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Annex A. Tables of initial case studies

The Advisory Committee on Novel Foods and Processes (ACNFP) Subcommittee on Products of Genetic Technologies (PGT) used a range of hypothetical example organisms which, based on the academic literature, may be developed and Precision Bred Organism (PBO) status subsequently sought from the Advisory Committee on Releases to the Environment (ACRE). These examples were used to support Subcommittee discussions concerning risks that may arise in PBO-derived products for food and feed use, as well as the development of a framework for the safety assessment of PBOs.

References for the academic literature used to develop hypothetical examples are listed in Tables A and B; these tables will be regularly updated as new examples are used by the Subcommittee.

Table A. Examples of plants, and their traits of interest, which could be produced by precision breeding for potential use in the food/feed industry

Host organisms	Nature of the edited genomic feature, and editing method used	Potential application	Reference
Tomato (*Solanum lycopersicum* L.)	Genes encoding enzymes of the GABA (Gamma-Amino-Butyric Acid) synthesis pathway Method: CRISPR/Cas9	Tomato with increased GABA (Gamma-Amino-Butyric Acid); potential health benefit (reduced blood pressure, stress relief)	Nonaka, S., et al. (2017) **Efficient increase of ɣ-am acid (GABA) content in to by targeted mutagenesis** Sci Rep, 7(1): 7057 https://doi.org/10.1038/s41 06400-y
Cocoa (*Theobroma cacao*)	Gene encoding a suppressor of the pathogen defence response Method: CRISPR/Cas9	Cocoa resistant to *Phytophthora tropicalis* infection; disease resistance	Fister, A.S., et al. (2018) **Transient Expression of C Machinery Targeting TcN Enhances Defense Respo *Theobroma cacao*.** Front Plant Sci, 2(9): 268 https://doi.org/10.3389/fpls.

Host organisms	Nature of the edited genomic feature, and editing method used	Potential application	Reference
Wheat (*Triticum aestivum*)	Genes encoding asparagine synthetase enzymes Method: CRISPR/Cas9	Low asparagine wheat; potential health benefit (reduction of carcinogenic acrylamide production from asparagine during processing)	Raffan, S., et al. (2021) **Wheat with greatly redu accumulation of free asp the grain, produced by C editing of asparagine sy gene TaASN2.** Plant Biotechnol J, 19(8): 16 https://doi.org/10.1111/pbi.
Tomato (*Solanum lycopersicum* L.)	Gene encoding a 7-dehydrocholesterol reductase Method: CRISPR/Cas9	Provitamin D3 biofortified tomato fruits for food and tomato leaves for food supplements; potential health benefit	Li, J., et al. (2022) **Biofortified tomatoes pro route to vitamin D suffic** Nat Plants, 8(6): 611 to 616 https://doi.org/10.1038/s41 01154-6
The laboratory model plant (*Arabidopsis thaliana*) but could also be applied to crops	Gene encoding a chloroplast thylakoid associated protein Method: CRISPR/Cas9	Increased crop oil yield (feed purposes)	Bhunia, R.K., et al. (2022) **A native promoter–gene created by CRISPR/Cas9- genomic deletion offers free method to drive oil in leaves.** FEBS Lett, 596(15): 1865 to https://doi.org/10.1002/187

Host organisms	Nature of the edited genomic feature, and editing method used	Potential application	Reference
Cottonseed (*Gossypium hirsutum* L.)	Genes encoding products involved in catalysing the desaturation of oleic acid to linoleic acid Method: CRISPR/Cas9	Increased shelf life and oxidative stability of oleic acid in cottonseed oil	Chen, Y., et al. (2021) **High-oleic acid content, nontransgenic allotetrap *Gossypium hirsutum* L.) knockout of GhFAD2 gen CRISPR/Cas9 system.** Plant Biotechnol J, 19(3): 42 https://doi.org/10.1111/pbi.
Potato (*Solanum stoloniferum, Solanum venturii*)	Genes responsible of late blight potato resistance Method: Random Insertion of cisgenes via marker-free *Agrobacterium* transformation	Potatoes resistant to *Phytophthora infestans* (late blight) disease	Jo, K.R., et al. (2014) **Development of late blig potatoes by cisgene stac** BMC Biotechnol, 14(1): 50 https://doi.org/10.1186/147

