GMWatch response to the FSA's "Responses to questions asked of FSA Board September 2023", 18 Oct 2023

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Following is GMWatch's response to some of the FSA's replies to questions we asked of the FSA Board for its September 2023 meeting. Due to time constraints, we have not attempted a comprehensive response to all the FSA's points, but focus on some key issues. We request that the FSA responds in turn.

We believe that it is important to respond to the FSA's points because they show a lack of scientific understanding of, or an unwillingness to admit to, the risks posed by new genetic modification (so-called "precision breeding" or PB) techniques in relation to food safety and public health. We therefore draw the FSA's attention to these issues in the expectation and hope that the agency will endeavour to improve its existing draft proposals for the assessment of genetically modified (GM) "precision bred" organisms (PBOs).

Invalid assumptions of equivalence between GM PB organisms and those conventionally bred

The FSA says, "The ACNFP recognised that most organisms produced by PB ["precision breeding"] will be similar in risk profile to their traditionally bred counterparts, where the same change has been achieved and a risk assessment is not required. By definition, the spectrum of genetic changes introduced by precision breeding techniques are identical to those that occur during natural mutagenesis. However, the off-target rate (i.e., the probability of genetic changes in genetic regions that were not intended to be altered) is dramatically lower. As a comparison, chemical mutagenesis of wheat (a technique that falls under the definition of traditional breeding) introduces around one mutation per 200,000 DNA base pairs (equivalent to 50,000 mutations per genome), whereas modern CRISPR techniques often produce no detectable off-target effects (i.e. they alter only a single DNA base-pair)."

The statement, "The ACNFP recognised that most organisms produced by PB will be similar in risk profile to their traditionally bred counterparts, where the same change has been achieved and a risk assessment is not required… the spectrum of genetic changes introduced by precision breeding techniques are identical to those that occur during natural mutagenesis" is not justifiable.

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First, the ACNFP's assertion that GM PB brings about "dramatically lower" unintended genetic alterations than conventional breeding is invalid, relying as it does on a deceptive "sleight-of-hand" definition – calling chemical-induced mutagenesis "natural mutagenesis". We are aware that in the Genetic Technology Act the UK government has classified "induced mutagenesis" (chemical- and radiation-induced mutagenesis) as "traditional processes", removing it from the GM organism (GMO) classification.[1] However, this move was accomplished without consulting a range of independent and qualified scientists and no scientific reasoning has been provided for it. (The majority of the experts on important UK committees evaluating the safety of GMOs have not been/are not independent, according to GMWatch analyses and a peer-reviewed article by eminent academics.[2]) It seems probable that the aim was to provide a comparator with GM "precision breeding (PB)" techniques that is so imprecise, mutagenic, and risky (to the plant, at least) that the GM PB techniques would look precise and safe in comparison.

This is equivalent to comparing an untested and potentially unsafe new aircraft with an old, potentially unsafe airplane and concluding that the new airplane is safe. This is clearly illogical and unscientific. The correct comparator for evaluating the risk profile of new GM PB plants is conventionally bred plants, which can be claimed to have a long safety record.

To the best of our knowledge there has been only one study that has directly compared genetic variation arising from GM PB employing CRISPR/Cas gene editing and conventional breeding not involving chemicals or radiation mutagenesis. This study found that the number of off-target mutations arising in rice plants that had undergone CRISPR/Cas gene editing (when all of the associated processes as a whole were considered, including tissue culture and Agrobacterium infection) was several times higher than those that had gone through a round of natural reproduction.[3]

Second, the statement that any off-target effects often "alter only a single DNA base pair" is simply untrue. Off-target effects are frequently reported from gene editing and can range from single DNA base pair changes to large deletions, insertions and rearrangements involving thousands of DNA base pairs.[4]

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[1] UK Government (2023). Genetic Technology (Precision Breeding) Act 2023 https://www.legislation.gov.uk/ukpga/2023/6/section/1/enacted

[2] Robinson C (2023). Majority of members of UK's new GMO regulatory committee have conflicts of interest. GMWatch, 16 Jan. https://www.gmwatch.org/en/106-news/latest-news/20157 ; Millstone E, Lang T (2022). An approach to conflicts of interest in UK food regulatory institutions. Nature Food 4:17-21. https://www.nature.com/articles/s43016-022-00666-w ; Robinson C (2022). 100% of members of UK government's GMO advisory body ACRE have potential or actual conflicts of interest. GMWatch, 2 March. https://www.gmwatch.org/en/106-news/latest-news/19999

