



Food and Agriculture
Organization of the
United Nations



World Health
Organization

FOOD SAFETY ASPECTS OF CELL-BASED FOOD





FOOD SAFETY ASPECTS OF
CELL-BASED FOOD

Food and Agriculture Organization of the United Nations
World Health Organization
Rome, 2023

Required citation:

FAO & WHO. 2023. *Food safety aspects of cell-based food*. Rome. <https://doi.org/10.4060/cc4855en>

The designations employed and the presentation of material in this information product do not imply the expression of any opinion whatsoever on the part of the Food and Agriculture Organization of the United Nations (FAO) or the World Health Organization (WHO) concerning the legal or development status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. The mention of specific companies or products of manufacturers, whether or not these have been patented, does not imply that these have been endorsed or recommended by FAO or WHO in preference to others of a similar nature that are not mentioned.

The views expressed in this information product are those of the author(s) and do not necessarily reflect the views or policies of FAO or WHO.

ISBN (FAO) 978-92-5-137723-9 (print)

ISBN (WHO) 978-92-4-007094-3 (electronic version)

ISBN (WHO) 978-92-4-007095-0 (print version)

© FAO and WHO, 2023



Some rights reserved. This work is made available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo/legalcode>).

Under the terms of this licence, this work may be copied, redistributed and adapted for non-commercial purposes, provided that the work is appropriately cited. In any use of this work, there should be no suggestion that FAO or WHO endorses any specific organization, products or services. The use of the FAO or WHO logo is not permitted. If the work is adapted, then it must be licensed under the same or equivalent Creative Commons licence. If a translation of this work is created, it must include the following disclaimer along with the required citation: "This translation was not created by the Food and Agriculture Organization of the United Nations (FAO) or the World Health Organization (WHO). Neither FAO nor WHO is responsible for the content or accuracy of this translation. The original English edition shall be the authoritative edition.

Disputes arising under the licence that cannot be settled amicably will be resolved by mediation and arbitration as described in Article 8 of the licence except as otherwise provided herein. The applicable mediation rules will be the mediation rules of the World Intellectual Property Organization <http://www.wipo.int/amc/en/mediation/rules> and any arbitration will be conducted in accordance with the Arbitration Rules of the United Nations Commission on International Trade Law (UNCITRAL).

Third-party materials. Users wishing to reuse material from this work that is attributed to a third party, such as tables, figures or images, are responsible for determining whether permission is needed for that reuse and for obtaining permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

Sales, rights and licensing. FAO information products are available on the FAO website (www.fao.org/publications) and can be purchased through publications-sales@fao.org. Requests for commercial use should be submitted via: www.fao.org/contact-us/licence-request. Queries regarding rights and licensing should be submitted to: copyright@fao.org.

CONTENTS

ACKNOWLEDGEMENTS	vii
ABBREVIATIONS AND ACRONYMS	viii
EXECUTIVE SUMMARY	ix
A. INTRODUCTION	1
1. Background	1
2. Working terminologies	3
3. Objectives and target audience	3
4. Scope of this document	3
5. Document composition	3
B. TECHNICAL BACKGROUND ISSUES	4
1. Terminologies	4
1.1. Introduction	4
1.2. Literature synthesis results	5
1.3. Impact of the terminologies	9
1.4. Discussion	17
2. Generic understanding of production processes	18
2.1. Introduction	18
2.2. Literature synthesis results	18
2.3. Discussion	28
3. Regulatory frameworks	29
3.1. Introduction	29
3.2. Literature synthesis results	30
3.3. Discussion	38
C. COUNTRY CASE STUDIES	40
1. Israel – country contexts	40
1.1. Terminology	40
1.2. Current status	40
1.3. Regulatory framework	42
1.4. Food safety assessment	47
1.5. Other key considerations outside food safety	48
1.6. Discussion	51

2. Qatar – country context	52
2.1. Terminology	52
2.2. Current status	52
2.3. Regulatory framework	52
2.4. Food safety assessment	58
2.5. Other key considerations outside food safety	60
2.6. Discussion	61
3. Singapore – country context	62
3.1. Terminology	62
3.2. Current status	62
3.3. Regulatory framework	62
3.4. Food safety assessment	67
3.5. Other key considerations outside food safety	70
3.6. Discussion	71
D. FOOD SAFETY HAZARD IDENTIFICATION	72
1. Overview of the Expert Consultation	72
2. Technical Panel experts and resource people	73
3. Expert Consultation methodologies	74
3.1. Approach for the hazard identification	74
3.2. Approach for developing practical guide for relevant communication	75
4. Results of the Expert Consultation	76
4.1. Overview	76
4.2. Hazard tables by four production stages	76
4.3. Explanations about the identified hazards	99
4.4. Concerns not included in the scope of hazard identification	110
4.5. Food safety communication and building consumer trusts	112
4.6. Special considerations on terminologies	116
E. CONCLUSIONS AND A WAY FORWARD	118
REFERENCES	120

BOXES, FIGURES AND TABLES

Boxes

Box 1.	A generic overview of the cell-based food production process	19
Box 2.	Cell sourcing and isolation of chicken and bovine muscle satellite cells	20
Box 3.	Cell sourcing and fluorescence-activated cell sorting to enrich bovine muscle satellite cells	21
Box 4.	Cell harvesting scenarios in cell-based food production	24

Figures

Figure 1.	Relative share of the synonyms of “cell-based” meat modifiers	7
Figure 2a.	The number of mentions of various terms for the period 2010–2021	8
Figure 2b.	Relative share of the various synonyms	8
Figure 3.	Product packaging shown to participants in the study	11
Figure 4.	Flow diagram for the sourcing and isolation of cultured muscle satellite cells	20
Figure 5.	Examples of potential food safety hazards and concerns at different phases of cell-based food production	28
Figure 6.	Global investments in cell-based food products in 2021	41
Figure 7.	Regulatory agencies and ministerial offices that may be involved in various stages of a cell-based food start-up company up to and including pre-market approval and issuing the required licences for commercial manufacturing	42
Figure 8.	Approval process for novel foods in Israel	45
Figure 9.	Summary of the food safety regulatory competent authority agencies in Qatar	53
Figure 10.	Process of seeking the Singapore Food Agency’s pre-market approval for cultured meat	65
Figure 11.	Generic components of food safety risk analysis paradigm	74
Figure 12.	Four stages of the cell-based food production	76

Tables

Table 1.	Synonyms of modifier terms for animal “cell-based” food products and their common use in professional sectors	5
Table 2.	Studies on modifier terminologies for cell-based food products, their preferred use and associated attributes	14
Table 3.	A generic map of potential hazards/concerns in production processes	25
Table 4.	Developments in different countries relevant for cell-based food products and their safety	31
Table 5.	Hazards identified by the Technical Panel for the cell sourcing stage	77
Table 6.	Hazards identified by the Technical Panel for the production stage	85
Table 7.	Hazards identified by the Technical Panel for the harvesting stage	91
Table 8.	Hazards identified by the Technical Panel for the processing stage	95



FOOD SAFETY ASPECTS OF
CELL-BASED FOOD

ACKNOWLEDGEMENTS

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) would like to express their appreciation to the many people who provided advice and guidance during the preparation of this document. It was prepared for FAO and WHO, and the development process of the document was coordinated by Masami Takeuchi (FAO) in collaboration with FAO and WHO colleagues under the overall guidance of Markus Lipp (FAO). This publication has been published as a joint publication of FAO and WHO, while the earlier chapters were initially drafted by various experts under the oversight of FAO. Technical contributions provided by Juliana De Oliveira Mota (WHO) and Moez Sanaa (WHO) throughout the process are herewith acknowledged.

Section B was authored by Mark Sturme and Gijs Kleter, Wageningen Food Safety Research, the Netherlands. Technical reviews were conducted by various international experts, namely Ousama Abubaker Abushahma, Joshua Ayers, Laura Braden, Stan Chan Siew Heng, Kern Rei Chng, Jonatan Darr, Breanna Duffy, Jeremiah Fasano, Antonio Fernandez, William Hallman, Ziva Hamama, Melissa Hammar, Natsuo Komoto, Teng Yong Low, Paul Mozdziaik, Rick Mumford, Glen Neal, Kimberly Ong, Atiq Rehman, Yadira Tejeda Saldana, Jo Anne Shatkin, Elliot Swartz, Mehdi Triki, Hanna Tuomisto, Ruth Willis and Johnny Yeung Chun Yin. Technical and editorial inputs were provided by various FAO colleagues and technical editing was provided by Jennifer Parkinson.

For the Section C, various government officials and experts have contributed to the country case studies and the following individuals have authored each chapter (alphabetical order).

