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Health Ministry Invites Comments on Genome Edited Food Policy

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Biotechnology and Other New Production Technologies
Agricultural Situation
Grain and Feed
Oilseeds and Products
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Report Highlights:
On January 24, 2019, Japan's Ministry of Health, Labour and Welfare (MHLW) opened a public comment period for its proposed regulatory policy for the handling of food products derived from genome editing technology. The proposed regulatory policy incorporates elements of the deliberations conducted by MHLW's expert members, and establishes conditions for when genome-edited products will be regulated and when they will not. Comments need to be submitted in Japanese via an online system, mail, or fax by February 24, 2019.

General Information:
After four meetings of scientific experts and a hearing including six interested parties (see, e.g., JA8077 and JA8106), the Research Sub-Committee for Genetically Modified Food (The Sub-Committee) issued a report proposing how to regulate foods derived from genome editing technology. After the report was reviewed by the Research Committee for Newly Developed Food (The Research Committee) on December 18 and 27, 2018, Japan finalized the proposed regulatory policy for food products derived from genome editing technology on January 17, 2019. On January 24, 2019, MHLW opened a 30 day public comment period for interested parties to weigh-in on the proposal. Comments must be submitted in Japanese and sent via one of three methods indicated below by February 24, 2019.

How to Submit Comments

1. Japanese Government's "e-Gov" system
   Comments can be sent electronically via the "e-Gov" system which enables electronic submission of comments on regulatory proposals by the Japanese Government. The site for commenting on the proposed regulatory policy for the handling of food products derived from genome editing technology can be found at: https://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495180327&Mode=0

2. Mail
   Comments can be mailed to the address below:

   Office of Health Policy on Newly Developed Food
   Food Safety Standards and Evaluation Division
   Pharmaceutical Safety and Environmental Health Bureau
   Ministry of Health, Labour and Welfare
   1-2-2, Kasumigaseki, Chiyoda-ku
   Tokyo 100-8916
   Japan

   The envelope containing comments should include the note "部会報告書（案）について"（meaning "Regarding the Research Committee's Report (Draft)" in Japanese). Mailed submissions must arrive to MHLW by February 24, 2019.

3. Facsimile
   It can be sent via fax to the number indicated below.

   Facsimile number: 03-3501-4868 (from outside Japan, +81-3-3501-4868)
   Office of Health Policy on Newly Developed Food
   Food Safety Standards and Evaluation Division
   Pharmaceutical Safety and Environmental Health Bureau

   The comment should have the title "部会報告書（案）について" (meaning "Regarding the Research Committee's Report (Draft)" in Japanese).

Comments must be submitted in Japanese and should contain the name (private individual or corporate body), address, and contact information (either phone number or email address) of the submitter. The filed comments may be released to the public without name, address and contact information.

Summary of Proposed Regulatory Policy for the Handling of Food Products Derived from Genome Editing Technology

The original report in Japanese can be found online at the e-Gov site (in Japanese).

1. **Point of Deliberation**

- With attention paid to: 1) the nucleic acid sequence of the food products derived from genome editing technology, 2) consideration of the selection process during breeding, and 3) the relative safety when compared to conventional breeding techniques (such as natural mutation and induced mutation), the Research Committee concluded that the report by the Sub-Committee is fundamentally appropriate.
- Major statements by the Research Committee included:
  - **i.** Insertion, substitution and deletion of one to several base pairs are not unique to genome editing technology, but can occur naturally. Such changes are difficult differentiate from mutational changes that occur in traditional breeding techniques.
  - **ii.** It should not be considered abnormal even if off-target mutations are observed by the application of genome editing technology, as off-target mutations have been observed in multiple locations (in genome) in traditional breeding such as using mutagenesis. Also, it will be difficult to determine whether off-target is due to genome editing technology, is occurring naturally or is a result of the breeding process.
  - **iii.** It would be unrealistic to analyze off-target mutation via the whole genome sequence as there are many species with no precise reference sequence data.
  - **iv.** There is a need to take full account for the risk of adverse effects to human health by off-target mutation. However, it is important to note that the products from traditional breeding (which face similar risks) have not presented adverse effects. Because the selection process over multiple generations is necessary to develop a specific cultivar during the breeding program, the risk of off-target causing adverse health effects is extremely unlikely.
  - **v.** The report by the Sub-Committee is fundamentally valid, however, it is still reasonable to continue the discussion on:
    - Mechanism to ensure effective reporting from developers;
    - Information to be reported and released to public;
    - Outreach activities to increase the understanding of various breeding techniques and regulations.

2. **Handling of Foods Derived from Genome Edited Technology from the Perspective of Food Hygiene**

The Research Committee proposes the policy for the handling of foods derived from genome editing technology under food hygiene perspective as detailed below. However, it is important to note that foods derived from new breeding techniques beyond the scope being discussed may not fall into the proposed policy below.

