INTRODUCTION

Bayer Crop Science, a division of Bayer AG which recorded annual sales of € 9.5 billion in 2017, is one of the world's leading innovative crop science companies in the areas of seeds and traits, crop protection and non-agricultural pest control.

The company has a global presence in over 120 countries and has operated in Australia for nearly 90 years. Bayer Crop Science Australia has a long history of leading innovation in sustainable agriculture and a strong focus on sales and Research & Development in Australia.

Access to Australia's diverse agricultural sector, a large research base and proximity to Asian markets are key factors which underpin Bayer Crop Science's investment in Australia.

Investment in Australian Innovation

Bayer operates two factories near Brisbane and Perth, ensuring year-round supply of some 400 agricultural chemical products. The Brisbane factory is also now a major export centre supplying Asia and New Zealand and other global Bayer markets with premium products supporting global food, feed and fibre production.

In 2014, Bayer opened a A$14 million state-of-the-art Wheat and Oilseeds Breeding Centre at Longerenong College, near Horsham, Victoria – the first of its kind in Australia. The Centre is focusing on the development of new wheat and oilseeds varieties with higher yields and productivity improvements specifically for Australian agriculture. Bayer has also opened an Animal Health Research Centre in New Zealand which has the proximity, experience and focus to provide tailored solutions for the local and regional markets.

These investments form the critical infrastructure for all facets of Bayer's agricultural business, including product manufacturing, crop protection, breeding, seed production and fundamental R&D.

We appreciate the opportunity to provide feedback to the FSANZ Consultation Paper reviewing how the Food Standards Code applies to foods derived from a range of new breeding methods discussed in the Consultation Paper, also frequently referred to as plant breeding innovations with respect to the Seeds industry.

This paper responds to the questions posed in the Consultation Paper as they apply to Bayer Crop Science's Research & Development activities and our knowledge of the global plant industry. We seek to offer opinion based on sound current research that will facilitate the

development of a wide variety of products in agriculture derived from applying breeding innovations that address areas of need for sustainable agricultural production systems required for the health, nutrition and wellbeing of our global population.

Bayer Crop Science holds the view that plant varieties developed through the newer breeding methods should not be differentially regulated based on the techniques employed during their development if the final product(s) are similar to or indistinguishable from varieties that could have been produced through earlier (or more "traditional") breeding methods.

SUMMARY

Bayer Crop Science strongly supports the exclusion of the products of mutagenesis such as oligo-directed mutagenesis (ODM), site-directed nuclease (SDN)-1, SDN-2, as well as the exclusion of cisgenesis and intragenesis from the scope of products requiring pre-market food safety assessment and elevation to inclusion in Standard 1.5.2 prior to commercialisation. We also strongly advocate for FSANZ to eliminate consideration of null segregants from the need for pre-market assessment on the basis that these products contain no remnant of genetic modification after passage through the breeding cycle and therefore they present no specific risks to humans, animals or the environment.

Our proposal, for reasons detailed in the wider discussion of this submission, is consistent with the principle that organisms created using gene technologies should be regulated in a manner that is commensurate with the risks they pose and not simply because of the use of specific methods to arrive at the final product. Thus methods that result in products that are indistinguishable from products made using long established techniques, such as chemical mutagenesis or conventional breeding should not be subject to pre-market food safety assessment and approval.

We support the efforts of FSANZ to review the innovative methods discussed in their Consultation Paper, and propose a revision of the Food Standards Code to amend the definitions surrounding gene technology and genetically modified food such that the exclusions discussed above can support clarity required for the on-going innovation and investment in efficient, safe and sustainable food production world-wide.

In providing our comments and answers to the consultation questions, we have taken into account the current process based triggers, their original purpose to distinguish functional DNA insertions sourced from an unrelated organism and the historical assumption that foods derived from such organisms are a potentially greater source of risk in contrast to conventional foods. It remains a matter of debate whether the choice of process based triggers has been a commensurate regulatory response to achieve the stated objectives of the regulation, namely to (a) protect public health and safety; (b) enable consumers to make informed choices by providing them with adequate information relating to food; and/or (c) prevent misleading or deceptive conduct. We note that it has not been demonstrated that the presence of “new” DNA in an organism is a reliable predictor of potential hazards or risk.

Outcomes of techniques on the genome of the organism from which food is obtained

In developing food regulatory measures, the FSANZ Application Handbook[1] indicates that the organisation must also have regard to "the need for standards to be based on risk analysis using the best available scientific evidence", and it is this scientific evidence with regard to plant breeding innovation that is discussed further in this submission.

We note that it has not been demonstrated that the presence of "new" DNA in an organism is a reliable predictor of potential hazards (and consequently risk) unless this new DNA is linked to a specific function that could lead to a health risk[2]. We share the view that the risks associated with gene technology are not unique, but are associated with particular products and their applications[3]. Ideally, regulatory scrutiny should be commensurate with the level of risk posed by the product, as determined against defined endpoints.

