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Food Safety Commission of Japan (FSCJ)

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Guidelines for the Safety Assessment of Genetically Modified Foods (Seed Plants)

Chapter 1. General Provisions

Section 1. Background

The Food Safety Commission of Japan (hereinafter referred to as "FSCJ") has issued guidelines for the safety assessment of food, based on the "Basic Matters Prescribed in Article 21, Paragraph 1 of the Food Safety Basic Act" (Cabinet Decision of June 29, 2012). These guidelines have been established for each subject of evaluation, with due consideration given to ensuring fairness and transparency in the "Assessment of the Effect of Food on Health" process (as defined in Article 11, Paragraph 1 of the Food Safety Basic Act [Act No. 48 of 2003]).

Regarding genetically modified foods, the "Guideline for the Safety Assessment of Foods and Food Additives Produced by Recombinant DNA Techniques" was issued in 1991 by the then Ministry of Health and Welfare. Based on this guideline, the first safety assessment of food additives produced by recombinant DNA technology was conducted in 1994, and the first safety assessment of genetically modified foods derived from seed plants was conducted in 1996. Thereafter, following a revision of "Specifications and Standards for Food, Food Additives, etc." [Ministry of Health and Welfare Notification No.370 of 1959] under the provisions of the Food Sanitation Act [Act No. 233 of 1947], the safety assessment of genetically modified foods has become mandatory since April 2001. At the international level, the Codex Alimentarius Commission issued guidelines, etc., for the safety assessment of genetically modified foods.

Following the enactment of the Food Safety Basic Act, FSCJ was appointed to conduct risk assessments of genetically modified foods and food additives in July 2003 to provide opinions in response to a request by the Ministry of Health, Labour and Welfare. Therefore, FSCJ established "Standards for the Safety of Genetically Modified Foods (Seed Plants)" (Decision of January 29, 2004, by the FSCJ) which laid down the principles necessary for safety assessments, with reference to both domestic and international guidelines in January 2004.

Based on the latest scientific knowledge, the content of this set of standards has been reevaluated and revised

in light of the outcomes of FSCJ's safety assessments to date, as well as international trends. Moving forward, safety assessments for this category of food shall, in principle, be conducted according to this set of guidelines.

Section 2. Objective and Type of Foods Applicable

This set of guidelines is applied to genetically modified foods (seed plants). It aims to ensure consistency in assessment methods across evaluation cases and alignment with international assessment methods to the extent possible, and to promote transparency and facilitate smooth deliberations.

Moreover, this set of guidelines is not intended to evaluate the environmental, ethical, moral or socio-economic aspects of research and development, production, or marketing of genetically modified foods (seed plants).

Section 3. Terminology Used in This Set of Guidelines

Terminology used in this set of guidelines follows the definitions provided in the "Food Safety Glossary" compiled by FSCJ (available in Japanese only).

Section 4. Principles and Fundamental Approach for the Safety Assessment of Genetically Modified Foods (Seed Plants)

For the safety assessment of genetically modified foods (seed plants), it is necessary to consider not only their direct adverse effects on human health, but also the potential indirect nutritional impacts of long-term consumption, among others. However, it has been established, based on a long history of consumption, that most foods consumed today pose either little or no harm, or harm that becomes tolerable through cooking or processing. Additionally, neither toxicological nor nutritional safety studies have been required for foods obtained through traditional breeding methods. These foods have been consumed based on evidence that, in most cases, breeding does not result in critical trait changes that pose safety concerns.

In general, due to significant technical difficulties, it is not common practice to evaluate the safety of foods in their intact form using conventional animal-based toxicological tests. Additionally, not all individual components of such foods have been scientifically proven to be safe. Thus, most foods have been known to be safe or not cause serious harm, based on their experience of consumption in their whole form, rather than through the safety assessment of each individual component.

In the safety assessment of genetically modified foods (seed plants), it is challenging to scientifically evaluate the safety of all components. Therefore, for the time being, it is reasonable to conduct safety assessments by comparing with existing plant varieties, focusing on traits that have been intentionally or unintentionally added or removed by recombinant DNA technology. Unintended changes can occur not only through the use of recombinant DNA technology but also through traditional breeding methods. It is crucial to evaluate and predict these unintended changes for assessing the safety of recombinant (genetically modified) plants as food. For new technologies without a long history of safe use, it is essential to preemptively exclude, to the extent

possible, the potential risks of drastic changes in harmful components or the generation of new toxic proteins resulting from unintended trait changes caused by such technologies.

