CropLife AUSTRALIA

*Representing **the best** of the plant science industry*

CropLife Submission to Consultation Paper on Food Derived Using New Breeding Techniques

10 April 2018

1 EXECUTIVE SUMMARY

CropLife Australia welcomes the opportunity to provide comments to the Food Standards Australia New Zealand (FSANZ) *Consultation Paper on Food Derived Using New Breeding Techniques*, and the consideration of the definitions in the Australia New Zealand Food Standards Code for 'food produced using gene technology' and 'gene technology'.

CropLife's long held view is that *food derived from plant varieties developed through the latest breeding methods should not be differentially regulated based on the techniques employed during the plant's development if they are similar to, or indistinguishable from foods that could have been produced using plants developed through earlier breeding methods.*

CropLife is concerned about the prospect of pre-market regulation of foods based simply on the technique employed during the development of specific traits and not on the characteristics of the final food product.

Food derived from conventional breeding methods, such as those that harness spontaneous or induced mutagenesis to generate large amounts of genomic variation is not subject to pre-market safety assessment. There is no risk-based argument to suggest that food derived from similar genetic variation, when generated using newer plant breeding innovations, should be subject to pre-market regulation purely on the process through which it was created.

Food derived from plants created by cisgenesis and intragenesis should be considered analogous to that which can be derived from plants created using conventional plant breeding methods as the transfer of the same genetic elements would be possible.

Food derived from null segregant organisms does not contain any elements of the transgenic event and therefore should not be subject to pre-market safety assessment and approval as a GM food.

Plant breeding methods represent a continuum, from traditional crossing of two varieties to using molecular methods to introduce genes from other species into a targeted plant species. In the same way, plant breeding innovation is considered as part of this continuum, with different applications fitting into the continuum of plant breeding methods.

A discriminatory application of regulation with no basis in risk would result in a situation where certain methods of gene technology are excluded from the scope of regulation based on their history of safe use, while regulation would be applied to methods that result in even more precise and more predictable outcomes than ever achievable with earlier excluded methods.

To be 'future proof', the Code needs to refrain from differentially regulating the latest breeding methods, if they do not result in food that poses new risks relative to the food derived from plants developed using conventional breeding methods, that are currently excluded from regulation.

The current process-based trigger in the Food Standards Code is no longer fit for purpose and no longer delivers appropriate risk-based outcomes in terms of what foods are captured for pre-market safety assessment.

CropLife believes it is important that new technologies are regulated as consistently as possible between Australian Government regulatory agencies. This is a matter of good regulatory practice and serves to avoid a situation whereby, for example, a product is regulated as a GMO regarding its release into the environment, but not as a GM food, and vice versa.

The final characteristics of foods derived from a new plant variety are the best indicator as to whether those foods will present a food safety risk and this needs to be recognised as part of the Food Standards Code.

2 INTRODUCTION

CropLife Australia is the national peak industry organisation representing the agricultural chemical and biotechnology (plant science) sector in Australia. CropLife represents the innovators, developers, manufacturers and formulators of crop protection and agricultural biotechnology products. CropLife's membership is made up of both patent holding and generic Australian and international and small and large companies and accordingly, advocates for policy positions that deliver whole of industry benefit. The plant science industry provides products to protect crops against pests, weeds and diseases, as well as developing crop biotechnologies that are key to the nation's agricultural productivity, sustainability and food security. The plant science industry is worth more than $20 billion a year to the Australian economy and directly employs thousands of people across the country. CropLife Australia is a member of CropLife Asia and part of the CropLife International Federation of 91 CropLife national associations globally.

CropLife welcomes the opportunity to provide comments to the Food Standards Australia New Zealand (FSANZ) *Consultation Paper on Food Derived Using New Breeding Techniques*, and the consideration of the definitions in the *Australia New Zealand Food Standards Code* for 'food produced using gene technology' and 'gene technology'.

CropLife supports the overarching objective of the Review to provide clarity regarding whether pre-market assessment and approval is appropriate for food derived using a diverse range of breeding innovations, referred to by FSANZ collectively as 'New Breeding Techniques'

CropLife's long held view is that *food derived from plant varieties developed through the latest breeding methods should not be differentially regulated based on the techniques employed during the plant's development if they are similar to, or indistinguishable from foods that could have been produced using plants developed through earlier breeding methods.*

CropLife's submissions to the 2016 Technical Review of the Gene Technology Regulations, to Phases 1 and 2 of the 2017 Review of the National Gene Technology Regulatory Scheme and to the 2017 draft amendments to the Gene Technology Regulations, have all reflected our member companies' collective concerns about the prospect of pre-market regulation of products developed using new breeding techniques (referred to hereon as plant breeding innovations), based simply on the technique employed during the development of specific traits and not on the characteristics of the final product.

