Genetic engineering: Keeping the promise of the 21st century or opening Pandora's box?

BY MANUELA ZWEIMÜLLER

It is 50 years since the biggest scientific breakthrough of the twentieth century - the discovery of the structure of DNA by Watson and Crick from the Cavendish Laboratory at Cambridge University. Their results were based on the data collected through X-ray experiments by Franklin and Wilkins from King's College in London. In April 1953, the double helical structure of DNA – the secret of life - was published in the prestigious scientific journal *Nature*. Rosalind Franklin sadly died in 1958, but in 1962 Watson, Crick and Wilkins were awarded the Nobel Prize for Physiology or Medicine "for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material."

In November 1973, the first successful transfer of a gene to a bacterium using gene technology was carried out. This marked the beginning of the modern biotechnology era, which has rapidly developed ever since into a wide variety of techniques for a broad spectrum of applications. Controversy erupted almost at the birth of this new technology. Opponents and proponents keep the issue in the public eye. Their arguments are fought more often on an emotional level than on a rational level. Little by little, however, early scepticism appears to be giving way to hard facts and sober approaches to the technology's positive uses. In general, there is a greater acceptance of genetic engineering techniques in the pharmaceutical and medical sector, where direct benefits can be seen. By contrast, food and agricultural sector applications continue to lack public support in various European countries. As a consequence, since 1998 a *de facto* moratorium on genetically engineered plants exists in Europe.

Genetic engineering basics and terminology

Genetic engineering technology functions, in a nutshell, like the "cut and paste" in your word processing software. Certain passages can be exchanged with others and single words or letters altered. In common practice, biological tools are used to take genetic material out of a living organism, and to transfer a selected advantageous gene to a different one.

A defined property or ability can thus be inserted into the recipient organism from a donor organism's genetic material. The main prerequisite for gene technology is that the genetic make-up in the living organisms involved consists of the same substance and that the information contained therein works in the same way. With few exceptions, the genetic code is universal. In other words, genetic material is composed of the same building blocks in human beings, plants, animals and micro-organisms. DNA – and its characteristic double helix – is the root of nearly all genetic material.

Genes produce proteins which accomplish many tasks necessary to life. They give skin, for example, its necessary elasticity; they contribute to the digestion of food; and they help to fend off illness and disease. They also assist in the circulation of oxygen through blood. Gene technology enables a bacterium injected with the human insulin gene to produce the human protein that regulates blood sugar levels.

The methodology allows foreign genetic material to be inserted into almost every cell in order to transfer desired traits to an array of different living organisms. It enables species barriers to be overcome as in the case of a bacterial gene being introduced into a plant. The transfer of an individual, specific gene becomes a relatively simple matter compared with previous reliance on traditional breeding methods of natural selection or hybridisation. The technology allows selected genes to be altered or silenced.

Biotech is big business

As one of the key technologies of the 21st century, biotechnology is a major economic force. The technology has developed rapidly and areas of application are expanding all the time. Experts estimate that sales from genetically altered products – including genetically modified food – will grow by a double-digit figure per year in coming years.

According to Ernst & Young's global biotechnology report 2003 – "Beyond Borders" – there are more than 4,300 entrepreneurial companies involved in biotechnology worldwide, roughly 15% of which are listed on the stock exchange. The combined sales revenues of the total number of US and European companies climbed to almost US$ 40bn in 2002. The number of employees in the US and European biotech industry reached nearly 180,000 people in 2002. Entrepreneurial life sciences companies posted net losses in 2002 of more than US$ 2.8bn in Europe and US$ 9.4bn in the US. According to Ernst & Young, “the best days of the industry are ahead, not behind” even if there was a significant market downturn in 2001 and 2002.

This data refers only to entrepreneurial bioscience companies which Ernst & Young defines as those that use modern biotech methods to develop products or services to serve the needs of human or animal health, agricultural productivity, food processing, renewable resources or environmental affairs. The data thus excludes a range of well-established companies.

The overall industry is highly diverse, ranging from small start-ups focused exclusively on R&D to large-scale production and distribution/marketing of products by large corporations. At the moment, agricultural products (including agrochemicals and foods) make up roughly one-third of the overall biotech industry market share, and the remaining two-thirds of sales are accounted for by healthcare products. Up to now, the environmental services sector has played only a minor role.

