3. Nutritional Information within supplementary guidance to applicants for assessment of Cell Cultivated Products (CCP) in food: Allergenicity & Nutrition

Nutritional information contained within the supplementary guidance to applicants for assessment of Cell Cultivated Products (CCP) in food: Allergenicity & Nutrition

3. Nutritional information

Under Regulation (EU) 2015/2283 and Section 2.9 of the 2016 EFSA guidance for novel foods, applications should demonstrate that a novel food is not nutritionally disadvantageous compared to any food it may replace. Evidence includes compositional data, bioavailability of nutrients and assessment of anticipated intake under the proposed conditions of use. This guidance intends to outline the scientific and regulatory requirements for assessing the nutritional quality and how this can apply to CCPs as novel foods.

Nutritional quality is a combination of multiple interrelated factors, including nutrient content (composition), digestibility, bioavailability, and the contribution of the CCP to the diet. To ensure it is not nutritionally disadvantageous under the proposed conditions of use considering the impact on different population subgroups who are anticipated to consume the novel food. This includes the impact on nutritional intake and status with replacement of conventional meats for CCPs.

Analytical methods, specifically used for nutritional assessment, should be completed by accredited laboratories using internationally recognised methods. Where in-house methods are used, these should be fully described and the method validated. Copies of the certificates(s) of analysis should be provided.

3.1 Composition

Applicants must provide both qualitative and quantitative data on the macro- and micronutrient composition of the CCP. The analysis should address the following key points:

- **Protein profile:** Clearly define the protein profile of the CCP, including any post-translational modifications where relevant, and compare it to the relevant conventional counterpart. Consideration should be given to any potential residues from culture media or scaffolds.
- **Scope of analysis:** Conduct compositional analysis on both the CCP as submitted for novel food authorisation (e.g., cell biomass) and, if applicable, the final food as it is intended to be consumed, including after any cooking or preparation steps.
- **Batch analysis:** Perform nutritional analysis on at least five independent, representative batches using validated or internationally recognised methods. If fewer batches are analysed (e.g., in continuous or semi-continuous manufacturing), provide a strong scientific

justification to ensure robust and reliable data. Justification may include evidence that fewer batches do not compromise safety or nutritional adequacy and that the product is homogeneous across production runs and representative of the novel food manufacture. For continuous processes, ensure batch representation from at least two different starting cell stocks. The definition and justification of a batch must be included in the application.
- **Batch consistency:** Demonstrate that batch analysis results are consistent within a predetermined specification. If variability is observed, explain its sources and how it will be controlled.
- **Presentation of results:** Present compositional data in a table, including batch specifications, minimum and maximum specification limits, and details of the analytical techniques used (including Limit of Detection (LOD) and Limit of Quantification (LOQ).
- **Micronutrients of concern:** Pay special attention to micronutrients relevant to public health in the UK, such as iron, zinc, selenium, vitamin B12, folate, riboflavin, vitamin D, essential amino acids, creatine, and long-chain fatty acids (such as omega-3). Compare these to conventional meat or seafood as appropriate. Additionally, consider and compare levels of any antinutrients present.
- **Comparator justification:** Justify the choice of comparator food (e.g., chicken breast for a CCP imitating chicken), considering the intended use of the CCP (full replacement or ingredient in a composite food). Refer to **Section 3.3**.

Best practice

Applications should include amino acid and fatty acid profiles of the defined novel food. Conventional meat contains all the essential amino acids and is a useful source of creatine the content of these nutrients should also be considered, also the bioavailability and digestibility of the form of certain nutrients e.g. haem/non-haem iron, folates/folic acid. The role of the novel food in the consumer's diet needs to be understood to evaluate the impact of the novel food on the nutritional status of the consumer e.g. total conventional meat replacement or ingredient added at a low percentage to a pre-existing product.

If the CCP's nutritional profile is not equivalent to its comparator (e.g., lower iron content than conventional meat), assess the potential impact on consumer nutritional status and provide a justification that its consumption will not adversely affect health or mitigations required.

It is recognised that, although the proposed uses and quantities of CCPs may not currently be sufficient to replace conventional meats, the impact of any nutritional disadvantage should still be assessed.

3.2 Absorption, Distribution, Metabolism and Excretion (ADME)

ADME investigations, including protein digestibility of the CCP or associated breakdown products should be assessed on the food as it is intended to be consumed.
The ADME profile should consider poorly digestible components within the novel food such as antinutritional factors, nutrients with poor bioavailability or non-protein nitrogen sources, including the impact in the colon and microbiome.

