ENVIRONMENTALLY SOUND MANAGEMENT OF BIOTECHNOLOGY IN JAPAN

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Summary

Biotechnology involves the application of biological knowledge and techniques to produce substances and services beneficial to agriculture, the environment, industry and medicine. In Japan, biotechnology methods, such as tissue culture and recombinant DNA (rDNA) techniques have been applied to agriculture, food, medicine, mining and manufacturing industries. The technique of tissue culture and rDNA was widely used for the production of virus-free seedlings and the breeding of new varieties of crops. Cell fusion techniques were applied to microorganisms used for food and food additive manufacturing as well as in medicine production. Embryo transfer techniques were

applied to the livestock and fishery.

The rDNA technique is expected to bring a great deal for the progress in the improvement of breeding technology and development of plants, animals and microorganisms. The application of rDNA technology among the different kinds of biotechnology has the possibility to create new gene combination which had not previously existed in nature. With this reasoning in mind, Japan has set the guidelines for the rDNA experiments and for the industrial usage of the rDNA. At the experiment level, the guidelines are set by Ministry of Education, Sports, Sciences and Technology (MEXT). Its describes about the basic discretion for safety assessment, training and health control of researchers, the organization of the institute and the system construction to ensure the security at the experiments. At the industrial level, the guidelines are set by Ministry of Agriculture Fishery and Forestry (MAFF), Ministry of Health, Labor, and Welfare (MHLW) and Ministry of Economic, Trade and Industry (METI). The guidelines of MAFF and METI are evaluating of mainly the environmental and ecological effects of the rDNA and the guidelines of MHLW are evaluating mainly the effects to the human health.

At present, many species of the transgenic plants have been developed in Japan and complied the safety assessment with the guidelines. One of the challenges of biotechnology currently is the feeling of anxiety regarding the safety of the genetically modified organisms (GMO) as food. Regarding these cases, the government of Japan started to establish its policy for the companies on the requirement for labeling of food containing GMO, so that people are informed and have choice.

1. Introduction

In view of the growing population on the earth, improvements in science and technology have assumed a great role in the 20th and 21st centuries. Biotechnology, such as tissue culture, cell and embryo manipulation techniques and recombinant DNA (rDNA) techniques, also had contributed greatly. Especially, since the establishment of the rDNA techniques, and with the progress in molecular biology, the technology using rDNA has been applied to agriculture, food, medicine, mining and manufacturing industries. Simultaneously, increased importance of this technology brought the necessity of appropriate management, such as ensuring safety and protection of the environment.

In Japan, biotechnology is already being widely used in such areas as breeding of plant, animal and microorganisms applied to agriculture, food and medicine production, mining and manufacturing industries, environmental conservation, and so on. And the Government of Japan is determined to continue to conduct these activities in each of the fields as given below. In addition, it is expected to continue to involve itself in the spread of the results of these activities in various fields and to promote international cooperation with regard to the above mentioned.

The council of ministers for Global Environmental Conservation decided the National Action Plan for Agenda 21 on 24 December, 1993, followed by the submission to the United Nations at the beginning of 1994. The Chapter 16 of this Agenda;

ENVIRONMENTALLY SOUND MANAGEMENT OF BIOTECHNOLOGY IN JAPAN, consists of five plans which were (A) Increasing availability of food, feed and Renewable Raw Materials, (B) Improving Human Health, (C) Enhancing Protection of the Environment, (D) Enhancing Safety and Developing International Mechanism and Cooperation, (E) Establishing Enabling Mechanisms for the Environment Sound Application of Biotechnology. At present, these plans were put into practice and the fruit of these were applied to the various fields.

In this chapter, the guidelines for rDNA technology on the levels of research and industrial uses in Japan which have been implemented by the ministries and agencies of Japanese government for the safety measures are introduced as well as the permitted case at the levels of industries; also, referenced to the recent issue of labeling genetically modified (GM) food in Japan.

2. Current Status of the Biotechnology Products Accepted in Japan

2.1. Food, Feed and Renewable Raw Materials

2.1.1. Crops

For the propagation and breeding of superior strains, the techniques of tissue culture, cell fusion and rDNA have been applied. As the application of the cell culture, the embryo culture and other culture techniques which involve mutant appearance are used for breeding of the new varieties of rice, vegetables and fruit trees. At present, seventy percent of the strawberry seedlings and most of the orchids sold in the Japanese market are virus free by using the results of the cell culture technique. As the application of the cell fusion, a novel plant oretachi which is a cross between orange (*Citrus sinensis*) and karatachi (*Citrus trifoliata*) has been developed. The varieties of rice, strawberry, spring onion, lily, citrus fruit, tobacco and hiratake (edible mushroom) are improved by using the cell fusion techniques and appear in the market. Using rDNA technique, it is expected to bring out a great progress in breeding technology. Transgenic carnation, developed by Suntory with light bluish purple flower has appeared since the October 1997. This flower is already started to be grown at the contracted farmers and commercialized. In Japan, great numbers of the transgenic plants have been already developed and are on going for examination (Appendixes 1 and 2) . At present in 1999, field 78 of the rDNA crops are under investigation for practical use including field examination. Pathogenic resistant rice (1994, Ministry of Agriculture and Forestry (MAFF), tomato(1992, 1996, MAFF), melon(1996, MAFF), petunia (1994, Suntory) and low allergen rice(1995, Mitsui Toatsu) have finished the examination at the ordinary field and approved to have complied with the Guidelines. Also, low protein sake brewery rice is ready for the open field cultivation. The researches using rDNA plant development have been carried out to enable growth at extreme situations such as cold tolerant, drought and salt resistant, and improved greatly high productivity through enhancing the ability of photosynthesis and nitrogen fixation, and containing physiologically functional ingredients, and the high efficient energy productive plants instead of fossil fuels. Further, Japan has been taking a leading part in investigating rice genome analysis as national project of the ‘Rice Genome Project’, obtaining good amount of positive results.

