Health Canada Santé Canada

Canada

Consultation Document:

Proposed Changes to Health Canada Guidance on the interpretation of Division 28 of Part B of the *Food and Drug Regulations* (the *Novel Food Regulations*):

When is a food that was derived from a plant developed through breeding a "novel food"?

March 2021

The goal of this public consultation is to obtain the views/perspectives of those for whom the new guidance is intended, including plant developers and the general public at large.

The final guidance will be published by the end of August 2021.

YOUR HEALTH AND SAFETY... OUR PRIORITY.

1. Introduction

Canada's *Novel Food Regulations* (Division 28, Part B, of the *Food and Drug Regulations*, *or FDRs*) were published in 1999. These regulations (set out in Annex 1) require a manufacturer to file a pre-market notification and for the regulator to determine that the information in that notification establishes that the food is safe before it can be sold. The scope of these requirements is delineated by a definition of novel food in these regulations. When a food is "novel" the regulations require pre-market notification and regulatory approval before sale.

To aid in the interpretation of these *Novel Foods Regulations*, Health Canada published the *Guidelines for the Safety Assessment of Novel Foods*. These guidelines describe how regulators conduct novel food pre-market safety assessments and the information that must be contained in a notification. This guidance document was last updated in 2006.

Since that time, technological advancements have created new tools of genetic modification by which new plant varieties can be developed. These tools have been collectively referred to as gene editing technologies.

Agricultural stakeholders have highlighted the need for clear, predictable and transparent regulation of products of plant breeding including those developed using gene editing technologies.

In August 2020, Health Canada announced its intent to develop and publish new guidance for novel foods to provide better clarity and predictability in how the *Novel Food Regulations* are applied to products of plant breeding. This new interpretive guidance takes account of the health and safety objectives of the regulations, making use of the regulator's experience as this field of science has evolved since the regulations were published. This new guidance seeks to interpret the *Novel Food Regulations* in a manner that takes account of the current scientific knowledge and the underlying scheme and purpose of these rules (to require pre-market assessment of novel foods that may pose a potential risk to the consumer) in a way that reflects the importance of innovation and a greater understanding of plant breeding technologies and the benefits of aligning with our international regulatory partners.

This proposal will supplement the existing novel foods guidance, focusing on foods derived from products of plant breeding. Further analysis will later be undertaken to assess the merits of updating the novel foods guidance as it pertains to foods derived from animals and microorganisms.

The development of this guidance represents the first phase of a broader, multi-year effort to modernize guidance for all novel foods as defined under the *Novel Food Regulations*. Based on what is learned during this phase, regulatory changes will be made, if needed.

The Department intends to add this new guidance to the 2006 *Guidelines for the Safety Assessment of Novel Foods* as an appendix to the existing guidance. This new guidance seeks to clarify which foods derived from products of plant breeding are novel foods subject to pre-

market notification and assessment under the *Novel Foods Regulations* (Division 28, Part B, of the *Food and Drug Regulations*).

As other parts of the 2006 *Guidelines* are updated in the coming years, Health Canada may revisit the overall organisation of these guidelines.

For over a century, plant developers[1] have used a large array of breeding methods to produce thousands of plant varieties which have been safely used in the Canadian food supply. Over the past 20 years, Health Canada has assessed many different foods derived from genetically modified plants as novel foods (including both products of conventional-breeding[2] and biotechnology). All of these foods have been assessed in accordance with the *Novel Food Regulations* and determined to be safe for consumption. Taking account of this experience and the evolving scientific knowledge about the safety of these foods, Health Canada is proposing to introduce new guidance to provide greater clarity and predictability to plant developers with regards to which foods derived from products of plant breeding do/do not meet the definition "novel food" in section B.28.001 of the *FDR*s.

