Regulatory Framework for Cultured Meat in the EU

12 September 2023, Jerome Diaz

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Report 2540, final

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This research project has been carried out by Wageningen Food & Biobased Research (WFBR), which is part of Wageningen University & Research.
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Objectives of the study

- The slide deck was made to:
  - give a general background regarding the emerging cultured meat industry
  - analyze the current EU regulatory landscape pertaining to cultured meat
  - describe potential safety and risks associated with cultured meat (according to a colloquium hosted by EFSA).
  - discuss environmental studies related to cultured meat
  - Evaluate relevant production scale for cultured meat

Disclaimer

- All the information obtained here are derived from published information (both scientific and publicly available resources were used)
- Several information sources used in this slide deck use the term “clean meat”, this is the same as cultured meat.
- No opinions were given from WFBR

Summary (1)

- Main food related EU regulations relevant for cultured meat:
  - GMO regulation (EU reg no. 2003/1283)
  - Novel food regulation (EU reg no. 2015/2283)
- Other food related regulations potentially affecting cultured meat derived food products:
  - General food law (EU reg no. 2002/178)
  - Information to consumers regulations (EU reg no. 2011/1169)
  - Food Hygiene (EU reg no. 2004/852)
  - Microbiological criteria for foodstuffs (EU reg no. 2005/2073)
  - Common organization of markets in agricultural products (EU reg no. 2013/1308)
- **There are no specific cell-culture derived food regulation or specific guidelines on food products derived from cellular agriculture in the EU.**

Summary (2)

- Cultured meat companies have knowledge about the EU regulatory framework affecting cultured cell/meat production
- However, cultured cell/meat companies may have difficulties regarding specific procedures/guidelines (e.g. related to dossier submissions, required information for risk assessment and approval)
- EFSA may provide some clarity regarding general procedures related to risk assessment

Summary (3)

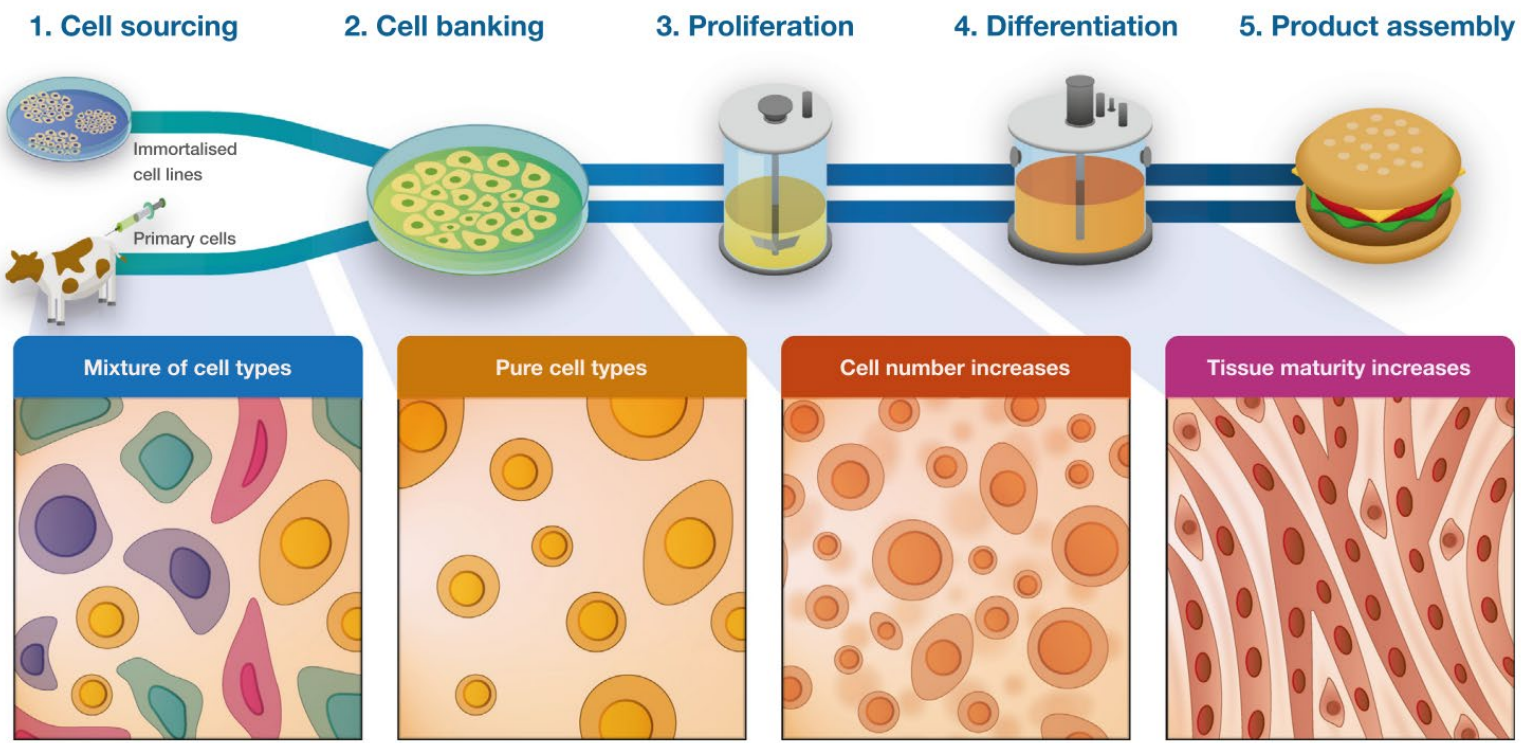
- **Legal constraints on production in small scale vs large scale:**
  - Currently, production scale is limited by technical constraints more than any existing legal constraints
  - Not enough public information/data is available to serve as basis what is needed for production in large (e.g. >10K liters) or small scales (<10K liters). Research and development is on-going related to:
    - Bio-reactor design (low shear mixing)
    - Mass production of cells (growth factors, culture media and standards)
    - Scaffolding design (material, 3D design)
    - Quality of end product (e.g. beyond pieces into large slices)
  - Most companies are currently following/adapting pharmaceutical guidelines for cultured cell production since no specific guidelines exists for cell-culture derived food products and ingredients.

I. Introduction

A. Approach for the study

- Using available public information/literature:
  - Identify regulatory framework relevant for cultured meat
  - Identify/collect challenges and opportunities in cultured meat based on existing EU regulatory framework
  - Identify potential safety hazards related to cultured meat
  - Characterize supply-chain for cultured meat
- This study is based on publicly available literature
- Summary and results of EFSA colloquium on cell culture-derived food

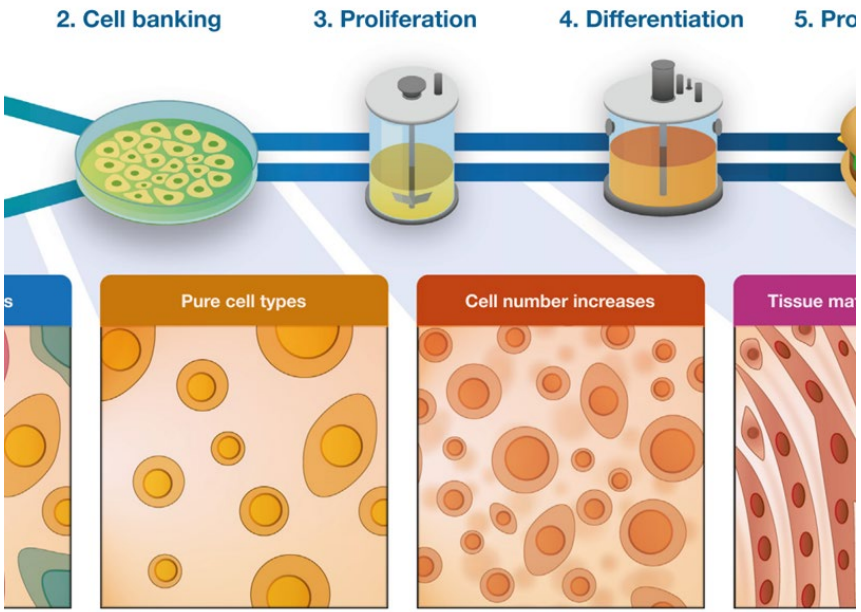
B. Background on cultured meat production



Andrew J. Stout, David L. Kaplan, and Joshua E. Flack. 2023. Cultured meat: creative solutions for a cell biological problem. Trends in Cell Biology, January 2023, Vol. 33, No. 1

Important aspects of cultured meat production

- Cultured cells can only tolerate low shear conditions
- Cell adhesion decreases as cell density and cell age increases
- In both cases, these limit current potential yields for cultured cells
- Therefore, bioreactor design and process control is crucial