[3] Tang X et al (2018). A large-scale whole-genome sequencing analysis reveals highly specific genome editing by both Cas9 and Cpf1 (Cas12a) nucleases in rice. Genome Biology 19:84. https://genomebiology.biomedcentral.com/articles/10.1186/s13059-018-1458-5

[4] Chu P, Agapito-Tenfen SZ (2022). Unintended genomic outcomes in current and next generation GM techniques: A systematic review. Plants 11(21). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9655061/ ; Koller F and Cieslak M (2023). A perspective from the EU: unintended genetic changes in plants caused by NGT — their relevance for a comprehensive molecular characterisation and risk assessment. Front. Bioeng. Biotechnol. 11. 27 October. Sec. Biosafety and Biosecurity. https://doi.org/10.3389/fbioe.2023.1276226

Third, and more crucially, the ACNFP has not produced any evidence that the genetic changes brought about by GM PB techniques, both intended and unintended, as analysed in an unbiased manner by whole genome sequencing (WGS), are "identical to" those brought about by traditional breeding. Conversely, it has ignored scientific evidence, which is accumulating, that gene editing can produce changes in regions of the genome that are not accessible to conventional breeding, including induced mutagenesis breeding, and that therefore different biological effects and risks may result from gene-edited plants.[5]

Furthermore, the ACNFP has not produced any evidence, via in-depth molecular profiling analytical techniques (proteomics, metabolomics) that any GM PB plant is the same as a conventionally bred plant, in terms of composition, nor has it produced any evidence that they are the same in terms of biological effects.

It must be remembered, however, that equivalence between a GM PB organism and a conventional plant is not just a matter of the type, size, and number of mutations. It is a matter of the quality genetic alterations made (both intended and unintended) in their totality; i.e. the spectrum of genes whose function has been altered – and their compositional and biological effects on the consumer and the environment. These aspects would not be considered in the FSA's proposed Tier 1 framework.

The FSA cannot claim that "by definition" the genetic changes in a PBO would be identical to those that would occur during natural mutagenesis, because neither the FSA nor the ACNFP are mandating the type of analyses that would provide such information. No meaningful normative values (on the crucial levels of the genome or the molecular characterisation) have been set that would constitute a "definition" of a PBO.

In this connection we bring to the FSA's attention the recent demolition by the French food safety agency ANSES (the French counterpart of the UK FSA) of the European Commission's proposal for a definition of Category 1 NGT plants,[6] which

[5] Koller F and Cieslak M (2023). A perspective from the EU: unintended genetic changes in plants caused by NGT — their relevance for a comprehensive molecular characterisation and risk assessment. Front. Bioeng. Biotechnol. 11. 27 October. Sec. Biosafety and Biosecurity. https://doi.org/10.3389/fbioe.2023.1276226 ; Kawall K (2019). New possibilities on the horizon: Genome editing makes the whole genome accessible for changes. Frontiers in Plant Science, 10:525. doi: 10.3389/fpls.2019.00525. https://www.frontiersin.org/articles/10.3389/fpls.2019.00525/full . See also this study, not relating to new GM techniques: Grey Monroe J et al (2022). Mutation bias reflects natural selection in Arabidopsis thaliana. Nature. 12 Jan. https://www.nature.com/articles/s41586-021-04269-6 , and for an explanation of how it is relevant to the discussion of changes brought about by new GM techniques vs conventional breeding, see: GMWatch (2022). New study highlights gulf between gene editing and conventional breeding. 20 Jan. https://www.gmwatch.org/en/2022/19971

[6] ANSES (2023). AVIS de l'Anses relatif à l'analyse scientifique de l'annexe I de la proposition de règlement de la Commission européenne du 5 juillet 2023 relative aux nouvelles techniques génomiques (NTG) – Examen des critères d'équivalence proposés pour définir les plantes NTG de catégorie 1. 29 Nov. https://www.anses.fr/fr/content/avis-2023-auto-0189

would be exempted from risk assessment, traceability and labelling on the claimed basis of their "equivalence… to conventional plants".[7]

Category 1 NGT is similar to the FSA's proposed Tier 1 PB and the Commission's reasoning is very similar to the FSA's and ACNFP's, with the exception that the Commission is specifically proposing as a criterion of equivalence thresholds of 20 genetic modifications per plant, at the target site and at sites with similar sequences, and a size of 20 nucleotides for insertions and substitutions.