- C-1 (Israel): Jonatan Darr, Ziva Hamama, Joseph Haskin, Yogev Magen and Shay Reicher
- C-2 (Qatar): Ousama Abubaker Abushahma, Irshad Ahmed Abdul Samad, Hend Ali Al-Tamimi and Mehdi Triki
- C-3 (Singapore): Joanne Chan Sheot Harn, Angela Li, Teng Yong Low, Kern Rei Chng, Johnny Yeung Chun Yin, Stan Chan Siew Heng, and How Chee Ong

Technical reviews for the country case studies were provided by various international experts who have participated in the relevant FAO initiative in the Technical Working Group, namely: Amie Adkin, Joshua Ayers, Darren Cutts, Jeremiah Fasano, Melissa Hammar, Rick Mumford, Glen Neal, Matthew O'Mullane and Atiq Rehman. The authors of each country case have also provided technical reviews on cases from other countries. Technical and editorial inputs on the country case studies were provided by various FAO colleagues including Shan Chen and Markus Lipp, and technical editing was provided by Jeannie Marshall.

Section D was developed based on the results of the Expert Consultation and all Technical Panel members have made substantial technical contributions to draft and review each section. Various FAO colleagues, including Maura DiMartino, Vittorio Fattori, and Keya Mukherjee, several Technical Working Group members and FAO experts have provided both technical and editorial contributions. In particular, significant contributions to the final text of the documents provided by Jeffrey Farber are gratefully acknowledged.

ABBREVIATIONS AND ACRONYMS

AMPS	Association for Meat, Poultry and Seafood Innovation
ANPR	Advance Notice of Proposed Rulemaking
CEPA	Canadian Environmental Protection Act
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
FBS	fetal bovine serum
FDA	Food and Drug Administration
FRESH	Future Ready Food Safety Hub
FSANZ	Food Standards Australia New Zealand
FSEH	Department of Food Safety and Environmental Health
FSIS	Food Safety and Inspection Service of the United States
GAP	good agricultural practices
GCC	Gulf Cooperation Council
GCCP	good cell culture practices
GHP	good hygiene practices
GLP	good laboratory practices
GM	genetically modified
GMO	genetically modified organism
GMP	good manufacturing practices
GRAS	generally recognized as safe
GSO	Gulf Standardization Organization
HACCP	hazard analysis and critical control points
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MME	Ministry of Municipality and Environment
MOCI	Ministry of Commerce and Industry
MOH	Ministry of Health
MOPH	Ministry of Public Health
NFS	National Food Service
NSNR	New Substances Notification Regulations
OECD	Organisation for Economic Co-operation and Development
QS	Qatar General Organization for Standards and Metrology
R&D	research and development
SD	standard deviation
SFA	Singapore Food Agency
USDA	United States Department of Agriculture
USDA-FSIS	United States Department of Agriculture's Food Safety and Inspection Service
US FDA	United States Food and Drug Administration
WHO	World Health Organization

EXECUTIVE SUMMARY

Animal-based meat production has evolved over thousands of years to meet the demand for safe and affordable sources of protein. Cell-based food production, which is the field of growing animal agricultural products directly from cell cultures, has been explored as an alleged sustainable alternative to the conventional livestock agricultural system. As commercial cell-based food production continues to expand, the urgency increases to address one of the most important questions of consumers, the question of food safety. Thus, the Food and Agriculture Organization of the United Nations (FAO), in collaboration with the World Health Organization (WHO), has developed the present document to engage with respective Members and relevant stakeholders by proactively sharing the current knowledge to identify concrete ways to inform consumers and all other stakeholders about the food safety considerations for cell-based food products.

This document includes a literature synthesis of relevant terminology issues, principles of cell-based food production processes and the global landscape of regulatory frameworks for cell-based food production. Case studies from Israel, Qatar and Singapore have been included to highlight different scopes, structures and contexts surrounding their regulatory frameworks for cell-based food. The results of the FAO-led Expert Consultation, where comprehensive food safety hazard identification was conducted, form the core of the document and the identified hazards are summarized with causal-chain examples.

Hazard identification is the first step of the formal risk assessment process. During the Expert Consultation, all potential hazards were discussed in the four stages of the cell-based food production, namely: 1) cell-sourcing; 2) cell growth and production; 3) cell harvesting; and 4) food processing. Experts agreed that while many hazards are already well known and existing equally as well in conventionally produced food, the focus may need to be put on the specific materials, inputs, ingredients (including potential allergens), and equipment that are more unique to cell-based food production.

While the list of hazards identified forms a strong basis for the next steps, more data generation and sharing at the global level are essential to create an atmosphere of openness and trust that will enable the positive engagement of all stakeholders. International collaborative efforts would benefit various food safety competent authorities, particularly those in low- and middle-income countries, to employ an evidence-based approach to prepare any necessary regulatory actions.

The way forward will consist of continuing to invest in research and development in order to understand whether the alleged benefits in increased sustainability can be realized. In this regard, it will be important to closely observe as to what extent, if any, cell-based foods result in differences from conventionally produced foods.

Keywords: food safety, cell-based food, cell culturing, cultured meat, cultivated meat, terminology, nomenclature, production process, regulatory framework, risk analysis, hazard identification, risk assessment, expert consultation, food standards, Codex Alimentarius

A. INTRODUCTION

1. Background

The world is facing tremendous food challenges as estimates are that our growing world population will reach 9–11 billion by 2050. In concert with this, as the global demand for proteins grows and because of potential health and environmental concerns, more consumers are looking to reduce their consumption of animal origin products. The increasing recognition of the challenges related to feeding a growing global population, while at the same time producing food more sustainably, is spurring food system innovations which are shaping our future agrifood landscape.

For example, many in the food sector are looking for opportunities to expand the sources of alternative proteins that can be both environmentally sustainable and nutritionally sound. In terms of traditional meat/protein production, there are also other mitigating factors such as there being a limited amount of global arable land as well as real and unknown threats due to climate change. Cell-based food production, or cellular agriculture, which is the field of growing animal agricultural products directly from cell cultures instead of using livestock, and which has been referred to as cell-based foods, cell-cultured foods and cultivated meat, has been explored as a potentially sustainable option to complement the conventional livestock agricultural system. Some of the cell-based food products are already under various stages of development across the world, making it critical to objectively assess the benefits they might bring, as well as any risks associated with them - including food safety and quality concerns.

Since the initial studies in the early 2000s, methodologies for cell-based food production, have been well characterized and have moved from laboratories to production facilities. In 2013, the first beef burger produced through this technology was presented to the world. In December 2020, the first cell-based chicken nuggets were approved in Singapore. In November 2022, the United States Food and Drug Administration (US FDA) completed its first pre-market consultation for human food (chicken) made using animal cell culture technology. The voluntary pre-market consultation is not an approval process; however, it means that after analyzing the data submitted by the company, the US FDA states that it has no further questions at this time about the safety conclusions. Currently, there are more than 100 start-ups developing various cell-based food products around the world. This commercial landscape is expanding very quickly, with many different types of products and commodities such as various meats, poultry, fish, aquatic products, dairy and eggs in the pipeline for future commercialization.

One of the most important questions consumers would raise is food safety. In addition to safety, there are several other legitimate issues that are important to consider, such as ethical issues, environmental considerations, animal welfare, consumer preference/acceptance, production cost, prices of the end products, as well as regulatory requirements such as approval mechanisms and labelling rules. As cell-based food production may involve a set of relatively new technologies, techniques and/or production steps, it is likely that many countries are currently thinking about and would consider implementing a regulatory process that addresses all the relevant issues, before such products become available in the marketplace.

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) consider that the time is ripe to initiate the discussion on the potential benefits and drawbacks of cell-based food production. It is important for FAO/WHO as well as the respective Members, to engage in the proactive sharing of relevant knowledge and information among various stakeholders to identify concrete ways to assure the safety of cell-based food products for consumers.

The intention of the present FAO/WHO work on cell-based food is to capture the key food safety issues in a timely manner, before the products can become widely available in the global market, so that competent authorities,

particularly those in low- and middle-income countries, will be equipped with up-to-date information and scientific knowledge related to cell-based food production, to consider potentially important regulatory actions. This document, extensively studying food safety aspects of cell-based food, does not have an intention to endorse the technology. It is not FAO/WHO's role to promote any types of food products or production methodologies, however, it is not FAO/WHO's intention to block any relevant technological developments and innovations. FAO and WHO support their Members to assure any food, no matter how it is produced, is safe for the consumer.

2. Working terminologies

Throughout this document, the terms “cell-based food”, “cell-based food products” and “cell-based food production” are used as a set of working terminologies to indicate the products or production processes involving culturing cells isolated from animals.

A literature synthesis was conducted on various relevant terminologies (see [Section B-1](#)) and the results showed that while some different preferences exist among different sectors, the term “cell-based food” was found to be less confusing, conveniently overarching and generally well-accepted by consumers. However, there is no term that is 100 percent scientifically correct. In theory, any organism made of cells can be described as “cell-based”, therefore, it does not automatically distinguish the technology to grow edible tissues from “cells”. Also, the term “cell-based” has never been used for food, therefore some food business operators may prefer not to use the term. The terms “cultured” and “cultivated” can be confusing as they are often used in the aquaculture sector to indicate farmed fish and fisheries products. The term “cellular agriculture” can be considered too general as it may include the topic of plant cell culturing or fermentation, which can use a wide variety of methodologies and techniques. There has also been a challenge identified on the use of commodity names such as “meat”, “chicken” or “fish” together within the terminologies (see [Section D-4.6.3](#)), thus the consistent use of “food” and “food products” has been maintained in the document.

