Bugs in the System?

ISSUES IN THE SCIENCE AND REGULATION OF GENETICALLY MODIFIED INSECTS

A Report Prepared by the Pew Initiative on Food and Biotechnology

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Preface

As biotechnology continues to develop, scientists are applying genetic engineering techniques to develop new varieties of plants, animals and microorganisms for a wide range of purposes. Our first report, *Harvest on the Horizon*, documented some of the diversity of biotechnology products under development for many purposes, ranging from increasing agricultural production to solving human health problems.

In this report, we examine the promises and potential problems associated with the genetic modification of insects.[1] Scientists are modifying insects for a number of purposes. One area of research involves the use of genetically modified (GM) insects to help solve agricultural pest problems. For example, scientists are attempting to modify insect pests that destroy crops in ways that weaken their ability to reproduce or that make them less harmful to crops. Alternatively, scientists are working to use biotechnology to make more effective predators of agricultural pests. For beneficial insects like honeybees that produce food or that provide important natural services such as pollination, scientists are using biotechnology to make them more disease- and pest-resistant. A major area of research involves using biotechnology to make insects much less effective vectors (organisms that transmit diseases) of animal and human diseases, such as malaria and Chagas' disease. Some of the approaches being explored involve the direct genetic modification of the insect (transgenesis), while other approaches involve modification of the symbiotic microorganisms carried by insects (paratransgenesis). The potential to reduce or even end age-old endemic insect-borne diseases without the use of potentially environmentally harmful chemical pesticides is a powerful vision.

As with other biotechnology applications, however, potential risks must be weighed against these potential dramatic benefits. A recent report from the National Academy of Sciences raises some environmental issues, expressing special concern about GM animals that can easily escape or breed with wild relatives. If the modified trait provides the genetically modified animal with a fitness advantage, it could disrupt ecosystems and lead to adverse results.

1 Throughout this paper, the term "insects" will be used to encompass not only the taxonomic class of insects, but also mites and other creatures the general public may refer to as "bugs," but which the scientific community would refer to as "arthropods."

In the broadest sense, "genetic modification" can refer to changes in the genetic makeup of organisms, including hybrids (offspring of parents from different species or sub-species). The focus of this paper is on GM insects where genetic material from a separate organism has been inserted into the heredity material (chromosomes) of an insect through recombinant DNA techniques (transgenesis). Additionally, some research is being carried out to genetically modify the microbes associated with the gut or reproductive systems of pest insects. This type of genetic modification has been termed "paratransgenesis" because, although the insect itself has not been modified, its microbial inhabitants have been. Discussion of microorganisms in this paper is limited to the use of them in paratransgenesis; direct modification of pathogen microorganisms will not be discussed. The term "GM insects," then, will be used to include both transgenic and paratransgenic insects, and transgenic and paratransgenic will be used when necessary to differentiate specifically between the two.

Environmental concerns are especially critical for some GM insects, particularly those planned for some biological and disease control uses. These GM insects differ from most other genetically modified organisms created to date in one very important respect: they are intended for permanent establishment in the environment and, in the case of those GM insects intended for population replacement, the new genetic trait has to be "driven" into the wild population to work at all. In other genetically modified organisms, scientists generally want to contain the GM variety to prevent the genetic trait from moving into related organisms. In contrast, some GM insects will not only be expected to survive in the wild, but also to pass their genes to the wild population. The potential to "recall" these GM insects, if unanticipated adverse results occur, will be difficult if not impossible. Because insects play valuable roles as predators, prey, recyclers, pollinators, and more in ecosystems throughout the world, scientists must carefully weigh the risks and benefits of their proposals for using GM insects.

Careful regulatory scrutiny will be needed to prevent possible environmental, public health, agricultural, and food safety risks from GM insects. In addition to these primary functions, a secondary critical function of an effective and credible regulatory system is to create public confidence and trust that regulators are adequately addressing the potential risks of new technologies. Despite the potential substantial benefits of GM insects, public concerns about the possible negative impacts will need to be assuaged through credible and transparent regulatory processes. At the same time, researchers need a fair and effective regulatory system that establishes a reasonable and predictable path through the regulatory review process.

Since 1986, a central tenet of the U.S. regulatory system has been that the regulation of biotechnology products should not differ from that covering comparable products made by conventional methods. In other words, regulation focuses on the product, and not the process by which it is made. Thus, what laws and regulations apply depends on the nature of the product.

One of the challenges of this regulatory approach, however, is that biotechnology has the capability of creating new varieties of plants and animals that do not readily fit in any pre-existing product categories -- or, alternatively, that could fit in several categories. For example, a corn crop modified to produce a pharmaceutical chemical could be a "plant pest," a food, or a "drug manufacturing facility." This is not just a problem of semantics; the category of the product determines how it is regulated. Because laws and regulations vary dramatically in their purposes and procedures, the decision as to which product category a particular application falls into is a critical one. A poor "fit" between the product and its regulatory review process can undermine the credibility of the regulatory process and threaten public acceptance of the product, and result in an inadequate review of the risks posed by the product.

It is apparent that, while a number of laws might conceivably apply to GM insects, the federal government lacks a coordinated regulatory approach to ensure that all GM insects are reviewed for potential environmental, agricultural, food safety, and public health risks. The regulations issued to date on genetically modified insects only cover plant pests. Depending on what kind of "product" a GM insect is considered to be, several agencies could conceivably have authority over some issues posed by GM insects. Given the number and range of laws that could apply, the issue is not so much the lack of legal authority as whether those authorities will be used in a coordinated way to ensure an adequate and credible regulatory review of all relevant risks. In the absence of such a coordinated policy framework, it is currently impossible to say whether federal regulation adequately protects against possible public health, environmental, agricultural, and food-safety risks.

This conclusion does not mean that there is any imminent threat to public health, agriculture, food safety, or the environment. To date, most research is still taking place in contained laboratory environments, and environmental releases are still several years away. The few field trials that have taken place received permits under the regulations for genetically modified plant pests. If a field test or experimental release were proposed that did not fall under the plant pest authority, some federal agency would likely have the legal authority to assert jurisdiction and review it, but it is not clear which legal authority would apply or whether the agency involved would have the tools it needed to assess and manage the risks involved. More field trials are on the horizon and the federal government will need to move deliberately, and quickly, to clarify how it intends to address the regulatory issues posed by GM insects.

GM insects raise several unique challenges. Because insects are relatively small, can move rapidly and over long distances, as well as the fact that many insects of interest are located in other nations, regulation of GM insects raises issues relating to international approvals. The international regulatory regime for approving such releases is not at all clear.

Development of many GM insects is likely to come from university or government researchers, not private companies interested in approval for a commercial product, as was the case for genetically modified crops. This critical difference raises several issues. As scientists move from the contained laboratory research governed by National Institutes of Health funding guidelines to field trials and general environmental releases, it will be critical for federal regulatory agencies, federal science-funding agencies, universities, and the scientific community to come together to develop a better understanding of the pathway for moving from laboratory to field and the appropriate role of the regulatory agencies. Finally, the non-commercial nature of much of the on-going research may determine which federal laws are applicable.

This report does not make policy recommendations, but instead highlights several key policy issues to help policymakers and the public understand the potential benefits, risks, and regulatory challenges posed by this area of cutting-edge genetic research. We would like to acknowledge the major contribution of Dr. Marjorie A. Hoy for authorship of a scientific review used in developing this paper, and the collaboration of Mr. Eric Olsen and Mr. Bob Nicholas for authorship of a regulatory review of GM insects. We would also like to thank the individuals to whom we circulated a draft of the report for review (names and affiliations are listed in Appendix A).

Michael Rodemeyer
Executive Director
January 2004

Chapter One

DEVELOPMENT AND STATUS OF GENETICALLY MODIFIED INSECTS

Chapter I

DEVELOPMENT AND STATUS OF GENETICALLY MODIFIED INSECTS

A Introduction

Scientists choose to target and focus on insects because of their enormous impact on human health, crop production, and animal health. For example, many insect species act as vectors of human diseases that sicken and kill millions of people worldwide each year. Insects that transmit diseases cause immense suffering to the individuals who contract the diseases, as well as enormous economic losses to the countries in which the diseases are endemic (Schneider 2000, Long and Hoffman 2002). Recent estimates suggest that malaria alone reduces the economic growth of Africa by more than one percent each year, which adds up to hundreds of billions of dollars of lost income over time.

In the United States each year, pest insects consume or destroy about 13 percent or $33 billion of the total potential crop production (Pimentel et al. 1999), yet the U.S. is far ahead of many countries in controlling agricultural pests. Worldwide each year, insects consume and destroy approximately 30 percent of all food produced (Entomological Society of America 2002). In forestry, the U.S. loses about 9 percent or $7 billion of all its forest products each year to insects.

In an effort to control insect pests, people often turn to chemical pesticides. According to USDA's National Agricultural Statistics Service (USDA NASS), U.S. farmers in the 2000 crop year applied insecticides to approximately 75 percent of the cotton acreage, 62 percent of sugar beet acreage, and 27 percent of corn acreage. The U.S. EPA estimated that approximately 82 million pounds of insecticides and 470 million pounds of herbicides[2] were used in agriculture, while another 47 million pounds of insecticides and 98 million pounds of herbicides were used in homeowner/governmental/commercial pesticide applicator settings in 1997. This accounts for about 9 percent of the total insecticides and 25 percent of the total herbicides used each year around the world (U.S. EPA 2001).

While pesticides have economic and public health benefits (Gianessi and Sankula 2003), they can also have negative health and ecological impacts (Benbrook 1996, National Research Council 2000). In the U.S., an average of 60,000 human insecticide poisonings and an average of 9,700 human herbicide poisonings were reported to authorities each year between 1997 and 2001 (Litovitz et al. 1998-2002). Historically, some pesticides have been shown to have detrimental ecological effects on non-target species, though the degree of the effect varies widely with the type of pesticide used (NRC 2000). Some pesticides may have direct adverse effects on non-target species through direct contact or through food intake, or they may harm them through indirect means such as decreasing local biodiversity. Non-target species include not only wild animals and plants, but also domestic animals, and of particular importance to agriculture, pollinators and other beneficial insects and microorganisms (NRC 2000).

2 Herbicide usage is relevant because insects can be used for biological control of weeds.

Although most developed nations, including the U.S., have attempted to move toward the use of pesticides that pose fewer human health and environmental risks, this has not occurred as rapidly as some would like (Benbrook 1996, Gianessi and Silvers 2000, G.A.O. 2001).

In addition to health and ecological impacts, pest managers must contend with the development of pesticide resistance in pest species, which renders the chemicals less effective (NRC 1986, NRC 2000, Hemingway et al. 2002). Because most populations contain individuals better able to cope with a selection agent such as a pesticide, selection pressure allows those individuals to survive and spread their resistance genes relatively rapidly to others in the population, eventually creating a population of resistant pests. Virtually all pest taxa have shown the ability to become resistant to a pesticide at one time or another (NRC 2000). This has been a particular problem in mosquitoes where resistance to DDT and pyrethroids has developed (Hemingway et al. 2002, Denholm et al. 2002).

Pesticides also carry economic costs. U.S. agricultural producers, homeowners, commercial applicators, and governments spent $3.5 billion on insecticides and $6.8 billion on herbicides in 1997 (EPA 2001). Of this amount, agricultural producers alone spent $1.6 billion on insecticides and $5.6 billion on herbicides, not including the costs of application equipment, fees paid to applicators of the pesticide, regulatory compliance, training for workers handling pesticides, storage or disposal costs, or emergency costs in case of an accident where medical attention is needed (Mayse 1991). A program that could reduce producers' pesticide applications would likely reduce their production expenses, provided the program does not add costs elsewhere (FAO 2002a, Benbrook 1996). Pressure continues to mount for producers to find alternatives to pesticides, while at the same time maintaining an affordable, safe, and abundant food supply (General Accounting Office 2001).

In agriculture, one alternative to using pesticides is to use living organisms to control pest insects and weeds through biological control programs. Biological control agents function as predators, parasites, pathogens, or phytophages (plant eaters) to control pest insects and weeds.[3] Biological control programs can be especially useful when foreign pests invade without their natural enemies and scientists are able to identify biological control agents from the pest's original home that are effective and attack only the target pest (van Driesche and Bellows 1996).[4]

3 Due to the scope of this paper, pathogens that function as biological control agents will not be discussed.

4 Many of the most serious pests in the U.S. are invaders, non-indigenous insects that have entered the U.S. environment (Office of Technology Assessment 1993). For example, a single species of ant, the red imported fire ant, that invaded the U.S. from South America causes over $1 billion in damage to U.S. livestock, wildlife, and human health. Another foreign pest, the Formosan termite, causes over $1 billion in structural damage (Pimentel et al. 1999). Invasive insects were estimated to cost the U.S. economy approximately $92 billion in damage between 1906 and 1991 (OTA 1993).

When biological control is successful, these programs can save millions of dollars in pest control costs and dramatically reduce the amount of pesticides applied, thus benefiting the environment as a whole (Hoy 2003). Biological control can provide inexpensive and long-lasting control because natural enemies establish and persist in the environment. Unfortunately, traditional biological control programs are often hindered by a lack of funding and scientific knowledge necessary to identify safe and effective agents. Biological control agents are also sometimes limited in their fundamental effectiveness, because of biological constraints such as susceptibility to pesticides or an inability to survive over winter; thus, scientists are working on genetically engineering biological control agents to help them perform better (Beckendorf and Hoy 1985, Heilmann et al. 1994, Hoy 1994, 2000).

In government-sponsored programs to control vector insects or agricultural pests in the U.S., pesticide use almost always provokes disagreements between government officials charged with protecting human health and agriculture, and individuals or groups who do not want people or the environment exposed to pesticides. Those managing programs, such as those used to control mosquitoes that transmit diseases to animals and humans, face the daunting task of trying to control an insect over vast geographic areas while also trying to make minimal environmental impacts. For this reason, researchers are seeking other options such as creating mosquitoes modified to no longer transmit the malaria parasite to people (James 2000, Nirmala and James 2003). Other scientists are doing similar work on insects that transmit other insect-borne diseases (Beard et al. 2000, Hao et al. 2001).

Another alternative pest control approach relies on the genetic control of pests. The term “genetic control” refers to programs in which the ability of the target insect population to reproduce is changed through radiation, chemical mutagenisis, or genetic engineering. To date, genetic control programs have only used insects altered by radiation or chemical mutagens. Scientists are now, however, experimenting with genetically engineering pest insects in an effort to improve genetic control programs (Robinson and Franz 2000). An example of one current genetic control program involves the Mediterranean fruit fly, which is mass reared and sterilized by irradiation prior to release of males. After release into the environment, these sterile males mate with wild females in the environment. The sterile males reduce the ability of the wild females to reproduce, and can even result in complete elimination of the pest in localized areas. Improvements in such genetic control programs could occur if genetically modified sterile males were better able to mate with wild females than the irradiated males, or if the mass-rearing programs could reduce costs by rearing male-only batches.

While much of the scientific focus is on insects that can cause harm to humans, animals, or crops, a few researchers are working on insects that greatly benefit humans, such as honeybees and silkworms. These two economically important insects provide billions of dollars worth of honey, pollination services, and silk (USDA NASS 2002, Southwick 1992, Wurm 2003). Researchers are trying to create disease- and pest-resistant honeybees and have considered making them pesticide-resistant as well. They are also altering silkworms to make them capable of producing biomedical proteins for use in human and animal pharmaceuticals (Tomita 2002). Scientists are also attempting to strengthen the silk that silkworms produce naturally in an effort to expand its uses in medicine and industry (Agrawal 1999, O'Neill 2000, Rennie 2000).

History of GM Insect Development

Insects have been used in genetic studies since 1910, when T. H. Morgan, a professor at Columbia University, started working with *Drosophila*, a fruit fly, for his research on heredity (Rubin and Lewis 2000). *Drosophila* offered researchers advantages over other animals for basic genetic research: a short time interval between generations (10 –12 days) and an ease in caring for and rearing them. By 1927, researchers had proven that radiation caused genetic changes (called mutations) in the fruit flies (Rubin and Lewis 2000). This fly remains a key tool in the basic research of heredity and evolution.

By the early 1980's, researchers had discovered a way to create genetic modifications to *Drosophila* fruit flies that were then passed on to the next generation (Rubin and Spradling 1982). The transformation system, however, was limited in its usefulness, because it only worked well in fruit flies. It took researchers another ten years to find ways to insert genes into other insects (Handler 2000).

By 2000, researchers had finished sequencing the fruit fly's genome (Rubin and Lewis 2000) and in 2002, the genome of the mosquito *Anopholes gambiae*, the major vector of malaria, was finished as well (Holt et al. 2002). The genomes of the mosquito *Aedes aegypti* and the honeybee *Apis mellifera* are currently being analyzed (Kaufman et al. 2002). The sequencing of genomes should increase the ability of scientists to identify useful genes to use in genetically modifying pests and beneficial insects. During the past decade, a few hundred researchers from around the world have been meeting regularly to exchange information related to the genetic modification of insects at Keystone Conferences called "Genetic Manipulation of Insects." Researchers have expanded their focus to additional insects, including tsetse flies, sandflies, pink bollworms, and silk moths, and, excluding the silkworm, the focus is on future applications in the field rather than just in the laboratory (Staten 2001, Aksoy et al. 2001, Hao et al. 2001).

In 1996, researchers performed the first field test of a transgenic predatory mite in the U.S. (Hoy 2000). Since then, genetically modified pink cotton bollworms (PBW) have been released in confined field cage trials (USDA APHIS 2001a). The initial confined field cage trials of GM pink bollworms demonstrated, however, that additional work is needed to "establish a usable genetically marked PBW" (Miller and Staten 2003). Researchers at the Centers for Disease Control and Prevention (CDC) in Atlanta are currently greenhouse testing a paratransgenic kissing bug designed to prevent the spread of Chagas' disease in Central and South America, and they will eventually need to field test it (Durvasula et al. 2002). If future confined field trials of the GM pink bollworm or the kissing bug achieve their goals, these GM insects could be considered ready for release in an operational pest management program in the relatively near future (Miller and Staten 2003, Beard et al. 2002).

Status of GM Insects

Table 1, though certainly not an exhaustive list of the current research on transgenic or para-transgenic insects, illustrates the breadth of projects now in the pipeline, from research through deployment, and summarizes the potential benefits and intended uses of each.[5]

TABLE 1

Examples of GM Insects in Research, Development, or Deployment

SPECIES *METHOD*	POTENTIAL BENEFIT	INTENDED END USE OF MODIFIED ORGANISM	PRODUCT STATUS
Honeybee *Transgenic*	Create an insecticide-resistant honeybee (Kimura 1997).	Protect this economically important insect from insecticides.	Laboratory research
Medfly *Transgenic*	Create medflies that carry a phenotypic marker and/or are male-only strains and/or pass along a fatal trait to developing offspring for use in an SIT program (Horn and Wimmer 2003, Robinson 2002a).	Control the medfly's impact on agriculture.	Laboratory research
Mites *Transgenic*	Researchers created a transgenic predatory mite with a marker gene (Hoy 2000).	Released as a model to test risk issues.	Initial field tests completed
Mosquitoes *Transgenic*	Create a mosquito that produces proteins that hinder the development of the malaria parasite within the mosquito (Ito et al., 2002, Nirmala and James 2003).	Protect human health by controlling the spread of malaria.	Laboratory research
	Boost the immune system of mosquitoes to destroy any bacteria taken up during a blood-feeding (Kokoza et al. 2000, James 2000, Nirmala and James 2003).	Protect human health by controlling the spread of malaria.	Laboratory research
	Create a mosquito that expresses antiparasite toxins (Nirmala and James 2003).	Protect human health by controlling the spread of malaria.	Laboratory research
	Creation of dengue-resistant mosquitoes (Olson et al. 1996).	Protect human health by controlling the spread of dengue.	Laboratory research
	Use mosquitoes to inject proteins into humans to induce immune response to diseases (vaccinate), such as malaria (Distribution on the Fly 2001, Crampton 1998).	Deliver vaccines to difficult-to-reach populations.	Laboratory research Patented

5 For a more complete look at current research on GM insects, see Hoy 2003.

TABLE 1 (CONTINUED)

Examples of GM Insects in Research, Development, or Deployment

SPECIES *METHOD*	POTENTIAL BENEFIT	INTENDED END USE OF MODIFIED ORGANISM	PRODUCT STATUS
Pink Bollworm *Transgenic*	Create a pink bollworm with a fluorescence marker gene to test field performance and for onsite experimentation (Staten 2001).	To eventually add other genes and establish an autocidal genetic control system for PBW.	Tested in confined field cage trials
Silkworm *Transgenic*	Create a silkworm capable of producing pharmaceutical or other proteins (Tomita et al. 2002, Wurm 2003, Tamura 2000).	Production of low-cost medical or industrial proteins.	Laboratory Research
Kissing Bug *Paratransgenic*	Engineer gut symbionts (bacteria) that live inside the kissing bug to kill the parasite responsible for Chagas' disease that also lives inside the kissing bug (Beard et al. 2002).	Protect human life by controlling Chagas' disease.	Greenhouse trials in preparation for field trials in Guatemala.
Glassy-winged sharpshooter *Paratransgenic*	Engineer a symbiont of the vector of Pierce's disease, the glassy-winged sharpshooter, to kill the bacteria that cause Pierce's disease in grapes (Miller et al. 2003, Cool 2003).	Protect vineyards from insect-transmitted disease.	Laboratory and preliminary field research with the bacterium.
Planthoppers *Paratransgenic*	Engineer endosymbionts (bacteria) to express proteins that block the transmission of rice stripe virus by planthoppers (Kang et al. 2003).	Protect rice production from insect-transmitted plant viruses.	Laboratory Research
Sand Fly *Paratransgenic*	Engineer gut symbionts (bacteria) that live inside the sand flies to kill the leishmania that can infect sandflies (Durvasula et al. 2002).	Protect human life by controlling leishmaniasis.	Laboratory Research
Tsetse Flies *Paratransgenic*	Hinder the development or transmission of trypanosomes in tsetse flies through paratransgenic symbionts or through boosting the fly's immune system (Aksoy et al. 2001, Hao et al. 2001).	Protect human health by controlling the spread of African trypanomiasis (Sleeping sickness).	Laboratory Research

HOW TO CREATE A TRANSGENIC INSECT

A Look at the Science: How GM Insects Are Created

Domesticated and semi-domesticated insects have been modified by traditional breeding methods for hundreds of years. Classical genetic manipulation, or breeding, has improved disease resistance and silk production in silkworms (Yokoyama 1979, Gopinathan 1992) as well as disease resistance and pollination attributes in honeybees (Rothenbuhler 1979). However, traditional genetic selection limited the development of traits and characteristics to the intrinsic genetic variability of the species under study or to genetic mutations introduced by agents that cause random DNA changes, like X-rays. Recombinant DNA methods, or genetic engineering, remove that limitation, greatly enhancing the number and type of genes potentially available for use, and allow researchers to make more precise genetic changes (Hoy 2003).