Post, M.J., Levenberg, S., Kaplan, D.L. et al. Scientific, sustainability and regulatory challenges of cultured meat. Nat Food 1, 403–415 (2020). https://doi.org/10.1038/s43016-020-0112-z

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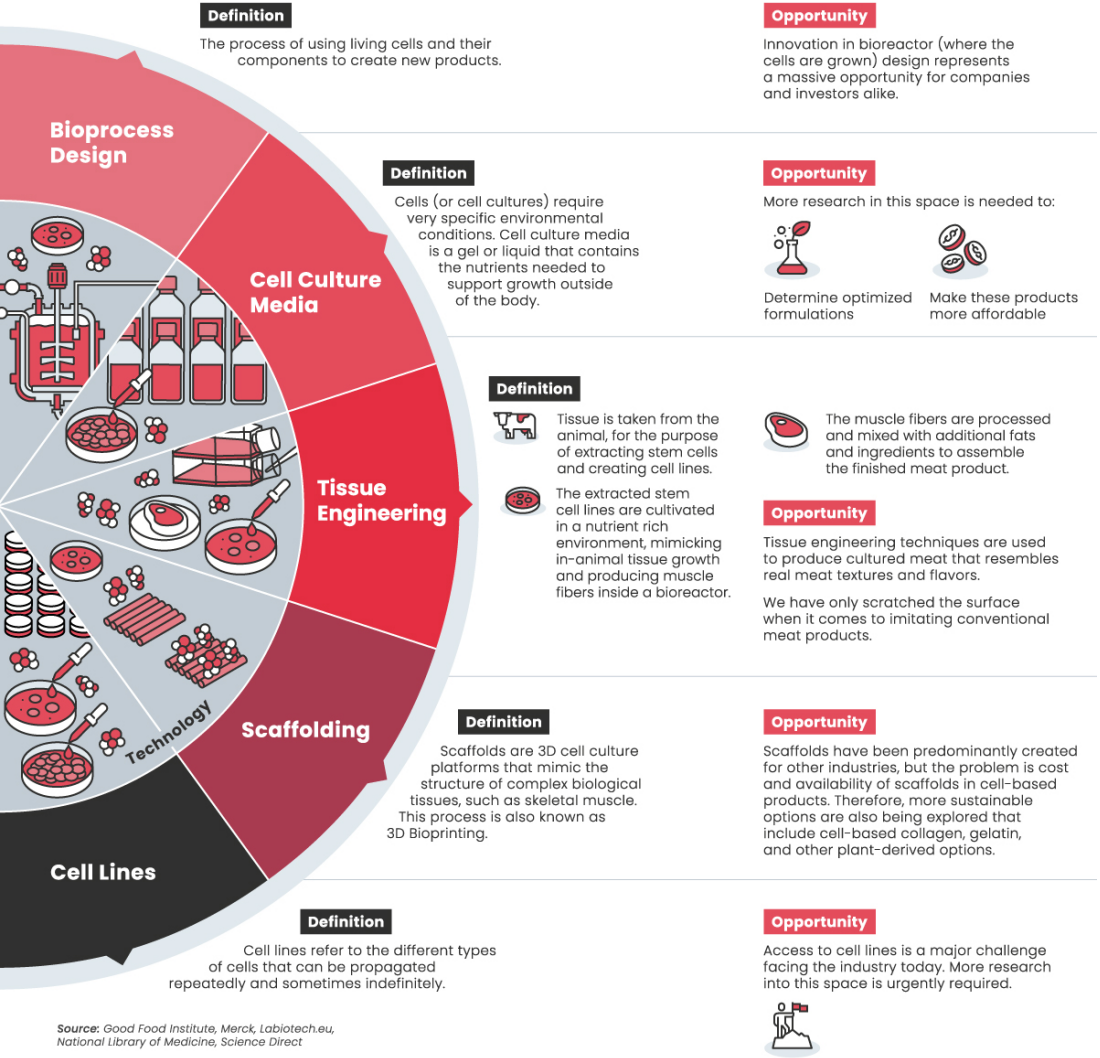


Innovations and Opportunities in Cultured meat

Main opportunities in cultured meat:

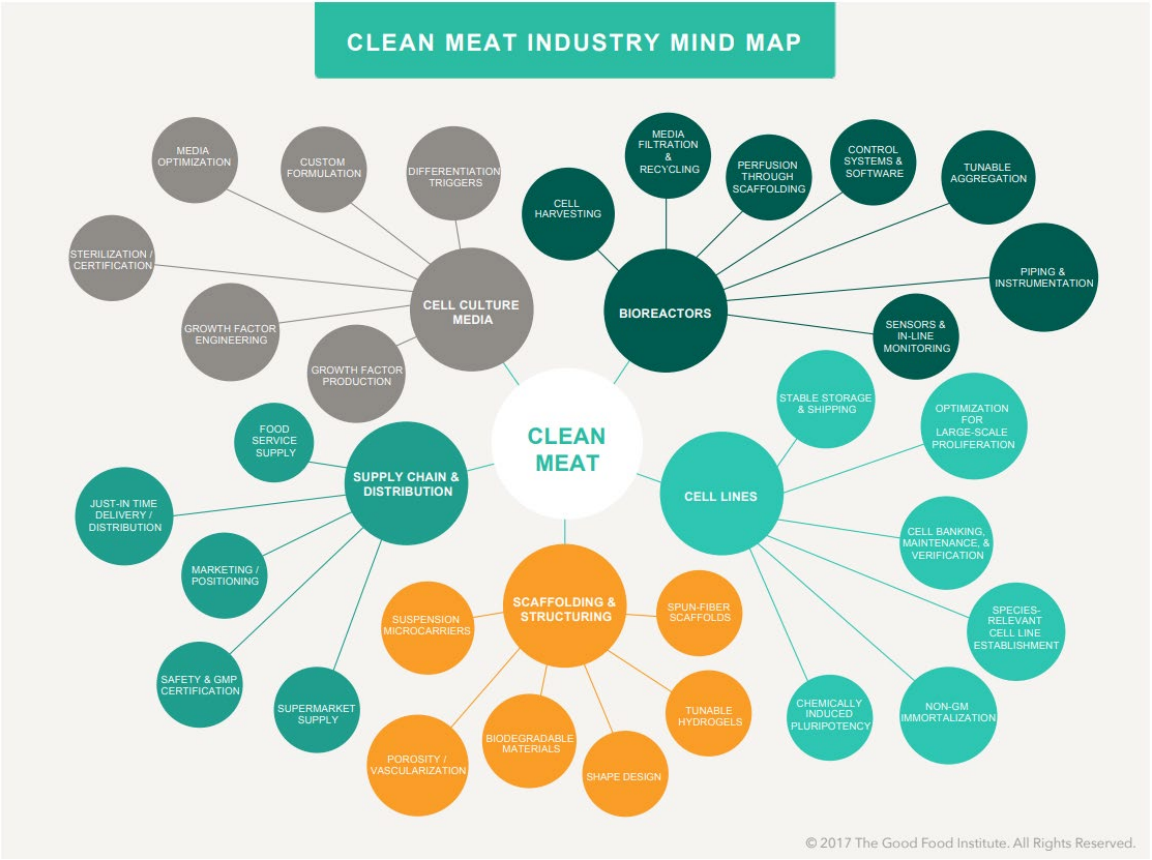
1. Development of culture media
   - efficient and effective media
2. Tissue engineering technology
   - high yield of tissue
3. Scaffolding
   - high yield of high quality tissue and obtain desired texture

Katie Jones and Sabrina Lam. 2022. A visual to the science behind cultured meat. https://www.visualcapitalist.com/sp/a-visual-guide-to-the-science-behind-cultured-meat/. Accessed 5 May 2023

Mind map for cultured meat production

Critical topics for cultured meat:

1. Cell lines
2. Cell culture media
3. Bioreactors
4. Scaffolding and structuring
5. Supply chain and distribution



Liz Specht and Christie Lagally. 2017. Mapping emerging industries: Clean Meat. The Good Food Institute. June 6, 2017. https://gfi.org/images/uploads/2017/06/Mapping-Emerging-Industries.pdf

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Consumer acceptability studies for cultured meat