Nomenclature can have a significant impact on consumer perception, marketing efforts and relevant regulatory actions such as labelling. While the present document uses the term “cell-based food”, experts (see [Section D-2](#) for more details about the Technical Panel experts) have suggested to have good studies before considering international harmonization of the terminology. While it is ideal to have an internationally harmonized set of terminologies, experts have indicated that it may be more important to start with recommending a set of key elements for the food safety competent authorities to consider and use within their cultural and geographical contexts as well as their languages. The experts also suggested not to use a direct translation of the English terms, without considering the impact of such terms in the local language.

3. Objectives and target audience

The primary objective of this document is to provide readers with up-to-date technical knowledge on the multidisciplinary topic of cell-based food production, with a focus on the food safety aspects, through the process of literature synthesis and expert elicitation.

Overarching specific objectives include:

1. to summarize the relevant technical matters for national food safety competent authorities, particularly those in low- and middle-income countries, to consider their potentially required actions;
2. to share information on technical knowledge and good practices among competent authorities on various regulatory frameworks on cell-based foods to learn from each other;
3. to summarize the results of the Expert Consultation where food safety hazard identification for cell-based food products has been conducted; and
4. to identify the needs for possible follow-up actions by international organizations like FAO/WHO. This will facilitate global discussions and action planning with the partner agencies and stakeholders at the global level.

More specific objectives include reviewing and describing information so that national food safety competent authorities can:

1. understand how various countries and organizations are describing and using terminology related to cell-based foods, so that this information can serve as a basis to support stakeholders worldwide in making informed decisions on selecting those cell-based food terminologies that could be used in communications or accepted in legislation on cell-based food products;
2. understand the various technologies that are currently being used to produce cell-based foods and the potential hazards that have been identified;
3. understand the results of food safety hazard identification conducted by the Technical Panel and initiate generation of relevant data for the next steps of risk assessment; and
4. learn about the current regulatory thinking and developments that currently exist for cell-based foods in different countries and jurisdictions.

While the primary target audience of this document was set for national food safety competent authorities, the global community of scientists, developers, the cell-based food industry as well as academics doing research in the area of cell-based food production may benefit from reading this document.

4. Scope of this document

The scope of this document is strictly technical and prioritizes any potential food safety issues associated with cell-based food products. The scope includes examining what are the existing terminologies that are now being used in the field, providing an overview of the scientific literature on the cell-based food production technologies currently being developed along with any potential hazards that have been identified, as well as discussing the current regulatory developments that apply for cell-based foods in different countries.

It is recognized that there are several other issues with respect to cell-based foods that are important to consider, including ethical issues, environmental considerations, animal welfare, consumer preference/acceptance, nutrition aspects, production costs, prices of the end products, and regulatory requirements such as approval mechanisms and labelling rules. Although these issues are critical in moving the whole area of cell-based foods forward, they are not within the scope of this document, however, they may be the subject of future FAO and/or WHO consultations.

In addition, besides cell-based foods, there are several other alternative protein sources that fall under the area of “new foods and production systems”, a field that is growing fast and it is very likely to grow even more so over time. Some of the more prominent topics covered under this category include seaweed, microalgae, edible insects, plant-based protein alternatives and 3-D printed foods. However, these latter potential alternative food protein sources are also not included within the scope of this document.

5. Document composition

This document has 5 sections from A to E. **Section A** is the present introductory chapter, and **Section B** consists of three technical background issues namely 1) terminologies, 2) production process and 3) regulatory frameworks. **Section C** has three country case studies from Israel, Qatar and Singapore. **Section D** summarizes the results of an Expert Consultation meeting where potential food safety hazards for cell-based food production have been identified by the Technical Panel experts and resource people. **Section E** concludes the document with a way forward.

B. TECHNICAL BACKGROUND ISSUES

1. Terminologies

1.1. Introduction

The increasing global demand for animal-sourced protein adds to the existing pressure on ecosystems and biodiversity (FAO, 2018). Intensifying animal production may also threaten broader sustainability objectives, such as climate change and public health, resulting in trade-offs in various aspects of environmental protection, food security and animal welfare (FAO, 2019, Henchion *et al.*, 2021, OECD, 2021). These factors have triggered research efforts for developing more sustainable ways of producing animal meat as well as a research focus on a “protein transition” wherein consumption of animal protein will be at least partially replaced by alternative protein sources, such as from plants and microorganisms but also *in vitro* produced animal protein (Aiking and de Boer, 2020), in order to accommodate the increased demand for protein and assure global food security.

One of the technological developments that could produce analogues of animal proteins without slaughtering animals is via *in vitro* cultivation of animal cells on a large scale, which could then be processed into products that are substantially equivalent to conventional meat. Such products are often called “cell-based”, “cultured” or “cultivated” meat, and currently there are several terms in use to define this type of products around the globe.

While research in this area has been ongoing since the early 2000s, the development of the products was presented to the general public in 2013, when researchers from the Netherlands demonstrated the first product describing it as a “lab-grown” beef burger at a press conference in London (BBC News, 2013). In December 2020, so-called “cultured” chicken nuggets became the first commercialized product of its kind, after market approval in Singapore; these particular nuggets are a blend of cultured chicken and plant-based ingredients (Carrington, 2020). On a broader scale, the production of analogues of animal products, such as meat, poultry, seafood, dairy, and eggs produced through cell-based culture techniques has been advancing quickly in the past few years and at least 76 companies have been developing similar products in 22 different countries since 2013 (Byrne, 2021).

Because of the novelty of the cell-based food production process and products, assurance of food safety is one of the main concerns of nutritionists, food technologists, the competent authorities and consumers. In addition, the national competent authorities will have to consider various socioeconomic issues relating to these products, including consumer preference, acceptance, ethical issues, production costs, trade issues and market prices. When there is a need for clear labelling of such products and/or special authorization processes are to be conducted by competent authorities, then appropriate regulatory frameworks need to be adjusted or newly employed, as these products may enter their jurisdictions or appear at the border at any time, via e-commerce for example.

In order to discuss the relevant technical issues about cell-based food production, it is important to use clear and consistent terminologies that can be accepted by all the stakeholders. Terminologies and labels are also an important and direct means of communicating information to consumers (FAO, 2021). However, currently many different terms and labels exist for these types of products in both the scientific literature and public communications, thereby potentially creating confusion. It is therefore important to make an inventory of these terms and their current usage, framing and legal consequences, in order to achieve a consensus on the terminology to use at the global level. This will also contribute to a better understanding of the topic as well as encourage further discussions on cell-based food products in different parts of the world.

To aid the scientific advice activities provided by the Food and Agriculture Organization of the United Nations (FAO), it is essential to use clear terminologies to describe the relevant processes, associated technologies, techniques and products in animal cell-based food production. The chapter focuses on the terminologies used in different sectors and describes the associated issues, by making a systematic inventory of the available scientific literature as well as non-scientific reports and public communications. This overview employed the systematic-review methodology, and it does not include any political nor opinion-based views. The aim of the chapter is not to define the relevant terminologies but to simply collect the existing ones with the attributed analyses, so that subject-matter experts and/or policymakers at the national level can use this overview as a reference to make informed decisions.

1.2. Literature synthesis results

1.2.1. Modifiers found in various literature

A list of the synonyms used for cell-based food products, such as cell-based meat and seafood products, and their use by different professional sectors is provided in **Table 1** based on the outcomes of several consumer and industry studies on the perception, acceptance and preference for terminologies for the modifier part (e.g. “cultured”) of the terminologies.

Table 1. Synonyms of modifier terms for animal “cell-based” food products and their common use in professional sectors

Modifier term ^a	Sector			
	Authorities	Industry and developers	Academia	Media
animal-free			X	X
artificial			X	X
cell-based	X	X	X	X
cell-cultivated ^b			X	
cell-cultured	X	X	X	X
cellular			X	X
clean		X		X
cruelty-free				X
cultivated	X	X	X	X
cultured	X	X	X	X
fake			X	X
Frankenmeat				X
healthy		X		X
imitation				X
<i>in vitro</i>			X	X
lab-grown			X	X
made				X
Meat 2.0 ^c				X
Shmeat				X
slaughter-free				X
synthetic			X	X
test tube				X
vat-grown				X

Notes: a) Based on scientific articles collected from the literature search, grey literature and media; b) Hallman, W. K., Hallman, W. K. II, & Hallman E. E. (2021) Cell-Based, Cell-Cultured, Cell-Cultivated, Cultured, or Cultivated. What is the best name for meat, poultry, and seafood made from the cells of animals? <https://www.biorxiv.org>; c) Meat 2.0 is a term that is used to cover “cell-based” meat, but also plant-based and microbe-based meat replacers.

Source: Authors' own elaboration.