In the Consultation Paper FSANZ has presented an illustrative figure of the different approaches used in plant and animal breeding. Gene technology is presented apart from "conventional breeding approaches" that include: simple selection; cross-breeding; mutagenesis and tissue culture and it is noted that [F]oods derived using conventional breeding, referred to as 'conventional foods', are generally considered to have a long history of safe use and are not typically subject to pre-market safety assessment. It is further stated that [T]here has been ongoing scientific and public debate about the nature of the risks associated with foods produced using specific modern methods and whether pre-market assessment and approval is appropriate for those foods.

We note that the breeding approaches described in the FSANZ Consultation Paper are never applied in isolation; rather they contribute to a varying degree, depending on the case, to the overall breeding process. With time, the knowledge and understanding about the underlying genetic determinants of traits has increased and has enabled the application of modern biotechnology for more efficient and effective development and selection of desirable traits. Within this continuum of developments, the creation of tools for introduction of precise genetic changes in the genome is enabling breeders to further optimise the breeding process and make it more efficient in terms of time taken to reach a final improved product. The introduction of targeted changes (mutations) in specific genes (via application of ODM, and SDN-1 and SND-2), the replacement of selected gene alleles with variants that confer desired characteristics or

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[1] Food Standards Australia New Zealand Application Handbook. 1 March 2016. http://www.foodstandards.gov.au/code/changes/Documents/Application%20Handbook%20as%20at%201%20March%202016.pdf

[2] McHughen, 2007. Fatal flaws in agbiotech regulatory policies. Nature Biotechnology 25(7), 725-727.

[3] National Research Council. (1987). Introduction of recombinant DNA-engineered organisms into the environment: Key issues. Washington, DC: National Academy Press.

their transfer from one genotype to another (via SDN-2, SDN-3, cisgenesis and intragenesis) is strongly dependent on prior knowledge and understanding of the gene(s) function(s). The perceived lack of history of safe use for modern breeding tools in comparison to the tools grouped under "conventional breeding methods" is counterbalanced by the significantly improved knowledge about the genomes today and the precision that the tools bring to the breeding process compared to earlier tools. The application of modern breeding methods is a logical, economic and science-based development in the fields of genetics and selective breeding that builds upon and further improves earlier breeding tools and approaches. In today's food production systems all methods remain relevant and are used in various combinations to address challenges and consumer demands. It appears that today there is much more public than scientific debate about the nature of the risks with foods produced using gene editing and we encourage all parties to participate transparently in support of informed consumer choice and science based regulatory decision making. [4] Below, we discuss in more detail the options discussed by the Consultation Paper.

In the consultation paper, new DNA is defined as: "*a fragment of DNA that is introduced to a host organism, irrespective of its source. That is, the DNA may be derived from an unrelated organism, the same species, or the host organism itself*." Further, examples are provided to illustrate this definition: the DNA sequence was *"not previously present in the host organism",* or "*is present in the host organism but has been reintroduced at a different location in the genome";* or *"is present in the host organism but has been rearranged or introduced into the host organism in a different orientation*."

Genome contains new DNA (transgenesis, cisgenesis, intragenesis) - 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?

Bayer Crop Science disagrees that as a general principle, food derived from an organism containing new pieces of DNA should require pre-market safety assessment and approval under the Standard 1.5.2 because it is the characteristics of the product that define its safety profile, not the process (e.g. gene technology) used in its development or the presence of new DNA sequence *per se*. However, we recognise that this trigger is well established for transgenic organisms. Consequently, we agree that organisms that carry DNA insertion(s) sourced from an unrelated organism that lead to the expression of a novel trait not previously present in the species and its cross-compatible gene pool require pre-market safety assessment and approval under the Standard 1.5.2. Example of such outcome of gene

[4] Sprink et al. (2016) Regulatory hurdles for genome editing: process- vs. product based approaches in different regulatory contexts. Plant Cell Reports 35, 1493-1506.

technology is insecticide resistance conferred by the insertion into the plant genome of *Bacillus thuringiensis* (Bt) derived *cry* toxin genes.

We do not agree however with the notion that sequences from cross-compatible or same species should be included in the same category for regulation. This is because plant breeders have been safely integrating genetic diversity from cross-compatible species and land races in the development of new plant varieties [5] without any new risks associated with derived food products. Therefore, our disagreement with the proposed general principle comes from a difference in understanding of what constitutes "new DNA" for an organism and to what extent this "new DNA" could lead to an increased risk for the derived food in comparison to food derived from conventionally bread organisms. When the "new DNA" is derived from the same or cross compatible species and is delivered to the organism via cisgenesis or intragenesis, such DNA is, in our understanding, not new. Similarly, the same DNA could be transferred to the organism via some of the conventional breeding approaches described in the Consultation Paper. The difference between the use of cisgenesis and intragenesis and crossing is that more precise transfer of desired genetic diversity[6] becomes possible and this is particularly relevant for species that are commonly propagated vegetatively[7,8,9].