Survey source	Year	Sample size and demographics	Question	Would eat	Do not know	Would not eat
YouGov[169]	2013	1,729 adults (18+ years) in the UK	Imagine artificial meat was available commercially, do you think you would eat it?	19%	19%	62%
Pew Research[147]	2014	1,001 adults (18+ years) in the US	Would you…eat meat that was grown in a lab?	20%	2%	78%
Flycatcher[145]	2013	1,296 adults (18+ years) in the Netherlands	Suppose that cultured meat is available at the supermarket. Would you buy cultured meat in order to try it?	52%	23%	25%
The Grocer[148]	2017	2,082 adults (16+ years) in the UK	Would you ever buy 'cultured meat' grown in a laboratory?	16%	33%	50%
Wilks and Phillips[146]	2017	673 adults adults (18+ years) in the US	Would you be willing to try in vitro meat?	65%	12%	21%
Surveygoo[162]	2018	1,000 adults (18+ years) in the UK and US	Would you be willing to eat cultured meat?	29%	38%	33%
Bryant et al.[152]	2019	3,030 adults in the US (18+ years), India and China (18+ years)	How likely are you to try clean meat?	52%	34%	13%

Post, M.J., Levenberg, S., Kaplan, D.L. et al. Scientific, sustainability and regulatory challenges of cultured meat. Nat Food 1, 403–415 (2020). https://doi.org/10.1038/s43016-020-0112-z

Cultured meat companies worldwide

Image Source: Cultured meat company database. https://bioinformant.com/product/cultured-meat-companies/

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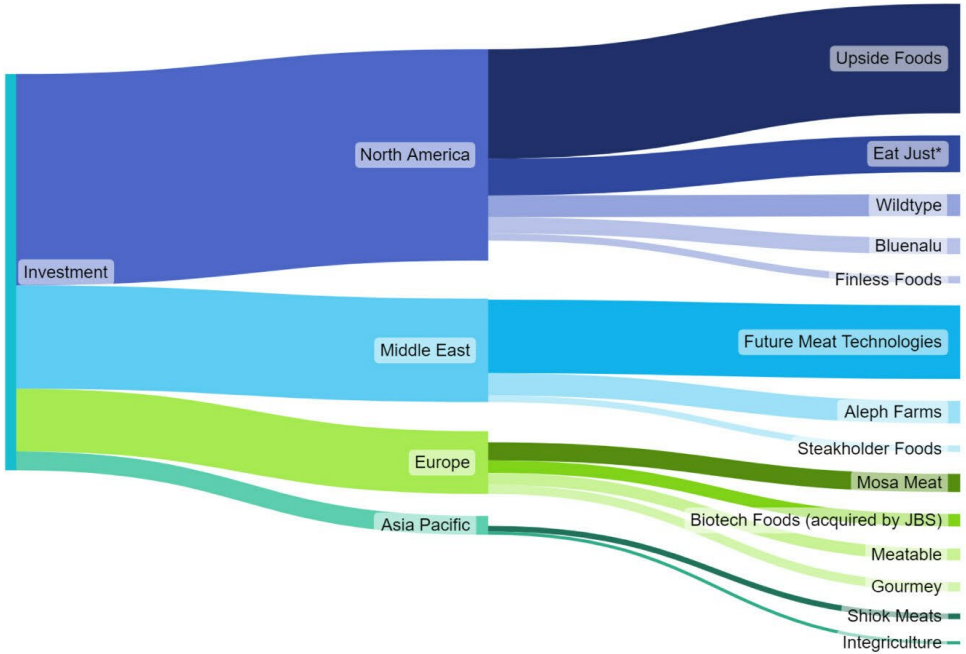
Total funding for Cultured Meat

Cultured Meat Industry Total Funding by Region and Major Companies

US$2.1bn
Invested 2015-2022

IDTechEx Research



*Note – Eat Just funding refers to GOOD meat product funds only

https://www.idtechex.com/en/research-report/cultured-meat-2023-2043/913

II. Overview of EU Regulations affecting Cultured Meat

Relevant EU regulations for cultured meat

- Precautionary principle is laid out in Article 191 (2) of the Treaty on the Functioning of the EU (**the Maastricht Treaty**)
- **In EU food law**, the precautionary principle applies to situations where there are reasonable grounds for concern that an unacceptable level of risk to health exists, and the available supporting information and data are not sufficiently complete to enable a comprehensive risk assessment (**Article 7 of the General Food Regulation, 178/2002**)
- The principles of non-discrimination and proportionality must be followed when taking risk management and consumer protection measures

https://doi.org/10.1016/j.foodcont.2021.108336

What the EU Precautionary Principle means for cultured meat ?

- It means certain foods need pre-market authorization; this include:
    - Novel foods
        - foods not consumed in the EU before May 15, 1997
        - Regulation (EU/2015/2283) – harmonized
    - Genetically modified organisms (GMO)
        - Regulation (EU/2003/1823) - harmonized

https://doi.org/10.1016/j.foodcont.2021.108336

Cultured meat from the perspective of novel food (EU Regulation 2015/2283)

- Cultured meat is considered a novel food since it has not been eaten in the EU before 15 May 1997
- Novel food regulation does not apply in cases where history of consumption is:
    - documented (e.g. published data such as production volumes, ingredients, recipes)
    - from significant consumption (i.e. consumed widely in the EU)
    - prior to May 1997

Definitions of the Novel Food Regulation in the EU

Operators uncertain on the legal status of a food are required to consult member state

Food

- Food
- Ingredients
- GM Foods
- Additives
- Enzymes
- Flavorings
- Extractions solvents

Novel food

Not consumed to a significant degree within the Union before 15 May 1997

i. Food with new or intentionally modified structure

ii. Food consisting of, isolated from or produced from microorganisms, fungi or algae

iii. Food consisting of, isolated from material of mineral origin

iv. Food consisting of, isolated from or produced from plants or their parts

v. Foods consisting of, isolated from or produced from animals or their parts

vi. Foods consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, micro-organisms, fungi or algae.

vii. Foods resulting from a production process not used for food production within the Union before 15 May 1997 which gives rise to significant changes in the composition or structure of a food, affecting its nutritional value, metabolism or level of undesirable substances

viii. Foods consisting of engineered nanomaterials

ix. Foods used exclusively in food supplements within the Union before 15 May 1997, where it is intended to be used in foods other than food supplements

x. Vitamins, minerals etc.

Not Food

Residues
e.g. processing aids residues

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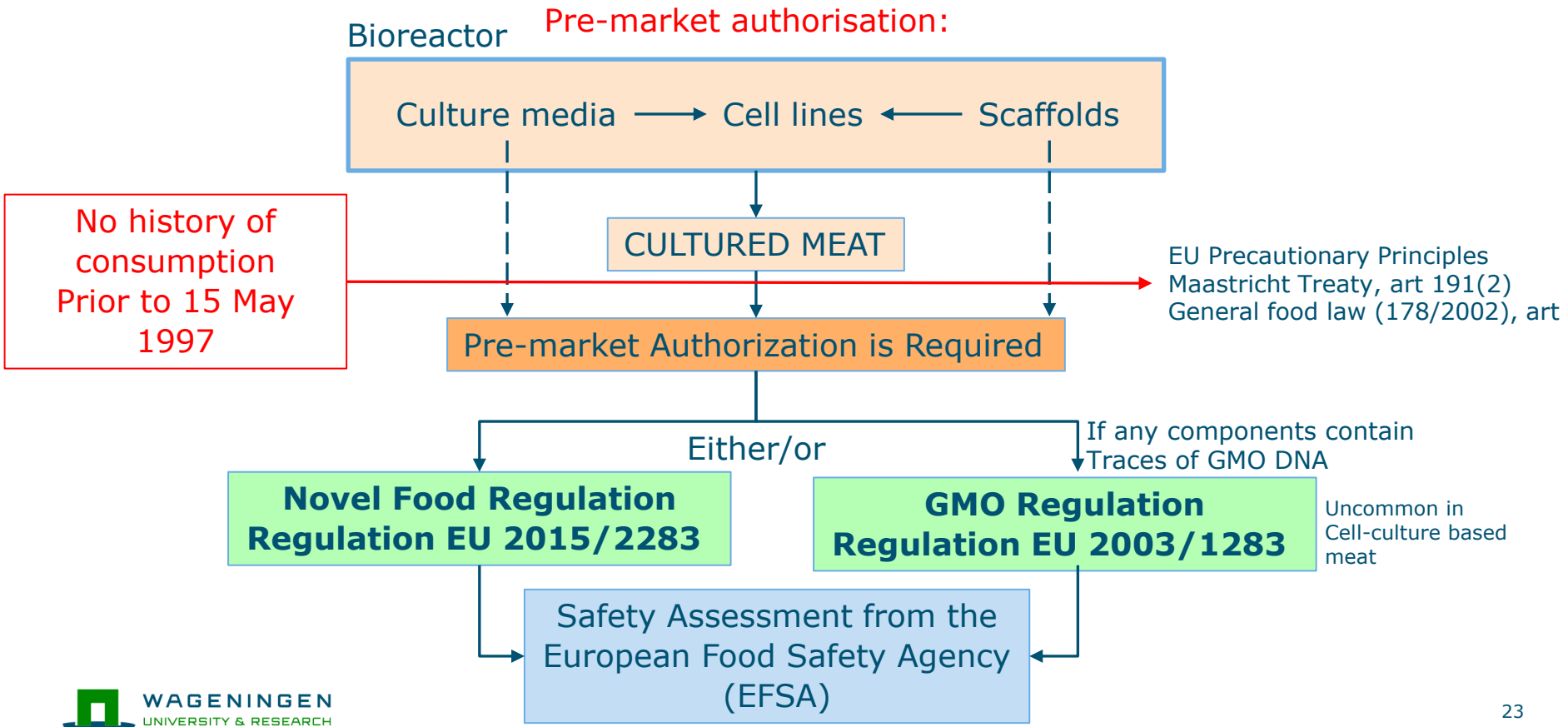
Cultured meat from the perspective of GMO Regulation (EU/2003/1823)