1.2.2. Modifier terminologies used by authorities

The use of terminologies by authorities such as governmental institutions and regulatory bodies is often expected to be guided by legally accepted terms. Besides, for example, Singapore and the European Union, regulatory bodies in most countries have not yet ruled as to what existing legislation cell-based food products fall under, or which specific terms for labelling of cell-based food products are to be used. As of February 2022, the Singapore Food Agency (SFA) is the only regulatory body that has implemented a specific section for cell-based food products in their “Requirements for the Safety Assessment of Novel Foods” document (SFA, 2021a). This document uses the term “cultured” meat, but this is not the only term allowed, as the SFA has indicated that product package labelling will require qualifying terms that clearly communicate the nature of “cultured” meat food products to consumers so that they can make informed choices. These terms may also include, for example, “cultured”, “cultivated” and “cell-based” (SFA, 2021b). Singapore has also published general food labelling guidelines that advise against the use of claims that would cast doubt on the safety of other foods or imply that a particular food is safer than other similar food, and these would also apply to cell-based food (SFA, 2021a).

In the United States, the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture (USDA) published in September 2021 an Advance Notice of Proposed Rulemaking (ANPR) in which it requests comments for “the labelling of meat and poultry products comprised of or containing cultured cells derived from animals” (USDA-FSIS, 2021). Similarly, the United States Food and Drug Administration (US FDA), which has labelling authority for cultured fish and seafood cell products, published in October 2020 a “Request for Information” in which it calls for comments for “the labelling of foods comprised of or containing cultured seafood cells.” (FDA, 2020). The FDA intends to use the information and data resulting from this notice to determine what type(s) of actions, if any, the agency should take to ensure that these foods are properly labelled. The FSIS and the FDA have agreed to develop joint principles for product labelling and claims to ensure that products are labelled consistently and transparently. Although the FSIS’s ANPR makes use of the term “cultured” meat, the US authorities are still in the process of defining the actual food labels that will be allowed in the future, which will impact the terms to be used by these authorities in the future. It is also worth considering that the authorities’ labelling regulations may have preference for terms that describe the process the food has undergone.

1.2.3. Modifier terminologies used by industry and developers

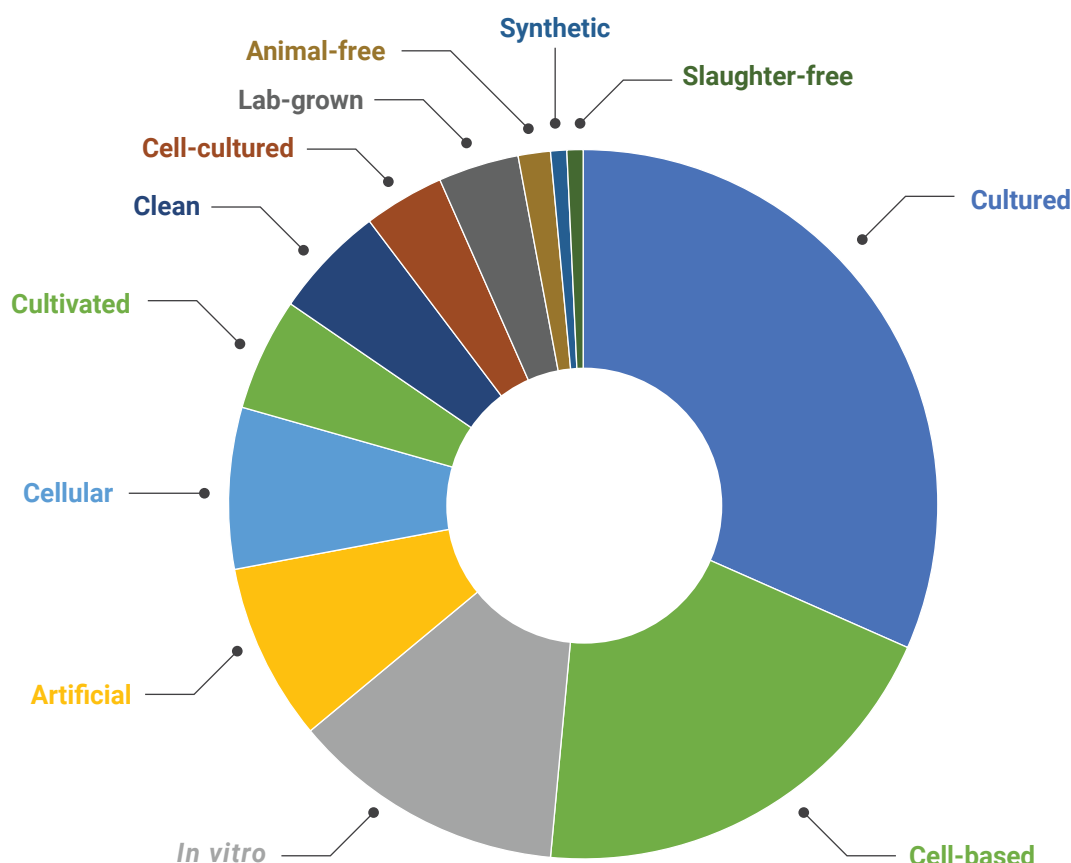
In September 2021, a focus group surveyed the Chief Executive Officers (CEOs) of 44 cell-based food companies globally about their preferred nomenclature for their products. Seventy five percent of the companies were found to use the modifier “cultivated”, 20 percent the concept “cultured” meat, and one company (~2 percent) “cell-based”. Several quotes from the interviewed CEOs appear to point to a shared view that the use of “cultivated” allows us to differentiate from other products and at the same time appeal to consumers and be amenable to consumer education. The use of “cultivated” might therefore align the industry viewpoint for the modifier term (Byrne, 2021). This survey indicates an increase in adoption of the term “cultivated” since a study in 2020, where this term was found to be used in 45 percent of relevant websites and promotional material from the cell-based food industry. This is partially in line with the recommendation from the American “cultured” meat industry trade group Association for Meat, Poultry and Seafood Innovation (AMPS) to use either “cultured”, “cultivated” or “cell-based” and in line with the recommendation by the cell-based meat industries based on the outcomes of the consumer study by Szejda *et al.* (2019). Following various post-hoc stakeholder meetings, the study executor and stakeholders chose the term “cultivated” meat to go forward with. Towards this end, a communication strategy was devised, where an analogy was drawn between cultivating meat and growing plants in a greenhouse.

In addition, the use of cultivation-related language, such as “cultivator” for the reaction vessel in which cells are grown, was considered to expand the narrative to engage people with the concept of meat cultivation (Szejda *et al.*, 2019). It is important to note that the terminologies used or preferred by industry are subject to change and indicates the need to harmonize terminologies in the industrial sector, which might come from legal approval of specific terms by the authorities.

1.2.4. Modifier terminologies used in academic research

The scientific community uses a wide variety of terminologies (Table 1). However, no studies have been performed to analyze the preferred modifier terminologies among scientists and, therefore, a consensus on accepted terminologies does not exist. Based on the scientific articles (N¹=144) collected from the literature search on this topic for the period 2013–2022, the most used terms are “cultured” (N=43) and “cell-based” (N=27), followed by “*in vitro*” (N=17), “artificial” (N=11) and “cellular” (N=10), while other modifier terms appear to be less commonly used (Figure 1).

Figure 1. Relative share of the synonyms of “cell-based” meat modifiers



Note: Terms used in the titles of scientific articles collected from the literature search for the years 2013–2021 (as mentioned in Table 1).

Source: Authors' own elaboration.

1.2.5. Modifier terminologies used by the media and others

Using the News on the Web corpus (Davies, 2016) via the website English-Corpora.org, a large collection of texts was searched through to verify the frequency that “cell-based” meat terms were mentioned in the media between 2010 and 2021 (Figure 2). This showed that media coverage of “cell-based” meat developments has markedly increased in the last 10 years (Figure 2a) and uses a wide variety of synonyms (Figure 2b and Table 1). The most frequently used terms since 2010 were, among others, “cultured” (30 percent), “lab-grown” (19 percent) and “fake” (14 percent) and “clean” (9 percent). It has to be noted that the preferentially used terms in the media have shifted in the last years: while in the initial years, terms such as “*in vitro*”, “cultured” or “clean” meat were often used alongside “cultured” meat, currently other terms are more frequently encountered, such as “cultivated” or “cell-based” meat (Southey, 2021).

¹ N=144 means that the number (N) of scientific articles was 144.

