Available online at www.ewijst.org

ISSN: 0975-7112 (Print)
ISSN: 0975-7120 (Online)

Environ. We Int. J. Sci. Tech. 6 (2011) 49-69

Environment & We
An International
Journal of Science
& Technology

Genetically Modified Crops: Their Effect on Agriculture and Food Security

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Abstract

Genetically modified organisms find several uses in the modern world. Genetically modified seed shows a potential threat to human welfare especially in developing countries including India. Technology fee, license to use, no seed storage facility, and agreement with the seed corporations, terms and conditions of use, limitations of use are certain conditions that involves scientific, ethical as well as economical issues of the farmers. Besides mixing of genetically modified seeds, untargeted gene transfer (both vertical and horizontal), use of different cultural conditions, no significant reduction in use of pesticides, no significant increase in harvest, are few issues which farmers need to analyze. Bio-piracy, monopoly of multinational seed corporations are the issues, at national and also at global level, that need to be analyzed. In this review few of the above issues are discussed with respect to scientific, ethical and economic aspects.

Keywords: GM crops, Agriculture, GMOs, Food Security.

Introduction

Traditional cross breeding in plants has limitation of breeding only within the species; it does not permit gene transfer across the species. Gene cloning makes it possible to transfer genes within or across species or across the kingdom in a shorter period (BIO, 1990; IFBC, 1990; *Watson et al*., 1996) Genes from any organism are transferred to any other organisms by transformation methods. This results in increase in the number of genetically modified organisms including microbes (bacteria, viruses, fungi) plants (lower and higher plants) and animals.

Either GMO's or the products obtained from GM plants finds several uses in the modern world; it includes several GM crops with improved nutritional values and/or improved agronomic features of the plants in order to tolerate biotic and abiotic stress, production of monoclonal antibodies, industrial enzymes, therapeutic proteins including nutritional, hormones, and enzymes, primary and secondary metabolites, carbohydrates

and feed. It also finds uses in agriculture, environment, medicines, fibers, vaccines and are commonly termed as Genetically modified food products (FAO/WHO, 1996)" "Genetically Modified" "Genetically Engineered." This technology involves the ability to manipulate, modify, alter, or otherwise 'engineer' genetic material to produce desired genetic characteristicsthat has been integral part of biotechnology (Liberman *et al*., 1991). Drastic improvement, especially in agriculture, took place during last decade due to gene manipulation. This is primarily for the improvement of agronomic traits as well as production traits. Several traits of plants were improved including herbicide tolerance trait, insect resistance and viral resistance, increase in vitamin and minerals e. g. iron contents (to alleviate malnutrition) in plants; eg. production of human vaccines in banana for curing hepatitis B. Some plants were genetically modified with more than one trait. Several plants were genetically modified, viz. soyabean, canola, cotton, alfa alfa, sweet potato, rice, wheat. (James, 1997; James and Krattiger, 1996)

In addition, improvement of several abiotic stress tolerances in plants has been achieved. It includes salt tolerant, temperature or drought tolerance, frost tolerance, in order to enhance abiotic as well as biotic stress respectively. GM plants are considered beneficial for mankind and are expected to meet food requirement as well as good health for the growing world population. Like two sides of a coin, the GM crops on one side have tremendous benefits and on the other side there exists serious threat for life, food, modern agriculture as well as environment.

GM crops – World wide: Globally about 1.6 billions of acres are planted with first generation of GE crops. Mostly these crops contain genes like herbicide tolerance, insect resistance and 70 different crop species has been trabnsformed in 34 different countries, 15000 individual field sites. (James and Krattiger, 1996; James, 1997)

GM Plants

Benefits and Controversies: GM plants are developed for various benefits. It is useful directly or otherwise to various areas including agriculture, human health, Animal Husbandry, Environment as a whole and to the society. Equally, GM plants raise numerous controversies for some ethical groups in several aspects including safety, ethical issue, and intellectual properties and patenting, labeling the GM seeds or GM products, Laws of biotechnology in developed (IFBC 1990) and international regulatory groups (FAO/WHO 1996)

Benefits

Crop plants: GM helps to develop enhanced flavor, taste and quality, reduced maturation time (e. g. sugarcane), increased in nutrient contents, improve in crop yields, and biotic and sbiotic stress tolerance, improved resistance to disease, pests, and herbicides and new products. (James and Krattiger, 1996)

Environment: "Eco-Friendly" bio-herbicides and bio-insecticides conservation of soil, water and energy, bio-processing for forestry products, better natural waste management

and more efficient processing are the issues that are addressed (BIO, 1990; Pimentel, 1988; Morrone *et al*., 1988; Russel 1978; Smith 1989)

Society: Increased food security for growing populations, good techniques to disease diagnosis as well as therapy includes recombinant proteins and antisense Therapy (Crooke 1992, 1998).

Controversial issues

Bio-Safety: Potential human health impacts include allergens, transfer of antibiotic resistance markers, unknown effects. Potential environmental impacts include unintended transfer of trans-genes through cross-pollination, unknown effects on other organisms (e.g., soil microbes) and loss of flora and fauna biodiversity. Terminator gene technology raises serious threat to the future food security as well as future agriculture

Access and Intellectual Property: Domination of world food production by a few companies, increasing dependence on industrialized nations by developing countries, bio-piracy or foreign exploitation of natural resources.