During the development of this new guidance, Health Canada evaluated how foods derived from plants developed using gene editing technologies have been regulated to date, how the science has evolved and whether the regulator's current approach to interpreting these regulations could be improved to better align with their safety objectives. A primer on gene editing technologies was developed that informs the Department's proposed position on how foods derived from gene-edited plants are to be regulated under a modified approach to applying these novel food rules as they apply to foods derived from plants developed using these technologies. This primer is attached to this Policy Consultation Document as Annex 2.

2. Background

2.1 Development of the Novel Foods Regulation

In 1999, Health Canada published new Regulations in part to address uncertainty in the safety of plants developed using biotechnology (i.e., recombinant DNA (rDNA) technologies). However, unlike most jurisdictions which developed legislation based on a specific process of genetic modification, Canada's *Novel Food Regulations* were written to broadly characterise (define) all these products – including certain conventionally-bred products – as "novel", requiring pre-market notification and safety assessment prior to sale. To date, these rules have been interpreted in a way that has not taken account of whether the breeding method used to develop the plant is well characterized as safe in determining whether these pre-market notification and assessment requirements apply to a food.

[1] For the purpose of this document, the term 'developer' is used as an umbrella term that represents all parties involved in the development of a new plant variety from concept to commercialisation.
[2] For a list of examples of conventional methods of plant breeding, see Annex 3 of this document.

2.2 Plant breeding practices that support food safety

Plant developers rigorously analyze and understand their new plant varieties in relation to food safety during the breeding process prior to commercialization, and throughout the commercial lifespan of the plant variety including one that is developed using biotechnology. In-depth product characterization limits the risk that plants can have unintended food safety effects related to an intentionally developed characteristic. These characterizations also provide assurance that any consequences of new characteristics are well-understood in relation to food safety.

The following points represent Health Canada's understanding of plant developer practices and competencies relating to the full characterization of a new product of plant breeding, regardless of what methods were used in its development and selection.

1. Plant developers are experts in their plant variety and the plant species in relation to its use in food, and related food safety. This means that:

    a. Developers understand the typical range of important analytes that make up the nutrients, anti-nutrients, allergens, and toxins of the plant variety they are developing or have developed;
    b. Developers understand the intended characteristic(s) in their new plant variety and how it can influence the exposure of Canadians to nutrients, anti-nutrients, allergens, and toxins of the plant-derived food; and
    c. Developers are aware of expected end uses of their products and how these end uses influence the exposure of Canadians to nutrients, anti-nutrients, allergens, and toxins of the plant-derived food.

2. It is well established that plant developers are current in their knowledge of how the intended characteristic(s) may affect the expression of other characteristics, and how this may affect food safety. For example, how changes in a metabolic pathway could influence nutrient bioavailability, or lead to the accumulation of other metabolites that may have allergenic and/or toxic and/or anti-nutrient properties.

3. It is well established that plant developers consider whether there are possible risks to food safety linked to the new characteristics that they have or plan to introduce in the plant. In this sense, plant developers are considering risk hypotheses involving altering the levels of nutrients, anti-nutrients, allergens, and toxins.

4. It is well established that throughout the plant development process, any plants with characteristics that can negatively affect food safety are noted and discarded.

5. It is well established that following commercialization, plant developers carefully observe their plant varieties for characteristics that can negatively affect food safety in relation to the plant variety they are working with. Any plants observed to possess characteristics that can negatively affect food safety are noted and discarded.

The data generated during plant variety development, as well as the post-commercialization variety stewardship, is of high quality and of sufficient rigor to adequately support the conclusion that this class of products is safe so as not to be within the meaning of novel food as defined in section B.28.001 of the *FDRs*.

