

Ministry of Health and Welfare Announcement No. 233

According to the Specifications and Standards for Foods, Food Additives and Other Related Products (Ministry of Health and Welfare Announcement No.370-December 1954) amended by new Announcement (Announcement No. 232), Procedure of Application for Safety Assessment of Foods and Food Additives Produced by Recombinant DNA Techniques is hereby determined as follows.

Even if application is not made based on the provision defined in paragraph 1 of Article 3 of this Announcement, the Minister can examine safety assessment of such foods and food additives, if the Minister has already possessed necessary documents for the safety assessments in applying this Announcement.

1st May, 2000

Minister for Health and Welfare Yuya Niwa

Procedures of Application for Safety Assessment of Foods and Food Additives Produced by Recombinant DNA Techniques

APPLICATION

Article 1. Regarding foods and food additives produced by recombinant DNA techniques, this Announcement determines procedure of application for safety assessment based on the provisions defined in paragraphs 3 and 4 of Part 1, Section A and in Part 2, Section D of the Specifications and Standards for Foods, Food Additives and Other Related Products (Ministry of Health and Welfare Announcement No. 370-Dec.1959).

DEFINITION

Article 2. In this Announcement, the term “recombinant DNA techniques” means a technology that DNA cleaved or recombined by, for example, by enzymes, is transferred to living cells for proliferation.

2. In this Announcement, the term “host” means a living cell or an individual organism to which DNA is transferred through recombinant DNA techniques.

3. In this Announcement, the term “vector” means a carrier DNA that transfers the target genes into hosts for proliferation and expression.

4. In this Announcement, the term “inserted gene” means a foreign gene inserted into vectors.

5. In this Announcement, the term “inserted DNA” means a foreign DNA inserted into vectors.

6. In this Announcement, the term “product” means any substance produced by recombinant DNA techniques.

7. In this Announcement, the term “recombinant” means a host containing recombinant DNA.

8. In this Announcement, the term “gene product” means nucleic acid or protein

originated by inserted genes.

SAFETY ASSESSMENT

Article 3. When an application document for safety assessment of food or food additive produced by recombinant DNA techniques is submitted by its developer, its agent or other party who can submit appropriate necessary information, the Minister for Health and Welfare shall examine the safety assessment of such food or food additive. If a food is an organism or made of / made from the organism produced by recombinant DNA techniques or includes such organisms, examination for the safety assessment of such food shall be performed on each organism basis. If foods or food additives are manufactured by use of organisms produced by recombinant DNA techniques or include such organisms, examination for the safety assessment of such foods or food additives shall be performed on each item of such food or food additive basis.

2. The examination for safety assessment designated in the preceding paragraph shall be based on consultation with the Food Safety Investigation Council. If any risk injurious to human health is not found on the assessment, the result of the examination for the safety assessment shall be officially announced.

3. Any person who intends to undergo examination for safety assessment in accordance with first paragraph of this Article shall submit an application form as stated in the attached exhibit together with the information as listed in the appendixes.

REASSESSMENT

Article 4. When, due to new scientific findings or any other reasons, it is deemed necessary to reassess safety of the foods and food additives that have already been undergone the examination in accordance with paragraph 2 of the preceding Article, the Minister for Health and Welfare shall reassess safety of such foods and food additives based on consultation with the Food Safety Investigation Council. The results of reassessment shall be officially announced, if any risk injurious to human health is found.

DIRECTIONS ON PROGENY CULTIVAR

Article 5. Among cultivars prepared by cross hybridization between a conventional cultivar and a recombinant cultivar that has been undergone examination for safety assessment in accordance with the provision stated in preceding Article, paragraph 2, by use of traditional breeding techniques (hereinafter referred to as "progeny cultivar"), if there are certain progeny cultivar that comply with the following requirements, such progeny cultivar can be regarded as the cultivar that has passed the examination based on the identical provision.

1. Properties that are newly acquired through recombinant DNA techniques have not changed in progeny cultivar.
2. Crossbreeding between subspecies has not been performed.
3. There is no change in the amount of ingestion, edible part or processing methods,

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etc.