Ethics: Violation of natural organisms' and their intrinsic values, tampering with nature by mixing genes among species, objections to incorporating animal genes in plants and *vice versa* and stress due to expression of foreign genes/proteins in plants (Gene Exchange, 1997; Harms, 1992; Chen and Gu, 1993; Pimentel *et al.,* 1989) and animals (Fox, 1992; Regal, 1994).

Labeling: Labeling is not mandatory in some countries; mixing GM crops with non-GM products (EC 2003b).

Society: New advances may be skewed to interests of developed countries

Befits of GM seeds or GM plants

Enhanced taste and Quality: Coffee producers use chemical solvents to remove the caffeine in coffee and some decaf coffee drinkers' fear of harmful residues that remain. Scientists have identified the genes responsible for caffeine production and hope to switch off the genes, thereby creating naturally caffeine-free coffee beans (ILSI 2004).

Reduced Maturation time: Certain crop takes longer time to grow and mature and harvest. Scientists believe that GMOs can reduce the duration to certain extent.

Inreased Maturation time: Some fruits like banana and tomato ripe faster and therefore there is loss due to damage of ripened fruits during transportation. In order to avoid this, the ethylene biosynthetic pathway has been blocked and/or slowed down by antisense RNA technology, thus delaying the ripening of the fruit. (Noteborn, 1998). This prevents damage of ripened fruits during transportation. In tomato, similar apporoach has been followed by increase in thickness of the skin

Increased **yields in food and enhanced cold and stress tolerance:** Scientists argue that GM crops end the hunger in globe. Increase in yields in rice, wheat, corn in Asia and cassava in Africa is needed to feed millions of people. GMOs boost agricultural production by making new cropland available. For example tomato made to grow in salty lands.

Scientists worked up to make the crops grow in cold conditions. Also, in the dry lands and deserted conditions the normal crops cannot grow. However, GM crops were developed to grow the crop in drought EFSA (2008).

Improved crop resistance to disease, pests and herbicides: Decreased use of the pesticides, herbicides and insecticides were made possible with GMOs. Hence lower risk of poisoning water and food crops. Gene of viral coat proteins were cloned in plants so as to express the viral coat protein in plants. Presence of one virus particle especially viral coat protein (Hayakawa *et al.*, 1992; Fitch *et al*., 1992) prevents the entry of other viruse particles and this gives a plant protection from viral diseases. The fungal resistant plants were obtained by expressing cellulose gene as the cell wall becomes thicker. Hence fungal hyphae can not penetrate the plant cell wall. Thus the plant is protected from fungal diseases. Another method is cloning of cellulase gene in plants, thus entry of the fungal hypae can be destroyed by the enzyme chitinase (Brogloe, *et al.*, 1991; 1993).

The insect tolerance plants were developed to prevent insect from feeding the crops. This is achieved by two different methods, one by the cloning of *Bt* gene. As a consequence the gut of the insect is made porous, by the activity of the crystal (*cry1Ab*) proteins in the insect gut (Gill, *et al.*1992; English and Slatin, 1992; Dean *et al.*, 1996; Yomamoto and Powel, 1993; Knowles, 1994; Huber and Luthy, 1981). The insect fed partially cannot digest the food and hence dies due to starvation. Another approach is the cloning of protease inhibitors to target the digestive enzymes in insects. Thus the insect takes very long time or can not digest the food and thus preventing the growth and developmental stages of the organisms.

The herbicide tolerant plants were made in order to maximize the use of herbicides. Glyphosate is a major herbicide used world wide (Pusztai *et al.,* 1990; Burks and Fuchs, 1995). This enzyme blocks the enol-pyrophosphate sikimic acid synthesis pathway (EPSP synthetase gene), which is a major aromatic acid symthetic pathway for synthesis of unusual aromatic aminoacids, thus the plant cannot grow and dies. This glyphosate does not differentiate between the crops as well as the weed. Thus the crop plants were also destroyed. In order to protect the crop plants, the EPSP synthase gene were cloned for over production. This helps the crop plants to tolerate herbicides and grow. It also destroys the non-GM weed. Thus all minerals, nutrients and water made available only to the crops and not to weeds

Improved nutrients by GM plants: GM crops were introduced so as to greatly improve the nutrition. In rice that lack vitamin A, β-carotene gene can be cloned, which is a precursor molecule for the synthesis of the Vitamin A. Thus cloning β-carotene leads to enhanced synthesis of the vitamin A in rice (ILSI 2004). Similarly, anaemia – an iron

deficiency disease, is caused due to lack of iron content in food. Ferritin, an iron storage protein was cloned in order to enhance iron content and therefore can release iron slowly and or when required (ILSI 2004).

New products and growing techniques

Plant tissue culture (PTC) techniques: Plant tissue is a gift by the god to us, used for cloning the plants. Using PTC any plant can be cultured and this technology is essential for gene cloning in plant. In addition to this, PTC technique facilitates generation of disease free plants. It can be used to maximise number of plantlets produced in a shorter period of time. This technique uses the differential plasticity of the plant cells using any cell or tissue of the plant and is used to culture in *in vitro* and grows them to plantlets.

Increased resistance, productivity, hardiness, and feed efficiency through GM plants

Development of edible vaccines by GM plants and their consumption by the needy individual will increase propylatic measure of treatment, for the human and animal husbandry. Several kinds of edible vaccines were developed to combat various diseases. This brought the demographic transition of the human population significantly. Recent advances include development of DNA vaccines (Berglund, *et al*., 1998; Leitner, et al., 1999; Lundstrom, 2000) in which the DNA of the vaccine is transferred to the needy individual and this DNA integrated in to the genome, keeps transcribing and translating. This ultimately gives the immunity to the individual.