Figure 2a. The number of mentions of various terms for the period 2010–2021

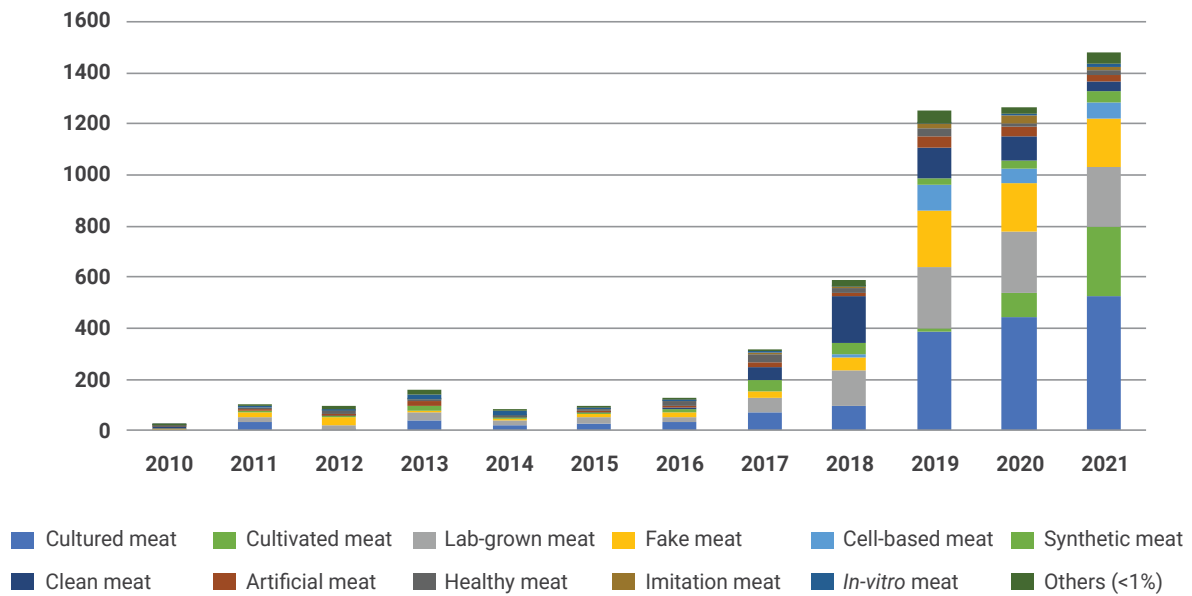
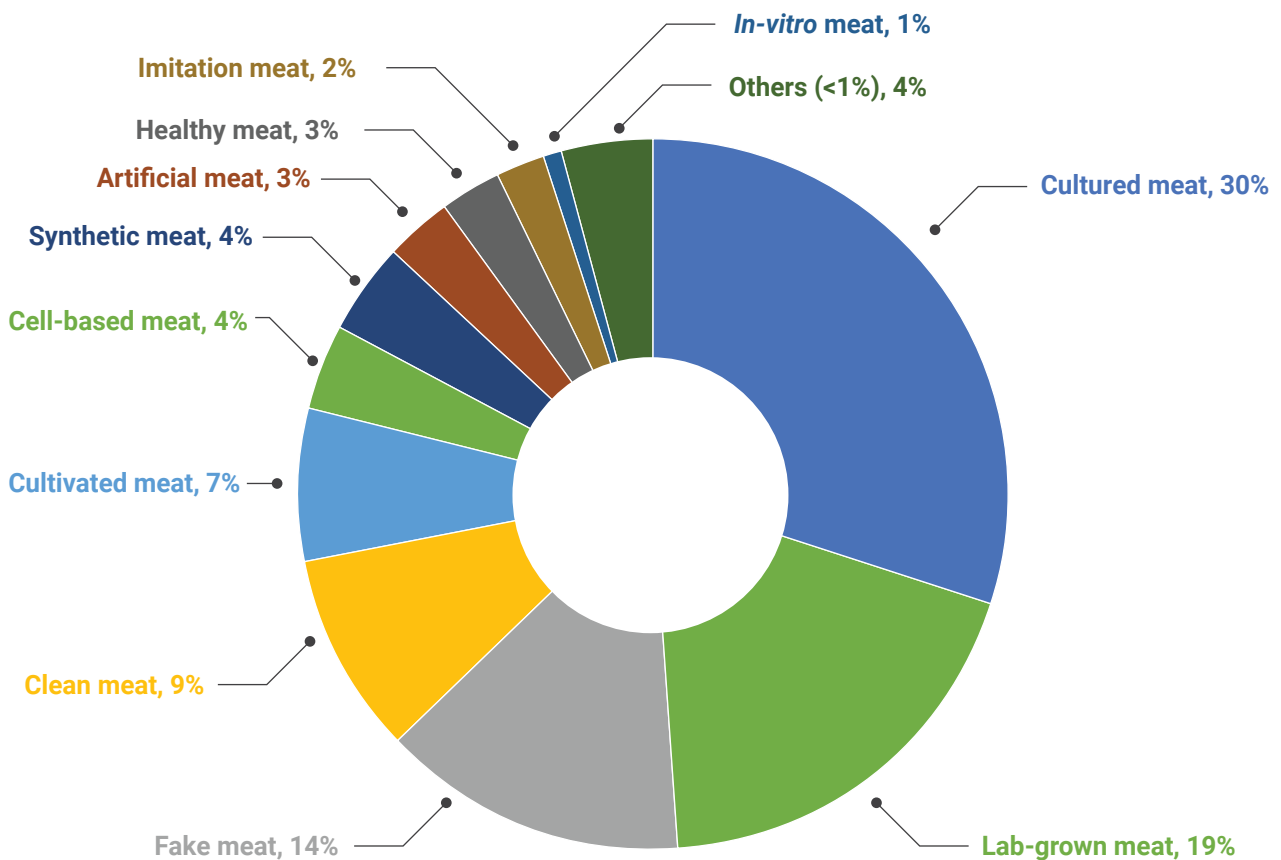


Figure 2b. Relative share of the various synonyms



Note: "fake meat" and "imitation meat" were also used for other meat analogue types; "healthy meat" occurred in many unrelated contexts

Source: Davies, M. 2016. *Corpus of News on the Web (NOW)*. <https://www.english-corpora.org/now/>

1.3. Impact of the terminologies

1.3.1. Public perception and acceptance of modifier terminologies

Participants in studies on acceptance of cell-based meat and the impact of terminology thereon are mainly from Western countries (United States of America, United Kingdom of Great Britain and Northern Ireland, European Union) with a few exceptions (Brazil, China). Studies carried out with other languages are not found with the current strategy. These are actually forward-looking studies because the products had not yet been launched on the markets at the time of study. Singapore might offer the opportunity to gauge consumer perception and acceptance in practice as “cultured” chicken products are already marketed and available in restaurants. Singapore’s Agency for Science Technology and Research has also put out articles in local media outlets as early as 2019 with the term “cultured meat”, which could have helped consumers become more familiar with both the terminology and technology around “cultured meat”. Singapore, as a high-income and high-tech country with a diverse ethnic population, might not be representative of other countries in the region, however.

In the introduction to their study, Bryant and Barnett (2019) provide an overview of the various terms for cell-based food encountered in the scientific literature and beyond. They also point out the importance of names and labels that directly or indirectly impact consumers’ perceptions and appeal of the product. These authors also note that certain widely used names, such as “artificial meat” or “synthetic meat”, may indirectly suggest vague and confusing concepts of “natural meat” to be associated with conventional meat. In the same study, the authors analyzed consumer perceptions of four concepts in more detail: “animal-free” meat, “clean” meat, “cultured” meat, and “lab-grown” meat. The participants (N=185) in this study made statistically significantly more positive associations with “clean” meat than with the other three concepts. In addition, “clean” meat and “animal-free” meat triggered more positive attitudes than “lab-grown” meat (Bryant and Barnett, 2019). In fact, negative associations arose particularly with “lab-grown” meat, whereas “clean meat” was associated with positive attributes. However, there is a problem with calling the product “clean” meat, as it implies that conventional meat is unclean in some way, which indirectly raises often unsubstantiated negative connotations for conventional meat. The outcomes were considered to prove the importance of *how* “cell-based” meat concepts are named in order to avoid negative perceptions and improve acceptance of these food products.

Possidonio *et al.* (2021) also noted that when the modifier term “lab-grown” was used for meat instead of the term plant-based meat (rather than other modifiers for cell-based meat), Portuguese consumers linked negative attributes to the concept of “cultured” meat more than to that of plant-based meat substitutes. “Lab-grown” meat was also perceived as having the lowest sustainability, the highest price and caloric value of all meat substitutes. The authors hypothesize that, indeed, the use of the term “lab-grown” alone might have evoked images of artificial production environments. In addition, consumer perceptions of the term “lab-grown” meat are affected by how the products are presented. This was supported by the observation that when terms were associated with pictures of the corresponding food products (alone or in a meal), a picture of “lab-grown” meat that was included into a meal markedly increased consumers’ positivity to it on many scores (Possidonio *et al.*, 2021).

In contrast to the findings of Bryant and Barnett (2019), Krings *et al.* (2022) attributed the lower popularity of “clean meat”-based dishes than of conventional meat dishes by consumers from Western countries who were omnivores, but neophobic towards food technology to the perceived lower safety and/or artificiality of “clean meat” dishes (Krings, Dhont and Hodson, 2022). These studies indicate that the choice of the comparators used for “cell-based” meat concepts and the way “cell-based” meat concepts and products are presented (such as a term alone or visualized together with a product) have an influence on consumer perception.