- **Nutritional quality:** Digestibility is a key factor determining the nutritional value of foods and allows the evaluation of protein quality. Protein quality and digestibility are to be assessed using in vitro appropriately validated methods such as Digestible Indispensable Amino Acid Score (DIAAS). Alternative methods can be used provided they are explained and justified within the application.
- **Allergenicity assessment:** Digestibility affects the way in which protein is presented to the gut mucosal immune system. Since peptides are poorly immunogenic, rapidly digested proteins will have a lower allergenic potential. In vitro digestibility tests for allergenicity

assessment should differ from those used in nutritional assessment by sampling earlier during digestion.

3.3 Comparator foods

When assessed against its comparator, the CCP should not be nutritionally disadvantageous and adversely affect the nutritional status of consumers by increasing the risk of inadequate or excess nutritional intake under the proposed conditions of use.
To establish a suitable comparator, consider whether the CCP novel food will be a replacement for conventional meat products or included as an ingredient in another food:

- **Conventional meat replacement:** the appropriate comparator should be the conventional meat it intends to replace.
- **Ingredient within food:** an appropriate comparator will require justification. Where inclusion of the novel food ingredient is more than 50% it should be justified whether conventional meat is an appropriate comparator.

The appropriate comparator is to be defined and justified within the application. Any rationale should include a justification for the cell types present within the novel food, as intended to be consumed, and a comparative assessment for the cell types and their prevalence within the conventional meat comparator.

- The expected role of the novel food within the consumer diet needs to be explained to understand the impact to the nutritional status of the consumer.
- Applicants should use analytical techniques that yield comparable results and employ technology to enable a comparison between the CCP analysis outcomes and a suitably justified comparator from published scientific literature. The results should be generated with equivalent techniques or there should be a justification as to why they are comparable.
- Applications should contain a summary of the systemic processes used to collect and report on the comprehensive literature review/research of micronutrients/macronutrients and allergens within the comparator.
- Where there is not a suitable direct comparator the applicant is to consider the appropriateness of an alternative (e.g. it is not appropriate for example to compare fat with muscle tissue).

3.4 Stability

The nutritional stability assessment of the CCP post-production is evaluated to assess hazards that may arise through storage (including transport). Stability testing considers constituents and parameters of the novel food that may be susceptible to changes during storage.
Applicants should consider:

- **Chemical, physiochemical, and microbiological stability** of the CCP under the intended/proposed storage conditions.
- **Degradation products** in the CCP, including the creation or reduction of antinutrient factors during storage and cooking.
- **Monitoring period of stability** testing to cover the end of the proposed shelf life with intermediate interval testing. Including testing of macro- and micronutrient at both beginning and end timepoints to evaluate any potential degradation of the nutrients and whether they pose a safety risk including the risk of allergens.

Where nutrient composition alters following storage, these should be fully explained and justified within the application.

3.5 Specifications

Specifications define the key parameters that characterise the CCP and are used to demonstrate safety in the CCP. A rationale for the specifications should be provided; it is recommended that data for the specifications is taken from a minimum of five batches, but fewer batches may be analysed if there is a strong scientific justification (see Section 3.1).

Specifications should be reflective of the CCP batches produced and set conditions for the novel food intended to be placed on the GB market after authorisation. Where there is intent to blend batches (e.g. a higher protein batch with a lower protein batch) as a part of the production process it must be demonstrated that safety implications have been considered to the mixing of batches and if there is change to the final protein profile.

Genetic stability should be monitored throughout the production process through appropriate controls e.g. monitoring of phenotypic characteristics. The number of cell divisions required in production and the impact on the final cell culture should be assessed. Further guidance on genetic stability will be addressed within future hazard guidance publications.

3.6 History of use

The history of use review should consider within a literature review the consumption of the source materials, including but not limited to the animal of origin, cell culture ingredients, and any scaffolds used. Although current data is limited, where possible it should be provided, including data from consumption of relevant CCPs which have been approved for use in other jurisdictions. These should be used to identify and consider potential hazards.

3.7 Proposed uses and intake levels

Applicants must review and specify the intended use for the CCP and how it’s use could impact the nutritional status of consumers within the GB population.

It is advisory for the applicant to estimate consumption/intake of the CCP based on the appropriate food categories for the intended use, and to estimate exposures accordingly.

Exposure assessment should typically be based on national dietary survey information and may be conducted using tools such as DietEx. For UK consumers the relevant dietary surveys are the National Diet and Nutrition Survey (NDNS) and the Diet and Nutrition Survey of Infants and Young Children (DNSIYC).

Estimations of the daily intake of the CCP should be calculated for all relevant age groups, independently. Exposure assessments should include a consideration of high intake consumers of the novel food, based on estimated consumption at the 95th or 97.5th percentile.

The assessment should consider the inclusion rate of the novel food within the product as intended to be consumed. Where the final product is a composite food, there should be consideration for the impact on the total nutritional intake for the consumer.