Foods and feed derived from crops produced using established techniques of genetic modification have been consumed since 1996 without a single documented adverse effect on human or animal health. As predicted by scientists early on, food derived from these genetically modified (GM) crops have posed no unique or incremental risks different to those foods derived from crop varieties produced through conventional breeding techniques, including mutagenesis.

3 QUESTIONS

3.1.1 Do you agree, as a general principle, that food derived from organisms containing new pieces of DNA should be captured for pre-market safety assessment and approval?

Should there be any exceptions to this general principle?

CropLife **disagrees** with the general principle that all food derived from organisms containing new pieces of DNA (as defined in Appendix 1 of the consultation paper) should be captured for pre-market safety assessment and approval. All regulation should be commensurate with risk, and the assumption that food derived from organisms containing 'new' pieces of DNA has a greater risk than food derived from organisms developed using 'conventional' breeding methods is inherently flawed.

CropLife is not arguing in this submission for the retrospective exclusion from regulation of existing GM foods currently listed in Standard 1.5.2. We do, however, strongly recommend that the future focus of assessing food safety risks should be on the final characteristics of the food derived from the new plant variety and not the breeding process used to produce that variety.

Food derived from conventional breeding methods, such as those that harness spontaneous or induced mutagenesis to generate large amounts of genomic variation is not subject to pre-market safety assessment. Food derived from similar genetic variation, when generated using newer plant breeding innovations, should not be subject to pre-market regulation purely on the process through which it was created.

In considering the different outcomes of plant breeding innovations, genetic changes can range from small nucleotide changes, deletions or additions, to re-creating an allele from a wild relative in a commercial variety. to introducing a transgene in a site-specific manner. Other products of genome editing, such as introducing a gene from an unrelated species, are similar to 'foods produced using gene technology' that are currently captured by the Code.

The US Food and Drug Administration's (FDA) 1992 policy statement on new plant varieties recognised that plant breeding methods represent a continuum, from traditional crossing of two varieties to using molecular methods to introduce genes from other species into a targeted plant species. In the same way, plant breeding innovation is considered as part of this continuum, with different applications fitting into the continuum of plant breeding methods[1].

Several of these products of genome editing applications could also be accomplished, albeit more slowly and with less precision, through more traditional plant breeding methods, such as crossing a commercial variety with a wild relative, or mutation breeding. This is an important point when considering the potential for any new food safety risks.

[1] Food For Human Consumption and Animal Drugs, Feeds, and Related Products: Foods Derived from New Plant Varieties; Policy Statement. 1992. Federal Register 57:104, 22984

Creating Genetic Variation through Spontaneous, Induced and Targeted Mutagenesis

Spontaneous and Induced Mutagenesis

Over the last several thousand years, humans have directed the evolution of plants by selectively saving and planting seed from wild, gathered plants with attributes of human value, for example, better flavors, larger fruits, fewer thorns, more nutrients and seeds that do not shatter. The process of constant genetic improvement continues today in a more formalised way using the science of plant breeding. As is true of evolution by natural selection, genetic variation is the essential resource upon which plant breeding programs are built.

Plant breeders have long utilised genetic variation created through mutations to develop plant varieties with improved characteristics. Foods derived from such variation, when generated using newer plant breeding innovations, should not be subject to pre-market safety assessment and approval.

Mutations are generally classified as spontaneous or induced, and mutation theory establishes that all are derived from premutagenic damage to DNA. Premutagenic damage that leads to spontaneous mutations is produced by a variety of factors present in normally growing cells.[2]

Spontaneous mutations are known to occur frequently and these bring about the genomic sequence changes that are the basis of evolution. Infidelities of the DNA replication and repair machinery can result in small local sequence changes, such as the deletion or insertion of one or a few adjacent nucleotides, or rearrangement of several neighbouring nucleotides. It is this mechanism that is exploited by the site-directed nuclease (SDN) genome editing technologies. In plants, estimates of mutation rates based on single nucleotide polymorphisms indicate more than ten spontaneous mutations per generation due to such mechanisms. Larger rearrangements of stretches of nucleotides may occur with the movement of transposable elements, which are known to be widespread in living organisms.[3] Transposition commonly results in gene gains, duplications and losses.[4]

Plants have considerable capacity to undergo genetic change and several additional mechanisms underlying natural mutation have been described that contribute to a process of constant genome restructuring and reprogramming. In comparison, animal genomes are relatively stable and conserved.[5] Greater plasticity in plants is believed to contribute to the maintenance of adaptive phenotypes and facilitate longevity, and to be a natural consequence of their immobility.[6] The presence of duplicated forms of genes is common in plants, and multigene families have been found that have arisen from the duplication of larger genomic regions and whole genomes.[7] Of note, these mechanisms are considered to have a greater

2 Maki, H (2002) Origins of spontaneous mutations: specificity and directionality of base-substitution, frameshift, and sequence-substitution mutageneses, *Annual Review of Genetics* 36: 279-303.

