CURRENT TRENDS IN **PHARMACEUTICAL RESEARCH 2013, 2(1): 45-59**

GENETICALLY MODIFIED ORGANISMS: ITS EMERGENCE AND CURRENT STATUS

Prakash Rajak*, Biman Bhuyan

Dept. of Pharmaceutical Sciences, Dibrugarh University,
Dibrugarh-786004, Assam.

ABSTRACT

A GMO is an animal, plant, or microorganism that has genes that have been modified using the gene technologies of molecular biology. This is a process where the traits or characteristics of an organism are changed by modifying genes within a species or transferring individual genes from one species to another (transgenics). The modification of genes can occur by: eliminating certain genes altogether within an organism, modifying genes by turning them off or on, or altering their location, or adding copies of specific genes from other organisms. Other associated terminology includes genetic engineering, and transgenics or recombinant DNA (inserting a gene from one species to another).

The use of genetically modified organisms represents an enormous advance in the science of biological and medical research, and GMOs are playing an increasingly important role in the discovery and development of new medicines.

The FSSAI now intends to meet its regulatory obligations by implementing a safety assessment and approval process for GM foods that leverages existing regulatory capacity within the Government of India, notably within DBT, MoEF and the Indian Council of Medical Research (ICMR).

In addition, the United Nations, World Health Organization, American Medical Association, and the National Academy of Sciences have examined the health and safety issues of GMOs. The UN recently reported that genetically modified crops "pose no more risk than conventionally grown crops" and "there have been no verifiable reports of their causing any significant health or environmental harm."

***Corresponding Author e-mail: prakashhhh@gmail.com**

INTRODUCTION

A genetically modified organism (GMO) is an organism whose genetic material has been altered using genetic engineering techniques. Organisms that have been genetically modified include micro-organisms such as bacteria and yeast, insects, plants, fish, and mammals. GMOs are the source of genetically modified foods, and are also widely used in scientific research and to produce goods other than food. The term GMO is very close to the technical legal term, 'living modified organism' defined in the Cartagena Protocol on Biosafety, which regulates international trade in living GMOs (specifically, "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology"). The acronym can apply to plants, animals or microorganisms, whereas the term genetically engineered microorganism (GEM) refers only to bacteria, fungi, yeast or other microorganisms. In both cases, however, these terms refer to a living organism that has been genetically altered using molecular genetics techniques such as gene cloning and protein engineering.

PRODUCTION METHOD

GMOs are produced using scientific methods that include recombinant DNA technology(Barta, A. *et al,* 1986*)* and reproductive cloning. Reproductive cloning technology generates offspring that are genetically identical to the parent by the transfer of an entire donor nucleus into the nucleated cytoplasm of a host egg. The first animal produced using this cloning technique was a sheep named Dolly, born in 1996. Since then a number of other animals, including pigs, horses, and dogs, have been generated using reproductive cloning technology.

Recombinant DNA technology, on the other hand, involves the insertion of one or more individual genes from an organism of one species into the DNA (deoxyribonucleic acid) of another (Fig.6).

Whole-genome replacement, involving the transplantation of one bacterial genome into the "cell body," or cytoplasm, of another microorganism, has been reported, although this technology is still limited to basic scientific applications (Guerrero-Andrade, O. *et al*, 2006).

GMOs produced through genetic technologies have become a part of everyday life, entering into society through agriculture, medicine, research, and environmental management (Hiatt, A. *et al*, 1989). However, while GMOs have benefited human society in many ways, some disadvantages exist; therefore, the production of GMOs remains a highly controversial topic in many parts of the world.

IMPACT OF GMOs

Bacteria were the first organisms to be modified in the laboratory, due to their simple genetics. These organisms are now used for several purposes, and are particularly important in producing large amounts of pure human proteins for use in medicine. Genetically modified bacteria are used to produce the protein insulin to treat diabetes. Similar bacteria have been used to produce biofuels, clotting factors to treat haemophilia and human growth hormone to treat various forms of dwarfism.

