

INTRODUCTION

Bayer CropScience, a division of Bayer AG which recorded annual sales of € 9.4 billion in 2014, 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 CropScience Australia has a long history of leading innovation in sustainable agriculture and a strong focus on sales and R&D in Australia.

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

Investment in Australian partnerships

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.

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 also recently opened an Animal Health Research Centre in New Zealand which has the proximity, experience and focus to provide tailored solutions for the Australian market.

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 OGTR's public consultation on the proposed changes to the Gene Technology Regulations (GT Regulations) regarding new breeding techniques, also known as plant breeding innovations (PBI) with respect to the Seeds industry.

The Option supported by Bayer CropScience reflects our 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 CropScience strongly supports **Option 4** as proposed in the Discussion Paper, to exclude the products of oligo-directed mutagenesis (ODM), site-directed nuclease (SDN)-1 and SDN-2 from the scope of regulation.

This option 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 the technique used to arrive at the final product. Thus techniques that result in products that are indistinguishable from products produced using long established techniques, such as chemical mutagenesis or conventional breeding should not be regulated under the GT Act.

Each of the three other options discussed in the Discussion Paper have significant “cons” associated with them as set out in the Discussion Paper. We agree in large part with the OGTR opinion expressed regarding the “cons” on Options 1, 2 and 3, and in addition wish to emphasise the following:

Option 1: This option from our perspective represents the least workable option moving forward as it offers no legal clarity to product developers on a suitable path to market for products developed using the new technologies mentioned in the Discussion Paper.

Option 2 and 3: In our opinion these two options are inadequate and do not reflect regulatory best practice. The cons raised in the OGTR discussion paper are cogent arguments as to why these options are not viable. We discuss this opinion in further detail within this submission.

Bayer CropScience also wishes to propose amendment of the GT Regulations to expressly exclude the technique of cisgenesis due to the similarity that the resultant products of cisgenesis have to those derived from conventional breeding and the organisms created by it, from the scope of regulation. The Regulator’s proposal to clarify that null segregants are not GMOs, and therefore not subject to regulation is also supported by Bayer CropScience.

Bayer CropScience’s position is consistent with that held by CropLife Australia and its members. As a result, our submission will reflect to a large extent the arguments raised in the CropLife Australia submission, with the addition of supplementary research papers that lend weight to the scientific rationale for adoption of Option 4. Nevertheless, the views held by Bayer CropScience and presented in this submission, although not unique, are expressly those of Bayer CropScience.

Option 4: Scientific Rationale and Supporting Evidence

The techniques included in the scope of Option 4, namely mutagenesis techniques based on cellular DNA repair (SDN-1, SDN-2 and ODM techniques), have been used by academic and

industry researchers for the targeted mutagenesis of endogenous genes to, for example, induce loss of function, modulate activity or alter function. These techniques enable the development of agronomically useful traits such as herbicide tolerance, changed nutritional composition, and resistance to biotic (e.g. disease) and abiotic stresses.¹

The SDN-1, SDN-2 and ODM techniques can be equated to long established or “conventional” induced mutagenesis techniques (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 techniques.² The difference between the new techniques and methods based on established mutagenic techniques is that the new techniques induce **targeted** genomic changes, meaning that the site of the genetic modification is known in advance and its effect can be predicted.^{3,4} In order to achieve the desired effect this requires prior knowledge of the gene or genes responsible for the desired trait. In contrast, conventional induced mutagenesis techniques cause unknown, random, genome-wide changes in addition to incorporation of the desired trait(s).^{5,6}

A concern with Option 4 raised in the Discussion Paper is that excluding these targeted mutagenesis techniques from regulation may not adequately manage risks their products may pose. Consideration of these risks should also take into account the effects of spontaneous, or

- 1 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.
- 2 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>
- 3 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.
- 4 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.
- 5 Hartung, F, Schiemann, J (2014) *The Plant Journal* 78: 742-752.
- 6 Podevin, N et al. (2013) *Op Cit.*

naturally occurring mutation mechanisms, and that of the conventional induced mutagenesis techniques that are excluded from regulation (Schedule 1A GT Regulations).