A number of challenges are involved in genetically modifying an insect or mite successfully. First, researchers need to identify a trait that, if altered or introduced into an organism, would be beneficial. Once identified, scientists have to pinpoint the gene responsible for generating this trait and use various techniques to isolate and duplicate (clone) it in large enough numbers to be useful for genetic engineering endeavors.

Theoretically, scientists can isolate genes from any organism, either closely or distantly related, for insertion into insects by recombinant DNA methods (Hoy 2003). For example, researchers can use genetic engineering to lift a gene for a luminescent protein from a marine jellyfish and insert it into a silkworm, thus creating fluorescent silkworms (Toshiki et al. 2000). Traits primarily determined by single major genes are most practical, because methods for manipulating and stabilizing traits that are determined by complex genetic mechanisms are not yet feasible with insects (Hoy 2003). In addition, scientists have to isolate the DNA sequences that can regulate the activity of the gene so that it functions properly once inserted into the “host” insect (Hoy 2003).

Scientists then stitch the desired genes and appropriate regulatory sequences together to form a "genetic construct" for delivery into the germ band chromosomes (those elements that later make sperm or eggs) of the target organism. The genetic construct would likely also include a vector, which is a genetic sequence capable of inserting itself and introducing the other piece of the genetic construct into a cell's DNA (Hoy 2003).[6]

Two types of vectors[7] are available to researchers modifying insects: transposons and viral vectors. Transposons are sections of DNA that may move to unique positions within the genome. Researchers have exploited transposons' natural ability to "cut and paste" themselves out of and into DNA in order to insert the desired DNA into target insects. Scientists cannot predict the exact site of a transposon insertion. They do know, however, that it is controlled by a specific site in the DNA, which occurs in multiple places in the genome. Furthermore, a bias may exist for some sites of the same nucleotide sequence over others (Handler 2002). The choice and deactivation of transposon may affect the stability of the inserted DNA and may have implications for environmental, agricultural, and public health safety. The section entitled "Potential Concerns Posed by GM Insects" will further discuss potential risks of using transposons to genetically modify insects.

Researchers also use the natural ability of viruses to invade a cell and integrate their DNA into the target genome to ferry desirable DNA into the target cell. Like transposons, viral vectors may have implications for environmental, agricultural, and public health safety (Hoy 2003).

Once scientists have created the genetic construct, they then need a way to deliver it into the germ band chromosomes (those elements that later make sperm or eggs) of target organisms, where the vector can then incorporate the desired genes and regulatory sequences into the target organism's DNA. Scientists have developed a number of methods for this purpose[8], including using a tiny micropipette to inject the DNA construct into insect eggs. Alternatively, scientists have soaked eggs in DNA, or used sperm to carry the foreign DNA into the eggs. Investigators have also used "gene guns" or electrical treatments to help introduced DNA molecules penetrate the nuclei of insect eggs (Hoy 2003).

Only a small portion of transformation attempts find success. Many of the injected eggs die and many do not keep the injected genes. Consequently, once scientists have attempted to insert desired genes into target organisms, they need to screen out those insects with the foreign genes added into their genomes. To do this, they include "marker genes" with the desirable genes to identify those insects containing the desired genes. Marker genes may code for traits such as a unique eye color, resistance to certain antibiotics or pesticides, or expression of a green fluorescent protein, though detection can be difficult depending on background fluorescence and in what tissue fluorescence is expressed. Some researchers have suggested that use of antibiotic or pesticide resistance markers is not as vital as once was thought because of both the availability of alternative markers (ffrench-Constant and Benedict 2000, Horn et al. 2002) and the fact that these markers are unreliable markers as resistance can develop in non-GM insects (FAO/IAEA 2002). Only those organisms that exhibit a marker trait will also have the other foreign genes. Once scientists identify the transformed insects, considerable back-crossing to non-modified insects, selection, care, and time is required to produce insects useful in the field, because transgenic insects are often very weak (Joron and Brakefield 2003, Catterucia et al. 2003).

6 For a complete list of available gene transfer methods, see Table 14.3 in Hoy 2003.

7 The word vector has more than one definition. Here vector is defined as "a sequence of genetic material used to introduce specific genes into the genome of an organism" (Merriam-Webster 2003). This use of the word vector here differs from earlier references in this report to disease vectors (organisms that can transmit disease).

8 For a more complete list of methods to deliver foreign DNA into insects, see Table 14.4 in Hoy 2003.

Chapter Two

POTENTIAL BENEFITS OF GENETICALLY MODIFIED INSECTS

Chapter II

POTENTIAL BENEFITS OF GENETICALLY MODIFIED INSECTS

The use of GM insects in agriculture could potentially reduce the need for producers to use pesticides on some crops. By altering biological control insects and pest insects themselves, scientists may provide producers viable alternative tools to protect their crops. In areas involving large acreages where pesticide application is not practical, such as rangeland, forests, and natural areas, GM biological control insects could provide managers of such lands an ecologically-friendly tool to fight invasive non-indigenous species. Finally, scientists may also be able to protect the nation's livestock herds from insect vectors of animal diseases.

A Potential Agricultural and Environmental Benefits

Transgenic insects may prove useful in agriculture for several different methods of controlling pests. In one case, transgenic insects could serve as biological control agents (i.e., used to control pest insects or weeds). Transgenic plant and animal pest insects could also be part of a genetic control program, where the insects are essentially used against themselves. It may also be possible to control the spread of animal diseases by insects, just as researchers are attempting to do with human diseases (see section on Potential Public Health Benefits). Finally, plant or animal diseases may be controlled through the use of paratransgenic insects. The following five sections describe the potential impact of GM insects on agricultural pest control.

i. Traditional Biological Control Programs

In traditional biological control programs, researchers look for natural enemies, or biological control agents, that function as predators, parasites, or phytophages (plant eaters) to control pest insects and weeds. Essentially, researchers use natural population control methods to keep pest species in line (Van Driesche and Bellows 1996).

For example, scientists have released leaf-feeding beetles, called *Galerucella*, to control purple loosestrife, an invasive wetlands weed capable of rooting out native plants and thus degrading habitat for wildlife. The beetles significantly reduced the amount of loosestrife in only a few years (Tu et al. 2001). Another example is the use of a parasitic wasp to control ash whiteflies in California ornamental plants and trees. Once introduced, the wasp brought the ash whitefly population under control within only two years and is credited with saving more than $200 million in tree replacement costs (OTA 1993).

ii. GM Insects as Biological Control Agents

Unfortunately, biological control agents are not always as successful or useful as scientists would like in controlling the target pest (Hoy 1976, 1993, Heilmann et al. 1994). For every success in biological control, several failures occur, particularly in annual crops where the establishment of equilibrium is much more difficult than in perennial crops. The preferred approach is to control pests by cultural practices (such as crop rotation, host plant resistance, etc.) in combination with natural enemies and possibly involving some selective insecticides. The economics of many large-scale monoculture crop production systems may dictate the use of pesticides. Classical biological control agents should be better able to control their targeted pests if they could survive longer and in more environments, and/or if they were tolerant to pesticides.

Researchers are working to understand how to alter life cycles in insects in hopes of providing biological control insects with longer, more productive lives, thus giving them more opportunities to attack pests. For example, some research on mechanisms of aging has resulted in the extended life span of the fruit fly in the laboratory (Tower 2000). Other researchers are enhancing progeny production or shortening the length of time it takes to grow the insect to its full size, and thus obtain effective biological control performance levels sooner (Hoy 1976). Still others are working to remove inactive periods that make up the lives of some insects (Hoy 1993). Pesticide resistance could also be beneficial in biological control agents, allowing farmers to use pesticides without harming the biological control insects (Hoy 1990). Altering the sex ratio (proportion of females) could also result in better pest control, because, in some species, only the female parasite attacks the target pest insect.

Work is also underway to expand the ability of biological control agents to survive in different environments. Because biological control agents are often not native to the environment in which they are placed, they may not adapt as well to their new environment as has their prey. Through traditional breeding, researchers have made some progress towards tolerance of temperature extremes among biological control agents (Hoy 1993). Genetic engineering allows researchers to use genes from non-related organisms to speed this process along. For example, scientists have demonstrated increased freeze resistance using antifreeze protein genes from two cold water fish in the *Drosophila* fruitfly (Rancourt et al. 1990, 1992, Peters et al. 1993, Duncker et al. 1995, 1996). While additional work is required to obtain insects that tolerate cold temperatures, the results suggest that subtropical or tropical species of biological control agents could become useful or adapted in a much broader range of climates. Other researchers are looking at extending temperature and relative humidity tolerances or altering host or habitat preferences (Hoy 1976).

iii. Conventional Genetic Control Methods

The sterile insect technique (SIT)[9] is the most commonly used genetic control method. In an SIT program, the pest is essentially used against itself to control its population. The males of a pest insect are mass-reared in a factory, sterilized by irradiation or chemicals, and then released in large numbers after tests confirm the males are indeed sterile (Robinson 2002). These males then compete with fertile wild males for the chance to mate with wild females. If the sterile males succeed, the wild females fail to reproduce or produce fewer progeny (LaChance 1979, Rechcigl and Rechcigl 2000).

During the past 40 years, use of the SIT has eradicated pests or reduced populations of pests having a significant impact on agriculture and human health, including the Mediterranean and Caribbean fruit flies, mosquitoes, tsetse flies and the New World screwworm (Wright and Pal 1967, Pal and Whitten 1974, Curtis 1979, LaChance 1979, Whitten 1979, Vreysen et al. 2000, Wyss 2000, Robinson 2002). For example, scientists used the SIT initially to eradicate the New World screwworm from the U.S. Later, the program was expanded to eliminate this pest from North and Central America (Mexico, Costa Rica, Belize, Guatemala, Honduras, El Salvador, Nicaragua and Panama) (Wyss 2000). In 1996, benefits of the screwworm SIT program to U.S., Mexican, and Central American cattle producers were estimated at $796 million, $292 million, and $77.9 million respectively. The benefit to cost ratios for the eradication programs ranged from an average of 12.2:1 for Central America to 18:1 for the U.S. and Mexican programs (Wyss 2000). In addition, screwworm eradication has a significant human and wildlife health component not included in these calculations (U.S. Embassy of San Jose 2003).

Other SIT programs have found equal success in eradicating pests. For example, the Medfly was eradicated from Chile using the SIT, allowing the country to gain approximately $400 million in trade with the U.S., which had previously banned imports of certain Chilean food products because of fears of accidental importation of the medfly. The SIT was used against the medfly in California as a preventive measure to preclude any accidental importations from establishing permanent populations. The ability to eradicate some pests is a unique aspect of the SIT compared to other insect control methods (LaChance 1979).

Another type of genetic control program has been proposed and tested, at least on a small scale (Pal and Whitten 1974, Whitten 1979). This program does not involve releasing sterile males; rather, through conventional methods (such as irradiation), insects are bred to carry a lethal gene, and both males and females are released to mate with the wild population. By transmitting the lethal trait to the progeny, subsequent generations of the insect populations can be reduced. This approach to genetic control of pests has not been used in any large-scale pest control program because it is more complex and difficult to achieve (LaChance 1979).

9 The Sterile Insect Technique is also known as the Sterile Insect Release Method or SIRM.

iv. GM Insects and Genetic Control Methods

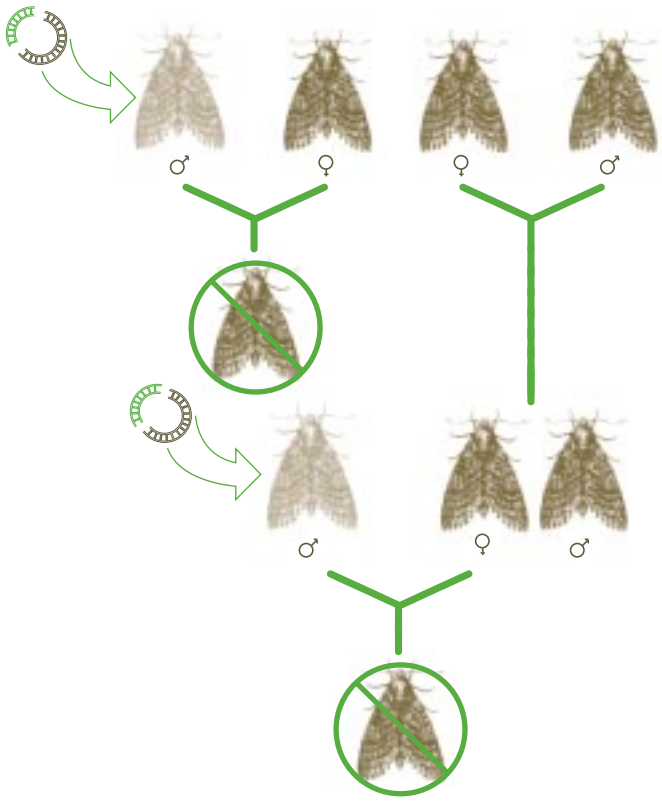
A big drawback to SIT programs is the damage to individual insects caused by the irradiation used to sterilize the male insects (LaChance 1979). During the irradiation process, the insect's whole body is irradiated, which damages all tissues and weakens the insect. As a result of this and problems caused by factory mass-rearing (disease, inbreeding, genetic adaptation), the SIT requires rearing very large numbers of males for release to "overflood" the native males. The number of sterile males released is usually a multiple of the estimated number of wild males; often 100 sterile males to 1 wild male. Rearing such huge numbers of insects is costly and difficult (LaChance 1979, Robinson and Franz 2000, Rechcigl and Rechcigl 2000).

Biotechnology could allow researchers to place lethal or sterility genes into insects, eliminating the problem of irradiation damage (Robinson and Franz 2000, Braig and Yan 2002). Sterility genes would take the place of exposure to irradiation, leaving male insects sterile but with none of the side effects of irradiation. Lethal genes would allow conception to occur, but the progeny would not live long enough to reproduce. Medfly researchers, for example, have been working to create medflies that pass along a fatal trait to their offspring, thus reducing the medfly population (Robinson and Franz 2000, Robinson 2002a). The fatal trait could be something like a "cold-sensitive gene" which would kill the recipient progeny when temperatures plunged (Marshall 1998). (For another example of the use of lethal genes, see the sidebar on Genetic Control of Pink Bollworms.)

Even where irradiation is the preferred method of sterilization, recombinant DNA techniques may help to improve the process by making insects more resistant to the tissue damage induced by irradiation (Robinson and Franz 2000). Additionally, the insertion of molecular markers into the sterile males would allow SIT program managers to differentiate more easily between released sterile males and wild males in traps, an important aspect of monitoring the progress of an SIT program. This would increase the efficiency and lower the costs and errors involved in SIT programs (Robinson and Franz 2000).

Genetic engineering may also make it possible to control the sex of insects reared in SIT programs (Hoy 1976, Robinson and Franz 2000). It is important in SIT programs to release only males. An SIT program should flood the environment with sterile males with which wild fertile females would mate; laboratory-reared females would compete with wild females for sterilized males and decrease the efficiency of the program. Furthermore, laboratory-reared females may be pests themselves, depending on the species. Conventional breeding methods allow insect breeders to develop "sexing" strains, but these methods are difficult to use, are not particularly stable, and are species specific (Robinson and Franz 2000, Robinson 2002). Biotechnology may allow researchers to put in sex-specific lethal genes designed to kill off the females under certain environmental conditions or in the presence of certain foods (Robinson and Franz, 2000). In this way, SIT programs could produce large batches of male-only insects.

TRANSGENIC MOTHS AS PART OF A GENETIC CONTROL PROGRAM



GENETIC CONTROL OF PINK BOLLWORMS

Agriculture already benefits from genetic control programs, both ecologically and economically. For example, the pink bollworm (PBW), a native of southern Asia, feeds on cotton plants throughout most of the southwestern cotton-growing states in the U.S., with the exception of the San Joaquin Valley of California. The bollworm causes damage when it eats the cotton flower or tunnels through the cotton boll to get at the seeds inside the boll. It later pupates and develops into a moth (USDA APHIS 1995a). PBWs are kept out of the San Joaquin Valley through a sterile insect technique (SIT) program, which protects more than 900,000 acres of cotton valued at more than $1 billion annually. The program rears millions of moths in a facility in Arizona, where they are irradiated to cause sterility and then released over cotton fields from planes as directed by the California Department of Food and Agriculture (CDFA). CDFA estimates that the genetic control program decreases by seven pounds per acre the amount of pesticides needed if PBW infested the San Joaquin Valley (CDFA 2002). USDA Animal and Plant Health Inspection Service (APHIS) estimates that pink bollworms cost the Imperial Valley approximately "$250 million, or about $300 per acre, each year between 1966 and 1980" (USDA APHIS 2001).

Because sterile moths, which are weakened by their exposure to radiation, need to outnumber wild fertile moths nearly 60:1, the costs of this program prohibit implementation in other areas of the nation where the pest already occurs (Robinson and Franz 2000). The National Cotton Council of America estimates that cotton producers in West Texas, New Mexico, Arizona, and California, annually lose about $21 million through costly pesticides, control methods, and crop yield loss to control the PBW (Carter 2001). Furthermore, this figure does not include any ecological costs or human health impacts from the use of pesticides.

For these reasons, some researchers have turned to biotechnology in hopes of creating a genetically modified PBW for use in infested areas. Researchers are working to design a PBW male moth that would pass on a lethal gene, which would prevent embryonic development, thereby eliminating the bollworm before it could do any damage (Staten 2001). Because such a moth would, theoretically, result in no viable offspring, the male moths would no longer need radiation exposure. In turn, they should be stronger and more able to compete with wild males, thus lowering the ratio of transgenic males to wild males needed for a successful SIT control program in heavily infested PBW areas. Furthermore, the lethal genes are conditional, meaning that they are suppressed in the presence of the tetracycline, an antibiotic currently used in mass-rearing facilities to suppress bacterial growth. The conditional lethality allows scientists to back-cross the PBW and breed in more viability, which should make them better competitors against wild males for wild females.

A recent progress report from the researchers indicated that "additional work needs to be done to establish a useable genetically marked PBW" (Staten 2003), the first step in creating a conditionally lethal GM PBW. In particular, the initial data suggests that the field life of the male transgenic PBW was not as long as the current male non-transgenic mass-reared PBW used in SIT programs. The transgenic PBW males also showed lower responses to pheromone traps than their non-transgenic counterparts, and transgenic PBW females mated significantly less than non-transgenic mass-reared PBW (Miller and Staten 2003). The researchers plan additional work before an open field release may be considered (Staten 2003).

v. The Use of Paratransgenesis in Controlling Agricultural Pests

Paratransgenesis refers to the genetic modification of insect symbionts (usually bacteria that live in the insect gut or reproductive systems) rather than the modification of the insects themselves. (For a more extensive look at how paratransgenesis works see the paragraph on Chagas' disease research under "Potential Public Health Benefits of GM Insects"). Some researchers hope to use a paratransgenic approach to reduce the transmission of rice stripe virus by planthoppers *(Laodelphax striatellus)* (McKnight Foundation 2003, Kang et al. 2003). They are trying to genetically modify *Wolbachia*, a bacterium present in the reproductive tissues of many insects, including planthoppers, to block transmission of the rice stripe virus by expressing particular proteins that interrupt transmission of the virus (McKnight Foundation 2003). Furthermore, *Wolbachia* infections can give the insects a reproductive advantage over non-infected insects, which should help spread (drive) the microbe through the population. Researchers plan to test this system in screenhouse conditions.

Another paratransgenic project involves altering symbionts of the glassy-winged sharpshooter (GWSS) in an attempt to cure or prevent Pierce's disease in vineyard grapes. Pierce's disease is an infection of grapevines caused by the bacterium *Xylella fastidiosa*. Known to exist in California for most of the last century, it was, except in rare cases, restricted to some California vineyards until recently, when the GWSS, *Homalodisca coagulata*, was introduced into the state. The GWSS is a much more efficient vector of Pierce's disease than the native leafhoppers, and Pierce's disease now seriously threatens all California vineyards (Miller et al. 2003). GWSS has spread from southern California to the southern end of the Central Valley, with pockets of GWSS found further north. Treatment of citrus with systemic insecticides in winter has slowed the onset of Pierce's disease by controlling the winter population of GWSS near vineyards, but an ultimate solution is not yet available. Continued spraying of alternative host plants unaffected by disease increases tensions amongst growers (Miller 2003).

Scientists are working on a paratransgenic approach to halt the spread of Pierce's disease. So far, they have altered *Alcaligenes xylosoxidans denitrificans*, a symbiont first isolated from the mouthparts of GWSS and present in plant xylem fluid, to carry a DsRed fluorescent marker gene (Miller et al. 2003). They received permission through EPA to apply this GM bacterium on grapevines in field cages in commercial vineyards in a confined field trial designed to elucidate the bacterium's biology, movement, and behavior within the vineyard ecosystem (Cool 2003, Miller et al. 2003). Once scientists know more about the symbiont's biology and behavior, they hope to further transform the bacterial symbiont to carry anti-Pierce's disease proteins and to insert the bacterial symbiont into the insect and plant disease cycle pathway in such a manner that Pierce's disease is neutralized (University of California 2001, Miller et al. 2003).

B Potential Public Health Benefits of GM Insects

The use of GM insects in public health programs could potentially have enormous impacts on quality of life, health care costs, and mortality rates in some areas of the world (See Table 2). Mosquitoes, tsetse flies, kissing bugs, ticks, fleas, lice and other insects notoriously act as vectors of human and animal illness; therefore, much of the work on GM insects focuses on disease prevention. Because complete elimination of vector insects remains impractical in most situations, researchers seek ways to alter insects to make them less capable of transmitting disease (James 2000, Aksoy 2000, Beard et al. 2000, Nirmala and James 2003).

i. The Use of Transgenic Vector Insects to Control Disease Transmission

Researchers are working on various methods to change the ability of disease vectors to transmit disease (vector competence). So far, much of the research has centered on mosquitoes, because mosquitoes are the vectors of many of the worst insect-borne diseases and the impact could be immense. At least eight teams (5 U.S., 3 E.U.) are researching transgenic mosquitoes (Enserink 2002).