Genetically modified mammals are an important category of genetically modified organisms. Ralph L. Brinster and Richard Palmiter developed the techniques responsible for transgenic mice, rats, rabbits, sheep, and pigs in the early 1980s, and established many of the first transgenic models of human disease, including the first carcinoma caused by a transgene. The process of genetically engineering animals is a slow, tedious, and expensive process. However, new technologies are making genetic modifications easier and more precise. The first transgenic (genetically modified) animal was produced by injecting DNA into mouse embryos then implanting the embryos in female mice.

Genetically modified animals currently being developed can be placed into six different broad classes based on the intended purpose of the genetic modification:

1. To research human diseases (for example, to develop animal models for these diseases);
2. To produce industrial or consumer products (fibres for multiple uses);
3. To produce products intended for human therapeutic use (pharmaceutical products or tissue for implantation);
4. To enrich or enhance the animals' interactions with humans (hypo-allergenic pets);
5. To enhance production or food quality traits (faster growing fish, pigs that digest food more efficiently);
6. To improve animal health (disease resistance)

In some ways, genetically modified organisms are simply carrying on the work that plant and animal breeders have been doing for centuries, i.e., enhancing traits like a racehorse's speed or a cow's milk production, while also eliminating bad traits like susceptibility to disease. Traditional breeding, however, is a slow process that's fraught with error.

Plants are genetically modified for disease resistance, for drought tolerance, for resistance to hot or cold temperatures, for added nutrition (Devlin, R. *et al*, 1994) and for resistance to insect pests. By genetically introducing pest resistance, scientists hope to reduce the use of chemical pesticides. Herbicide resistance can also be genetically induced, and crops plants that have a tolerance to herbicides can survive even when nearby plants specifically, weeds are sprayed with a deadly herbicide

GMOs have been developed for pharmaceutical uses, and for "phytoremediation," the use of plants to clean up toxins and other hazardous materials from contaminated soil and water. Some trees, for example, have been genetically engineered to pull dangerous heavy metals out of contaminated soil (Ma, J. *et al*, 2003).

Positive Aspect of Genetically Modified Organisms (GMOs)

GMOs have been on the market since 1996, so if all GMOs were an immediate health threat, we would know it by now. GMO technology can develop crops with higher yield, with less fertilizer, less pesticides, and more nutrients.

GMO technology is more predictable than traditional breeding, in which thousands of genes from each parent are transferred randomly to the offspring. Genetic engineering moves discrete genes or blocks of genes at a time. Traditional breeding can be very slow because it might take several generations before the desired trait is sufficiently brought out and the offspring must reach sexual maturity before they can be bred. With GMO technology, the desired genotype can be created instantly in the current generation (Demont, M. *et al*, 2007).

Food additives that are Generally Recognized as Safe (GRAS) do not have to undergo rigorous toxicity testing to prove their safety. Instead, their safety is generally based on published past toxicity studies. The FDA has awarded GRAS status to 95% of the GMOs that have been submitted.

Negative Aspect of Genetically Modified Organisms (GMOs)

- Studies have already shown that GMOs are dangerous to rats. A review of 19 studies in which genetically modified soy and corn were fed to mammals found that a GMO diet often led to liver and kidney problems. While results on rats may or may not be relevant to humans, these results show that GMOs may have unintended effects on wildlife and livestock.

- GMOs have not been tested thoroughly. GMO safety tests are sometimes as short as 90 days, which is not long enough to prove that a substance is safe for long-term, multi-generational human consumption (Muir, W., & Howard, R., 1999)
- GMOs are transferring genes in a much more unpredictable way compared to natural breeding. One of the built-in safeguards of natural breeding is that a member of one species will not produce fertile offspring with a member of another species. With transgenic technology, scientists are transferring genes not just across species but even across kingdoms, inserting animal genes into microbes or plants. This produces genotypes that could never exist in nature.
- Genetically modified products contain novel proteins that could trigger allergic reactions in people who are either allergic to one of the components of the GMO or in people who are allergic only to the new substance.
- Genetically modified plants or animals could interbreed with wild populations, creating problems such as population explosions or crashes, problems with corresponding predator or prey species, or offspring with dangerous traits.
- Even if some GMOs are safe for human consumption, this does not mean that all GMOs are safe. Each new GMO has its own benefits and risks.
- GMOs have led to more herbicides (weed killer) being used. Herbicide-resistant GMO crops were developed so that the desired crop plants could survive higher amounts of herbicides to kill weeds.
- GMOs will inevitably lead to more monoculture, which is dangerous because it threatens the biological diversity of our food supply.