The location of a specific DNA sequence within the genome of an individual organism may be relatively fixed but in the context of a species this is not the case and is readily observed when performing genetic analysis of breeding lines[10]. Such differences can be explained by recombination events that occur naturally during meiosis or by movement of transposable elements within the genome to name but two examples. The change of position of a DNA sequence within the genome of an organism does not make such DNA sequence new but more

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[5] Mondal, S., Rutkoski, J. E., Velu, G., Singh, P. K., Crespo-Herrera, L. A., Guzmán, C., … Singh, R. P. (2016). Harnessing Diversity in Wheat to Enhance Grain Yield, Climate Resilience, Disease and Insect Pest Resistance and Nutrition Through Conventional and Modern Breeding Approaches. Frontiers in Plant Science, 7, 991. http://doi.org/10.3389/fpls.2016.00991

[6] Holme I.B., Wendt T., Holm P.B. (2013) Intragenesis and cisgenesis as alternatives to transgenic crop development. Plant Biotechnol. J. 11(4), 395-407.

[7] Broggini, G. A. L., Wöhner, T., Fahrentrapp, J., Kost, T. D., Flachowsky, H., Peil, A., Hanke, M.-V., Richter, K., Patocchi, A. and Gessler, C. (2014), Engineering fire blight resistance into the apple cultivar 'Gala' using the FB_MR5 CC-NBS-LRR resistance gene of Malus × robusta 5. Plant Biotechnol J, 12: 728–733.

[8] Schouten, H. J., Krens, F. A., & Jacobsen, E. (2006). Cisgenic plants are similar to traditionally bred plants: International regulations for genetically modified organisms should be altered to exempt cisgenesis. EMBO Reports, 7(8), 750–753.

[9] Jo, K.-R., Kim, C.-J., Kim, S.-J., Kim, T.-Y., Bergervoet, M., Jongsma, M. A., … Vossen, J. H. (2014). Development of late blight resistant potatoes by cisgene stacking. BMC Biotechnology, 14, 50.

[10] Wingen, L. U., West, C., Leverington-Waite, M., Collier, S., Orford, S., Goram, R., … Griffiths, S. (2017). Wheat Landrace Genome Diversity. Genetics, 205(4), 1657–1676. http://doi.org/10.1534/genetics.116.194688.

importantly, does not lead to an increased risk for the derived food unless the function of the DNA can be associated with an adverse effect.

Cisgenesis and Intragenesis

In plants, cisgenesis and intragenesis may involve the use of established genetic engineering methods, i.e. random integration of recombinant DNA molecules into the genome, or SDN-3 techniques for site-specific integration of a gene. These methods are characterised by 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 for cisgenesis the resulting organisms *could in principle be developed using conventional breeding techniques*, although the same is not true for the products of intragenesis.[11] 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[12], and intragenesis has been utilised to develop breeding lines of potato with resistance to black spot bruising[11] and lower acrylamide content after high temperature processing.[11] Transgenesis is differentiated from cisgenesis in that it allows for the integration of donor DNA from an unrelated, cross-incompatible species.[13]

In cisgenesis, the introduced DNA is a naturally occurring fragment of genomic DNA that contains the gene of interest with its own regulatory sequences, i.e. promoter, coding region including its introns, terminator sequences, and 5' and 3' untranslated regions in the normal-sense orientation.[14] 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 in antisense orientation.[14]

The use of cisgenesis and intragenesis requires prior knowledge of the gene sequence, its position, and its function in the genome of origin. In the case of cisgenesis, when the cisgene is integrated into the genome of the recipient, it is expected to show comparable expression levels with the donor, along with comparable fitness, toxicity/allergenicity, and effects on non-target

[11] 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.

[12] 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.

[13] Araki, M, Ishii, T (2015) Towards social acceptance of plant breeding by genome editing, Trends in Plant Science 20: 145-149.

[14] Holme, IB, Wendt, T, Holm PB (2013) Intragenesis and cisgenesis as alternatives to transgenic crop development, Plant Biotechnology Journal 11: 395-407.

organisms to organisms created using conventional methods.[15] 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.[16] 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.[17]

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 methods are specific to the new breeding lines resulting from these breeding methods, 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 unintended changes owing to somaclonal variation will be similar in both cases.[18]

In agriculture, wild relatives of domesticated crops and landraces have long been used in intra- and inter-specific hybridisation. The primary advantages of cisgenesis and intragenesis over conventional breeding methods is improved efficiency and ability to respond to agricultural challenges.[19] This arises as a result of more targeted access to:

i. Specific beneficial traits that are present in the crossable breeders' pool and wild relatives but not in commercial crop plants. This scenario arises due to breeder-controlled selection of progeny for improved traits and narrowing of the available genetic variation. In contrast, exotic breeding lines, and wild relatives have broader

[15] 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; Schouten, HJ, Krens FA, Jacobsen E (2006) Cisgenic plants are similar to traditionally bred plants, EMBO Reports 7: 750-753.

[16] 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.

[17] Schouten, H.J., Krens, FA (2006) Do cisgenic plants warrant less stringent oversight? *Nature Biotechnology*, 24: 753; Jacobsen, E., Schouten, H.J.(2008) Cisgenesis, a new tool for traditional plant breeding, should be exempted from the regulation on genetically modified organisms in a step by step approach. *Potato Research* https://www.researchgate.net/profile/Henk_Schouten/publication/225613807_Cisgenesis_a_New_Tool_for_Traditional_Plant_Breeding_Should_be_Exempted_from_the_Regulation_on_Genetically_Modified_Organisms_in_a_Step_by_Step_Approach/links/00b49539eb68757f6f000000.pdf.