Safety assessment is feasible only when changes in the characteristics of genetically modified foods (seed plants) can be adequately predicted through scientific analysis, based on the characteristics of the introduced transgene or inserted DNA and any resulting genomic modifications, and when sufficient comparison can be made between the existing plant variety and the recombinant plant.

Based on the aforementioned principles, safety assessments should be conducted by applying the following fundamental approach.

1. Characteristics other than traits newly introduced by genetic modification in recombinant plants are either already widely accepted as safe without requiring any additional consideration or are supported by a substantial body of scientific knowledge necessary for safety assessment. Accordingly, genetically modified foods (seed plants) for which safety assessment is possible are those that can be compared with existing plant varieties with a long history of safe use and foods derived from these existing plant varieties.
2. The most critical elements to be considered in safety assessments are the impacts on human health such as those resulting from traits that have been intentionally added, altered, or eliminated through recombinant DNA technology, as well as the risks from potential increases in newly generated harmful components, and changes in major nutrients. Additionally, the possibility that unintentional traits may be added, or that existing traits may be eliminated or modified, must also be considered. Furthermore, for recombinant plants developed with the intent of modifying the content of nutrients, functional components, or harmful components through recombinant DNA technology, it is necessary to evaluate their safety on human health by considering the levels and intake of these components from other foods. Moreover, in conducting safety assessments, a tiered approach based on the weight of evidence (WOE)[1] should be considered, in light of the aforementioned fundamental principles and prior assessment outcomes.
3. For genetically modified foods (seed plants), the potential effects of food processing, including home cooking, should also be considered. Additionally, some recombinant plants may exhibit traits (e.g. herbicide tolerance) that could indirectly lead to the accumulation of pesticide residues and their metabolites, toxic metabolites, contaminants, or other substances that may pose safety concerns over human health. Such possibilities must also be considered in safety assessments.
4. In safety assessments, all potential forms of the recombinant plant that may be used as food should be considered. If the forms in which it is used as food are limited to specific edible parts or non-protein extracts, this must also be considered. However, even in cases such as rapeseed oil, where typically only non-protein extracts from the recombinant plant are consumed, the possibility that other parts of the plant may also be ingested should be considered in the safety assessment of genetically modified food (seed plants).
5. In conducting safety assessments, sufficient test data and information are required to minimize the likelihood of unforeseen adverse effects on humans from genetically modified food (seed plants). Studies for safety assessment must be designed and conducted following scientifically reliable approaches and principles to

[1] The assessment is conducted in a stepwise manner based on the relevance of the source information.

ensure confidence and must adhere to Good Laboratory Practice (GLP)[2] wherever appropriate. Additionally, raw data must be submitted upon request. Data or information necessary for safety assessment include experimental data obtained by developers, etc., published scientific papers, and scientifically reliable information provided by third parties, etc. These data must be prepared using scientifically reliable methods and analyzed using scientifically appropriate technology. Moreover, the limit of quantification (LOQ) of all analytical methods should be documented wherever possible.

6. In safety assessments of genetically modified food (seed plants), it may be necessary to use substances produced by different methods or from different sources when testing novel substances expressed in such foods. In such cases, the substances used in the tests should be demonstrated to be biochemically, structurally, and functionally equivalent to those produced in the recombinant plant.

Section 5. Future Reevaluations to This Set of Standards

As recombinant DNA technology continues to advance, this set of standards should be reevaluated as necessary, taking into account the latest trends in safety evaluations and scientific knowledge from both Japan and abroad.

Chapter 2. Points to Consider in Safety Assessments When Using Part or Whole of Genetically Modified Food (Seed Plants)

Section 1. Outline of Items Subject to Assessment

History of development as well as outlines described in the following Section 2 through Section 6 must be explained for items subject to assessment.

Section 2. Characteristics of the Existing Plant Varieties Used as Comparators in Safety Assessments

An outline of items 1 through 8 below should be provided to demonstrate that an existing plant variety is available as a comparator for the safety assessment of the genetically modified food (seed plant), and to clearly identify the differences between the recombinant plant and said existing plant variety, as described in Section 3.