EXAMPLES OF GMOs

Bt corn

The European corn borer, *Ostrinia nubilalis*, has been known to cause major damage to corn crops in the U.S. and Canada. The larval stage of this organism bores holes in the corn plants as they feed. However, scientists discovered that there was a gene that they could insert into the corn plant's genome that would help them be resistant to these larva. The gene that is inserted comes from the bacteria *Bacillus thuringiensis* and codes for an endotoxin protein that acts as an insect stomach poison. The endotoxin protein binds to cells in the intestinal lining of the larva and the cells burst (Losey, J. *et al*, 1999). This causes the larva to stop eating quickly and die within a few days depending on how much toxin is ingested. While this protein is toxic to the European corn borer larva, it is harmless and safe for most other organisms including humans. Genetically modified corn with the Bacillus endotoxin, commonly called Bt corn (Figure 1 & 2), was introduced in 1996 and its use in corn fields is expanding (Jesse, H., & Obrycki, J., 2000)

The Umbuku Lizard

The fabrication of this little lizard has no practical and scientific reason behind it. It was done simply to prove that it can be done. Scientists managed to find a gene in the DNA of the Umbuku, a rare species of lizards living in Africa, which once altered gave them the ability to fly. Currently, there are six flying Umbuku reported to have been created (Figure 3)

The Lemur Cat

The lemur cat, a cross between a cat and a lemur, is the offspring of Chinese researchers. There is a tradition amongst Chinese wealthy women to show off their richness through the acquisition of exotic and rare animals, which has left scientific and medical research companies competing to find a new breed of pets (Figure 4).

Golden Rice

Food scientists have also been applying genetic modification to crops with the goal of making them more nutritious. This would be particularly beneficial in parts of the world where nutritional deficiencies are common and a diet full of fruits and vegetables is not possible. Vitamin A deficiency is thought to be responsible for at least 1 million deaths annually worldwide. Golden rice has been developed in attempt to make rice more nutritious by inserting genes that produce beta-carotene, a precursor to vitamin A (Beyer, P. *et al*, 2002*)*. It is intended for this rice to be grown and eaten by the poor and malnourished populations of the world and give them more of a vitamin that is lacking in their diets (Figure 5).

OPERATIONALIZING THE REGULATION OF GM FOODS IN INDIA

In India, the regulation of all activities related to GMOs and products derived from GMOs is governed by "Rules for the Manufacture/Use/Import/Export and Storage of Hazardous Microorganisms, Genetically Engineered Organisms or Cells, 1989" (commonly referred to as Rules, 1989) under the provisions of the Environment (Protection) Act, 1986 through the Ministry of Environment and Forests (MoEF). The Rules, 1989 are primarily implemented by MoEF and the Department of Biotechnology (DBT), Ministry of Science and Technology through six competent authorities: the Recombinant DNA Advisory Committee (RDAC); the Review Committee on Genetic Manipulation (RCGM); the Genetic Engineering Approval Committee (GEAC); Institutional Biosafety Committees (IBSC); State Biosafety Coordination Committees (SBCC), and; District Level Committees (DLC). The Rules, 1989 are very broad in scope and essentially capture all activities, products and processes related to or derived from biotechnology including foods derived from biotechnology, thereby making GEAC as the competent authority to approve or disapprove the release of GM foods in the market place.

ETHICAL ISSUES

Genetically modified organisms have been a hot topic of debate among environmentalists, scientists, and policy makers. There are enormous benefits that can come from genetically modified crops and animals; however there are also serious concerns about the consequences on the environment and human health (Devos, Y., *et al*, 2007).