[18] EFSA (2012) Scientific opinion of the EFSA GMO Panel addressing the safety assessment of plants developed through cisgenesis and intragenesis. *EFSA J* **10:** 2561

[19] 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.

genetic variability that allows adaptation to changing environmental conditions via natural evolutionary processes.[20]

ii. Specific beneficial traits without the disadvantages of unwanted traits associated with linkage drag which reduces performance and viability of the final product. Overcoming linkage drag requires successive generations of backcrossing, however this is not always possible and depends on the chromosomal positon of the desired trait.[21]

iii. Previously inaccessible beneficial traits. In some cases, beneficial traits are positioned in chromosome regions that have very low recombination frequencies, which mean 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.[22]

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

Plants created by cisgenesis are considered to be analogous to that which can be 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.[23] 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.[24] For both products of cisgenesis and intragenesis, changes that may occur with the insertion include rearrangements or

[20] 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.

[21] Ibid.; Jacobsen, E. and Schouten, H.J. (2007) Cisgenesis strongly improves introgression breeding and induced translocation breeding of plants, Trends Biotechnol. doi:10.1016/j.tibtech.2007.03.008

[22] 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.

[23] 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.

[24] 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.

translocations in the flanking regions, which could impact on genes and open reading frames. However, such changes are reported to occur spontaneously in plants, and are especially common in regions where transposons are active and with the use of conventional induced mutagenesis techniques could result in larger changes.[25] The potential risks posed by cisgenesis and intragenesis and the organisms created from these breeding methods should be assessed by comparison with conventional breeding approaches rather than with transgenesis, so that regulation is commensurate with the comparable risk of their derived products.

We therefore propose that if the discussed general principle is retained, it is applied to organisms where the new DNA sequence was "not previously present in the host organism or cross compatible breeding species", and that it is not applied when the "new DNA" is derived from the host organism, or the breeder's gene pool for that host organism, this "new DNA" having been reintroduced at a different location in the genome or when it has been rearranged or introduced into the host organism in a different orientation.

Genome unchanged by gene technology (null segregants) - 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? If no, what are your specific safety concerns for food derived from null segregants?

Bayer Crop Science considers that null segregants are not genetically modified organisms, they do not have novel traits derived from the integration of new pieces of DNA and as such should not be subject to pre-market safety assessment. There is no scientific basis for organisms that are derived from GMOs (included in Food Standard 1.5.2) but which no longer contain foreign DNA to undergo pre-market safety assessment for inclusion in Food Standard 1.5.2. Such organisms have lost the transgenic event (i.e. "new" DNA) due to segregation during breeding. These organisms are identical (in terms of food risk and performance) to that obtained through conventional breeding methods and should be treated in the same manner by FSANZ.

Genome changed but no new DNA (genome editing – refer Section 3.1.3 of Consultation Paper) - Are foods from genome edited organisms likely to be the same in terms of risk to foods derived using chemical or radiation mutagenesis? If no, how are they different? 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?

[25] Schouten, HJ, Krens, FA, Jacobsen, E (2006) EMBO Reports 7(8): 750-753; Forsbach, A, Schubert, D, Lechtenburg, B, Gils, M, Schmidt, R. (2003) A comprehensive characterization of single-copy T-DNA insertions in Arabadopsis thaliana genome. Plant Mol Biol 52: 161-176; Tax, FE, Vernon DM (2001) T-DNA associated duplication/translocations in Arabidopsis. Implications for mutant analysis and functional genomics. Plant Physiol 126: 1527-1538.

Foods derived from genome edited organisms, in particular from plants, we propose are the same in terms of risks to foods derived using conventional breeding methods, including chemical or radiation mutagenesis. We support this proposal with the discussion below.

Genome editing based on DNA break induction and repair for targeted mutagenesis of endogenous genes, i.e. SDN-1, SDN-2 and ODM methods, have been used to, for example, induce loss of function, modulate activity or alter function of native genes. These methods enable more targeted and efficient development of agronomically useful traits such as resistance to biotic (e.g. disease) and abiotic stresses, herbicide tolerance, changed nutritional composition.[26]

The SDN-1, SDN-2 and ODM methods can be equated to long established or "conventional" induced mutagenesis approaches (e.g. based on the use of chemicals or radiation), as the SDN or oligomer essentially acts as a mutagenic substance, resulting in comparable genetic changes resulting from the earlier approaches.[27] The difference between newer methods and those based on established mutagenisis is that the modern approaches induce **targeted** genomic changes, meaning that the site of the genetic change is known in advance and its effect can be predicted. [28,29] In order to achieve the desired effect this requires prior knowledge of the gene or genes responsible for the desired trait. In contrast, induced mutagenesis approaches cause genome-wide changes in addition to incorporation of the desired trait(s).[30,31]

The issue considered to be of key importance under this question in the Consultation Paper is "the nature of the genome changes that may be introduced (both targeted and off-target) and

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[26] Podevin, N, Davies, HV, Hartung, F, Nogue F, Casacuberta, JM (2013) Site-directed nucleases: A paradigm shift in predictable, knowledge-based plant breeding, *Trends in Biotechnology* 31: 375-383; Beetham, P.R., Kipp, P. B., Sawycky, X. L., Arntzen, C. J., May, G. D. (1999) A tool for functional plant genomics: Chimeric RNA/DNA oligonucleotides cause in vivo gene-specific mutations, PNA 96, 8774-8778; Dong, C., Beetham, P.R., Vincent, K., Sharp, P. (2006) Oligonucleotide-directed gene repair in wheat using a transient plasmid gene repair assay system. Plant Cell Reports 25, 457-465.