1. Taxonomic position of existing plant varieties
   The scientific name of the species must be identified, including, as necessary, the subspecies name, the name of the existing plant variety used in the development of the recombinant plant, and the line name, along with its origin.
2. Usage of existing plant varieties as food
   The plant must have a long history of use as food (food culture) and an extensive record of safe human consumption.
3. Usage of existing plant varieties as food

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[2] OECD Principles on Good Laboratory Practice (1998, OECD)

(1) Harvest time (degree of ripeness) and storage method
(2) Edible parts
(3) Consumption volume
(4) Cooking and processing methods

4. Genetic ancestry of existing plant varieties, history of breeding and development, and closely related plant species

It should be clearly indicated whether the genetic ancestry of the existing plant variety is capable of producing harmful bioactive substances such as toxins and anti-nutrients. If any ancestral plant produces harmful bioactive substances, the breeding process employed to reduce or eliminate these harmful bioactive substances such as toxins and anti-nutrients should be described as thoroughly as possible.

If closely related species of the existing plant variety used in the development of the recombinant plant are known to produce harmful bioactive substances, it must be clarified whether these substances are also expressed in the recombinant plant. If such substances are expressed in the recombinant plant, scientific rationale, such as an assessment based on estimated intake, must be provided to demonstrate that their presence does not pose safety concerns, as outlined in Section 5, 6 (1).

5. Food components, etc., derived from existing plant varieties
   (1) Overview of the types and quantities of major nutrients (such as protein, lipids, etc.) in the edible parts of existing plant varieties
   (2) Overview of the types and quantities of toxic constituents and inhibitors for nutrients (substances that inhibit the digestion and absorption of nutrients, for example, trypsin inhibitors and phytic acid, etc.) present in existing plant varieties
6. Allergenicity of existing plant varieties

Characterization of the allergenicity (including the potential to induce gluten-sensitive enteropathy) of the existing plant variety used in the development of the recombinant plant should be provided.

7. Potential exogenous factors that may have an impact on human health during the cultivation and distribution of the existing plant variety used

If any exogenous factor is known to contaminate the existing plant variety used for developing the recombinant plant, it should be demonstrated that the exogenous factor does not impact human health.

8. Safe consumption of the existing plant variety

If there is any history of processing or technological practices used to ensure safe consumption of the existing plant variety used for developing the recombinant plant, they should be clearly described (e.g. certain pulses containing cyanogenic compounds).

Section 3. Purpose and Use of the Recombinant Plant, and Differences from the Existing Plant Variety

1. Newly added and modified traits

2. Purpose

3. Use

(1) Cultivation method, time of harvest, and production and management method of seeds

(i) Regarding the cultivation method, difference between the existing plant variety and the recombinant plant must be provided. There should be no significant differences in principle. If any differences do exist, scientific rationale demonstrating their safety must be provided, as

indicated in Section 4 below.

(ii) Regarding the cultivation method, the use of pesticides should be identified.

(iii) Regarding the cultivation method, if pesticide tolerance is achieved through the metabolism of the pesticide, the resulting metabolites must be clearly described. Additionally, the safety of the major metabolites must be verified.

(iv) Regarding the production and management methods of seeds, the degree of difference between the existing plant variety and the recombinant plant must be provided. There should be no significant differences in principle. If any differences do exist, scientific rationale demonstrating their safety must be provided, as indicated in Section 4 below. Furthermore, seeds from the existing plant variety used in the development of the recombinant plant, as well as seeds from each generation following genetic modification, should be preserved.

(2) Edible parts, cooking, and processing methods

(3) Consumption volume

4. Differences that need to be considered when evaluating safety

If there are any differences in (i) and (iv) of 3(1), scientific rationale demonstrating that safety is not compromised must be provided.

5. Justification for using a comparator other than the existing plant variety

Section 4. Inserted DNA, Gene Products and Generation of Construct

1. Name and origin of the vector

The name and origin of the vector (e.g., plasmid) used for gene introduction should be identified.

2. Characteristics of the vector

(1) Number of nucleotides in the vector and its nucleotide sequence

The number of nucleotides in the vector and its nucleotide sequence should be identified. Furthermore, if the sequence is publicly available, the components of the region corresponding to the vector backbone and the accession number in public databases must also be provided. If Southern blotting is performed, the restriction map of the vector must be clearly identified, including the names of the restriction enzymes used, as well as the number and sizes of the resulting DNA fragments.