Host organisms	Nature of the edited genomic feature, and editing method used	Potential application	Reference
Rice (*Oryza alta*)	Genes encoding for grain yield, grain quality, fertility, heading date, biotic and abiotic resistance, and nutrient-use efficiency Method: CRISPR/Cas9, *de novo* domestication	Improvement of six agronomically important traits in a staple cereal; potential benefits for world food production/security	Yu, H., et al. (2021) **A route to de novo dome wild allotetraploid rice.** Cell, 184(5): 1156 to 1170 https://doi.org/10.1016/j.cel
Rice (*Oryza sativa japonica*)	Gene encoding the Acetolactate Synthase (ALS), target of Imidazolinone (IMI) herbicides and responsible of interaction with IMI herbicides Method: CRISPR/Cas9	Control of weed proliferation in field by herbicide treatment without concomitant phytotoxicity on rice	Wang, F., et al. (2021) **Creating a novel herbicid *OsALS* allele using CRISP mediated gene editing.** The Crop Journal, 9(2): 305 https://doi.org/10.1016/j.cj.2

Host organisms	Nature of the edited genomic feature, and editing method used	Potential application	Reference
Peanut (*Arachis hypogaea* L.)	Genes encoding the Fatty Acid Desaturase 2 (FAD2) enzyme, that converts oleic acid to linoleic acid Method: CRISPR/Cas9	Peanuts with increased oleic acid content for improved oil quality and flavour and improved nut shelf-life; potential health benefit (cardiovascular)	Neelakandan Anjanasree, K **CRISPR/Cas9 Based Site-Modification of FAD2 cis-Motifs in Peanut (*Arachis* L).** Frontiers in Genetics, 27(13 https://doi.org/10.3389/fger

Table B. Examples of animals, and their traits of interest, which could be produced by precision breeding for potential use in the food industry

Host organisms	Nature of the edited genomic feature and editing method used	Potential application	Reference

Chicken (*Gallus gallus domesticus*)	Gene encoding the receptor required for avian leukosis virus subgroup J to infect chicken cells Method: CRISPR/Cas9	Chickens resistant to infection by Avian leukosis virus subgroup J	Koslová, A., et al. (2020) **Precise CRISPR/Cas9 editing of the NHE1 gene renders chickens resistant to the J subgroup of avian leukosis virus.** Proc Natl Acad Sci USA, 117(4): 2108 to 2112 https://doi.org/10.1073/pnas.1913827117
Pacific bluefin tuna (*Thunnus orientalis*)	Gene encoding a receptor expressed in muscle cells that leads to muscle contraction Method: TALEN	Less aggressive tuna not capable of fast swimming in aquaculture; reduction in deaths from collisions with walls	Higuchi, K., et al. (2019) **Targeted mutagenesis of the ryanodine receptor by Platinum TALENs causes slow swimming behaviour in Pacific bluefin tuna (*Thunnus orientalis*).** Sci Rep, 9(1):13871 https://doi.org/10.1038/s41598-019-50418-3

Pig (*Sus domesticus*)	Gene encoding a receptor for Porcine Reproductive and Respiratory Syndrome Virus 1 (PRRSV1) Method: CRISPR/Cas9	Pigs resistant to infection by Porcine Reproductive and Respiratory Syndrome Virus 1	C. Burkard, et al. (2017) **Precision engineering for PRRSV resistance in pigs: Macrophages from genome edited pigs lacking CD163 SRCR5 domain are fully resistant to both PRRSV genotypes while maintaining biological function.** PLoS Pathog, 23;13(2): e1006206 https://doi.org/10.1371/journal.ppat.1006206

Annex B. Technical justifications for the data requirements for triaging, assignment to Tier 1 and Tier 2 and for assessment in both Tiers

1. In developing the Models for the assessment of the safety of PBOs, the ACNFP-PGT considered case studies (Annex A) and used its expert knowledge to identify scenarios where scrutiny beyond the current due diligence measures for traditionally bred crops and animals would be justified. Based on the discussion, a number of key considerations were identified to inform the development of the information and data required to support tier assignment and safety assessment. The Committee sought to ensure foreseen risks could be identified while ensuring the requirements were proportionate. The key considerations are explored below.