[27] EFSA (European Food Safety Authority) (2015) Genetically modified organisms UNIT. Mandate Number: M-2015-0183. http://registerofquestions.efsa.europa.eu/roqFrontend ; Sprink, T., Metje, J., Schiemann, J. et al. Plant Biotechnol Rep (2016). doi:10.1007/s11816-016-0418-3; European Academies Science Advisory Council (2015) Statement: New Breeding Techniques. http://www.easac.eu/home/reports-and-statements/detail-view/article/easac-statem-2.html

[28] Hartung, F, Schiemann, J (2014) Precise plant breeding using new genome editing techniques: opportunities, safety and regulation in the EU, *The Plant Journal* 78: 742-752.

[29] Podevin, N et al. (2013) *Op Cit*.; Pauwels, K., Podevin, N., Breyer, D., Carroll, D., Herman, P. (2014) Engineering nucleases for gene targeting: safety and regulatory considerations *New Biotechnology* 31(1): 18-27.

[30] Hartung, F, Schiemann, J (2014) *The Plant Journal* 78: 742-752.

[31] Podevin, N et al. (2013) *Op Cit*.

the extent to which they may be similar to changes introduced using conventional approaches such as chemical or radiation mutagenesis (which introduce similar changes to genome editing except at random sites in the genome), or that occur spontaneously in nature (and are representative of natural variation)". Our understanding is that the regulator is concerned that the exclusion of targeted mutagenesis techniques (i.e. genome editing) from pre-market safety assessment may not adequately manage food risks the resulting products may pose. As pointed out in the paragraph above, consideration of these risks should take into account and compare the effects of spontaneous or naturally occurring mutations and that of the induced mutagenesis techniques that are excluded from pre-market food safety assessment based on history of safe use.

Genome changes brought about through induced mutagenic methods are generally more extensive than that brought about through the application of SDN-1, SDN-2 or ODM approaches. Subjecting the latter to pre-market safety assessment under Food Standard 1.5.2 while exempting the former, would result in with application of regulatory measures that are not commensurate to the risks posed by the latter.

Spontaneous mutations are known to occur frequently in nature, and these bring about the genomic sequence changes that are the basis of evolution. These 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 SDN technologies, and the same mechanism is involved in the integration of rDNA in transgenesis, cisgenesis and intragenesis. 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[32] and can lead to gene gain, duplication or loss and hence contribute to a change in the phenotype of the resultant organism.[33]

Plants in particular have considerable capacity to undergo genetic change, and several additional mechanisms underlying spontaneous mutation have been described that contribute to a process of constant genome restructuring and reprogramming. In comparison, animal

[32] 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; Ossowski, S. *et al*. (2010) The rate and molecular spectrum of spontaneous mutations in *Arabidopsis thaliana*. *Science* 327: (5961) 92. 94.

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

genomes are relatively stable and conserved.[34] Greater plasticity in plants is believed to contribute to the maintenance of adaptive phenotypes, and to be an adaptation mechanism to their immobility.[35] 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.[36] Of note, these mechanisms are considered to have a greater impact on genome sequence and function than gene insertion using genetic engineering.[37] 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.[38]

Parallels may be drawn between the movement of transposable elements and the insertion of transgenes in terms of their size (from hundreds to thousands of base pairs), and impact, in that they may contain one or more open reading frames, they may increase gene copy number and activate or inactivate genes. These changes can alter gene expression and the nature of proteins expressed, leading to modified or novel traits. In plants, transposable elements can account for substantial portions of the genome, e.g. 25% in rice and 57% in maize, and their insertion near genes have been associated with some important traits, e.g. the anthocyanin biosynthesis pathway in grapes that is responsible for berry colour.[39]

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.[40]

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

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[34] 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.

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

[36] 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.

[37] Strauss SH, Sax JK (2016) *Nature Biotechnology* 34: 474-477; Schnell et al. (2015) *Transgenic Research* 24: 1-17.

[38] Strauss SH, Sax JK (2016) *Nature Biotechnology* 34: 474-477.

[39] Arber, W (2010) *New Biotechnology* 27: 517-521; Schnell et al (2015) *Transgenic Research* 24: 1-17.