(2) Absence of known harmful nucleotide sequences

The expression vector to be introduced into the host must not contain nucleotide sequences that produce known harmful proteins.

(3) Genes involved in the selection of the recombinant plant

If the vector contains any gene involved in the selection of the recombinant plant (including antibiotic resistance marker genes), the characteristics of these genes must be described.

(4) Transmissibility and related considerations

In principle, the vector should not exhibit transmissibility (i.e., the characteristic of being transferable between different species). If the vector exhibits transmissibility, the host range must be clearly defined.

Furthermore, the vector must not contain any genetic sequence capable of autonomous mobility, such as transposons.

3. Donor organism of the inserted DNA

(1) Name, origin, and taxonomy

The name, origin, and taxonomic status of the donor organism should be identified.

(2) Safety (including allergenicity and toxin production)

(i) The donor organism for the inserted DNA must neither exhibit pathogenicity to humans nor produce toxins. Additionally, if pathogenic strains are known within the donor organism, such as Escherichia coli, it must be demonstrated that the inserted DNA is derived from a non-pathogenic strain.

(ii) If the donor organism has been reported to be pathogenic to humans or to produce toxins, it must be demonstrated that the inserted DNA itself does not produce any toxins, and that the proteins derived from the inserted DNA are non-pathogenic.

(iii) The presence or absence of a documented history of safe consumption for the donor of the inserted DNA must be identified

4. Characteristics of the transgene (including genes involved in the selection of the recombinant plant) and their gene products (RNA and proteins).

(1) Properties of the transgene function

The function of the transgene and the characteristics and functions of its gene products (RNA and proteins) must be clearly characterized. Scientific rationale is necessary to demonstrate that the expressed protein does not exert any adverse effects. These requirements also apply to any cleavage or degradation products of the protein that may result following transcription and translation of the transgene within the plant cell. The methods and results of the sequence homology searches comparing the transgene-derived protein with known toxic proteins must be provided. In principle, no significant sequence homology must be observed. If such homology is observed, scientific rationale must be provided to demonstrate that the protein does not pose safety concerns.

(2) Antibiotic resistance marker genes among the genes involved in the selection of recombinant plants

Address the following criteria as needed:

i) The administration route of antibiotics (po or iv, etc.) must be clearly indicated.

ii) The mechanism of resistance development must be clearly indicated.

iii) There must be scientific rationale demonstrating that the metabolites associated with the development of resistance do not pose safety concerns.

iv) The usage status (regimen, dosage, purpose, etc.) of the antibiotic subject to resistance must be clearly indicated.

(3) The transgene and regulatory regions involved in the expression of genes related to the selection of the recombinant plant.

i) Promotors

The origin and characteristics of the promoters used must be clearly indicated.

ii) Terminators

The origin and characteristics of the terminators used must be clearly indicated.

iii) Additionally, if any nucleotide sequences have been inserted to regulate the expression of the transgene, their origin and characteristics must be clearly indicated.

5. Additional information on the functions of the transgenes and the characteristics and functions of the expressed proteins

If proteins are produced from genes that are introduced into the cells of the host but are not integrated into the genome, their origin, function, and safety must be clearly indicated.

6. Methods for inserting foreign DNA into the vector and related information

(1) Cloning or synthesis methods of the inserted DNA

The cloning or synthesis methods of the inserted DNA must be clearly indicated.

(2) Methods for inserting foreign DNA into the vector

Address the following criteria concerning the methods for inserting foreign DNA into the vector.

i) The methods used to generate the construct to be introduced into the existing plant variety must be clearly indicated. In particular, if multiple gene fragments are intended to be assembled, the procedures used for their assembly must also be shown.

ii) The order and methods used to introduce promoters, open reading frames (hereinafter referred to as "ORFs"), terminators, and genes involved in the selection of recombinant plants into a vector must be clearly described.

7. Genetic construct

(1) Number of nucleotides, nucleotide sequences, and restriction maps generated by restriction enzymes

Concerning the genetic construct and the DNA fragments intended for insertion into the host, the number of nucleotides and the nucleotide sequence of the inserted DNA must be clearly indicated. Additionally, if Southern blotting is performed on the construct, the name of the restriction enzyme, the number of fragments, and their sizes must also be clearly specified.