Unintended effects, Intended effects, Anticipated effects

2. When discussing the uncertainties associated with the generation of PBOs, the ACNFP considered whether basic phenotypic information should be requested not only to capture the intended changes but also to provide some evidence to identify any unintended changes in composition. In both Models, information on phenotype as a result of intended changes is requested.

3. Some Members thought that, in the initial stages of PBO authorisation, it would provide additional reassurance and contribute to public confidence if it could be shown that no significant unintended changes in composition are produced. For example, whether new toxins or increased levels of toxins had been inadvertently generated. Conceptually, such unintended consequences are also possible with TBOs, arguably more so if the approach to breeding is not precise and targeted, though not in such short a time frame as with PBOs. However, it was considered by Defra and during the development of the Act, that the history of use of TBOs shows only very rare occurrences of safety concerns as a consequence of unintended changes and these have been managed through due diligence and food and feed law post market.

4. Taking the reasoning of the Act that PBOs could have been generated by TB, by definition, the risk presented by potential unintended changes to PBOs is inherently being considered comparable to TBOs. Some Members of ACNFP remain concerned that the potential for generating traits that are unintended and unknown is there for both TBOs and PBOs, and there is a risk the unknowns are not being covered in either case. However, assessing intended changes, dealing with the knowns and any reasonably anticipated unintended consequence is a pragmatic starting point, appreciating the residual risks that may also be present due to unknowns in a risk management context.

5. There was no suggestion of a need to routinely screen for unintended changes in composition through proteomics, metabolomics, or any other very detailed analysis, given that such monitoring is not done as part of TBO production. It was also highlighted that if such analyses were carried out, it could be difficult to set parameters for identification of an unintended change - particularly a minor change - above the level that could be expected to be found within natural variation. As such changes are no more likely to take place in PBOs when compared to TBOs, the risks associated with unintended changes could reasonably be controlled by due diligence under the GFL. Therefore, Members proposed that only intended changes and unintended changes that could be anticipated be considered, as reflected by the triage questions (Table 1).

6. It would be desirable for applicants to understand and describe any anticipated resulting changes in composition relevant for consumer safety, resulting from, for example:

- genetic changes impacting metabolic or regulatory pathways affecting the nutrient profile associated with such pathways, or potentially impacting known hazards (for example, intentional increases in toxins for pest

resistance (for example) could also change the metabolic pathway of other, unrelated toxins and/or allergens);
- loss or change of function of the endogenous DNA at the site of the edit, including downstream effects (for example, this could be the result of the insertion of a cisgene), possibly impacting on additional phenotypes.

7. It was noted that while breeders are aware of the anti-nutrients/toxins that are present in their crops and may monitor this during product development, these might justify greater scrutiny as part of the assessment.

Tissue used in food and/or feed

8. The approach to the assessment being developed is specifically related to edible tissues. For this reason, understanding which parts of the PB plant or animal are destined to be used for food and/or feed can determine whether further scrutiny is necessary (for example, when the genetic change would have phenotypic consequences exclusively in a part of the plant or animal PBO that is not consumed either as part of feed or food, no safety impact would be anticipated on the food and/or feed).

Novelty

9. With regards to novelty, the policy intention is to explicitly remove PBOs from the scope of NF via a consequential amendment to retained Regulation (EC) 2015/2283. Because of this intention, ACNFP was informed that there was a need to ensure there is a clear route for any PBOs which have modified an organism that had not previously been significantly consumed by humans. This would avoid legal loopholes for species where the potential risks are not well understood. These should be subject to the necessary assessment based on that for NF, which has been identified as requiring a deeper level of assessment of risk. As such whether there was a history of consumption of the species modified, was identified as a key parameter for tier assignment.

10. When considering the taxonomic information that could, in part, inform determination of the novelty of a PBO, ACNFP observed that there would be no additional risks associated with a different variety of a commonly eaten species, so differentiation at the species level was preferred. It was noted that this would also align well with the NF regulations, which are also at the species level.

11. While the NF regulation does not include feeds, PBOs for feed that are novel may also present risks and will also need assessment in Tier 2.