3 Arber, W (2010) Genetic Engineering Compared to Natural Genetic Variations, *New Biotechnology* 27: 517-521; Schnell, J, Steele, M, Bean, J, Neuspiel, M, Girard, C, Dormann N, Peason, C, Savoie, A, Bourbonniérre, L, Macdonald, P (2015) A Comparative Analysis of Insertional Effects in Genetically Engineered Plants: Considerations for Pre-market Assessment, *Transgenic Research* 24: 1-17.

4 Strauss SH, Sax JK (2016) Ending event-based regulation of GMO crops, *Nature Biotechnology* 34: 474-477;

5 Murat, F, Van de Peer, Y, Salase J (2012) Decoding plant and animal genome plasticity from differential paleo-evolutionary patterns and processes, *Genome Biology and Evolution* 4: 917-928.

6 Borges, RM (2008) Plasticity comparisons between plants and animals, *Plant Signalling and Behaviour*, 3: 367-375.

7 Weber, N, Halpin, C, Hannah, LC, Jez, JM (2012) Editors choice: Crop Genome Plasticity and its relevance for food and feed safety of genetically engineered breeding stacks, *Plant Physiology* 160: 1842-1853.

impact on genome sequence and function than gene insertion using genetic engineering.[8] Also notable, is the lack of evidence that a naturally occurring random genetic change has resulted in a novel safety concern, e.g. due to the creation of new genes or alleles, changes in gene expression level, expression of novel proteins, or production of novel metabolites.[9]

Spontaneous mutations may result in no effect on the phenotype of the organism, i.e. the mutations are neutral or silent, or they may modify a characteristic (in terms of level of gene expression), introduce a newly expressed characteristic, or cause the loss of a previously expressed characteristic. These effects may be selectively advantageous or disadvantageous, however evolutionary beneficial mutations are relatively rare.[10]

Plant breeding has long exploited the genetic variation that results from spontaneous mutation mechanisms in selecting for important traits, and such spontaneous mutations may result in modified or new characteristics that are selected for and preserved in crop breeding, e.g. the semi-dwarf variation in cereal crops, which has contributed significantly to improved grain yield.[11] Limitations of spontaneous mutations in this context include their low frequency and that only a small number of such mutations lead to phenotypic characteristics of interest. Therefore, induced mutagenesis via physical (e.g. irradiation) or chemical treatments may be used to accelerate the process.[12]

Such induced mutagenesis techniques result in random mutations, which may include deletions ranging in size from tens to millions of base pairs, and rearrangements that include inversions and chromosomal translocations.[13] A limitation of this approach is that large populations of mutagenized plants must be screened to select plants with desired changes to be included in breeding programs. Generations of crossing may then be needed to segregate away unwanted mutations that may impact on plant performance.[14]

Foods derived from induced mutagenesis techniques commonly used for the development of new or improved traits in plant breeding are excluded from pre-market regulation on the basis of their demonstrated history of safe use, with chemical and irradiation techniques in use for the development of new crop varieties for at least 60 years.[15],[16] The breeding and selection process that is applied to new lines/varieties developed using these methods has continued to result in thousands of commercial food products that are safe to consume.

The FAO/IAEA Mutant Variety Database lists 3275 officially released cultivars in more than 200 plant species registered since 1950.[17] In the past 20 years, these techniques have been complemented by biotechnology, with the early techniques (e.g. rDNA) now also having a demonstrated history of safe use.

8 Strauss SH, Sax JK (2016) *Nature Biotechnology* 34: 474-477; Schnell et al. (2015) *Transgenic Research* 24: 1-17.
9 Strauss SH, Sax JK (2016) *Nature Biotechnology* 34: 474-477.
10 Arber, W (2010) *New Biotechnology* 27: 517-521; Schnell et al. (2015) *Transgenic Research* 24: 1-17.
11 Xiong, J-S, Ding, J, Li, Y (2015) Genome-editing technologies and their potential application in horticultural crop breeding, *Horticultural Research* 2: 15019, doi:10.1038/hortres.2015.19.
12 Andersen, MM, Landes X, Xiang W, Anyshchenko A, Falhof, J, Østerberg, JT, Olsen, LI, Edenbrandt, AK, Vedel, SE, Thorsen, BJ, Sandøe P, Gamborg, C, Kappel, K, Palmgren, MG (2015) Feasibility of New Breeding Techniques for Organic Farming, Trends in Plant Science 20: 426-434; Xiong, J-S, Ding, J, Li, Y (2015) *Horticultural Research* 2: 15019, doi:10.1038/hortres.2015.19
13 Schnell et al. (2015) *Transgenic Research* 24: 1-17.
14 Podevin, N et al. (2013) *Trends in Biotechnology* 31: 375-383.
15 Hartung, F, Schiemann, J (2014) *The Plant Journal* 78: 742-752
16 Ahloowalia, B. S., Maluszynski, M., & Nichterlein, K. (2004). Global impact of mutation-derived varieties. *Euphytica* 135(2), 187-204.
17 https://mvd.iaea.org/#!Home, accessed 21 March 2018; Podevin, N et al. (2013) *Trends in Biotechnology* 31:375-383.

