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Gentechnik und Lebensmittel

Genetic Engineering and Food

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Genetic Engineering and Food

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für Grundsatzfragen der Genforschung

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Genetic Engineering and Food

Statement of the Senate Commission
on Genetic Research,
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1 Preface

It has been slightly more than five years since the Deutsche Forschungsgemeinschaft (DFG) passed its first statement of March 1996 on the subject of "Gene Technology and Food"*.

The DFG is now presenting a statement on the subject of gene technology and food that has been completely revised by the Senate Commission on Genetic Research. This statement has also been agreed on by the Senate Commission on Food Safety. The statement concentrates on food made from genetically modified plants. The subject does not exclude animal-based foodstuffs, though these will be covered in a separate statement. With this statement, the DFG is fulfilling its statutory obligation to advise parliament and authorities on scientific issues. This is done at a time when the production of animal- and plant-based food is a controversial matter of public debate. "Gene Food" or "Frankenstein Food" are the pejorative terms for food that contains components made from genetically modified plants or micro-organisms.

With this statement, the DFG would like to make an objective contribution to this discussion, which has often been extremely emotional in recent times. The Senate Commission comments on the aims and applications of "Green Gene Technology" in agriculture and considers the conceivable risks of the cultivation of genetically modified plants as well as the consumption of genetically modified food. It also gives advice about the legal safety precautions for the protection of consumers.

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* Gentechnik und Lebensmittel, Stellungnahme vom 1. März 1996. Published in "Genforschung – Therapie, Technik, Patentierung", Report 1 of the Senate Commission on Genetic Research, Wiley-VCH Verlag, Weinheim 1997.

From this statement it is clear that genetically modified plants with high-quality components and improved resistance to pests and diseases can make an important contribution to sustainable agriculture. Thus, the DFG highly recommends that the responsible development of gene technology in the food industry is pursued. This requires an open and transparent dialogue between scientists and the public. Under discussion will be not only complex scientific correlations but also less well-known regulations for anything from seeds to "novel food", each of which are governed by detailed safety aspects.

Gene technology is not incompatible with new agriculture policies, which focusses increasingly on quality rather than on quantity. Thus, I hope that this communication helps to integrate into national law the recently approved EC guidelines for the release of genetically engineered organisms into the environment.

A great deal of time was invested in discussions and collection of material in order to tackle such a complex subject in a proper and comprehensive way. Particular thanks are due to the members of the working group on "Genetically Modified Plants and Food" of the Senate Commission on Genetic Research, and above all to H. G. Gassen, H. Saedler, W. P. Hammes, L. Honnefelder, and J. Straus.

I hope that the second statement concerning "Gene Technology and Food" will receive a great deal of attention and that this will be to the advantage of the objective discussion of this subject both in scientific and political circles.

Bonn, April 2001

Professor Dr. Ernst-Ludwig Winnacker
President of the Deutsche
Forschungsgemeinschaft (DFG)

2 Conclusions and recommendations

- The Commission confirms its statement of 1996, in which it recommends to emphasize promotion of the responsible development of genetic engineering in plant breeding and food-related microbiology to the benefit of humans and the environment.
- Rules and regulations of Genetic Engineering Law and Food Law have largely stood the test of assessment of health safety of genetically modified crop plants and foods. Rather, a call for action seems appropriate for the substantiation and consistent implementation of national and European regulations. Supplementary regulations (threshold limits for contamination, labelling) are needed for seeds to be used for the production of feeding stuff and foods.
- The assessment principle of "Substantial Equivalence", which is based on a comparison of genetically modified and traditional foods is still valid. Novel scientific findings are to be taken into account.
- Technical realization of open-field experiments with genetically modified plants does not require any modification. Previous safety research should be extended by including cultivation-linked ecological aspects. For this purpose, it is necessary to develop suitable approaches. Risk assessment should be carried out on the basis of single-case evaluation by careful assessment of chances and risks in consideration of current agricultural practice.

- With respect to safeguarding world nutrition and protection of natural resources, it is necessary to develop and promote intensive and environmentally friendly production processes. The principle of sustained development in agriculture and the food sector must be observed.
- Since advanced technologies increasingly determine global economic development, industrialized and developing countries should make use of possibilities offered to them within the framework of the Convention on Biological Diversity and participate in this development. In particular, developing countries should be enabled to utilize novel technologies to their advantage and to prioritize research, development and applications according to their own needs.
- Increasing privatization of research (private companies are responsible for approximately 80 per cent of research investments in agricultural biotechnology) necessitates a fundamental reconsideration of the modes of co-operation between publicly and privately funded research. The increasing activity of biotechnology companies in research, development, and production of seeds, their legitimate request for industrial property rights (patents and/or protection of cultivar and varieties), as well as the emerging market concentration in this area should put no strains on co-operation with developing countries. Rather, this should lead to improved plant breeding and cultivation in these countries.
- The application of genetic engineering to the benefit of mankind and the environment requires the consent of the broad public. The public debate about this topic therefore must be carried on as a constructive dialogue, i.e. in an atmosphere of mutual understanding between the scientific community and the public. The information of consumers by open and perspicuous presentation of complex scientific facts, a meaningful labelling of genetically modified foods, as well as the transparency of research and approval procedures must be guaranteed.

3 Introduction

In fulfilment of its statutory obligations to give expert policy advice, the Senate Commission on Genetic Research in co-operation with the Senate Commission on Food Safety has dealt with the topic of "Genetic Engineering and Food" in a first statement issued in March 1996. Meanwhile, research and commercialization in this area have advanced, and important basic conditions have changed. Therefore, a reappraisal is due. Currently, most species of crop plants are subject to breeding by means of genetic engineering techniques. On a world-wide scale, the cultivation of genetically modified crop plants (in particular soybeans, maize, cotton, and oil-seed rape) almost reached 40 million hectares in 1999, including approximately 20 million hectares in the US. Most enzymes, amino acids, some vitamins, and other additives employed in food processing are produced by means of genetically modified micro-organisms. Foods from genetically modified plants and micro-organisms have been consumed by millions of people without any reported cases of health problems attributable specifically to genetic engineering.

For seed producers and other parties involved in the chain of food production, economic advantages are obvious. By cultivating genetically modified crops, farmers expect a more cost-effective high-yield production and reduced utilization of agrochemicals for pest and weed management in comparison to traditional cultivation techniques. On the other hand, in Europe the commercial exploitation of genetically modified plants has only been possible to a very small extent due to a lack of official authorization. To what extent this situation will change due to a revision of guideline 90/220/EWG (Release Guideline) remains to be seen.

In addition, there are problems of acceptance within large parts of the European public. For many citizens the benefits of plant ge-

netic engineering ("Green" Gene Technology) have not become sufficiently clear. While genetic engineering applications in medicine ("Red" Gene Technology) have been widely accepted, genetic engineering applications in agriculture and food technology are subject to strong criticism. Critical attitudes of large parts of the public towards genetic engineering appear to reflect a general distrust in economy and society rather than anxieties hastened by concrete risks (Hampel and Renn 1999). Other problems pertaining to food and nutrition (BSE, dioxine) and controversial scientific publications may have contributed towards such negative attitudes.