THE ECONOMIC AND SOCIETAL COSTS OF MALARIA

The World Health Organization estimates that between 300 and 500 million clinical cases of malaria occur each year, and over one million people, mostly children under the age of five, die from malaria. Including the impact of malaria on death from other diseases, the actual death toll per year from malaria reaches closer to three million. About 2000 children a day, or one every 40 seconds, dies directly from malaria (Sachs and Malaney 2002).

Of children that survive the disease, some are cognitively or developmentally impaired. Studies have shown that children with malaria are less able to perform fine motor functions. Furthermore, between 5 and 20 percent of children that survive cerebral malaria (when malaria affects the central nervous system) exhibit both behavioral and cognitive disorders. Additionally, pregnant women are particularly susceptible to malaria, and malaria-caused anemia in the mother can lead to low birth weight for the baby, which is associated with developmental problems (Sachs and Malaney 2002).

In endemic areas, adults may develop immunity from malaria, but only partially. People leaving a malaria area risk losing their immunity if not re-infected every year or so. Because leaving an endemic region may mean catching the disease upon returning, people hesitate to move into and out of endemic regions, thus preventing people from seeking additional education or better jobs (Sachs and Malaney 2002).

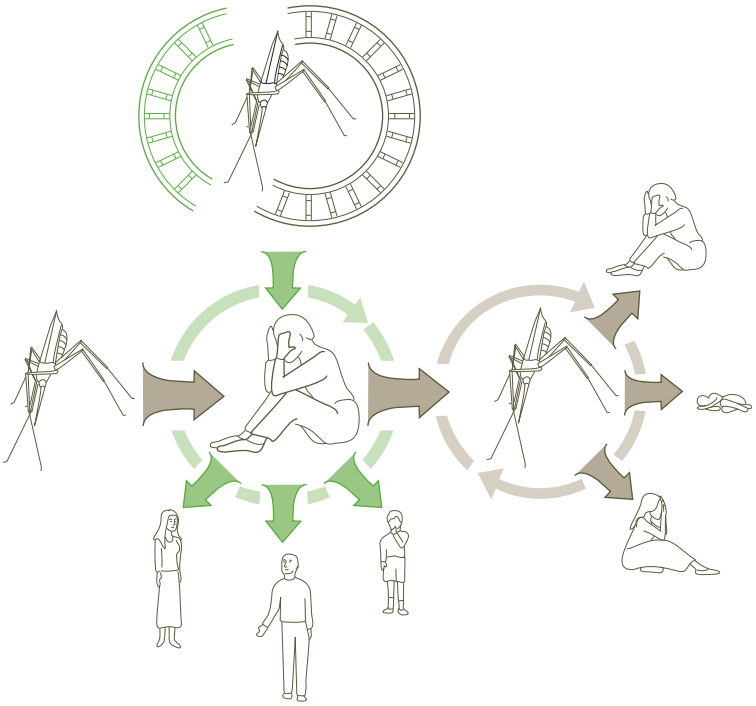
Malaria affects economies by discouraging tourism and foreign investments in endemic areas. For example, when malaria was brought under control in Greece, Portugal, and Spain in the 1950's, their tourism rates increased dramatically (Sachs and Malaney 2002). More recently, when a London-based mining company, Billiton, built a $1.4 billion aluminum smelter in Mozambique, the company's employees experienced 7,000 cases of malaria, and 13 workers died from the disease in their first two years of operation (Thurow 2001).

Besides these costs, estimates show malaria slowing economic growth by 1.3 percent per year in countries in which malaria is endemic, leaving these countries further and further behind (World Bank 1999). Malaria-endemic countries average a gross domestic product per person three times lower than malaria-free countries, even after including the effects of government policies, geographical locations, and other impacts on economic vigor (WHO 2000).

Significant sums of money are spent on treating and preventing malaria in countries that are not wealthy (Mills 1991). A family of five in several Sub-Saharan African nations may spend as much as $55 annually on prevention methods such as mosquito coils, insecticide sprays, bednets, and repellents, while the median per capita income in these nations is approximately $800 (World Bank 1999). Currently, international spending on malaria totals about $100 million, whereas estimated needs are closer to $1 billion. The WHO Commission on Macroeconomics and Health estimate that the expenditure needs by 2007 will reach $2.5 billion and rise to $4 billion by 2015 (Sachs and Malaney 2002).

Perhaps the greatest measure of the magnitude of malaria's impact on humans is its effect on human biology and evolution.

"Long before economists attempted to estimate the costs of malaria, natural selection had already demonstrated the phenomenal burden of the disease. Certain genetic polymorphisms, such as sickle cell trait, were selected for because of their protective effect against malaria when inherited from one parent, even though the same allele inherited from both parents is fatal. In essence, the chance of death from malaria was so high as to justify welcoming a potentially fatal mutation into the [human] gene pool" (Sachs and Malaney 2002).



Researchers have genetically engineered one type of mosquito to reduce transmission of the malaria parasite (Ito et al. 2002). The researchers transformed the mosquito to produce a protein that binds to the same receptor site in the mosquito midgut to which the malaria parasite must bind to complete its life cycle. By preventing the malaria parasite from binding, the malaria parasite's life cycle is interrupted, resulting in fewer transmissions of the parasite. This is a significant milestone but, because the scientists were working on a parasite that causes malaria in rodents, it remains to be seen whether this protein will work against parasites that cause disease in humans (Lycett and Kafatos 2002).

Other researchers are focusing on boosting the immune systems of mosquitoes to produce more defensin, a protein which destroys bacterial cell walls and may be useful in controlling the malarial protozoa and elephantiasis-causing filarial worms (James 2000). Scientists are creating mosquitoes that will produce defensin whenever they take a blood meal so that any bacteria and malaria parasites taken into the mosquito's digestive tract during feeding would be destroyed by the defensin. Similar work is underway to stop the spread of dengue fever, yellow fever, and encephalitides by mosquito vectors.

Some researchers are experimenting with making transgenic mosquitoes that vaccinate people or animals against malaria or other infections (Distribution on the Fly 2001, Crampton 1998), although this application is in preliminary stages and is years away from fruition. A mosquito bite would trigger the production of proteins in the individual bitten. These proteins, or antibodies, would then act like a vaccine to halt disease.

TABLE 2

Sample of Worldwide Infection and Mortality Caused by Insect-Borne Diseases

DISEASE	INSECT VECTOR	NUMBER OF PEOPLE INFECTED EACH YEAR	NUMBER OF DEATHS EACH YEAR
Dengue Fever (WHO 2002)	Mosquitoes	50 million	12,500 but could be much higher
Elephantiasis or Lymphatic Filariasis (Global Alliance)	Mosquitoes	120 million*	0[a]
Malaria	Mosquitoes	300-500 million	1-3 million
Yellow Fever (WHO 2001a)	Mosquitoes	200,000	30,000
Encephalitides (Zalinski 2002)	Mosquitoes	No Reliable Data	No Reliable Data
Plague (WHO 2002a)	Fleas	2500	200
Typhus (WHO 1997)	Lice	Varies from a few thousand to tens of thousands	1-20% of those infected
Lyme Disease (CDC 2001)	Ticks	16,000	0[b]
Chagas' Disease (CDC 1999)	Kissing Bugs	16-18 million*	50,000
Sleeping Sickness or African Trypanosomiasis (WHO 2001)	Tsetse Flies	300,000-500,000*	Very high, but unestimated; in some areas, it kills more people than AIDS
Leishmaniases (WHO 2000a)	Sandflies	1.5-2 million	<500,000
River Blindness (WHO 2000b)	Black Flies	18 million*	0[c]

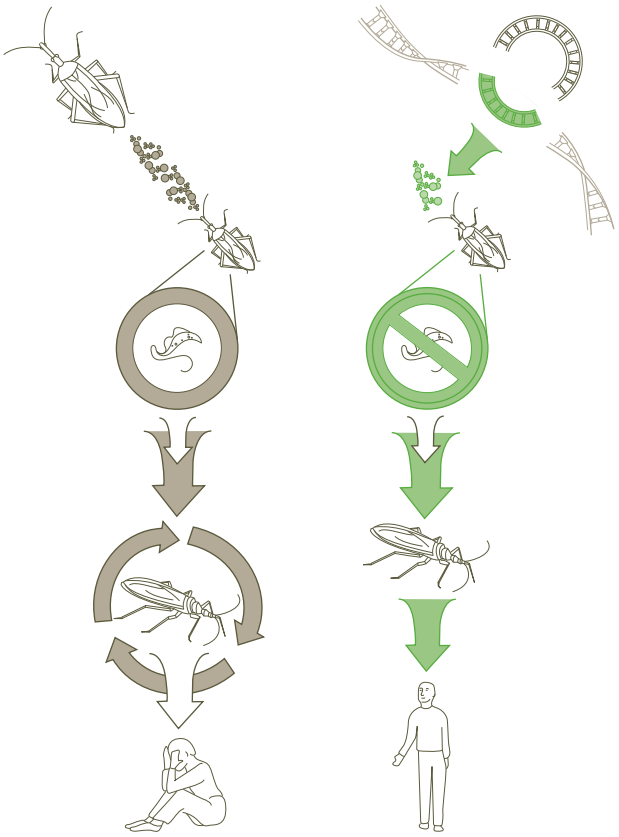
* Total infected with the disease. Not a yearly basis.
a Causes severe deformities in victims.
b Can cause painful arthritis and debilitate victims.
c In severe cases, causes permanent blindness in victims.

ii. The Use of Paratransgenesis to Control Disease Transmission

One advanced paratransgenic project is the work the CDC is doing on Chagas' disease, a parasitic disease endemic through much of Central and South America that affects about 16 to 18 million people, killing approximately 50,000 people each year (Beard et al. 2000, 2002). Chagas' disease is caused by the parasitic protozoan, *Trypanosoma cruzi*. The protozoa are transmitted by the blood-sucking triatomine bug *Rhodnius prolixus*, known colloquially as the kissing bug, which becomes infected with protozoa while feeding on an infected person. Upon entering the kissing bug, the protozoa travel through the bug's digestive tract and are transmitted to humans when the kissing bug feeds on an individual and releases fecal material containing the protozoa near the bite wound. The protozoa then enter the wound when the individual scratches the affected area (Beard et al. 2000).

Researchers hope to use the movement of the protozoa through the kissing bug's digestive system against the protozoa (Beard et al. 2000). Inside the kissing bug's gut live bacterial symbionts, which are vital to the survival of the kissing bug. Researchers have engineered the gut bacterium to kill the protozoa as they travel through the kissing bug's gut. The kissing bug itself is not transformed through genetic engineering, but its gut symbionts are. This type of insect would be called paratransgenic (Beard et al. 2002).

Young kissing bugs obtain the vital gut symbionts by consuming the fecal droppings of their parents. Researchers plan to exploit this transfer of gut symbionts to introduce their genetically modified gut symbionts. Laboratory tests have shown that the GM gut symbionts can be moved into young kissing bugs through placement in synthetic "dung," which the bugs eat at an early stage in their development. This paratransgenic kissing bug could potentially lower the number of Chagas' disease cases each year (Beard et al. 2002).



Scientists are applying similar methods to tsetse flies, the insect vector for trypanosomes, the parasite that causes African sleeping sickness in people and a similar disease in cattle. Nearly 60 million people in Africa live with the threat of contracting sleeping sickness from tsetse flies. Furthermore, tsetse-borne trypanosomiasis also affects livestock, killing an estimated three million livestock animals a year (FAO 2002). Approximately ten million square kilometers of Africa are virtually off-limits to cattle and other farm animals, thus lowering the productive capacity of the land and the job opportunities of the people (Cheng and Aksoy 1999, Aksoy Laboratory 2001, Aksoy et al. 2001). The thirty-seven countries infested with tsetse are estimated to lose approximately $600 million to $1.2 billion a year in agricultural losses and control costs (FAO 2002). The World Health Organization puts this figure closer to $4.5 billion (WHO 2002b).

Some scientists are researching any symbionts carried by the tsetse fly to see if they might transform them to attack the trypanosomes in the same way scientists transformed the gut symbionts in kissing bugs (Aksoy Laboratory 2001, Aksoy 2000, Aksoy et al. 2001). Other researchers are examining the possibility of boosting the tsetse flies' immune system to ward off infection by trypanosomes, similar to the work underway on mosquitoes' immune systems (Dale and Welburn 2001, Hao et al. 2001).

GM Economically Beneficial Insects

In addition to what it might contribute to biological control or genetic control programs, biotechnology also has the potential to make the genetic improvement of silkworms *(Bombyx mori)* and honeybees *(Apis mellifera)* more efficient and less expensive than traditional breeding techniques (Beckendorf and Hoy 1985, Walker 1989, Heilmann et al. 1994, Walker et al. 1995, Beckage 1998).

i. Honeybees

Honeybees provide two important services to agricultural producers: production of honey and pollination of many agricultural crops. In 2001, honey production in the U.S. was worth about $127 million according to the National Agricultural Statistics Services of USDA (USDA NASS 2002). As pollinators, honeybees are essential for the output of many crops that require insects to move pollen from one plant to another, such as many of our fruit and vegetable crops, alfalfa, and almonds. Without honeybee pollination, many of these crops would be unproductive. The value of honeybees as pollinators of agricultural crops is estimated at between $1.6 and $8.3 billion, depending on the availability of native pollinators (Southwick 1992).

Unfortunately, honeybees suffer from several debilitating diseases and parasites that have devastated their populations in the U.S. during the past decade. For this reason, scientists have been working to genetically engineer honeybees (Robinson et al. 2000), to make them resistant to diseases and parasites. Scientists also aim to make them resistant to certain insecticides. Because honeybees forage for food among agricultural crops, they are sometimes exposed to insecticides used by farmers to protect crops against pest insects. Researchers may also focus on characteristics, such as cold tolerance and pollination abilities, because bees are susceptible to the cold and will freeze to death if their colonies are not protected and in good health.

ii. Silkworms

Domestic use of silkworms has taken place for approximately 4,500 years, primarily to produce silk but more recently to produce cosmetic and food products (Sumitomo 2001, Nishiyama 2000). Recently, scientists proved they could transform silkworms using biotechnology by inserting a luminescence gene from a jellyfish into the silkworm. The silkworms now produce fluorescent silk, although the main goal of the experiment was to prove that silkworms could be genetically modified in a stable and permanent manner (Toshiki et al. 2000).

Silkworms could be made to produce spider silk which, because of its strength, could be used in bulletproof vests or parachutes, or for medical purposes to produce artificial ligaments (Agrawal 1999, O'Neill 2000, Rennie 2000). Researchers have shown that they can insert genes that allow silkworms to produce pharmaceutical proteins (Tomita et al. 2003). Many new medications rely on recombinant protein production, but production facilities are limited even as demand for them grows (Pew 2003a, Wurm 2003). With worldwide production of silk at 60,000 tons per year, silkworms could offer the pharmaceutical industry a viable option for bulk recombinant protein production (Wurm 2003).

Researchers also believe that they could make silkworms less susceptible to disease. Furthermore, scientists are hopeful that they could expand the range of silkworm cultivation by making the worms more tolerant of hot climates (Reuters 2000).

III

Chapter Three

POTENTIAL CONCERNS POSED BY GENETICALLY MODIFIED INSECTS

Chapter III

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As with any new technology, the use of biotechnology with insects raises concerns about the safety of the technology. Because most GM insect research is still in an early stage and confined mainly to the laboratory, an analysis of the risks posed by GM insects is necessarily speculative. Consequently, this section focuses on the *potential* environmental, public health, and food safety issues related to GM insects and the full range of concerns that they raise. This is not intended as an exhaustive look at the risks of GM insects, but instead as an introduction to some concerns raised within the research and public policy community.

A Potential Environmental Concerns Related to GM Insects

The primary environmental concerns related to GM insects are the potential for creating new pests and ecosystem disruption. GM insects could have expanded environmental tolerances, enhanced reproductive capacities, or altered life cycles. Because their additional traits remove some of the biological boundaries that hold their non-GM counterparts in check, GM insects could become agricultural or environmental pests. Additionally, they could potentially pass their modified traits on to wild relatives, or through horizontal gene transfer, to non-related organisms.

A recent analysis of animal biotechnology by the National Research Council's (NRC) Committee on Defining Science-Based Concerns Associated with Products of Animal Biotechnology concluded that among the topics considered by the Committee such as food safety, environmental concerns, and animal health and welfare, "the effects on the environment were considered to have the greatest potential for long-term impact." The Committee went on to explain that "the taxonomic groups that present the greatest environmental concerns are aquatic organisms and insects because their mobility poses serious containment problems and because, unlike domestic farm birds and mammals, they can easily become feral and compete with indigenous populations" (NRC 2002a).

The NRC Committee focused its concerns around the probability of the establishment of a GM animal in the environment, because it viewed establishment as the critical factor in risk assessment of GM organisms. However, the NRC Committee's concerns regarding establishment immediately run into one of the unique aspects of some GM insects: Unlike most GM organisms, which are designed to be contained, GM insects designed to no longer transmit diseases will *need* to be established in the environment to work. The NRC Committee acknowledged this situation and expressed "a high level of concern regarding the intentional release of GE organisms into the environment."

For GM animals *not* intended for wide release in the environment, the Committee viewed the likelihood of establishment in the environment as dependent on three primary factors: the fitness of the GM organism, the ability of that organism to escape and disperse, and the qualities of the receiving community (NRC 2002a).

The NRC Committee examined how the specific traits conferred by genetic modification might affect a GM animal's fitness (its ability to survive and pass its genes to fertile offspring). For example, traits that improve the adaptability of a GM organism improve its fitness and increase the probability of its establishment in the environment and, thus, the Committee expressed a high level of concern for the alteration of these traits. In order to make biological control insects more effective, however, researchers working on these insects would likely target traits that improve adaptability. For example, traditional genetic improvement of biological control agents used for suppressing pest insects and mites has involved selecting for pesticide resistance, lengthening active phases in life cycles, and increased tolerance to temperature extremes (Hoy 1990, 1993). Scientists would likely continue transforming these characteristics in addition to working on others that could also increase the adaptability of biological control insects.

Besides examining the traits that researchers might modify, the NRC Committee examined factors naturally found in the non-GM animal which could contribute to an animal's ability to become established in the environment: the ability to become feral, the likelihood of escape from captivity, and the mobility of the animal involved. For insects specifically, the level of concern for all three factors was "high" (NRC 2002a).

The planned uses of GM insects range between confined mass-rearing and deliberate release for establishment in the environment, which will, of course, affect their ability to escape or become feral. For example, insects used for agricultural biological control or for blocking disease transmission will be deliberately released and intended for at least seasonal, if not permanent, establishment in the environment. Insects in SIT programs would be deliberately released, but they would not be intended to establish in the environment because of their sterility or lethal genes. Honeybees are domesticated and would be intended for use in pollination and honey production, but they are known to escape and form feral colonies. It could be expected that GM honeybees could do the same. Silkworms are generally kept in factory-type settings, would not be intended for release into the environment, and are normally unable to survive on their own in the wild (Daly et al. 1998).

The mobility of insects was also a factor of high concern for the Committee (NRC 2002a). Less is known about dispersal behavior of many insects than might be needed for a thorough risk assessment. For example, some research suggests that a worldwide migration of mosquitoes carrying pesticide-resistance genes has taken place, perhaps aided by accidental human transport (Raymond et al. 1991). If migration is the basis for these widespread genes, then dispersal of some GM insect strains could be far more rapid and extensive than anticipated. Again, some GM insects, specifically those engineered to stop disease transmission, will be expected to disperse, at least moderately, in the areas where the disease is found (Boete and Koella 2002).

At a 2002 Consultants Meeting of the Joint FAO/IAEA meeting on "Risk Assessment of Transgenic Arthropods," participants outlined potential hazards related to GM insects. They felt that hazards could arise from the GM insect itself, the genetic construct used in the insect, or genes used in the transformation process (FAO/IAEA 2002). They outlined general hazards as follows:

1) alterations in the GM insect's biology (alterations in environmental tolerances such as tolerance to humidity or temperature leading to increased adaptability; changes in physiology such as reproductive behavior, pesticide resistance, or susceptibility to post-harvest treatment, which could alter the compatibility of the pest with other pest management programs; alterations in pathogenicity, feeding behavior on normal hosts, or length or timing of development, which could increase disease transmission);

2) effects on non-target organisms (alterations in suitability of the GM insect to parasites or predators that could lead to a reduction in natural enemies; adverse effects on pollinators causing altered pollination patterns; effects on symbionts that could alter survival, fitness, etc.; adverse effects on soil or aquatic species that could alter soil productivity); and

3) the stability of the construct used in transforming the insect (its recombination potential, mobility of the gene, transfer of transposon by hybridization, or horizontal transfer to related species or other organisms that could have various effects on ecosystems).

The group noted that this was not an exhaustive list, the hazards listed would have varying probabilities, and the consequences would vary in magnitude (FAO/IAEA 2002).

i. Environmental Concerns of Biological Control Programs

When considering the release and establishment of GM insects, it is useful to examine the environmental concerns related to classical non-GM biological control programs. In these cases, scientists have some historical knowledge of the risks associated with release of insects into the environment.

Biological control usually involves the introduction of an exotic species into an ecosystem. In other words, one exotic species is imported and used against another exotic species. The idea behind biological control is that the pest species has "escaped" its natural enemies by traveling (often aided through human activities) to a new ecosystem. If the insect survives and succeeds in the new ecosystem, the newcomer may become a pest because native species may not be adapted to control the newcomer. If researchers can find effective natural enemies of the pest species in its native home, they may then be able to utilize them as biological control agents, but to do so they must introduce another exotic species (Follett and Duan 2000). Unfortunately, the behavior of an exotic species in an ecosystem can never be fully predicted. If the predators and parasites used for biological control extend their feeding range to include native flora or fauna, they can cause serious or permanent damage to the native ecology.