Some of the benefits of genetically modified crops are that genes can be inserted that cause the plant to be resistant to many harmful things such as weeds, insects, and disease. This would allow for less herbicide to be used on the crops and more crops to survive and produce food. Crops can also be modified to have a longer shelf life in stores, grow in dryer/colder climates, be resistant to pests, and even to have increased nutritional value.

Despite the fact that the genes being transferred occur naturally in other species, there are unknown consequences to altering the natural state of an organism through foreign gene expression. After all, such alterations can change the organism's metabolism, growth rate, and/or response to external environmental factors. These consequences influence not only the GMO itself, but also the natural environment in which that organism is allowed to proliferate. Potential health risks to humans include the possibility of exposure to new allergens in genetically modified foods, as well as the transfer of antibiotic-resistant genes to gut flora.

Horizontal gene transfer of pesticide, herbicide, or antibiotic resistance to other organisms would not only put humans at risk, but it would also cause ecological imbalances, allowing previously innocuous plants to grow uncontrolled, thus promoting the spread of disease among both plants and animals. Although the possibility of horizontal gene transfer between GMOs and other organisms cannot be denied, in reality, this risk is considered to be quite low. Horizontal gene transfer occurs naturally at a very low rate and, in most cases, cannot be simulated in an optimized laboratory environment without active modification of the target genome to increase susceptibility (Takeda, S., & Matsuoka, M, 2008).

In contrast, the alarming consequences of vertical gene transfer between GMOs and their wild-type counterparts have been highlighted by studying transgenic fish released into wild populations of the same species. The enhanced mating advantages of the genetically modified fish led to a reduction in the viability of their offspring. Thus, when a new transgene is introduced into a wild fish population, it propagates and may eventually threaten the viability of both the wild-type and the genetically modified organisms.

The concerns regarding genetic modification deal with the possible unknown effects on human health and the environment. Some new allergies have emerged due to the consumption of genetically modified foods. A study in 1998 cited that a soybean allergy was developed in people who ingested transgenic soybeans that were produced to be animal feed. Additionally, there are other issues related to possible harmful side effects on other organisms that live with or depend on the organism that is genetically modified. One example of this is Bt corn. While the modification is helpful in making the corn toxic to caterpillars, the pollen from these modified plants might also be fatal to the monarch butterflies (Sears, M. *et al*, 2001). There are many issues to think about when discussing the viability of genetically modified organisms.

GMOs and the General Public: Philosophical and Religious Concerns

In a 2007 survey of 1,000 American adults conducted by the International Food Information Council (IFIC), 33% of respondents believed that biotech food products would benefit them or their families, but 23% of respondents did not know biotech foods had already reached the market. In addition, only 5% of those polled said they would take action by altering their purchasing habits as a result of concerns associated with using biotech products (United States Department of Energy, 2007).

According to the Food and Agriculture Organization of the United Nations, public acceptance trends in Europe and Asia are mixed depending on the country and current mood at the time of the survey (Hoban, 2004). Attitudes toward cloning, biotechnology, and genetically modified products differ depending upon people's level of education and interpretations of what each of these terms mean. Support varies for different types of biotechnology; however, it is consistently lower when animals are mentioned.

Furthermore, even if the technologies are shared fairly, there are people who would still resist consumable GMOs, even with thorough testing for safety, because of personal or religious beliefs. The ethical issues surrounding GMOs include debate over our right to "play God," as well as the introduction of foreign material into foods that are abstained from for religious reasons. Some people believe that tampering with nature is intrinsically wrong, and others maintain that inserting plant genes in animals, or vice versa, is immoral. When it comes to genetically modified foods, those who feel strongly that the development of GMOs is against nature or religion have called for clear labeling rules so they can make informed selections when choosing which items to purchase (Spurgeon, D, 2001). Respect for consumer choice and assumed risk is as important as having safeguards to prevent mixing of genetically modified products with non-genetically modified foods. In order to determine the requirements for such safeguards, there must be a definitive assessment of what constitutes a GMO and universal agreement on how products should be labeled.