As explained in more detail below, changes brought about through conventional induced mutagenic techniques are generally more extensive than that brought about through the SDN-1, SDN-2 or ODM techniques. Regulating the latter while exempting the former, given that it is not possible to distinguish changes brought about by using SDN-1, SDN-2 or ODM from changes brought about by conventional induced mutagenic techniques, would not be proportionate to the risks posed by the latter.

Spontaneous mutations are known to occur frequently, 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 and cisgenesis. 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.⁷ Transposition commonly results in gene gains, duplications and losses and hence the phenotype of the resultant organism.⁸

Plants in particular 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.⁹ 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.¹⁰ The presence of duplicated forms of genes is common in plants, and multigene families have been found that have arisen from the

7 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, Bourbonni re, 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.

⁸ Strauss SH, Sax JK (2016) Ending event-based regulation of GMO crops, *Nature Biotechnology* 34: 474-477;

⁹ 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.

¹⁰ Borges, RM (2008) Plasticity comparisons between plants and animals, *Plant Signalling and Behaviour*, 3: 367-375.

duplication of larger genomic regions and whole genomes.¹¹ Of note, these mechanisms are considered to have a greater impact on genome sequence and function than gene insertion using genetic engineering.¹² 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.¹³

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.¹⁴

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.¹⁵

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.¹⁶ 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

¹¹ 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.

¹² Strauss SH, Sax JK (2016) *Nature Biotechnology* 34: 474-477; Schnell et al. (2015) *Transgenic Research* 24: 1-17.

¹³ Strauss SH, Sax JK (2016) *Nature Biotechnology* 34: 474-477.

¹⁴ Arber, W (2010) *New Biotechnology* 27: 517-521; Schnell et al (2015) *Transgenic Research* 24: 1-17.

¹⁵ Arber, W (2010) *New Biotechnology* 27: 517-521; Schnell et al. (2015) *Transgenic Research* 24: 1-17.

¹⁶ 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.

may be used to accelerate the process.¹⁷ Such conventional 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.¹⁸ 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.¹⁹

Conventionally induced mutagenesis techniques used for the development of new or improved traits in plant breeding are excluded from regulation (Schedule 1A GT Regulations) 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.²⁰ The FAO/IAEA Mutant Variety Database lists 3241 officially released cultivars in more than 200 plant species registered since 1950.²¹ 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.

¹⁷ 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

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

¹⁹ Podevin, N et al. (2013) Op cit.

²⁰ Hartung, F, Schiemann, J (2014) Op Cit.

²¹ <https://mvd.iaea.org/#!/Home>, accessed 21 November 2016; Podevin, N et al. (2013) Op cit.

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 induced using conventional mutagenesis techniques (e.g. ionising radiation and ultra violet light), and sites flanking transposon movement or DNA insertions in genetically engineered plants.²² The exact sequence of mutated organisms cannot be predicted but their phenotypes can be screened for the presence of the intended change.²³

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.²⁴

The ODM mutagenesis technique differs from 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 with the exception of the nucleotide changes intended to be incorporated during repair.²⁵

An argument raised to support claims of risk associated with these technologies is the possibility for unintended, off-target effects. However, the site-directed nature of SDN-1, SDN-2 and ODM techniques reduces these effects in comparison with conventionally induced mutagenesis techniques. Furthermore, in plants, while off-target effects have been reported with SDN techniques, their frequency is considered to be well below that which occurs with other non-regulated conventional mutagenesis techniques, and comparable to that which occurs in cross breeding.²⁶ 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,

²² Schnell et al. (2015) *Transgenic Research* 24: 1-17.

²³ Jones, HD (2015) Future of breeding by genome editing is in the hands of regulators, *GM Crops & Food* 6: 223-232.

²⁴ 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.

²⁵ Sprink et al (2016) *Plant Cell Reports* 35: 1493-1506; Jones, HD (2015) *GM Crops & Food* 6: 223-232.

²⁶ 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*.