(2) In the method used for introducing the construct into the host, the intended insertion region must be clearly identified on the construct.

(3) The construct intended to be introduced must be purified to prevent contamination by unintended genes.

Section 5. Development of recombinant plants and subsequent transgenic plant lines

1. Gene introduction

(1) Methods for introducing transgenes into the host

The methods used for introduction of the transgene into the host should be presented. Specifically, the

following must be described clearly:

i) The method used to introduce the transgene into the host

ii) The selection method (the method used for selecting the recombinant plant)

iii) The method used for regenerating into a plant organism

(2) Description of transgenic plant lines (line-oriented descriptions such as diagrams of the breeding processes)

The generations and the range of plant lines subject to the safety assessment must be clearly identified, for example, using a tree-diagram to illustrate the breeding process.

(3) Copy number and sequences flanking the insertion

The nucleotide sequence, structure, copy number, size and origin of the transgene introduced into the host must be characterized by DNA sequencing analysis etc. (including details such as the method of introduction, the structure of the transgene introduced, whether the transgene is single or multiple, and whether there are any deletions). The nucleotide sequences flanking the inserted DNA in the genome of the host should be identified.

Additionally, it should be demonstrated, wherever possible, that the insertion does not cause any alterations in the nucleotide sequences of the host. If any sequence alterations are detected, it must be demonstrated that these alterations do not pose safety concerns.

(4) Stability of the transgene introduced into the transgenic plant line

i) The stability of the transgene(s) should be demonstrated by verifying that their structure, expression sites, and expression levels remain unchanged over a sufficient number of subsequent generations, by conducting DNA sequencing, Southern blotting, Western blotting, or other appropriate methods based on the results of cultivation trials. Furthermore, it must be specified which line and generation of recombinant plants in the breeding process were subjected to these tests.

ii) The trait conferred by the introduced transgene, as well as its expression levels, should be monitored over multiple generations to determine whether any changes occur. Based on these observations, the structural integrity and copy number of the transgenes must be confirmed as stable.

(5) Presence of ORFs and the potential for their transcription and expression

i) The construct and the transgenes introduced into the host or the inserted DNA (including DNA sequences flanking the insertion site in the genome of the host) have been analyzed for ORFs, and scientific rationale must be provided to demonstrate that no ORFs are present which could lead to the expression of proteins other than the intended product in the recombinant plant, in principle. Specifically, if mutations, deletions, or rearrangements occur during the gene introduction process, the resulting changes to the ORF must be identified through nucleotide sequencing analysis. Furthermore, the absence of any potential for unintended protein expression must be verified using methods such as DNA sequencing, Northern blotting, or RT-PCR.

ii) If any ORF that can express an unintended protein is identified, scientific rationale must be provided

to demonstrate that the ORF and the protein it expresses do not pose safety concerns, including allergenicity.

2. Spatial and temporal expression, and expression level of the gene product in the transgenic plant lines

The method for quantifying the gene product derived from the inserted gene (including genes used for the selection of the recombinant plants) should be available, and the expression site, timing, and levels of these gene products in the recombinant plant should be identified.

Any changes in expression site, timing, and level of the gene product in the recombinant plant should be thoroughly reviewed, and a scientific rationale must be provided to demonstrate that these changes do not pose any safety concerns.

3. Whether the intake of the gene product constitutes a significant proportion of total protein consumption

(1) The proportion of the gene product in the total daily protein intake of humans should be estimated. In principle, the intake of the gene product should not constitute a significant portion of the total daily protein intake. If it does, scientific rationale must be provided to demonstrate that this intake does not pose safety concerns.

(2) If an antibiotic resistance marker gene is used, scientific rationale should be provided to demonstrate that there are no concerns relating to the inactivation of the antibiotic. This should be based on data such as the amount of the expressed protein ingested (the enzyme that metabolizes the antibiotic), its breakdown by artificial gastric or intestinal fluids, its degradation during cooking processes such as heating, and the status of antibiotic usage, etc.

4. Allergenicity of the gene product (protein) (including the gene product used for the selection of recombinant plants)

The safety of the gene product must be confirmed by comprehensively reviewing the following items (1) to (4). If the safety cannot be confirmed by the information on items (1) to (4), it should be assessed by considering item (5) in addition to items (1) to (4). Furthermore, some items may be omitted if appropriate scientific rationale is provided.