Better yields of meat, eggs, and milk

The slaughter wastes were reprocessed and dried, powdered mixed in feed and given back to the cow. This makes the cow grow faster and gain weight. In broilers, the numbers of eggs laid by the fowl were increased by using the recombinant growth hormones. Usually the fowl produces 2-3 eggs/day. By injecting the recombinant growth hormone/peptides the fowl produces more than 5 eggs / day. This results in enormous stress to the chicken

Improved animal health and diagnostic methods

Prior to genetic engineering, insulin were obtained from cadaver and were injected to the needy persons. Later, insulin isolated from the pig and other ruminants were used. With the development of gene cloning techniques, the insulin gene were isolated and cloned in high expression vectors and transformed in appropriate hosts and over-expressed and then purified (Kane, 1995; Chen and Inouye, 1994)

Recently, the monoclonal antibodies were produced and were targetted towards pathogenic diseases. This technology is useful in both disease diagnosis as well as therapy. Using the monoclonal antibodies the infectious diseases as well as cancerous diseases were diagnosed (Natali and Siccardi (1990); Jorge Leon *et al*., 1994)

Environment

"Eco-Friendly" bio-herbicides and bio-insecticide: Use of pesticides, insecticides and other toxic chemicals like herbicide is harmful to the environment. These toxic chemicals are non-degradable and therefore stable in the environment. Bio-control agents as well as eco-friendly procedures / techniques were identified and implemented in order to preserve the ecological balance. Genetic engineering has brought much improvement in the field of environmentally safe products. All the above discussed products are of genetic origin including the monoclonal antibodies, vaccines, *Bacillus thuringiensis*,-crystal protein, growth hormones. No synthetic chemicals or drugs can be utilized, hence environmentally safe, in addition no side effects (EC 2003b)

Conservation of soil, water, and energy

The possibilities for soil microbes exposed to transgenic products are high. Toxins from GMCs remain active in the soil, decreasing soil fertility. There is long term persistence of insecticidal products (for example: *Bt* and proteinase inhibitors) in soil. The insecticidal toxin produced by *Bacillus thuringiensis* remains active in the soil, where it binds rapidly and tightly to clays and humic acids. The bound toxin retains its insecticidal properties and is protected against microbial degradation by being bound to soil particles, persisting in various soils (Devare1, *et al*., 2007; Yuanjiao Feng *et al*., 2011) If transgenic crops substantially alter soil biota and affect processes such as soil organic matter decomposition and mineralization, this would be of serious concern to organic farmers and most poor farmers in the developing world. These farmers cannot purchase or don't want to use expensive chemical fertilizers. They rely instead on local residues, organic matter and especially soil organisms for soil fertility (e.g., key invertebrate, fungal or bacterial species) which can be affected by the soil bound toxin. Soil fertility could be dramatically reduced if crop leachates inhibit the activity of the soil biota and slow down natural rates of decomposition and nutrient release

Bio-processing for forestry products Forest products can also be processed in an efficient manner by rapid biotechnological methods to improve quality.

Better natural waste management Cloning of microbes with suitable plasmids will degrade the oil wastes and which is an efficient process that is not available in nature. *Pseudomonas putida* is a microbe cleans up the oil leaked from the oil tanker in the mid ocean. These organisms were developed to degrade the multiple oil degradation.

More efficient processing Plant tissue culture and other bioprocess methods are very relevant, fast for efficient development of the products.

Other direct Environmental benefits of GmOs: Reduces use of synthetic insecticides and pesticides (up to 72% in some countries). Minimizes bioleaching of pesticides and minimizes exposure of farmers to toxic chemicals. It is a biological control of pests an "Eco-friendly" environmental management. Development of new techniques, new culture methods etc. Helps to conserve forests and Soil conservation

Society : Increased food security for growing populations

Controversial risks of GM plants/seeds.

Harmful to other organisms A study reported by Richard Hellmicha and Blair Siegfriedb (2001) that a gene for a bacterial toxin is inserted into corn and proved poisonous to monarch butterfly larvae that ate the leaves of those plants. Possibilities of unintended effects transgenic designed to resist pests might have on beneficial insects or how they could upset various balances in nature.

Risk of uncontrolled cross-pollination Genetically modified plants can unintentionally cross-pollinate with other plants. Hence the crops grown at some distance from a field of GM crops, greater distance than scientists had thought, involve in pollination. Larger buffer zones than previously thought may be necessary to prevent transgenics from spreading. Scientists also warned of the rapid spread of pollen from GM rapeseed, or canola, to an extent that makes it nearly impossible to grow uncontaminated rapeseed.

Risk of development of "super-weeds" and "super-pests" Transgenic crops could presumably crossbreed with weeds and transfer their herbicide resistance, creating a class of super-weeds that would be difficult to wipe out. A group of super-weeds resistant to several widely used herbicides. Concerns surround the inadvertent creation of new super-pests, or insects that would be resistant to many pesticides. Overuse of antibiotics has led some bacteria to develop resistance to most antibiotics, widespread GMO agriculture could lead to pesticide-resistant super-pests.

Risk of potential allergies An adverse allergic reaction to GM food or mixing genes from different food sources will only increase the risk of additional food allergies. Food allergies are especially common among children, and GMOs could create new allergens (Mills, *et al.,* 2003) (allergy-causing substances). Moreover, if the gene from a nut or other common allergen are transferred to another food crop, people with an allergy to nuts could unknowingly consume the allergen with potentially severe consequences.