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Exhibit Form

(Date)

The Minister for Health and Welfare:

Address (Principal office address for corporate entity)
Name (Corporate name and corporate representative name for corporate entity)

In accordance with “Procedures of Application for Safety Assessment of Foods and Food Additives Produced by Recombinant DNA Techniques” (The Ministry of Health and Welfare Announcement No.233 -May 2000), we hereby request for your examination for safety assessment of the attached items:

Foods produced by recombinant DNA techniques
Food Additives produced by recombinant DNA techniques

Note:

1. Use Japan Industrial Standard A4 size paper
2. Write in block letter with India ink, black ink, *etc.*

Appendix 1 INFORMATION REQUIRED FOR SAFETY ASSESSMENT WHEN
FOODS ARE OR INCLUDE ORGANISMS OBTAINED THROUGH RECOMBINANT
DNA TECHNIQUES

- I. Information Regarding equivalency between Produced Food and Existing Food
 1. Information on the genetic materials
 2. Information on broad human consumption history
 3. Information on nutritional components of foods
 4. Information on differences in usage between the conventional variety and the new variety

- II. Purposes and usage of recombinants

- III. Information Regarding Host
 1. Taxonomy (Scientific name, species and strain)
 2. Genetic origin
 3. Production of harmful physiologically active substances
 4. Allergenicity
 5. Capability of becoming parasitic and striking root
 6. Foreign pathogenic factors (*e.g.* virus) (a host should not be contaminated with pathogenic exogenous factors.)
 7. Ability for survival and propagation under experimental conditions simulating ordinary or natural environments
 8. Sexual reproduction cycle and out crossing
 9. History of utilization as food
 10. Safe consumption
 11. Restrictive conditions on survival and proliferation abilities
 12. Pathogenicity and production of harmful physiologically active substances in ancestral of related species to the host

- IV. Vector
 1. Name and its origin
 2. Properties
 - (1) DNA molecular weight
 - (2) Cleavage map using restriction enzymes
 - (3) Presence of any potentially harmful nucleic acid sequence
 3. Drug resistance
 4. Transmission
 5. Host dependency
 6. Expression vector preparation method
 7. Insertion method and site of the expression vector insertion

- V. Inserted Gene and its Genetic Products
 1. Donor
 - (1) Name, origin and taxonomy
 - (2) Safety

2. Method of gene insertion
 - (1) Method of vector construction
 - (2) Method of gene insertion
 3. Construction
 - (1) Promoter
 - (2) Terminator
 - (3) Hazardous DNA sequence
 4. Properties
 - (1) Function of inserted DNA
 - (2) Cleavage map using restriction enzymes
 - (3) DNA molecular weight
 5. Purity
 6. Stability
 7. Number of inserted gene copies
 8. Site, timing and level of gene expression
 9. Safety of antibiotic-resistant maker gene
 - (1) Properties of the gene and gene product
 - Structure and function
 - Mechanism of resistance, the method of use and related metabolites
 - Method of identification and quantification
 - Changes accompanying cooking or processing (stability against heat and physical pressure)
 - Changes in gastrointestinal tract environment (stability against acid and digestive enzymes)
 - Allergenicity
 - (2) Consumption of genes and their products
 - Expected amounts of consumption
 - Present usage of antibiotics associated with resistance
 - Comparison with normally existing antibiotic-resistant microorganisms
 - Estimated amount of antibiotics inactivated after oral administration and the possibility that inactivation may cause problems
 10. Presence or absence of exogenous open leading frames and the possibility of their transcription and expression
- VI. Recombinants
1. New properties acquired by recombinant DNA techniques
 2. Allergenicity of recombinant products (If there is rational reasons, some portions can be omitted.)
 - (1) Consumption history of the donor
 - (2) Whether the gene product is known to be an allergen
 - (3) Sensitivity of the gene product to physicochemical treatment
 - (4) Consumption volume of the gene product
 - (5) Structural homology of gene products with known food allergens
 - (6) Whether the gene product constitutes a considerable part of the total protein intake per day
 - (7) Information on binding ability of patient IgE antibody and the gene product

relative to allergens with structural homologies to the gene product and information on binding ability of patient IgE antibody and the gene product relative major allergens, if safety is not confirmed on the basis of (1) to (6).

3. Toxicity of recombinant products (other than allergenicity)
4. Effect of recombinant products on metabolic pathways (including information of possibility of reaction with basic properties of existing seeds)
5. Difference from the host (including information of nutrition & anti-nutrition and information of changes in composing elements that may be potentially harmful after changes in content volume)
6. Survival and proliferation in the external environment
7. Restrictive conditions on survival and proliferation abilities of recombinants
8. Inactivation method of recombinants
9. Approval and usage as food in other countries
10. Methods of preparation, breeding and cultivation
11. Methods of seed production and management

VII. Information regarding results of the following studies(The results shall be obtained by studies performed at a GLP (Good Laboratory Practice) compliant facilities following GLP standard) if safety assessment can not be accomplished from the information listed in II through VI(If there is rational reasons, a portion or the entire set of studies can be exempted):

1. Acute toxicity study
2. Sub acute toxicity study
3. Chronic toxicity study
4. Reproduction study
5. Mutagenicity study
6. Carcinogenicity study
7. Other necessary studies (e.g. intestinal tract toxicity, immunological toxin, neurological toxicity, nutrition etc.)