Endless applications

Many of the application possibilities for biotechnology are in the healthcare sector (including pharmaceuticals and diagnostics). Farming, foods and environmental areas can also benefit from these methods. The broadest public acceptance for genetic engineering has been in the medical field, while less acceptance – particularly in Europe – has been seen for genetically modified foods. Detailed examples of the main genetic engineering applications are:

- *Medical:* Diagnosis and therapy possibilities for many different illnesses as well as the production of a variety of medicines. This sector also includes the transfer of genetic material to animals to provide disease resistance. However, the main prospective use of animals in healthcare is as drug factories, producing medicines – a method that is also called "gene *ph*arming." The most well-known substance manufactured for research purposes in such a way is alpha-1-antitrypsin for cystic fibrosis and was produced by using transgenic sheep in Scotland. The milk from these sheep contains the drug in significant amounts.

- *Food:* Here, experiments with plants and animals are carried out with a view to increasing the level and quality of agricultural and livestock food output. At present, the focus is on plants. The emergence of transgenic animals or products made from these is not on the immediate horizon. Nonetheless, some fish farms already breed genetically altered salmon, trout and carp which are larger than natural fish.

- *Environmental:* This area of research is aimed at reducing hazardous waste or pollution via transgenic organisms. Bioremediation employs micro-organisms engineered to degrade or detoxify targeted pollutants such as spilled oil. Phytoremediation uses plants to extract or promote degradation of toxic substances. So far there has been only basic research and no product marketing in this area.

Genetically modified organisms – To have and to have not

Genetically modified organisms can be used to produce individual substances or can be contained in the finished product such as a genetically altered plant or animal. They can be either part or the whole of the final product. Among the well-known substances produced using genetic engineering methods are human insulin and chymosin. Micro-organisms can manufacture both of these proteins in large quantities and to a high degree of purity when they carry the necessary gene. Millions of diabetics worldwide rely on genetically produced insulin. This medication has been available since the US Food and Drug Administration first approved it in 1982. Chymosin, for its part, is the first genetically engineered industrial food ingredient ever approved. This protein-degrading enzyme, which curdles milk, is used in cheese-making. In traditional cheese production cow's rennet fosters coagulation. Biotechnological production of chymosin enables UK cheese-makers to offer consumers a "vegetarian cheddar," and the product has been highly successful. These applications do not leave genetically modified organisms – living or dead – in the final products. Genetically modified organisms can also be directly added to products. One example is in fermentation processes such as beer brewing. Genetically optimised beer yeast can considerably simplify the entire brewing process as it transforms barley starch directly into malt sugars. These methods have already been approved for use in the UK. Genetically altered bacteria, too, will increasingly be used for waste reduction. For many years these natural properties of micro-organisms have been employed in public and industrial water purification and in soil decontamination. Gene technology will take this a step further as cell enzymes known to break down certain types of contamination can be transferred and produced. And the new "Mr. Clean" cells can be programmed to eat away at previously unreachable contamination. Along these lines, bio-filters are being discussed which should be able to filter and purify industrial pollution before it enters the atmosphere. There have been pilot tests using fungi to break down styrene resulting from plastics production. A classical example of genetically engineered organisms being marketed as products is the FlavrSavr™ tomato introduced in 1994 in the US. Scientists simply switched off the gene responsible for the tomato's spoiling. As a result, these tomatoes can ripen longer on the vine and they are more aromatic than green tomatoes picked too early and ripened artificially. In another case, oil and fats used to produce candy or salad oil are tailor-made for that purpose. Product optimisation is the watch-word in all these instances.