12. Changes which are likely to trigger novelty assessment in Tier 2 include those made in the context of *de novo* domestication of a wild species not commonly consumed: this could raise potential concerns because of uncertainty about composition (including the possible presence of compounds not known to be normally present in the diet) and the nature of any hazards in the host organism. Moreover, *de novo* domestication would inevitably require multiple genome edits to a wild species in order to obtain the desirable domesticated traits (for example, improvement of crop yield, making the organism or its products more edible/attractive), and the phenotypic differences between the derived PBO and the wild progenitor might further increase uncertainty about composition and potentially impact risk. Additionally, *de novo* domesticated species could change their adaptation to a certain climate/environment leading to, for example, altered levels of toxic compounds, justifying further scrutiny.

13. It was noted that early identification of applications needing a Tier 2 assessment on the grounds of novelty would enable the FSA to support the applicant to supply relevant data that would assist a subsequent review by the ACNFP.

Nutrition

14. With regards to nutrition, the ACNFP agreed that when a “PBO is designed to introduce significant changes to the nutritional quality of the organism currently consumed that are likely to be disadvantageous to the consumer” (Table 1), it would be important to determine whether further scrutiny of the nutritional quality would be needed in Tier 2 and to provide the evidence base for any risk management that was required.

15. In this context, the greater focus is on deliberate changes to nutrients that may have consequences for the nutritional profile more widely and may result in nutritional disadvantage (this captures both increases and decreases in relevant compounds). Predicted wider impacts on relevant metabolic pathways and the nutritional profile associated with such pathways might justify greater scrutiny (for example, information on the anticipated effects of the manipulation of enzymes involved in the production of secondary metabolites). Known antinutritional factors must also be considered in the assessment, as substantial increases in their level are potential hazards which might pose a greater risk if not identified.

16. Answering the nutrition triage question involves determining the changes in nutritional quality and understanding their impact by comparison to an

appropriate reference. For instance, any impact of changes in nutrient profile would also depend on what food is being considered and its contribution to the UK diet as a source of key nutrients (for example, non-staple source would be more likely to be assigned to Tier 1, while staple source might require assessment in Tier 2). Important considerations include:

- How the upper intake levels impact on different sub-populations of consumers.
- Whether increased or decreased levels of nutrients may represent a risk, with potential consequences for all or some consumers.
- Presence of compounds known not to be normally present in the specific food; this should take into account that stacked effects on the diet could result from consumption of several PBOs developed for the same nutritional benefit.
- Whether other foods with similar composition are consumed.
- Wider dietary consideration (for example, information on and an appreciation of the levels of nutrients in an enhanced nutrient crop in the context of other contributions of that nutrient to the diet could avoid the potential for further review; similarly, a decrease in levels of a single amino acid in a PBO might not really be disadvantageous when the rest of the diet is taken into consideration). Information on the protein quality may support consideration of this point.
- It was noted that a mitigating factor for risk managers might be whether the developer intends to market the PBO food via a labelled, identity-preserved route.

17. Any safety concerns regarding intakes to a population subgroup would assign the PBO to a Tier 2 assessment for further review of the impact; however, changes in nutrient profile alone should not be sufficient for allocation to Tier 2; rather, this should depend on the significance of the impact. For example, for an increase (or decrease) to be considered for Tier 2, it would need to be significantly outside the range of current varieties and at the same time represent a potential hazard. To define this significance scientifically and statistically raises the challenge of how best to analyse this and what data/nutritional information would be required to allow comparison. As such significance should be considered on a case-by-case basis.

The question of benchmarking will be further explored when guidelines for applicants are developed.

18. It was suggested that breeders should take steps to be aware of the antinutritional factors that are present in their crops and should monitor this during product development. Any developer marketing a product with increased nutrient levels would likely already have the data to support their claims. Major changes to nutritional quality would also have to be labelled under GFL.

Toxicity

19. Substantial increases in toxic compounds in a crop are a cause for concern above certain levels and would likely require a safety assessment. Therefore, the ACNFP agreed that a PBO “designed to introduce changes that are expected to elevate significantly the toxicity of any foods/feeds derived from the organism” (Table 1) would require further scrutiny in Tier 2; this will capture both intended and anticipated increases in known toxic compounds. To understand potential hazards, information on the following would inform review:

- Whether the target of the change is the organism’s response to pathogens, due to the likely variation in production of toxic compounds frequently known to be produced as part of the organism’s response, which may involve different metabolic pathways.
- Whether the target of the change is stress resistance, due to the potential variation in production of toxic compounds that may be produced under stressful growth conditions.
- Whether the target of the change is an alteration in ion uptake capacity, due to the crossover of use between some essential ion channels in plants and hyperaccumulation of heavy metal contaminants.