- There have been no publicly available reports that stem cells used for cultured meat are genetically modified
- Due to lack of literature and public information available, it can be concluded that GMO stem cells for the purpose of cultured meat production is uncommon practice
- In case gene modification technologies are used, then the GMO regulation becomes applicable.

EU Regulatory landscape for Cultured meat (1)



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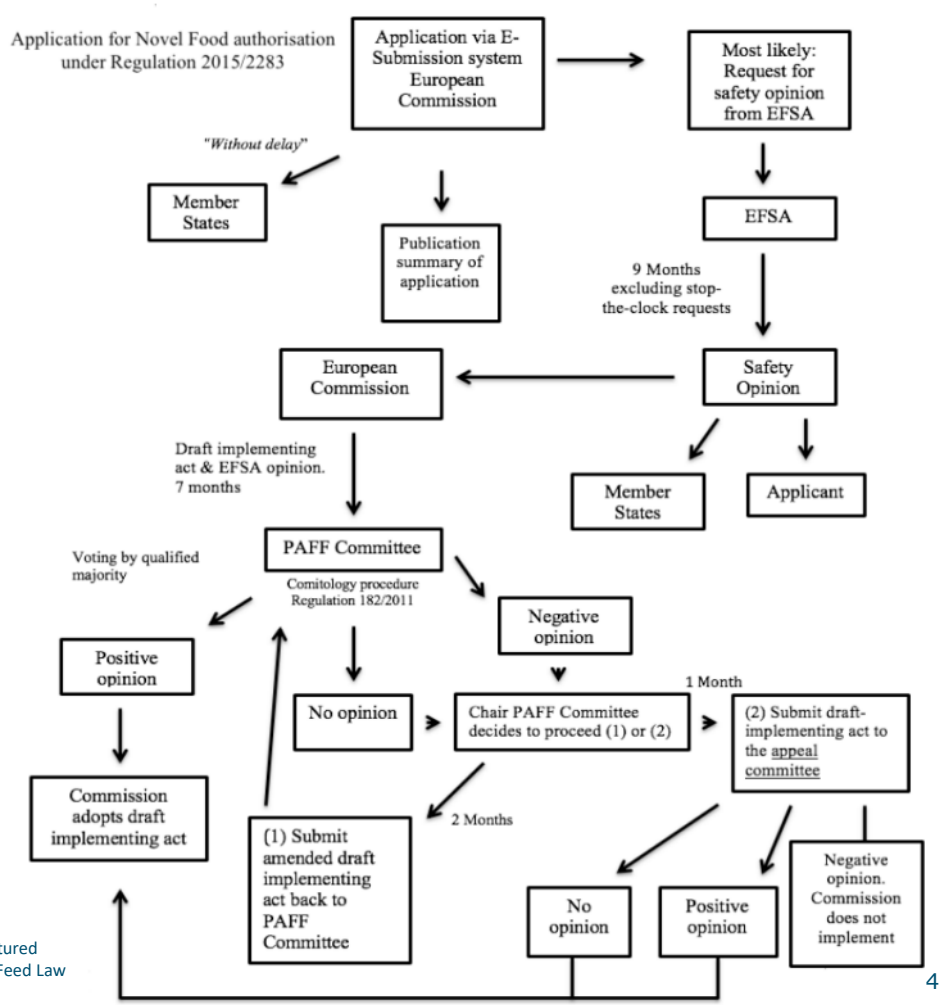
Application process NFA

Novel food authorization (NFA):

1. Application/dossier submitted to the e-submission system of the EC
2. Goes to EFSA. Member states informed by EFSA
3. EFSA reviews application and forms safety opinion
4. EC reviews EFSA opinion (delegated acts: SCOPAFF)
5. Results in (**positive**, **no opinion**, **negative**)

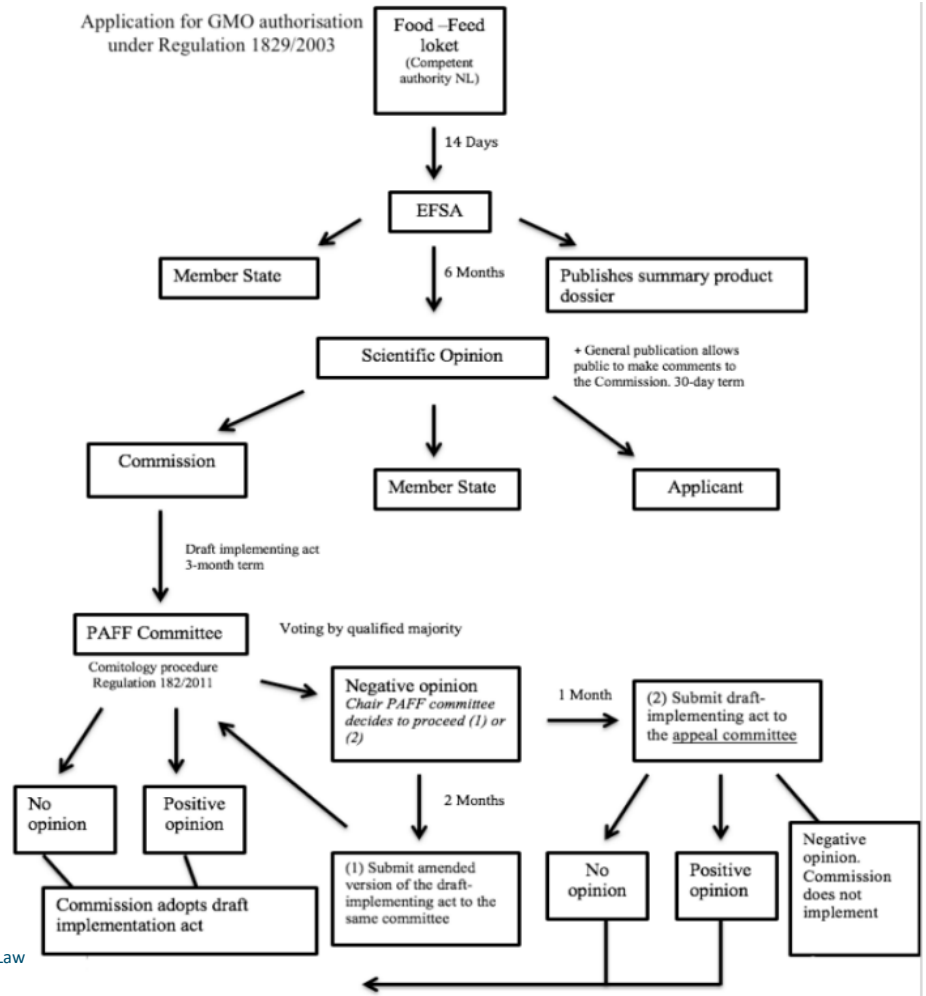


Karin Verzijden and Jasmin Buijs. 2020.Meat 3.0 — How Cultured Meat is Making its Way to the Market. European Food and Feed Law Review, Vol. 15, No. 2 (2020), pp. 96-107. https://www.jstor.org/stable/26998475

Application process for GMO authorization

GMO authorization:

1. Application submitted to competent authority of member state
2. Member state forwards to EFSA
3. EFSA Scientific Opinion
4. Informs member state, EC, applicant
5. EC determines final opinion (**Positive opinion**, **No opinion**, **Negative opinion**)
6. Will require GMO labelling, if DNA fragments are present in final product



Karin Verzijden and Jasmin Buijs. 2020.Meat 3.0 — How Cultured Meat is Making its Way to the Market. European Food and Feed Law Review, Vol. 15, No. 2 (2020), pp. 96-107. https://www.jstor.org/stable/26998475