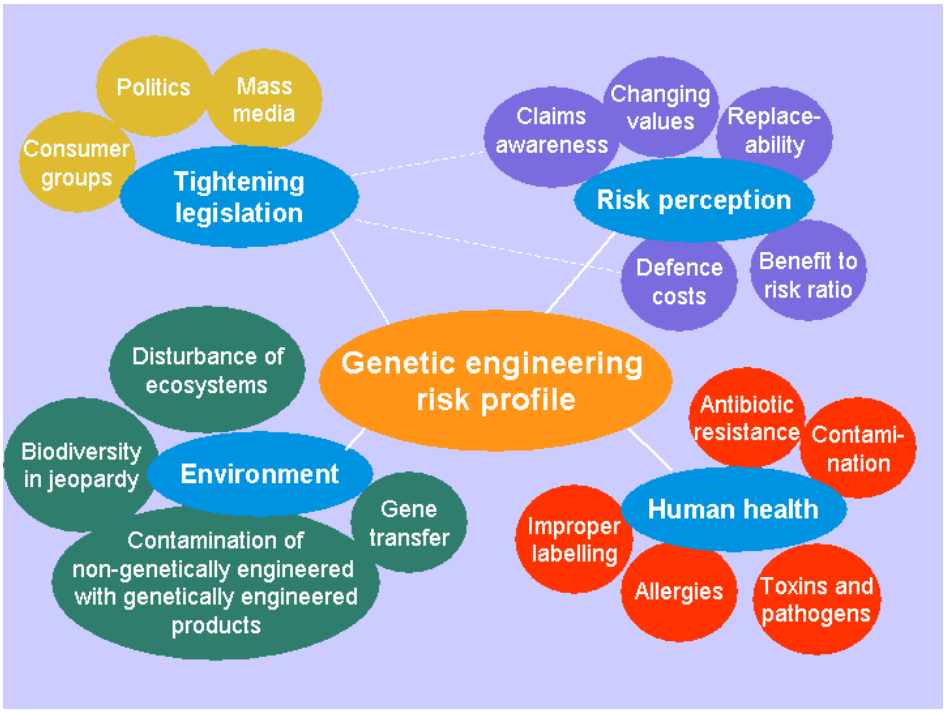

Fig. 1: Genetic engineering risk profile

Risks of genetic engineering

Niels Bohr – Nobel Prize Laureate for Physics in 1922 – pointed out that "predictions are difficult, especially about the future". It is indeed very difficult to determine the exact risk profile of genetic engineering as it is a very complex issue composed of diverse facets – social, ethical, scientific and legal. It is impossible to predict all future hazards linked to genetic engineering and their consequences. In addition, as genetic engineering enters new markets with new applications, problems may take time to show up.

Very early in the history of genetic engineering, the scientists involved took risks seriously. In 1974 they initiated voluntary deferment of certain experiments involving animal viruses, antibiotic resistance genes, toxins and cancer-promoting genes until disarmed (weakened) safe strains were developed and suitable safety procedures were established. The Asilomar Conference in 1975 resulted in a vote both to continue research and to develop a useful safety code. The following year the US National Institutes of Health (NIH) published guidelines which defined various safety levels and specific biological and physical containment measures. This NIH standard became the model for numerous national regulations worldwide guaranteeing a high degree of biosafety. However, regulation of genetic engineering liability varies from country to country. European Union directives on deliberate release and on contained use of genetically modified organisms have also been based upon these guidelines. The former already became stricter and includes now a far more thorough analysis of the consequences for agriculture and the ecosystem prior to approval (Directive 2001/18/EC). The amendment came into force in March 2001 and had to be implemented by the Member States by October 2002. However, at present most of the Member States have not yet transferred this directive into national legislation. In addition, new regulations on traceability and labelling of genetically modified organisms of food and feed products produced from genetically modified organisms will come into force in spring 2004.

In general, in the industrialized nations, genetic engineering is effectively regulated. Scientists must register experiments with regulators; at higher biosafety levels, official authorization is necessary. Marketing and sales of genetically engineered products also requires regulatory approval. It is said that no food products are tested more rigorously than genetically engineered food. Germany is the world leader in biosafety research. However, some countries in South America and Eastern Europe, for example, do not yet have such regulations. So far there have been no serious accidents affecting either human health or the environment.

Genetic engineering risk assessment follows the same main rules as for any other industry regarding risk prevention, loss limitation and damage repair measures. A genetically modified organism, for example, has to be tested to see if it is infectious or can cause diseases, whether the gene could be transferred to another organism, and whether medications exist to prevent infection or to treat disease. Genetic engineering risks are also compared to traditional manufacturing or conventional product hazards.

Although sophisticated biosafety systems and regulations are in place, the question about potential hazards, which could convert into losses, remains. The following real-life examples illustrate the genetic engineering risk problem:

- An 18-year-old boy died shortly after having been treated with genetically altered viruses during gene therapy. Allegedly, the dose was too high.

- In Paris, France several infants received new genetic material to combat a life-threatening disease called Severe Combined Immunodeficiency (SCID). Usually, patients with SCID are forced to live in tightly-controlled, sterile "bubbles" to avoid threats to their non-existent immune systems. However, last December two of the eleven successfully treated “bubble babies” developed leukaemia as a severe side effect. As a consequence, several gene therapy trials have been suspended.

- In May 1999, the public was horrified by findings that monarch butterfly larvae do not survive ingestion of Bt maize pollen. Bt is a bacterial toxin – harmless to humans, but very effective against insect larvae. It has been used in biological pest control for decades. Concerns have been raised that not only pests, but also useful species may be affected as the transgenic pollen is spread with the wind. However, the laboratory results could not be proven in field trials.