As for Brazil, various large meat-producing companies have indicated their intention to develop and market cell-based meat within the next few years. Regulation on approval and labelling still has to be developed, though, pending the outcomes of research on food hazards (Costa, 2022). Consumer research in Portuguese shows that a significant proportion (>34 percent) of interviewed Brazilian respondents were willing to consume cell-based meat (Bryant and Krelling, 2021; Forte Maiolino Molento *et al.*, 2021). There is variability, though, between interviewees of different age groups and from different urban areas of Brazil when asked if they would consume “meat from cellular agriculture”

(Forte Maiolino Molento *et al.*, 2021). After having been presented texts with one out of four different names for cell-based meat, subjects in another study found “clean meat” to be less descriptive and less distinguishable from conventional meat and plant-based alternatives than “cultivated meat”, “cell-based meat”, and “slaughter-free meat” (Bryant and Krelling, 2021). It should be noted that both these studies were performed using the Portuguese equivalents of the English modifier terms. Bryant *et al.* (2019) did a pre-test among Chinese consumers to rank various potential names for cell-based meat in Mandarin for appeal and descriptiveness. Based on the outcomes, these authors selected the term “purity meat” (similar to “clean meat”), for use in a survey to further study consumer perception.

1.3.2. Language barriers and translation issues

Language-specific perception barriers may also exist for the use of certain terminologies. Direct translation from English may not always be straightforward or might be problematic due to non-familiarity or negative connotations of the translated terms. For example, several respondents to a consumer survey in Japan expressed their dislike of the translation of “cultured” meat into Japanese (*Baiyo-niku*) (CAIC, 2021).

Among ten cell-based meat-related terms submitted to a cross-section of German society in a study survey, “direct meat” (*Direktfleisch* in German) attained the highest scores for appeal, accuracy, and clear differentiation. This term was nonetheless excluded from further study due to its dissimilarity to the English synonyms currently used and the low acceptability among industrial stakeholders (Janat *et al.*, 2020). Similar issues in perception of specific terms might also exist in other languages and should be evaluated before using terms.

Bryant *et al.* (2019) employed back-translation of the related terms and a study questionnaire from English into Mandarin to achieve equivalent meaning. Back-translation entails the translation of a questionnaire into a target language by a bilingual person as a first step. This translated text is subsequently translated back into the source language by another bilingual person who is unaware of the original text. The original text and the second translation can then be compared. Any ambiguities and discrepancies can then be resolved, and the text revised and refined accordingly (Jones, 1998).

1.3.3. Modifier terminologies that are fit for purpose

Hallman and Hallman (2020) extended on the findings by Bryant and Barnett (2019) in their study on possible names for “cultured” seafood products. They noted that past consumer studies had focused on meat, yet that the category of “cultured” seafood products was also at an advanced stage of development. Moreover, previous studies had not addressed the distinguishability between “cultured” and conventional products. In the case of seafood, there is already a need to distinguish products of farmed and wild-caught seafood, and this now needs to be further clarified for the term “cultured” seafood as well.

The authors formulated three additional requirements for a designation for cell-based food products, namely that they 1) are appropriate from the consumers’ point of view; 2) do not disparage one or any other category of foods; and 3) do not raise a response inconsistent with the idea that “cultured” seafood is safe, healthy and nutritious. The term chosen should be able to modify not only seafood but also poultry and meat. Three additional phrases were used for the investigation, including “produced using cellular aquaculture”, “cultivated from the cells of...”, and “grown directly from the cells of...” (Hallman and Hallman, 2020).

All the concepts using the term “cell” were most accurately identified as being neither farm-raised nor caught in the wild, and also scored significantly lower in consumer acceptance than the conventional products (Hallman and Hallman, 2020). All concepts used were equally well identified as products not to be consumed by people who are allergic to seafood. The phrases “cultivated from the cells of...” and “grown directly from the cells of...” were most accurately identified as not being “ocean-caught” or “farm-raised”. They were also somewhat less appetizing (17–18 percent versus 26 percent) than the other concepts and evoked the least positive initial responses. With several others, participants imagined products labelled with these two phrases to be less tasty and less safe to eat as well. They also thought products labelled with the concepts “cell-cultured” and “cultivated from the cells of ...” to be less nutritious than conventionally farmed and wild-caught seafood (Hallman and Hallman, 2020). The authors abandoned “cultivated”, “cultured”, and “produced using cellular aquaculture” due to an apparent misidentification

The outcomes confirmed those of the previous study in that many participants correctly identified both products as not being derived from farm-raised or wild-caught fish, and that they should not be consumed by persons with allergies. For the remaining incorrect identifications, “cell-cultured” was more often associated with farm-raised products than “cell-based”, which was also the case for ocean-caught fish. Moreover, many participants correctly assumed that both products were derived from salmon cells. Initial, subsequent, and overall reactions to “cell-based” were more positive than to “cell-cultured”. Products with both concepts performed equally positive in some respects: consumers considered both somewhat-to-moderately safe to eat, moderately nutritious, slightly good-tasting, and neither natural nor unnatural. “Cell-cultured” was associated more with genetic modification than “cell-based”, while purchasing and tasting intentions were slightly greater for “cell-based” than for “cell-cultured” products (Hallman and Hallman, 2021).

Ong *et al.* (2020) also studied the term “cell-based” meats, reviewing the evolving production and regulatory landscapes for these products. As regards nomenclature, they considered the possibility of adding additional terms implying edibility, healthiness, sustainability and no involvement of animals. While for edibility, the ingredients and production processes used should be proven to be safe, various claims and labelling rules and guidelines may apply to claims of healthiness, sustainability and absence of cruelty to animals. As regards healthiness, depending on the regulatory frameworks, certain claims may be permitted provided that evidence can be provided in support of these claims. The authors considered that reference to “animal-free” might still be controversial as cells from animals will be used as donors in the initial stage, although the use of lines of immortalized cells could further decrease dependency on animals, as does the avoidance of the use of animal-derived additives to the production media (Ong *et al.*, 2020).

Szejda *et al.* (2019), in collaboration with several cell-based food companies, carried out a study in which focus groups (N=27) discussed a narrative for the “cultured” meat presented to them, followed by another study with segmented consumer groups (enthusiasts, sceptics, opponents). They concluded that, for example, the concepts “cultivated” meat and “cultured” meat had the most appeal and were moderately descriptive. “Cell-based” and “cell-cultured” were only somewhat appealing yet scored better on the descriptiveness scale as being moderately to very descriptive. The modifiers “cultivated”, “cultured”, and “cell-based” differentiated moderately and moderately to very much from conventional meat. It was argued that “cultivated” evoked positive responses, considering appeal, neutrality, and descriptiveness criteria, for many of the participants.

1.3.4. Other considerations for terminologies

Allergen labelling

The product noun, such as “salmon” in the collocation “cultured salmon” might impart important information to allergy patients who are allergic to the traditional form of the product from the same animal species (salmon in this example). It is important to ensure that the modifiers do not conceal this, such as in the example “cell-based artificial salmon product” (Lamb, 2018).

In addition, it is also important to consider proper allergen labelling, as cell-based food products can have the same level of risks for allergic reactions as conventional counterparts (Hallman and Hallman, 2020). This will entail the declaration of ingredients (listed on the product label) that may cause hypersensitivities, such as egg, crustaceans, fish, and milk (Codex Alimentarius, 2018). These may then have to be highlighted in bold font, for example, so as to stand out for consumers reading the product label.

Commodity terminologies in the regulatory framework

While no internationally harmonized definition of the term exists and nothing indicates restrictions on the use of any terms, there are potential and significant restrictions in many countries on using commodity terms such as “meat”, “chicken”, “fish”, “milk” and so forth. Cell-based food can be considered as “novel food” in certain jurisdictions (e.g. in the European Union), which may place additional requirements on the terms used and provides an opportunity to define terms, as certain regulatory requirements of “meat” may not apply to this type of product (Seehafer and Bartels, 2019). In the United States of America, new agency regulations for labelling of meat and poultry products derived from animal cells is under consultation in a so-called “advance notice of proposed regulation (ANPR)” (USDA, 2021).

While the ANPR touches upon issues of regulation and safety, it is notable that it also addresses the various aspects identified by the scientific investigations into the impact of naming of these products on acceptance and interpretation accuracy.

The term “cellular agriculture”

As of February 2022, several terms are in use in science, industry and the media, such as “cellular agriculture”, “cellular food technologies”, “cell-based techniques” and “cell-based food production”. The use of these terms is currently dictated by the end user, and no studies have been performed on the perception and acceptance of alternative terms by different social or professional groups.

The term “cellular agriculture” is used by many stakeholders and it indicates the production method that can be used to make acellular or cellular products, where acellular products are made of organic molecules like proteins and fats and contain no cellular or living material in the final product, while cellular products are made of living or once-living cells. For example, acellular animal-sourced foods (like milk proteins or gelatine) are produced without animals through fermentation using microorganisms like yeast or bacteria (often referred to as precision fermentation). In contrast, cellular products are formed by growing cells from a particular animal species and tissue type *in vitro*, followed by assembly of cells on a scaffold to form tissue-like structures and further processing into products (Rischer *et al.*, 2020). The use of the term is also documented in various sources (CAIC, 2021).

However, it should also be noted that for the scientific community, the term “cellular agriculture” encompasses not only the production of cell-based food but also the utilization of cell cultures of a whole variety of host organisms (animals, plants, microorganisms) for the production of agricultural food products rather than production from farmed animals or crops (Mattick, 2018; Rischer *et al.*, 2020).