Targeted mutagenesis

The targeted mutagenesis techniques of SDN-1 and SDN-2 employ a site-directed nuclease (SDN) to create a double-stranded break at a defined site in the genome, and exploit the natural cellular mechanisms for DNA repair.

For SDN-1, deletions, insertions and rearrangements are often observed at repair sites, and these are analogous and indistinguishable at the DNA sequence level from deletions, insertions and rearrangements that are obtained using induced mutagenesis techniques, and observed in sites flanking transposon movement or DNA insertions in genetically engineered plants.[18] The exact sequence of mutated organisms cannot be predicted but their phenotypes can be screened for the presence of the intended change.[19]

For SDN-2, the outcomes are more predictable than for SDN-1 due to the use of a template to direct repair of the DNA double-stranded break. The repair template is introduced to the cell at the same time as the SDN and results in the precise change defined by the repair template.[20]

The ODM mutagenesis technique differs to the SDN techniques in that it does not employ a nuclease to create DNA double-stranded breaks at target sites in the genome, and it uses a short oligonucleotide to direct DNA repair. In both ODM and SDN-2, the oligonucleotide/repair template is identical to the corresponding site in the genome except for the nucleotide changes intended to be incorporated during repair.[21]

An argument raised to support claims of risk associated with these technologies is the possibility for unintended, off-target edits. However, the site-directed nature of SDN-1, SDN-2 and ODM techniques reduces these genomic changes in comparison with tools that induce random mutagenesis. Furthermore, in plants, while off-target edits have been reported with SDN techniques, their frequency is well below that which occurs with other mutagenesis techniques, and comparable to that which occurs in cross breeding.[22]

The ODM and SDN techniques require careful target design, which depends on the availability of precise genome sequence and knowledge of gene function. Further, their precision/specificity and efficiency must be optimised through experimentation, and optimal methods for delivery into the relevant target cells need to be determined. Thus, these techniques are not as technically simple to employ in any eukaryote as the general media suggests. Though the general finding to date has been that often no off-target target edits are observed; when they have been observed they are typically similar to, or less than the generation to generation variability or variability among individuals in the genome of a species.[23]

18 Schnell et al. (2015) *Transgenic Research* 24: 1-17.

19 Jones, HD (2015) Future of breeding by genome editing is in the hands of regulators, *GM Crops & Food* 6: 223-232.

20 Sprink, T, Eriksson, D, Schiemann, J, Hartung, F (2016) Regulatory Hurdles for Genome Editing: Process- vs Product-Based Approaches in Different Regulatory Contexts, *Plant Cell Reports* 35: 1493-1506; Jones, HD (2015) GM Crops & Food 6: 223-232.

21 Sprink et al (2016) *Plant Cell Reports* 35: 1493-1506; Jones, HD (2015) *GM Crops & Food* 6: 223-232.

22 European Food Safety Authority Panel on Genetically Modified Organisms (2012) Scientific opinion addressing the safety assessment of plants developed using Zinc Finger Nuclease 3 and other Site-Directed Nucleases with similar function, *EFSA Journal* 10: 2943; Podevin, N et al. (2013) *Trends in Biotechnology* 31: 375-383.

23 See e.g. Cho, SW, Kim, S, Kim Y, Kweon, J, Kim HS, Bae, S, Kim, J-S (2014) Analysis of off-target effects of CRISPR/Cas-derived RNA-guided endonucleases and nickases, *Genome Research* 24: 132-141; Shen, B, Zhang, W, Zhang, J, Zhou, J, Wang, J, Chen, L, Wang, L, Hodgkins, A, Iyer, V, Huang, X, Skarnes, WC (2014) Efficient genome modification by CRISPR-Cas9 nickase with minimal off-target effects, *Nature Methods* 11: 399-404; Cho, SW, Kim, S, Kim, JM, Kim, J-S (2013) Targeted genome engineering in human cells with the Cas9 RNA-guided endonuclease, *Nature Biotechnology* 31: 230-232; Gaj, T, Gersbach, CA, Carlos FB (2013) ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering, *Trends in Biotechnology* 31: 397-405; Hwang, WY, Fu, Y, Reyon, D, Maeder, ML, Tsai, SQ, Sander, JD, Peterson, RT, Yeh J-RJ, Joung, JK (2013) Efficient genome editing in zebrafish using a CRISPR-Cas system, *Nature Biotechnology* 31: 227-229.