ANSES writes (section 3.2.3.2, p25, Deepl translation from the French, our emphases):

"Questions of scientific basis:

"The Commission's technical document states that 'similar genetic modifications obtained by different techniques are not assumed to present different risks', and 'if certain types and numbers of mutations can be introduced by conventional breeding techniques as well as by NTGs, then the type of traits associated with these mutations will not differ between these techniques'. It concludes that it is sufficient to consider only the type and number of mutations to assess equivalence between these plants, and that it is not necessary to consider the associated effects.

"The Biotechnology WG considers that **there is no scientific basis for equivalence of type of trait or level of risk between two categories of plants on the basis of equivalent content of genetic variations or modifications defined solely by their type, size and number**.

"The WG points out that **genetic variability or genetic variations observed in nature are the product of thousands of years of evolution, drift or natural selection. Genetic variations or modifications observed in varieties produced by conventional breeding techniques have undergone selection by breeders.**

"In both cases, genetic variations or modifications associated with deleterious effects are eliminated, whether in terms of the plant's fitness or its selective value in nature, or in terms of the agronomic and qualitative characteristics sought by man in conventional breeding programmes. The elimination or selection of these variations and modifications is not based on their type, size or number, but on their potential impact on a biological function.

"The Biotechnology WG emphasises that **the functional or biological consequences of a given genetic variation or modification are not determined by its type or size.**

"Nevertheless, when analysing the proposed equivalence approach, which focuses on the types, sizes and number of genetic modifications, the Biotechnology WG

[7] European Commission (2023). ANNEX I: Criteria of equivalence of NGT plants to conventional plants. 5 Jul. https://food.ec.europa.eu/system/files/2023-09/gmo_biotech_ngt_proposal_2023-411_annex_en.pdf

considers that the thresholds of 20 genetic modifications per plant, at the target site and at sites with similar sequences, and a size of 20 nucleotides for insertions and substitutions, are not justified. Nor is the acceptance of any deletion or inversion without conditions, or, to a lesser extent, of targeted cisgenesis without target orthology conditions. Nor is the lack of consideration for potential modifications outside the targeted sites and similar sequences (with the exception of transgenic elements, due to the definition of the NGT plant) justified."

ANSES adds, "**The possibility or probability that a given modification or combination of modifications could be obtained by conventional techniques should be considered**."

This last point is important. While it is theoretically possible for a chimpanzee with a word processor to write this submission, the likelihood that this will happen in any realistic timeframe is practically zero. Nowhere has the FSA or the ACNFP defined the probability of the claim that any given GM PBO could occur through traditional processes or that such a GM PBO would have equivalent biological effects with those of a conventional plant.

We agree with ANSES's analysis. The FSA, in basing its assumptions of equivalence between GM PBOs and conventional organisms on arguments related to type, number, and size of mutations ("the spectrum of genetic changes introduced by precision breeding techniques are identical to those that occur during natural mutagenesis"), cannot fulfil its mandate "to safeguard public health and protect the interests of consumers in relation to food".

Comparison of PB techniques with chemical-induced mutagenesis

It is significant that the FSA chooses to compare the (completely unknown) risk profile of GM PB techniques with chemical-induced mutagenesis. Chemical-induced mutagenesis is known to be a highly risky technique *for the plant*, producing large numbers of infertile, deformed, and non-viable organisms. Experts conclude that most induced mutations are harmful and lead to unhealthy and/or infertile plants.[8] The safety of such plants for the consumer has never been tested in controlled feeding studies, so their risk profile remains unknown, except insofar as it can be claimed that those that have persisted in breeding programmes are not acutely toxic.