For example, the cactus moth or prickly pear moth, *Cactoblastis*, was introduced to Australia from Argentina in 1925 to control cacti. Non-native to Australia, the cacti caused serious damage to farming by their explosive growth (Zimmermann et al. 2001). The moth successfully controlled the cacti and was later introduced into other places around the world, including Nevis in 1957. The moth then spread, either by accidental importation in cacti imported from the Dominican Republic or by its own movement, throughout much of the Carribean and eventually to Florida in 1989 (Mahr 2001). The moth is now attacking rare cacti in Florida. Scientists are worried that the moth may eventually move into the desert southwest, where it could damage the extensive native cactus species there, and into Mexico where cacti are important sources of food, fodder, and traditional medicines (OTA 1993, Zimmermann et al. 2001). It should be noted that "such an introduction would not be sanctioned nowadays because of the risk of attack by *C. cactorum* on non-target native opuntias [a genus of cacti] and because biological control of native plants that are pests is now considered to be unwise" according to Zimmerman et al. (2001).

The debate over possible non-target effects of biological control agents is highly polarized (Follett and Duan 2000) and GM insects used as biological control agents could raise similar concerns. As noted by Follett and Duan (2000) "the practice of biological control has been viewed as a progressive and environmentally friendly method of insect and weed pest management. Biological control has many benefits, including essentially permanent management of the target species, no harmful residues, nonrecurrent costs, host specificity, and, for successful programs, a favorable cost-benefit ratio...it may be one of the few methods of reducing pest numbers over a broad geographical range." Recently, however, biological control scientists have come under fire to justify the introduction of organisms, given the potential for unintended environmental effects. Despite this, Follett and Duan (2000) note, "The strict conservationist's point of view of no intentional introductions of alien species whatsoever has proved hard to defend because evidence for non-target effects of arthropod biological control introductions is thin and often circumstantial."

The risks of biological control agents emerge from the same qualities that can make them successful. They exhibit the ability to disperse widely, have a high reproductive rate, establish permanently in the new environment, and are intrinsically programmed to harm other insects or plants. For this reason, the USDA's Animal and Plant Health Inspection Service (APHIS) and many state departments of agriculture regulate the introduction of classical biological control agents. Generalist predators are no longer introduced into the U.S., and there is an increased focus on only introducing parasites that very specifically attack only the target pest. Biological control of weeds is subject to some of the strictest evaluations made for planned release of natural enemies; tests are conducted on insects proposed for introduction to control weeds to resolve whether the weed-control agent is likely to attack crops or other non-target plants (Ruesinki et al. 1995).

ii. GM Insects as Biological Control Agents

One primary difference between GM insects and their traditional counterparts would be the additional traits provided them by genetic engineering, such as pesticide resistance, changes in life cycles, or increased tolerance to heat, cold, or humidity. An evaluation of those traits should help determine whether the insects would likely become pests or be capable of displacing native insects. Traits that increase the fitness of an insect, and thus make it a better biological control agent, could also increase the risk that the GM insect could expand into ecosystems where it could not previously survive, displace other insects through competition for habitat, or become a pest. Biotechnology could enhance those characteristics that make an insect a good biological control agent, but in doing so, it may also result in unintended consequences.

iii. Gene Flow

Besides the risk that GM insects may pose by dispersing and surviving in the environment, the risk also exists that GM insects could spread their novel traits to other organisms through gene flow, which is the movement of genes. There are two possible methods of gene flow: through reproduction and through horizontal gene transfer. Gene flow through reproduction (vertical inheritance) is simply the passing of genes from one generation to the next and generally involves individuals of the same species or closely related species being able to mate and produce fertile offspring. Horizontal gene transfer, on the other hand, is the movement of genes from one organism to another through means other than sexual transmission and can involve completely unrelated species. The discussion below outlines the risks associated with both types of gene flow.

a. Vertical Inheritance

Insects, like other biological organisms, exchange DNA with members of their own species or closely related ones as part of the reproductive process. One environmental concern with GM insects is that they will exchange their DNA with wild relatives and thus pass on their novel traits. Of course, passing on novel traits is the intent of some genetic control programs such as those that involve releasing GM mosquitoes that are unable to transmit a disease (Scott et al. 2002, Dobson 2003).

1. Consequences of Vertical Inheritance

Vertical gene flow has always occurred in nature, and it will continue to happen with GM insects, except those designed to be sterile or to carry genes lethal to any offspring they produce. The primary ecological concerns of vertical gene flow are the potential creation of new pests or the possible disruption of ecosystems. The effects of gene flow from GM insects on wild populations or the environment will depend on whether the novel traits conferred by those genes bestow more fitness upon the recipient insect. For example, if a biological control insect altered to carry genes that make it more fit (cold tolerance, pesticide resistance, disease resistance, etc.) passes those genes to a related insect, will the advantage in fitness given to the receiving insect turn it into a public health, agricultural, or environmental pest by allowing it to adapt to new ecosystems where it could not previously live? Conversely, what impact would a gene conferring reduced fitness to a biological control organism have on native populations if the GM insect spread to the native habitat? Or, if researchers engineer honeybees for resistance to certain diseases and the bees pass those genes to feral relatives, the feral relatives might well benefit from receiving the transgenes. This could be a benefit if the feral bees provide pollination services to rare plants or it could be detrimental if the feral honeybees displaced other bee species that pollinated those plants better. To answer these questions, scientists will need to evaluate factors specific to the insect involved.

Whether gene flow occurs and what effects it might have will depend on several factors: the availability of wild relatives; whether the GM insect had been sterilized, carried a gene lethal to its offspring, or was intended to establish permanently in the environment; whether the transgene conferred any enhanced or reduced fitness to the wild relative; and the ability of the GM insect to disperse. Of course, assessing the risk of gene flow requires that the risk assessors have pertinent information about the GM insect's habitat, enemies, primary and secondary food sources, wild relatives, etc., allowing, of course, for the fact that a certain amount of scientific uncertainty is inevitable and is part of the risk assessment process. The scientific knowledge of insect population biology and ecology may be limited, however, for some species. For example, scientists admit that "too little is known about natural populations and gene flow between mosquito subspecies to allow us to predict the fate of introduced genes" (Lycett and Kafatos 2002). The section entitled "Regulation of GM Insects" will further examine the risk assessment of GM insects.

b. Horizontal Gene Transfer

Horizontal gene flow is the movement of genetic information from one organism to another through means other than sexual transmission. The primary ecological and health concerns with horizontal gene flow are the same as those for gene flow through sexual transmission, with the exception that sexual transmission is limited to related organisms. Horizontal gene flow, on the other hand, could occur between completely unrelated organisms (Bushman 2002).

As mentioned in the section on "How GM Insects Are Created," scientists use "vectors" to insert DNA into the genome of the target organism. Vectors, however, carry with them certain risks, particularly for increasing the potential for horizontal gene flow. Scientists use two common types of vectors to insert foreign DNA into a genome: transposons and viruses.

1. Transposons

"Transposable elements," or "transposons" for short, are sections of DNA that may move to new locations within the genome. Transposons naturally exist in many organisms; in fact, whenever researchers have looked for transposable elements they have found them. Generally, transposons rearrange DNA, causing mutations by disrupting genes or by altering gene regulation. Some transposons can move between cells and may carry genes with them when they do so. Because of this natural ability to "cut" themselves from a genome and then "insert" themselves elsewhere, transposons play an important part in horizontal gene transfer (Bushman 2002).

Transposons sometimes escape their hosts and move to new ones. For example, the transposon, *mariner*, is found in numerous species including humans, centipedes, almond moths, house ants, and many others (Bushman 2002). One theory poses that transposons may "piggyback" on some viruses and actually move with a virus into a new host. Once in the new host, the transposon then inserts itself into the host organism's DNA.

Researchers do know that horizontal transfer of genes may occur between insect species by movement of naturally occurring transposons (Houck et al. 1991, Plasterk 1993). While considered rare, researchers have observed more than one such horizontal transfer within the last fifty years in the fruit fly and may have missed other examples because no one was looking for them (Bonnivard et al. 2000).

Scientists are still discovering new aspects of the biology and ecology of transposable elements, and this lack of knowledge makes it difficult to predict precisely what would happen upon the release of insects containing either active or inactive transposable elements. Some transposons remain "dormant" within insect genomes. One possibility is that some newly introduced transposons will mobilize such inactive transposons, resulting in mutations and other genetic damage (Hoy 2000). Some researchers have shown that inactive transposons can be activated when a genome is stressed by exposure to DNA-damaging agents such as UV light (Petrov et al. 1995).

2. Transduction

Insect viruses could mediate horizontal transfer of DNA. Movement of DNA from one cell to another via a virus is known as transduction. Viruses reproduce themselves using the reproductive tools of the invaded host cell. During this reproduction, some of the host cell's DNA may be accidentally packaged into the viruses. When the virus moves to a new host, it injects the DNA it carries and thus, it may inadvertently transfer DNA from one organism to another (Bushman 2002). Scientists have utilized the natural ability of viruses to insert DNA into the genome of an organism. Because viruses naturally transmit DNA from one species to another on occasion, questions arise about whether the genes inserted into an insect species using genetic engineering techniques would remain within that species.

3. Horizontal Gene Transfer between Gut Bacteria and Other Bacteria

Genetic engineering of bacteria that reside in the insect gut (paratransgenesis), such as the kissing bug, could allow movement of introduced genes into other non-targeted bacteria found within the insect gut (Watanabe et al. 1998). For example, scientists found that *Enterobacter cloacae,* a bacterium found in the guts of insects, and *Erwinia herbicola*, a bacterium that grows on the surface of plants, both grow in the guts of silkworm larvae and exchange genes at very high rates via circular packages of genetic material known as plasmids (Watanabe and Sato 1998). The bacteria containing the new genetic information were found in the feces of the insects, suggesting that this method of horizontal gene transfer is a frequent event in nature.

4. State of Scientific Knowledge about and Consequences of Horizontal Gene Transfer

Risks associated with horizontal gene transfer are difficult to quantify because researchers lack fundamental information on the frequencies and mechanisms of it. Scientists have shown differences between horizontal gene transfer among less-complex organisms, such as bacteria, and more-complex organisms, such as plants and animals. Researchers have found that less-complex organisms can incorporate whole blocks of genes, allowing for expression of intact traits from lateral transfers, whereas more complex organisms do not readily incorporate whole blocks of genes, but may instead, incorporate bits and pieces (Bushman 2002).

The problems associated with horizontal gene flow could be very similar to those associated with gene flow through traditional sexual transmission. However, the list of possible recipients of novel traits would no longer be limited to sexually compatible species. Whether the horizontal gene transfer resulted in particular environmental, agricultural, or public health problems would depend, again, on whether the recipient organism expressed the transferred genes, and if so, whether those traits conferred an increase in fitness or other benefit to the recipient organism. For example, horizontal gene transfer could drive some recipient populations to extinction due to increased mutation rates if active transposable elements were moved into a new host as has happened with small populations of the fruitfly *Drosophila* (French et al. 1999). The NRC report states, "The risk of horizontal gene transfer…is of considerably lower probability but of high risk should it occur in some ecosystems" (NRC 2002a).

Researchers face difficulties in assessing the risk to the environment of rare events. Specific to GM pink bollworms, Peloquin and Schweizer state, "Without unlimited resources it may indeed be impossible to obtain reasonable estimates of such rare frequencies." They do, however, lay out some potential methods for assessing horizontal transfer of genes and estimating the frequency of rare events. They also note, "Perhaps, the risk associated with horizontal transmission should be assessed in terms of the possible damage that could result from this event" (Peloquin and Schweizer 2002).

B Public Health Concerns Raised by GM Insects

i. Gene Silencing

A possible public health risk involves releasing a GM insect population into the field, yet having them fail to function as expected due to a phenomenon called "gene silencing." Plants and mammals can, at times, inactivate multiple copies of introduced genes, in particular those that overexpress proteins or are otherwise abnormal (Dorer and Henikoff 1994, Wolffe 1997, Henikoff 1998). Researchers are not certain why genes are sometimes silenced or even removed entirely from the chromosomes, but they theorize that it may be a defense mechanism intended to prevent genetic damage.

Gene silencing could pose risks if it occurs in a pest insect that was genetically modified to produce some sort of benefit (Hoy 2000). If that benefit is lost, then scientists will just introduce more pest species into the environment (Hoy 2000). For example, if scientists genetically engineer malaria-carrying mosquitoes to become inhospitable to the malaria parasite, but that trait is lost due to gene silencing, the introduction of these engineered mosquitoes could spread, rather than contain, malaria (Spielman 1994).

ii. Laboratory versus the Field

Researchers working with GM insects will also face the possibility that what they planned in the laboratory may not work in the field or may have unintended consequences. For example, if the kissing bug research is tested in the field, will impacts on the kissing bug itself occur that were not observed in the laboratory? If so, what wider public health effects would it have? Would the protozoa that cause Chagas' disease adapt so that the kissing bug could once again transmit them?

In the case of the sandfly, researchers are working on engineering bacteria in the sandfly's gut in hopes of stopping the spread of leishmaniasis. Sandflies, however, differ from kissing bugs in that the parasite that causes leishmaniasis affects the fly itself (Hurd 2003). In this case, the parasite "chokes" the sandfly, forcing it to eat many small meals, thus effectively causing it to bite more and spread the parasite more effectively (Schlein et al. 1992). If the parasite population were killed, what would happen to the sandfly populations and their feeding behavior? Field trials may answer some of these questions, but even field trials, given their scale and temporal restrictions, are limited in the answers they can provide.

a. State of Scientific Knowledge about Vector Ecology

In June of 2002, vector ecologists met in Wageningen, Netherlands, to discuss key aspects of mosquito ecology that scientists should answer before they deploy transgenic mosquitoes for disease control (Scott et al. 2002). The ecologists identified key areas in need of additional research. First, scientists need to understand the spread and stability of introduced transgenes in mosquito populations. This will be critical for predicting how quickly and stably introduced genes can spread through the target mosquito population, whether all forms of the target mosquito can receive the transgenes,[10] how the target mosquito population size will effect the flow of the transgenes, and whether the drive mechanism can overcome any loss of fitness in the transgenic mosquito.

A second area of research is pathogen transmission. The vector ecologists stated that scientists "need to know the extent to which vector populations must be reduced in order to elicit required public health outcomes" (Scott et al. 2002). For example, several types of mosquitoes can transmit malaria, so introduction of one species of GM mosquito may not greatly affect malaria transmission. The ecologists noted that dengue researchers have had more trouble than malaria researchers in estimating the relationship between vector density and human infection. Nevertheless, such information will be critical in planning a GM approach to dengue control.

A third recommendation made by the vector ecologists was to develop models to predict accurately the outcome of releasing GM mosquitoes under specific circumstances. Finally, the vector ecologists noted that more research is needed on the evolutionary consequences of mosquito transformation. For example, they ask, "What effects will natural environmental conditions have on the expression of refractoriness[11] of GMM [genetically modified mosquitoes]?" (Scott et al. 2002). Furthermore, they are concerned that the malarial parasite might evolve resistance to GM mosquitoes. If that happened, they wondered, "Will changes in parasite populations in response to GMM affect the efficacy of vaccines or antiparasitic drugs?" (Scott et al. 2002). They questioned whether altering mosquitoes could alter their ability to carry other diseases (Scott et al. 2002, Curtis 2002b). The ecologists also asked what the fitness costs of genetically modifying mosquitoes would be, and how those costs would affect plans to reduce disease transmission.

A partial answer to the question of fitness of GM mosquitoes in relation to their wild counterparts appeared in 2003. Researchers demonstrated that mosquitoes transformed with fluorescent marker genes had altered fitness levels compared to wild mosquitoes (Catteruccia et al. 2003). Researchers concluded that the transformed mosquitoes had lower fitness levels due to two elements: 1) the mosquitoes were highly inbred (a problem common to laboratory or factory-reared insects) and thus likely carried deleterious recessive alleles against which selection would act, and 2) the insertion and/or the expression of the transgenes may have reduced their fitness. Researchers point out, however, that each transgene and its associate promoter could give different results. In the end, researchers suggest that if fitness is reduced and GM mosquitoes are still used for malaria control, compensation for the fitness reduction will be needed. They suggest using either larger numbers of mosquitoes in a manner similar to an SIT program or inserting a stronger genetic drive mechanism.

10 Chromosomal variations within a mosquito species, such as the primary malaria vector *Anopheles gambiea*, could create reproductive barriers which could deter the spread of transgenes (Torre et al. 2002).

11 Refractoriness in this case means the resistance or immunity of the mosquito to the malarial parasite.

iii. Drivers

Potential programs for replacing vector populations will require a way to "drive" desired genes into wild populations. Gene-drive systems spread the gene of interest into the target pest population at rates faster than would be achieved through Mendelian genetics (Alphey et al. 2002, Dobson 2003). The gene-drive approach has the possible advantage of requiring relatively smaller releases of transgenic pest individuals because the approach, in theory, can result in population replacement with transgenic individuals even if the released insects have a lower fitness relative to the wild population (Dobson 2003).

Though scientists are searching for additional types, there are currently two possible types of gene drivers: autonomous transposons or a paratransgenic approach using transgenic bacteria. Transposon gene-drive strategies rely on "the replicative movement of transposable elements between chromosomes at the time of mating" (Dobson 2003). Ideally, the mating of a mosquito carrying the transposon and one not carrying the transposon would result in a majority of their offspring carrying the transposon. Scientists have demonstrated such transfers through the spread of the *P* element in fruit flies and through modeling and cage experiments (Dobson 2003). Transposons, and the risks associated with them, were discussed previously, but specifically related to their use as drivers, Alphey et al. state, "Autonomous transposons ... could increase the mutation rate through multiple genomic insertions, leading to unanticipated alterations in the biology of the target species" (Alphey et al. 2002).

The paratransgenic approach to drivers involves the use of symbiont bacteria such as *Wolbachia*. As discussed in the section on paratransgenesis in agriculture, *Wolbachia* are a bacterium present in the reproductive tissues of many insects, including mosquitoes. In the case of mosquitoes, researchers hope to use *Wolbachia* either to express transgenes within or drive transgenes through mosquito populations (Townson 2002, Sinkins and O'Neill 2000). Infection by *Wolbachia* can confer a reproductive advantage to host insects, and in turn, enhance the chance of transmitting the *Wolbachia* further (Sinkins and O-Neill 2000). Additionally, if the transgene should become inactive or ineffective, it may be possible to replace the mosquito population repeatedly through new infections, because host insects can be infected with more than one type of *Wolbachia* (Dobson 2003). One potential advantage of using *Wolbachia* would be that model simulations have shown the possibility of slowing or reversing *Wolbachia* infections, thereby slowing or even removing transgenes from the host populations (Dobson 2003). Dobson states, "This capability would provide a prudent safeguard in the event that unexpected, undesired results become associated with transgene spread."

Whatever driver is used, it must be tightly linked to the transgene, because tight linkage should make it less likely that the transgene and driver could become separated (Alphey et al. 2002, Scott et al. 2002, Sinkins and O'Neill 2000). Loss of the transgene in subsequent generations could have potential public health impacts like those described in the following section on "Effectiveness" (Alphey et al. 2002).

iv. Effectiveness

Even if the GM mosquito successfully halts transmission of malaria, there could still be problems related to its success rate (Boete and Koella 2002). In some cases, reducing the rate of transmission of malaria could result in more serious disease problems. A low rate of infection can result in a low level of immunity in people to the protozoa that cause malaria. People in Africa are well aware that if they move to a new area they will become more susceptible to malaria in the new environment, because of genetic differences in malaria-causing protozoa. As a result, GM mosquitoes may have to function very efficiently to suppress malaria transmission. One theoretical model suggests that, "If refractoriness is less than 100% effective (because of, for example, environmentally induced variation in the effectiveness of the mosquito's immune response), control programmes based on genetic manipulation of mosquitoes will have very little impact on the epidemiology of malaria, at least in areas with intense transmission" (Boete and Koella 2002). Curtis (2002b) noted that even if "one succeeded in driving a refractoriness gene to a high frequency there would be intense selection pressure on the local *Plasmodium* to evolve a genotype which evaded the action of the refractoriness gene." He suggested that it might be necessary to incorporate two or more independently acting genes into the mosquito or the malaria protozoa could develop resistance—as they have to many drugs.

The research community is aware that it must address the issue of effectiveness before release. Lycett and Kafatos (2002) note, "The consensus in the mosquito-research community is strongly against premature field experiments. It is felt that even fully contained field trials must await stringent laboratory experiments and long-term population studies, and that transformed mosquitoes should meet the requirement of a 'significant probability' of reducing malaria prevalence before being released."

Food-Safety Concerns Raised by GM Insects

In the United States, insects are generally not eaten by people. Honey, however, is the product of an insect targeted by scientists for transformation. Additionally, the Japanese have started manufacturing "silk powder," an edible form of silk used in noodles, confectionery, and drink mixes (Sumitomo 2001). An analysis, then, of potential food-safety issues related to the honey or silk produced from transgenic bees or silkworms is necessary.

Some people are allergic to honey. Although research on food allergies is limited, scientists do know that allergic reactions are responses to proteins in a select food and that different people may be allergic to different parts of a protein. Reactions to food allergies vary in symptoms from mild such as skin rashes to severe such as life-threatening anaphylactic shock (Pew 2003).

It is possible that the process of genetically engineering honeybees and silkworms could alter the allergic potential of honey and silk. The gene introduced could cause the honeybee to produce a protein it previously had not produced, or change the composition of a protein such that it now triggers the allergic reaction. Researchers could also use a gene from an organism people traditionally do not eat, for which allergic potential is unknown (Pew 2003).

Most of the traits considered for alteration or addition in the honeybee are not directly related to honey production, with the exception of enhancing pollination abilities. Because some individuals are naturally allergic to honey to begin with, however, honey from GM honeybees will likely need to be examined for possible food safety risks, regardless of whether or not the altered trait is tied to honey production. In silkworms, silk protein production is itself the primary target for transformation (Toshiki et al. 2000), but because silkworms are kept confined in factories, scientists would hopefully be able to keep GM silk production separate from silk production intended for the food supply.

D Societal Issues

All societies must weigh the risks and benefits of any new technology and accept or reject that technology based on their perceptions of the risks and benefits; GM insects will be no exception to this. This public deliberation will likely touch on the use of limited financial and human resources, research priorities, and public perceptions—whether accurate or not—about safety. And, the deliberation will differ from one community to another.

For instance, the use of GM mosquitoes to prevent malaria raises issues about whether the intended recipients of this new technology—countries in which malaria is endemic—feel this approach to mosquito control would work for them, given their resources and abilities. This technology offers challenges that individual nations may not be willing to meet (Hoy et al. 1997, Spielman 1994, Spielman et al. 2002, Scott et al. 2002). For example, public health programs would likely only release male mosquitoes, which do not bite, and therefore would not themselves add to the overall vector burden of the release area. However, the intent of releasing those males would be to pass along the GM traits to the next generation of mosquitoes. The next generation, in order to successfully replace their non-GM wild relatives, would need to: feed on blood, prefer humans as their source of blood, and live in areas populated with humans. This could mean then, that while they could not transmit the malaria parasite, they could transmit other diseases. Furthermore, because the progeny of GM mosquitoes must survive in order to successfully do their job, the agency charged with releasing the mosquitoes would also need to monitor their density among the total mosquito population and might want to prevent people from taking precautionary measures against mosquitoes (Spielman 1994).