3. Guidance for Implementation: Foods derived from genetically modified[3] products of plant breeding that are not novel foods that require pre-market notification

Taking account of these conclusions, it is Health Canada's position that the following five categories of foods would not add to our body of knowledge about their safety, if assessed individually as novel foods in accordance with sections B.28.002-B.28.003 of the *FDRs* because their safety is already well characterized:

1. Foods derived from plants with genetic modifications that do not alter an endogenous protein so that it now demonstrates significant homology with a known allergen or toxin relevant to human health; or

2. Foods derived from plants with genetic modifications that do not increase levels of an endogenous allergen, an endogenous toxin or an endogenous anti-nutrient beyond the documented range; or

3. Foods derived from plants with genetic modifications that do not have an impact on key nutritional composition and/or metabolism; or

4. Foods derived from plants with genetic modifications that do not change the food use of the plant; or

5. Foods derived from plants with genetic modifications that are not the result of the insertion of foreign DNA[4].

The Department proposes to interpret the *Novel Food Regulations* narrowly to classify foods within these categories as ones that do not meet the threshold of novelty of characteristics required for them to meet the definition of a "novel food" set out in section B.28.001 of the *FDRs*. The definition, interpreted narrowly in this way takes account of the precautionary safety objectives that underlie these pre-market safety assessment regulations.

[3] As defined in Section B.28.001 of the *FDRs*, "genetically modify" means to change the heritable traits of a plant, animal or microorganism by means of intentional manipulation.
[4] The term 'foreign DNA' commonly refers to DNA that is not currently a part of the organism's genome and is introduced through *in vitro* means. For example, a DNA sequence encoding a gene from a bacterial species is considered to be foreign DNA to the plant for which the sequence is introduced.

Section 4 below, further explains the Department's position that the safety of these categories of foods is well characterized so that an assessment of them would not add to what is known about their safety, if they were subject to pre-market notification as a novel food in accordance with the *Novel Food Regulations*.

4. Rationale for the Guidance: Impacts on food safety and nutrition

While most characteristics introduced or altered in plants are known to not affect food safety, there are certain characteristics that would pose a potential safety concern and would be considered "novel food" and require a pre-market assessment.

The following explains when characteristics do pose potential safety or nutritional concerns that merit a food derived from a plant to be classified as novel:

4.1 Impacts on allergens, toxins, and anti-nutrients

The expression of an altered endogenous protein that now demonstrates significant[5] homology with a known allergen or toxin relevant to human health; increased expression of an endogenous allergen or toxin; or an increase in the expression of an endogenous anti-nutrient is considered to be a trigger for a food being "novel", requiring a pre-market notification and safety assessment prior to sale.

4.2 Impacts on key nutritional composition and metabolism

In recognition of the variability in nutritional composition that is present due to a variety of factors, Health Canada believes that the use of documented ranges[6] remains a useful approach to identifying those products that require pre-market assessment. As a result, Health Canada will concentrate on those key nutrients[7] identified as potential nutrients of concern due to an existing high prevalence of inadequacy (e.g., more than 10% of the population has usual intakes

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[5] Significant homology is typically >35 % overall sequence identity between amino acid sequences, or 100 % sequence identity over 8 consecutive amino acid residues with the sequence of a known allergen.
[6] For the purpose of this guidance, documented ranges refers to the ranges documented in the Organisation for Economic Co-operation and Development (OECD) Consensus Documents on Compositional Considerations for New Varieties and other crop composition databases (e.g., the Agriculture and Food Systems Institute Crop Composition Database). Documented ranges from the published literature and the developers own experience are also acceptable sources of information where they refer to commercialised varieties.
[7] For the purpose of this guidance, a key nutrient is a nutrient of food that has an Estimated Average Requirement (EAR) and/or a Tolerable Upper Intake Level (UL) as described in the Dietary Reference Intakes published by the National Academy of Medicine.

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that are below the Estimated Average requirement (EAR)) or high prevalence of intakes that exceed the Tolerable Upper Intake Level (UL) in the Canadian population.

All products where a key nutrient of concern is outside the documented range and for which consumption is likely to result in a higher prevalence of inadequacy or over-consumption among Canadians require pre-market notification and assessment as a novel food.

Similarly, developers should consider the bioavailability of key nutrients or the manner in which derived foods are metabolized in the body. If a characteristic of a plant results in key nutrients becoming more or less available upon consumption of the plant-derived food, this may in turn worsen the prevalence of nutritional inadequacy or of intakes that exceed the UL. Products with an altered bioavailability of a key nutrient(s) require pre-market notification and assessment as a novel food.