Risk includes unscripted responses A project to transfer a gene from the *Brazil nut* to *soybeans* was halted (Mills, *et al.,* 2003) after tests revealed that the modified soybean triggered an allergic response in people with allergies to nuts. In this case the source of the gene was known to produce allergies, but skeptics of GM plants argue that such knowledge may not always be available.

Risk of widening the gap Some opponents of GM plants fear that the biggest gainers from bioengineered crops will be agribusinesses, the large corporations that develop GM plants for agricultural use. Creating GM plants and bringing them to market is costly, and businesses are patenting their GM plants. Critics fear that this may make the products too costly for developing countries or small farmers, thus widening the gap between rich and poor countries.

Environmental risks of GM Plants Potentiality of un-anticipated gene mixing Damage to non-targeted organisms.

1. Evolution of 'super weeds'
2. Development of new or potential allergen.
3. Crop turns to become weed and vice versa
4. Enhanced pest resistance
5. Weed gets the gene transferred and hence vigorous growth of weeds.

Discussion

GM crops introduced first and occupied 63% of soy and 20% of maize in 2002. Advent of GMOs in the international scenario have initiated various debate/controversial about safety and other issues. Biotechnology promises the potentiality to lessen some of the world serious problems including hunger, poverty and others including environment and health. GMOs for example can increase crop yield and alleviate world's hunger; and reduce dependence of chemical pesticides and herbicides. In addition, GMO have ability to repair damaged terrain by eliminating toxins more efficiently than an organic plant. On the other hand GMOs are also associated with health and environmental risks. With regard to the health, controversial studies have been conducted on the effects of the transgenic pesticides in rats that resulted in detoriation of their intestines. This evidence however has been contested due to deficiencies in the methodology employed.

GM foods increase the possibility of food allergen (Mills, *et al.,* 2003) reactions in the consumer, when modified foods are made of proteins or components of plants or products that are known to cause such detrimental medical effects. GM crops have potential to transfer their traits to their organic relatives, thus perhaps affecting the integrity of the biological diversity.

Risks World Health Organization (WHO) has recommended an agent risk group classification for laboratory use that describes four general risk groups based on these principal characteristics and the route of transmission of the natural disease. The four groups address the risk to both the laboratory worker and the community. The NIH Guidelines (NIH, 2002) established a comparable classification and assigned human etiological agents into four risk groups on the basis of hazard. The descriptions of the WHO and NIH risk group classifications are presented. They correlate with but do not equate to biosafety levels. A risk assessment will determine the degree of correlation between an agent's risk group classification and biosafety level.

Genetically modified agent hazards The identification and assessment of hazardous characteristics of genetically modified agents involve consideration of the same factors used in risk assessment of the wild-type organism. It is particularly important to address the possibility that the genetic modification could increase an agent's pathogenicity or affect its susceptibility to antibiotics or other effective treatments. The risk assessment can be difficult or incomplete, because important information may not be available for a newly engineered agent. Several investigators have reported that they observed

unanticipated enhanced virulence, in recent studies, with engineered agents (Jackson *et al.,* 2001). These observations give reason to remain alert to the possibility that experimental alteration of virulence genes may lead to increased risk. It also suggests that risk assessment is a continuing process that requires updating as research progresses.

The NIH Guidelines are the key reference in assessing risk and establishing an appropriate bio-safety level for work involving recombinant DNA molecules (NIH, 2002). The purpose of the NIH Guidelines is to promote the safe conduct of research involving recombinant DNA. The guidelines specify appropriate practices and procedures for research involving constructing and handling both recombinant DNA molecules and organisms and viruses that contain recombinant DNA. They define recombinant DNA as a molecule constructed outside of a living cell with the capability to replicate in a living cell. The NIH Guidelines explicitly address experiments that involve introduction of recombinant DNA into Risk Groups 2, 3, and 4 agents, and experiments in which the DNA from Risk Groups 2, 3, and 4 agents is cloned into nonpathogenic prokaryotic or lower eukaryotic host-vector systems. Compliance with the NIH Guidelines is mandatory for investigators conducting recombinant DNA research funded by the NIH or performed at, or sponsored by, any public or private entity that receives any NIH funding for recombinant DNA research. Many other institutions have adopted these guidelines as the best current practice.

The NIH Guidelines were first published in 1976 and are revised on an ongoing basis in response to scientific and policy developments. They outline the roles and responsibilities of various entities affiliated with recombinant DNA research, including institutions, investigators, and the NIH. Recombinant DNA research subject to the NIH Guidelines may require:

1. approval by the NIH Director, review by the NIH Recombinant DNA Advisory Committee (RAC), and approval by the IBC; or
2. review by the NIH Office of Biotechnology Activities (OBA) and approval by the IBC; or
3. review by the RAC and approvals by the IBC and Institutional Review Board; or
4. approval by the IBC prior to initiation of the research; or
5. notification of the IBC simultaneous with initiation of the work. It is important to note that review by an IBC is required for all non-exempt experiments as defined by the NIH Guidelines.