In the course of globalization and international dependencies, it is necessary not to disregard the food situation in developing countries. Despite the utilization of plant protective agents, approximately one third of all crops is still lost world-wide due to diseases, pests, and weeds (Oerke and Steiner 1996). Due to the increasing population, the world will have to produce more food in the next 50 years than it did before, i.e. since the onset of agricultural production approximately 10,000 years ago. However, the agricultural area available can hardly be enlarged. For this reason, the global challenge is to secure high and top quality yields and to make agricultural production environmentally compatible.

Against this background and based on current scientific knowledge, aims and applications – as well as conceivable risks concerning genetic engineering and food production – shall be reviewed and assessed. Recommendations will also be given.

4 Aims and applications

4.1 Genetically modified plants in agriculture

Approximately 10,000 years ago, man has begun to select crop plants from feral forms. However, classical breeding based on the application of Mendelian rules and scientific principles has been carried out only for approximately 100 years. Breeding aims have changed little. They can be classified into three main groups:

– yield increase,
– yield maintenance,
– quality and processing criteria.

Modern biotechnological techniques that rapidly entered plant breeding have been developed based on novel scientific knowledge in molecular biology and genetics. By means of cell and tissue culture techniques, for example, complete plants can be regenerated from individual cells and tissue components. Cell and tissue culture techniques, therefore, are important prerequisites for the application of genetic engineering. While traditional breeding is restricted to crosses between closely related species, genetic engineering permits the transfer of individual genes, which may also come from other species, e.g. bacteria. Genetic engineering therefore supplements classical breeding approaches. The following paragraphs will cite some examples of genetically modified plants and vistas for their utilization that are relevant for practical applications.

4.1.1 Resistance against phytophagous pests

By now, approximately 40 genes which cause resistance against phytophagous pests have been transferred to agricultural crop plants (Schuler et al. 1998). The best known examples are genes of the bacterium *Bacillus thuringiensis*, known as Bt genes. Preparations of this Bt bacterium (spores and protein crystals) have been used as insecticides for 40 years predominantly in ecological farming, horticulture, and forestry. The bacterium produces a toxic protein that is poisonous for certain insects such as butterfly larvae but is harmless for other animals. The effect of this spray is short-lived, however, as the active ingredient, i.e. the Bt protein, is rapidly degraded and inactivated. At least 10 genes encoding different Bt toxins which confer selective resistance against harmful insects have been implanted into various crop plants by now (Schuler et al. 1998).

"Transgenic" plants equipped with the bacterial gene by means of genetic engineering make their own toxin and thus protect themselves against being eaten by insects. In maize, another advantage is apparent. Since damages due to insect infestation are reduced, the incorporated Bt genes indirectly also reduce infestation with harmful fungi which can invade the maize plant through damaged tissues and which may produce hazardous toxins (mycotoxins) such as Fumonisin. At present, five different Bt gene constructs have been approved for use in maize in the US (Munkvold and Hellmich 1999). Species of maize and cotton harbouring Bt genes protecting them against phytophagous pests are being cultivated on a large scale in the US. In some instances, cultivation of resistant varieties can reduce the use of insecticides considerably.

4.1.2 Resistance against pathogens

Fungi and bacteria

A currently tested defence is the utilization of chitinases, as these enzymes are capable of degrading polysaccharides of the fungal cell wall (chitins). These enzymes attack the fungal hyphae invading the plant cell and block fungal growth. Genes encoding chitinases have been isolated, for example, from barley and a soil bacterium (Jach

et al. 1995). Genes encoding so-called osmotins that are capable of destroying fungal membranes have been found in tobacco, potato, and tomato plants. Pilot experiments with potato plants infected with the causative agent of late potato blight show that the expression of these genes slows down the development of disease symptoms (Zhu et al. 1996). Another approach uses a so-called ribonuclease gene that causes a cell infected with a fungus to die due to the degradation of RNA. This is thought to prevent further spreading of the fungal infection (Strittmatter et al. 1995). Cultivation of fungus-resistant varieties is expected to reduce the utilization of fungicides markedly; in wine growing, this still comprises up to seven spray campaigns.

Molecular defence mechanisms, for example based on lysozyme genes that were transferred to potato plants, are also investigated for bacterial diseases that are difficult to attack. Lysozymes (enzymes that can destroy cells) are ubiquitous and have toxic effects for bacteria. By transferring the genes encoding these enzymes to plants, invading bacteria can be attacked at an early stage of infection so that massive reproduction can be prevented (Düring et al. 1993).

Viruses

Plant-virus diseases are a particular problem in agriculture, as there are no specific means to counteract infections directly. At best, the transmission of viruses can be prevented indirectly in certain instances by attacking those insects that serve as vectors for the spread of viruses. Several novel protective strategies are now being pursued by means of genetic engineering. Some viruses cannot replicate within plants if certain harmless parts of the infectious agent are already present in the plant cell. The transfer of genes encoding certain viral coat or transport proteins, for example, is being investigated as one way to improve resistance against viruses. This approach is pursued, for example, with sugar beets and resistance against *Rizomania* virus, the causative agent of rizomania (Mannerlöf et al. 1996). In potatoes it is pursued with resistance against leaf roll virus (Tacke et al. 1996) and tested in open-field release experiments in Germany.

Cultivation of suitably genetically modified varieties offers a perspective of abandoning largely the use of synthetic spraying agents against insects transmitting viruses.

4.1.3 Tolerance against herbicides

Crop plants are exposed not only to diseases and to pests but also compete with feral plants for light, water, and nutrients under open-field conditions. These feral plants overgrow cultivated crops and may lead to considerable yield losses. Herbicides are used to prevent this. Herbicides are usually applied before or a short time after sowing in order to provide developmental advantages for crop plants. Certain broad-band herbicides are degraded quickly and therefore are deemed relatively environmentally friendly. However, such herbicides block important enzymes of plant metabolism and damage feral and crop plants to the same extent. Therefore, they could not be used so far during the growth periods of crop plants.

Agrochemical industry has modified important crop plants such as soybeans, maize, cotton, and oilseed rape by means of genetic engineering so that these plants can now tolerate such herbicides. In these approaches, two strategies play a prominent role:

- Plants produce an enzyme that inactivates the herbicide, for example by attaching an acetyl moiety.
- The enzyme resembles the target protein of the herbicide. However, it has been altered by genetic engineering in such a way that the herbicide can no longer block it.

Herbicides that are degraded rapidly by micro-organisms in the soil can now be employed without disadvantages for the crop plants. This can be done effectively by a post-emergent treatment. At this stage, it can be foreseen that the yield will be threatened and feral species will have reached a later stage of development. In the US, these herbicide-tolerant plants are being cultivated on a large scale.