4.3 Changes in the food use of the plant

In some cases, new plant varieties may exhibit altered or new characteristic(s) that change the expected usage of the plant-derived foods. Such changes may result from altering a component of the edible tissues such that consumers are expected to consume greater or lesser amounts of the plant-derived foods, or the plant has been modified such that a new part/tissue of the plant will be consumed as food. Plant varieties that have altered or new characteristics that result in such a change in food use continue to be considered “novel food” that require pre-market notification and assessment prior to sale.

4.4 Food products derived from plants that contain foreign DNA

Foods derived from plants that have been genetically modified such that they contain DNA not previously found in that species (i.e., foreign DNA) require pre-market notification and assessment as novel foods.

Of specific importance for gene-edited plants, the DNA encoding gene editing machinery (e.g., CRISPR Cas protein(s) and associated guide RNAs) is considered to be foreign DNA (as it is bacterial in origin). Most plant developers will remove these genes through subsequent plant breeding however, in the event that a gene-edited plant still contains the DNA encoding this machinery within its genome, foods derived from such a gene-edited plant require pre-market notification and assessment as novel foods.

5. Requesting a Novelty Determination for foods derived from a new plant variety

The Department has a voluntary process by which developers can request a novelty determination for foods derived from their new plant variety. Plant developers are encouraged to contact the Food Directorate Submission Management and Information Unit at hc.smiu-ugdi.sc@canada.ca to make a request.

Health Canada maintains a list of non-novel determinations for food and food ingredients that have been made since 2012. This list, available here, is intended to increase transparency and provide predictability to plant developers.

6. Voluntary Transparency Initiative expanded for foods derived from plant breeding using gene editing technologies that fall outside the scope of this Guidance:

Plants that are developed using gene editing technologies that fall outside the scope of the definition of a “novel food” according to this guidance will not be subject to pre-market notification. However, there is great interest from and benefit for regulators, plant developers, and the public in greater transparency regarding all products developed using these technologies that are present in the Canadian food supply.

To address this interest, Health Canada will expand its transparency approach beyond the recently launched List of non-novel determinations for food and food ingredients. Health Canada Voluntary Transparency Initiative will also include gene-edited plants developed for food use that are not novel foods, and for which developers are invited to submit to Health Canada a concise set of information. Health Canada will publish this information online for public access.

The goal of this initiative is to provide Canadians with a clearer understanding of the gene-edited products in the Canadian market with the goal of enhancing public trust in these products and the regulatory system. This initiative will also assist developers in understanding how the regulatory framework applies to their products.

Should it be determined that developers are not voluntarily disclosing this information, amendments to the *FDRs* to require such reporting in the future may be considered.

It is important to note that this voluntary system is to be used for products ready for commercialization and not for theoretical products.

Plant developers should provide the following information:

- Contact and company information
- Name of plant variety / identifier

- Intended date of commercialization
- Name of plant species
- A description of the altered or new characteristic(s) of the new plant variety. This description should explain what change(s) were made to the plant genome, what result this change(s) has within the plant's cells, and the observed phenotype that results from this change(s). No data is required for this description
- A description of how the altered or new characteristic(s) was developed in the new plant variety
- Information regarding which analyses were performed to confirm that the new plant variety does not contain any DNA sequence related to the gene editing technology used in the plant's development. Furthermore, confirmation that any DNA sequences in the plant's genome which may be susceptible to "off-target" edits based on the gene editing technology used have been analysed.
- A rationale to support the developer's self-determination that their new gene-edited plant is not Novel, including the lack of any substantial differences that would be relevant to food safety.
- A description of the intended food use(s) of the plant variety
- A description of the regulatory status of the plant variety as an animal feed and environmental release in Canada (if applicable)

Plant developers are encouraged to provide the above-mentioned information to Health Canada's Submission Management and Information Unit (SMIU) at least 90 calendar days prior to commercialization of their product. This information will be provided in a form (to be developed) that will be available on Health Canada's website. As the Department's "single-window" for submissions/inquiries related to novel foods, the SMIU will forward the notification to the Novel Foods Section for further review.