Compounding the issue of whether to use GM insects is the question of whether there will be other possibilities of controlling malaria in the future and how to use scarce financial and human resources to the best effect. Currently, in some areas, malaria control is attempted by using bednets impregnated with pesticides, which can be very effective when used properly, and the destruction of habitats suitable for mosquito breeding. In the future, however, malaria control may occur through improved vaccines, the development of better anti-malarial drugs now that the malarial protozoan's genome has been completely sequenced, and improved pesticides for mosquito control (Gelb and Hol 2002, Long and Hoffman 2002, Schofield et al. 2002, Tuteja 2002). Some have suggested spending more money on these techniques rather than on research on GM vectors (Spielman 1994, Curtis 2002a, 2000). Most experts in malaria, however, recognize that control of malaria, and that of other tropical diseases transmitted by insects, is unlikely through a single tactic; rather, multiple tactics are probably necessary to maintain long-term control over the mosquitoes and other insects that transmit disease (Lycett and Kafatos 2002).

Another societal consideration is whether the general public in the recipient countries will accept the technology. All societies must weigh the risks and benefits of any new technology and accept or reject that technology based on their perceptions of the risks and benefits. For example, in the case of genetically modified food, some societies rejected the technology because they felt the risks associated with such food outweighed the benefits, while others have embraced GM foods, believing the benefits outweigh the risks. GM insects are likely to face similar problems with acceptance.

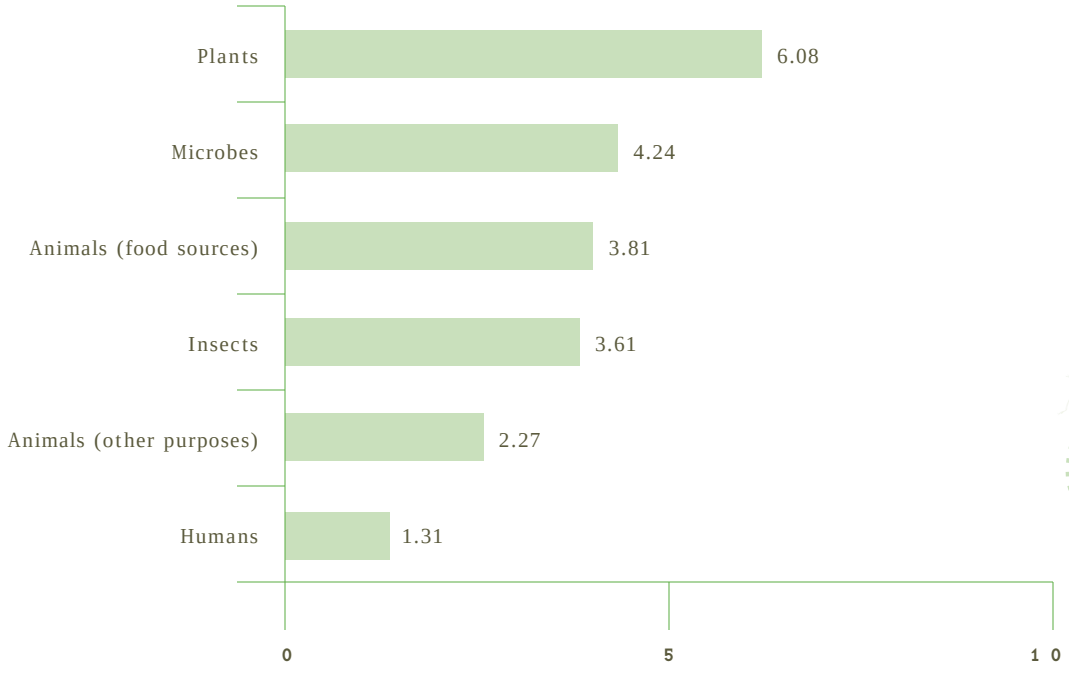
For instance, researchers working on the paratransgenic approach to Pierce's disease acknowledge that their work may not be accepted by the owners of vineyards if the GM-bacteria make their way into the fruit of table grapes (Miller 2003). The vineyards are concerned about their ability to sell grapes and wine and are anxious that customers might reject their products if they were considered GM. Thus, they are first testing the bacterium in confined field trials (Miller 2003, Miller et al. 2003).

Research from a poll taken in May of 2001 indicates that a majority of the American population are uncomfortable with the idea of genetically modifying insects to prevent them from carrying diseases (Pew and the Gene Media Forum 2001). In a poll conducted in August of 2003, Americans were asked to rate their comfort with the genetic modification of different life forms. As Figure 1 demonstrates, Americans are far less comfortable with the genetic modification of insects than they are with genetically modifying plants (Pew 2003b).

Release of GM mosquitoes, or other GM insects, could generate considerable concern by the public. In the past, when scientists have attempted to release large numbers of mosquitoes for genetic control programs or to obtain scientific information, public outcry has stopped them from going forward. For example, residents of southern California blocked a research effort by scientists in 1988 to release 20,000 mosquitoes in an effort to monitor dispersal patterns, because they feared the spread of St. Louis encephalitis (Hoy et al. 1997).

AMERICANS ARE MOST COMFORTABLE WITH THE GENETIC MODIFICATION OF PLANTS

RANKED BY MEAN (OUT OF 10)



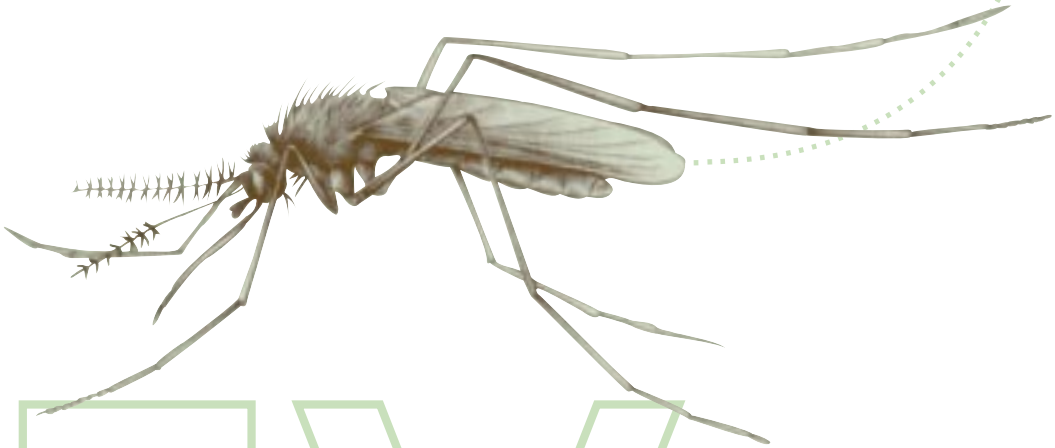
The Mellman Group and Public Opinion Strategies 8/03

In 1975, residents and the government of India halted a World Health Organization-backed research program to release sterile male mosquitoes as part of a genetic control program designed to reduce cases of malaria, dengue, chikungunya (a painful, but not deadly, viral flu-like disease), and filariasis. A newspaper erroneously reported that U.S. researchers involved in the program were developing mosquitoes as agents of biological warfare and implied that Indians were being used as guinea pigs for tests the U.S. deemed too dangerous for its own population (Anon. 1975, Seghal 1974). The article resulted in a political witch-hunt, and WHO eventually pulled the program and all of its researchers from India (Anon. 1975). As a result of this debacle, one researcher lamented ten years later that the question of whether one of the mosquitoes involved could be controlled through the sterile-male technique remained unanswered (Grover 1985).

The scientists working with GM insects, particularly those working on vector insects, have noted the difficulties they face regarding public acceptance and have made suggestions in an attempt to alleviate some of the public concern. For example, researchers involved in a recent workshop examining the risks and benefits of GM insect vectors as public health tools report, "Perhaps the most important theme emerging from the workshop was the recognition that control strategies involving GMOs could potentially provoke serious public mistrust and resistance to their implementation. Therefore it was strongly recommended that all work leading to the development of specific genetic control strategies targeted at malaria vectors should involve both public health specialists and scientists from disease-endemic countries and (where possible) the general public in areas where field trials could be implemented" (Alphey et al. 2002).

Furthermore, Alphey et al. note, "The goal of producing GMOs intended to benefit human health has been perceived more favorably by the public than that of producing GMOs for agricultural or domestic animal research. However, meeting participants strongly argued that this positive public perception could be rapidly undermined by an actual field trial of a transgenic arthropod that failed to provide a significant and tangible health benefit to the resident human community. It was therefore recommended that all preliminary research designed to lead to field trials of the efficacy of a transgenic arthropod-based disease control strategy should involve fully contained laboratory or cage environments. Release should be permitted only when all relevant parameters had been investigated in either contained environments or in open field studies that did not involve transgenic arthropods. Furthermore, field trials involving release of transgenic arthropods should take place only when members of both scientific and local community review groups were assured that such trials had a very high probability of producing a significant and measurable public health benefit for the local community" (Alphey et al. 2002).

The scientific community involved in the research has attempted to devise guidelines for field research and release (FAO/IAEA 2002, ACME/ASTMH 2000, Alphey et al. 2002). While their efforts are to be commended, the larger society will likely also want to participate in controlling GM insects. To that end, a clear, transparent, and effective regulatory oversight of GM insects would go a long ways toward meeting GM insect researchers' need for guidelines or rules and in building public confidence and acceptance of this technology. The next section of the paper will examine the regulatory oversight of GM insects.



Chapter Four

REGULATION OF GENETICALLY MODIFIED INSECTS

Chapter IV

REGULATION OF GENETICALLY MODIFIED INSECTS

Guide to Federal Agencies and Their Acronyms

USDA-APHIS	U.S. Department of Agriculture–Agriculture Pest & Health Inspection Service
USDA-CVB	U.S. Department of Agriculture–Center for Veterinary Biologics
FDA-CVM	Food and Drug Administration–Center for Veterinary Medicine
FDA-CFSAN	Food and Drug Administration–Center for Food Safety and Nutrition
FDA-CDER	Food and Drug Administration–Center for Drug Evaluation and Research
HHS-PHS	U.S. Department of Health and Human Service–Public Health Service
EPA	U.S. Environmental Protection Agency

Guide to Federal Laws and Their Acronyms

FFDCA	Federal Food, Drug, and Cosmetic Act
TSCA	Toxic Substances Control Act
PPA	Plant Protection Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
AHPA	Animal Health Protection Act

A Overview

Since the mid-1980s, when the first GM products began to move from the laboratory towards commercialization, it has been federal policy to regulate biotechnology products no differently than similar products developed in a conventional manner. In 1986 the Coordinated Framework for Regulation of Biotechnology codified this principle, stating that products should be regulated based on their characteristics, rather than on the process by which they were made (OSTP 1986).

As a result, biotechnology products are regulated today based on what they are and their intended use. For example, GM food crops are reviewed for safety under the same laws that apply to conventional foods, while pesticides produced by GM plants are reviewed under laws that apply to chemical pesticides.

In 1986, federal regulators believed that existing laws would adequately cover all of the biotechnology products then foreseen. Since that time, three federal agencies—the Food and Drug Administration (FDA), the Department of Agriculture (USDA), and the Environmental Protection Agency (EPA)—have used their authorities under existing laws to review hundreds of field trials of genetically modified plants for possible impact on human health, agricultural, and environmental safety. While agencies have in some cases needed to interpret their laws creatively and expansively to cover some of the biotechnology products, all biotechnology products on the market in the U.S. have received some regulatory review, if not approval.

Now, seventeen years later, biotechnology research is poised to produce new products that will be more challenging to fit into existing statutes. As noted in the first section, using biotechnology to modify the genetic makeup of insects or their bacterial symbionts raises a range of issues, including concerns about public health, agricultural, environmental, and food safety risks.

GM insects, however, do not fall neatly within any pre-existing product category. No law specifically addresses GM insects. Depending on the intended purpose of the GM insect, seven different laws could be interpreted to apply to research, field trials, and environmental releases of GM insects or associated GM microorganisms. Some laws could apply to many, if not all, GM insects, while others would have more limited scope. The different laws have widely varying standards and procedures; the choice of which law to apply could therefore have significant consequences both for the public and for the developers of this technology.

To date, however, the federal government has not indicated which of these laws will apply to GM insects or their associated GM microorganisms, or how they would operate together to ensure a full review of all potential environmental, food safety, agricultural, and public health risks.[12] No single agency appears to have authority over the full range of GM insects under development or authority to consider the full range of risks they might present. Only the USDA's Animal and Plant Health Inspection Service (APHIS) has officially asserted authority over some GM insects, requiring prior APHIS approval for field tests or environmental releases of any GM insects that could harm plants or crops. How GM insects developed for other purposes will be regulated remains unclear. Nor is it clear how any overlap with APHIS's authority by other agencies will be resolved.

The policy issue presented by GM insects is not so much the lack of legal authority but whether existing legal authorities will be used in a coordinated way to ensure an adequate and publicly credible regulatory review of risks. In the absence of a clearly articulated and coordinated federal policy for addressing GM insects, it is currently impossible to assess the adequacy of the federal regulatory process for reviewing the potential public health, agricultural, environmental, and food-safety risks of GM insects. Moreover, the lack of a clear regulatory pathway imposes uncertainty and costs on researchers and developers, delaying any potential benefits that these new technologies may bring.

12 In early 2001, at the end of the Clinton Administration, the Office of Science and Technology Policy and the Council on Environmental Quality (CEQ-OSTP) jointly issued a series of case studies that described the various legal authorities that have been or could be used to cover various types of genetically-modified products (CEQ-OSTP 2001). The case studies included an example of a GM insect virus used as a biocontrol, and included a brief discussion of legal authorities that could be used to address GM arthropods (pp 69-70). The discussion noted the USDA's authority to regulate plant pests and the EPA's authority to regulate new chemicals, but did not discuss how these two regulatory processes would interact. In any event, the case studies were intended to be illustrative only and explicitly did not set out any new requirements or establish binding policy.

The lack of a clear federal regulatory framework does not suggest an imminent threat to public health, agriculture, food safety, or the environment. At the moment, most work remains at the laboratory research stage, and in the event that a field test were required, some federal agency likely has the authority to review it. Moreover, at present, only a few hundred researchers worldwide work on transgenic insects. Their work, however, will eventually reach the field trial stage and shortly thereafter experimental releases will have to be considered. Therefore, the federal government needs to move deliberately, and quickly, to clarify how it intends to address the regulatory issues posed by GM insects.

GM insects pose several important issues not raised by GM crops. First, given the range and mobility of insects and the fact that many insects of interest to public health researchers are native to countries other than the U.S., releases of GM insects will raise international regulatory issues in addition to domestic regulatory questions. The application of U.S. and international laws and procedures for field-testing GM insects in other nations are not at all clear.

Second, achieving the public health or agricultural benefits of GM insects often requires that they spread and persist in the environment. In contrast, GM plants are generally managed to prevent the unintended spread of GM traits. Given the need to drive the trait broadly into the population, as well as the small size and mobility of insects, "recalling" a GM insect once released is likely to be very difficult.

Third, the basis of the regulatory process for GM crops is a system of approvals for commercial products. In contrast, the aim of much of the work in the area of GM insects is public health or public agricultural purposes, and is conducted by federal researchers or university scientists without a clear commercial product in mind. This difference has several implications. Public research scientists likely have less familiarity with formal government regulatory processes than scientists from private companies. In addition, the regulatory process does not always provide a smooth or clear pathway between the stages of laboratory research, field trials, and "operational" releases for non-commercial applications. Furthermore, the non-commercial nature of these applications may limit which laws apply to them.

This section of the report examines the existing legal authorities that could address the public health, environmental, animal health, plant health, and food safety issues posed by GM insects. The analysis compares the different authorities used by USDA, EPA, and FDA that could apply to GM insects and considers the adequacy of each agency's authority and procedures to assess and manage the risks of GM insects in a credible and effective way. Following the discussion of the formal federal regulatory process, the report also examines the role that National Institutes of Health guidelines play in setting research standards to ensure environmental safety and protect the rights of human research subjects.

B Federal Regulatory Authority for GM Insects

i. Summary

Which law applies to GM insects depends both on the nature of the organism and its intended use. Table 3 summarizes the laws that could potentially apply to regulate transgenic insects and the agencies associated with them. Table 4 sets out the jurisdiction of agencies over symbiotic microorganisms that are genetically modified to control human, plant, or animal pathogens and operate in the biological system of the insect vector, which could otherwise remain unmodified (paratransgenic).

TABLE 3

Potential Agency Jurisdiction by Composition and Intended Use of Transgenic Insect

COMPOSITION/USE	AGENCY	PRODUCT CATEGORY	LAW	RISKS CONSIDERED
All Uses				
Transgenic insects	FDA-CVM	New animal drug	FFDCA	Human and animal safety
Transgenic insects (except for food, drugs, and pesticides)	EPA	New chemical substance	TSCA	Unreasonable risks to environment
Transgenic insects that are or could be plant pests (regardless of use)	USDA-APHIS	Plant pests	PPA	Harm to plants and plant products

TABLE 3 (CONTINUED)

Potential Agency Jurisdiction by Composition and Intended Use of Transgenic Insect

COMPOSITION/USE	AGENCY	PRODUCT CATEGORY	LAW	RISKS CONSIDERED
Agricultural & Industrial Uses				
Transgenic insects as bio-control agents (control plant pests or noxious weeds)	EPA	Pesticide	FIFRA	Unreasonable risks to the environment
	USDA-APHIS	Plant pest	PPA	Harm to plants
Transgenic insect vectors of livestock diseases	USDA-APHIS	Livestock disease control	AHPA	Animal health
Transgenic insect vectors of animal disease, modified to induce immune system reaction	USDA-CVB	Animal biologic drugs	VSTA	Safety and efficacy of drug on animals
Transgenic insect food product (i.e., honey)	FDA-CFSAN	Food safety	FFDCA	Food safety
Transgenic insects to make chemicals or products (i.e., silk)	EPA	New chemical substance	TSCA	Unreasonable risks to the environment
Transgenic honeybees	USDA-APHIS	Honeybees	Honeybee Act	Undesirable species and subspecies of honeybees
Public Health Uses				
Transgenic insect vectors of human diseases	HHS-PHS	Human disease control	PHSA	Public health
	FDA-CDER	Human drugs	FFDCA	Efficacy and safety
	FDA-CBER	Human biologic drugs	FFDCA	Efficacy and safety

USDA-APHIS: U.S. Department of Agriculture–Agriculture Pest & Health Inspection Service
USDA-CVB: U.S. Department of Agriculture–Center for Veterinary Biologics
FDA-CVM: Food and Drug Administration–Center for Veterinary Medicine
FDA-CFSAN: Food and Drug Administration–Center for Food Safety and Nutrition
FDA-CBER: Food and Drug Administration–Center for Biologics Evaluation and Research
FDA-CDER: Food and Drug Administration–Center for Drug Evaluation and Research
HHS-PHS: U.S. Department of Health and Human Service–Public Health Service
EPA: U.S. Environmental Protection Agency
FFDCA – Federal Food, Drug, and Cosmetic Act
TSCA – Toxic Substances Control Act
PPA – Plant Protection Act
FIFRA – Federal Insecticide, Fungicide, and Rodenticide Act
AHPA – Animal Health Protection Act
VSTA – Virus-Serum-Toxin Act
PHSA – Public Health Service Act

TABLE 4

Potential Agency Jurisdiction by Composition and Intended Use of Transgenic Insect Symbionts (Paratransgenesis)

COMPOSITION/USE	AGENCY	PRODUCT CATEGORY	LAW	RISKS CONSIDERED
All Uses				
GM insect symbionts (except for food, drugs, and pesticides)	EPA	New chemical substance	TSCA	Unreasonable risks to environment
GM insect symbionts that control plant, pathogens in insect vectors	USDA-APHIS	Plant pest - biocontrol	PPA	Harm to plants
Agricultural & Industrial Uses				
GM insect symbionts that control livestock disease pathogens in insect vectors	USDA-APHIS	Livestock disease control	AHPA	Animal health
Public Health Uses				
GM insect symbionts that control human pathogens in insect vectors	HHS-PHS FDA-CDER FDA-CVM	Human disease control Human drugs New animal drug	PHSA FFDCA	Public health Efficacy and safety of human or animal drug
GM insect symbionts that control zoonotic disease pathogens in insect vectors	USDA-APHIS	Livestock disease control	AHPA	Animal health

USDA-APHIS: U.S. Department of Agriculture–Agriculture Pest & Health Inspection Service
FDA-CVM: Food and Drug Administration–Center for Veterinary Medicine
FDA-CDER: Food and Drug Administration–Center for Drug Evaluation and Research
HHS-PHS: U.S. Department of Health and Human Service, Public Health Service
EPA: U.S. Environmental Protection Agency
FFDCA – Federal Food, Drug, and Cosmetic Act
TSCA – Toxic Substances Control Act
PPA – Plant Protection Act
AHPA – Animal Health Protection Act
PHSA – Public Health Service Act

ii. Agency Authority and Procedure

Because no coordinated federal regulatory approach to GM insects has been developed and only one agency has published any official guidance, an analysis of the adequacy of the regulatory systems is somewhat speculative. Consequently, this section examines in detail the *potential* of existing laws to cover anticipated GM insect applications and the full range of risk issues raised by those applications. It also considers whether those laws give the agencies adequate authority to prevent harm and to respond to problems if they occur.

No existing laws explicitly mention products of insect biotechnology. Lawmakers wrote them for other purposes, such as controlling conventional plant pests, animal diseases, and preventing the spread of human diseases. Many were written well before the advent of biotechnology. As a result, genetically modified organisms come within the scope of existing laws only insofar as they fall within the "product" definitions of those laws. Consequently, determining what types of GM organisms could be covered – and what could not – inevitably involves an interpretation of those laws, regulations, and definitions.