These issues are increasingly important to consider as the number of GMOs continues to increase due to improved laboratory techniques and tools for sequencing whole genomes, better processes for cloning and transferring genes, and improved understanding of gene expression systems. Thus, legislative practices that regulate this research have to keep pace. Prior to permitting commercial use of GMOs, governments perform risk assessments to determine the possible consequences of their use, but difficulties in estimating the impact of commercial GMO use makes regulation of these organisms a challenge.

CONCLUSION

Proponents of the use of GMOs believe that, with adequate research, these organisms can be safely commercialized. There are many experimental variations for expression and control of engineered genes that can be applied to minimize potential risks. Some of these practices are already necessary as a result of new legislation, such as avoiding superfluous DNA transfer (vector sequences) and replacing selectable marker genes commonly used in the lab (antibiotic resistance) with innocuous plant-derived markers. Issues such as the risk of vaccine-expressing plants being mixed in with normal foodstuffs might be overcome by having built-in identification factors, such as pigmentation, that facilitate monitoring and separation of genetically modified products from non-GMOs. Other built-in control techniques include having inducible promoters (e.g., induced by stress, chemicals, etc.), geographic isolation, using male-sterile plants, and separate growing seasons.

GMOs benefit mankind when used for purposes such as increasing the availability and quality of food and medical care, and contributing to a cleaner environment. If used wisely, they could result in an improved economy without doing more harm than good, and they could also make the most of their potential to alleviate hunger and disease worldwide. However, the full potential of GMOs cannot be realized without due diligence and thorough attention to the risks associated with each new GMO on a case-by-case basis.

REFERENCES

Barta, A., *et al*. The expression of a nopaline synthase-human growth hormone chimaeric gene in transformed tobacco and sunflower callus tissue. *Plant Molecular Biology* **6**, 347–357 (1986)

Beyer, P., *et al*. Golden rice: Introducing the β-carotene biosynthesis pathway into rice endosperm by genetic engineering to defeat vitamin A deficiency. *Journal of Nutrition* **132**, 506S–510S (2002)

Demont, M., *et al*. GM crops in Europe: How much value and for whom? *EuroChoices* **6**, 46–53 (2007)

Devlin, R., *et al*. Extraordinary salmon growth. *Nature* **371**, 209–210 (1994)

Devos, Y., *et al*. Ethics in the societal debate on genetically modified organisms: A (re)quest for sense and sensibility. *Journal of Agricultural and Environmental Ethics* **21**, 29–61 (2007) doi:10.1007/s10806-007-9057-6

Guerrero-Andrade, O., *et al*. Expression of the Newcastle disease virus fusion protein in transgenic maize and immunological studies. *Transgenic Research* **15**, 455–463(2006) doi:10.1007/s11248-006-0017-0

Hiatt, A., *et al*. Production of antibodies in transgenic plants. *Nature* **342**, 76–79 (1989)

Hoban, T. Public attitudes towards agricultural biotechnology. ESA working papers nos. 4-9. Agricultural and Development Economics Division, Food and Agricultural Organization of the United Nations (2004)

Jesse, H., & Obrycki, J. Field deposition of Bt transgenic corn pollen: Lethal effects on the monarch butterfly. *Oecologia* **125**, 241–248 (2000)

Losey, J., *et al*. Transgenic pollen harms monarch larvae. *Nature* **399**, 214 (1999) doi:10.1038/20338

Ma, J., *et al*. The production of recombinant pharmaceutical proteins in plants. *Nature Reviews Genetics* **4**, 794–805 (2003) doi:10.1038/nrg1177

Muir, W., & Howard, R. Possible ecological risks of transgenic organism release when transgenes affect mating success: Sexual selection and the Trojan gene hypothesis. *Proceedings of the National Academy of Sciences* **96**, 13853–13856 (1999)

Sears, M., *et al*. Impact of Bt corn on monarch butterfly populations: A risk assessment. *Proceedings of the National Academy of Sciences* **98**, 11937–11942 (2001)

Spurgeon, D. Call for tighter controls on transgenic foods. *Nature* **409**, 749 (2001)