20. Important considerations when examining toxicity include:

- Differing impacts can exist for different parts of the population, particularly the most vulnerable groups for example, infants, children, the elderly, those with compromised digestive or immune system based on the consequences that the level of a compound can cause; for PBOs assigned to Tier 2, how toxicity would be managed through marketing could be explored.
- (mitigating factor) High levels of processing can inactivate toxins, reducing concern over their presence. Applicants should reassure themselves that the organism as consumed was subject to effective processing to mitigate this risk.
- (mitigating factor) Presence of toxic compounds in food and/or feed is regulated by GFL, therefore it might be mitigated by testing during development before variety trial and as part of due diligence. However there

are no legal limits imposed by UK regulation, except for substances representing a high risk for consumers (for example, erucic acid, mycotoxins; Chemical Food Safety Law).

21. The concern over levels of compounds that might exceed typical levels was explored, raising here again the challenge of how best to define and analyse this. The question of benchmarking will be further explored when the technical guidelines for the applicant are developed according to the chosen Model.

22. It was noted that developers of traditionally bred toxin-containing organisms would typically check levels of toxins throughout product development, but don't necessarily test for everything in new organisms (for example, potato developers monitoring levels of glycoalkaloids).

Allergenicity

23. How PB could influence the level of allergenicity, particularly of crops, is especially pertinent in the context of the UK population which shows a high prevalence of hypersensitivity and with food allergy being a significant cause of hospital admissions. Substantial increases in the levels of known allergenic proteins would change the allergenic potency of a substance such as pollen or food. This would have the potential to alter the capacity of a substance to initiate new allergies (a process known as sensitisation) or trigger a reaction in an allergic individual (a process known as elicitation). It may also increase the severity of a reaction. Identifying such a potential hazard is crucial to ensure any increased risk is adequately managed. This is relevant to those species that are already known to be allergenic and especially the so-called priority allergenic foods which are listed in Annex II of the Food Information for Consumers Regulation as retained in UK law.

24. Modifying the allergenic potential of an organism is a potential risk posed by any breeding process, and can be further modified by many factors, including abiotic stress, post-harvest management and other food chain production processes. In all cases the risk of elevating the levels of existing allergens would be left to the developer to assess and monitor. Where significant / major changes in levels of allergens can be predicted from the genetic changes made in the PBO, the organism would likely be assigned to Tier 2.

25. The latest expert consultations on risk assessment of food allergens (for example, FAO and WHO. 2022. Risk Assessment of Food Allergens, Part 1; Risk Assessment of Food Allergens, Part 2) provides a risk assessment framework

which should be taken into account when considering what would constitute a significant / major change in allergenicity, and in assessing its risk in the context of PBOs.

26. Assessing the risks posed by the introduction of “new” allergenic proteins is currently beset by uncertainty. PBOs, unlike GMOs that involve transgenesis (where a new gene (and hence protein, usually) is introduced into an organism from another organism), would only alter the risk if either the expression of minor allergenic proteins was radically increased or the genetic event in the PBO radically altered the allergenic potential of a protein.

27. In considering whether PB “introduces changes that are expected to alter the allergenicity of any foods/feeds derived from the organism” (Table 1) the applicants should confirm that there are no inadvertent significant changes in allergenic protein levels including, but may not be limited to:

- Whether the host organism for PB is known for its allergenic potential: priority allergenic organisms should receive increased scrutiny at triage, in order to understand any impact on the use of thresholds for allergenic risk management. Knowledge of organisms or products with similar traits in major allergenic food, where tests or history of use have evidenced unchanged allergenicity, may prevent triggering Tier 2 for allergenicity. It was noted that some people do have reactions (including severe reaction such as anaphylaxis) to non-regulated allergenic foods, which might be taken into consideration (Review and validation of Codex priority allergen list, FAO/WHO joint report, 2021).
- Whether modifications to recognised pathways in the PBO may have direct and indirect impacts on allergens (for example, stress and pathogen resistance in particular are traits that are known to increase expression of allergenic proteins and increase the allergenicity of foods and can significantly change allergenicity during post-harvest storage (for example, the presence and potency of an allergen can change in some fruits during storage, maturation and post-harvest)). Such changes may be mitigated if the particular organism is consumed in a processed form which may inactivate allergens and reduce allergenic potency of a food, reducing concern over their presence.
- The design of the PBO needs to consider whether it is likely to result in a radical alteration in protein expression and/or change its allergenic potential; both intended and anticipated increases in known allergenic compounds should be considered.