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. Off-target effects of different types of SDN techniques have been described in the scientific literature as highly homologous to on-target effects, with the possibility of predicting them based on sequence homology and detecting them using sequencing.²⁷

In plants, off-target effects can be greatly limited by designing highly binding-specific SDNs or oligonucleotides, and mutant plants can be subject to downstream selection to remove undesired phenotypes.²⁸ In plants, while it is theoretically possible, unintended effects arising from cross-breeding or transgenesis do not automatically contribute to increased hazard or impact on biosafety, e.g. production of a new toxin or allergen, and there are no documented cases of this occurring.²⁹

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 SDN-3 technique, which like SDN-1 and SDN-2 induces DNA double-stranded breaks at specific locations and like SDN-2 utilises a repair template.

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

The SDN-1, SDN-2 and ODM techniques are distinguished from established genetic engineering (rDNA) and SDN-3 techniques 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 or

²⁷ 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.

²⁸ Wolt, JD, Wang, K, Yang, B (2016) The Regulatory Status of Genome-edited Crops, *Plant Biotechnology Journal* 14: 510-518.

²⁹ Schnell et al. (2015) *Transgenic Research* 24: 1-17.

SDN-3-type techniques 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.³⁰

As described in the Discussion Paper, a difference between SDN-2 and SDN-3 is the extent of the genetic modification 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). Where SDN-3 is used for transgenesis, the resulting product **could not be achieved using established breeding methods**, and this differentiates transgenesis from cisgenesis (see section on cisgenesis below).

Another consideration, as noted in the Discussion Paper, is that organisms created using ODM, SDN-1 and SDN-2 may not be easily identifiable, even with DNA sequencing, as the genetic changes may not be distinguishable from spontaneous or induced mutations. The Discussion Paper notes that this is an issue for enforcement and compliance. Bayer CropScience agrees with this assessment. When detection and enforcement are not possible, this puts the credibility of such a regulatory scheme at risk and creates regulations that are impractical and unworkable.

Use of Successive Rounds of SDN-2 or ODM

The Discussion Paper refers to the use of successive rounds of SDN-2 to achieve substantial modifications that are more comparable to SDN-3 in terms of the risk posed by resulting organisms. While it is questionable whether this approach is technically or practically feasible for the development of a commercial product given the time and cost involved compared to only using SDN-3, these products can still be differentiated from SDN-3.

As noted above, SDN-2 aims to **modify endogenous gene function**, whereas SDN-3 intends to **integrate a novel gene**. Where repeated rounds of SDN-2 result in an outcome that modifies the function of an endogenous gene it will remain SDN-2. Where the outcome is equivalent to the insertion of a gene outside of the sexually compatible breeding pool, this is consistent with transgenesis (SDN-3). Where the outcome is equivalent to the insertion of a gene that is within the sexually compatible breeding pool, this will be consistent with cisgenesis, which Bayer CropScience argues should be excluded from regulation.

Additionally, established breeding techniques could be used to achieve the same result as successive rounds of SDN-2 or ODM. For example mutagenic techniques may be used to generate multiple mutations which are then combined by crossing. This has been done with

³⁰ 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.

barley in Australia by creating a breeding stack of a gamma-radiated mutant, an EMS-derived mutant and a spontaneous mutant from Ethiopia.³¹

Cisgenesis

In plants, cisgenesis 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. The technique is 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 the resulting organisms could in principle be developed using conventional breeding techniques.³² 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.³³ Transgenesis is differentiated from cisgenesis in that it allows for the integration of donor DNA from an unrelated, cross-incompatible species.³⁴

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.³⁵ 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. The use of cisgenesis 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 expression levels with the donor, along with comparable fitness, toxicity/allergenicity, and effects on non-target organisms to organisms created using conventional methods.³⁶ 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

31 Tanner, G. J., Blundell, M. J., Colgrave, M. L. and Howitt, C. A. (2016), Creation of the first ultra-low gluten barley (*Hordeum vulgare* L.) for coeliac and gluten-intolerant populations. *Plant Biotechnol J*, 14: 1139–1150. doi:10.1111/pbi.12482

32 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.