Takeda, S., & Matsuoka, M. Genetic approaches to crop improvement: Responding to environmental and population changes. *Nature Reviews Genetics* **9**, 444–457 (2008) doi:10.1038/nrg2342

United States Department of Energy, Office of Biological and Environmental Research, Human Genome Program. Human Genome Project information: Genetically modified foods and organisms, http://www.ornl.gov/sci/techresources/Human_Genome/elsi/gmfood.shtml (2007)

Table 1: Examples of GMOs Resulting from Agricultural Biotechnology

Genetically Conferred Trait	Example Organism	Genetic Change
APPROVED COMMERCIAL PRODUCTS		
Herbicide tolerance	Soybean	Glyphosate herbicide (Roundup) tolerance conferred by expression of a glyphosate-tolerant form of the plant enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) isolated from the soil bacterium *Agrobacterium tumefaciens*, strain CP4
Insect resistance	Corn	Resistance to insect pests, specifically the European corn borer, through expression of the insecticidal protein Cryl Ab from *Bacillus thuringiensis*
Altered fatty acid composition	Canola	High laurate levels achieved by inserting the gene for ACP thioesterase from the California bay tree *Umbellularia californica*
Virus resistance	Plum	Resistance to plum pox virus conferred by insertion of a coat protein (CP) gene from the virus
PRODUCTS STILL IN DEVELOPMENT		
Vitamin enrichment	Rice	Three genes for the manufacture of beta-carotene, a precursor to vitamin A, in the endosperm of the rice prevent its removal (from husks) during milling
Vaccines	Tobacco	Hepatitis B virus surface antigen (HBsAg) produced in transgenic tobacco induces immune response when injected into mice
Oral vaccines	Maize	Fusion protein (F) from Newcastle disease virus (NDV) expressed in corn seeds induces an immune response when fed to chickens
Faster maturation	Coho salmon	A type 1 growth hormone gene injected into fertilized fish eggs results in 6.2%

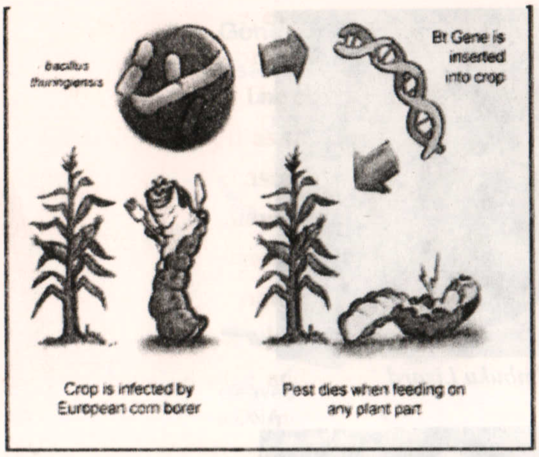

Fig.1: *Engineering resistant corn. Following the insertion of a gene from the bacteria Bacillus thuringiensis, corn becomes resistant to corn borer infection. This allows farmers to use fewer insecticides*