The laws summarized in this section could potentially cover most, if not all, of the potential uses of GM insects. In many cases, however, covering GM insects requires an expansive and creative interpretation of existing laws, creating at least some legal question about how far an agency's jurisdiction can be asserted. Agencies cannot exceed the authority delegated to them by Congress. While courts give an agency due deference to interpret its authority, courts have struck down agency regulations when they found agencies exercising their authority "in a manner that is inconsistent with the administrative structure that Congress enacted into law" (*Food and Drug Administration v. Brown & Williamson Tobacco Co.*, 529 U.S. 120, 120 S. Ct. 1291 (March 21, 2000)).

The analysis below raises legal questions about some of the jurisdictional claims that have been, or could be, made by several federal agencies. It is important to note that even with some legal uncertainty about an agency's position, the question may never get resolved unless someone chooses to challenge it in court. To the extent that developers comply with an agency's assertion of authority, the question of whether an agency is lawfully exercising its authority has little practical significance. However, there remains a risk that, at some point, the agency's authority could be successfully challenged in court, leaving the agency with no immediately viable authority for regulating some GM insect applications.

In addition to asking whether the laws give agencies jurisdiction over a particular category of GM insect, it is also important to consider the scope of the agencies' authority to assess relevant risks. Agencies have the authority to review only those issues within the authority delegated to them by Congress. The fact that an agency may have jurisdiction over a particular GM organism for one issue does not necessarily give it authority to consider any other issue that may be of concern. So, for example, an agency authorized to consider food safety aspects for GM honeybees may not have authority to consider environmental risks of GM honeybees.

Agencies have widely different powers to assess and manage relevant risks. In some cases, agencies have the authority to approve product safety, while in other cases agencies can act only when, and if, problems occur. For example, the FDA approves new human and animal drugs as safe and effective before their lawful use, but has no similar pre-market approval authority for novel whole foods and can act only when evidence of harm exists. This report will also examine issues around the adequacy of an agency's tools to assess and manage the potential risks of GM insects.

Whether an agency carries out its regulatory responsibilities in a way that builds public trust and confidence is also a critical issue. Credibility and confidence are particularly important to the acceptance of new technologies like biotechnology. While the potential benefits of biotechnology may be great, such as the potential elimination of certain insect-borne diseases, there may also be risks—and the public can remain skeptical about risks. A strong and credible regulatory process can help provide public assurance that agencies are carefully assessing and managing risks. Key procedural elements that contribute to public trust are clarity, transparency, and public participation. Clarity means that the process for making a regulatory decision is widely known and generally understandable, both to the public at large and to the regulated community in particular. Transparency means that the basis for an agency decision is made public – both the data on which the agency relied, as well as the rationale for the agency decision. Public participation gives an opportunity for the public and interested groups to have input into an agency's decision-making process before a final decision is made. All of these elements help ensure agency decisions are sound, rational, and respected. The analysis below also considers the extent to which various laws that might apply to GM insects permit clarity, transparency, and public participation.

A regulatory system that looks efficient, effective, and credible on paper may mean little if an agency does not have sufficient resources to carry out its regulatory responsibilities. Agencies need to have (or have access to) a critical mix and level of scientific expertise to conduct credible risk assessments that ask the appropriate questions and analyze the supporting data.

Finally, the regulatory system, taken as a whole, should avoid duplication and unnecessary regulatory burdens and ensure coordination among agencies that might share jurisdiction.

a. USDA Authority and Procedure

1. Overview

USDA's Animal and Plant Health Inspection Service (APHIS) administers three laws that give it authority over some types of GM insects.

Under the Plant Protection Act (PPA), APHIS has broad authority to regulate plant pests to protect crops and other plants (7 U.S.C. §7701 et seq.). The PPA definition of a plant pest includes any insect or microorganism that "can directly or indirectly injure, cause damage to, or cause disease in any plant or plant product" (Section 403(14)).[13]

13 Section 403(14) defines a plant pest as "any living stage of any of the following that can directly or indirectly injure, cause damage to, or cause disease in any plant or plant product: (A) a protozoan. (B) a nonhuman animal. (C) a parasitic plant. (D) a bacterium. (E) a fungus. (F) a virus or viroid. (G) an infectious agent or other pathogen. (H) any article similar to or allied with any of the articles specified in the preceding paragraphs."

APHIS has issued regulations covering genetically modified organisms, including insects and microorganisms that are or could be plant pests (7 C.F.R. Part 340).[14] The regulations set out notification and permitting requirements for field trials and environmental releases for a broad range of organisms that are or could be plant pests. Because there are so many potential plant pests, these regulations cover many insects (Young et al. 2000). To date, APHIS is the only regulatory agency that has articulated and implemented a regulatory program for transgenic insects.

The second law that provides APHIS with authority over GM insects is the Animal Health Protection Act (AHPA), which gives broad authority to the USDA to act against the spread of livestock diseases and pests, including insect-borne diseases[15] (7 U.S.C. §8301 et seq.). APHIS subjects insect vectors of animal disease to regulation; in theory, APHIS could use the authority under the AHPA to develop a regulatory permit program for GM vectors of livestock disease similar to the program that APHIS has implemented for plant pests. APHIS has previously indicated that it is developing such regulations (Young et al. 2000; CEQ-OSTP 2001), but to date has not published proposed rules or otherwise indicated whether, or how, it intends to regulate insect vectors of animal diseases.

A third law that might apply is the Honeybee Act (7 U.S.C. §281 et seq.) which gives APHIS authority to prevent the introduction and spread of "undesirable" species or subspecies of honeybees into the U.S. The primary purpose of the Act is to prevent the introduction of honeybee diseases and "africanized" honeybees, but conceivably, the Act could be applied to require permits for novel varieties of honeybees created through biotechnology. However, to date, APHIS has not indicated any intention to use the Honeybee Act in this way.

In addition to these three laws regulated by APHIS, the USDA's Center for Veterinary Biologics has responsibility for regulating the safety and efficacy of new animal biologic drugs under the Virus-Serum-Toxin Act (21 U.S.C. 151 et seq.). (Other types of animal drugs, such as antibiotics, fall under the jurisdiction of the FDA's Center for Veterinary Medicine.) In theory, under this Act, the USDA could have authority over insect vectors modified to produce an immune system reaction in the animal, should such a product be developed. To date, however, the USDA has not indicated whether it intends to exercise such authority under this Act.

14 Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which are Plant Pests or Which There is Reason to Believe are Plant Pests, 7 C.F.R. 340. APHIS promulgated this regulation under the Plant Pest Act, which predated the current Plant Protection Act. However, the Plant Protection Act expressly confirmed the continuing validity of regulations issued under the older act.

15 The Animal Health Protection Act, passed by Congress in 2002, consolidated a variety of laws giving the Secretary of Agriculture authority to regulate diseases and pests of livestock. Under AHPA, the Secretary has broad authority to act against the spread of livestock diseases and pests by quarantining, destroying, or otherwise prohibiting use and movement of infected and exposed animals, articles, or means of conveyance.

2. Scope Issues

i. Transgenic Plant Pests

APHIS has issued specific regulations for genetically-engineered organisms under its authority to regulate plant pests (7 CFR Part 340). The regulations define "regulated articles" as any organism that have been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent is classified as being a pest, or organisms which the Administrator determines or has reason to believe is a plant pest (7 CFR 340.1). In essence, the regulations assume that any genetically-engineered organism derived in some way from a known or suspected plant pest may well be a plant pest itself, and therefore should be subjected to regulatory scrutiny before release into the environment.[16]

APHIS' definition of a "regulated article" clearly includes any genetic modification, for any purpose, of an insect or a microorganism known as a plant pest. So, for example, a silkworm modified to produce greater quantities of silk would be subject to the APHIS regulations because a silkworm is a known plant pest. Similarly, a virus, bacterium, or fungus that causes plant diseases or damages plant products (e.g., food) is subject to the regulation, regardless of the purpose of the modification. To date, APHIS has issued five permits for GM insects under this regulation for field trials or interstate movement (USDA APHIS 2001b). (See sidebar, Environmental Impact Assessment of Transgenic Pink Bollworms.)

APHIS also has asserted that the definition of "regulated article" covers organisms that cause "indirect" harm to plants, such as biological control organisms and beneficial insects that do not themselves directly harm plants or plant products (CEQ-OSTP 2001; USDA APHIS 1995). A "biological control organism" is an organism, including insects and microorganisms, that is a predator, parasite, or competitor of a plant pest. A "beneficial insect" is one that provides valuable services, such as pollination.

APHIS' assertion that it can regulate biological control organisms as part of the Plant Protection Act raises some questions and seems to conflict with other provisions of the Act. Section 412 of the PPA suggests that APHIS has authority to regulate biological control organisms solely for the purpose of preventing those organisms from becoming plant pests themselves. (See sidebar, Regulation of Conventional Biological Control Organisms.) Under APHIS' rule, however, genetically-modified biological control organisms are effectively presumed to be plant pests, erasing the distinction made in Section 412.[17] Since some of the ongoing insect modification research is focused precisely on creating more effective biological control agents or hardier beneficial insects, the question of whether APHIS has clear jurisdiction over such organisms is an important one to clarify. At this point, it is not clear how APHIS will regulate genetically modified biological control organisms.

16 Under this definition, a GM organism may be regulated without prior evidence that it is a plant pest – i.e., that it harms plants or plant products. However, the USDA would still need a "reasonable basis" for the conclusion that such organisms were in some way capable of harming plants or plant products. As a practical matter, the developer probably bears the burden of showing that a covered organism is not a plant pest because it is not capable of harming plants or plant products.

17 While APHIS does not explictly make this argument, it may be relying upon the PPA's definition of plant pest as including "any article similar to or allied with" a plant pest. Arguably, an enemy of a plant pest is "allied with" the plant pest, as in a predator-prey relationship. Of course, an organism can function both as a biological control organism and still be capable of harming plants or plant products; in such a case, jurisdiction is not an issue.

ii. Insect Symbionts

As noted in the preceding section of this report, scientists are modifying symbiotic microorganisms that live in the digestive or reproductive systems of insects that are vectors of plant, animal, or human diseases. The goal is to modify the symbiotic microorganisms to attack or otherwise control the disease pathogens carried by the vector insect. APHIS clearly would have authority over the pathogenic microorganism itself if it is a plant pest under PPA or a source of a livestock disease under AHPA. In these cases, however, it is not the disease-causing microorganism that is being genetically modified, but rather the usually benign symbiont microorganism. In effect, the symbiotic organism is being made into a biological control organism, although its operation is within the insect – not in the open environment. Under AHPA, the USDA has broad authority to act to prevent or control livestock diseases, including specific authority over vectors of such diseases. APHA would grant the agency the authority to regulate such GM vectors, however, APHIS has not asserted this authority to date. APHIS's authority over similar efforts with respect to plant pests depends on its broader authority over biological control agents, questions about which were discussed above.[18]

There is also a question whether this is an area in which EPA might share jurisdiction. Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), EPA has regulatory responsibility for pesticides. EPA has, however, relinquished authority over most biological control agents to APHIS (40 C.F.R. Part 152.20). The exception is that EPA has retained authority over most microbial pesticides, including the genetic construct from the *Bt* bacteria that has been inserted into GM corn and GM cotton as a pesticide against certain moths and larvae. Because the purpose of modifying symbiotic microorganisms is to kill or control a plant, animal, or human pest, EPA would arguably have jurisdiction over any field trial or environmental release of a paratransgenic insect. In an analogous area, however, EPA has stated that it holds authority over antimicrobial pesticides only if they work on inanimate surfaces; if they instead work on, or within, a biological organism, it is considered a drug, and EPA would not have jurisdiction under FIFRA (U.S. EPA 2003). (Possible overlaps with FDA and with EPA under the Toxic Substances Control Act are discussed later.)

18 The CEQ-OSTP Case Studies include a case in which a baculovirus, a biological control organism, was modified to become a more lethal killer of insect plant pests. In that particular case, APHIS concluded that it did not have authority over the modified baculovirus because it did not pose a plant risk, and that EPA would have the primary authority over the modified baculovirus under the pesticide laws (CEQ-OSTP 2001).

3. Risk Considerations

Laws give agencies authority only for particular purposes. In the case of the PPA, the primary purpose of the Act is to prevent and control the spread of plant pests (i.e., organisms that harm plants and plant products). In the case of the AHPA, the primary purpose is to prevent or contain diseases or pests that might harm livestock. APHIS does not have authority to act on the basis of additional issues that are not relevant to its specific legal authority, such as risks to wildlife or human health concerns.[19]

The fact that APHIS, like all federal agencies, must comply with the National Environmental Policy Act (NEPA) (42 U.S.C. §11011 et seq.) in carrying out the PPA and AHPA does not expand APHIS's authority to act on the basis of environmental risks beyond those addressed in the specific laws. NEPA requires federal agencies to conduct an environmental assessment to determine if a major federal action, such as granting a permit, would have a significant impact on the environment. If the agency cannot find that the proposed action will have "no significant impact" on the environment, it must conduct a more extensive Environmental Impact Statement (EIS).

The environmental assessment required by NEPA does consider broad environmental impacts of the proposed action. Based on that assessment, APHIS must find that the proposed permit, with appropriate conditions such as confinement, will pose no significant impact on the environment, or else be forced to undergo the additional expense and delay of conducting a more extensive EIS. On that basis, APHIS can negotiate the terms of a permit with an applicant to reduce environmental impacts to make a finding of no significant impact. However, while NEPA requires an analysis of environmental impacts, it is not a substantive law; in other words, it does not provide an independent legal basis for an agency determination. APHIS would have no legal basis for denying a permit under PPA where the developer could demonstrate no harm to plants or plant products, even if the EIS showed a significant adverse impact on wildlife or non-target organisms.

As noted in the first section of this paper, the potential environmental impact of GM insects is more difficult to assess in many ways than the impact of current GM crops. Significantly, APHIS announced that it would conduct a full Environmental Impact Statement for the proposed field trial of a transgenic pink bollworm, the first time it will conduct an EIS of any genetically modified organism under its jurisdiction. (See sidebar, Environmental Impact Assessment of Transgenic Pink Bollworms.) However, the scope of the PPA and the AHPA limit APHIS' ability to respond to environmental risks.[20]

19 As long as agencies act within their authority, their actions can permissibly have an impact on matters beyond their specific authority unless the agency is specifically prohibited from doing so. For example, some livestock diseases are also human diseases or could involve identical insect vectors (e.g. the West Nile virus). As long as there is a connection to animal health, APHIS has authority to take actions that could also benefit public health. For example, the court upheld the USDA's regulations on the bacterium *Salmonella enteritidis* in chicken eggs even though the primary impact was on human health (Rose Acre Farms, Inc. v. Madigan, 956 F.2d 670 (7th Cir. 1992)). Similarly, a permit that requires the applicant to destroy all the plants on a test field to ensure that a plant pest is not introduced, also has the practical effect of protecting against other environmental risks.

20 The plant pest provisions of the PPA are concerned with whether an organism causes harm to plants – not on whether the organism has a broader environmental impact (such as impacts on wildlife). The PPA includes an expanded definition of a "noxious weed" as a plant that, among other things, causes injury or damage to "the natural resources of the United States, the public health, or the environment" (7 U.S.C. §7702(10)). While this appears to allow USDA to consider broad environmental impacts of plants, this provision does not apply to other organisms like insects. Nothing in the AHPA addresses environmental risks.

REGULATION OF CONVENTIONAL BIOLOGICAL CONTROL ORGANISMS

While using biotechnology to modify insects and microorganisms to control plant pests is new, the concept of using organisms to combat plant pests – biological control – is a longstanding practice with an existing regulatory regime. The two principal agencies involved in biological control are USDA's APHIS and EPA. Generally, EPA's role has been to look at microbes used to control pests while USDA has considered larger organisms.

APHIS Permitting Process

Section 412 of the Plant Protection Act provides the Secretary of Agriculture with broad authority to prohibit or restrict the movement of biological control organisms "if necessary to prevent the introduction into the United States or the dissemination of a plant pest or noxious weed within the United States." The Act defines a "biological control organism" as "any enemy, antagonist, or competitor" used to control a plant pest or noxious weed. The Act permits APHIS to regulate biological control organisms primarily to make sure that such organisms do not themselves become plant pests.

APHIS has established a permitting process for regulating the importation and release of biological control organisms. (APHIS proposed a revised permitting and regulatory scheme for biological control organisms in late 2001, but it has not been finalized at this time. USDA APHIS, Proposed Rule: Plant Pest Regulations: Update of Current Provisions (66 FR 51340, Oct. 9, 2001).) Permit applications must contain a range of information, such as the purpose and need for the release, information about the target pest and the biological control organism, the estimated impact of the release, and any post release monitoring program. APHIS reviews the application to assess the risks and benefits, including the imposition of measures to mitigate the risk, if necessary.

APHIS regulates: 1) entomopathogens (bacteria, fungi, viruses) to control insects and mites, 2) predators and parasitoids (predatory mites, lady beetles, parasitic wasps, etc.) of arthropods, insects, and mites, and 3) organisms for biological control of weeds, such as insects, mites, nematodes, or plant pathogens (USDA APHIS 2002). By agreement between the agencies, APHIS limits its jurisdiction over entomopathogens to their importation and interstate movement, including release into the environment. APHIS generally regulates confined field releases, while EPA regulates large-scale experimental or commercial use.

EPA Role

Under FIFRA, EPA regulates microorganisms (fungi, bacteria, protozoans, viruses) intended for use in "preventing, destroying, repelling or mitigating any pest." For example, EPA regulates the use of *Bacillus thuringiensis* (Bt), a naturally occurring bacterium widely used by gardeners and farmers as a pesticide against certain moths and larvae. By rule, EPA has exempted most other biological control agents from FIFRA in recognition that USDA adequately regulates them (40 C.F.R. 152.20).

4. Risk Management Tools

APHIS has a broad range of tools with which to regulate GM insects that fall within its jurisdiction. APHIS tries to prevent harm by requiring USDA approval before the release of any covered GM insect into the environment.

Under AHPA, APHIS has broad authority to take action to prevent the spread of animal disease vectors, presumably including GM insects that carry animal diseases. (APHIS has yet to indicate whether or how AHPA will apply to genetically modified organisms or to propose implementing regulations to establish a permit process.)

APHIS can impose conditions on field trials or general releases through its permit process under the PPA. The PPA prohibits the introduction or movement of any plant pest unless USDA has granted a permit and the release is consistent with USDA regulations (Section 411 of the Plant Protection Act). USDA has the authority to exempt certain "regulated articles" that meet a range of requirements and performance standards from these pre-release or pre-market requirements (but USDA still requires notification of the release of such articles). For example, USDA has determined that GM crops that pose minimal risks to the environment and that are completely contained may be grown with only a notification to the agency (7 CFR 340.3). This exception, however, does not apply to GM insects at this time, due to a variety of specific requirements in the PPA that apply only to plants (7 CFR 340.3).

Under the PPA permit process, APHIS requires applicants to submit a wide range of data, including a description of the expression of the altered genetic material and how that expression differs from the non-modified organism; a detailed description of the molecular biology used to produce the GM organism; information regarding the source of the vector, donor, and recipient organisms; and how the organism will be transported, held, used and disposed of, including safeguards to prevent contamination, escape, or release of the regulated article (7 CFR 340.4).

APHIS can deny a permit under PPA for a number of reasons, including if "acceptable safeguards adequate to prevent plant pest dissemination can[not] be arranged;" or if the potential risks of pest dissemination, despite safeguards, outweighs the potential benefits (7 CFR 330.204). If it grants a permit, APHIS also imposes an array of conditions on the permit to prevent the dissemination and establishment of plant pests (7 CFR 340.4). This includes a requirement that APHIS be "orally notified immediately upon discovery and notif[ied] in writing within 24 hours in the event of any accidental or unauthorized release of the regulated article." APHIS must also be notified "[i]n writing as soon as possible but not later than 5 working days if the regulated article…is found to have characteristics substantially different from [the permit application] or suffers any unusual occurrence [such as] excessive mortality or morbidity, or unanticipated effect on non-target organisms."

In addition to having authority to withdraw a permit application if non-compliance with the permit conditions occurs, APHIS also has broad statutory authorities to prevent the dissemination of a GM insect defined as a plant pest. This includes the authority to hold, seize, quarantine, treat, destroy, or otherwise dispose of new plant pests, including declaring an extraordinary emergency (Plant Protection Act, Sections 414 and 415).

APHIS also has broad statutory authorities to address livestock pest and disease risks. Although APHIS has indicated it is developing specific authorities and guidance to address the risks presented by GM insects that act as vectors of animal diseases, and that such a regulatory program would be similar to the program for potential plant pests (Young et al. 2000), APHIS has not established such a regulatory program to date. Thus, no framework exists in which to handle permit applications and address specific risks of GM insects that are or may be vectors of animal diseases.

5. Transparency, Clarity, and Public Participation

The APHIS process for regulating GM insects is generally accessible to the public. APHIS requires applicants to submit two applications, one with confidential business information (CBI) deleted, that will be made available to the public. APHIS informs the public when permit requests are filed. However, a recent National Academy of Sciences review criticized the amount of CBI in applications for GM plants (National Research Council 2002). The Academy's report found that "[t]he extent of CBI in registrant documents sent to APHIS hampers external review and transparency of the decision-making process." So far, the developers of GM insects have not extensively deleted CBI from their applications (USDA APHIS 2001b).

APHIS has solicited public input in the NEPA process, both for environmental assessments, as well as through the decision to pursue an EIS for the field release of the GM pink bollworm (See sidebar, Environmental Impact Assessment of Transgenic Pink Bollworms). Although this process has enabled the public to comment on a range of procedural and substantive issues, including such critical issues as the stability of the genetic construct, the National Academy report also suggested that APHIS expand its efforts to involve the public and affected parties in its risk analysis process beyond mere publication in the Federal Register (National Research Council 2002).

Notably, APHIS regulations implementing NEPA presume that the release of genetically engineered organisms will normally require only an environmental assessment (7 C.F.R. 372.5), a presumption that at least one interested party has suggested APHIS remove (Center for Food Safety Petition 2001).

6. Resources and Expertise

APHIS has extensive expertise to assess risks from insect plant pests and insect-borne livestock diseases. The National Academy of Sciences' review of APHIS' regulation of GM plants made a number of suggestions for improving the scientific rigor of APHIS' assessment process, including the use of external scientific advisory committees (National Research Council 2002). While APHIS has the appropriate expertise to assess threats to crops, some have expressed concern that its ability to review permit applications and to inspect field trials to ensure compliance is constrained by limited resources. A recent review of APHIS's ability to respond to threats from traditional plant pests that are frequently unintentionally imported into this country concluded that APHIS is already stretched thin to monitor and act against such threats.[21]

21 The National Plant Board summarized this view in a report commissioned by USDA-APHIS-PPQ in 1999. The report states, "Recent breaches of the APHIS-PPQ safeguarding system that allowed entry of dangerous invasive plant pests into the U.S. have raised concerns that current organizational practices and procedures are inadequate to execute these [Agency] functions."