Experience demonstrates that in comparison to traditional production methods this novel strategy of weed control reduces the amount of herbicides (Carpenter and Gianessi 1999, Fulton and Keyowski 1999). Moreover, prolonged coverage of the soil by feral

plants prevents erosion by wind and water (heavy rainfall). Practically oriented open-field release experiments will have to show if this procedure will also lead to reductions in herbicides in the cultivation of maize, sugar beets, and oilseed rape in our latitudes.

4.1.4 Crop plants for unfavourable habitats

In large areas of the world, adverse environmental conditions such as dryness, high salinity or aluminium content of the soil or extreme temperatures make the cultivation of crop plants difficult. What is needed are high-yield crops that will grow even under such unfavourable conditions. Attempts to study the stress tolerance of plants are therefore made with particular emphasis on the difficult production conditions in many developing countries. Research is focussed on so-called osmoprotective substances (osmolytes) as well as special protective proteins that allow plant cells to survive stress caused by droughts, salt or cold temperatures. Osmoprotective substances are low molecular weight compounds that are often derived from sugar and amino acid metabolism.

Plants produce certain proteins under conditions of stress. The expression of some of these proteins is induced by drought. It appears that some of these proteins can acquire the function of water molecules necessary for the maintenance of protein structures. It is of interest that one such group of proteins from barley shows structural similarities with proteins found in arctic fishes, which protect cells from freezing (Holmberg and Bülow 1998). Recently, a regulatory gene (CBF1) has been identified in the model plant *Arabidopsis thaliana* (Thale Cress). This gene appears to play an essential role in the activation of genes protecting against cold temperatures (Sarhan and Danyluk 1998). Genetically modified stress-tolerant plants are still in the stage of development and have not yet reached the application stage.

4.1.5 Foodstuff with improved quality

Many research projects world-wide are focussed on the improvement of foodstuff quality by means of genetic engineering techniques. Genes for the production of oils, proteins, carbohydrates and vitamins are being modified selectively in order to improve the health value for humans or to prevent diseases. Two approaches that may be of importance especially for developing countries shall be discussed briefly.

Maize is an important staple food for many people. However, maize kernels contain only little amounts of the protein building block lysine, which is vital for humans. In many regions of Central America and Africa, deficiency diseases are observed, because other plant or animal foods cannot balance the deficit. Lysine-rich maize would be useful for the prevention of such deficiency diseases. Against this background, research projects are aimed at producing maize with a sufficiently high lysine content in the kernels. Initial experiments show that introducing a bacterial gene for an important enzyme of lysine biosynthesis could raise the lysine content of maize kernels (Krebbers et al. 1999).

More than 400 million people world-wide suffer from vitamin A deficiency, which can cause blindness. It mainly affects children in Asian countries, in which rice is the predominant staple food. Scientists of the *Eidgenössische Technische Hochschule (ETH)* in Zürich have developed rice plants that produce β-carotene in their kernels, a precursor of vitamin A. This was achieved by transferring genes encoding key enzymes of terpenoid metabolism from narcissus and the bacterium *Erwinia uredovora*, respectively, to rice plants (Potrykus 1999). This novel trait will be bred into several local rice varieties at the International Rice Research Institute in the Philippines. It is clearly intended to donate this material free of charge to rice farmers.

4.1.6 Breeding of hybrids

Around 1930, it was observed that crosses of inbred maize lines obtained by self-fertilization resulted in particularly strong and high-yielding hybrids. Currently, most market varieties of maize, sugar beet, or sunflower are such hybrids. If hybrid seeds are used for the next growth period this results in genetic segregation and yield losses, so that every year, farmers will have to buy fresh hybrid seeds.

Apomixis is a form of vegetative reproduction that regularly occurs in some grasses. It can be induced by applying genetic engineering techniques. This now opens the perspective of retaining favourable traits of important crop plants, particularly in hybrids, over several generations. Through apomixis, seeds develop directly from a diploid cell without fertilization by eliminating reduction division. Currently, the genes responsible for this are being identified. Farmers in developing countries in particular might profit from this approach. A prerequisite would be an appropriately priced access to apomictic crop plant cultivars.

The exact opposite is a strategy known as "gene protection" or, as critics call it, "gene terminator" technology aimed at seed protection. The corresponding patent, "Control of Plant Gene Expression", has been granted recently to the US Ministry of Agriculture and the Delta & Pine Land Company (Monsanto 1998). In cereals, the so-called terminator genes cause the death of the seed embryo before it reaches maturity. The seed is sterile and cannot be used for planting the next generation. Farmers are therefore forced to purchase new seed stocks. Rightly, there are considerable objections to this kind of cultivar protection.

4.2 Genetically modified micro-organisms in foodstuff production

The number of genetically modified micro-organisms employed in food technology currently exceeds the number of genetically modified plants by far. Such micro-organisms are used

- as producers of metabolites,
- as producers of enzymes,
- as fermenting organisms in foodstuffs.

4.2.1 Production of metabolites

Due to their extremely high metabolic activities and their simple modes of propagation, micro-organisms (bacteria, yeasts, and moulds) are particularly well suited for the production of metabolic products such as amino acids, vitamins, alcohols, organic acids, and flavours. For this purpose, selected strains of micro-organisms are grown in optimized fermentation procedures. The metabolic products have many uses in food technology, e.g. during production, in the improvement of shelf life, flavour, taste, texture, colour, or nutritional value. A frequently used compound, for example, is citric acid, which was originally obtained from lemon. To date, citric acid is obtained by fermentation, using the filamentous fungus *Aspergillus niger* in volumes of 300 000 tons per year. It is utilized as an acidifier and antioxidant in products such as non-alcoholic soft drinks, candies, marmalades, desserts, fats, and oils.

Increasingly, these compounds obtained by biotechnology are produced by genetically modified micro-organisms. One goal is to manipulate the metabolism of such micro-organisms in a manner that the desired products are released at elevated rates. In the laboratory it has been possible, for example, to establish novel metabolic pathways in certain strains of lactic acid fermenting bacteria (*Lactococci*). These bacteria no longer produce lactic acid, acetic acid, or formic acid as products of fermentation. Instead, they produce butter flavour, diacetyl (Hugenholtz 1993), or the amino acid L-alanine, which contributes to natural sweetness in dairy drinks (Hols et al. 1999).

4.2.2 Production of enzymes

Traditionally, micro-organisms have been frequently used as sources of enzymes employed in the production of foodstuffs. The production of enzymes by means of genetically modified micro-organisms has a particular advantage in view of aspects of economic efficiency, protection of resources, protection of the environment, and health safety. This can be seen most impressively from a comparison of α-glucosidase derived from genetically modified yeasts and fresh yeasts (source: Boehringer Mannheim). Glucosidases are utilized largely, for example, in pastry industries.