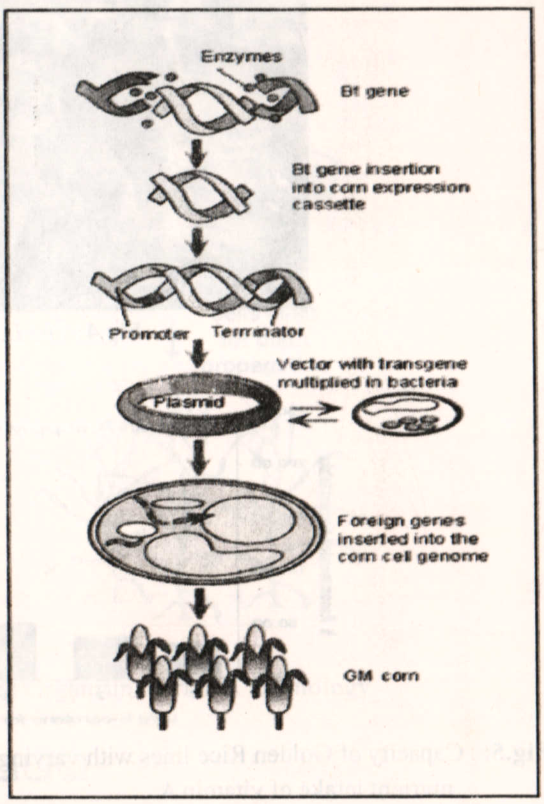

Fig.2: *General schematic of GM crop production*

Fig.3: *The Umbuku Lizard*

Fig.4: *The Lemur Cat*

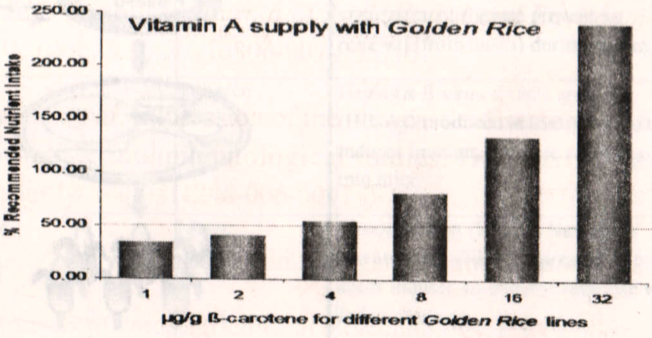

Fig.5: Capacity of Golden Rice lines with varying carotene content to supply the recommended nutrient intake of vitamin A.

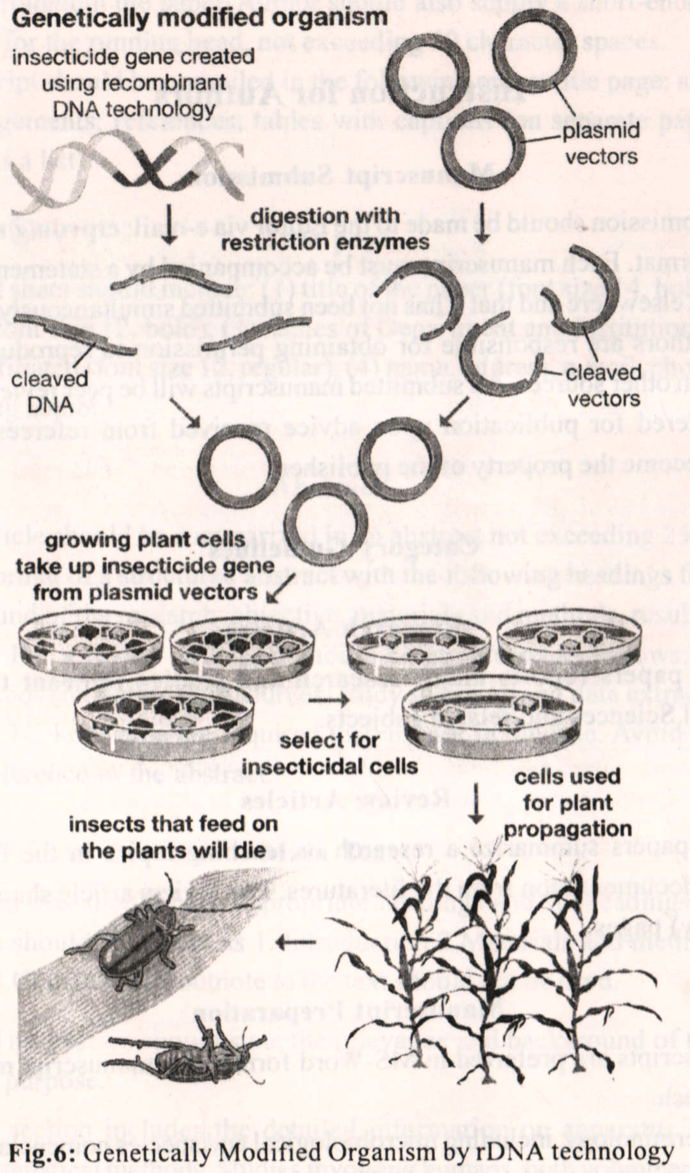

Fig.6: Genetically Modified Organism by rDNA technology