Table 2 provides a summary of the various studies analyzed in detail examining the impact of terminology on the perception of cell-based meat products by consumers. The results show that “cultivated” was the preferred modifier in 5 studies, while “cultured” and “cell-based” were preferred twice in separate studies and “clean” in one study.

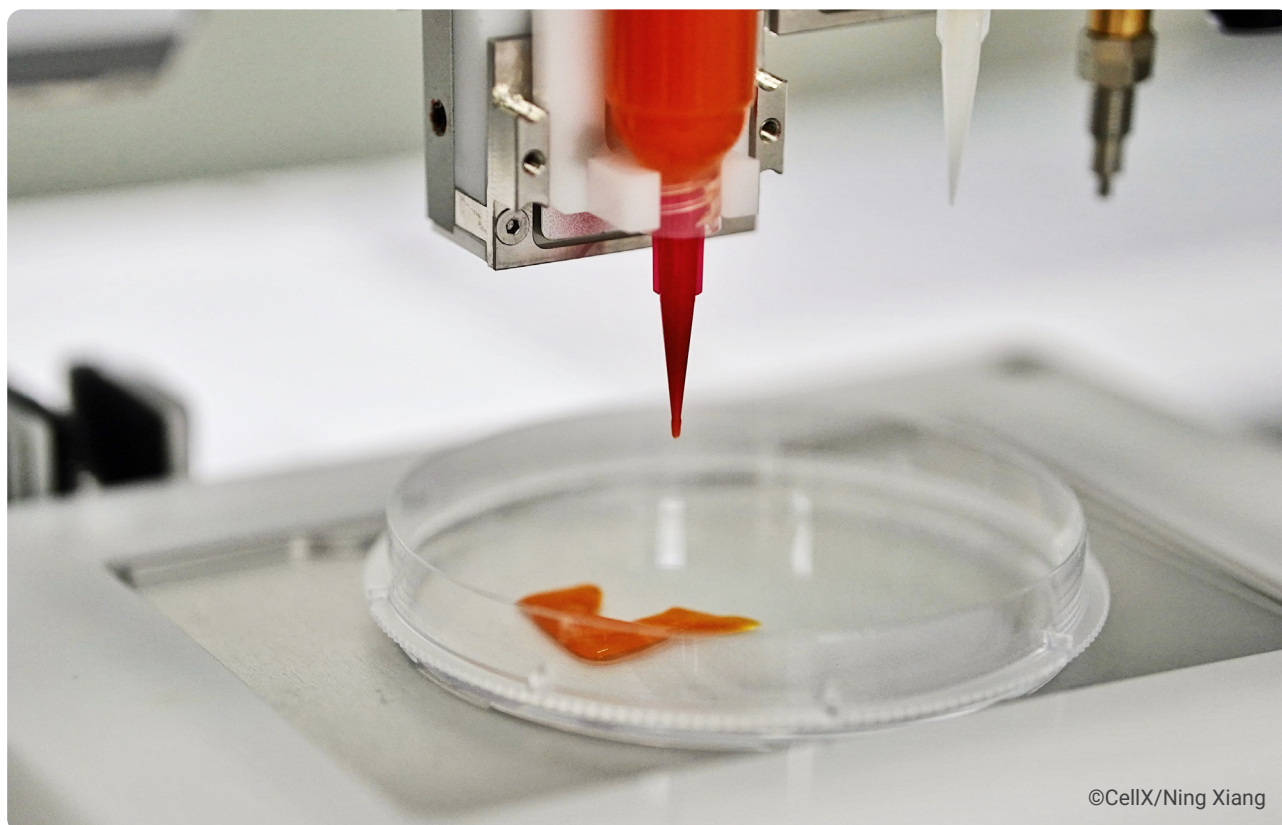


Table 2. Studies on modifier terminologies for cell-based food products, their preferred use and associated attributes

Sector/social group	Country	Term preference	Preference (%) or best perception/acceptance	Study set-up	Reference
Consumers Cell-based food industry Non-profit advocates	United States of America	Cultivated	<p>Preference of consumers based on survey, and of relevant companies and associations.</p> <p>Appeal: cultivated and cultured more appealing than cell-based and cell-cultured.</p> <p>Descriptiveness: cell-based and cell-cultured more descriptive than cultivated and cultured.</p> <p>Differentiation from conventional meat: cultivated, cell-based, and cultured were moderately and cell-cultured was moderately to very differentiating.</p> <p>all terms were moderately differentiating.</p>	<p>Mixed methods consumer survey and focus groups (N=27).</p> <p>University students: participants expressed a diverse range of political views, skewed toward a younger age (primarily 18–21 years), majority female (59%), and the majority were omnivores.</p>	(Szejda, 2019) <i>Survey report</i>
Consumers	United States of America	Clean	<p>“Clean meat” showed significantly more positive associations than “animal-free”, “cultured” or “lab-grown”.</p> <p>“Clean meat” and “animal-free meat” also triggered more positive attitudes - and “clean meat” more positive intentional behaviours -than “lab-grown meat”.</p>	<p>Between-subjects design (N = 185).</p> <p>Participants’ perception assessed for 4 product names: (1) “cultured meat”, (2) “clean meat”, (3) “lab-grown meat”, and (4) “animal-free meat”.</p> <p>Participants were recruited through Amazon MTurk (online platform), and were 57.8% male, 42.2% female, aged 20–68 years (mean = 34.86, standard deviation (SD) = 10.38). The country was not recorded, though 75% of MTurk workers are in the United States of America.</p>	(Bryant and Barnett, 2019) <i>Scientific article</i>
Cell-based food industry	Worldwide	Cultivated Cultured	75% preference. 20% preference.	Study poll - 49 company CEOs consulted.	(Friedrich, 2021) <i>Poll report</i>
Cell-based food industry	Worldwide	Cultivated Cultured Cell-based Cell-cultured	37% preference. 25% preference. 18% preference. 7% preference.	Analysis of websites, LinkedIn profiles, and media statements of all known cultivated meat start-ups.	(Byrne, 2021) <i>Survey report</i>
Cell-based food industry	United States of America	Cultivated Cell-based Cultured Cell-cultured	Preferred terms – neutral and scientifically accurate, and clear distinction from “plant-based protein” and “animal-based meat”.	Statement by AMPS Innovation member companies.	(AMPS, 2022) <i>Opinion</i>

Sector/social group	Country	Term preference	Preference (%) or best perception/acceptance	Study set-up	Reference
Consumers	United States of America	Cell-based	<p>Cell-based best term for clarity, perception and acceptance.</p> <p>Cell-based seafood, cell-cultured seafood, cultivated seafood, and cultured seafood were compared.</p>	<p>Between-subjects online experiments (N=3186).</p> <p>Study participants were recruited from a web-based consumer panel with more than 3.2 million active members enrolled in the United States. The experiment was performed during an 18-day period in 2020. A total of 8 485 randomly selected E-rewards panel members were sent an e-mail invitation to participate in the study.</p> <p>Demographic information (education level, year of birth, ethnicity, race, and gender) was used to produce a sample balanced to 2010 United States of America census data.</p>	(Hallman and Hallman, 2020) <i>Scientific article</i>
Consumers	United States of America	Cell-based	Cell-based versus cell-cultured seafood was compared.	<p>Two-group between-subjects design (N=1200). Data were collected in 2020.</p> <p>Study participants consisted of adult American consumers (18 and older) recruited from the YouGov.com web-based consumer panel. A sample of 1 600 participants were selected to produce the final dataset, matching a sampling frame derived from the 2018 American Community Survey. Of these 1 600 participants, 1 200 were randomly assigned to one of the two experimental conditions. A total of 591 participants viewed packages displaying the "Cell-Based Seafood," and 609 viewed packages displaying "Cell-Cultured Seafood".</p> <p>Median length of the experiment was 11.8 minutes. Consistent with census data, 51.3% of the 1 200 participants were female. Mean age was 47.41, SD = 17.69.</p>	(Hallman and Hallman, 2021) <i>Scientific article</i>
Consumers	United Kingdom of Great Britain and Northern Ireland, United States of America	Cultivated Cultured	<p>Preferred terms for social context and product packaging, and considered more appealing. Both terms were perceived very similar.</p> <p>Cell-based and Cell-cultured not the preferred terms, but considered more descriptive. Both terms were also perceived as very similar.</p>	<p>Survey and experiments - (N=2 292 for United States of America and N=2 270 for United Kingdom of Great Britain and Northern Ireland).</p> <p>Sampling protocol to match adult population aged 18–74 years, by interlocked sex and age groups to fit within generational groups. Geographical region and race/ethnicity quotas in the United States of America, and region quotas in the United Kingdom of Great Britain and Northern Ireland were accounted for.</p>	(Szejda, 2021) <i>Scientific article</i>