Nevertheless, while the EU legislator has classified chemical- and radiation-induced mutagenesis as GM techniques (in contrast to the UK government's Genetic Technology Act), it has exempted them from the requirements of the legislation (risk assessment, traceability and labelling) due to their "long safety record".[9]

[8] Acquaah G (2007). Principles of Plant Genetics and Breeding. Wiley-Blackwell ; Van Harten AM (1998). Mutation Breeding: Theory and Practical Applications. Cambridge UP.
[9] Directive 2001/18/EC. http://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32001L0018 Annex 1B and Preamble, para 17; ECJ (2023). https://curia.europa.eu/jcms/upload/docs/application/pdf/2023-02/cp230022en.pdf ; Judgment of the Court in Case C-688/21: Confédération paysanne and Others (in vitro random mutagenesis)

In contrast, new GM techniques such as gene editing cannot be claimed to have such a “long safety record”. They have not been in use in our food and feed systems long enough to have any safety record at all.

Improper use of a reference

FSA’s statement, “modern CRISPR techniques often produce no detectable off-target effects”, is referenced with a study by Zhang et al (2019).[10] However, this is not a valid citation to back FSA’s claim. This is because Zhang et al did not use unbiased WGS to assess genetic alterations but instead used a biased screening method that only looks for off-target mutations based on computer software prediction tools. In addition, they do not appear to have looked for unintended on-target mutations at all.

It is surprising and disappointing that the FSA and the ACNFP are not basing their analyses of the risk profile of new GM PB plants on up-to-date scientific knowledge and screening methods, especially when many independent scientists have for the past several years emphasised the importance of using such methods in evaluating the safety of new GM gene-edited plants.[11]

In addition, when looking for unintended changes from gene editing and other GM processes, it is necessary to consider the entire process, including the obligatory plant tissue culture and cell transformation (including the commonly used Agrobacterium infection process) phases, which induce large numbers (hundreds or thousands) of mutations over and above those induced by the action of the gene-editing tool.[12]

Mischaracterisation of the scientific literature

FSA says, "Where potential risks are identified, FSA officials are able to request the particular information necessary to ensure that the specific PBO under scrutiny can safely be placed on the market. This would be the case for many of the products,

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[10] Zhang S et al (2019). Highly efficient and heritable targeted mutagenesis in wheat via the Agrobacterium tumefaciens-mediated CRISPR/Cas9 system. Int J Mol Sci. 20(17): 4257. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6747105/

[11] Chu P, Agapito-Tenfen SZ (2022). Unintended genomic outcomes in current and next generation GM techniques: A systematic review. Plants 11(21). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9655061/ ; Biswas S et al (2020). Investigation of CRISPR/Cas9-induced SD1 rice mutants highlights the importance of molecular characterization in plant molecular breeding. Journal of Genetics and Genomics 47(5). http://www.sciencedirect.com/science/article/pii/S1673852720300916 ; Kawall K et al (2020). Broadening the GMO risk assessment in the EU for genome editing technologies in agriculture. Environmental Science Europe 32(1). https://doi.org/10.1186/s12302-020-00361-2 ; Eckerstorfer MF et al (2019). An EU perspective on biosafety considerations for plants developed by genome editing and other new genetic modification techniques (nGMs). Front. Bioeng. Biotechnol. 7. https://www.frontiersin.org/articles/10.3389/fbioe.2019.00031/full

[12] Tang X et al (2018). A large-scale whole-genome sequencing analysis reveals highly specific genome editing by both Cas9 and Cpf1 (Cas12a) nucleases in rice. Genome Biology 19:84. https://genomebiology.biomedcentral.com/articles/10.1186/s13059-018-1458-5 ; Latham JR et al (2006). The mutational consequences of plant transformation. J Biomed Biotechnol 2006(2):25376. http://www.ncbi.nlm.nih.gov/pubmed/16883050

such as those exhibiting ‘traits previously unknown in conventional breeding’, described in the reference cited above. [ref 3: Kawall, K. (2021) The Generic risks and the potential of SDN-1 applications in crop plants. Plants 10 (11), 2259. http://dx.doi.org/10.3390/plants10112259] If such information and/or data is not provided for an assessment to be made or does not satisfactorily address concerns over potential risks to safety or any other concerns, the FSA will not put forward the PBO for authorisation to be placed on the market. Notably, the scientific literature referenced above [ref 4: Eckerstorfer M F et al (2023) Recommendations for the assessment of potential environmental effects of genome-editing applications in plants in the EU. Plants. 12 (9):1764. http://dx.doi.org/10.3390/plants12091764.] recommends this ‘product-based’ rather than ‘technology-based’ assessment process."