Though, except the transgenic carnation, rDNA plants are still not made to be commercialized. At present in 1999, 29 transgenic crops, i.e., soybean, canola, corn, potato, cotton and sugar beet which were resistant to herbicides and diseases or ripening delayed, have complied with the safety assessments with the guidelines required in Japan, either in the means of food, feed or human usage, or the means of environmental effect. Public acceptance is necessary for further promotion towards consumption.

2.1.2. Livestock

Especially for calves production which has progressed in Japan, mass production of excellent calves has been carried out using embryo from one superior cow transferred to other ordinary cows. This technique is already made practicable in Japan. The number of the calves born through embryo transfer techniques is increasing and some 13,000 calves were born in 1995. Research on *in vitro* fertilization and nuclear transplantation is also carried out. Some 1,200 calves were born through *in vitro* fertilization in 1995, and successful experiments for producing clone calves through nuclear transplantation were reported in1993. The techniques using an embryo or a somatic cell for mass production of the cloned calves are carried out for experiments in Japan. Current topic was the somatic cell clone of animal since the first sheep 'Dolly' was born at Roslin Institute, Edinburgh, in 1996. Following this, in Japan, in September 1998, there were seven somatic clone calves growing and 68 pregnant cows on the experiments. The rDNA techniques were used for the production of recombinant live vaccine for cattle leukemia with which the inoculation test has been already started. Live vaccine of swine Aujesky disease virus developed by genetic engineering and also a cat interferon produced in silk worm are practically applied. Development of recombinant livestock for the production of useful substances or recombinant swine for organ transplant with the experiments of the test production has been carried out. DNA analysis of the fertilized egg is used for the selection of the sex in cattle production. Genome analysis of the livestock is also on going within cattle and swine, in Japan.

2.1.3. Forest and Aquatic Products

Investigations for the breeding of cedar which scatters lower amount of pollen, low lignin containing cedar for pulp production for paper manufacturing have been carried out as well as the mass production of the difficult-to- raise nursery trees are carried out using cell or tissue culture and rDNA techniques.

For the increase of the fish productivity, triploid and female fish were produced by ova and embryo manipulation (e.g. rainbow trout, flat fish). The Fisheries Agency showed the guidelines for the Utilization of Triploid Fish and others in 1992 for appropriate application of this technology in aquaculture. The guidelines pointed out the characteristics which should be tested before the practical application of such fish. Eleven lines had been tested by 1996.

Novel materials for the surgery thread were produced from the shell of shrimps and crabs. Fibronectin used for pearl cultivation was produced using rDNA techniques. The rDNA researches applied for the development of eel cultivation technologies through

embryo manipulation, and producing recombinant rainbow trout in Japan are now taking a leading part in the world.

2.1.4. Microorganisms

Japan has been leading the technology in the field of microbiology or fermentation for some decades such as amino acid and nucleotide fermentation (production of sodium mono glutamate, sodium inosinate etc). Baker's yeast available for freeze stock as well as novel strains of koji (mold used in the saccharification of rice starch before brewing of sake) and improvement of brewer's yeast used in shochu (Japanese spirit) production has been developed using cell fusion techniques. Bioreactors containing fixed enzymes and microorganisms are applied for sugar production (high fructose syrups and cyclo-dextrin and erythritol) and for the fermentation of alcohol nowadays. Chymosin, the enzyme used in cheese manufacturing, was produced using recombinant microorganisms at present in the EU and USA which also will be commercialized soon in Japan.

2.2. Improvement in Human Health

Many of medical supplies, industrial enzymes and reagents are produced by using recombinant DNA techniques. Human interferon and insulin are already put on practical use as well as the detergent additive enzymes. These are now sharing a big part in the market. Japan is one of the world's largest markets of pharmaceuticals. The In fiscal year 1989 about 8 per cent of all pharmaceuticals is imported, 17 per cent is manufactured by foreign companies, while an additional 20 per cent is produced by a Japanese company. At present, many of medical supplies, industrial enzymes and reagents are produced by using rDNA techniques in Japan. The most successful biotechnological drug is interferon produced in cell culture, which is used in the treatment of hepatitis C. Important manufacturers are *Takeda Chemical*, the largest Japanese drug company, and *Yamanouchi*. Other successful biomedicines produced by rDNA technology are human insulin by *Shionogi*, human growth hormone by *Sumitomo Chemical* and *Yamanouchi*, granulocyte colony stimulating factor (GCSF) and erythropoietin (EPO) by *Chugai*, *Kirin* and *Sankyo*. Human interferon and insulin are already put on practical use as well as the detergent additive enzymes. These are now sharing a big part in the market in Japan.