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Important considerations regarding NFA and GMO application processes

- In both novel food authorization and GMO authorization, EFSA forms a scientific opinion (main task of EFSA) purely from a food safety perspective
- The actual authorization/ implementing act is given by the European Commission (EC) based on existing regulations
- Through delegated acts (comitology) the SCOPAFF (Standing Committee On Plants, Animals, Food and Feed) will give the final decision whether the authorization is given

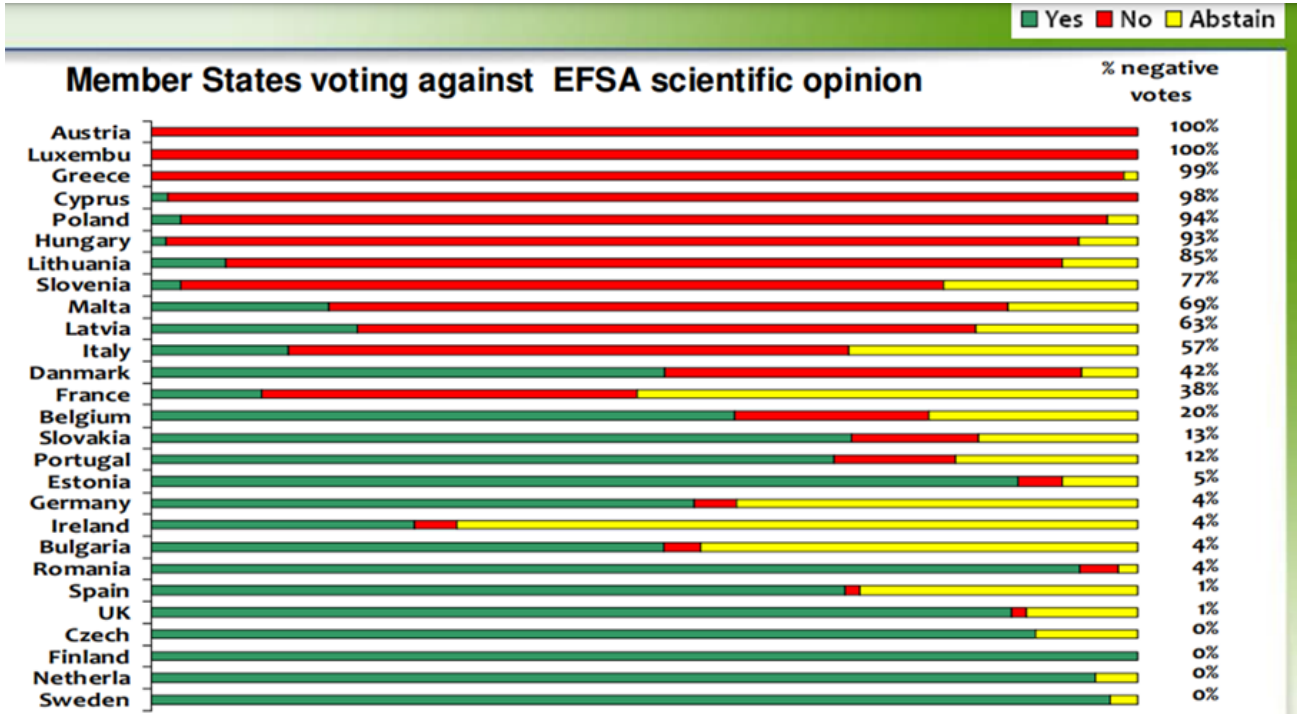
At this moment, the review process for cultured meat pre-market authorization is not clear

- Based on the EFSA colloquium on cultured meat (Brussels, May 11-12 2023), it is not clear for companies which safety data are required for the EFSA and EC authorization.
- Both the EFSA and the EC are not able to specify which safety data are required (a priori), since they are not familiar yet in detail with the production process(es) for cultured meat
- The EFSA review process lasts normally 9 months. However, this process may be delayed during stop clock events such as when additional information/data will be requested from the applicant
- The current lack of clarity and potential stop clock events contribute to the hesitation of cultured meat companies in submitting an application for pre-market authorization

Member states voting against GMO EFSA scientific opinion

Beyond the scientific risk and safety assessment conducted by EFSA, EU politics also play a role in the approval process.

In the end, a qualified majority from voting members is required for approval of Novel foods and GMOs



The chart shows that 10 countries vote against the EFSA scientific opinion ranging upwards of 63% of the time.

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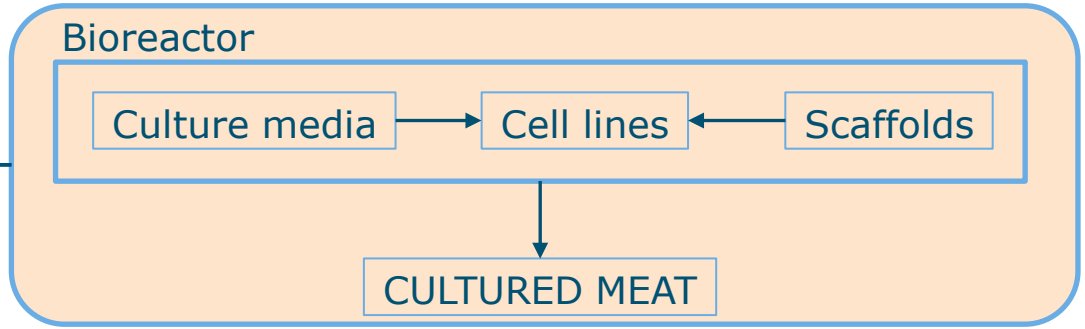
Source: 10.15252/embr.202154529

EU Regulatory landscape for Cultured Meat (2)

After authorization* is granted, the existing EU food regulations should be followed



General Food Law (Regulation 2002/178)
foods must be safe; it is the responsibility of the food operator to ensure this

Food additives regulation (Regulation 1333/2008)
Concerning food additives permitted for use in foods

Food information to consumers (Regulation 1169/2011)
Concerning labelling and right to information of consumers

All other specific/pertinent EU food regulations (next slide)

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Other existing relevant EU Regulations affecting cultured meat:

- **EU Regulation 2004/1935**: Food contact materials
- **Directive 2000/54/EC**: protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC)
- **Directive 2008/98/EC** : waste handling covering waste handling, recovery and disposal
- **Regulation (EU) 2019/624 and 2004/852 and 853**: official control measures on the production of and handling meat
- **Regulation (EU) 2019/627**: official control measures on products of animal origin intended for human consumption
- **Regulation (EU) 2021/405** : list of third countries or regions thereof authorised for the entry into the Union of certain animals and goods intended for human consumption in accordance with Regulation (EU) 2017/625
- **Regulation (EU) 2073/2005**: establishes the microbiological criteria for foodstuffs
- **Regulation (EU) 1308/2013** : establishes the temperature requirements for storage and transport of food products that are not stable at ambient conditions.

Comparison between US FDA and EU regulatory landscapes

	US FDA (pre-harvest)	EU
1	Pre-market consultation to evaluate production materials and processes.	No formal pre-market consultation procedure in EU novel foods framework, except the optional consultation at member state level in the case of doubt whether the product qualifies as a novel food (which is clear in the case of cultured meat). Changes to be implemented as of 26 March 2021.
2	Oversee cell collection and quality of cell banks.	Oversight of preparatory production steps, as well as registration of a company as an FBO, will be done at member state level. In the Netherlands, FBOs working with products from animal origin require a so-called recognition (erkenning). This is a more detailed procedure (average term of 8 weeks) than FBO registration (average term of a few days).
3	Oversee production process until harvest.	
4	Ensure companies comply with FDA requirements: facility registration, cGMP and other applicable food legislation.	
5	Where needed — issuing regulations or guidance or additional requirements regarding sections 2 and 3 to ensure that biological materials exiting the culturing process are safe (FFDCA).	EU hygiene rules for food of animal origin[164] to apply, and potential national legislation. In the Netherlands, the Commodities Act decrees on hygiene[165] and the preparation and packaging of foodstuffs[166] are applicable. Additional requirements (conditions of use) may also be included in individual novel food authorizations.
6	Inspections and enforcement directed at safety of cell banks and culturing facilities.	Inspections and enforcement are done at member state level. In the Netherlands, the responsible entity is the Dutch Food Safety Authority.
	USDA (post-harvest)	**EU**
7	Determine whether harvested cells are eligible to be processed in meat or poultry products.	The novel food framework requires FBOs to specify the source of the product, its production process and typical compositional features in their market authorization applicaiton[141]. No additional eligibility test is required for cell harvest prior to production of food products.
8	Require each cultured meat company to obtain a so-called grant of inspection.	Not required under EU legal framework. Registration (or recognition) with the competent food safety authority provides the authority with the legal basis for inspection. A novel food authorization must be obtained before placing the product on the market.
9	Conduct inspections in establishments where cells cultured from livestock and poultry are harvested, processed, packaged or labelled to ensure that the resulting products are safe, unadulterated, wholesome and properly labelled.	Inspections will be executed at a member state level based on the Official Controls Regulation 2017/625 (ref. [167]), which targets products of animal origin for human consumption inter alia.
10	Pre-approval of labeling of cultured meat products and inspection thereof.	No pre-approval of product labels under EU novel food framework. It is the responsibility of the FBO to comply with applicable labeling legislation, such as the Food Information to Consumers Regulation 1169/2011 (ref. [136]).
11	Where needed — develop additional requirements to ensure the safety and accurate labeling of cultured meat products.	Safety and labelling provisions are already in place at EU level. These are embodied in the General Food Law Regulation 178/2002 (ref. [168]) and the Food Information to Consumers Regulation 1169/2011, respectively. Specific labelling requirements may be included in novel food authorizations. Post-market monitoring requirements may be imposed. In any event, FBOs should inform the European Commission of any new information that arises regarding the safety of the novel food placed on the market.
12	Enforcement actions regarding adulterated or misbranded food products.	See section 6. Competitors, consumers and watchdog organizations may also bring cases regarding misleading food information before self-regulatory bodies. For example, unpermitted references to 'meat' could be a topic of such cases.