The Novel Foods Section will review the information provided and, upon concurrence with the developer's rationale for the non-novel status of foods derived from their gene-edited plant, will publish a summary of this information on Health Canada's website within 60 calendar days under a new table titled "Health Canada's List of Non-Novel Gene-Edited Plants for Food Use".

This review is not a pre-market safety assessment of the gene-edited plant, rather a determination of concurrence with the non-novel status of the foods derived from the gene-edited plant. Prior to publication, Health Canada will give the developer the opportunity to review the information that will be published for the purpose of identifying and redacting any information that is considered to be confidential business information (CBI).

It is important to note that Health Canada reserves the right to conduct a pre-market safety assessment of foods derived from a specific gene-edited plant and request additional information if the Department believes that such foods meet the definition of a "novel food", as described in this guidance.

Annex 1: *Novel Food Regulations*

***Food and Drug Regulations*, Part B, Division 28**

Novel Foods

Interpretation

B.28.001 The definitions in this section apply in this Division.

genetically modify means to change the heritable traits of a plant, animal or microorganism by means of intentional manipulation. (*modifier génétiquement*)

major change means, in respect of a food, a change in the food that, based on the manufacturer's experience or generally accepted nutritional or food science theory, places the modified food outside the accepted limits of natural variations for that food with regard to

(a) the composition, structure or nutritional quality of the food or its generally recognized physiological effects;

(b) the manner in which the food is metabolized in the body; or

(c) the microbiological safety, the chemical safety or the safe use of the food. (*changement majeur*)

novel food means

(a) a substance, including a microorganism, that does not have a history of safe use as a food;

(b) a food that has been manufactured, prepared, preserved or packaged by a process that

(i) has not been previously applied to that food, and
(ii) causes the food to undergo a major change; and

(c) a food that is derived from a plant, animal or microorganism that has been genetically modified such that

(i) the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism,
(ii) the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism, or
(iii) one or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism. (*aliment nouveau*)

Pre-Market Notification

B.28.002 (1) No person shall sell or advertise for sale a novel food unless the manufacturer or importer of the novel food

(a) has notified the Minister in writing of their intention to sell or advertise for sale the novel food; and

(b) has received a written notice from the Minister under paragraph B.28.003(1)(a) or subsection B.28.003(2).

(2) A notification referred to in paragraph (1)(a) shall be signed by the manufacturer or importer, or a person authorized to sign on behalf of the manufacturer or importer, and shall include the following information:

(a) the common name under which the novel food will be sold;

(b) the name and address of the principal place of business of the manufacturer and, if the address is outside Canada, the name and address of the principal place of business of the importer;

(c) a description of the novel food, together with

(i) information respecting its development,
(ii) details of the method by which it is manufactured, prepared, preserved, packaged and stored,
(iii) details of the major change, if any,
(iv) information respecting its intended use and directions for its preparation,
(v) information respecting its history of use as a food in a country other than Canada, if applicable, and
(vi) information relied on to establish that the novel food is safe for consumption;

(d) information respecting the estimated levels of consumption by consumers of the novel food;

(e) the text of all labels to be used in connection with the novel food; and

(f) the name and title of the person who signed the notification and the date of signing.

B.28.003 (1) Within 45 days after receiving a notification referred to in paragraph B.28.002(1)(a), the Minister shall review the information included in the notification and

(a) if the information establishes that the novel food is safe for consumption, notify the manufacturer or importer in writing that the information is sufficient; or

(b) if additional information of a scientific nature is necessary in order to assess the safety of the novel food, request in writing that the manufacturer or importer submit that information.

(2) Within 90 days after receiving the additional information requested under paragraph (1)(b) the Minister shall assess it and, if it establishes that the novel food is safe for consumption, notify the manufacturer or importer in writing that the information is sufficient.