3. The Management carried out for Biotechnology Techniques in Japan

Cell and tissue cultures including the embryo and other culture techniques were widely used for the production of virus-free seedlings and the breeding of new varieties of crops. Most of the strawberry seedlings in Japan are virus-free using the tissue culture techniques, and also the new variety of rice, vegetables and fruit trees were bred by using these techniques. Cell fusion techniques were also applied to breeding not only for plants but also for microorganisms used for food and food additive manufacturing as well as in medicine production. Embryo transfer techniques were applied to the livestock and fishery. Especially for calves production which has progressed in Japan, mass production of superior calves has been carried out using transfer techniques of fertilized eggs from one cow. Current topic was the somatic cell clone of animal since

the first sheep 'Dolly' was born at Roslin Institute, Edinburgh, in 1996. Following this, in Japan, in September 1998, there are seven somatic clone calves growing and 68 pregnant cows to be going on for the experiments. The techniques mentioned above are not considered to be the targets for controls because the genes of these organisms have not been modified. Though, applying of these techniques to produce the clone of human must be argued as a problem of bioethics which most of the advanced countries including Japan have not permitted.

The rDNA technique is expected to bring a great deal of progress in the improvement of breeding technology and development of plants, animals and microorganisms which having novel characteristics. A great number of the researches have been carried out in Japan so far and some of the results were to be marketed. Blue carnation could be given as an instance. On the other hand, there was anxiety that the genetically engineered organisms may get out of human control and may be cause the appearance of unexpected creatures. For this reason, following the National Institute of Health (NIH) of the U.S.A., Japan has set the guidelines for the rDNA experiments and for the industrial usage of the rDNA.

Japan has taken adopted safety measures and conducted scientifically and appropriately rDNA research, taking maximum account of potential risks of each research at the various stages, until sufficient knowledge has been accumulated. Because the application of rDNA technology, among the different kinds of biotechnology, has the possibility to create new gene combinations which had not previously existed in nature. However, as the recent scientific knowledge accumulated so far has clarified that initial imaginary risks of rDNA technology were too exaggerated, Japan has gradually relaxed these restrictions. In the fact, on the basis of several guidelines established by some ministries and agencies, research and industrial application of rDNA has been managed, and at present there has not been known of any environmental problems due to the use of biotechnology, including rDNA technology.

3.1. Background

The discussion of the measures for the security concerning to rDNA techniques were started to work out at the Asilomar Conference on Recombinant DNA Molecules at California, 1975. In this conference, the details for the security measures were discussed on the assumption of the existence of 'unknown risk' to the rDNA as a new technology with the prudential view, on the basis that self-control should be exercised by those who are concerned. Based on the discussion in this conference, 'NIH Guidelines for Research Involving Recombinant DNA Molecules' was established in 1976, which has been playing the leading part of the global standard there after. The Reports of National Academy of Science U.S.A. of 1987 and 1989 have shown the view that there is no evidence of any particular danger in rDNA techniques.

For the industrial usage of this technology, security measures concerning rDNA techniques were started in 1983 at Organization of Economic Cooperation and Development (OECD)/ Committee for Scientific and Technological Policy (CSTP) in the Organization for Economic Cooperation and Development on the basis of the accumulation of scientific knowledge as well as from the view of promoting

international harmonization in regard to safety policies. In 1986, the report by the OECD, 'Recombinant DNA Safety Considerations' on the industrial, agricultural and environmental application was published which showed the perception that there is no scientific reason to regulate the usage of rDNA by law.

In Japan, referring to NIH guideline, with the basic recognition for the security measures of rDNA at the level of research as 'It is not appropriate to impose legal controls on the research which has no evidence for the dangerousness', the guidelines were set by Ministry of Education, Science, Sports and Culture (MONBU) and Science and Technology Agency (STA) within a short time span from each other in 1979 for the purpose to promote self-control of the researcher. On the other hand, discussions on the guidelines for safety measures at industrial level were carried out on the basis of OECD counsel of 1986. As the result, the guidelines were set by the Ministry of Health and Welfare (MHW), Ministry of Agriculture Fishery and Forestry (MAFF) and Ministry of International Trade and Industry (MITI), and so far the measures for safety are promoted by the organizations or its operator with the principle of the self-control.

Since the reorganization of the government carried out in 2001, these guidelines are implemented by Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labor and Welfare (MHLW), Ministry of Agriculture Fishery and Forestry (MAFF) and Ministry of Economy, Trade and Industry (METT) in present.

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Biographical Sketches

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