[40] Arber, W (2010) Op. Cit; Schnell et al. (2015) Op. Cit.

semi-dwarf variation in cereal crops which has contributed significantly to improved grain yield.[41] Limitation of exploitation of spontaneous mutations for crop breeding 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.[42] Such conventional induced mutagenesis methods 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.[43] A limitation of this approach is that large populations of mutant plants must be screened in order to select plants with desired phenotype to be included in breeding programs. Generations of crossing may then be needed to segregate away unwanted mutations that may impact on plant performance.[44]

Conventionally induced mutagenesis (chemical and radiation mutagenesis) used for the development of new or improved traits in plant breeding are excluded from pre-market food safety assessment by FSANZ 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.[45] The FAO/IAEA Mutant Variety Database lists 3275 officially released cultivars in more than 200 plant species registered since 1950.[46] In the past 20 years, these methods have been complemented by biotechnology tools, with the early approaches (e.g. rDNA) now also having a demonstrated history of safe use, exemplified by the many products derived from the application of recombinant DNA methods in their development having successfully undergone food safety assessment, with consumption of those foods having occurred over an extended period without any evidence of ill-effects from human or animal consumption.[47] [48]

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[41] 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.

[42] 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

[43] Schnell et al. (2015) Transgenic Research 24: 1-17.

[44] Podevin, N et al. (2013) Op cit.

[45] Hartung, F, Schiemann, J (2014) Op Cit.

[46] https://mvd.iaea.org/#!Home, accessed 20 March 2018; Podevin, N et al. (2013) Op cit.

[47] https://www.nature.com/articles/s41598-018-21284-2 Pellegrino, E., Bedini, S., Nuti, M., Ercoli, L., Impact of genetically engineered maize on agronomic, environmental and toxicological traits: a meta-analysis of 21 years of field data *Scientific Reports,* **Vol 8**, Article number:3113 (2018), doi:10.1038/s41598-018-21284-2

[48] Van Eenennaam, A. L. and Young, A. E. Prevalence and impacts of genetically engineered feedstuffs on livestock populations. J. Anim. Sci. 2014.92:4255–4278. doi:10.2527/jas2014-8124.

The targeted mutagenesis approaches 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 induced using conventional mutagenesis applications(e.g. ionising radiation and ultra violet light), and sites flanking transposon movement or DNA insertions in genetically modified plants.[49] The exact sequence of mutated organisms cannot be predicted but their phenotypes can be screened for the presence of the intended change.[50]

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 modifications defined by the repair template.[51]

The ODM approach differs from SDN approaches 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 with the exception of the nucleotide changes intended to be incorporated during repair.[52]

An argument raised to support claims of risk associated with genome editing is the possibility for unintended, off-target effects, a point raised in the Consultation Paper where further information was requested (refer Section 3.1.3 of the Consultation Paper). We note that off-target mutations (changes in DNA sequence) beyond those intended to be introduced in the target location in the genome should not be equated with off-target effects, as off-target effects are the phenotypic manifestation of a mutation.

To our knowledge, the site-directed nature of SDN-1, SDN-2 and ODM approaches can only reduce the number of off-target mutations in comparison with chemical or radiation induced mutagenesis approaches. Furthermore, any potential off-target effects would be addressed in the breeding and selection process in a similar way to the one used to reduce the level of background mutations due to chemical and radiation mutagenesis. Furthermore, in plants, while

[49] Schnell et al. (2015) Transgenic Research 24: 1-17.

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

[51] 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.

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

off-target mutations have been reported with SDN approaches , their frequency is considered to be well below that which occurs with other non-regulated conventional mutagenesis, and comparable to that which occurs in cross breeding.[53] The ODM and SDN approaches 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 methods are not as technically simple to employ in any plant as the general media suggests. Off-target mutations due to the application of SDN approaches have been described in the scientific literature as highly homologous to on-target mutations, with the possibility to predict and detect them based on sequence homology.[54]

In plants, off-target mutations can be greatly controlled by careful design and selection of the site directed nuclease or oligonucleotides, and the resulting mutant plants can be further selected to eliminate undesired phenotypes.[55] In plants, while possible, unintended effects arising from cross-breeding or transgenesis do not automatically contribute to increased hazard or impact on food safety, e.g. production of a new toxin or allergen, and there are no documented cases of this occurring.[56]

The targeted nature of genome editing techniques differentiates them from transgenesis which is characterised by the random integration of recombinant DNA. Targeted integration of transgenes is possible with SDN-3 methods, which like SDN-1 and SDN-2 induces DNA double-stranded breaks at specific locations and like SDN-2 utilises a repair template. The following section discusses how products derived from the SDN-3 technique are captured under the definition of products containing “new pieces of DNA”. **We believe that SDN-3 derived products should be included for pre-market food safety assessment, due to the possibility of expression of novel proteins, and the need to characterise potential toxins**

[53] 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) Op cit.

[54] 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.

[55] Wolt, JD, Wang, K, Yang, B (2016) The Regulatory Status of Genome-edited Crops, Plant *Biotechnology Journal* 14: 510-518.