FBO, food business operator.

Post, M.J., Levenberg, S., Kaplan, D.L. et al. Scientific, sustainability and regulatory challenges of cultured meat. Nat Food 1, 403–415 (2020). https://doi.org/10.1038/s43016-020-0112-z

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III. Production, Labelling and Marketing issues affecting Cultured Meat

Production issues

- Production scale is limited by process technology at the moment:
  - Cell culture technologies are derived from pharmaceutical practices and scale up for food purposes is main theme of research
  - Majority of companies involved in cultured meat are still developing production capacity to meet potential food demand
  - No public information available on current capacity for cultured meat production

- Large scale vs Small scale production
  - Currently, limited by process technology not practice or policy yet
  - Technical constraints limit production scale than any existing legal constraints

Overview of production and scale-up challenges

Cell lines	Cell culture medium	Scaffolding	Bioreactor design	Supply chain
• Food standards for establishing cell lines for cultured meat does not yet exist	• Lack of animal free alternatives	• Lack of established materials • Most materials are still under development	• Low shear designs still needs to be developed • Development of a high efficiency conversion of media to cells	• Still underdeveloped • Sourcing of sustainable media components • Sourcing of sustainable energy for bioreactors

Grey areas related in EU regulations related to cultured cell derived foods and ingredients

- **Some grey areas related to cultured cell derived food products/ingredients:**
  - How do we label cultured-cell derived food products ?
  - What standards are adapted for obtaining cell cultures for food use?
  - What standards are adapted for cellular agriculture for food in general?
  - Should standards exist for cell-cultured derived food? For cellular agriculture in general?
- **Who should answer these grey areas ?**
  - Who is responsible: Member state? EC? EFSA?
  - Should the Dutch government give indication who has the mandate to decide on the grey areas ?

Labelling and marketing issues not resolved yet

- According to EU regulation on Food Information to consumers (EU Regulation EC No. 1169/2011) producers should **not mislead consumers**
- Therefore, **how do we label cultured meat?**
    - How should cultured meats be marketed? The same as 'regular' meat? Or differently? If yes, what should we call them? Which name should be use for labelling?
    - Do cultured meat products replace "traditional" meat products? (or are they equivalent ?)
    - Should nutritional value be similar to "traditional" meat products?
    - What other information should be considered?
    - Is cultured meat considered as fresh products or a processed products?
    - Does cultured meat have to follow labelling similar to plant-based foods?
- EU regulations do not provide a clear pathway for labelling food products derived from cultured cell cultivation

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IV. Environmental issues (based on published scientific literature)

Carbon dioxide emission from cultured meat

Based on published study (https://doi.org/10.3389/fsufs.2019.00005)

Production system	Annotation	CO_2	CH_4	N_2O	GWP_{100} CO_2e
CULTURED MEAT					
Tuomisto and Teixeira de Mattos (2011)—low	Cultured-a	1.69			1.69
Tuomisto et al. (2014)—average	Cultured-b	3.67			3.67
Mattick et al. (2015b)—average	Cultured-c	6.64	0.019	0.0013	7.5
Mattick et al. (2015b)—high	Cultured-d	22.1	0.062	0.0043	25
BEEF CATTLE					
Swedish ranch	Sweden	0.90	0.8	0.02	28.6
Brazilian pasture	Brazil	0.90	1.2	0.03	42.45
USA Midwestern pasture	Mid-West USA	5.4	0.8	0.06	43.7

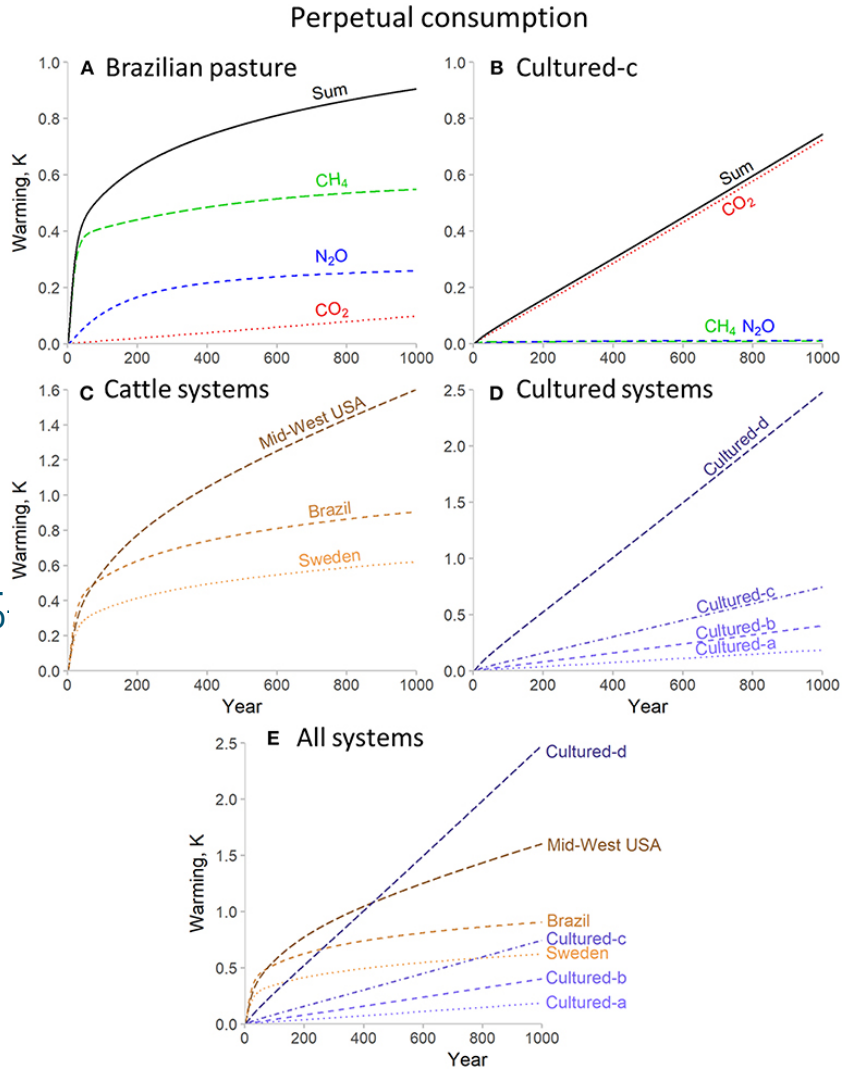
GWP100: looks at the Global Warming Potential (GWP) of the greenhouse gases over 100 years

Front. Sustain. Food Syst., 19 February 2019
Sec. Sustainable Food Processing . Volume 3 – 2019
https://doi.org/10.3389/fsufs.2019.00005

Warming impact for perpetual consumption at (250 Mt per year) for beef cattle and cultured meat production systems for 1,000 years

Conclusions from the study (https://doi.org/10.3389/fsufs.2019.00005):

- it is **not yet clear** whether cultured meat production would provide a more climatically sustainable alternative
- climate impacts of cultured meat production will depend on what level of **decarbonized energy generation can be achieved**, and the specific environmental footprints o production
- need for detailed and transparent **LCA of real cultured meat production systems**.
- Based on currently available data, **cultured production does not necessarily give license for unrestrained meat consumption**