Cell cultures: Workers who handle or manipulate human or animal cells and tissues are at risk for possible exposure to potentially infectious latent and adventitious agents that may be present in those cells and tissues. This risk is well understood and illustrated by the reactivation of herpes viruses from latency (Efstathiou and Preston, 2005). The inadvertent transmission of disease to organ recipients, (CDC, 2004; 2005) and the persistence of human immunodeficiency virus (HIV), HBV and hepatitis C virus (HCV) within infected individuals in the U.S. population. There is also evidence of accidental transplantation of human tumor cells to healthy recipients which indicates that these cells

are potentially hazardous to laboratory workers who handle them. (Gather *et al.,* 1996) In addition, human and animal cell lines that are not well characterized or are obtained from secondary sources may introduce an infectious hazard to the laboratory. For example, the handling of nude mice inoculated with a tumor cell line unknowingly infected with lymphocytic chorio-meningitis virus resulted in multiple LAIs (Dykewicz *et al.,* 1992). The potential for human cell lines to harbor a blood borne pathogen led the Occupational Health and Safety Administration (OSHA) to interpret that the occupational exposure to blood borne pathogens final rule would include human cell lines.

Labeling GMO's Although labeling is essential, it is the question of the product derived from the GMOs or Derived out of GO derived products, Labeling is mandatory for GM foods or not, is controversial. International Dairy Foods Association is the primary case in which a federal court has dealt with a state initiative to compel labeling of a GM product.

In Amestoy, the Second Circuit of Appeals was presented with a challenge to a Vermont statute that compelled disclosure of dairy products produced with the hormone rBST ("BGH") or "recombinant bovine somatotropin", which is a protein growth hormone that stimulates milk production (and has other physiological effects), is produced naturally by the cow pituitary gland. rBST is given to cows by intravenous injection, and although milk production. Stimulated by the administration of rBST, the milk itself is not genetically modified.

Bovine somatotropin (BST) is a protein, also a growth hormone that stimulates milk production (and has other physiological effects), and is produced naturally by the cow pituitary gland. The gene that codes for the production of BST has been genetically engineered into bacteria so that the hormone can be produced commercially and used as animal drug, rBST. rBST is given to cows by intravenous injection, and although milk production is stimulated by the administration of rbST, the milk itself is not genetically modified. Nonetheless, milk produced with the use of rbST has raised many of the same concerns as GM food. Because milk generated with the use of rbST is not a GM food product, the issue of whether milk generated with its use should be labeled as such forcefully illustrates the dichotomy between labeling based on method of production and labeling based on safety concerns raised by the product itself. In addition, there is extensive data on the safety of rbST because rbST is an animal drug subject to premarket review. Accordingly, by examining the efforts to label rbST generated milk, one can evaluate whether public pressure to label it stems from scientifically grounded safety concerns or other considerations.

Although the court did not address this argument directly, they nevertheless applied

1. Whether the expression concerns lawful activity and is not misleading;
2. Whether the government's interest is substantial;
3. Whether the labeling law directly serves the asserted interest; and
4. Whether the labeling law is no more extensive than necessary.

Beaudoin (1999) explains about this decision that Amestoy "is curious in light of the contemporary commercial speech jurisprudence, including those cases applying the Central Hudson test." The author's opinion circumscribes to: First, observers have noted that the Supreme Court appears to be taking a new approach to commercial speech, showing a "growing acceptance of the preservation of a fair bargaining process as the rationale for commercial speech regulation." In most instances where a court recognizes a state interest in informed consumers, it has been an interest in informing them of a difference in product characteristics and preventing the suppression of accurate information.

Second, the policy of providing information to consumers has always been a primary concern in commercial speech and disclosure cases and has overcome even the higher standard of review applied to complete bans of speech.

Specifically, the FFDCA requires labeling regarding rbST treatment because milk from rbST-treated cows is organo-leptically different from ordinary milk, and because "there is widespread consumer desire for mandatory labeling of rbST derived milk, and that such a degree of demand is also a material fact requiring labeling." The court did not agree that these were material facts requiring labeling. While the court agreed that orgono-leptic differences, which are differences that are capable of being detected by a human sense organ and differences in performance characteristics such as flavor, shelf life, or physical properties are material facts that would require labeling, it found no evidence of such differences in the administrative record, which concluded that rbST "has no significant effect on the overall composition of milk."

As for consumer demand, the court held that; Consumer opinion alone was insufficient to require labeling without a determination that a product differs materially from the type of product it purports to be if the product does not differ in any significant way from what purports to be, then it would be misbranding to label the product as different, even if consumers misperceived the product as different. In the absence of evidence of a material difference between rbST derived milk and ordinary milk, the use of consumer demand as a rationale for labeling would violate the Food, Drug and Cosmetic Act.

EU Regulation on Labeling GM Foods

EC Novel Foods and Novel Food Ingredients Regulation provide for special labeling:

1. if a GM food is judged not to be equivalent to the relevant existing (i.e. non-GM) food;
2. if a GM food contains material that might give rise to health concerns (e.g. a protein from a known food allergen such as peanuts);
3. if a GM food contains material that might give rise to ethical concerns (e.g. animal genes in vegetable products).

In addition, all foods which contain or consist of GM plants themselves should be labeled, although because segregation of GM and conventional products may not be possible, the Regulation recognizes that a label stating that GMOs "may be present" would fulfill the labeling obligation.

Policies on GMOs:

The Assembly recommends that governments of member states, when defining their policies on GMOs:

A. To take into account four general principles:

a. Respecting the freedom of choice for consumers and producers: Maintaining simple access to GMO-free foods is the central objective of GMO regulation. The viability of Agriculture without GMOs can be safeguarded in the long term. In contrast to other forms of traditional agriculture, regional organic farming cannot be safeguarded by threshold values above the limit of technical detection. In any case, consumers of organic products will not accept a tolerance threshold of 0.9% GMOs.

b. Preserving sustainability in agriculture: GMO-free agriculture should be guaranteed in law without ruling out the cultivation of GMO crops and the confined release of GMO for scientific purposes.

