Guidance on regulatory framework for genome edited crops for use as food and/or feed

1 Aug 2024

Contents

1 Overview

1.1 Modern biotechnology has accelerated the breeding of new crop varieties[1] with desirable agronomic traits, such as disease resistance, drought tolerance, and improved nutrition, for use as food and animal feed. These traits can bring benefits for the farmer and the consumer. Genome editing represents a set of tools from modern biotechnology that enables crop developers to make precise changes within an organism's genome.[2] Examples of genome editing tools that have been used to generate new food crop varieties include zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALENs), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) nucleases.

1.2 Genome editing has been employed to expedite the breeding of new crop varieties that could have been generated via conventional breeding[3]. This is because genome editing can be used to generate precise changes in an organism's genome that are equivalent to the changes that occur naturally or during conventional crop breeding. SFA does not consider such crop varieties to contain foreign DNA. This is because SFA considers foreign DNA to be DNA sequences derived from source organism(s), or DNA sequences not found in nature, that are introduced into a host organism's genome and could not have been inserted naturally or been introduced into said organism using conventional breeding techniques.

1.3 Genome editing can also be employed to generate new crop varieties that contain foreign DNA. SFA considers such GEd crops to be equivalent to genetically modified organisms (GMOs).

1.4 SFA encourages crop developers intending to sell or offer their **GEd crops that do not contain foreign DNA** for feed and/or feed to notify SFA by providing information

[1] A crop is a plant, a macroscopic fungus (e.g., mushroom), or a macroscopic alga (e.g., seaweed).

[2] The genome of an organism includes its entire hereditary material, which is made from deoxyribonucleic acid (DNA). The genome includes, but is not limited to, the chromosomal DNA, mitochondrial DNA, chloroplast DNA and plasmid DNA.

[3] Conventional crop breeding techniques include selective breeding, cross breeding, *in vitro* cell fusion between related species, and mutagenesis via ionising radiation or chemical mutagens, but excludes modern biotechnology techniques such as genome editing and genetic modification.

on said crop to SFA (see Section 3 for Information Checklist). Based on the information provided, SFA will verify that said crop indeed does not contain foreign DNA and is therefore equivalent to conventionally bred crops. Upon verification, SFA will inform the crop developer that said GEd crop does not need to undergo GMO pre-market assessment.

1.5 GMO crops and genome edited (GEd) crops equivalent to GMOs are required to obtain SFA's pre-market approval before they can be sold or offered for use in food and/or feed. Please refer to the Conditions related to Genetically Modified Crops on SFA's website for further information on the GMO pre-market approval process: https://www.sfa.gov.sg/food-import-export/commercial-food-imports

1.6 To promote transparency towards joint responsibility in food safety, the List of GEd crops that have completed Notification will be made publicly available on SFA's website. Only the common / scientific name of the crop, commercial / proprietary name, marketed traits, and intended use (as food and/or feed) will be made publicly known. Confidential business information submitted by developers will not be disclosed outside of SFA without the developer's explicit consent.

1.7 SFA understands that genome editing is an emerging technology and will update this guidance document periodically as the technology evolves. Please submit enquiries and feedback via the online feedback form: https://csp.sfa.gov.sg/feedback

2 Procedure for notifying SFA on genome edited crops without foreign DNA

2.1 A crop developer intending to sell a GEd crop in Singapore for use as food and/or animal feed must first determine whether said crop contains foreign DNA. If the crop does not contain foreign DNA, SFA encourages the developer to notify SFA on the crop (**Pathway A** in the Flowchart below). A non-exhaustive list of examples of GEd crops that are considered to not contain foreign DNA include:

(a) A crop with a non-functional gene arising from cellular repair of a targeted DNA strand break (i.e., gene knock-out).
(b) A crop containing a targeted single base pair substitution in any part of the genome.
(c) A crop (host) where an endogenous gene has been substituted with a homologous gene variant (i.e., allele) originating from another crop that can reproduce with said host via conventional breeding (e.g., breeding between two tomato varieties).