In plants, off-target edits may be greatly limited by downstream selection to remove undesired phenotypes.[24] In plants, while it is theoretically possible, unintended effects arising from cross-breeding do not correspond to increased impacts on safety, e.g. production of a new toxin or allergen, as there are no documented cases of this occurring.[25]

The targeted nature of SDN-1, SDN-2 and ODM techniques differentiates them from transgenesis which is characterised by the random integration of recombinant DNA. Targeted integration of transgenes is possible with the SDN-3 technique, which like SDN-1 and SDN-2 induces DNA double-stranded breaks at specific locations.

There are no strong risk-based arguments to suggest food derived from plants created using newer targeted mutagenic techniques should be differentially regulated based on the techniques employed during the plant's development if they are similar to, or indistinguishable from foods that could have been produced using plants developed through earlier breeding methods.

Cisgenesis and Intragenesis

In plants, cisgenesis and intragenesis may involve the use of established techniques for genetic modification methods, i.e. random integration of recombinant DNA molecules into the genome, or SDN-3 techniques for site-specific integration of a gene. Cisgenic organisms are characterised using donor DNA that originates from the species itself or a cross-compatible species, i.e. the wider sexually compatible gene pool for the species, and the resulting organisms could in principle be developed using conventional breeding techniques, although this is not true for intragenesis.[26]

In crops, the use of cisgenesis has been reported for improving pathogen resistance, e.g. scab resistance in apple and late blight resistance in potato[27], and intragenesis has been utilised to develop breeding lines of potato with resistance to black spot bruising and lower acrylamide content after high temperature processing. Transgenesis is differentiated from cisgenesis and intragenesis in that it allows for the integration of DNA from an unrelated, cross-incompatible species.[28]

It is important to recall that some conventional breeding methods, such as embryo rescue, can be used to create interspecific crosses (in instances where the phylogenetic difference is not large), and food derived from these plants is not subject to pre-market safety assessment and approval.

24 Wolt, JD, Wang, K, Yang, B (2016) The Regulatory Status of Genome-edited Crops, *Plant Biotechnology Journal* 14: 510-518.
25 Schnell et al. (2015) *Transgenic Research* 24: 1-17.
26 Cardi, T (2016) Cisgenesis and genome editing: Combining concepts and efforts for a smarter use of genetic resources in crop breeding, *Plant Breeding* 135: 139-147.
27 Cardi, T (2016) *Plant Breeding* 135: 139-147.
28 Araki, M, Ishii, T (2015) Towards social acceptance of plant breeding by genome editing, *Trends in Plant Science* 20:145-149.

In cisgenesis, the introduced DNA is a naturally occurring fragment of genomic DNA that contains the gene of interest with its associated regulatory sequences, i.e. promoter, coding region including its introns, terminator sequences and 5' and 3' untranslated regions in the normal-sense orientation.[29] This genomic DNA, the protein(s) it encodes, and the phenotype it confers already exist in nature and are not novel to the germplasm pool. In intragenesis, different coding and regulatory sequences are assembled either in sense or antisense orientation.[30]

The use of cisgenesis and intragenesis requires prior knowledge of the gene sequence, its position and its function in the genome of origin. When the cisgene is integrated into the genome of the recipient, it is expected to show comparable fitness, toxicity/allergenicity, and potential effects on non-target organisms to organisms developed using conventional methods.[31] It is also possible that the expression of the cisgene may fall outside the range of expression variation observed in conventional varieties, however such an outcome is also possible via conventional breeding.[32] This contrasts with transgenesis for the introduction of a novel trait that does not occur in the species and cannot be introduced using conventional breeding methods.[33]

As many of the changes introduced via cisgenesis and intragenesis are comparable to those that could be obtained through conventional breeding, it is important to consider whether any unintended changes arising from these techniques are specific to the new breeding lines from these breeding techniques, or whether they differ from those caused by conventional breeding. The *in vitro* procedures (for example, cell and tissue culture) used to arrive at products of cisgenesis and intragenesis are also used in conventional plant breeding, so any unintended changes owing to somaclonal variation will be similar in both cases.[34]

In agriculture, wild relatives of domesticated crops and landraces have long been used in intra- and inter-specific hybridisation. The primary advantage of cisgenesis over conventional breeding methods is improved efficiency and ability to respond to agricultural challenges.[35] This arises because of more targeted access to:

i. Specific beneficial traits that are present in the crossable breeders' pool and wild relatives but not in crop plants. This will help widen the available genetic variation and allow breeders greater ability to utilise genetic potential present in wild relatives. Exotic breeding lines and wild relatives have broader genetic variability that allow adaptation to changing environmental conditions via natural evolutionary processes.[36]