Organic farming in particular deserves protection because it is the best form of agriculture in terms of ecological sustainability, as mentioned in the Assembly's Recommendation 1636 (2003) on the development of organic farming.

c. Precaution: Large gaps in scientific knowledge, both in the field of molecular genetics and with regard to ecological consequences, irreversible manipulation of nature and creeping contamination with transgenes should be avoided and the environmental precautionary principle recognised at all times.

d. Objectivity of the scientific debate and public participation: It is in the interests of all concerned to construct a sound scientific base at various levels of safety research, to make it possible for standards and regulations to be redirected, eased or tightened under agreed procedures. Only on the basis of broad social discussion can clear political decisions be taken. Research should also be more open to this debate. A debate involving the whole of society should focus not only on the risks of green genetic engineering but also on the question of whether or not social models, objectives and practical expectations justify the move into green biotechnology on a larger scale;

Bring safety standards relating to the use of GMOs into line with EU legislation as a minimum standard.

a. Labeling of GMOs: the labeling of animal products following the use of genetically modified feedstuffs should be a mandatory requirement.

b. Labeling of seeds: following the precautionary principle, compulsory labeling of seeds at the limit of technical detection (0.1%) is the most effective means of checking environmental consequences and securing conformity with threshold values for labeling purposes.

c. Liability regime: clear regulations on the questions of liability, together with clear decisions on who is to bear the additional costs incurred in making possible the co-existence of different forms of agriculture. These rules should obey the causal agent principle.

d. Good agricultural practices: regulation of good agricultural practice in terms of production and use of GMOs (minimum distances, public register, etc.).

e. GMO-free zones: GMO-free reference areas should be established to fix natural baselines. Regional agreements for GMO-free zones should be possible to safeguard the co-existence of different methods of cultivation and ecologically sensitive areas.

f. Prohibition of the cultivation of GMO crops which contain marker-genes for antibiotic resistance.

iv. Take the following steps in view of the fact that the commercial introduction of transgenic domestic animals is imminent:

a. Risk investigations: A thorough risk investigation in all areas including (human health, animal health, ecological effects) is urgent. The use of genetically modified micro-organisms in livestock farming should consider the animal and its life cycle as a whole.

b. Secure fencing systems: under no circumstances should genetically modified livestock be kept in open herds.

In order to restrict the risks to the surrounding ecosystem arising from transgenic fish, these should not be kept in cage systems in the open sea;

c. Pharmaceutical products: transgenic plants and animals used for the production of pharmaceutical products should be kept only in enclosed areas.

A distinction must be drawn between health-promoting and therapeutic effects.

Safety tests on commercial GM crops

GM tomatoes The first and only safety evaluation of a GM crop, the FLAVR SAVRT^{M} tomato, was commissioned by Calgene, as required by the FDA. This GM tomato was produced by inserting kanr genes into a tomato by an ‘antisense’ GM method. The test has not been peer-reviewed or published but is on the internet. The results claim there were no significant alterations in total protein, vitamins and mineral contents and in toxic

glycol-alkaloids. Therefore, the GM and parent tomatoes were deemed to be "substantially equivalent." In acute toxicity studies with male/female rats, which were tube-fed homogenized GM tomatoes, toxic effects were claimed to be absent. In addition, it was concluded that mean body and organ weights, weight gains, food consumption and clinical chemistry or blood parameters were not significantly different between GM-fed and control groups. However, some rats died within a few weeks after eating GM tomatoes. The unacceptably wide range of rat starting weights (±18% to ±23%) invalidated these findings. No histology on the intestines was done even though stomach sections showed mild/moderate erosive/necrotic lesions in up to seven out of twenty female rats but none in the controls. However, these were considered to be of no importance, although in humans they could lead to life-endangering hemorrhage, particularly in the elderly who use aspirin to prevent thrombosis. Seven out of forty rats on GM tomatoes died within two weeks for unstated reasons. These studies were poorly designed and therefore the conclusion that FLAVR SAVRT^{M} tomatoes were safe does not rest on good science, questioning the validity of the FDA's decision that no toxicological testing of other GM foods will in future be required.

GM maize

Two lines of Chardon LL herbicide-resistant GM maize expressing the gene of Phosphinothricin Acetyltransferase Enzyme "Pat-Protein" before and after ensiling showed significant differences in fat and carbohydrate contents compared with non-GM maize and were therefore substantially different.

Toxicity tests were only performed with the "Pat-Protein" even though with this the unpredictable effects of the gene transfer or the vector or gene insertion could not be demonstrated or excluded.

The design of these experiments was also flawed because [a] the rats' ability to digest was decreased after eating GM corn Richard Hellmicha and Blair Siegfriedb (2001); [b] the starting weight of the rats varied by more than ±20% and individual feed intakes were not monitored; [c] feed conversion efficiency on "Pat-Protein"' was significantly reduced; [d] urine output increased and several clinical parameters were also different; [e] the weight and histology of the digestive tract (and pancreas) was not measured. Thus, GM maize expressing Pat-protein may present unacceptable health risks.

Compositional studies Allergen content increased when soybeans were genetically modified (Mills, *et al.,* 2003).