By using genetically modified yeasts, the amount of waste products or waste water and energy costs can be reduced dramatically. In addition, the enzymes obtained contain markedly less potential allergenic impurities. According to data provided by the organization of producers of microbial enzymes, there exist more than 30 enzyme preparations from genetically modified bacteria, moulds, and yeasts.

In the meantime, genetically engineered chymosine, used for 80 per cent of all cheeses produced in the US, has found the broadest application. Genetically engineered chymosine is identical with the active ingredient contained in traditionally used calf rennin.

4.2.3 Starter and protective cultures

In food technology, micro-organisms are also used as starter and protective cultures. Complex processes are mediated by microbial metabolism in fermented foodstuffs. In raw goods of plant and animal origin microbes are responsible for the conversion of components that are perishable, inedible or of reduced nutritional value into refined, usually stable products without adverse health effects. The result of the fermentation process is subject to a plethora of imponderabilities (state of the raw good, microbial load, infection with bacteriophages).

Advances in microbiology and biotechnology have initiated developments that have led to technologically and biologically controlled production processes. The important issue in these developments is the utilization of starter and protective cultures. These are selected micro-organisms isolated initially from particularly success-

ful fermentations and subjected subsequently to comprehensive characterization. The first cultures in food technology were yeasts and lactic acid bacteria utilized for the manufacture of beer and the production of sour cream butter, respectively. Currently, the use of starter cultures is considered state of the art. For example, without using them it would be impossible for the dairy industry to produce cheese, yoghurt, soured milk, or curds with defined sensory characteristics from several 100 000 litres of milk with high precision in an industrial plant in a single day.

Due to their great significance, micro-organisms employed in foodstuff fermentation processes have undergone rigorous scientific analysis and have been modified genetically. Aims of genetic modifications are:

- resistance against bacterial viruses to provide reliable and safe fermentation procedures,
- improvement of foodstuff hygiene through degradation of natural toxic compounds and prevention of food poisoning,
- enhancement of technological efficiency.

5 Risk considerations

Foodstuffs obtained from genetically modified plants and micro-organisms must be as safe as traditional ones. For this reason, possible risks must be recognized and assessed already while they are being developed.

5.1 Conceivable risks of cultivated genetically modified plants

When developing genetically modified plants – and this is also the case with traditional breeding approaches – the generation of plants with undesirable or unexpected traits cannot be ruled out beforehand. Genetically modified plants therefore are subject to intensive risk assessment.

5.1.1 Naturalization and outcrossing

Ecological risks due to cultivation under open-field conditions might come from uncontrolled spread of a crop plant (naturalization) or the transfer of the novel gene to feral species (outcrossing).

Because of their long breeding history, most crop plants in current use are no longer capable of competing with wild species without protective human interference. This equally applies to crop plants obtained by classical breeding and those obtained by genetic modification. Typical wild-type traits such as loose mounting of seeds in conjunction with small size have been bred out in favour of larger crops and simplified harvests.

However, through outcrossing (vertical gene transfer) the novel gene might be transmitted by pollen to related species. A trait that is desirable in crop plants but undesirable in feral species might then spread. The probability of outcrossing and uncontrolled spread of a foreign gene depends on the presence of suitable breeding partners in the vicinity, and on the generation of fertile progeny. It also depends on a distinct advantage the progeny might have outside of the field due to the presence of the foreign gene, for example, through improved pest or disease resistance, as well as through cold, drought, or salt tolerance. These interrelationships need to be investigated on a regional-specific basis.

In Central Europe, there are no feral plants related to potato, maize, or soy beans which might be able to produce fertile progeny in case of pollen transfer. However, in Central Europe, this scenario cannot be ruled out, for example, for oilseed rape, sugar beets, and oat (Dietz-Pfeilstetter et al. 1999, Bartsch and Pohl-Orff 1996, Ammann et al. 1996). As a matter of principle, regions or gene centres harbouring feral varieties of crop plants therefore deserve special attention with respect to problems of outcrossing.

The question of whether the transferred foreign gene will negatively affect an ecosystem is closely linked to the question of whether it confers selective advantage to its host. Such a selective advantage would result, for example, if transgenic plants dominated over feral varieties due to the newly acquired trait and if they consequently established themselves permanently in an ecosystem. This is to be assessed for each new trait and cultivated area on a case-to-case basis. Currently, it is not clear, if and how far genes introduced by genetic engineering that do not provide selective advantages in nature would establish themselves permanently in feral populations (WBGU 1998).

It cannot be ruled out that cultivation of genetically modified genes in large areas – this applies especially to cross-pollinators – may occasionally be associated with pollen transfer to conventionally bred crop plants. Therefore, ecological farming in the end will not be able to guarantee that certain products will be free of recombinant DNA (Meyer et al. 1998). An interesting prospect of preventing such undesirable transfer of genes by pollen may be offered by approaches that involve genetic interventions in chloroplasts rather than cellular nuclei, since chloroplasts do not occur in pollen cells (Chamberlain and Stewart 1999).

5.1.2 Horizontal gene transfer

Apart from this type of vertical gene transfer, a possible horizontal gene transfer is controversely discussed, i. e. the cross-species transfer of genes introduced into plants, for example into micro-organisms. There are concerns that such genes may end up in micro-organisms after plant decomposition in soil or digestion in human or animal intestines, and that this may have undesired effects. What worries many people in particular is the notion that antibiotic resistance genes used as markers in breeding transgenic plants may interfere with the activities of therapeutic antibiotics.

Genes are constantly being exchanged between bacteria of different species in human and animal intestines as well as in water treatment plants or in soil. A horizontal gene transfer between plants and micro-organisms has not yet been experimentally proven. However, for theoretical reasons this cannot be ruled out (Pühler 1998). The key to a solution of antibiotic resistance problems lies in the drastic reduction of existing selection pressures by responsible handling of antibiotics (Smalla et al. 2000). Novel technological developments also make the use of antibiotic resistance genes dispensable. For these reasons, the use of such resistance genes in combination with other DNA sequences should be discontinued. In consideration of the public debate about the spread of antibiotic resistance and also to minimize risks, breeders now try to obtain genetically modified plants that no longer contain antibiotic resistance genes.

5.1.3 Generation of novel viruses

Risk assessment during the development of transgenic virus-resistant plants focuses on the possibility of the evolution of novel viruses. It is known that viral gene sequences may be exchanged through viral infections. The real extent of such recombination events is not known. This is a natural process that principally can also take place in transgenic plants containing viral genes. For example, recombination might produce a novel virus that causes more pronounced disease symptoms or one that has a broader host range. This risk can be lowered by using incomplete viral gene sequences in the development of transgenic virus-resistant plants. The selected

gene pieces should bestow resistance against viruses but should not allow successful recombination and hence the formation of new viruses (Stiletto and Käppeli 1997).