(1) Information on the allergenicity of the donor of the transgene (including the donor of the gene used for the selection of recombinant plants), including the potential to induce gluten-sensitive enteropathy, should be provided.

(2) Available knowledge regarding the allergenicity of the gene product (protein) must be provided.

(3) Susceptibility of the gene product (protein) to physicochemical treatments

It should be demonstrated whether the molecular weight, enzymatic activity, and immunoreactivity of the gene product (protein), etc., change as a result of the following treatments (i) to (iii). The molecular weight should be determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The immunoreactivity should be demonstrated by Western blotting, ELISA, or an equivalent method using specific antibodies against the untreated gene product (protein).

(i) Acidic and enzymatic (pepsin) treatment with artificial gastric fluid

(ii) Alkaline and enzymatic (pancreatin) treatment with artificial intestinal fluid

(iii) Heat treatment

Heat treatment should be conducted under conditions similar to those used when the food is prepared or processed for human consumption.

(4) Sequence similarity between the gene product (protein) and known allergens (including proteins involved in gluten-sensitive enteropathy)

The gene product (protein) should be compared with known allergens at the level of primary structure to confirm the absence of sequence similarity with known allergens. To identify potential epitope regions (antigenic determinant), sequence similarity searches based on amino acid sequences should be conducted. In doing so, the name of the allergen database used, search parameters, methods, and results must be provided.

(5) IgE-binding activity of the gene product (protein)

If it cannot be determined that the gene product (protein) poses no risk to human health based on items (1) to (4), its IgE-binding activity should be assessed.

The sera of allergic patients to be used should be selected according to the following (i) to (iv):

(i) In cases where the donor of the transgene has allergenicity, sera with high titers of donor-specific IgE should be used.

(ii) In cases where the gene product has sequence homology with a known allergen, sera with high titers of IgE specific for the organism bearing the known allergen should be used.

(iii) In cases where the gene product does not exhibit sequence homology with any known allergen, but its potential allergenicity cannot be completely ruled out based on the information provided in items (1) through (3), sera with high titers of IgE specific to a species closely related to the gene donor should be used.

(iv) In cases where appropriate sera for (i) to (iii) are not available, sera with high titers of IgE specific for major food allergens (egg, milk, soybean, rice, wheat, buckwheat, cod, shrimp and peanut) should be used.

In cases where the donor of the transgene is known to have allergenicity, and its safety cannot be sufficiently confirmed despite negative IgE binding assay results using the sera from patients allergic to the gene product (protein), supplementary clinical data, such as basophil activation tests, skin tests, or oral food challenge tests must be reviewed.

5. Impact of the transgenic plant lines on metabolic pathways including potential interactions with substrates found in existing plant varieties and closely related species

If the protein produced by the gene product is an enzyme, its substrate specificity must be clearly established, and in principle, the substrate specificity should be high. It should be demonstrated that the substrate specificity has not been changed through the gene introduction event. If the substrate specificity has been changed or was initially low, scientific rationale should be provided to demonstrate that it does not pose safety

concerns.

In addition, if the gene product acts as an enzyme within the recombinant plant's metabolic pathways and causes alterations in related components, an analysis of these changes should be conducted, and scientific rationale should be provided to demonstrate that these alterations do not pose safety concerns.

6. Differences from existing plant varieties and classification of traits conferred to transgenic plant lines

(1) Based on comparative data between the recombinant plants and known non-recombinant plants, including existing plant varieties, it should be determined whether there are significant differences in terms of nutritional components, toxins, anti-nutrients, and other harmful bioactive substances. In principle, no significant differences should be observed. If significant differences are observed, scientific rationale must be provided to demonstrate that these differences do not pose safety concerns. Additionally, if there are variations in the protein components in relation to allergenicity compared to existing plant varieties, the potential impact of these variations on allergenicity, etc., must be clearly described.

In cases where harmful bioactive substances are generated in the recombinant plants in Section 2.4, scientific rationale should be provided to demonstrate that their intake level, etc., do not pose safety concerns.

(2) If the genetic modification is intended to alter nutritional composition or metabolic pathways, scientific rationale must be provided to demonstrate that the intended components of the recombinant plant do not pose safety concerns. In principle, any unintended components should not differ significantly from those of existing plant varieties. If significant differences are observed, scientific rationale must also be provided to demonstrate that these differences do not raise safety concerns.