SOR/99-392, s. 1; SOR/2018-69, s. 27

Annex 2: A Primer on Gene editing technologies in relation to Health Canada's product-based regulatory framework for Novel Foods

1. What is gene editing technology?

Gene editing technology refers to biotechnology tools that can be used to generate modifications to the genome of living organisms by adding, removing, or altering genetic sequences at precise locations. Gene editing can accomplish the same objectives as conventional breeding methods, including plant crossing and hybridization, chemical and/or physical (e.g., ionizing) mutagenesis, and/or genomic modifications that arise through the use of rDNA technologies. However, gene editing tools accomplish these objectives with higher precision and with no more unintentional effects than the technologies used to date (Chen et al., 2019; Graham et al., 2020).

The term 'gene editing technology' describes a number of tools used in biological sciences. Today, it is mainly used to describe CRISPR-Cas9, but it also captures Oligonucleotide Directed Mutagenesis (ODM), Transcription Activator-like Effector Nucleases (TALENs), Zinc-Finger Nucleases (ZFNs) and mega nucleases, as well as variations of these tools. These technologies continue to evolve to improve their precision, efficiency, and to identify experimental conditions to expand the plant species that developers can improve through gene editing (Young et al., 2019; references within Graham et al., 2020). For the sake of clarifying terminology, these technologies are also commonly referred to as plant breeding innovations (PBI). In Europe, they are also referred to as new breeding techniques (NBTs) or new genomic techniques (NGTs).

To date, gene editing has been successfully used to modify the genomes of numerous plants (Zaman et al., 2019) and it is expected that plant developers will use gene editing tools to improve many other plants and crops for food use, among other uses.

2. How can gene editing technology be applied to plant breeding?

Plant developers have indicated that gene editing will be used to introduce new or alter existing characteristics to improve agricultural performance, nutritional composition, and/or consumer preference of plants (Zhang et al., 2018). The ways plant developers will use gene editing tools to accomplish these objectives could involve introduction of small insertions or deletions at precise genomic sites, precise deletions of larger segments of genomic DNA, as well as insertions of whole genes and their regulatory elements in ways that would be considered rDNA (Chen et al., 2019; Zhang et al., 2018). Furthermore, plant developers have indicated that gene editing can help identify useful characteristics in regions of plant genomes that developers currently have difficulty manipulating using conventional breeding methods. As a result, gene editing has the potential to identify and improve new characteristics within the plant species not previously accessible to plant developers.

3. Gene editing technologies – creating genetic variation in plants.

Plant breeding depends on having genetic variation from which to select. In conventional breeding programs, this variation has evolved and continues to evolve naturally within plant species over time, and/or is introduced into the species by means of wide crosses, tissue culture techniques, or the application of chemical and/or physical mutagens. rDNA technology, where genetic sequences are inserted in to a plant's genome using biotechnology tools, is yet another approach to expand on the genetic variation that plant developers depend upon. Though these are different sources of genetic variation, this variation all occurs randomly in terms of its location within the plant genome (Schnell et al., 2015).

Gene editing technologies are the most recent tools that have been developed to expand the genetic variation that plant developers need to meet the demands of growers and consumers and assist with global food security and sustainability objectives. How gene editing differs in relation to conventional and rDNA-based plant breeding genetic variation is that the gene-edited variation can be introduced at precise, predetermined locations within the plant genome (Chen et al., 2019). The precision aspect of gene editing can simplify the food safety evaluation of a new, gene-edited crop and therefore offers the possibility for new products to be developed and commercialized in a timely and efficient manner.

4. Gene editing technologies – unintentional off-target edits.

Off-target edits are genetic changes that result from the gene editing tools working at genomic sites other than the intended edit site (Wolt et al. 2016). Off-target edits can introduce unintended characteristics, and alter the risk profile of the plant-derived foods (Wolt et al., 2016; Zhao and Wolt, 2017).