5.1.4 Influence on "non-target" organisms

Man's agricultural activities have a massive impact on ecosystems. The goal of a long-term development must be to minimize the negative consequences of such activities. Environmentally friendly strategies of plant protection should take precautions against disease and pest infestations and should minimize possible negative consequences for the rest of the flora and fauna. Assessment of disease and pest resistance mediated by genetic engineering must also be seen from this angle.

A recent study demonstrating that larvae of the monarch butterfly (*Danaus plexippus*) may be damaged if fed on leaves of milkweed (*Asclepias syriaca*), their host plant, which had been dusted with pollen from Bt maize has caused public debates. This is a preliminary laboratory study the results of which cannot be applied directly to open-field conditions. From what is known currently, the negative effects for the monarch butterfly appear to be minimal. Pollen of maize are formed only during a short phase of the vegetation period, at best overlapping minimally with the sensitive developmental stage of the butterfly. Since pollen grains are relatively heavy, they are dispersed by the wind only over modest distances away from the maize field. Therefore, milkweed plants in the immediate vicinity of the maize field may be a potential threat for the larvae. It is currently not known if monarch butterflies use milkweed "contaminated" with pollen at all as host plants, if other food sources are available elsewhere (USDA 1999). For these reasons, more practically oriented open-field tests are now underway.

Likewise, laboratory tests with maize plants secreting Bt toxins by their roots, which might damage "non-target" organisms (Saxena et al. 1999), do not allow direct conclusions to be drawn for the situation under practical open-field conditions. Until now, there are only a few open-field tests concerning the impact of Bt plants on "non-target" organisms (De Maagd et al. 1999). There is a considerable need for further research in this area. Any risk-benefit analysis should be carried out always with a view towards current agricultur-

al practice. It should take into account the extent to which conventional insecticides may also damage "non-target" organisms. Using tissue-specific and inducible genetic regulatory units (promoters), which localize defence reactions and induce them only in case of infestation, could further reduce risks.

5.1.5 Resistance against Bt toxins

Against the background of extensive cultivation of genetically modified plants containing Bt toxins for the protection against phytophagous pests concerns have been voiced that this could accelerate the evolution of Bt-resistant pests. Use of this environmentally friendly Bt spray thus could become ineffective. This is not a risk specific for genetic engineering. From agricultural practice it is known that close crop rotation strategies or, under extreme circumstances, monocultures in conjunction with frequent use of the same herbicides can favour the development of resistant pests.

Until now, only a few resistances against Bt preparations in pests of crop plants have been found, for example in the Diamondback moth (*Plutella xylostella*) (Tabashnik 1994). Laboratory tests have demonstrated that insects can become resistant against individual Bt toxins (De Maagd et al. 1999). Resistant strains of the Diamondback moth (*Plutella xylostella*) were reported first for Bt oilseed rape (Rachmandran et al. 1998). Resistant strains of tobacco budworm larvae (*Heliothis virescens*) and of the pink bollworm moth (*Pectinophora gossypiella*) were reported first for Bt cotton (Liu et al. 1999, Gould et al. 1997). The resistance is probably inherited as a recessive trait.

In order to prevent increased rates of pest resistance against Bt toxins of transgenic plants, several strategies of resistance management are now being investigated (De Maagd et al. 1999):

- establishment of a "refuge" of non-transgenic host plant in the vicinity of transgenic plants containing high concentrations of Bt toxins,
- use of several different Bt toxins,
- use of toxin genes with inducible promoters.

Further research will be necessary because the mechanisms of resistance development under open-field conditions are not yet understood in detail.

5.2 Conceivable risks of ingestion of genetically modified food

A confirmation that food is safe is compounded by influences of eating habits, the natural variability in the concentrations of ingredients, processing procedures, as well as the differential susceptibility of individuals or sections of the population. These problems apply to all types of foodstuffs and are not restricted to food modified by genetic engineering.

5.2.1 Toxic ingredients

The development of foods must guarantee that toxic ingredients will not be generated. A great feeling of unease in the general population has been caused by the publication of a research project of the Rowet Research Institute in Scotland. According to a statement of the Royal Society (1999), scientific attitudes have been neglected in this study. The case in question concerns the generation of genetically modified potatoes containing a snowdrop gene encoding a lectin. With such a construct the efforts involved in confirming health safety must satisfy most stringent requirements. On the one hand, there is no experience with the ingestion of snowdrop genes. On the other hand, lectins are known to be highly effective toxins and in particular antinutritive compounds, i.e. they cause deficiencies or influence function and utilization of nutrients. The said potatoes were fed to rats as cooked and raw food. Subsequently, the health status of these experimental animals was determined. According to statements of one scientist carrying out the investigations, the raw transgenic potatoes damaged the health of the rats in contrast to rats that were fed with conventional control potatoes. It should be noted, however, that raw potatoes are principally not fit for con-

sumption, as by nature they contain quite high amounts of toxins and antinutritive compounds.

Great Britain has been hit hard by BSE and its handling by the state authorities. These findings of a toxicological test have precipitated, therefore, a feeling of disapproval and rejection with respect to utilization of genetic engineering in the food industry. It had been impossible to convey to the public that even now a comprehensive assessment much more strict than the rat experiment is European standard and that the data presented do not hint at an unanticipated adverse effect of genetically modified potatoes.

5.2.2 Antibiotic resistance

The exchange of genes between micro-organisms is carried out by several mechanisms. Micro-organisms constitute the intestinal flora and thus have direct effects on humans. A particular problem is manifested by the evolution of micro-organisms that are resistant against chemotherapeutic agents such as antibiotics. These agents are used, for example, to kill pathogenic germs and thus to cure humans from infectious diseases. The increased use of antibiotics has led to a threatening increase of resistant germs. For these reasons, many people fear that this situation could be aggravated by organisms having undergone genetic modifications.

The spread of antibiotic resistance clearly demonstrates that gene transfer among micro-organisms principally cannot be prevented and that micro-organisms acquiring a selective advantage by obtaining a foreign gene can be accumulated in the environment. Therefore, a generally applicable assessment strategy cannot be forwarded and risks must be assessed always on a case-to-case basis.

5.2.3 Allergies

In the context of genetic engineering and foodstuffs, possible allergic reactions from consumers are particularly relevant. In most instances, allergies are caused by proteins. Proteins derived from foodstuffs with known allergenic potential can be tested for this allergenic potential because sera from allergic individuals containing corresponding antibodies are normally available. For example, a

Brazil-nut gene, i.e. the corresponding protein, introduced to improve the nutritional quality of soybeans, has been identified as a major foreign allergen (Nordlee et al. 1996). Thereupon, further development was blocked. Last but not least, it is also possible by means of genetic engineering to suppress the formation of allergenic proteins in crop plants.

Typical properties of allergenic proteins such as molecular size, modification by glycosylation, and stability during processing procedures and passage through the gastrointestinal tracts are known (Jany and Greiner 1998). However, in many instances it is still not clear which particular proteins are responsible for allergic reactions. The allergic potential of proteins that have not yet been components of foodstuffs cannot be predicted and therefore still has to be verified.