28. In addition, when the purpose of altering a crop is to reduce its allergenicity (for example, a reduced or allergen-free PBO), the claim should be supported by clinical studies considering the potential to elicit a reaction in sensitive people; a pre-existing, published clinical study of the same trait may support assessment as part of Tier 1.

Other Safety Concerns

29. The question on “any additional features of the PBO that cause food/feed safety concerns” (Table 1) should capture PBOs with changes that may present a greater degree of uncertainty with regards to food and feed safety and that would not be suitably addressed by the nutritional, toxicology, or allergenicity triage questions.

30. Examples of features that may raise other safety concerns include but are not limited to:

- Complex or rare combinations of novel genomic features; with the development of molecular biology techniques, multiple sequential edits are becoming more viable, and may be performed within elite breeding lines rather than donor lines.
- PBOs with stacked PB modifications, each previously authorised individually; these could present new risks.
- Possible pharmaceutical drug interactions (for example, in cases of biofortification).
- Engineering of an organism to produce something that it doesn’t produce normally (rather than a change in level of production).
- Engineering of an organism to produce compounds not known to be normally present in the diet.

31. There are “Other Safety Concerns” where the impact of the trait may alter the degree of novelty that would need to be taken into account to understand any risk, and which may only require limited data to address focused areas of review; these include for example:

- Where an organism is engineered to produce something that it doesn’t produce normally, rather than a change in level of production (for example, by the intentional alteration of a metabolic pathway or pathways; as a result of significant alteration to a protein, changing its properties).
- Where a cisgene from a donor species with no history of safe use has been introduced, and knowledge of the cisgene donor species – particularly in the

context of consumed food – would be critical in considering the level of uncertainty). To note, introduction of a cisgene is not considered a scenario of concern by itself, rather the nature of the protein sequence it encodes and whether this might be associated with a hazard (for example, impact on composition) could be important for understanding any potential risk.
- Where an organism is altered to allow a new part of the organism to be consumed, and no plant or animal from the same species provides an history of safe use of the part (tissue), for example where the part of the plant now edible would previously have been toxic.
- Where an organism is altered to allow a change in traditional processing techniques, and there could be concomitant removal of control measures for a hazard (for example, new trait removing the previously required heat processing necessary to allow consumption, and potentially removing control of antinutritional or allergenic compounds and of microbial contaminations).

32. Due to the unforeseen/unanticipated nature of ‘other’ safety concerns that could be identified, the need for a case-by-case approach to additional data that will be required in Tier 2 becomes more acute.

Special considerations for animal feed

33. A single PBO may contribute a more significant portion of an animal diet than it would as part of the human diet, therefore resulting in different level of significance for changes when used as food or feed. Antinutritional factors and digestibility are particularly relevant in this context. The animal(s) the feed is intended for should be identified, as the nutritional needs vary depending on the animal species, for example, ruminants have very different nutritional needs than poultry or pigs.

34. In addition, the part of the plant to be used as feed for animals may be different from that used as food for humans, or the feed might be a by-product of a plant otherwise used to produce non-edible materials. The impact of any change on the edible part of the plant destined for feed should be taken into consideration when assessing a PBO for feed.

Special considerations for animal PBOs

35. Traits introduced precisely to alter the composition of the animal tissues may impact the nutritional content of foods produced from the animal parts. Traits introduced into an animal to allow them to digest a new feed, if they were developed, may also have such an impact.

36. Particular consideration should be given to how PB could affect the composition of products derived from the animal PBO, such as milk from cows or eggs from chicken and other similar staple foods in the diet. Milk and eggs in particular are a key dietary component for young children.

37. Some animals and animal products can contain allergens (for example, fish, shellfish, insects, eggs, milk) and these should also be taken into consideration when determining impact of PB on the quality of foods from animal PBOs.