29 Holme, IB, Wendt, T, Holm PB (2013) Intragenesis and cisgenesis as alternatives to transgenic crop development, *Plant Biotechnology Journal* 11: 395-407.
30 Holme, IB et al (2013) *Plant Biotechnology Journal* 11: 395-407
31 Cardi, T (2016) *Plant Breeding* 135: 139-147; Schouten, HJ, Krens FA, Jacobsen E (2006) Cisgenic plants are similar to traditionally bred plants, *EMBO Reports* 7: 750-753.
32 European Food Safety Authority Panel on Genetically Modified Organisms (2012) Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis, *EFSA Journal* 10: 2561.
33 Schouten, HJ, Krens, FA (2006) Do cisgenic plants warrant less stringent oversight? *Nature Biotechnology*, 24:753.
34 EFSA (2012) EFSA Journal 10: 2561
35 Cardi, T (2016) *Plant Breeding* 135: 139-147.
36 Andersen, MM et al (2015) *Trends in Plant Science* 20: 426-434.

ii. Specific beneficial traits without the disadvantages of unwanted traits associated with linkage drag. Overcoming linkage drag requires successive generations of backcrossing, however, this is not always possible and depends on the chromosomal position of the desired trait.[37]

iii. Previously inaccessible beneficial traits. In some cases, beneficial traits are positioned in chromosome regions that have very low recombination frequencies, which means that the chance of transferring the specific trait via conventional breeding to a breeding line is very low or impossible.

iv. In the case of intragenesis, different coding and regulatory sequences may be assembled in sense or antisense orientations, the latter if the aim is to reduce gene expression by activating the RNA interference (RNAi) pathway. This technique has been used to effect reduction in gene expression to improve quality traits in potato as an example.[38]

Cisgenesis also allows for overcoming the inability to introgress valuable traits via conventional breeding in commercial species that are clonally propagated or sterile.

Food derived from plants created by cisgenesis should be analogous to that which can be derived from plants created using conventional plant breeding methods as the transfer of the same genetic material would be possible. This is consistent with the conclusion reached by the GMO Panel of the European Food Safety Authority that similar hazards can be associated with cisgenic and conventionally bred plants.[39] The types of changes that may occur in the genome due to cellular DNA repair mechanisms during conventional breeding are also expected to occur at the integration site in cisgenic and intragenic plants, but only at that locus.[40]

For products of both cisgenesis and intragenesis, changes that may occur with the insertion include rearrangements or translocations in the flanking regions, which could impact on genes and open reading frames. However, as detailed above, such changes are reported to occur spontaneously in plants, and are especially common in regions where transposons are active, and with the use of induced mutagenesis techniques. The potential risks posed by cisgenesis and intragenesis and the food derived from these plant breeding innovations should be assessed by comparison with conventional breeding techniques rather than transgenesis, with regulation commensurate with the comparable risk of the derived products.

Section 3.1.1 of the Consultation Paper appears to have an incorrect interpretation in the description of cisgenesis. It states that:

> "The new DNA that is inserted typically gives rise to the expression of a new or modified form of protein."

Since a cisgene or an intrgeneuses an expression cassette derived from DNA elements of the same species, the protein(s) expressed by the resultant cisgenenic or intragenic product are not 'new' to that species. The phrase 'new DNA' is also used several times in Section 3.1.1, but it is unclear in regard to cisgenesis and intragenesis whether all introduced genetic elements need to be from the same species, or simply from a sexually cross-compatible species.

37 Andersen, MM et al (2015) *Trends in Plant Science* 20: 426-434.
38 Cardi, T (2016) *Plant Breeding* 135: 139-147
39 European Food Safety Authority Panel on Genetically Modified Organisms (2012) *EFSA Journal* 10: 2561.
40 European Food Safety Authority Panel on Genetically Modified Organisms (2012*) EFSA Journal* 10: 2561.

3.1.2 Should food from null segregant organisms be excluded from pre-assessment and approval?

If yes, should that exclusion be conditional on specific criteria and what should those criteria be?

CropLife **strongly recommends** that food derived from null segregant organisms should be excluded from pre-assessment and approval.

There is no scientific risk basis to regulate food obtained from organisms that are derived from GMOs (that would be regulated under the *Gene Technology Act 2000*) that have not inherited traits that occurred because of gene technology. Such organisms have lost the transgenic event (insert) due to normal segregation following conventional breeding with an organism that did not contain the transgenic event. Food derived from these organisms does not contain any elements of the transgenic event and therefore should not be subject to pre-market safety assessment and approval as a GM food.

CropLife has identified some logical inconsistency in the Consultation Paper in Section 3.1.2 on null segregants and in Section 3.1.3 where FSANZ have implied that they are going to consider and look at factors not related to definitional interpretation but based on potential risk. For example:

> "The question for this category is whether there is sufficient justification (based on risk) to require pre-market assessment and approval for food obtained from null-segregants."

CropLife **recommends** that if FSANZ can make a risk-based distinction for food obtained from null segregants, they should be able to make the same risk-based distinction for food obtained from gene-edited organisms.