2.2 If the crop contains foreign DNA, said crop will need to undergo SFA's pre-market approval process (**Pathway B**). A non-exhaustive list of examples of GEd crops that are considered to contain foreign DNA include:

(a) A crop containing DNA from a bacterial, animal, viral sources, or containing DNA sequences not found in nature.
(b) A crop containing DNA from another crop that cannot undergo conventional breeding with the GEd crop (e.g., insertion of corn DNA into tomato).

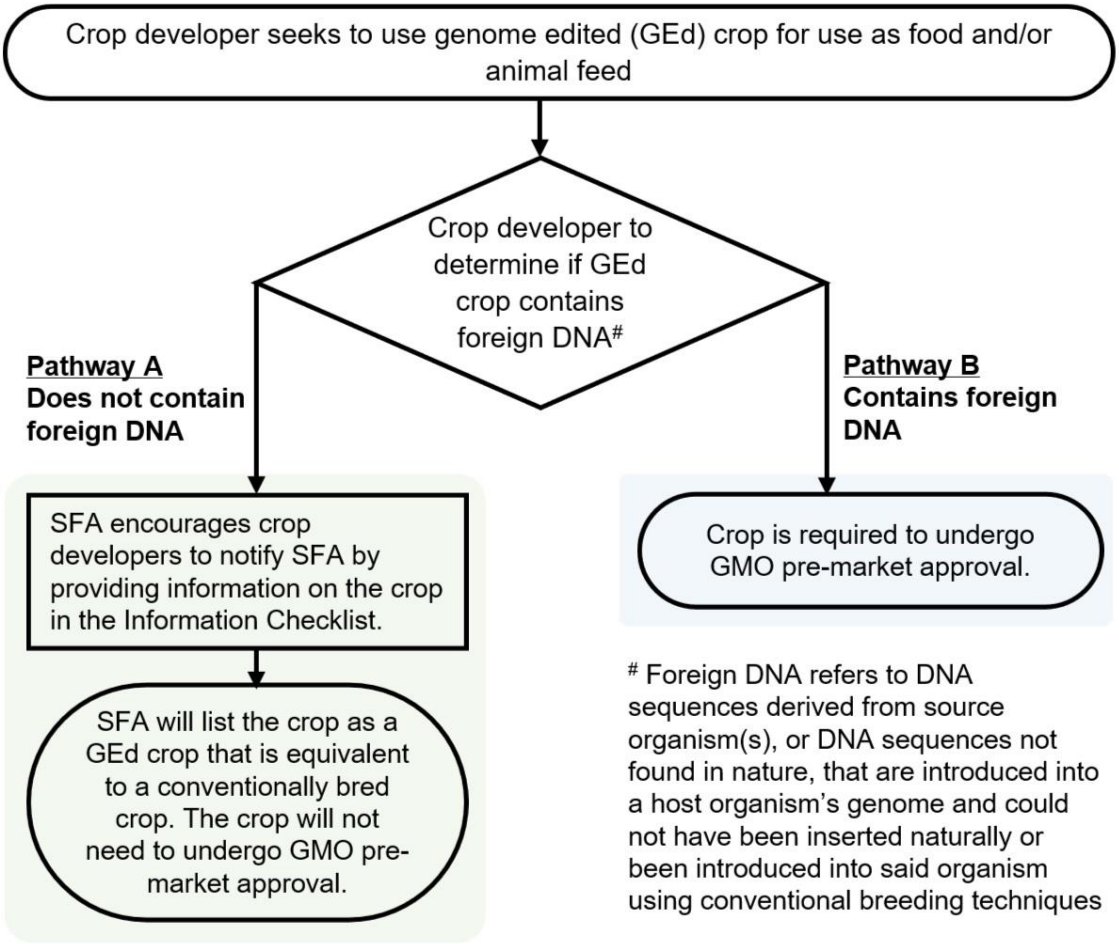

Figure 1. Flowchart of regulatory framework for GEd crops

2.3. To notify SFA on GEd crops without foreign DNA (**Pathway A**), please provide full information in the Information Checklist found in Section 3 below. Please submit the completed Information Checklist to the following SFA officers:

- Dr Tan Yong Quan: tan_yong_quan@sfa.gov.sg
- Dr Wang Yanwen: wang_yanwen@sfa.gov.sg

2.4 Upon receipt of complete information in the Information Checklist, SFA will verify the developer's determination that the GEd crop does not contain foreign DNA based on the information provided. After SFA has verified that the GEd crop does not contain foreign DNA, SFA will list the crop under a list of GEd crops that have completed the Notification process. SFA will not require these crops to undergo GMO pre-market assessment.

2.5 SFA does not charge any fees to process Notifications on GEd crops without foreign DNA. SFA expects to inform developers on whether SFA agrees that the GEd crop does not contain foreign DNA within 60 – 90 calendar days, **upon receipt of complete information in the Information Checklist**.

3 Information Checklist for Notification of GEd crop without foreign DNA for use as food and/or feed

Q1. Developer information

(a) Company name

(b) Unique Entity Number (applicable for entities based in Singapore)

(c) Address

(d) Name and designation of contact person

(e) Contact information

Q2. Basic information on GEd crop

Note: SFA will include only the company name and information provided in Q2 in the List of GEd crops that have completed Notification that is published on SFA's website.

(a) Scientific / common name of the crop from which the GEd crop was bred

(b) Commercial / proprietary name of the GEd crop

(c) Marketed traits (e.g., pest resistance, increased vitamin production, longer shelf life)

(d) Intended use of GEd crop (i.e., as human food and/or animal feed)

Q3. Further information on GEd crop

(a) Provide information on complete and ongoing international regulatory approvals / registrations / notifications in other countries and jurisdictions.

(b) Is there a scientific basis to identify and analyse any food safety hazard(s) that is/are new or at increased levels in the GEd crop compared to the conventional counterpart? If so, please provide results of analysis.

Q4. Information on genome editing process and verification

(a) Provide the name(s) of genome editing technique(s) used, along with a summary of the genome editing process.

(b) Provide name(s) and genomic location(s) of the genetic sequence(s) in the organism's genome that has/have been edited, along with known function(s) of the edited sequence(s).

(c) Provide a description of the obtained phenotypic traits resulting from the genome editing process on the crop.

(d) Provide a summary of how the sequence alterations in the organism were verified. Verification should be performed using standard molecular biology techniques, such as targeted sequencing, or Next Generation Sequencing (NGS).

(e) For the final GEd crop, provide evidence verifying the complete removal of foreign nucleotides (e.g., plasmids, guide RNA, oligonucleotides, carrier DNA) and/or proteins that were transiently present in the organism at some point during the genome editing process. Evidence provided should be based on standard molecular biology methodologies such as whole genome sequencing or genomic Southern blotting. Provide a summary of the removal process, including details of the number of generations of segregation or backcrossing where applicable.

(f) Provide a summary of how the phenotypic trait(s) in the final GEd crop was/were verified.

(g) Provide evidence that the genome alterations resulting from genome editing, as well as the phenotypic traits resulting from said alterations, are stably inherited through several generations and are consistent with applicable laws of inheritance.

Q5. Other information

(a) Please provide information on the GEd crop that the developer thinks may be relevant but was not requested above.

3.6 Please note that incomplete information or information that is not substantiated by scientific evidence or reasoning may delay the Notification processing time.

3.7 Business confidential information submitted by developers will not be disclosed outside of SFA without the developer's explicit consent. Please note that SFA does not sign non-disclosure agreements (NDA) with companies for the purposes of evaluating the information submitted, as SFA employees are bound to the preservation of secrecy under Section 34 of the Singapore Food Agency Act 2019.