- In September 2000, some 300 products containing StarLink™ maize were recalled in the USA, including taco chips and corn flakes. This genetically modified pest-resistant maize variety which had only been approved for use as animal feed had been mixed with conventional maize varieties for human consumption. The financial consequences for the manufacturer were considerable and included – among other things – buying back contaminated shipments, a decline in price, monitoring and test programmes as well as provisions for liability claims and recall costs.

- To date, between 70 and 80 potential allergy cases have been reported in the USA in conjunction with StarLink™. The conclusion reached so far is that only 28 people suffered from genuine allergies. However, antibodies against the foreign protein Cry9c could not be detected in any of these people. Experts believe that these results make it highly unlikely that the allergies were caused by this protein introduced by genetic engineering. Further studies will follow, nevertheless.

- In a field trial, genetically engineered rapeseed pollen spread to a weedy wild relative producing hybrid plants, which kept their weedy nature and, in addition, propagated

well. The transfer of genetically engineered maize genes to neighbouring fields with unaltered maize has also been observed.

All these examples show the main problems of genetic engineering-related risks and claims: establishing a clear causal link could be difficult. Defining or determining a genetic engineering damage is equally problematic, but the general public's view will probably play a key role.

Human health risks

The health of a consumer, an employee working in a genetic engineering lab or a third party could be affected by the technology. A few health risks are outlined here:

- *Antibiotic resistance genes:* These genes were initially used to label the successful transfer of a foreign gene. Now there are other means of tracing gene insertion. It is well known that the treatment of bacterial infection is becoming more and more difficult due to the excess use of antibiotics in animal feeding as well as in hospitals. Although the public fears that antibiotic resistance genes could be transferred to bacteria living in the human digestive tract, this risk is scientifically negligible. Amongst other provisions, the revised deliberate release Directive (2001/18/EC) calls for the phasing out of antibiotic resistance marker genes for genetically modified organisms placed on the market by 31 December 2004 and for experimental genetically modified organisms possibly by 31 December 2008. The EU action is seen to be a precautionary approach to antibiotic resistance marker genes since no clear evidence regarding their health impacts currently exists.

- *Food allergies:* The labelling of genetically engineered food is important so that consumers know which new proteins or other substances have been added. There may be increased complaints and even claims when consumers blame their allergies on genetically engineered food. In general, genetic engineering may contribute to the increased prevalence of food allergies because almost every protein can be transferred into any species, and this could be done more frequently. On the other hand, genetic engineering assists in the production of some allergen-free food such as anti-allergy peanuts. In any case, genetically engineered food undergoes rigorous allergy testing.

- *Pathogenic contamination and toxins:* The risks of disease-causing or poisonous effects also have to be considered with any foodstuff or pharmaceutical drugs. They cannot be regarded as specific to genetic engineering.

Environmental risks

Presently, hazards arising out of the deliberate release of genetically modified organisms are the most difficult to assess. Once released in field trials or on a commercial scale, genetically modified organisms cannot be withdrawn. We can observe a peaceful coexistence of natural and biotech flora and fauna, but we could also be confronted with the possibility of a reduction in the number of natural species or a spread of genetic material disturbing the ecological balance.

- *Gene transfer:* The main risk in the environmental sector is the transfer of genetically altered or newly integrated foreign genes. Control and safety measures are possible, however, like sterile pollen, excluding wild relatives nearby, avoiding neighbouring fields with the same crop species and keeping a certain distance to the next field. The risk of cross-pollination to weedy wild relatives (“out-crossing”) is considered low in

Europe and in the US but significantly higher in countries like Mexico or Costa Rica where wild relatives of crop species are native. However, for organic farmers, "genetic contamination" through gene transfer via pollen or soil bacteria could lead to substantial financial loss. Cross-contamination could also occur during harvest, transport, storage or further processing.

- *Loss of engineered traits, adaptation:* The loss of specifically engineered resistance genes could have an effect on the environment or at least present a financial loss if the product fails to perform as expected. Engineered resistance is estimated to last only between 7 and 15 years. Adaptation of pests or weeds to genetically engineered resistance may additionally occur, but this also takes place with chemical pesticides.