As discussed in CropLife's response to Question 3.4 below, the consistency of regulation between government agencies is desirable. FSANZ should be aware that through the proposed interim amendments to the Gene Technology Regulations 2001, the OGTR is proposing to clarify the regulatory status of "organisms that are not themselves categorised as GMOs but have been derived from GMOs."[41] The OGTR is clear that the definition of 'GMO' in the *Gene Technology Act 2000* does not include organisms derived from GMOs that have not inherited traits that occurred because of gene technology, also known as null segregants.

41 See http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/amendment%20proposals-1 accessed 21 March 2018.

3.1.3 Are foods from genome edited organisms likely to be the same in terms of risk to foods derived using chemical or radiation mutagenesis?

If yes, would this apply to all derived food products or are there likely to be some foods that carry a greater risk and therefore warrant pre-market safety assessment and approval?

CropLife has provided a detailed technical answer to this question in our response to Question 3.1.1. New plant varieties developed using genome editing applications that are essentially a more precise way of cross-breeding or inducing mutagenesis should not be treated differently from a regulatory perspective than those new plant varieties developed through conventional breeding methods. There is no reason to believe that a genetic change (i.e. insertions, deletions or substitutions) that relies on the existing inherent diversity in a plant's gene pool would be more or less likely to present a new or novel food safety risk.

As discussed previously, spontaneous or induced mutations could result in these same types of changes at the genetic level. Substituting an allele from a wild relative, either through cross-breeding or genome editing, would not result in a differing food safety profile. Food derived from transgenic plants, developed through either rDNA methods or genome editing, does not necessarily differ in its food safety profile either; this has been confirmed over more than 20 years of pre-market safety assessment and consumption of the derived foods without any food safety risk being established at any step of the process from review to consumption.

Food products derived from plants produced using genome editing represent a step forward in the precision of change that can be brought about as part of the continuum of breeding processes available. Due to these significant improvements in the precision of genome modification processes, concomitant improvements in the food safety profiles of derived foods can be achieved.[42]

A discriminatory application of regulation would result in a situation where foods derived from certain methods of gene technology are excluded from the scope of regulation based on their history of safe use, while regulation would be applied to foods derived from methods that result in even more precise and more predictable outcomes than ever achievable with earlier excluded methods.

In CropLife's view, this is inconsistent with the principles of proportionate and science-based regulation. Furthermore, such discrimination between various induced mutagenesis tools and genetic transfer methods, does not help in addressing any potential risks associated with the food derived from the resulting organisms. In our understanding, identical foods could be derived from the application of different methods, some of which are more recent and more efficient than earlier ones. It is not scientifically justified to regulate the process based on it being more recent while not considering the outcome of the method – the resulting product. As the outcomes of genome editing can be equivalent to those of non-regulated breeding methods, the presumption of history of safe use should logically extend to these products as well.

[42] Podevin, N et al. (2013) *Trends in Biotechnology* 31:375 383.

Plant breeders use common and well-established practices to evaluate the quality and safety of new varieties introduced into the market. There will undoubtedly be instances when food derived from a genome edited plant warrants pre-market safety assessment and approval, for example, if the nutritional profile of the food is significantly changed.

3.2 Are you aware of other techniques not currently addressed by this paper which have the potential to be used in the future for development of food products?

The use of DNA methylation as a technology remains very speculative today and is a subject of active research. If successful applications are developed in the future, based on knowledge about DNA methylation in specific organisms, these should not be subject to pre-market safety assessment and approval under the Standard 1.5.2 as no "new DNA" has been inserted in the organism and the likely phenotype that may be achieved through modulation of DNA methylation would be in the range of natural variation for the species.

Another specific technique is 'base editing', which could be considered as similar to genome editing, but does not rely on double-stranded breaks. However, while technology development is accelerating and the pace of change is growing, food regulators need to be agile and regulations as future proof as possible to avoid stifling much needed innovation in the food industry.

While technology tools continue to advance, the same principle that "*food derived from plant varieties developed through the latest breeding methods should not be differentially regulated based on the techniques employed during the plant's development if they are similar to, or indistinguishable from foods that could have been produced using plants developed through earlier breeding methods"* should still apply.

To be 'future proof', the Code needs to refrain from differentially regulating the latest breeding methods, if they do not result in food that poses new risks relative to the food derived from plants developed using conventional breeding methods, that are currently excluded from regulation.

Mechanisms for the regular review and revision of the Code are crucial: foods derived from technologies to be excluded from pre-market assessment and approval can be identified based on scientific evidence, and the body of accumulated knowledge and experience with gene technology. Where that is not available today it should be considered as it develops.

Such an approach promotes regulation that is proportionate to risk, and regulation that is focussed on the protection of human health and safety.

While this question invites technological advances that can be 'foreseen', it is not appropriate to attempt to regulate concepts that are today merely speculation. The focus of this review should therefore be on providing regulatory certainty in the short to medium term, but also to provide the mechanisms that will enable the Code to be reactive in the longer term. A practical approach could be implementing the necessary legislative mechanisms or policy approaches that permit FSANZ to continuously 'scan the horizon' for new processes and products that could present novel food risks, and to ensure their approach to risk assessment remains robust and effective.