4 Frequently Asked Questions

Q4.1 **I am not entirely sure if the food crop I am intending to import for the local market is eligible for Notification (Pathway A). How can I seek further clarification?**

SFA encourages developers of GEd crops to engage SFA early to clarify various issues regarding the applicability of their products for Notification. Importers are advised to consult with the crop developers/suppliers on the characteristics (e.g., has it undergone genome editing) of the crops that they are obtaining from the developers/suppliers. Please submit enquiries and feedback via the online feedback form: https://csp.sfa.gov.sg/feedback

Q4.2 **Does SFA require raw chemical and biological analysis data for the information requested?**

For first submission of the Information Checklist, summary figures or tables of the characterisation data would be preferred. Nonetheless, if further information is needed to clarify if the crop contains foreign DNA, SFA may request for companies to provide further data, including raw data from chemical and biological analysis.

Q4.3 **How is the Notification process for GEd crops without foreign DNA different from the GMO pre-market approval process?**

Upon receipt of complete information as denoted in the Information Checklist, SFA expects to inform the developers on the outcome of the Notification within 60 – 90 calendar days.

The pre-market approval process for GMOs involves submission of the product dossier to Singapore's Genetic Modification Advisory Committee (GMAC) for holistic biosafety evaluation of the genetic modifications made. Upon endorsement by GMAC, SFA will follow up with a food safety assessment before an approval can be given for said GMO to be imported into Singapore for use as food. Overall, the GMO pre-market approval process generally takes an estimated 12 – 18 months.

Q4.4 **Foreign DNA, nucleotides, and/or proteins were introduced into the host crop during genome editing. Does this disqualify the host crop from notification?**

SFA is aware that transient introduction of foreign DNA, nucleotides, and/or proteins is often used during the genome editing process to make the necessary DNA changes. If foreign DNA, nucleotides and/or proteins remain in the GEd final crop, the crop would be required to obtain GMO pre-market approval before it is allowed to be sold or offered as food and/or feed. If foreign DNA, nucleotides and/or proteins are completely removed from the final crop, and removal was verified based on the criteria indicated in the Information Checklist, the product would be eligible for Notification.

Q4.5 **How might more recently developed genome editing techniques, such as base editing, prime editing or retron editing, be regulated under this guideline?**

SFA focuses on the product when looking at the food safety of GEd crops. Products generated using very recent or other genome editing techniques not developed at the point of writing can still be eligible for Notification as long as the final crop does not contain foreign DNA, nucleotides, and/or proteins.

Q4.6 **Is genome editing the same as gene editing?**

Genome editing is used interchangeably with gene editing by scientific researchers and by various food agencies all over the world. Both terms have the same meaning, and genome editing is the term used by SFA for consistency.

Genome editing can fall under terms used by other food safety agencies. These terms include but are not limited to:

- New Genomic Techniques (NGT)
- New Breeding Techniques (NBT)
- Precision breeding

Q4.7 **Is genome editing the same as genetic modification?**

From SFA's perspective, genome editing is not the same as genetic modification. While both genome editing and genetic modification refer to the use of modern biotechnology tools to alter an organism's genome, genome editing represents a more

recent set of tools, which include ZFN, TALENs, and CRISPR nucleases, that allow researchers to make precise changes to an organism's genome. Many of these changes do not insert foreign DNA into the final product.

In contrast, genetic modification generally involves insertion of foreign DNA, generating organisms that could not have been produced via conventional breeding.

Q4.8 **Why does SFA ask crop developers to indicate if there is a basis to identify and analyse any food safety hazard(s) that is/are new or at increased levels in the GEd crop compared to the conventional counterpart?**

SFA would like to highlight that all food businesses have a continuing responsibility to ensure the safety of their food products sold or offered to the public. This includes developers of new crop varieties that have been obtained through genome editing. Therefore, for GEd crops where there is a scientific basis to investigate if new food safety hazards could be introduced or existing hazards could be produced at increased levels, SFA expects developers to have already analysed these hazards as part of their product development process. For example, a tomato variety that has undergone genome editing to increase its plant sterol levels should also be analysed for potentially increased levels of toxic glycoalkaloids, such as tomatine. This is because plant sterols and glycoalkaloids share a similar biosynthesis pathway.