ENVIRONMENTAL IMPACT ASSESSMENT OF TRANSGENIC PINK BOLLWORMS

APHIS recently approved a confined field cage study of a genetically modified pink bollworm, a cotton pest that causes an estimated $24 million in damages per year. Since the late 1960s, a Sterile Insect Technique (SIT) control program has been used to prevent the spread of the pink bollworm in California. Recently, scientists have genetically modified the pink bollworm to express a fluorescent protein to improve the efficiency and effectiveness of the SIT program by identifying if a bollworm is a lab-reared moth or its progeny, or indicative of a potential infestation. It was also designed to study the effects of GM insects on the environment (66 FR 33226, June 21, 2001; USDA APHIS 2001a).

In response to the application for this confined field cage release, APHIS published a notice in the Federal Register requesting comments on the permit application (June 21, 2001, 66 FR 33226), conducted an environmental assessment under NEPA, and issued a Finding of No Significant Impact (FONSI) on October 1, 2001.

Subsequently, APHIS took the unprecedented step of announcing that it would conduct a full environmental impact statement (EIS) of the proposed field release of the GM bollworm (67 FR 5086-5087, Feb. 4, 2002). Some critics of the existing regulatory regime had recommended this approach, as it would be more comprehensive than the environmental assessment done to evaluate the confined field release. APHIS requested public comment on a number of critical issues for the EIS, including "potential genetic transformation affecting the environment; persistence of the genetically modified pink bollworm versus wild-type pink bollworm; physical and biological containment measures...; potential gene transfer to other insect species; potential gene transfer to non-insect species; potential impacts on humans...; potential effects...on chemical loads in the environment; and risk to non-target plants and animals, including threatened and endangered species."

A progress report from the researchers, however, indicated that they planned to conduct more research before further field tests would occur (Staten 2003, Miller and Staten 2003). No word was available at press time about when further field tests would take place and whether APHIS would maintain its commitment to performing an EIS if and when such an application is received. This would have been the first time that APHIS has conducted an EIS of any GM organism under its jurisdiction. APHIS has approved all other releases of GM organisms on the basis of an environmental assessment.

b. FDA Authority and Procedure

1. Overview

The Federal Food, Drug, and Cosmetic Act (FFDCA) gives FDA several possible jurisdictional claims for authority over GM insects and related microorganisms.

The most extensive authority comes from the FFDCA's provisions requiring the approval of new animal drugs as safe and effective before they can go to market.[22] FDA has informally asserted that the genetic construct used to genetically modify animals, as well as the expression products in the animal, fall within the definition of "drug" because they are "intended to affect the structure or function of the body of man or other animals" (Pew 2003, CEQ-OSTP Case Studies 2001). FDA has asserted this authority over fish that have been genetically modified to grow more quickly than conventionally bred fish.

Since insects are animals,[23] FDA could presumably assert its jurisdiction over GM insects, although to date it has not indicated that it would do so. If FDA applied its interpretation of the new animal drug approval provisions of the FFDCA to insects, FDA's jurisdiction would arguably apply to all GM insects, regardless of their intended use.[24] FDA's Center for Veterinary Medicine (CVM) is responsible for new animal drugs, and therefore, would likely lead any jurisdictional claims made under the new animal drug provision of FFDCA.

A second source of regulatory authority comes from the authority given to FDA under the FFDCA to oversee the safety of the nation's food supply and animal feed. (USDA overseas the safety of meat, poultry and egg products.) FDA's Center for Food Safety and Nutrition (CFSAN) holds the responsibility for food safety and CFSAN's authority could apply, for example, to honey produced by transgenic bees.

Finally, some GM insects, such as a mosquito engineered to be unable to carry diseases like malaria or West Nile, could possibly be considered a human drug or a drug delivery device under the FFDCA because they could be "intended for use in the ... prevention of disease in man." Evaluating the safety and efficacy of human drugs is the responsibility of FDA's Center for Drug Evaluation and Research (CDER), while drug delivery devices are the responsibility of FDA's Center for Devices and Radiological Health (CDRH). CDER would also have the authority to review the safety and efficacy of any human pharmaceuticals produced by a transgenic insect, and possibly over the transgenic insect itself under the theory that the insect is a "drug manufacturing facility" subject to FDA's regulations on good manufacturing practices. Similarly, FDA could assert authority over a GM insect modified to produce a protein that causes an immune system response in bitten humans, as FDA's Center for Biologics Evaluation and Research reviews human biologics.

22 Under the FFDCA, a drug sponsor cannot sell a new animal drug on the market until it has been approved by the FDA as (1) effective, (2) safe for the target animal, and (3) safe for humans who consume foods derived from the treated animal. Among other things, the drug sponsor must demonstrate through "adequate tests by all methods reasonably applicable" that the drug is "safe for use under the conditions prescribed..." and must demonstrate a "reasonable certainty of no harm" for foods derived from the animal treated by the drug (21 U.S.C. §361b). The "reasonable certainty of no harm" standard has not been further defined by FDA or by a court.

23 Insects are the largest class of the phylum Arthropoda, which is itself the largest of the animal phyla.

24 Under FDA's interpretation, the intention of genetic modification does not need to serve a specific purpose to come under the statutory definition. The "intent" is simply to "change the structure or function" of the animal which is accomplished by the insertion of the novel genetic material. The modification need not be for the purpose of treating a livestock disease or even improving an animal's function. A benign (color) or adverse (bioterrorism) change would presumably be equally subject to FDA jurisdiction. Therefore, the end result of the modification is irrelevant to FDA's jurisdiction.

2. Scope Issues

i. Scope of Organisms Covered - New Animal Drugs?

As has been noted in the context of GM fish (Pew 2003), FDA's interpretation of the new animal drug provisions of FFDCA as applied to the genetic modification of animals expands the boundaries of the definition of animal drugs. Conventional animal drugs operate on individual animals and herds/flocks, and their effects are not inherited; their impact is usually temporary. In contrast, genetic alterations result in permanent change to the altered animal, and the new genetic trait may be passed on to subsequent generations. FDA has not yet indicated how it will apply the concepts of "safety" and "effectiveness" to GM animals and their progeny. The FDA's assertion that the definition of new animal drug encompasses genetic engineering has not been challenged and might never be tested in a court, but at least some chance exists that a court would not agree with FDA's interpretation.

It is not clear at what point a GM insect would be subject to FDA's authority. Presumably, at the point at which a genetic construct has been introduced into an insect and the intended purpose of the genetic construct has been achieved. At least in theory, such use would be considered "unsafe" and therefore unlawful without prior FDA approval. As a practical matter, however, the involvement of the FDA at such an early stage is unlikely. A developer can conduct research on an unapproved new animal drug under an exemption for an investigational new animal drug (INAD) (21 U.S.C. 360b(j);21 CFR 511.1). Until FDA provides guidance, however, it is unclear at what point in the research of transgenic insects the INAD requirement would be triggered.[25]

To date, FDA has not indicated whether it intends to exercise its asserted authority over GM insects.[26] If it does, however, its authority would be very broad. FDA would have authority over all GM insects because the very process of genetically modifying them makes them "new animal drugs" for the purposes of the FFDCA. As noted above, however, FDA could also assert authority over a narrower class of GM insects.

25 At a minimum, an INAD is currently required if the GM animal will be disposed of into the food or feed chain.

26 In the CEQ-OSTP case studies that discuss authority over arthropods, FDA's potential authority is not mentioned; only USDA and EPA authorities are cited. In another case study in the document, however, FDA's authority over transgenic livestock ("biofarm animals") is extensively noted. See Case Study No IV, Farm Animal (Goat) that Produces Human Drugs. In that case, FDA has a double hook on jurisdiction, because the product made by the goat would clearly be a human biologic coming under FDA's human drug approval authority.

ii. Symbiotic Microorganisms

GM microorganisms that are insect symbionts could potentially be considered new animal drugs as well. While microorganisms are not animals, the use of them in other animals (including insects) could possibly be considered the administration of a drug intended to alter the "structure or function" of the animal into which it is placed. Certainly, if an antibiotic were injected into an insect to kill a disease-causing virus harbored by the insect, it would be considered an animal drug; the insertion of a GM symbiont microorganism into an insect to do the same thing could be treated in the same way.

Alternatively, a GM symbiotic microorganism modified to kill or control a human disease-causing microbe in the gut of an insect could also conceivably be considered a "human drug" since the intent would be to prevent the transmission of human diseases. In either case, the developer would need to prove both the safety (for humans and the insects) and the efficacy of the technique before it could be lawfully used to help prevent disease transmission. To date, the FDA has not indicated how, or whether, it would assert authority over GM symbiotic microorganisms intended to kill or control human pathogens in insect vectors.

3. Risks Considerations

If FDA's potential authority over GM insects is broad, the scope of the risks that it can consider under the applicable laws is more limited. This factor could be an issue if the federal government decides to place primary or exclusive regulatory authority for GM insects in the hands of the FDA.

FDA assesses new animal drugs to carry out the statutory requirement that the drugs be safe and effective. FDA evaluates drugs to ensure their safety both for animals and for humans. For example, FDA examines the food safety of any animal drug residue in an animal destined for the food supply. FDA also has authority to look at indirect health impacts on humans caused by new animal drugs, and presumably could also consider public health risks, such as in the case of a GM insect vector of human diseases (CEQ-OSTP 2001).

It is unclear, however, how far FDA can go under its new animal drug approval authority to consider potential environmental risks (CEQ-OSTP 2001; Pew 2003). The law itself does not refer to environmental harm or contain a legal standard for evaluating environmental risks. FDA asserts that the Act's requirement to show safety thus permits the agency to consider environmental impacts that could indirectly result in harm to humans or animals. For instance, in the approval process for recombinant bovine somatotropin (rBST), a hormone made by GM bacteria, the FDA expressly considered broad environmental risks that could potentially be presented through the use of the drug. For example, the FDA considered the possibility that approval of the drug (1) might affect land-use patterns and water quality by affecting the types of feed ingredients grown for dairy cows, (2) might affect carbon dioxide emissions due to changed ration requirements and dairy populations, and (3) might present a used syringe disposal problem (CEQ-OSTP 2001). The FDA's authority to consider these environmental impacts was not challenged in the process. The FDA approved rBST as a new animal drug in 1993.

However, FDA's authority to look at purely ecological risks that could stem from gene flow from GM animals is uncertain (Pew 2003). Further, it is unclear what standard FDA would apply to assess such risks, or the basis for a decision to deny a permit that otherwise meets FDA's standards. Like other federal agencies, FDA is subject to NEPA. When issuing a permit or taking action, FDA conducts an environmental assessment and may impose conditions in the permit that mitigate other environmental concerns, so that it can find that its action poses "no significant impact" on the environment and avoid a full EIS. But NEPA does not give FDA any substantive legal authority to deny a permit on grounds other than those set out in the FFDCA.

4. Risk Management Tools

The drug approval provisions of the FFDCA are broad, flexible, and afford the FDA a great deal of authority before and after approval of a new product. FDA requires product developers to prove the safety and efficacy of a drug when used under prescribed conditions. FDA can impose labeling and use restrictions as part of its approval and requires developers to report adverse events.

The legal regime with respect to food safety differs in several important respects from that for human or animal drugs. Foods that have been a part of the human food supply for many years are effectively presumed safe, and FDA has generally considered new food varieties, whether bred conventionally or through biotechnology, to be as safe as prior foods. As a result, the FFDCA does not require FDA to approve new whole food varieties before they can go to market. Manufacturers are, however, legally responsible for the safety of the food they make, and FDA has the authority to enjoin the sale and distribution of "adulterated" foods on the market – i.e., foods that cause harm. In the case of GM crops, FDA presumes that they are substantially equivalent to their conventionally bred counterparts, and encourages companies to share safety data with FDA before taking new foods derived from GM crops to the market. If the modification adds an element not found in the conventional variety, FDA could regulate the element as a food additive, which does require FDA pre-market approval for safety.

For example, it is unclear how FDA would proceed if faced with a transgenic honeybee. It might choose to regulate the insect itself under the new animal drug law provisions, under which the developer would need to prove a "reasonable certainty of no harm" from the honey made by the GM bee. Alternatively, the FDA could consider the honey simply as substantially equivalent to honey produced by conventional bees, and not require any pre-market review.

5. Transparency, Clarity, and Public Participation

If FDA asserted jurisdiction over GM insects under its new animal drug authority, FDA would likely follow a very closed process that would provide little transparency, clarity, and public participation in FDA's decision making process. By law, new animal drug applications are confidential and FDA is precluded from notifying the public of even the existence of an application for approval of a new animal drug (CEQ-OSTP 2001). The public would not be aware if FDA were considering an application for GM insects unless the developer voluntarily released this information.

If FDA approves a GM insect under the new animal drug authority, FDA would publicly announce the approval and at that time make available a summary of the data contained in the application, excluding CBI. While this process provides some transparency after the regulatory decision has been made, it does not provide for disclosure of all of the health or environmental data relied upon by the agency before the decision is made. In addition, the process affords no opportunity to comment on the application nor permits others to submit relevant information or views. Thus, no public discussion would occur about risks and benefits of particular applications. The public would not have any opportunity to assess whether the benefits of a particular GM insect outweigh the risks or to define what it thinks is an acceptable risk, issues which are informed both by policy and science. (In the past, CVM has used draft risk assessments and advisory committees to obtain public comment and external views on more general policy and science issues.) FDA has noted the conflict between these confidentiality requirements and the requirement to provide the opportunity for public notice and comment on environmental assessments under NEPA, which requires FDA to assess the environmental effects of its actions. The agency has indicated that it is evaluating its options to resolve this tension (CEQ-OSTP 2001, Pew 2003).

6. Resources and Expertise

FDA clearly has the expertise to address human health and food safety issues. It may not, however, have the expertise to assess the full range of environmental effects that could arise from the release of GM insects, including, for example, risks to plants, an expertise housed in other agencies like APHIS or the Department of the Interior (Pew 2003). Moreover, while FDA has a regulatory program in place for plant-based biotechnology that could form the basis for a GM insect regulatory program, FDA will need additional staff and resources, including field personnel, to develop an effective regulatory program for GM insects.

c. EPA Authority and Procedures

1. Overview

EPA has two potential legal authorities that could apply to regulate GM insects: the Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Both statutes, however, may only apply to a narrow class of GM insects, and the applicability of both these statutes may hinge on whether FDA asserts jurisdiction under its new animal drug authorities.

FIFRA provides EPA with broad authority to regulate pesticides, which it defines as "any substance or mixtures of substances intended to prevent, destroy, repel or mitigate any pest" (7 U.S.C. §136(u)). In order to market a pesticide, a developer must get prior approval ("registration") from EPA, which considers both environmental risks and human health risks and imposes labeling and use restrictions to prevent unreasonable environmental risks. EPA is also responsible for establishing tolerances for pesticide residues in food under the FFDCA.

Under Section 5 of TSCA, a manufacturer or importer of a "new" chemical substance must submit a notice to EPA at least 90 days before beginning to manufacture it (15 U.S.C. 2604). A "new" chemical substance is defined as one not listed on the TSCA Inventory. During this 90-day period, EPA reviews the substance to determine whether any aspect of its manufacture, use, distribution in commerce, or disposal warrant regulation. EPA is authorized to regulate when insufficient information exists to demonstrate a risk, as well as in the face of information demonstrating a risk, and can require the generation and submission of data either before or after the submission of the notice. While EPA has historically relied upon the "pre-manufacturing notice" requirements of Section 5 to regulate microbes, other sections of TSCA provide EPA with authority to require testing (Section 4) or to regulate unreasonable risks (Section 6).

In addition to providing EPA with authority over the organism, TSCA may also provide EPA with authority over substances made by GM insects, such as silk, provided that the product meets the definition of a "new chemical substance" or that the substance has been designated as a "significant new use" of an existing chemical substance. The product also could not fall within one of specific exclusions in Section 3, such as a food, drug, or pesticide.

2. Scope Issues

Under FIFRA, GM insects modified to kill, repel, or mitigate animal, plant, or human pests would come under the definition of a pesticide. However, as noted previously, EPA has disclaimed authority over most biological-control organisms used to control pests except for certain microorganisms used as "bio-pesticides" (40 C.F.R. 152.20). EPA regulates microbial pesticides, such as the Bt bacterial toxin, as well as the pesticidal substances produced within some GM crops. If EPA followed these precedents, it might not assert authority over GM insects. (In the CEQ-OSTP case studies, EPA did not assert authority under FIFRA for regulating GM arthropods, but did assert authority under TSCA.) Arguably, however, EPA could still regulate the pesticidal proteins produced by a GM insect, or assert authority over a symbiotic microorganism genetically modified to kill a pathogen (see the previous discussion under APHIS). The question then arises whether EPA would assert authority over paratransgenic insects, genetically engineered or not, that host GM micro-organisms.

A second issue is that both FIFRA and TSCA specifically exclude substances regulated as human and animal drugs (7 U.S.C. §136 (u); 15 USC § 2602). If FDA asserts its authority to regulate GM insects or GM microorganisms as human or animal drugs, it could preclude EPA regulation under both FIFRA and TSCA. Arguably, EPA might still be able to regulate a GM insect on the grounds that the actual "drug" regulated by FDA is the genetic construct and its expression product, not the whole organism itself. This argument would not seem to apply to GM microorganisms, however, which would likely be considered new drugs if intended for insertion into a host insect.

TSCA's application to GM insects and GM microorganisms also raises questions. Under TSCA, EPA has promulgated regulations addressing microbial products of biotechnology (40 C.F.R. Part 725). In those regulations, EPA asserts that "intergeneric" (i.e., GM) combinations of microorganisms are "new chemical substances" within the meaning of TSCA, and developers must notify EPA prior to manufacturing. TSCA therefore covers all microorganisms modified through rDNA techniques, unless those microrganisms are exempted or specifically covered by other laws, such as drugs (noted above), food, and pesticides. While EPA's argument that TSCA applies to whole living organisms has drawn criticism,[27] to date EPA's assertion of jurisdiction over GM microorganisms has not been challenged.

EPA has also claimed that TSCA would similarly give it the authority to regulate higher level organisms, including GM animals and insects (CEQ-OSTP 2001). EPA has not indicated whether it will assert its authority under TSCA to regulate GM insects, but the argument that TSCA applies to higher level whole living organisms is subject to at least some legal uncertainty.

In addition, the pre-manufacturing notice requirement of Section 5 of TSCA is limited to substances "with a commercial purpose." In its regulations on GM microbes, EPA has interpreted this requirement broadly to encompass activities conducted "with the purpose of obtaining an immediate or eventual commercial advantage" for the manufacturer or distributor (40 C.F.R. § 725.3). However, many of the GM insects under development are non-commercial or are being developed by the public sector for public health or other non-profit purposes. As a result, Section 5 of TSCA may not provide authority over the full range of GM insects under development, particularly non-commercial research.

27 See, e.g., McGarity 1983.

3. Risk Management Tools

TSCA and FIFRA provide different risk management tools with which to regulate GM insects. For example, under Section 5 of TSCA, EPA reviews "new" microorganisms and has authority to impose measures necessary to prevent unreasonable risk to human health and the environment and to regulate when there is insufficient information to determine whether the microorganism may present such a risk. Before manufacture or importation, including release into the environment, developers must provide EPA with extensive data regarding the genetic construction of the new microorganism, its use and ability to survive in various environments, its effect on other target and non-target organisms, and all test data regarding the health and environmental effects of the new microorganism (40 CFR 725.155 and 725.160). EPA has asserted broad authority to impose conditions to address unreasonable risks (CEQ-OSTP 2001). Under TSCA, EPA is required to evaluate both the costs and benefits of the new microorganism as well as the economic effects of regulation; thus, it does not look solely at health and safety effects in evaluating whether a new microorganism presents unreasonable risks. EPA also has power under Sections 6 and 8 to require testing and to regulate chemicals to protect against unreasonable risks to the environment and human health.[28]

Under FIFRA, EPA reviews the potential impacts of pesticides on human health and the environment, including non-target organisms, to ensure that they do not impose unreasonable risks. EPA requires manufacturers to register and re-register pesticides, during which time manufacturers submit extensive data to EPA regarding the human health and environmental effects of their products. EPA also imposes restrictions or conditions on the use of such products, including adverse event reporting and storage restrictions, and can force a recall of a pesticide. In addition, EPA has the authority to cancel or suspend registrations, effectively prohibiting use of the product, including in emergency situations. Under the FFDCA, EPA also establishes tolerances for pesticide residues in food to ensure that they pose "a reasonable certainty of no harm"; it is illegal to sell foods containing pesticide residues that exceed EPA's tolerance. The standard applied for evaluating dietary exposures is purely risk-based, while other human health risks, including farm worker risks, are subjected to a balancing test that evaluates an array of costs and benefits of the pesticide (although non-occupational exposures are factored into the assessment of the safety of dietary exposure).

28 While beyond the scope of this paper, the powers of EPA to regulate chemicals under Section 6 has been constrained by court decisions construing the requirement that EPA use the "least burdensome" regulatory approach. (See, e.g., Corrosion Proof Fittings vs. EPA, 947 F.2d 1201, 5th Cir. (October 18, 1991).)

4. Transparency, Clarity, and Public Participation

Under TSCA, FIFRA, and FFDCA, the public would be provided with information about GM insects in the regulatory pipeline and would be afforded an opportunity to have input into the agency's decision making process. For example, under TSCA, the public would be notified when a notice is submitted to EPA and would have access to any non-confidential information. Similarly, EPA publishes notices in the Federal Register, without confidential information, when it is petitioned to establish a tolerance under the FFDCA, including a summary of the data and information supporting the petition. The tolerance process also provides the public with certain hearing rights.

5. Resources and Expertise

EPA has expertise relative to environmental and human health risks, but it may not have expertise relative to animal health risks presented by GM insects. Since EPA does not have a regulatory program in place for GM insects, an infusion of funding and staff would be needed to establish a credible regulatory program.

d. Public Health Service — Authorities

The Public Health Service (PHS), within the Department of Health and Human Services (HHS), has statutory responsibility under the Public Health Service Act (42 U.S.C. §264) for preventing and controlling the spread of communicable human diseases, including insect-borne diseases such as West Nile and malaria. HHS has promulgated regulations regarding the importation and interstate shipment of agents like insects that can cause disease (42 C.F.R. §71-§72). However, outside of such restrictions, the PHS has not traditionally regulated the use of such insects in research or field trials, leaving matters such as environmental safety and informed human subject consent to research guidelines issued by the NIH (discussed in the next section).