33 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.

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

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

36 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.

outcome is also possible via conventional breeding.³⁷ 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.³⁸

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.³⁹ 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 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 genetic variability that allows adaptation to changing environmental conditions via natural evolutionary processes.⁴⁰
- 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, 41}
- 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.

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

³⁷ 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.

³⁸ 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.

³⁹ 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.

⁴⁰ 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.

⁴¹ 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

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.⁴²The 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 plants, but only at that locus.⁴³ 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 conventional induced mutagenesis techniques could result in larger changes.⁴⁴The potential risks posed by cisgenesis and the organisms created should be assessed by comparison with conventional breeding techniques rather than transgenesis, with regulation commensurate with its comparable risk.

⁴² 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.

⁴³ 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.

⁴⁴ 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 *Arabidopsis 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.

Null Segregants

Bayer CropScience also supports the Regulator's intention to clarify that null segregants are not GMOs. There is no scientific basis for organisms that are derived from GMOs (that would be regulated under the Act) that no longer contain DNA that was integrated into the genome of that GMO to be regulated under the Act. Such organisms have lost the transgenic event due to normal segregation during generations of crosses with non-GMOs. These organisms do not contain any elements of the transgenic event and cannot be identified as being a GMO, or derived from one, using detection tools for the detection of the original transgenic event. These organisms are therefore indistinguishable from that obtained through conventional breeding methods and should be regulated in the same manner. We note that it is for the same reasons that the products of ODM, SDN-1 and SDN-2 should also not be regulated.

ADDITIONAL COMMENTARY

In the Discussion Paper, the Regulator calls for commentary in a number of different areas, some of which are addressed in this submission. Additional commentary on the areas of RNA interference and the importance of consistency in regulation between Australian Government agencies is provided below.

RNA interference

RNA interference (RNAi) is a natural eukaryotic cellular mechanism that results in silencing or modulation of gene expression that is triggered by small interfering RNA molecules.⁴⁵ The use of RNA interference triggered by the topical application of double-stranded RNA (dsRNA) should not be included in the scope of gene technology regulation because such applications do not involve the creation of GMOs.⁴⁶ and are non-transgenic approach⁴⁷ The delivery of dsRNA to cells of target crop pests to induce RNAi and silencing of genes impacting on fitness or mortality have been reported, e.g. in nematodes, and lepidopteran and coleopteran insect, however optimal strategies for efficient delivery and uptake remain under investigation.⁴⁸ Products based on this technology should be regulated in accordance with existing schemes for biological plant protection products.

Consistency of Regulation between Australian Government Agencies

Bayer CropScience seeks that the Australian Government agencies with regulatory overview of the new technologies treat these technologies consistently, for example, to avoid a situation whereby a product is regulated as a GMO in regard to its release into the environment, but not as a GM food, and vice versa.

⁴⁵ Baum, JA, Bogaert, T, Clinton, W, Heck, GR, Feldmann, P, Ilagan, O, Johnson, S, Plaetinck, G, Munyikwa, T, Pleau, M, Vaughn, T, Roberts, J (2007) Control of coleopteran insect pests through RNA interference, *Nature Biotechnology* 25: 1322-1326.

⁴⁶ Robinson, KE, Worrall, EA, Mitter, N (2014) Double stranded RNA expression and its topical application for non-transgenic resistance to plant viruses, *Journal of Plant Biochemistry and Biotechnology* 23: 231-237.

⁴⁷ Scott, JG, Michel, K, Bartholomay, LC, Siegfried, BD, Hunter, WB, Smagghe, G, Zhu, KY, Douglas, AE (2013) Towards the elements of successful insect RNAi, *Journal of Insect Physiology* 59: 1212-1221.