With this in mind, there is some important context when thinking about off-target edits. Genetic variations that occur because of conventional breeding practices, or rDNA technology, can also introduce unintended characteristics, and therefore alter the risk profile of the plant-derived food. Health Canada and the Canadian Food Inspection Agency (CFIA) have previously determined that these sources of unintended characteristics have not posed higher risks than other genetic modification technologies and therefore do not require a higher level of scrutiny (Schnell et al., 2015).

As mentioned previously, conventionally-derived genetic variations occur randomly. However, off-target edits from gene editing are largely predictable because gene editing tools work on genome sites similar to the intended edit site. Based on the targeted DNA sequence to be edited, plant developers can use programs which predict other genomic sites that may be altered due to their degree of sequence similarity. Based on how off-target edits manifest, and as product developers will be primarily targeting genetic sequences that will alter biological processes to generate new or alter existing characteristics of plants, the off-target edit sites are more likely to inadvertently impact secondary biological processes when compared to random sources of unintentional characteristics that have been previously analyzed. As a result, it is not clear if the same risk analysis that was previously reported (Schnell et al., 2015) can be extended to off-target edits that result from gene editing technologies.

Though the probability of affecting a biological process is higher, it is important to acknowledge that affecting a biological process does not necessarily create a food safety risk. Also, it is important to point out that because off-target edits can be predicted, they can also be mitigated with good gene editing tool design. Furthermore, the presence of off-target edits can be directly investigated using targeted DNA sequencing (Wolt et al., 2016; Liang et al., 2017); something that cannot be reasonably accomplished for conventional, random variations.

Scientific studies evaluating off-target edits suggest that, though they are possible, they rarely occur even at predicted off-target sites in plants (Young et al., 2019, Hahn and Nekrasov, 2019 and reviewed in Fichtner et al., 2014).

Lastly, should off-target edits be present in a gene-edited plant, plant developers are able to remove them in most crops using breeding and selection, and/or backcrossing (Kaiser et al., 2020).

In summary, Health Canada will be expecting plant developers to characterize the potential off-target edit sites of their gene-edited plants.

5. Gene editing technologies – delivering the gene editing tools to living cells.

Gene editing tools, like all other forms of biotechnology used to modify plants, need to be delivered to living cells to work. Where gene editing technologies differ from conventional and rDNA breeding tools is in the way that DNA sequences encoding the components of gene editing technologies can, in some cases, become part of the product, and therefore the technology itself can contribute a new characteristic to the product (Wolt et al., 2016; Zhao and Wolt, 2017).

It is important to note that although this is one way to perform gene editing, it is not necessary to include these DNA sequences in the plant genome to successfully gene edit the plant. It is expected that plant developers are unlikely to use this approach (i.e., genomic integration of the gene editing technology) unless it is the only way to successfully gene edit the plant. Furthermore, during an October 16, 2020 Expert Panel meeting between government regulators and plant developers in both areas of academia and industry explained that should they choose to use this approach, they are unlikely to advance this particular product to commercialization without having subsequently removed these sequences.

Should a plant developer advance a gene-edited plant to commercialization where the DNA sequences encoding the gene editing tools are retained in the plant genome, then this product would be considered a Novel Food and the safety of this new characteristic would have to be substantiated as part of a pre-market safety assessment.

6. Gene editing technologies – one of many tools plant developers use together to create new plants.

Gene editing technology is unlikely to be used as an isolated tool when developing a new plant. With the exception of vegetatively propagated plants (e.g., sugarcane, potato, apples, etc.), gene-edited plants will undergo extensive crossing and selection. As part of this step, plant developers use conventional breeding methods to create large populations of plants from which

the majority are eliminated, and only a few plants are selected and retained for further development. Through this process of crossing and selection, plant developers eliminate undesirable characteristics from the population while advancing desirable characteristics (Kaiser et al., 2020; Glenn et al., 2017). Much of this field trial work occurs over the course of 5 or more years, and in diverse growing environments to evaluate the agronomic performance and crop quality (Kaiser et al., 2020).