(3) In accordance with "1. Recombinant Plants" in the Appendix: "Safety Assessments of Cross-bred Recombinant Plants Whose Parent Plants Have Already Undergone Safety Assessments," the classification of the recombinant breeding line must be clearly defined.

7. Approval status and usage in genetically modified seed plants as food, etc., abroad

Information on the approval status of genetically modified seed plants as food by foreign authorities and their utilization as food products should be provided.

Section 6 Additional Studies Required When Safety Cannot be Confirmed Based on Sections 2 to 5

The safety of the genetically modified plant as food should be confirmed based on results of appropriate studies from the following list:

(1) Genotoxicity study

(2) Repeated dose toxicity study

(3) Carcinogenicity study

(4) Reproductive toxicity study

(5) Developmental toxicity study

(6) Other required studies (e.g. immunotoxicity study, neurotoxicity study, etc.)

(7) Scientific knowledge from clinical observation

Attachment

Safety Assessments of Crossbred Plants Derived from Previously Assessed Genetically Modified Parent Plants ‡

1. Recombinant plants

Recombinant plants are categorized into the following three types depending on the traits conferred, with each requiring safety assessments:

(i) Traits conferred by the introduced transgene that do not affect the metabolic pathways of existing plant varieties.

(ii) Traits conferred by the introduced transgenes that modify the metabolic pathways of existing plant varieties and promote or inhibit specific metabolic pathways.

(iii) Traits conferred by the introduced transgenes that enable the synthesis of new metabolites not produced by existing plant varieties through the utilization of certain metabolites within the metabolic pathways.

2. Crossbreeding of recombinant plants

(1) Crossbreeding between existing plant varieties and any of the categories described in (i), (ii), or (iii) above, or crossbreeding within (i), or crossbreeding between (i) and (ii)

a) Demonstration of safety is required for the time being for plants generated through

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‡ Assessments of recombinant plants as food are conducted to establish that they are equivalent in safety to existing foods. This document establishes the approach to the evaluation of crossbreeding involving genetically modified plants that have been evaluated for safety. In accordance with the "Procedure of Application for Safety Assessment of foods and food additives produced by recombinant DNA techniques " (Ministry of Health and Welfare Notification No. 233 of 2000), plants produced through traditional breeding by crossing genetically modified plants that have already been evaluated for safety with existing varieties are referred to as "progeny crosses."

If the following three requirements are met, the product is considered to have undergone safety assessment:
・Newly acquired characteristics remain unchanged
・No crossbreeding occurs between subspecies
・No change in intake volumes, edible parts, processing methods, etc.

hybridization beyond the subspecies level

b) Demonstration of safety is required for the time being for plants for which intake, edible parts, or processing methods, etc. are changed, even if the hybridization is not above the subspecies level.

(2) For the time being, safety assessments are required for crossbreeding between (i) and (iii)

(3) Safety assessments are required for crossbreeding within (ii), within (iii), and between (ii) and (iii)

References

Section 1: Technical Documents

To supplement the technical aspects of this set of guidelines, separate technical documents are provided (available in Japanese language only), detailing the fundamental approach, technical criteria, and specific considerations and assessment points as established by the Expert Committee for Genetically Modified Foods, FSCJ.

Section 2: Relevant Documents

1. FSCJ Food Safety Glossary (in Japanese only: https://www.fsc.go.jp/yougoshu.html).
2. PRINCIPLES FOR THE RISK ANALYSIS OF FOODS DERIVED FROM MODERN BIOTECHNOLOGY (CAC/GL 44-2003).
3. GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANTDNA PLANTS CAC/GL 45-2003.
4. GUIDELINE FOR THE CONDUCT OF FOOD SAFETY ASSESSMENT OF FOODS DERIVED FROM RECOMBINANT-DNA PLANTS (CAC/GL 45-2003) Adopted in 2003, Annexes II and III adopted in 2008.
5. Survey on the Utilization of Next-Generation Sequencers (FY2016 Comprehensive Survey on Food Safety Assurance) FSCJ, Cabinet Office, Government of Japan.
6. Survey for the Development of Guidance on the Evaluation of Compositional Data in the Safety Assessment of Genetically Modified Foods (FY2018 Comprehensive Survey on Food Safety Assurance) FSCJ, Cabinet Office, Government of Japan.