5.2.4 Examination of health safety

Recommendations of the EC Scientific Committee for Food (97/618/EC) serve as guidelines for the assessment of health hazards of novel food, in particular those of genetically modified products, which are assigned as such. These recommendations take into account the internationally obtained scientific consensus and are addressed to producers of transgenic organisms as well as to institutions of European countries in charge of food control.

The recommendations consider long-term experience with one foodstuff to be a significant criterion for assessment. Experience gained over centuries demonstrates that even those foodstuffs that are known to contain toxins or antinutritive compounds are suitable for human consumption. Since all plants may contain potentially hazardous metabolic products, the beneficial quality of foodstuffs is determined by product-processing procedures and amounts consumed.

Considering the fact that traditional foodstuffs are not subject to scientific assessments with respect to health safety, genetically modified novel foodstuffs can only be assessed by comparison. Thus, a general strategy, labelled 'concept of substantial equivalence', has been suggested. It is based on a comparison of the novel food with traditional foodstuffs. In doing so, chemical, biological, agronomic and a plethora of other properties are compared with the

aim to determine if significant differences exist between the organisms or foods derived thereof.

If a novel foodstuff turns out to be basically identical to a traditional foodstuff, then the novel foodstuff can be treated in the same way as the reference product in terms of health hazards. If there are significant differences, then the extent to which they might compromise human health – for example by causing allergic reactions – will have to be assessed.

As occasion demands, additional in-vitro and in-vivo toxicity assays will be carried out, which may also comprise mutagenicity, reproductive, teratogenicity, and feeding tests over an extended period of time. Like additives, colouring agents and flavours obtained by means of transgenic organisms, isolated, chemically defined ingredients can be assayed with respect to health hazards by well-tried methods of food toxicology. For this purpose, comprehensive toxicity and mutagenicity tests as well as feedings tests with rodents are carried out. In addition, further tests assaying the metabolisms of compounds, their toxikokinetics, chronic toxicity, cancerogenesis, reproductive functions, teratogenicity, immunotoxicity, and neurotoxicity may be required. A conclusive assessment can only be settled by taking all results into account, because in animal experiments only certain quantities of complex foodstuffs can be administered without causing nutritional defects that compromise statements about toxicity.

6 Legal safety provisions

Important special provisions of law with respect to genetically modified plants and foodstuffs are the Genetic Engineering Law (based among other things on European guidelines), and the EC Novel Foods Directive.

6.1 Genetic Engineering Law

In Germany, the production and utilization of genetically modified organisms is regulated comprehensively by the Genetic Engineering Law in its revised form of December 16, 1993. The aim of the Genetic Engineering Law, among other things, is the protection of humans, animals, plants, and the environment against possible hazards of genetic engineering techniques and genetically engineered products as well as the prevention of such risks.

6.1.1 Generation and utilization of genetically modified plants

In contrast to plants obtained by conventional breeding techniques, plants modified by genetic engineering techniques are subject to an extensive safety assessment. This risk assessment is carried out in a step-by-step fashion and on a case-to-case basis. Findings are first obtained in the laboratory, then in the greenhouse, and eventually in the open field.

The generation and utilization of plants modified by genetic engineering in the laboratory or greenhouse, i. e. in closed systems, are already covered by provisions of the Genetic Engineering Law.

This law provides for four different safety levels, depending upon the risk potential for humans and the environment. At levels two to four, the establishment as well as the operation of the corresponding laboratories or facilities must be certified by the proper competent authorities, before organisms can be genetically modified or used. Level one just requires that competent authorities be notified.

The admissibility of each intended project has to be assessed by a case-specific authorization procedure. The applicant is obliged to thoroughly explain the project, to point out the safety measures, and to demonstrate that the facilities per se as well as the genetically modified plants do not bear risks for humans and the environment.

According to the Genetic Engineering Law, open-field trials involving genetically modified plants are also subject to approval in as much as they involve the release of genetically modified organisms. Deliberate release trials are those in which a genetically modified organism (GMO) is selectively set free in the environment. In contrast to closed systems, deliberate release does not involve a physical barrier preventing the contact of GMOs with the environment. In every single case, the crucial point is whether a physical barrier will prevent the horizontal gene transfer between GMOs and other organisms and hence the uncontrolled spread of GMOs into the natural environment. As a rule, this may not be possible with plants in open-field trials.

The licensing authority for deliberate release experiments with genetically modified plants is the Robert-Koch-Institut in Berlin. Other specific authorities involved in the assessment of a release application are the Biologische Bundesanstalt für Land- und Forstwirtschaft (Federal Biological Office for Agriculture and Forestry) and the Umweltbundesamt (Federal Office for the Environment). The Zentrale Kommission für die Biologische Sicherheit (ZKBS; Central Commission for Biological Safety), an expert advisory board, reviews and assesses the projected release experiment with respect to possible hazards for the environment.

Approval by state authorities is given only if all necessary safety requirements are guaranteed to be in compliance with current status of science and technology. In addition, it has to be demonstrated that adverse effects on humans and the environment that would be unjustifiable in proportion to the purpose of the release trial are not to be expected.

For these reasons, extensive information about the nature of the genetic modification, the genetically modified plant, as well as possible effects on the environment must be presented already upon application. The application must contain detailed statements concerning the biological safety of the genetically modified organism in the environment. The risk of outcrossing of newly introduced genes must be assessed and measures for the extensive prevention of outcrossing must be delineated (for example: shelter crops, protective zones). Open-field cultivation is only granted, if a comparison with conventionally bred crop plants shows that there are no further unjustifiable risks.

As with conventional breeds, *commercial cultivation* of genetically modified crop plants additionally requires registration at the Bundessortenamt (Federal Bureau for Plant Varieties) in Hannover according to the German Seed Act. If the variety was already licensed in other EC countries, it must be registered in the joint EC catalogue of varieties. Registration in the National List of Varieties is required for the putting on the market of seeds and presupposes successful completion of the review process. In the case of agricultural plant species, this also comprises, among other things, assessment in field tests, which may take several years.

6.1.2 Utilization of genetically modified micro-organisms in the production of foodstuffs

Also subject to regulation by the Genetic Engineering Law is the utilization of genetically modified micro-organisms (GMMO) such as bacteria, moulds, and yeasts in the production of foodstuffs. GMMOs are micro-organisms the generation and utilization of which is classified by the Genetic Engineering Law as work involving the use of genetic engineering techniques. Hence, generation and utilization consequently need to be carried out in an approved facility. By the same token, the release of GMMOs also requires approval.

6.1.3 Revision of the EC Deliberate Release Directive

After the Council of Ministers, the European Parliament too has approved the revised form of the EC Directive for GMO Deliberate Release on February 14, 2001.

