

12 September 2023

**Subject: Impact of the Use of New Genomic Techniques in Animal Cells (Cell Cultured Meat) and Microorganisms in Light of the European Commission's Proposal**

Dear [REDACTED],

I would like to follow up on a response letter from the European Commission that I received on 17 November 2020 (Annex I). In this response letter, the European Commission services expressed their view on whether the use of non-integrative techniques (not introducing any DNA but remodelling the epigenetics of the cells) would result in genetically modified (GM) cells, in view of cell cultured meat. In their opinion, the European Commission services interpreted that cells obtained by non-integrative techniques would be covered by the definition of a genetically modified organism (GMO) as per Article 2(2) of Directive 2001/18/EC, i.e., *organisms in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination*. The European Commission also indicated that they could not yet provide any information whether the Commission study on new genomic techniques, which would be presented in April 2021, would result in any changes regarding this interpretation.

Considering the progress that the European Commission made in relation to this topic since the reception of the original response letter, and the proposal for a new Regulation on plants produced by certain new genomic techniques (NGTs) that has been adopted by the European Commission on 5 July 2023, I would like to receive input from the European Commission on whether this proposal will have an impact on the use of NGTs in animal cells and microorganisms? In the specific case of cell cultured meat, is there a chance that animal cells that are modified with NGTs in which the DNA is altered in a way that also could occur naturally, would be exempted from the requirements of the GMO legislation (similar to 'category 1 NGT plants', as per the proposal)? Is there any indication from the European Commission that a similar proposal will be prepared in the future covering animal cells and microorganisms, or that the current proposal will be amended to cover animal cells and microorganisms, besides plants?

Article 22(3) and Article 22(4) of the proposal also proposes that EFSA, or the competent Member State authority to which the application is going to be submitted, will offer pre-submission advice to small or medium-sized enterprises (SMEs) for 'category 2 NGT plants' and 'category 2 NGT products containing traits relevant for sustainability' to help applicants prepare the dossier. Can we expect a similar procedure for pre-submission advice for products containing animal cells and microorganisms that are modified using NGTs?

Cell cultured meat is gaining a lot of attention globally, and many companies are using NGTs and other more traditional techniques to edit their cell lines so that they become immortalised and can consistently produce the same product, which ultimately leads to a safer and more stable product. In many instances, the final product produced from the edited cells does not contain heterologous DNA.

We welcome the proposal for a new Regulation on plants produced by NGTs and welcome the two-tiered approach depending on the presence of heterologous DNA on the final product, which gives applicants producing innovative products greater regulatory flexibility and predictability when accessing the EU market. It is also very interesting to hear that the EC proposes regulatory incentives such as support to SMEs. Hence, it would be interesting to understand if the same approach will be extrapolated to food products derived from cell culture and microorganisms.

I would be grateful for your assistance on this matter.

Yours sincerely,

[REDACTED]  
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**Annex I: Response letter from the European Commission received on 17 November 2020**



EUROPEAN COMMISSION  
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Food and feed safety, innovation  
**Biotechnology**

Brussels  
SANTE.DDG2.E.3/[REDACTED] (2020)7344894

Dear [REDACTED],

**Subject: Your letter of 9 October 2020 – Classification of induced pluripotent stem cells, intended for production of cultured meat for use in human food**

Thank you for your letter of 9 October, requesting views of the European Commission on whether induced pluripotent stem cells (iPSCs), intended for the production of cultivated meat for use in human food and which are obtained by non-integrative techniques, are genetically modified organisms (GMOs) in accordance with EU GMO legislation. You also enquire whether the study on new genomic techniques, which is being conducted by the European Commission, will bring any changes to your interpretation that such iPSCs are not GMOs.

In your letter, you indicate that iPSCs are a type of pluripotent stem cell derived from a somatic cell through the (over)expression of certain endogenous transcription factor genes. You further explain that techniques to (over)express these genes in the somatic cells include integrative techniques (introducing foreign DNA in the genome of the somatic cells) and non-integrative techniques (not introducing any DNA but remodelling the epigenetics of the cells). In the case of non-integrative techniques, the somatic cells are exposed to specific chemicals or RNA, resulting in pluripotency inducing transcription factor genes being activated and expressed, converting those somatic cells into stem cells. In that regard, you consider that iPSCs obtained from the non-integrative techniques are not GMOs in accordance with EU legislation, because those techniques do not introduce any DNA in the genome of the somatic cells or alter their genetic information, and therefore the material introduced into the cells is not integrated into the genome and is not heritable.

Firstly, I would like to stress that the legal status and requirements for particular organisms or products under the Union legislation are assessed on a case-by-case basis. It follows that we are only in the position to provide you with a general response to your question as a concrete and specific answer can only be given following an in-depth regulatory analysis of a specific application. Therefore, please note that the advice given below cannot replace the specific analysis when an application is submitted and is based only on the information you have provided.

Mr [REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]

Spain

GMOs are defined in Article 2(2) of Directive 2001/18/EC as organisms *‘with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination’*. Article 2(2) further provides that genetic modification occurs at least through the use of the techniques listed in part 1 of Annex IA, and that the techniques listed in part 2 of Annex IA are not considered to result in genetic modification.

The list in part 1 of Annex IA is non-exhaustive, as reflected by the terms *‘inter alia’* in the first sentence of the annex, and as confirmed by the EU Court of Justice in its judgment in Case C-528/16 (par. 35). Therefore, the fact that the above-described non-integrative techniques are not listed in part 1 of Annex IA of Directive 2001/18 does not mean necessarily that organisms obtained with them are not GMOs.

Furthermore, the definition of GMO in Article 2(2) of Directive 2001/18 refers to organisms *‘in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination’*. While the term *‘altered’* is not defined in the directive, in our view it is not restricted to modifications of the nucleic acid sequence, but encompasses any modifications of the genetic material that do not occur naturally by mating and/or natural recombination. Accordingly, chemical alterations of the DNA molecule affecting the expression of genes would be covered by the GMO definition.

Based on the above considerations, we are of the view that iPSCs obtained by the activation and (over)expression of pluripotency inducing transcription factor genes resulting from exposure of somatic cells to specific chemicals or RNA are not excluded from the GMO definition in Article 2 of Directive 2001/18.

With regard to your second question, concerning possible changes in the interpretation of the GMO definition in the light of the Commission study on new genomic techniques under preparation, that study is due to be completed in April 2021. It is therefore too early to provide any information on the outcome of the study.

Please note that this letter expresses the view of the Commission services and does not commit the European Commission. Only the Court of Justice of the European Union is competent to authoritatively interpret Union law.

Yours faithfully,