On the other hand, for GEd crops where there is no scientific basis to identify and conduct analysis on hazards that are new or at increased levels, there will not be a need to conduct hazard analysis. For example, a GEd tomato variety that has a disease susceptibility gene inactivated is unlikely to produce new or increased levels of food safety hazards if the gene is not involved in biosynthesis of components that are food safety hazards.

Due to the complexities of plant biology, SFA understands that for some GEd crop varieties, developers may have uncertainties on whether these varieties could have new food safety hazards or increased production of existing hazards. In such cases, developers may consider discussing further with SFA on their specific products.

Q4.9 **What is SFA's perspective on potential off-target DNA changes that can arise during the genome editing process?**

SFA notes that conventional crop breeding routinely introduces off-target DNA changes. SFA also notes that while there are existing scientific tools and genome editing protocols to reduce the probability of off-target DNA changes, it is not possible for current genome editing tools to have zero probability of off-target DNA changes.

Off-target DNA alterations can either have no impact or negatively impact the resulting crop's characteristics. For conventional breeding, SFA is aware that developers routinely identify crops with undesirable characteristics and eliminate them from further development. Therefore, SFA anticipates that developers who utilise genome editing will likewise identify and eliminate crops with undesirable characteristics as part of the crop development process.

SFA encourages crop developers to refer to scientific resources, such as those provided below, that provide technical guidance on reducing the probability of off-target changes.

- Liang, Z., Chen, K., Zhang, Y. et al. Genome editing of bread wheat using biolistic delivery of CRISPR/Cas9 in vitro transcripts or ribonucleoproteins. *Nat Protoc* **13**, 413–430 (2018). https://doi.org/10.1038/nprot.2017.145
- Osakabe, Y., Liang, Z., Ren, C. et al. CRISPR–Cas9-mediated genome editing in apple and grapevine. *Nat Protoc* **13**, 2844–2863 (2018). https://doi.org/10.1038/s41596-018-0067-9
- Sturme, M. H. J. et al. Occurrence and Nature of Off-Target Modifications by CRISPR-Cas Genome Editing in Plants. *ACS Agric. Sci. Technol.* **2**, 192–201 (2022). https://doi.org/10.1021/acsagscitech.1c00270
- Stroik, S. CRISPR 101: Off-Target Effects. https://blog.addgene.org/crispr-101-off-target-effects

Q4.10 **Does SFA consider mutagenesis using cosmic rays ("space breeding") or proton beams to be conventional breeding techniques?**

SFA considers new modalities in mutagenesis via ionising radiation, such as using cosmic rays (also termed "space breeding") and proton beams to be conventional breeding techniques. This is because the nature of mutagenesis (using high energy particles / radiation to induce DNA mutations) is the same.

Q4.11 **How do I know if the Information Checklist that I have submitted is complete?**

SFA will inform you if the Information Checklist is complete. If it is incomplete, SFA will contact you with our comments and questions to assist you in submitting a complete Information Checklist.

5 Revision History

Version	Date	Changes made
1	01 Aug 2024	First issue

6 Annex: Glossary of Terms and Abbreviations

Term / abbreviation	Meaning or full name
Allele	A gene variant that is observed at a given location on a chromosome
Base pair	A fundamental unit in double stranded nucleic acids consisting of the adenine-thymine nucleobase pair or guanine-cytosine nucleobase pair
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats, a genome editing tool
DNA	Deoxyribonucleic acid
GEd	Genome edited
GM	Genetically modified
GMO	Genetically modified organism
Host	Organism that is undergoing or has undergone any form of genetic engineering, including genome editing
Nuclease	An enzyme that cuts nucleic acid sequences (DNA or RNA)
NGS	Next-generation sequencing
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
TALEN	Transcription activator-like effector nuclease, a genome editing tool
ZFN	Zinc finger nuclease, a genome editing tool