- *Biodiversity loss:* Some fear that genetic engineering may deplete genetic variety such as for crop plants, thereby eliminating important genetic traits. However, the reduction of genetic resources has occurred for years through inbreeding. In fact, genetic engineering methods could contribute to preserving a broad genetic basis. In February 2000, the European Commission has adopted the White Paper on Environmental Liability including compensation for damage to biodiversity. The White Paper also mentions genetically modified organisms as a potential cause of damage to natural resources. In addition, the Cartagena Protocol on Biosafety enters into force on September 11, 2003. It deals with the safe transfer, handling and use of living genetically modified organisms across country boundaries.

Risk perception and insurability

Scientifically, genetic engineering is much less hazardous than the public perceives it to be. In the medical field, there is no longer any discussion about using drugs or vaccines manufactured with the help of genetic engineering methods. In the agricultural and food sector, where a direct benefit for the consumer has not yet been recognized, genetic engineering rejection is prevalent. Interestingly, scientists consider some medical applications (such as xenotransplantation or gene therapy) to be far more risky than food sector applications. The insurance industry, for its part, sees genetic engineering as a new risk characterized by a lack of experience in losses and underwriting practice. In addition, genetic engineering is a potential long-tail and development risk. Scenarios with cumulative exposure exist where genetic engineering could affect several insurance policyholders, e.g. seed companies, farmers and food manufacturers. At present, most genetically engineered product and lab risks are covered under existing insurance policies for large corporations. However, pure biotech start-ups may find it difficult to insure all of their activities. While some markets offer specific biotech coverage, others operate with genetic engineering exclusions. Few insurers offer property coverage for the genetically modified organism itself which would encompass replacement and disposal costs in case of damage. In the past, some UK insurers were even willing to provide cross-pollination coverage to farmers. For organic farmers, "genetic contamination" through gene transfer could lead to substantial financial loss. However, such "pollution" could also occur during harvest or further processing as measures for strict separation of genetically engineered and non-genetically engineered crops are not 100% effective. Therefore, permissible thresholds of 0.9% of product contamination have now been set in the European Union. Ecological damage reducing biodiversity and disturbing ecosystems cannot generally be insured with conventional products. Changes in the European Union's Products Liability Directive already led to strict liability for primary agricultural products (e.g. tomatoes, potatoes) – genetically engineered or not – facilitating potential claims for compensation.

Conclusion

In sum, the biotechnology sector offers something for everyone. Many people afflicted with various diseases can no longer live without new medications such as genetically engineered insulin and diagnostic tests.

Consumers, for their part, gain a greater choice of products with new properties. Here, it is imperative that clear and sufficient labelling of products underscore this freedom of choice – now having been taken care of by new European regulations. The overall verdict is that the positive opportunities of genetic engineering outweigh potential risks: the cure for AIDS or cancer could be right around the corner. Nevertheless, the potential risks to human health and the environment should not be overlooked. Public perceptions of these risks, however, diverge greatly from scientifically proven dangers. Public risk perception is thus a critical issue with a powerful influence on claims. In response to public pressure, courts may, for example, apply new and unforeseen standards retrospectively, imposing liability on industry and its insurers.

Thorough risk assessment and further biosafety research are indispensable. Genetic engineering is a typical example of a risk of change where an early-warning system should be installed to recognize trends and review risk analysis. Genetic engineering should not be looked at solely with a view towards opportunities or hazards. This complicated issue demands a comprehensive examination. In the future, a more open dialogue between consumers, biotech experts, industry, insurers and legal bodies is desirable.

Internet links

http://www.rki.de/GENTEC/INVERKEHR/INVKLIST_E.HTM
http://vm.cfsan.fda.gov/~lrd/biocon.html
http://webdomino1.oecd.org/ehs/bioprod.nsf
http://www.binas.unido.org/binas

For further information contact

Dr. Manuela Zweimüller
Munich Re Group
Corporate Underwriting Global Clients CUGC1.4.1
Casualty Risk Consulting (CRC)
80791 Munich
Germany
E-mail: mzweimueller@munichre.com

About the author

Dr. Manuela Zweimüller has been a biosciences risk consultant with Munich Re since January 2001 and is responsible for assessing the risks of biotech, pharmaceutical and food companies. She has many years of experience in primary insurance, having worked also in London, Sydney and Singapore. Dr. Zweimüller headed an international and interdisciplinary working group on genetic engineering and is author of various publications on this topic. She was also an invited speaker to several insurance conferences. Within Munich Re's Centre of Competence for Biosciences, Manuela Zweimüller represents the casualty field of business. This year, Dr. Zweimüller completed an intensive course in economics with focus on strategic management, marketing, leadership and organizational skills as well as business process optimisation and workflow management. Manuela Zweimüller holds a PhD in biochemistry from the University of Munich.

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