The PHS is not a regulatory agency in the sense that it reviews products or awards licenses. However, the Secretary of HHS and the Surgeon General have broad powers to act to prevent the introduction and dissemination of insect-borne diseases, including the power to investigate, quarantine, inspect, and seize, as demonstrated by the recent SARS outbreak. Under the Public Health Service Act, PHS clearly has the authority to develop a broader regulatory and permitting program for GM insects that are the vectors of human diseases, though such a program would require a dramatic change in the PHS's institutional culture and traditional mission. To date, PHS has not indicated any intention to do so despite requests by some public interest groups (Center for Food Safety Petition 2001a).

C NIH Research Guidelines

i. Overview

In 1975, molecular biologists began exploring the potential of genetic engineering, often using bacteria common in the environment and in humans. Many researchers believed that genetic alterations would make bacteria too weak to survive in nature, but others began to raise ethical and safety concerns about the potential consequences if altered microorganisms escaped from the laboratory, and entered the environment, and potentially resulted in human exposure. Scientists met in Asilomar, California, that same year to agree on guidelines to ensure the safe use of genetically engineered organisms until scientists gained additional experience.

The tradition of establishing guidelines for the safe and ethical conduct of scientific research continues today. Following Asilomar, the National Institutes of Health (NIH) codified this approach with the establishment of the Recombinant DNA Advisory Committee (RAC) to advise the NIH Director on ethical and safety matters involving recombinant DNA research. In 1976, NIH issued the first Guidelines for Research Involving Recombinant DNA molecules (Guidelines), which, although modified frequently since then, continue to apply to all recombinant DNA research at institutions receiving NIH funding.

As the technology advanced, however, and as research moved from the laboratory to the field and from basic research to commercial applications, mandatory regulatory regimes at FDA, EPA, and USDA largely replaced the RAC as the principal federal mechanism governing recombinant DNA technology. Today, the RAC focuses largely on human gene therapy experiments and other recombinant DNA research seen as more controversial than agricultural applications.

However, the institutional research review and approval structure created by NIH remains very much in place and continues to cover all recombinant DNA research at federal laboratories and institutions funded by NIH or most federal agencies, including research on GM insects. While NIH is not a regulatory agency, its influence in the conduct of research is pervasive. All research conducted at a federal laboratory, or at a research facility that receives virtually any federal research funding, is obligated to follow the NIH guidelines or face the potential withdrawal of federal funds.

In laboratories across the country, scientists work with thousands of animals (including insects) that have been genetically modified for research purposes without ever needing any review or approval from any federal or state regulatory agency. NIH guidelines, as interpreted by the researchers and the research institutions, provide instructions on appropriate standards of containment. Scientific societies provide further expert guidance.[29] No external review or approval by a federal agency is usually expected or required. (In some cases, transport of hazardous substances or organisms do require permits.)

Researchers working with transgenic and paratransgenic insects under the NIH guidelines may soon collide with federal regulatory authority and public concerns about environmental releases of GM insects and microorganisms. NIH guidelines have focused mainly on the appropriate containment of laboratory experiments to prevent environmental or human exposure. They do not address many of the critical environmental, animal health, or plant health issues that will be generated by field trials and more general environmental releases. Researchers' assertions that such releases will pose little or no risk are unlikely to reassure the public. Yet, with the exception of APHIS, no federal rules are in place to assess those risks or to provide a pathway for answering those questions. In this policy vacuum, several scientists and scientific groups are attempting to grapple with appropriate standards for releases that will safeguard the environment and protect the rights of human subjects in those experiments involving public health.[30] It is, however, critical that the federal regulatory agencies, NIH and the Public Health Service, researchers and research institutions begin a dialogue to determine how to handle field trials and general releases.

29 See, e.g., The American Committee of Medical Entomology of the American Society of Tropical Medicine and Hygiene 2000; Hoy et al. 1997.

30 The American Committee of Medical Entomology of the American Society of Tropical Medicine and Hygiene 2000; Aultman et al. 2000, which discusses the need for Institutional Biosafety Committee and Institution Review Board approvals of trial releases of genetically-modified insect vectors; UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases 2003, which discusses the need to obtain community consent; Beard et al. 2002, which discusses the potential regulatory role of APHIS, EPA, FDA, and the Public Health Service.

ii. NIH and Institutional Biosafety Committees

This section describes how the NIH guidelines help ensure the safe and ethical handling of genetically modified organisms and the informed prior consent of patients in medical research.

a. Overview – Biosafety and Containment

NIH is not a regulatory agency. Instead, the primary mission of the organization is to carry out research and make research grants to promote the discovery of scientific knowledge in the biomedical area. As one of the largest sources of research funding, NIH can and does regulate the conduct of its grantees through provisions included in grant agreements. The NIH Guidelines for Research Involving Recombinant DNA Molecules (National Institutes of Health 2002) are contractually binding on NIH grantees; and, many other federal agencies that fund research have incorporated the NIH guidelines by reference into their own research agreements. (Research at federal laboratories also complies with the NIH guidelines.) The NIH guidelines cover any institution that receives any NIH funding and can even extend to privately funded research carried out at an institution that receives any funding from NIH.

Under its guidelines for recombinant DNA research, NIH categorizes research into certain risk categories and then specifies the level of containment needed to protect against the accidental release of the modified organism. Depending on the type of research and the level of risk involved, approvals might also be needed. Relatively low-risk experiments may involve review and approval by an institution's Institutional Biosafety Advisory Committee (IBC). Each institution subject to the NIH guidelines must establish IBCs, which are composed of individuals with specified expertise (including persons not affiliated with the institution), who are charged with the responsibility of initial review, approval, and on-going oversight of research conducted under the guidelines. Riskier research (such as human gene therapy) would require approval by the NIH's Recombinant DNA Advisory Committee (RAC) and the NIH Director.

It is important to note that responsibility falls to the individual researcher, not the NIH, to assess the risk and the appropriate biosafety containment level and obtain IBC review for the particular research project.[31] NIH does not have regulatory tools to ensure enforcement and compliance with the guidelines. Enforcement is accomplished primarily through oversight by an institution's IBC, which is required to report annually to the NIH as well as to report any adverse events. Non-compliance can lead to withdrawal of NIH funding for the specific research and, potentially, to the entire institution at which the research is conducted.

31 In addition to NIH guidelines, scientific groups work to develop additional "best practices" relevant to their particular discipline. See., e.g., American Committee of Medical Entomology of the American Society of Tropical Medicine and Hygiene 2000, whose standards have been recommended by USDA.

The NIH guidelines and process used to evaluate research provides a relatively transparent, largely predictable, and established public process for oversight. The NIH posts the minutes (and sometimes archived webcasts) of RAC meetings on its website. However, the IBCs of individual institutions review the great majority of recombinant DNA research projects. According to a recent survey of the nearly 400 IBCs that have registered with NIH, 48 percent of those responding reported that their meetings were not open to the public and 51 percent of those responding reported that IBC minutes are not available to the public, despite NIH guidance to the contrary.[32]

In addition, the annual reports required by NIH contain little or no information about the actual projects reviewed and approved by IBCs. As a result, it is impossible to determine how well the IBCs apply the NIH guidelines, or to draw any conclusions about the scope or nature of the research being conducted or reviewed. The guidelines also require appropriate expertise on an IBC. While the annual reports do contain the identities and expertise of the IBC members, without knowing the nature of the research projects under review, it is impossible to determine the level of the IBCs compliance with that NIH requirement.

b. Application of Guidelines to GM Insect Research

According to NIH's Office of Biotechnology Activities, the provisions of the NIH guidelines relating to animals (specifically Section III-D-4) would cover genetic modification of insects and the modification of microorganisms carried by animals. Almost all experiments involving whole animals, including insects, are required to be conducted under a minimum biosafety level (BL1) that would preclude any field test or release into the environment.[33] For example, an experiment with a mosquito that carries the malaria parasite would need to take place at the more secure BL2 or BL2-N biosafety level. Additional provisions relating to containment are included in Appendix Q and P of the NIH guidelines.[34]

Because NIH primarily focuses on early stage contained laboratory research, its activities do not overlap significantly with the federal regulatory agencies. As noted above, in general, the NIH guidelines may be superceded once a product enters an established regulatory process, such as for approval of field trials. In some instances, concurrent requirements exist. For example, researchers working with animal or plant pathogens will also need to comply with USDA permit requirements for interstate transport.

32 Hackney, Survey of Institutional Biosafety Committees, Presentation at the "The Future Face of Institutional Biosafety Committees: Evolving Roles and Responsibilities, Upcoming Challenges and Opportunities", San Diego, CA (February, 2003); http://www.capcon-corp.com/ibc2003/presentations/Hackney2.ppt

33 Zerhouni, DHHS, PHS, Letter to Center for Food Safety, June 19, 2003.

34 http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html

iii. Informed Human Subject Consent

DHHS' Office for Human Research Protections also operates a separate program focused on protecting human subjects in biomedical research and insuring informed consent (45 C.F.R.§46 et seq.). As in the case of research with recombinant DNA molecules, the regulations require federal laboratories and research institutions receiving federal funding to establish an Institutional Review Board (IRB) to review proposed research on human subjects to ensure that ethical standards are met. In addition to ensuring that the human subjects provide informed consent, the IRB ensures that proposed research minimizes risks to subjects, imposes risks that are reasonable in relation to anticipated benefits, and selects subjects in an equitable way (45 C.F.R. §46.111).

In theory, the release of vector insects begets a need to inform individuals that might be affected. Such notification, however, is difficult, if not impossible, in areas with large populations. Scientists working on GM insects to control insect-borne diseases like malaria and Chagas' disease have grappled with plans to provide informed consent during any field trials (Aultman et al. 2000; Macer 2003; Beard et al. 2002). Ultimately, approval will be needed from the IRBs of the institutions conducting the research, whether the research takes place in the United States or abroad.

International Issues

Because the potential benefits of GM insects in disease prevention could be found in tropical nations with the highest incidence of such diseases, researchers have taken a particular interest in the procedures for approval and testing in other nations. While an increasing number of researchers have pointed to the need for regulatory oversight of GM insects, developing regulatory frameworks has received little concrete attention. To date, the scientific communities involved primarily in public health have carried out most of the discussions (FAO/IAEA 2002, Scott et al. 2002, Alphey et al. 2002, Hoy 2002).

This interest, coupled with concern about a lack of international risk assessment guidelines and expertise, resulted in an international workshop in April 2002 sponsored by the Food and Agricultural Organization and the International Atomic Energy Association (FAO/IAEA 2002). At the workshop, experts in the fields of insect biotechnology and risk assessment attempted to outline the potential risks associated with the release of a transgenic insect and to establish preliminary risk assessment protocols. The proceedings from the conference note that "Current national regulatory processes, including the availability of suitable risk analysis protocols, may be insufficient to address any eventual release of transgenic arthropods." Given the interest in permanently releasing such insects into the environment, important questions ensue about the ability of any country to contain these insects within borders, making risk assessment an international issue. A further complication to the internal U.S. debate is the fact that some of the GM insects used in pest management programs will not be intended for use here in the U.S., but for deployment elsewhere in the world, or could invade other countries through accidental or natural spread.

A number of international agreements could impact the transboundary movement of GM insects and microorganisms, as described below.

The International Plant Protection Convention (IPPC) aims to protect plant health from introduced plant pests (International Plant Protection Convention 1997). The International Standards for Phytosanitary Measures (ISPM) established for the IPPC will likely cover GM insects that are plant pests, but it is not likely to cover insects that vector human or animal diseases.

Transboundary movement of GM insects, whether intentional or not, fall within the scope of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity. The Biosafety Protocol applies to "the transboundary movement, transit, handling and use of all living modified organisms that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health," where living modified organisms (LMOs) are defined as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology" (Cartagena 2000). The Protocol exempts those LMOs that are contained and will not be released into the environment, as well as LMOs used for pharmaceutical uses. The Protocol also establishes a system of advanced notice for situations where scientists plan to intentionally introduce LMOs into the environment of the importing nation; exemptions are given for advanced notice for LMOs used for food, feed, or processing uses. The Protocol will eventually establish a system for liability and redress "for damage resulting from the transboundary movements" of LMOs. While all of the issues surrounding the implementation of the Protocol, such as liability and compliance, remain to be sorted out, the Protocol may provide a minimal first layer of international standards to the international transportation and release of GM insects.

NIH guidelines on recombinant DNA research and the protection of human subjects apply to NIH-funded research, even research conducted abroad. However, NIH guidelines do not permit uncontained field trials of GM insects. As a result, the NIH guidelines appear to operate as a ban on uncontained field trials abroad by NIH-funded and federal researchers. The regulatory requirements that apply to field trials or releases in the U.S. are unlikely to apply, because U.S. laws are generally presumed not to have extra-territorial application absent some clear intent from Congress to the contrary. Consequently, field trials or permanent releases into the environment could be conducted abroad without review and approval from FDA, EPA, or USDA. (Because those regulatory approvals are not required, those agencies would not need to do an environmental assessment under NEPA.) NEPA might, however, apply to federal agencies that fund the research or field trials abroad. In that case, the federal funding agency would need to conduct an environmental assessment or an Environmental Impact Statement in the event that the release would be considered to have a significant environmental impact.

Chapter Five

CONCLUSIONS

Chapter V

CONCLUSIONS

Authority: Scope of Organisms Covered & Risks Considered

As the above analysis demonstrates, a number of laws could theoretically apply to most, if not all, kinds of genetically modified insects and their associated microorganisms. However, no single law provides both a comprehensive coverage of GM insects and authority to look at the food safety, environmental, agricultural, and public health risks that GM insects and GM microorganisms might pose.

At least two laws have the potential to cover many, if not all, GM insects. FDA's interpretation of the new animal drug approval provisions of the FFDCA would cover all GM insects modified for any purpose. Similarly, because many insects are also plant pests, USDA's APHIS would have jurisdiction over many GM insects, without regard to their intended purpose. If EPA's interpretation of TSCA is sound, EPA would also have authority over many GM insects, regardless of their intended use—assuming it is not precluded by FDA's new animal drug characterization. In addition to these broad jurisdictional claims, other laws could apply to more specific applications, such as honey from a transgenic honeybee.

With respect to GM microorganisms associated with paratransgenic insects, several agencies could lay claim authority. The FDA could regulate these microorganisms intended for insertion into insects as new animal drugs or in some cases as human biologics. EPA would regulate microorganisms modified to be pesticides, while Section 5 of TSCA would cover other novel microorganisms. However, EPA's authority may be constrained if FDA asserts the authority to regulate GM microorganisms as drugs, because both FIFRA and TSCA exclude substances regulated as drugs. APHIS could also lay claim to a microorganism which could harm plants either in its natural or genetically modified form.

While some law likely exists that would apply to almost all currently expected applications of transgenic and paratransgenic insects, it is less clear that an agency with jurisdiction has the authority to assess and manage the full range of risks potentially posed by these insects. For example, if FDA's interpretation of its new animal drug approval authority is sound, the agency would have authority to assess and manage risks for public health, animal health and safety, and food safety, but only limited power to consider environmental risks. The FFDCA does not explicitly provide any authority for FDA to regulate on the basis of environmental risks that do not impact human health or animal health. Even in its most expansive interpretation, FDA has acknowledged that it lacks authority to consider some kinds of environmental risks (CEQ-OSTP 2001). Ironically, FDA's assertion of jurisdiction could also preclude EPA, the one agency with authority to review all of the potential environmental impacts, from having jurisdiction over GM insects.

Similarly, APHIS focuses on injury to livestock, crops, and plants. APHIS considers other environmental impacts as part of the NEPA process, but neither the PPA nor NEPA provide substantive legal authority for APHIS to deny a permit for GM insects because of unacceptable environmental risks. Moreover, APHIS has no explicit authority to consider public health or food safety risks.

Much of the above analysis is based on what agencies might or might not do under existing laws. With the exception of APHIS' regulation of GM plant pests, no agency has formally indicated how it intends to use its authority to regulate GM insects, and the federal government has not indicated how it intends to use these various authorities in a coordinated way to cover the range of potential applications and potential concerns raised by GM insects. In the absence of a clear policy, it is impossible to judge the adequacy of the federal regulatory system to prevent and mitigate risks from GM insects. However, the above analysis suggests that, even when combining the statutory authorities, gaps may remain in both the coverage and in the scope of risks that agencies can cover.

B Transparency, Clarity, and Public Participation

In the absence of a clear federal policy on the regulation of GM insects, researchers and developers lack a clear regulatory pathway. This lack of clarity can also threaten public trust in the regulatory system. Any effort to compile a comprehensive regulatory framework by coordinating different legal authorities and agencies faces difficulties because each of the laws provides different standards and processes for making regulatory decisions. It will be difficult using existing statutory authorities to develop a relatively uniform process that provides for public access and participation in the regulation of GM products.

This reinforces a broader point about the importance of ensuring that the public believes that the regulatory system is, in fact, asking the right questions and has the capacity or regulatory tools necessary to address issues presented by particular applications of the technology. In this regard, the public transparency and participation provided by the current APHIS process helps to mitigate public concerns regarding adequate regulation, but the closed process in the new animal drug approach used by FDA could aggravate public concerns. As a result, even if the federal government proactively established a framework for handling these products, concerns may still exist about the adequacy of the process under existing statutory authorities.

C Adequacy of Risk Management Tools—Determining and Managing Risk

Even with a strong statutory authority and an array of risk management tools, many difficult questions must be addressed regarding the range of risks presented by GM insects. One of the most difficult sets of questions involves determining and managing risk.

For example, one of the risks of GM insects is the potential for genes to move into other species as a result of horizontal gene flow from transpons. Fundamental scientific information regarding the nature and extent of such horizontal gene flow is limited. How will agencies evaluate and regulate this risk of horizontal gene flow? Will the agencies conduct a comprehensive risk assessment of the likelihood of this occurrence and apply general restrictions, such as requiring the removal of the transposable element vector from the GM insects before release in the environment?

In turn, the previous questions raise more questions: Instead of general restrictions, will the agencies analyze each insect and the likelihood that it presents a risk of horizontal gene flow, and impose appropriate restrictions? Will a public discussion of the particular risks of each GM insect occur? How is risk measured? Put another way, what level of risk of horizontal gene flow is safe or acceptable from a public policy and a risk management perspective? For GM insects developed specifically to address human diseases, how will developers and regulators go about ensuring informed consent, when the insects are released into areas for experimental field trials?

Further, questions arise about the methods by which agencies will evaluate and regulate the plant, animal, and environmental risks presented by GM insects. Will they impose biological, geographic, and climatic controls that limit the ability of the GM insect to survive? How will the agencies handle a situation where the transgenic insect population needs to survive permanently in the environment in order to achieve an important public benefit, like a dramatic reduction in pesticide use? How would the agencies withdraw a GM insect that had been released into the wild? The government's ability to manage invasive species has been criticized for lack of authority and resources. How would the agencies monitor whether a GM insect has become an invasive pest species? How do you remove genes that have already entered nature's gene pool?

As the development of GM insects continues, these and other difficult questions related to defining and managing risks need careful evaluation and answers from the regulatory agencies in a transparent and clear manner. This is not likely to be achieved without some controversy, including legal challenges. For example, while not in the context of GM organisms, APHIS was recently challenged regarding its failure to define "negligible risk" regarding the importation of Argentine citrus. In the risk assessment that supported the rulemaking, APHIS found that the risk of pest introduction was negligible, but did not define what it meant by "negligible." The court remanded the issue to APHIS for the development of a negligible risk standard for each of the pests involved (Harlan Land Company et al., vs. U.S. Department of Agriculture, Sept. 27, 2001, United States District Court of the Eastern District Of California). In April 2002, the government withdrew its appeal of this decision. As the agencies struggle to define and manage the risks presented by GM insects, legal challenges may well continue and expand.

Efficiency and Coordination

This analysis clearly shows that there are multiple potential claims of overlapping jurisdiction over GM insects and GM microorganisms. In the absence of a policy that sorts out the roles of each agency with some claim to review, the potential exists for significant duplication and overlap of regulatory effort. In particular, many GM insects could be characterized by APHIS not only as a potential plant or animal pest, vector of livestock disease, or undesirable species of honeybee, but also as a new animal drug by FDA, and as a new chemical substance by EPA. The many insects that act as vectors for both human and animal diseases, along with the disease-causing organisms, could likely be claimed by USDA, the Public Health Service and, possibly, FDA. This presents the potential for inefficient and unnecessary duplication of government regulation.

Resources and Expertise

Given that transgenic and paratransgenic insects potentially raise human health, food safety, animal and plant health, and environmental issues, it is unclear whether any single agency has the expertise to evaluate the full range of risks. Without an articulated framework that establishes how the various regulatory agencies will coordinate and manage the myriad of issues involved with GM insects, it is difficult to evaluate whether sufficient resources and expertise are or will be made available to fully evaluate and effectively address these potential risks. Until such a framework is established, and the issues raised by GM insects are fully and publicly discussed, it may be difficult to assure the public that all of the relevant agencies have all the authorities, tools, resources, and expertise necessary to assess and address these risks.

Guidelines for Field Trials and Environmental Releases

For over twenty years, the NIH guidelines have provided effective and practical standards for ensuring the safe and ethical use of biotechnology in research. As transgenic plants moved from the laboratory toward commercialization, the regulatory agencies picked up the responsibility for establishing standards and providing regulatory review for field trials and general releases. GM insects now face that same transition, but it is made more complicated by the conflicting and unclear federal jurisdiction, the difficult assessment of environmental risks, the non-commercial nature of the work, and the potential international context of many of the proposed applications. To date, federal agencies have done little to provide concrete guidance to the scientific community.

The International Context

Just as the world's borders are proving highly permeable by invasive animal and plant species, the small size, mobility, and range of insects pose international regulatory challenges never faced by GM crops. Scientists are grappling with these issues at international meetings, but the lack of regulatory infrastructures in many countries make it difficult to see a clear pathway for development and deployment, despite the truly dramatic benefits that might flow. Federal leadership is needed to help mobilize efforts on the international front.

Chapter Six

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VII

Chapter Seven

APPENDIX

APPENDIX

A Reviewers

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