The issue with the FSA’s statement “Where potential risks are identified…” is that without whole genome sequencing and full molecular profiling (omics) analysis of the PBO – in other words, consideration of the entire process of creating the PBO – potential risks are highly unlikely to be identified.

In this connection, the FSA’s characterisation of the review cited in reference 4 (and reference 3, if this was meant to be included) is incorrect. The reviews cited in references 3 and 4 emphasise the importance of considering process as well as product in risk assessment.

For example, Kawall (ref 3) says, "The resulting [SDN-1 gene-edited] plants can contain modified **alleles and** associated traits, which are either known or unknown in conventionally bred plants." These **alleles** or gene variants are caused by the **process**.

Kawall emphasises the importance of the specific GM applications and associated processes used (process-based risks). "However, the generic risks associated with CRISPR/Cas arise equally from its potential, and can lead to new types of risks compared to previous genetic engineering applications: the ability of CRISPR/Cas to recognize and induce DSBs at all DNA regions carrying the same DNA sequence is highly relevant to risk assessment. If a plant contains several off-target sites – for example, in the DNA sequence of a gene within a gene family – then several or all of the genes in this gene family can be altered simultaneously. If an off-target site exists several times in a polyploid plant, off-target effects and other effects can occur at multiple sites of the genome. Therefore, CRISPR/Cas can modify an off-target region as often as gene variants (e.g., alleles or gene copies) with this DNA sequence are present in the genome in such plants."

She says that regarding even the "simplest" form of new GMOs, SDN1, "Overall, a case-specific risk assessment considering both process- and product-based risks seems to be best suited to analyse plants derived from SDN-1 applications." In the abstract she points to intrinsic risks from the gene editing processes: "This review highlights the need for a case-specific risk assessment of crop plants derived from SDN-1 applications considering both the characteristics of the product and the process to ensure a high level of protection of human and animal health and the environment.... In summary, it was found that nearly half of plants with so-called

market-oriented traits contain complex genomic alterations induced by SDN-1 applications, which may also pose new types of risks. It further underscores the need for data on both the process and the end-product for a case-by-case risk assessment of plants derived from SDN-1 applications."

In the review cited in reference 4, Eckerstorfer et al say, "The comparison of genome-edited plants with plants developed using conventional breeding methods should be conducted at the level of a scientific case-by-case assessment of individual applications rather than at a general, technology-based level."

In other words, it is not scientifically justified to generalise about the safety of new GMOs based on the assumption that they are equivalent to natural plants. It is certainly not justified to exempt the proposed Tier 1 PB plants from risk assessment without considering their risk in a scientific case-by-case assessment of individual applications ("applications" in this context would include the processes used).

The crucial importance of process in assessing risk is made clear throughout Eckerstorfer et al's paper. For example, they write, "Assumptions that the mutations introduced with spontaneous natural processes and classical mutagenesis are 'similar' to the ones introduced with genome editing are not scientifically sound. Thus, an assumption of general 'likeness' may be misleading... An earlier review indicated that the theoretical comparison of the range of mutations generated with conventional and genome-editing methods is flawed: conventional mutagenesis does not generate a random distribution of mutational events across the genome of a plant, whereas genome-editing methods allow the introduction of mutations into parts of the genome that are somewhat protected against spontaneous genetic alteration."

They also state: "Recent scientific findings indicate that spontaneous mutations are not distributed randomly throughout the plant genome, as assumed previously, but occur at a higher frequency in internecine regions of the genome… Genome editing using SDN methods, on the other hand, is capable of introducing mutations in functionally important genome regions that are 'protected' to some extent from mutations induced with conventional techniques…; this is one of the reasons why genome editing is regarded to be a very powerful technique. However, it also implies that there are relevant differences between mutations induced with genome editing as compared to sequence changes introduced using conventional breeding techniques."

They further state: "In their 2020 opinion, the EFSA stated that genome editing will result in fewer unintended genetic modifications compared to certain conventional breeding techniques, such as classical mutagenesis... However, this does not take into consideration the removal of unintended modifications during subsequent breeding steps that are inherently necessary for conventional breeding schemes. Additionally, the effects of the in vitro steps necessary to express genome-editing tools in the target cells and the different tendencies of the existing methods for genome editing to induce unintended modifications… are disregarded.