In future, permits are only to be issued after intensified safety tests are passed in accordance with the precautionary principle. As a basic principle, permits to put GMO products into circulation will be limited to a period of ten years at most. Additionally, monitoring accompanying cultivation (ecological long-term surveillance) will be required to identify unexpected adverse effects for the environment or for human health as early as possible.

The use of antibiotic resistance markers in GMOs that may have detrimental effects for human health or the environment is to be abandoned gradually. The respective deadlines are the end of 2004 for putting GMO products into circulation and the end of 2008 for the release of GMOs.

The revised Deliberate Release Directive provides for more transparency of the application process as well as for the participation of the public therein. Information concerning all GMO release projects in the respective territory is to be made accessible to the public as well as the exchange of information between the competent authorities in charge and the commission. In the future, evaluation reports and statements of scientific committees for GMO products will also be open to the public.

The new provisions will have to be implemented as national laws by the end of 2002. Still in 2001, the European Commission plans to issue suitable regulatory propositions for the implementation of obligatory labelling of GMO products. So far, the directive merely contains arrangements requiring that the note "This product contains genetically modified organisms" be printed on the label or in a document accompanying the product. Furthermore, the commission has pledged to advance a legislative proposition before the end of 2001 that will also comprise damages caused by GMOs.

6.2 The Novel-Foods Directive of the EC

Since May 1997, EC Directive 258/97 concerning novel foods and food ingredients (Novel-Foods Directive) regulates in a legally binding fashion for all member states the putting on the market of novel foods. In contrast to traditional foods, these novel foods are subject to registration or notification and also have to meet additional requirements with respect to labelling. "Novel" foods, among other things, comprises foods that have not yet been used in the European Community at appreciable levels for human consumption and

– contain genetically modified organisms or are composed thereof, or
– were produced from genetically modified organisms but do not contain such organisms.

The Novel-Foods Directive thus also comprises genetically modified plants or products derived from such plants, as well as foods obtained by using GMMOs. There are certain prerequisites for the putting on the market of novel foods: they must not involve risks for the consumer, they must not deceive consumers, and normal consumption should not cause dietary deficiencies. Market introduction must be approved by the European Commission.

On principle, the Novel-Foods Directive does not cover food additives, flavours and extraction media, for which there are separate legal EC stipulations. In Germany, additives may be used only if they were approved specifically for this purpose in compliance with general Food Law.

6.3 Labelling regulations

In addition to general labelling regulations covered by Food Laws, the Novel-Foods Directive demands a particular label for foods that contain or consist of genetically modified organisms. In addition, foods that are no longer substantially equivalent to existing foods due to the application of genetic engineering are subject to specific labelling. This follows from the principle of consumer sovereignty,

i. e. the public must have a choice between conventional and genetically modified foods.

Special labelling regulations exist since September 1, 1998 for products derived from genetically modified maize or soybeans. Foods containing genetically modified soybeans or maize constituents must be labelled with "produced from genetically modified soybeans (or maize)".

A decree of the EC Commission from January 10, 2000 has introduced a threshold limit for labelling of products containing such additives. Additives containing at most one per cent of genetically modified soybean or maize constituents are exempt from compulsory labelling. However, this applies only if the genetically modified material is present in the additive, for example just by accidental unintentional contamination brought about by cultivation, harvest, transport, storage or processing.

In addition, a further decree of the Commission of January 20, 2000 stipulates labelling of foods and food ingredients obtained from additives and flavours produced from genetically modified organisms. Both decrees became effective on April 20, 2000. In Germany, food quality control authorities survey compliance with these decrees.

One additional decree of the Federal Ministry for Health from October 1998 must be mentioned. It specifies conditions under which foods may be labelled "free of genetic modification". This labelling is voluntary and may be used only if utilization of genetic engineering techniques has actually been excluded at all processing stages.

Supplementary suggestions aim at the extension of labelling to semi-finished goods and the integration and consolidation of individual labelling directives into a single regulation.

6.4 First draft of a Novel-Feed Directive of the EC

In July 2000, the EC Commission presented the first draft of a Novel-Feed Directive. Its aim is to establish a unified system for the assessment, registration, and labelling of genetically modified feeds. This directive comprises feeds that consist of, contain, or are derived

from genetically modified organisms. Exempt from this directive are additives and enzymes, even if they were obtained by means of genetically modified micro-organisms.

According to the draft of the EC Commission, Novel Feed should only be put on the market or utilized if, among other things, they do not bear any hazards to animal health, human health, or the environment. In addition, feedstuffs must not impair the quality of the animal product in a way that may be hazardous to the consumer. As a basic principle, approval of Novel Feed will be limited to ten years at most and can be withdrawn, if continuous scientific surveillance should suggest withdrawal. If Novel Feed consist of genetically modified organisms or if such organisms are detectable, arrangements are to be made for labelling either in the accompanying documents or on the packaging. The draft also requires that detailed information be provided about possible deviations of nutritional values, composition, and other variant properties in comparison to conventionally produced feeding stuffs.

7 References

Ammann, K., Y. Jacot and P. Rufener Al Mazayad (1996) Field release of transgenic crops in Switzerland, an ecological risk assessment of vertical gene flow. In: Schulze und Käppeli (eds.) (1996) Gentechnisch veränderte krankheits- und schädlingsresistente Nutzpflanzen. Eine Option für die Landwirtschaft? Vol. 1, Materialien, BATS, Basel.

Bartsch, D. and M. Pohl-Orff (1996) Ecological aspects of transgenic sugar beet: Transfer and expression of herbicide resistance in hybrids with wild beets. *Euphytica* **91**, 55–58.

Carpenter, J. and L. Gianessi (1999) Herbicide Tolerant Soybeans: Why Growers are Adopting Roundup Ready Varieties. AgBioForum Vol. 2 No. 2, http://www.agbioforum.org/

Chamberlain, D. and C. Neal Stewart (1999) Transgene escape and transplastomics. Nature Biotechnol. **17** (4), 330–331.

De Maagd, R.A., D. Bosch and W. Stiekema (1999) *Bacillus thuringiensis* toxin-mediated insect resistance in plants. Trends Plant Sci. **4** (1), 9–13.

Dietz-Pfeilstetter, A., A. Gland-Zwerger and V. Garbe (1999) Potential und Bewertung von Auskreuzungen aus gentechnisch verändertem Raps. Nachrichtenblatt des Deutschen Pflanzenschutzdienstes **51** (1), 14–19.

Düring, K., P. Porsch, M. Fladung and H. Lörz (1993) Transgenic potato plants resistant to the phytopathogenic bacterium *Erwinia caratovora*. Plant J. **3**, 587–598.

Fulton, F. and L. Keyowski (1999) The Producer Benefits of Herbicide-Resistant Canola. AgBioForum Vol. 2, No. 2, http://www.agbioforum.org/

Gould, F., A. Anderson, A. Jones, D. Sumerford, D.G. Heckel, J. Lopez, S. Micinski, R. Leonard and M. Laster (1997) Initial frequency of alleles for resistance to *Bacillus thuringiensis* toxins in field populations of *Heliothis virescens*. Proc. Natl. Acad. Sci. USA **94**, 3519–3523.