Front. Sustain. Food Syst., 19 February 2019
Sec. Sustainable Food Processing
Volume 3 - 2019 | https://doi.org/10.3389/fsufs.2019.00005

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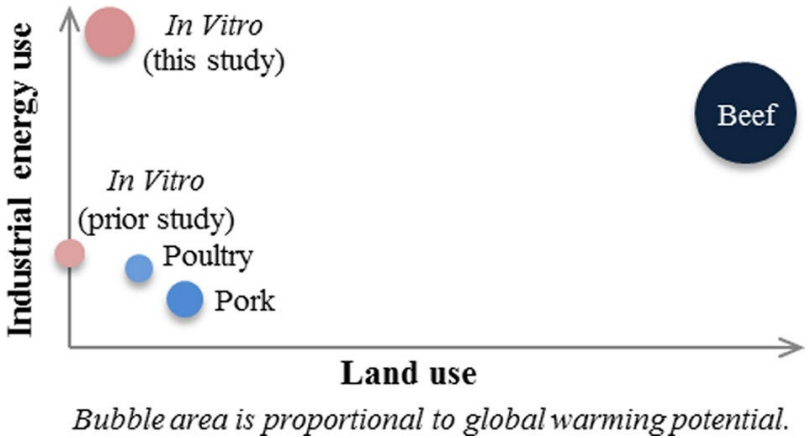
Energy use versus land use



Environ. Sci. Technol. 2015, 49, 19, 11941–11949
Publication Date:September 18, 2015
https://doi-org.ezproxy.library.wur.nl/10.1021/acs.est.5b01614

- Conclusions from the study (https://doi-org.ezproxy.library.wur.nl/10.1021/acs.est.5b01614):
- While uncertainty ranges are large, the findings suggest that in vitro biomass cultivation could **require smaller quantities of agricultural inputs and land** than livestock;
- however, those benefits could come at the expense of more intensive energy use as biological functions such as digestion and nutrient circulation are replaced by industrial equivalents.
- From this perspective, large-scale cultivation of in vitro meat and other bioengineered products could represent **a new phase of industrialization with inherently complex and challenging trade-offs**.

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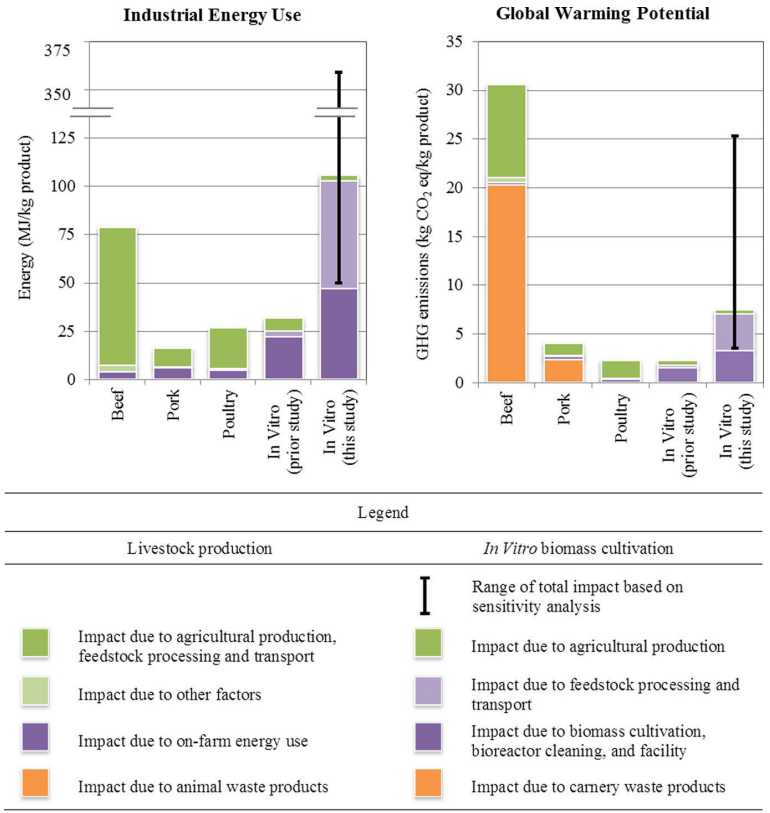
Industrial energy use and GHG emissions

Based on the study (https://doi-org.ezproxy.library.wur.nl/10.1021/acs.est.5b01614):

- Biomass cultivation requires high on-farm energy use (energy source determinative for GHG impact) and has high environmental impact due to biomass cultivation and bioreactor processes
- Livestock production requires high energy for production, processing, transport and has high environmental impact due to waste products



Environ. Sci. Technol. 2015, 49, 19, 11941–11949
Publication Date:September 18, 2015
https://doi-org.ezproxy.library.wur.nl/10.1021/acs.est.5b01614

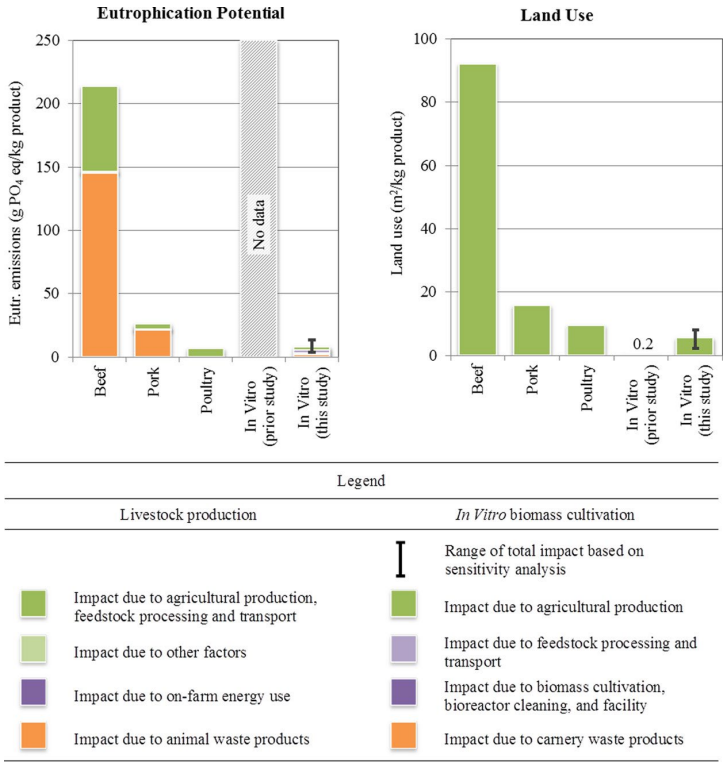
Eutrophication potential and land use

Based on the study (https://doi-org.ezproxy.library.wur.nl/10.1021/acs.est.5b01614):

- With limited data, cultured meat offers less eutrophication potential and land use compared to livestock production

Eutrophication potential:

- Nitrates and phosphates are essential for life, but increased concentrations in water can encourage excessive growth of algae and reduce the oxygen within the water. Eutrophication can therefore be classified as the over-enrichment of water courses.



Environ. Sci. Technol. 2015, 49, 19, 11941–11949
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Other potential issues: Italy against cultured meat

Despite existing EU level regulations, countries can exercise their voting rights during the approval process (See slide 27)

The new Food Sovereignty Ministry is trying to live up to its name by prohibiting lab-grown food in defence of the country's farming traditions. But how likely is an outright ban?

Italy is moving to become the first country in the world to ban its companies from producing lab-cultivated meat, threatening fines of up to €60,000.

Upon introducing the bill to the Senate, the country's Agriculture and Food Sovereignty Minister, Francesco Lollobrigida, said:

> ***It damages small food producers.***
> ***It damages the environment.***
> ***It standardises food habits.***
> ***Studies do not guarantee it's safe.*** ”

https://www.euronews.com/2023/04/04/frankenstein-food-why-italys-crusade-against-cultured-meat-probably-wont-work

VI. Conclusions

EU Regulatory Framework affecting cultured meat

The existing EU regulatory landscape has mechanisms to deal with cultured meat and other cell culture-derived food via the precautionary principles enshrined in the EU food law:

a. Cultured meat and other cell culture-derived food as such is covered by novel food (NF) regulation

b. GMO regulation covers all genetically modified organisms (including cell cultures, if they are so modified)

c. Both NF and GMO requires pre-market approval

d. Submission of a dossier for the risk and safety evaluation by the EFSA and pre-authorization from the European commission

What it means for the Netherlands ?