GM soybeans: To make soybeans herbicide resistant, the gene of 5 enolpyruvylshikimate-3-phosphate synthase from Agrobacterium was used. Safety tests claim the GM variety to be "substantially equivalent" to conventional soybeans (Padgette *et al.,* 1996). The same was claimed for GTS (glyphosate-resistant soybeans) sprayed with this herbicide (Taylor *et al.,* 1999). However, several significant differences between the GM and control lines were recorded. (Padgette *et al.,* 1996) and the

statistical method used was flawed because: There were also differences in the contents of natural isoflavones (genistein, etc.) with potential importance for health (Lappe *et al.,* 1999). Additionally, the trypsin inhibitor (a major allergen) content was significantly increased in GTS. Because of this, and the large variability (± 10% or more), the lines could not be regarded as "substantially equivalent."

GM potatoes: There is only one peer-reviewed publication on GM potatoes that express the soybean glycinin gene (Hashimoto *et al.,* 1999). However, the expression level was very low and no improvements in the protein content or amino acid profile were obtained.

GM rice: The kind that expresses soybean glycinin gene (40-50 mg glycinin/g protein) has been developed (Momma Hashimoto *et al* 1999) and is claimed to contain 20% more protein. However, the increased protein content was probably due to a decrease in moisture rather than true increase in protein putting a question mark over the significance of this GM crop.

GM cotton: The toxin level of GM cotton is unpredictable. Several lines of GM cotton plants have been developed using a gene from *Bacillus thuringiensis* subsp. *kurstaki* providing increased protection against major lepidopteran pests. The lines were claimed to be "substantially equivalent" to parent lines (Berberich *et al.,* 1996) in levels of macronutrients and gossypol, cyclopropenoid fatty acids and aflatoxin levels were less than those in conventional seeds. However, because of the use of inappropriate statistics it is questionable whether the GM and non-GM lines were truly equivalent, particularly as environmental stresses could have unpredictable effects on antinutrient/toxin levels (Novak and Hasberger, 2000).

Nutritional and toxicological studies

Herbicide-resistant soybean: Studies have been conducted on the feeding value (Hammond *et al.,* 1996) and possible toxicity (Harrison *et al.,* 1996) for rats, broiler chickens, catfish and dairy cows of two GM lines of glyphosate-resistant soybean (GTS). The growth, feed conversion efficiency, catfish fillet composition, broiler breast muscle and fat pad weights and milk production, rumen fermentation and digestibilities in cows were claimed to be similar for GTS and non-GTS. However, these experiments were poorly designed since the high dietary protein concentration and the low inclusion level of GTS could have masked any GM effect. No individual feed intakes, body or organ weights were given and no histology was performed, except some qualitative microscopy on the pancreas. The feeding value of the two GTS lines was not substantially equivalent either because the rats grew significantly better on one of the GTS lines than on the other.

The experiment with **broiler chicken** was a commercial and not a scientific study. The **catfish** experiment showed again that the feeding value of one of the GTS lines was superior to the other. In **milk production** and performance of lactating cows also showed significant differences between cows fed GM and non-GM feeds. Moreover, testing of the safety of 5-enolpyruvylshikimate-3-phosphate synthase which renders

soybeans glyphosate-resistant (Harrison *et al.,* 1996) was irrelevant because in the gavage studies an *E. coli* recombinant and not the GTS product were used. Their effects could be different as the differences in post-translational modification could have impaired their stability to gut proteolysis. Thus, the claim that the feeding value of GTS and non-GTS lines was substantially equivalent is at best premature. Rats had meager weight gain when fed GM soybeans. In a separate study (Teshima *et al.,* 2000) it was claimed that rats and mice which were fed with 30% toasted GTS or non-GTS in their diet had no significant differences in nutritional performance, organ weights, histopathology and production of IgE and IgG antibodies. However, under the unphysiological, starvation conditions of these experiments when, instead of the normal daily growth of 5-8 g per day, the rats grew less than 0.3 g and mice not at all, no valid conclusions could be drawn.

GM corn One broiler chicken feeding study with rations containing transgenic Event 176 derived *Bt* corn (Novartis) has been published

GM peas The nutritional value of diets containing GM peas expressing bean alpha-amylase inhibitor when fed to rats for 10 days at two different (30% or 65%) dietary inclusions, was shown to be similar to that of parent-line peas (Puszatai *et al.,* 1999) GM peas seem to have no harmful effects on animals but that doesn't mean they are safe for humans. Even at 65% level the difference was small mainly because the alpha-amylase inhibitor expressed in the peas was quickly digested in the rat gut and its anti-nutritive effect abolished. Unfortunately no gut histology was done or lymphocyte responsiveness measured. Although some organ weights, mainly the caecum and pancreas were different, those of others were remarkably similar suggesting that GM peas may be used in the diets of farm animals at low/moderate levels if their progress was carefully monitored. However, to establish its safety for humans a more rigorous specific risk assessment will have to be carried out with several GM lines. This should include: An initial nutritional/toxicological testing on laboratory animals. If no harmful effects are then detected, it should be followed by clinical, double-blind, placebo-type tests with human volunteers, keeping in mind that any possible harmful effects would be particularly serious with the young, old, and disabled. A protocol for such testing was given at the OECD conference in Edinburgh, February 2000 (Puzatai, 2000).