Appendix 2. INFORMATION REQUIRED FOR SAFETY ASSESSMENT WHEN FOODS AND FOOD ADDITIVES ARE MANUFACTURED BY USE OF LIVING ORGANISMS OBTAINED THROUGH RECOMBINANT DNA TECHNIQUES

I. Substantial equivalence between produced substances and existing substances

II. Recombinants

1. Confirmation that a non-pathogenic recombinant can be utilized in GILSP or Category 1 manufacturing (see “Ministry of Health and Welfare Announcement No. 234”)
2. Purpose and usage of recombinants
3. Host
 - (1) Taxonomy (scientific name, stain name)
 - (2) Production of pathogens or harmful physiologically active substances
 - (3) Parasiticity and specificity
 - (4) Foreign pathogenic factors (e.g. virus) (a host should not be contaminated with

- pathogenic exogenous factors)
 - (5) Survival and proliferation abilities under experimental conditions simulating ordinary or natural environments
 - (6) Sexual or asexual reproduction cycle and cross reactivity on sexual life cycle
 - (7) History of utilization as food
 - (8) Restrictive conditions on survival and proliferation abilities
 - (9) Pathogenicity and production of harmful physiologically active substances of host-related strains
4. Vector
- (1) Name and origin
 - (2) Properties
 - DNA molecular weight
 - Cleavage map using restriction enzymes
 - Presence of any potentially harmful nucleic acid sequence
 - (3) Drug resistance
 - (4) Transmission to other species
 - (5) Host dependency
 - (6) Preparation method of expression vector
 - (7) Insertion method and site of the expression vector
5. Inserted gene and its gene product
- (1) Name, origin, and taxonomy of donor
 - (2) Method of gene insertion
 - Method of vector construction
 - Method of gene insertion
 - (3) Construction
 - Promoter
 - Terminator
 - Hazardous DNA sequence
 - (4) Properties
 - Function of inserted DNA
 - Cleavage map using restriction enzymes
 - DNA molecular weight
 - (5) Purity on DNA sequences
 - (6) Safety of antibiotic-resistant makers
 - Properties of the gene and gene product:
 - *Structure and function
 - *Expression mechanism of resistance, the method of use and related metabolites
 - *Method of identification and quantification
 - *Changes accompanying cooking or processing (stability against heat and physical pressure)
 - *Changes in gastrointestinal tract environment (stability against acid and digestive enzymes)
 - *Allergenicity
 - Consumption of genes and their products:
 - *Estimated amounts of consumption

- *Present usage of antibiotics associated with resistance
 - *Comparison with existing antibiotic resistance
 - *Estimated amount of antibiotics inactivated after oral administration and the possibility that cause any problem by inactivation process
 - (7) Presence or absence of exogenous open reading frames and the possibility of their transcription and expression
6. Recombinants
- (1) New properties acquired by recombinant DNA techniques(must be non-pathogenic)
 - (2) Survival and proliferation in the external environments
 - (3) Restrictive conditions on survival and proliferation abilities
 - (4) Inactivation method of recombinants
 - (5) Difference from the host
- III. Miscellaneous ingredients and manufacturing apparatus other than the recombinant
- 1. The history of the actual use as a manufacturing apparatus on manufacturing process or as raw ingredients for foods or food additives.
 - 2. Existing knowledge regarding its safety in use as a manufacturing apparatus or ingredients for foods or additives.
- IV. Products
- 1. Absence of contamination by recombinants
 - 2. Purity and amounts of impurity
 - 3. Purifying process
 - 4. Changes in levels of normal ingredients which may be harmful
 - 5. Approval status and usage of products in other countries

Information regarding results of the following studies

(The results shall be obtained by studies performed at a GLP (Good Laboratory Practice) compliant facilities following GLP standard) if safety assessment can not be fully accomplished from the information listed in II through VI (If there is rational reasons, a portion or the entire set of studies can be exempted):)

- 1. Acute toxicity study
- 2. Sub acute toxicity study
- 3. Chronic toxicity study
- 4. Reproduction study
- 5. Mutagenicity study
- 6. Carcinogenicity study
- 7. Other necessary studies (e.g. intestinal tract toxicity, immunological toxin, neurological toxicity etc.)

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Note: This English version of the Notice is translated to meet the need of the non-Japanese speaking people. In the case of any discrepancy between the Japanese original and the English translation, the former will take priority.