For the most part, field trials are controlled and administered by the plant developer because the vast majority of characteristics being worked with in plants do not present any hazards to food safety. In the cases where a plant does possess a characteristic which may have an impact on food safety, key nutritional composition and/or metabolism, etc. and is considered Novel, developers are required to conduct their field trials in coordination with the CFIA's confined research field trial program (CFIA, 2012).

This matters in relation to off-target edits and the transfer of DNA sequences encoding the components of the gene editing technology to the plant genome because undesirable characteristics would include off-target edits, and may also include the DNA encoding the gene editing tools. As a result, these unique characteristics of gene editing technology will be eliminated from most products destined for the Canadian food supply.

7. Gene editing technologies – pre-market and post-market product safety

The food derived from gene-edited plants is what consumers will be exposed to, not the technology used to create these plants. As a result, it is the characteristics retained in the plant from which a food product is derived that determine product safety and whether or not the product will require a pre-market safety assessment.

It is important to also note that there are post-market requirements that provide for further controls which ensure product safety. Under Section 4 of the *Food and Drugs Act*, no person may sell a food that is harmful or unit for human consumption. Furthermore, in terms of food derived from plant sources, the *Seeds Regulations* (*Seed Regulations*, C.R.C., C. 1400, Part III, Variety Registration) require that if a food safety risk is identified for a registered plant variety then the registration of this plant variety must be canceled and the variety be removed from the market.

8. Summary

Using gene editing technologies, plant developers have the ability to create new plant varieties that are Novel and others that are not Novel. Plant developers have expressed the need for clear and predictable guidance to help in the determination of the regulatory status of their gene-edited plants. Through a review of the current scientific knowledge regarding the use of gene editing technologies to develop new plant varieties, Health Canada concludes that the use of gene editing technologies does not present any unique safety concerns compared to other methods of plant breeding. By consequence, foods derived from gene-edited plants are subject to the same considerations that determine the novelty status of all products of plant breeding, including the new elements of guidance presented in this consultation document.

Health Canada recognizes the need for greater transparency surrounding gene-edited plants as many of these plants will not be considered Novel, and thus they will not undergo pre-market

safety assessment prior to entering the Canadian food supply. To increase transparency regarding gene-edited plant varieties that are present in the Canadian food supply, this guidance describes a Voluntary Transparency Initiative whereby plant developers are encouraged to inform Health Canada of any non-novel gene-edited plant variety that they have developed for commercial use.

Annex 3: Examples of Conventional Methods of Plant Breeding

Techniques for overcoming reproductive barriers
• Bridge cross • Pollination through use of sub- or supra-optimal stigma age, or suboptimal conditions • Chemical-facilitated pollination • Pollination using pollen mixture treatments • Pollination through treatment and/or manipulation of the style • *In vitro* pollination • *In vitro* culture of excised ovaries • *In vitro* culture of excised ovules • *In vitro* culture of excised embryos (embryo rescue) • *In vitro* fertilization
Techniques for chromosome and genome manipulation
• Haploidization • Genome doubling, polyploidization • Production of alien addition or substitution lines • Chromosome translocation breeding • Manipulation of chromosome pairing in meiosis • Mutagenesis (via chemical mutagens or ionizing radiation) • Cell fusion (i.e., somatic hybridization) • Partial genome transfer
Other plant-breeding techniques
• Interspecific grafting • Hybrid variety production • *In vitro* tissue culture • Sex expression in monoecious or dioecious species • Apomixis • Marker-assisted breeding (MAB) • TILLING • Cell sorting

* Detailed descriptions and examples of the listed techniques can be found in van de Wiel et al., 2010. Traditional plant breeding methods. Wageningen UR Plant Breeding, Wageningen. Report 338.

** This table represents a list of methods which were, at the minimum, researched as potential tools for plant breeding. The majority of these methods were adopted by plant breeders and are used in current breeding programs.

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