[56] Schnell et al. (2015) *Transgenic Research* 24: 1-17.

and allergens that may occur in the derived food. We note that, the possibility of this occurring is minimised in products derived from SDN-3 compared to those derived from random transgenesis techniques.[57]

Workshops convened by FSANZ in 2012 and 2013 explored the necessity to undertake food safety assessment for products derived from new breeding techniques. [58] For the targeted mutagenesis approaches (genome editing) of ODM, SDN-1 and SDN-2, it was recognised that the genomic changes were typically small and definable with predictable outcomes, and these outcomes were comparable to that possible with conventional mutagenesis. **Thus, food derived from plants developed using these methods should not be regarded as GM food.**

The scientific interpretation of these methods is consistent with recommendations made by the EFSA GMO unit, EASAC and the Swedish Board of Agriculture[27] and most recently the USDA.[59] The US authorities have also exempted from regulations a number of products derived from plant breeding innovation approaches – for example, non-browning mushrooms, waxy corn and Group B herbicide tolerant canola produced using ODM.

For cisgenesis, it was recognised that derived food would be similar to that produced using standard transgenic approaches, but the transferred genes will be derived from the same or a closely related species which is likely to be commonly used as food and have a history of safe use. For this reason, a reduced food safety assessment was considered proportional to the risk posed, and this proposal has taken effect within the FSANZ Application Handbook published in March 2016.[60]

The view on cisgenesis taken in the FSANZ workshops on the innovations in plant breeding 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.[61]

Bayer Crop Science believes that in the context of the food safety assessments managed by FSANZ that organisms developed using cisgenesis and intragenesis pose equivalent food safety risks to those developed using conventional plant breeding methods, and regulation of cisgenic and intragenic plants in the same manner as transgenic plants is

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[57] Podevin, N et al. (2013) *Op Cit*.

[58] http://www.foodstandards.gov.au/publications/Documents/New%20Plant%20Breeding%20Techniques%20-2013%20Workshop%20Report.pdf

[59] https://www.the-scientist.com/?articles.view/articleNo/52209/title/USDA-Will-Not-Regulate-CRISPR-Edited-Crops/

[60] http://www.foodstandards.gov.au/code/changes/pages/applicationshandbook.aspx

[61] 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.

disproportionate to their risks. The key reason for differentiation of the products of cisgenesis and intragenesis from products of transgenesis, on a food safety assessment basis, is that the resultant cisgenic and intragenic products introduce no new DNA which is foreign to the host species, and therefore the resultant plant lines would have comparable risks to those derived from other, non-regulated breeding methods. We therefore propose that the products of cisgenesis and intragenesis should also be included in the group of products derived from genome editing (SDN-1, SDN-2 and ODM) which may be excluded from pre-market food safety assessment and approval. This is consistent with the proposal that methods that result in products similar to those that may be derived from conventional plant breeding methods should be excluded from the necessity for food safety assessment.

Differentiating SDN-1, SDN-2 and ODM from SDN-3

The SDN-1, SDN-2 and ODM are distinguished from established genetic engineering (rDNA) and SDN-3 approaches in one critical way: the changes to the DNA sequence induced by these methods brings about changes in **endogenous gene sequence and function** that are in principle **possible to create using well established methods** (i.e. crossing/breeding, mutagenesis). Furthermore, the genes or genetic material altered by these techniques and the respective organisms that carry these changes are **indistinguishable at the DNA sequence level from organisms which can be obtained with alternative mutagenesis or breeding methods.** In contrast, traditional genetic engineering techniques including SDN-3-approaches result in the **integration of a novel functional gene(s)**. SDN-3 may also potentially be used to introduce gene stacks at a specific single locus.[62]

A difference between SDN-2 and SDN-3 is the extent of the change introduced using the repair template. SDN-2 aims to make a site-specific modification to **endogenous gene function**, whereas SDN-3 intends targeted **insertion of a novel gene(s)**. With SDN-3, the inserted gene may not already be present in the genome sequence of the host organism or its sexually compatible breeding pool (transgenesis), or it may be present in its sexually compatible breeding pool (cisgenesis and intragenesis). Where SDN-3 is used for transgenesis, the resulting product **could not be achieved using established breeding methods**, and this differentiates transgenesis from cisgenesis and intragenesis (see section on cisgenesis and intragenesis above).

When SDN-3 is used to introduce transgenes into a host organism, it is pertinent to compare the process and outcomes with transgenesis, because the aim and the final products derived from

[62] Podevin et al. (2013) Op cit.; Chen, K., Gao, C. (2014) Targeted genome modification technologies and their applications in crop improvements. *Plant Cell Rep* 33: 575-583.

the two processes will be similar. However, although in transgenesis the DNA is integrated into natural DNA breaks that occur at random positions in the genome (often close to actively transcribed genes),[63] SDN-3 techniques target DNA insertion to a predefined site in the genome. Targeting of the transgene in a predefined locus can optimise the genomic environment for gene expression and minimise hazards associated with the disruption of genes and/or regulatory elements in the recipient genome. Moreover, because the junctions between the transgene and the recipient genome are predefined by the sequence of the donor used, the SDN-3 approach should avoid the creation of new open reading frames with similarity to toxins or allergens. Therefore, the use of the SDN-3 technique could be seen as a way to decrease substantially these perceived risks and therefore warrants a reduced data package to prove safety in comparison to transgenesis.[64]

Other techniques - Are you aware of other techniques not currently addressed by this paper which have the potential to be used in the future for the development of food products? Should food derived from other techniques, such as DNA methylation, be subject to pre-market safety assessment and approval?