3.3 Do you think a process-based definition is appropriate as a trigger for pre-market approval in the case of NBTs?

If no, what other approaches could be used?

Are there any aspects of the current definitions that should be retained or remain applicable?

CropLife **agrees** with the statement in the Consultation Paper that as a mechanism for capturing foods with new DNA inserted, the process-based approach has generally worked well over nearly 20 years of application. However, CropLife **submits** that the current process-based definitions are no longer fit for purpose and no longer deliver appropriate risk-based outcomes in terms of what foods are captured for pre-market safety assessment.

As stated in CropLife's response to Questions 3.1.1 and 3.1.3 above, the final characteristics of a food derived from a new plant variety are the best indicator as to whether the food will present a food safety risk.

This review provides the opportunity to improve the definitions used by FSANZ, particularly that of 'gene technology'. For example, CropLife proposed the following amendment to the definition of 'gene technology' in the *Gene Technology Act 2000*:

> ***gene technology*** means any technique for the modification of genes or other genetic material, but does not include:
>
> (a) sexual reproduction; OR
>
> (b) homologous recombination; OR
>
> (c) techniques that do not result in the integration of one or more genes in a defined genetic construct into the genome; OR
>
> (d) any other technique specified in the regulations for the purposes of this paragraph.

The inserted text (underlined) above would exclude upfront from regulatory scope foods derived from organisms developed using the techniques of ODM, SDN-1 and SDN-2. It also does not change the regulatory status of food derived from organisms that are currently, and have historically been within regulatory scope of the Food Standards Code.

As discussed in CropLife's response to Question 3.4 below, the consistency of regulation between government agencies is desirable. The alignment of the definition of gene technology in the Food Standards Code and the *Gene Technology Act 2000* would be a step in the right direction.

3.4 Are there other issues not mentioned in this paper that FSANZ should also consider, either as part of this Review or any subsequent proposal to amend the Code?

Consistency regulation of new technologies across government agencies

There are currently three reviews underway into the way Australia regulates Gene Technology, namely:

- 2016 Technical Review of the Gene Technology Regulations
- 2017 Review of the National Gene Technology Regulatory Scheme
- 2018 FSANZ Review of Food Derived Using New Breeding Techniques

CropLife believes it is important that new technologies are regulated as consistently as possible between Australian Government regulatory agencies. This is a matter of good regulatory practice and serves to avoid a situation whereby, for example, a product is regulated as a GMO regarding its release into the environment, but not as a GM food, and vice versa.

CropLife recognises that the OGTR and FSANZ operate under separate pieces of legislation and that they regulate different products of biotechnologies for different risks, therefore there may be unavoidable areas of divergence (differentiation of regulation of cisgenic organisms may be one example). We strongly believe, however, that efforts should be made to harmonise the way in which new technologies are regulated as far as possible, consistent with the Australian Government's high-level policy priority of minimising regulatory 'red tape'. CropLife believes this is achievable as an outcome of the current reviews.

Development of an 'unstacking' policy

Gene stacking refers to the process of combining genes of interest into a single plant line. Plants with stacked genes now form a significant part of GM crops grown throughout the world. FSANZ does not require separate approval or safety assessment for foods derived from a stacked GM line that is the result of traditional breeding between several GM parent lines for which food has already been approved.

CropLife requests that FSANZ may consider clarification regarding the 'unstacking' of genes through conventional breeding. For example, if you have a plant with three unlinked GM events (i.e. insect resistance, herbicide tolerance and drought tolerance) that had been approved by FSANZ (as a stack, no individual approvals sought); then if a new plant variety is brought to market containing one or two or those events segregated by conventional breeding, would it be subject to separate regulatory oversight?

4 CONCLUSION

Food derived from conventional breeding methods, such as those that harness spontaneous or induced mutagenesis to generate large amounts of genomic variation is not subject to pre-market safety assessment. Food derived from similar genetic variation, when generated using newer plant breeding innovations, should not be subject to pre-market regulation purely on the process through which it was created.

CropLife's long held view is that food derived from plant varieties developed through the latest breeding methods should not be differentially regulated based on the techniques employed during the plant's development if they are similar to, or indistinguishable from foods that could have been produced using plants developed through earlier breeding methods.

Food derived from new plant varieties developed using genome editing applications that are essentially a more precise way of cross-breeding or inducing mutagenesis should not be treated differently from a regulatory perspective than those new plant varieties developed through conventional breeding methods. There is no reason to believe that a genetic change (i.e. insertions, deletions or substitutions) that relies on the existing inherent diversity in a plant's gene pool would be more or less likely to present a new or novel food safety risk.

The final characteristics of foods derived from a new plant variety are the best indicator as to whether those foods will present a food safety risk and this needs to be recognised as part of the Food Standards Code.