GM potatoes: In a feeding study to establish the safety of GM potatoes expressing the soybean glycinin gene, rats were daily force-fed with 2 g of GM or control potatoes/kg body weight (Hashimoto *et al.,* 1999). No differences in growth, feed intake, blood cell count and composition and organ weights between the groups was found, the potato intake of the animals was too low and unclear, whether the potatoes were raw or boiled. Toxins were found in mice after eating GM potatoes. Feeding mice with potatoes transformed with a *Bacillus thuringiensis* var. *kurstaki Cry1* toxin gene or the toxin itself was shown (Hashimoto *et al.,* 1999) to have caused villus epithelial cell hypertrophy and multinucleation, disrupted microvilli, mitochondrial degeneration, increased numbers of lysosomes and autophagic vacuoles and activation of crypt Paneth cells. The results showed that despite claims to the contrary, *Cry I* toxin was stable in the mouse gut and therefore GM crops expressing it need to be subjected to "thorough tests…to avoid the risks before marketing. When the health risks of GM potatoes were revealed in some

studies, a debate ensued. In another study, young, growing rats were pair-fed on iso-proteinic and iso-caloric balanced diets containing raw or boiled non-GM potatoes and GM potatoes with the snowdrop (*Galanthus nivalis*) (Ewen and Pusztai 1999b; Pusztai *et al.,* 1990, 1990, Pusztai, 2000) bulb lectin (GNA) gene. (Ewan and Puzszatai, 1999b) The results showed that the mucosal thickness of the stomach and the crypt length of the intestines of rats fed GM potatoes were significantly increased. Most of these effects were due to the insertion of the construct and not to GNA which had been been pre-selected as a non-mitotic lectin unable to induce hyperplastic intestinal growth (Puszatai *et al.,* 1990) and epithelial T lymphocyte infiltration.

Although there is controversy about the tests, most of the adverse comments on this Lancet paper were personal, non-peer reviewed opinions and, as such, of limited scientific value. The findings, on the other hand, were published in a peer-reviewed publication (Ewan and Puzszatai 1999b). The work, however, has not been repeated nor the results contradicted and it is therefore imperative that the effects on the gut structure and metabolism of all other GM crops developed using similar techniques and genetic vectors should be thoroughly investigated before their release into the food chain.

GM tomatoes: This study with a GM tomato expressing *B. thuringiensis* toxin *Cry IA (b)* gene was published, its importance was underlined by the immunocytochemical demonstration of *in vitro* binding of *Bt* toxin to the caecum/colon from humans and rhesus monkeys (Noteborn *et al.,* 1995). Although *in vivo* the *Bt* toxin was not bound by the rat gut, this was possibly due to the authors' use of recombinant *Bt* toxin.

Allergenicity studies: One of the major health concerns with GM food is its potential to increase allergies and anaphylaxis in humans eating unlabeled GM foodstuffs. Allergies are a major concern with GM food (Mills, *et al.,* 2003), especially if ingredients are not labeled in packaged food.When the gene is from a crop of known allergenicity, it is easy to establish whether the GM food is allergenic using *in vitro* tests, such as immunoblotting, with sera from individuals sensitised to the original crop. This was demonstrated in GM soybeans expressing the brasil nut 2S protein (Nordlee *et al.,* 1996) or in GM potatoes expressing cod protein genes (Bindslev-Jensen and Poulsen, 1997).

It is also relatively easy to assess whether genetic engineering affected the potency of endogenous allergens (Burks and Fuchs, 1995). Some farm workers exposed to *B. thuringiensis* pesticide were shown to have developed skin sensitization and IgE antibodies to the *Bt* spore extract. With their sera it may now therefore be possible to test for the allergenic potential of GM crops expressing *Bt* toxin (Bernstein *et al.,* 1999). It is all the more important because Bt toxin Cry1Ac has recently been shown to be a potent oral/nasal antigen and adjuvant (Vazquez-Padron *et al.,* 2000). There are no reliable ways to test GM foods for allergies. Assessment of the allergenicity of a GM foodcrop, however, is difficult when the gene is transferred from a source not eaten before or with unknown allergenicity or on gene transfer/insertion a new allergen or adjuvant is developed or the expression of a minor allergen is increased. Unfortunately, while there are good animal models for nutritional/ toxicological testing, no such models exist for allergenicity testing. Presently only indirect and rather scientifically unsound methods,

such as finding short sequence homologies (at least 8 contiguous amino acids) to any of the about 200 known allergens, are used for the assessment of allergenicity. The decision-tree type of indirect approach based on factors (such as size and stability) of the transgenically expressed protein (O'Neil *et al.,* 1998) is even more unsound, particularly as its stability to gut proteolysis is assessed by an in vitro (simulated) testing (Metcalf *et al.,* 1996) instead of *in vivo*(human/animal) testing and this is fundamentally wrong.

The concept that most allergens are abundant proteins is also misleading because for example *Gad c1*, the major allergen in codfish, is not a predominant protein (Bindslev-Jensen and Poulsen, 1997). However, when the gene responsible for the allergenicity is known, such as the gene of the alpha-amylase/trypsin inhibitors/allergens in rice, cloning and sequencing opens the way for reducing their level by antisense RNA strategy (Nakamura and Matsuda, 1996). Thus, in the absence of reliable methods for allergenicity testing, it is at present impossible to definitely establish whether a new GM crop is allergenic or not before its release into the human/animal food/feed chain.

Authors' contributions: Dr. **T. B. Sridharan** (Associate Professor) *contributed in preparation, performance, editing and also corresponding authors of the manuscript.*

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