⁴⁸ Killiny, N, Hajeri, S, Tiwari, S, Gowdam S, Stelinski, L (2014) Double-stranded RNA uptake through topical application, mediates silencing of five CYP4 genes and suppresses insecticide resistance in *Diaphorina citri*, PLOS ONE 9: e110536; Burand, JP, Hunter, WB (2013) RNAi: Future in insect management, *Journal of Invertebrate Pathology* 112: S68-S74; Baum, JA, Bogaert, T, Clinton, W, Heck, GR, Feldmann, P, Ilagan, O, Johnson, S, Plaetinck, G, Munyikwa, T, Pleau, M, Vaughn, T, Roberts, J (2007) Control of coleopteran insect pests through RNA interference, *Nature Biotechnology* 25: 1322-1326.

Food Standards Australia New Zealand (FSANZ) has held two scientific workshops that considered a range of new technologies to provide advice on regulation of derived food.⁴⁹ A summary of the workshop outcomes is outlined below:

Technique	Regulated as GM food
Targeted transgene addition or replacement (c.f. SDN-3)	Yes
Cisgenesis / Intragenesis	Yes – but should only require a simplified food safety assessment
Oligo-directed mutagenesis	No
Targeted mutagenesis (c.f. SDN-1; SDN-2)	No – so long as not used to introduce a new gene

For the targeted mutagenesis techniques 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 techniques. Thus, food derived from plants developed using these techniques should not be regarded as GM food. The scientific interpretation of these techniques from the FSANZ workshops is consistent with this submission supporting the exclusion of the products of ODM, SDN-1 and SDN-2 from the scope of the OGTR's regulatory scheme. It is also consistent with recommendations on the techniques made by the EFSA GMO unit, EASAC and the Swedish Board of Agriculture.² The US authorities have also exempted from regulations a number of products derived from the new techniques – for example non-browning mushrooms, waxy corn and Group B herbicide tolerant canola produced through the ODM technique.

For cisgenesis, it was recognised that derived food would be similar to that produced using standard transgenic techniques, 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 required was considered proportional to the risk posed, and this proposal has taken effect within the FSANZ Application Handbook published in March 2016.⁵⁰

⁴⁹ <http://www.foodstandards.gov.au/consumer/gmfood/Pages/New-plant-breeding-techniques-in-the-spotlight.aspx>

⁵⁰ <http://www.foodstandards.gov.au/code/changes/pages/applicationshandbook.aspx>

The view on cisgenesis taken in the FSANZ workshops on the new technologies 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.⁵¹ Bayer CropScience believes that in the context of the environmental risks managed by OGTR that organisms developed using cisgenesis pose equivalent biosafety risks to those developed using conventional plant breeding methods, and regulation of cisgenic plants in the same manner as transgenic plants is disproportionate to their risks. The proposal to treat cisgenesis as a new technology within the group of techniques proposed for exclusion from regulation as discussed in Option 4. This idea is consistent with the proposal that techniques that deliver products similar to those that may be derived from conventional plant breeding methods should be excluded from regulation.

Bayer CropScience recognises that OGTR and FSANZ regulate different products of biotechnologies for different risks. Bayer CropScience believes that harmonisation of the way in which the new technologies are regulated is achievable as an outcome of the current technical review of the regulations.

⁵¹ 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.

CONCLUSION

The potential risks posed by the SDN-1, SDN-2 and ODM techniques and the organisms that result from such changes should be assessed against the risks posed by conventional breeding and established mutagenesis techniques. We believe that in this submission we have scientifically argued for the similarity of the products derived from the SDN-1, SDN-2 and ODM techniques to those products derived from conventional breeding techniques which have an established history of safe use. Option 4 as proposed by the regulator represents a regulation scheme commensurate with the biosafety risk associated with the products derived from SDN-1, SDN-2 and ODM techniques.

We welcome OGTR's clarification on the definition of null segregants within the regulatory scheme. In addition to this we hope that OGTR can consider our commentary on products of cisgenesis within the scope of this public consultation on the regulatory scheme. We feel that it is timely that this technique is considered within the proposal to vary the scope of the definitions of those products that are and are not considered to be defined as GMOs under the gene technology regulations.

Bayer CropScience looks forward to the opportunity to comment upon any proposed changes that OGTR publishes in regards to the regulations moving forward.