We believe that progress in science and innovation in plant breeding is a continuous process and leads to the refinement and optimisation of existing approaches in addition to development of further new tools. Whilst continuously improving on existing processes brings more cost efficient and effective product outcomes, in practice it is the combination of multiple approaches that significantly support breakthrough innovations. Considering this continued progress in innovation and demand for solutions to significant ongoing challenges in sustainable food production, we believe that it is very relevant to consider whether the regulatory process should continue to use a technology-based regulatory trigger in the longer term. In particular, the application of gene technology (and whatever tools and methods may be included in this category) to food production would greatly benefit from further scientific evaluation of the proportionality of the regulation in comparison to risk of the resulting products. We believe that there may be instances where the application of modern biotechnology approaches would reduce the risks due to the greater predictability that is inherent with some innovative methods such as gene editing in comparison to alternative methods used in isolation.

Finally, we would like to comment on the question whether DNA methylation should be subject to pre-market safety assessment and approval. **DNA methylation, in our view is not a technique but a biological phenomenon that is linked to multiple aspects of gene and**

[63] Fu, F.F. et al. (2009) Studies on rice seed quality through analysis of a large-scale T-DNA insertion population. Cell Res. 19, 380–391.

[64] Podevin et al. (2013) Op cit.

genome regulation in all organisms, including plants[65]. The recent advancements in the study of DNA methylation[66], indicate that variants in DNA methylation can have, in some cases, phenotypic consequences and because of this have been discussed as a potential source of diversity in plant breeding. However, much remains to be studied and understood about the different layers of regulation that contribute to the expression of a given phenotype, and the role that DNA methylation plays in this complex regulatory network. Multiple genetic and environmental factors contribute to phenotypic variations in plants and with time the understanding of specific elements in this complex regulatory network will be elucidated better. However, 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.

Regulatory trigger - *Do you think a process-based definition is appropriate as a trigger for pre-market approval in the case of New Breeding Techniques? If no, what other approaches could be used? If yes, how could a process-based approach be applied to New Breeding Techniques? Are there any aspects of the current definitions that should be retained or remain applicable?*

Bayer Crop Science, in general, **agrees** with the statement in the Consultation Paper that as a mechanism for food safety assessment of foods with new DNA inserted, the process-based approach has generally worked well over nearly 20 years of application. However, as we have discussed earlier in this submission, the current process-based definitions are no longer appropriate due to the fact that products derived from current innovative breeding methods including SDN-1, SDN-2, ODM can in large part be arrived at via conventional breeding approaches. The most important and driving feature that differentiates products derived from conventional breeding and those obtained from SDN-1, SDN-2 and ODM is the significantly enhanced speed of breeding as supported by directed accuracy in achieving the desired final product. The economic consequences of this optimised timeframe should not be underestimated as compelling further innovation in plant breeding now and in future. As a consequence, **the process-based trigger for food safety assessment no longer delivers**

[65] Chad E. Niederhuth, Robert J. Schmitz (2017). Putting DNA methylation in context: from genomes to gene expression in plants, *Biochimica et Biophysica Acta* (BBA) - Gene Regulatory Mechanisms, Volume 1860 (1), 149-156.

[66] Chad E. Niederhuth, Adam J. Bewick, Lexiang Ji, Magdy S. Alabady, Kyung Do Kim, Qing Li, Nicholas A. Rohr, Aditi Rambani, John M. Burke, Joshua A. Udall, Chiedozie Egesi, Jeremy Schmutz, Jane Grimwood, Scott A. Jackson, Nathan M. Springer ,Robert J. Schmitz (2016). Widespread natural variation of DNA methylation within angiosperms. *Genome Biology* 17:194.

appropriate risk-based outcomes in terms of what foods are considered for pre-market safety assessment.

As stated in our answers to Questions 3.1.1 and 3.1.3 from the Consultation Paper, the final characteristics of the new plant variety are the best indicator as to whether a new plant variety will present a food safety risk.

In addition, to discussion provided on the products of continuous plant breeding innovation, we have extensively discussed the relevance of the products of cisgenesis and intragenesis in the food safety assessment scheme, in the context of what constitutes "new DNA". The presence of "new DNA" is part of the current process trigger for inclusion of such products in the pre-market food safety assessment scheme. For products of cisgenesis and intragenesis pre-market food safety assessment under Standard 1.5.2 is not relevant due to the fact that cisgenic and intragenic products do not contain "new DNA" or foreign DNA, and the DNA sequences utilised in breeding of these products are all derived from the host species.

If the discussed general principle is retained, it should be applied to organisms where the new DNA sequence was not previously present in the host organism or cross compatible breeding species.

Premarket safety assessment and approval under the Food Standards Code should therefore <u>not</u> be applied when the "new DNA" is derived from the host organism, or the breeder's gene pool for that host organism, this "new DNA" having been reintroduced at a different location in the genome or when it has been rearranged or introduced into the host organism in a different orientation.