Hampel, J. and O. Renn (eds.) (1999) Gentechnik in der Öffentlichkeit. Wahrnehmung und Bewertung einer umstrittenen Technologie. Campus-Verlag, Frankfurt/New York.

Holmberg, N. and L. Bülow (1998) Improving stress tolerance in plants by gene transfer. Trends Plant Sci. **3** (2), 61–66.

Hols, P., M. Kleerebezem, A. N. Schank, T. Ferain, J. Hugenholtz, J. Delcour and W.M. De Vos (1999) Conversion of *Lactococcus lactis* from homo-

lactic to homoalanine fermentation through metabolic engineering. Nat. Biotechnol. **17**, 588–592.

Hugenholtz, J. (1993) Citrate metabolism in lactic bacteria. FEMS Microbiol. Rev. **12**, 165–178.

Jach, G., B. Görnhardt, J. Logemann, E. Pinsdorf, J. Mundy, J. Schell and C. Maas (1995) Enhanced quantitative resistance against fungal disease by combinatorial expression of different antifungal proteins in transgenic tabacco. Plant J. **8** (1), 97–109.

Jany, K.D. and R. Greiner (1998) Gentechnik und Lebensmittel. Berichte der Bundesforschungsanstalt für Ernährung, Karlsruhe.

Krebbers, E., S.C. Falco and G. Fader (1999) Modification of seed amino acid and protein composition for feed and food application. In: Plant Biotechnology and Food for the 21st Century, Nov. 3/4, 1999 (Colmar, France) – Nov. 5, 1999 (Freiburg, Germany), p. 10.

Liu, Y.-B., B.E. Tabashnik, T.J. Denehy, A.L. Patin and A.C. Bartlett (1999) Development time and resistance to Bt crops. Nature **400**, 519.

Losey, J.E., L.S. Rayor and M.E. Carter (1999) Transgenic pollen harms monarch larvae. Nature **399**, 214.

Mannerlöf, M., B.-L. Lennerfors and P. Tenning (1996) Reduced titer of BNYVV in transgenic sugar beets expressing the BNYVV coat protein. Euphytica **90**, 293–299.

Meyer R., C. Revermann and A. Sauter (1998) TA-Projekt „Gentechnik, Züchtung und Biodiversität“, TAB Arbeitsbericht Nr. 55, Büro für Technikfolgenabschätzung beim Deutschen Bundestag.

Monsanto (1998) Positionspapier: Gene Protection: Ein neues Verfahren zum Saatgutschutz. Unser Standpunkt.

Munkvold, G.P. and R.L. Helmich (1999) Genetically modified, insect resistant corn: Implications for disease management, APSnet Feature. http://www.apsnet.org/feature/Btcorn/Top.htm.

Nordlee, J.A., S.L. Taylor, J.A. Townsend, L.A. Thomas and R. Townsend (1996) Investigations of the Allergenicity of Brazil Nut 2S Seed Storage Protein in Transgenic Soybean. In: Food Safety Evaluation. OECD Documents 1996, 151–155.

Oerke, E.-C. and U. Steiner (1996) Ertragsverluste und Pflanzenschutz. Die Anbausituation für die wirtschaftlich wichtigsten Kulturpflanzen. Schriftenreihe der Deutschen Phytomedizinischen Gesellschaft, Band 6. Ulmer-Verlag, Stuttgart.

Potrykus, I. (1999) Genetic engineering for food security. In: Plant Biotechnology and Food for the 21st Century, Nov. 3/4, 1999 (Colmar, France) – Nov. 5, 1999 (Freiburg, Germany), p. 41.

Pühler, A. (1998): Gentechnik und Ökologie – Anmerkungen zum horizontalen Gentransfer beim landwirtschaftlichen Einsatz von transgenen Pflanzen. In: Thüringer Ministerium für Ernährung, Landwirtschaft, Naturschutz und Umwelt (ed.) Chancen und Risiken der Gentechnik im Umweltschutz. Tagungsband zur öffentlichen Anhörung der Umweltministerkonferenz am 06.–07. November 1997 in Erfurt, 35–39.

Ramachandran, S. et al. (1998) Survival, development, and oviposition of resistant diamondback moth (Lepidoptera: *Plutellidae*) on transgenic canola producing a *Bacillus thuringiensis* toxin. J. Economic Entomol. **91**, 1239–1244.

Royal Society (1999) GMOs and Pusztai – the Royal Society reviews the evidence. http://www.royalsoc.ac.uk/press/pr_15_99.htm.

Sarhan, F. and J. Danyluk (1998) Engineering cold tolerant crops – throwing the master switch. Trends Plant Sci. **3** (8), 289–290.

Saxena, D., S. Flaures and G. Stotzky (1999) Transgenic plants: Insecticidal toxin in root exudates from Bt corn. Nature **402**, 408.

Schuler T.H., G.M. Poppy, B.R. Kerry and I. Denholm (1998) Insect-resistant transgenic plants. TIBTECH April 1998, Vol. 16, 168–175.

Schulze, E. and O. Käppeli (1997) Gentechnisch veränderte krankheits- und schädlingsresistente Nutzpflanzen. Eine Option für die Landwirtschaft? Vol. 2, final report. BATS, Basel.

Smalla, K., F. Gebhard and H. Heuer (2000) Antibiotika-Resistenzgene als Marker in gentechnisch veränderten Pflanzen – Gefahr durch horizontalen Gentransfer? Nachrichtenblatt des Deutschen Pflanzenschutzdienstes **52** (3), 62–68.

Strittmatter, G., J. Janssens, C. Opsomer and J. Botterman (1995) Inhibition of Fungal Disease Development in Plants by Engineering Controlled Cell Death. Biotechnology **13**, 1085–1089.

Tabashnik, B.E. (1994) Evolution of resistance to *Bacillus thuringiensis*. Ann. Rev. Entomol. **39**, 47–79.

Tacke, E., F. Salamini and W. Rohde (1996) Genetic engineering of potato for broad spectrum protection against virus infection. Nature Biotechnol. **14**, 1597–1601.

USDA (1999) Frequently asked questions. What about the recent monarch butterfly study? http://www.aphis.usda.gov/biotechnology.

WBGU (Wissenschaftlicher Beirat der Bundesregierung Globale Umweltveränderungen) (1998) Welt im Wandel. Strategien zur Bewältigung globaler Umweltrisiken. Jahresgutachten (1998). Springer, Berlin Heidelberg New York, 108–117.

Zhu, B., T.H.H. Chen and P.H. Li (1996) Analysis of late-blight disease resistance and freezing tolerance in transgenic potato plants expressing sense and antisense genes for an osmotin-like protein. Planta **198**, 70–77.

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