"Of importance for drawing a comparison is also the fact that unintended modifications will likely occur at different frequencies and at different genomic

locations using genome-editing or conventional techniques, respectively. Modifications due to classical mutagenesis are thought to be induced randomly throughout the genome and — at lower mutational rates — would be subject to the same bias of distribution in the genome as detected for spontaneous mutations… In contrast, off-target modifications introduced with genome-editing tools are occurring predominantly at genomic loci sharing sequence homologies with the intended target sites... Thus, the frequencies of off-target modifications will be considerably higher at genomic locations sharing functional similarities with the targeted genetic sequence. Concerning the final number of unintended modifications present in a marketable plant variety, the effects of breeding steps following the genetic modification need to be considered as well. The probability that unintended modifications—in particular those, which are not genetically linked to the intended trait—are removed is increasing with the number of subsequent backcrossing steps. Classical mutagenesis typically involves a significant number of backcrossing steps to ideally retain only the intended trait(s) and remove any unintended mutations. Sidestepping or considerably curtailing such a backcrossing regime, e.g., when fast-track genome editing is conducted directly in elite germplasm... will reduce the margin of safety inherent to the approach used for classical mutagenesis. The number of mutations initially present in the mutagenized plants may be higher for classical mutagenesis compared to genome editing – as highlighted by the EFSA... and the EC... However, this difference may not be reflected similarly in the number of unintended modifications present in the final breeding products."

These authors recommend whole genome sequencing to look for unintended effects.

Based on their analysis of the importance of considering process as well as product in the risk assessment, the authors conclude, “Considering the different characteristics of specific examples of genome edited plants and the respective risk issues relevant for these genome edited plants… we believe that it is neither appropriate nor scientifically justified to draw general conclusions for whole groups of genome-editing applications, such as for all SDN-1/2 applications. Rather, a case-specific risk assessment approach, which is focused by a scientifically-based problem formulation to identify and address plausible risk issues, needs to be pursued.”

Desirability of whole genome sequencing

The FSA says, “Defra will not be mandating whole genome sequencing (WGS) as part of this evidence package. This is because WGS datasets are generally less precise than other shorter sequencing methods, as well as being more difficult to interpret. This becomes even more pronounced when considering the types of changes typically introduced through precision breeding (i.e. very small, single DNA base pair edits), in which it is often impossible to determine what is a true off-target impact of the genome editing technique, and what is an alteration that has arisen spontaneously during the natural breeding process that followed. There are other methods that provide more effective testing such as SITE-Seq, which involves mapping all potential off targets of the editing construct that is being used and then individually sequencing those regions of the genome to ascertain whether the precision bred animal contains off-targets in those regions.”

We find this extraordinary, given the now significant number of researchers and regulators who recommend, employ, and indicate the desirability of, whole genome sequencing and long-read sequencing to check for off-target and unintended on-target effects of gene editing in both plants and animals.[13] Analytical software is available to enable interpretation of the data and again, the fact that at least some scientists are using it in order to understand their results indicates that these best practices are feasible.

SITE-Seq, in contrast, is a limited and biased screening method that will miss the vast majority of important unintended effects of gene editing, including the large numbers of mutations caused by the tissue culture process and cell transformation used in gene editing applications. Nevertheless, given that the FSA favours the SITE-Seq method, it is incomprehensible that the agency is not requiring its use by GMO developers. The public could be forgiven for concluding that the FSA does not want anything to be found that would derail the rush to bring insufficiently tested and analysed new GM products to market.

FSA's comment, "Moreover, if ACRE feel that the information provided is not sufficient to assess regulatory status, more evidence may be requested from the notifier before concluding the appraisal and making a recommendation to Defra SoS" is disingenuous. The "information provided" is not sufficient to show problems, so ACRE will likely not notice any problems, and as a consequence they will not have grounds to require more information.