Dutch universities and research institutes may play a leading role in collaborating with the cultured meat industry in the following areas:

a. Generating protocols and data to help in the risk assessment of cultured meat and other cell culture-derived foods and ingredients (currently no published data and protocols are available)

b. The development of safe-by-design cultured meat and cell culture derived food systems (this is currently difficult since the process for cultured meat is not yet established)

c. Generating data to establish sustainability of cultured meat and cell culture-derived food and ingredients

What it means for the Netherlands ?

The Netherlands may play a role at the EU level (in collaboration with other EU entities such as EFSA and other member states), by helping establish standards for the cultured meat and cell culture-derived food and ingredients. Currently these standards does not exist. These standards may include:

a. Guidelines for cell sourcing and cell-banking for food purposes
b. Safe-by-design cultured meat and cell culture-derived food and ingredients
c. Labelling/Marketing guidelines for cultured meat and products of cell culture-derived food and ingredients

Thank you very much for your attention

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WAGENINGEN
UNIVERSITY & RESEARCH

Appendix 1. Risks and hazards associated with cultured meat

Summary from EFSA colloquium on:
Cell-culture derived foods and food ingredients
May 11-12, 2023. Brussels, BE

Meeting minutes will be available from EFSA website
(not yet available as of September 2023)

Participants of the colloquium

- 720 registrants from 62 countries
- 120 participants in Brussels:
    - 41% private sector
    - 26% universities and public research institutes
    - 5% NGOs
    - 4% EU institutions and 4% EU national authorities
    - 5% international organizations
    - Among others (EFSA staff, panel members, etc)
- 600+ following on-line
- 24 programme affiliates (EFSA and EC)

Objectives

- The colloquium organized by EFSA was meant to discuss the potential risks and safety issues related to precision fermentation and cultured meat.
- The colloquium invited stakeholders representing interested companies, research institutes and universities

Definition: cell culture-derived foods

- In the absence of a legal definition, cell culture-derived foods of animal or plant origin refers to:
    - Foods produced by the propagation of animal or plant cells, assisted by tissue engineering techniques
    - Adapted for the purposes of the colloquium

Potential safety and risks in cultured meat in relation to the following were discussed:

- Establishment and use of animal- or plant- derived cells to ensure a safe and consistent product
- Use of bioreactors, culture media and their components
- Nutritional value and information
- Scaffolding structures (properties and types)
- Toxicology and allergenicity aspects

Issues related to establishment and use of animal or plant-derived cells towards ensuring a safe and consistent product (1)

- How relevant are the health status of the source animals, their herd and clinical examination of the source animals to cell culture-derived foods before the biopsy?
    - Health of the animal and/or the herd relevant to food safety (information related to eg vaccinations, treatment of diseases)
    - Use of immortalized cell lines vs primary cells (recurring biopsies and isolation) does not necessarily lead to a final product with the same degree of consistency
- Is it necessary that specific requirements for establishing and maintaining cell lines (to enhance identity and quality aspects) are relevant and what are these?
    - Establishment and maintenance of cell banks is important. Existing guidelines from breeding and pharmaceutical sectors could be adapted to enhance robustness, variety and reproducibility of the production process

Issues related to establishment and use of animal or plant-derived cells towards ensuring a safe and consistent product (2)

- Is it needed that cells intended for cell-culture derived foods are GMO?
- Is there a risk of (epi)genetic drift in cell lines due to constant sub-culturing? How could this be linked to food safety?
    - Example: Cell isolation and subsequent cell treatment towards establishing a cell line could introduce chemical hazards and are methods readily available for monitoring occurrence ?
- How can it be ensured that a product is manufactured with consistent characteristics regarding its identity (types of cells, (epi)genetic drift, phenotype of cells (expressed proteins) and composition?
    - Phenotypic and generic stability of cells should be tested throughout the different production steps

Issues related to establishment and use of animal or plant-derived cells towards ensuring a safe and consistent product (3)

- Zoonotic agents could be present, as well as anti-biotic resistance, genetic diseases, prions, mycoplasma, viruses
- Outstanding issue whether cells should be sourced from different animals vs from 1 animal for product consistency
- How can we ensure that cell banking practices are sufficient to prevent contamination of cell lines?
- How can we monitor DNA transformation during cell culture ?
- Are applicable guidelines regarding harvesting and growing of cell lines needed to be established ?

Issues related to bioreactors, culture media and their components (1)

- Current start-ups take efforts to substitute the use of fetal animal serum. Which components could be present during the initial phases of the production, and which may be present in the end product?
- Which steps of the process would ensure removal of undesirable substances unnecessary for food production (e.g. growth factors, antimicrobials)?
    - Cryo-preservants, antibiotics, and other substances might be added during the process (process inputs)
    - Growth media components and other residues might remain in final product
- Could the presence of components inducing cell differentiation impact behaviour of cells and activate dormant expression pathways?

Issues related to bioreactors, culture media and their components (2)

- Regarding bioreactors, could scaling up with cost reduction introduce new hazards/risks (eg recycling input materials)?
    - Growth factor safety is a new theme in food safety
    - Bioaccumulation of compounds (e.g. animal growth serum and alternatives)
- How is microbial contamination monitored and prevented? Are antimicrobials used? What are alternatives?
    - Microbial contamination […]

Issues related to nutritional value and information (1)

Key questions:

- Which nutrition-related parameters should be addressed? Keeping in mind that differences per se do not necessarily result in a disadvantages for the consumer product, from a nutrition point of view
- Could these new food matrices and their composition (including but not limited to the presence or absence of other components) affect the dietary bioavailability of nutrients and other components present in the produced cell cultured-derived food?

Issues related to nutritional value and information (2)

- Nutritional quality should be evaluated in terms of protein content, fat content, amino acid profile, purine/ pyrimidine contents, like all food products
- Amino acid profile should be investigated, because it is possibly affected by different extracellular matrix composition, degree of cell differentiation and maturation
- Polysaccharide content (from scaffolds) is also relevant to be analysed
- Vitamin B12, iron, and other nutrients will be lacking compared with traditional meat and may need to be added at specific stages of the process before harvesting the biomass.
- "The bioavailability of nutrients might not be that different" vs "composition and matrices can affect bioavailability"
- Oxalic acid, trypsin inhibitors, and hydrocyanic acid are to be tested (antinutrients)
- All nutrition-related parameters that are used for classic meat products should be analyzed for these products too

Issues related to scaffolding structures-properties and types (1)

- When present in the final product and subsequently cooked by the consumers, could this lead to the formation of substances of potential concern to human health? In the case of auto-dissolvable scaffolds, which would be the food safety impact of any potential residues in the final product?
- When re-usable scaffolds are used, how could the migration of contact material actually impact the composition of the harvested biomass?
- How investigating the composition and behaviour of scaffolds under various steps and conditions (e.g., sterilisation process in the bioreactor, culturing, boiling, grilling) would contribute to investigating safety aspects, including toxicity and allergenicity?

Issues related to toxicology and allergenicity aspects (1)

- Can a detailed description of the manufacturing process, accompanied by a thorough characterisation of the composition compensate for not performing all the toxicological studies indicated in EFSA's tiered toxicity approach? Which toxicity studies (e.g., genotoxicity, read-across or other in vitro/in silico tests) might be more appropriate and on which production system components (harvested biomass, culture media etc.)?
    - A comprehensive compositional characterization of the components/materials used and of the final product could potentially mitigate the need for 90-day toxicological study.
    - Untargeted analyses (-omics) of the media after harvesting the biomass could help to understand further the toxicological properties of the production process (components, materials, by-products). The implementation of such analyses is currently challenging.

Issues related to toxicology and allergenicity aspects (2)

- Considering that the environment of the cultured cells and their state of differentiation differ from that of the cells comprised in meat, which methods could be used to elucidate the presence of proteins and their allergenicity in cell culture-derived food?
    - Allergenicity could be caused by:
        - new proteins produced (different genes expressed)
        - components
        - scaffolds
    - In silico approaches could be informative towards allergenicity prediction
    - Allergens not linked to conventional animal products may be present (but consumers, would not expect them).
- How could data derived from Omics and other New Approach Methodologies (NAMs) contribute to the toxicological and allergenicity assessment of cell culture-derived foods?

Relevant literature

- An official EFSA colloquium report will be available by the end of summer.
- For a more international view on the safety and potential hazard from cell cultured-derived food and ingredients, an WHO/FAO study have been published and available on-line
- WHO/FAO report is available here:
    - https://www.fao.org/documents/card/en/c/cc4855en
    - 132-page report relating to case studies, regulatory landscape across the globe, safety and risk analysis, among other topics
    - Section 4 details hazards related to cell-culture derived foods