- Foods derived from genome editing technology that contain transgenic genes and/or fragments of transgenic genes are considered as (the foods derived from) recombinant DNA technology and are required to undergo a safety review under the current standards and regulations.

- When there are no transgenic genes and/or fragments of transgenic genes in the final product, however, the genome edited foods will not be considered to be foods derived from recombinant DNA technology, as long as, the DNA double-strand break induced by engineered restriction enzyme and following repair (i.e., mutation) is:

    a) base-pair deletion;
    b) substitution;
    c) naturally occurring gene deletion; and/or,
    d) concomitant insertion (mutation) of one to several base pairs

As these mutations can occur during the natural process of repairing a break site and in traditional breeding technology, neither of which falls into recombinant DNA technology, it is appropriate to handle it differently from genetically engineered (GE) foods.

- In addition to confirming that food from genome editing is as safe as the food obtained by conventional breeding technologies, for the understanding and monitoring of the spread of the technology in the market, it is reasonable to request information from developers on their developed food(s). Some of this information should be published for public understanding, while respecting the need to protect certain elements that constitute proprietary information.

- The degree of mutation in non-GE genome edited foods is not to exceed the range of mutation by conventional breeding technology. . Furthermore, non-GE genome edited food products are not be distinguishable from the product derived from conventional breeding technology. Therefore, the mandatory submission of product information by developers is not required. However, this policy may be revised in the future to ensure the effectiveness of reporting, if deemed necessary.

    The information developers should provide includes:

    a) Crop type, cultivar name, how to use/eat and the purpose of use;
    b) The method and content of genome editing (target gene, function and altered function of the target gene, phenotypic change, whether the induced change is maintained before and after the breeding process, etc.);
    c) Information confirming that there has been no production of new toxic substances or increases in pre-existing toxic substances observed due to the DNA mutation (including off-target) as well as the methods being used for the confirmation of no adverse effect to human health;
    d) Information confirming the absence of transgenic gene(s) and fragments of transgenic gene(s) in the product; and,

e) With regard to the modified metabolic pathway to increase or decrease specific substances, information on the changes in major components (e.g., nutritional components, etc.).

The information reported from developers to be released to the public includes:

a) Crop type, cultivar name, how to use/eat and the purpose of use, method of genome editing and outline of genetic change;
b) Outline of the confirmation of no adverse effects to human health;
c) With regard to the modified metabolic pathway to increase or decrease specific substances, the outline of the changes in major components (e.g., nutritional components, etc.).

- In addition to determining the applicability of the non-GE classification (by confirming the absence of transgenic gene and fragments of transgenic gene(s)), it is necessary for developers to confirm the presence of off-target mutation in the regions of high probability of off-target mutation by using search tools (developers are recommended to use multiple tools such as CRISPRdirect). If off-target mutation is confirmed in the regions of target or there is a high probability of off-target mutation, developers need to confirm there is no production of new protein(s) with allergenicity and/or toxicity by frameshift mutation.

- If a developer cannot make a clear decision on the applicability of the non-GE classification and/or there is an absence of allergenic substance production due to the sequence condition, they should hold a consultation with MHLW. Based on the result of consultation on the applicability to the non-GE classification and/or absence of allergenic substance production, the product may need to be subjected to a safety review as a GE product.

- A consultation mechanism for the safety of foods derived from genome editing technology needs to be established for developers.

- Regarding the handling of recombinant DNA technology (including self-cloning and natural-occurring), it should be further evaluated as technology develops and knowledge is accumulated. Also, the issue needs to be discussed consistent with MHLW's policies of recombinant DNA and genome editing technologies.

3. Handling of Food Additives Derived From Genome Edited Organisms

- Additives manufactured from genome edited organisms and whose technology is considered recombinant DNA technology need to go through the safety review process under the GE regulations and standards.

- Additives manufactured from genomic edited organisms and whose technology applied is <u>not</u> considered recombinant DNA technology are subjected to the MHLW reporting requirements specific to food additive substances. Regarding the highly purified

additives derived from genome edited organisms, reporting information may not be necessary because the highly purified additives from genetically modified organisms have expedited approval processes already.

- Based on the current practice for the handling of additives with recombinant DNA technology, it is not necessary to report information on additives from genome edited microorganisms which fall under the self-cloning and natural occurrence.

4. Risk Communications Need to Continue for the Public

- The risk communication for all breeding technologies, including genome editing and recombinant DNA, as well as its food safety and its relation to legal regulations, needs to continue to increase consumer understanding.

5. Refinements Should be Considered as Technology Develops

- As genome editing technology and detection methods are expected to develop continuously, the food safety aspect of genome editing technology needs to continue to be monitored.

- A survey of how genome editing technology is handled in other countries needs to be conducted from a food safety perspective. When new scientific knowledge and/or concerns with regard to food safety emerge, Japan's policy should be reviewed, as needed.