Risk of unknown/new allergens

The FSA says, "Developers wishing to market PBOs are subject to General Food Law and Food Safety Act requirements. This requires them to follow due diligence at all steps of development, which includes consideration of aspects such as allergen levels. Plant breeders who wish to market their precision bred plant varieties on national lists will also need to add their varieties to a new 'England-only Variety List for Precision Bred Varieties' through an application process. Existing labelling legislation on allergens – for example, Article 21 of retained EU Regulation 1169/2011, would still apply to PB food as it does for traditionally bred food. In practice, a Precision Bred product that created an allergen risk that was not present

[13] Examples include: Kondo K, Taguchi C (2022). Japanese regulatory framework and approach for genome-edited foods based on latest scientific findings. Food Saf (Tokyo) 10(4): 113–128. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9789915/ ; Eckerstorfer M F et al (2023) Recommendations for the assessment of potential environmental effects of genome-editing applications in plants in the EU. Plants. 12 (9):1764. http://dx.doi.org/10.3390/plants12091764 ; Norris AL et al (2020). Template plasmid integration in germline genome-edited cattle. Nature Biotechnology 38: 163–164. https://doi.org/10.1038/s41587-019-0394-6 ; Chu P, Agapito-Tenfen SZ (2022). Unintended genomic outcomes in current and next generation GM techniques: A systematic review. Plants 11(2997). https://doi.org/10.3390/plants11212997 ; Biswas S et al (2020). Investigation of CRISPR/Cas9-induced SD1 rice mutants highlights the importance of molecular characterization in plant molecular breeding. Journal of Genetics and Genomics 47(5). http://www.sciencedirect.com/science/article/pii/S1673852720300916

in traditionally-bred equivalent products would, by definition, be subject to a bespoke risk assessment via Tier 2."

This legal framework (including Article 21 of retained EU Regulation 1169/2011) is not able to pick up on new and unknown allergens that may be created as a result of the GM processes used in the development of a PBO. And without the requirement for metabolomics and proteomics analysis for each PBO to provide a first indication of such unexpected allergens, they will not be identified in advance of marketing of the PBO.

The findings of certain studies show that the implications of such knowledge gaps are alarming.

For example, a study in human cells shows that gene editing is apt to produce new and mutant proteins.[14] Another study in mice showed that CRISPR/Cas gene editing induced insertions of multiple copies of the DNA molecules used as a template for bringing about the desired gene modifications. The researchers were concerned by the fact that the insertions could not be detected using standard PCR analysis and noted the false claims of precision for CRISPR/Cas gene editing.[15] The lead authors of the study commented that their findings could have relevance for gene editing across all kingdoms of life, from plants to human cells. They warned that duplications could lead to dangerous frameshift mutations, resulting in misshapen proteins.[16]

Both these studies have worrying implications regarding the risk of the presence of unknown and unexpected allergens in PBOs.

Conclusion

The FSA is ignoring or overlooking serious risks from GM “PB” foods, despite the warnings of many scientists, including those working for regulatory agencies in Europe. It is accomplishing this by ignoring the processes used to make PB organisms, which are widely acknowledged as being prone to large-scale, genome-wide unintended effects that cannot be identified by the routinely used screening methods employed by developers and therefore require special scrutiny.

However, the FSA, the ACNFP, ACRE, and Defra are refusing to require that developers conduct suitable analyses (such as whole genome sequencing and molecular compositional profiling “omics” investigations) that could potentially identify the unintended effects of GM PB processes and indicate their risks.

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[14] Smits AH et al (2019). Biological plasticity rescues target activity in CRISPR knock outs. Nat Methods 16, 1087–1093. https://www.ncbi.nlm.nih.gov/pubmed/31659326

[15] Skryabin BV et al. (2020). Pervasive head-to-tail insertions of DNA templates mask desired CRISPR-Cas9–mediated genome editing events. Science Advances 12 Feb 2020: Vol. 6, no. 7, eaax2941. DOI: 10.1126/sciadv.aax2941. https://advances.sciencemag.org/content/6/7/eaax2941

[16] Zimmer K (2020). CRISPR can create unwanted duplications during knock-ins. The Scientist, 19 Feb. https://www.the-scientist.com/news-opinion/crispr-can-create-unwanted-duplications-during-knock-ins-67126

If these omissions are allowed to persist, the very least that is required of the regulator to fulfil their responsibilities to the public is that they mandate labelling of all GMOs, including “PB” foods, to inform consumers and enable them to choose to avoid such foods. We note that while the Genetic Technology Act does not explicitly provide for such labelling, it does not ban it either.

Given the FSA’s declared independence from the UK government, it should fulfil its role as the food safety watchdog by establishing a stringent risk assessment process for all PB foods and demanding clear on-package labelling.