Sector/social group	Country	Term preference	Preference (%) or best perception/acceptance	Study set-up	Reference
Consumers	Portugal	N.A.	Only the term "lab-grown" was included in comparison between eight different food products: red and white meat, fish and seafood, insects, legumes, tofu, seitan, and lab-grown meat. "Lab-grown" meat was perceived negatively as the least natural and most processed of all meat alternatives, associated with health risks and artificiality and it was seen as the least sustainable and most expensive.	<p>Study 1 (N=138) - participants 58.1% female, aged 18–52 years (Median age = 26.77, SD = 8.89). More than half (58.9%) had a higher education degree (BSc, MSc or Doctorate), 38.8% had completed secondary education and 2.3% primary education. Most participants included animal products (meat or fish) in their diets (82.8%), 3.7% followed a vegetarian diet, and 6% a vegan diet; 7.5% reported to have "other" dietary orientations.</p> <p>Study 2 (N=285) - participants (68% female) aged 18–66 years (M = 30.21, SD = 10.19). More than half (56.8%) had a higher education degree (BSc, MSc or Doctorate), 41.1% completed secondary education, and 2.1% primary education. Most participants were employed (60.4%) or students (22.1%). Most participants included meat or fish in their diets (59.6%), and 15.1% followed a vegetarian diet, 21.1% had a vegan diet, and 4.2% reported "other" dietary orientations. On average, participants lived in predominantly urban areas.</p>	(Possidonio <i>et al.</i> , 2021) <i>Scientific article</i>
Consumers	European Union, United Kingdom of Great Britain and Northern Ireland, United States of America	Cell-based	<p>The "clean meat" label was evaluated negatively. The authors mention that the term "clean" meat was chosen, as it tends to be associated with more positive evaluations of the product compared with other labels such as "cultured", "in vitro", or "lab-grown" meat. Thus one of the more positive labels was used to avoid strong negative effects induced by the label alone.</p> <p>Images of "clean meat"-labelled dishes were more negatively evaluated than images of "regular meat"-labelled dishes by omnivores. "Clean meat"-based dishes were perceived as lower in safety and/or lower in naturalness.</p>	<p>Experiment 1 - participants (N = 270) recruited through the crowdsourcing platform Prolific and received financial compensation. Only omnivores were retained. The sample consisted of 54.9% men and 45.1% women, with a mean age of 30.42 years (SD age = 10.95). Most participants were from the European Union (45.3%), United Kingdom of Great Britain and Northern Ireland (27.9%), or the United States of America (11.4%).</p> <p>Experiment 2 - participants (N = 626) were recruited through opportunity sampling on social media and received no financial compensation. Only omnivores and vegans retained. Sample consisted of 21.8% men and 78.2% women, with a mean age of 36.41 years (SD age = 16.41). Of this sample, 455 were omnivores (74.7% women; Median age = 37.47 years, SD age = 17.07) and 171 were vegan (87.8% women; Median age = 33.35 years; SD age = 14.45). Participants were not asked for their nationality.</p> <p>Experiment 3 - participants (N = 273) were recruited through the crowdsourcing platform Prolific and received financial compensation. Only omnivores were retained. The sample consisted of 56.1% men and 43.9% women, with a mean age of 28.19 years (SD age = 9.36). Most participants were from the European Union (57.4%), the United Kingdom of Great Britain and Northern Ireland (18.7%), and the United States of America (6.7%).</p>	(Krings, Dhont and Hodson, 2022) <i>Scientific article</i>

Source: Authors' own elaboration.

1.4. Discussion

Overall, through the examination of both scientific and grey literature, “cell-based”, “cultivated” and “cultured” are the three major terminologies used or preferred by consumers, industry and the authorities. These terms are also commonly used in scientific publications, but a broader range of terms can also be found in many cases in science, including the terms “*in vitro*”, “artificial” and “clean” that were used more frequently in the early days of the technology developments. However, industry prefers to use “cultured”, “cultivated” or cell-based”, while the media use a more diverse array of terms including, but not limited to, “cultured”, “lab-grown”, “fake”, “clean”, “cultivated”, or “cell-based”.

As for consumers, only a small number of well-designed quantitative studies in a limited number of countries have addressed the appropriateness and relevant consumer perception and acceptance of different terminologies. Moreover, these studies did not always include the same set of terms to be analyzed and compared. Despite these limitations, consumer studies indicated that the term “cultivated” was often considered the most appealing, and “cultured”, “cell-based” and “clean” to a lesser extent. These studies did not always test whether these four terms were also considered to be the clearest.

It is recommended that, from the early stages, the national competent authorities establish clear and consistent terminologies that fit in with their national and language contexts so that they can mitigate potential miscommunications on this subject in the future. If English is the language to be used, based on the data currently available and consumer studies, the potential candidates are “cell-based”, “cultivated” or “cultured”, whereby the specific use might be further determined by the target audience or language-specific associations of these terms. It is important to note that “cultured” and “cultivated” may be wrongly interpreted when used for cell-based seafood products, as both terms can be perceived as being “farmed fish” (Hallman and Hallman, 2020). In addition, United States’ federal agencies use the term “cultivated” to identify farmed shellfish. To make the terminology non-commodity-specific, “cell-based” may be useful as in cell-based food, cell-based food products, or cell-based food production, while “cultivated” and “cultured” most likely need to be followed by a commodity name, such as meat, chicken, fish and so forth.



2. Generic understanding of production processes

2.1. Introduction

Food safety is an essential element to achieve food security, and regardless of how food is produced, consumers expect all food products to be safe to eat. While various steps are involved in overall food safety assurance, one of the first practical and important steps to ensure food safety is the identification of potential hazards in food production chains, in order to further assess the risks associated with implementing measures to reduce or mitigate any adverse health impact.

Cell-based food production encompasses the *in vitro* cultivation of animal cells or microbial cells for the production of analogues of animal or plant products (e.g. animal tissues or specific animal or plant proteins and fats), with nutritional properties matching those of conventionally produced components. Technologies in this area are rapidly developing and various types of large-scale cell-based food production are on the horizon. These technologies could possibly play an important role in supporting the increasing global demand for animal-sourced protein (Henchion *et al.*, 2021) and provide more sustainable ways of producing animal protein in the so-called “protein transition” (Aiking and de Boer, 2020).

It is important to apply the same level of food safety assurance of currently commercialized food products to animal cell-based food products as well, thus a basic understanding of the cell-based food production processes is an important preliminary step prior to food safety hazard identification. To this end, the aim of this chapter is to provide an overview of the available literature for a generic understanding of the relevant technologies and production processes for animal cell-based food and the potential food safety hazards and/or relevant concerns.

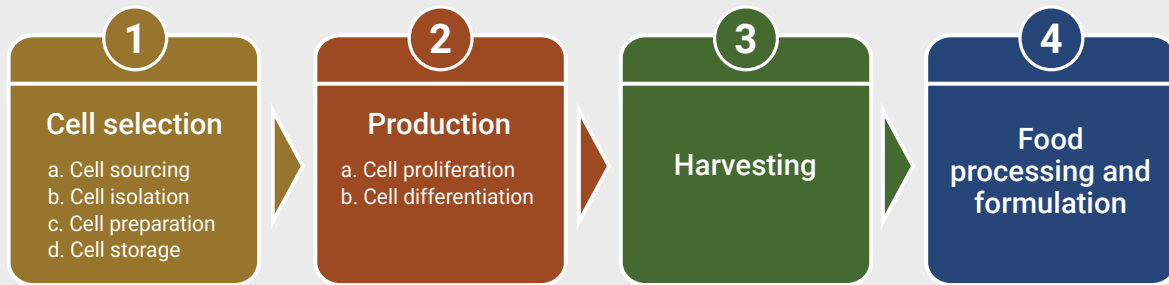
Animal cell-based food production can employ a wide variety of cells to initiate the production process in order to develop cellular products such as proteins, fats or tissues from whole animal cells of poultry, cattle, pork, fish (e.g. salmon and tuna), game animals (e.g. kangaroo and quail), shrimp, crab, and lobster (Hong *et al.*, 2021; Miller, 2020). The specific production processes for each cell-based food product may vary considerably. This chapter therefore primarily focuses on the processes that are common for the majority of production chains for animal cell-based food products. Therefore, this chapter can be interpreted as an overview of the main characteristics of generic production process steps and the relevant potential food safety hazards or concerns. In addition, as FAO aims to provide scientific information to the relevant competent authorities, particularly those in low- and middle-income countries, key considerations for countries with limited knowledge, resources and capacity are included.

2.2. Literature synthesis results

2.2.1. General processes for animal cell-based food production

Manufacturing processes for animal cell-based food products may significantly vary depending on the type of cell line used (livestock, poultry, fish or seafood) and the nature of the final product (e.g. a burger, steak or nuggets). Nevertheless, a general process includes four key production stages (i) target tissue or cell selection, isolation, preparation and storage, (ii) cell proliferation and possible cell differentiation during large-scale biomass production (iii) tissue or cell harvesting, and (iv) processing and formulation of food products (Ong *et al.*, 2021). Depending on the commodity and desired final product, each of these stages can have different sub-steps for completing the specific stage. To present a high-level understanding of the production process, an overview of the common cell-based food production process has been summarized in **Box 1**.

Box 1. A generic overview of the cell-based food production process



Source: FAO. 2022. Thinking about the future of food safety - A foresight report. Rome. www.fao.org/3/cb8667en/cb8667en.pdf

2.2.2. Cell selection – sourcing, storage, isolation and preparation

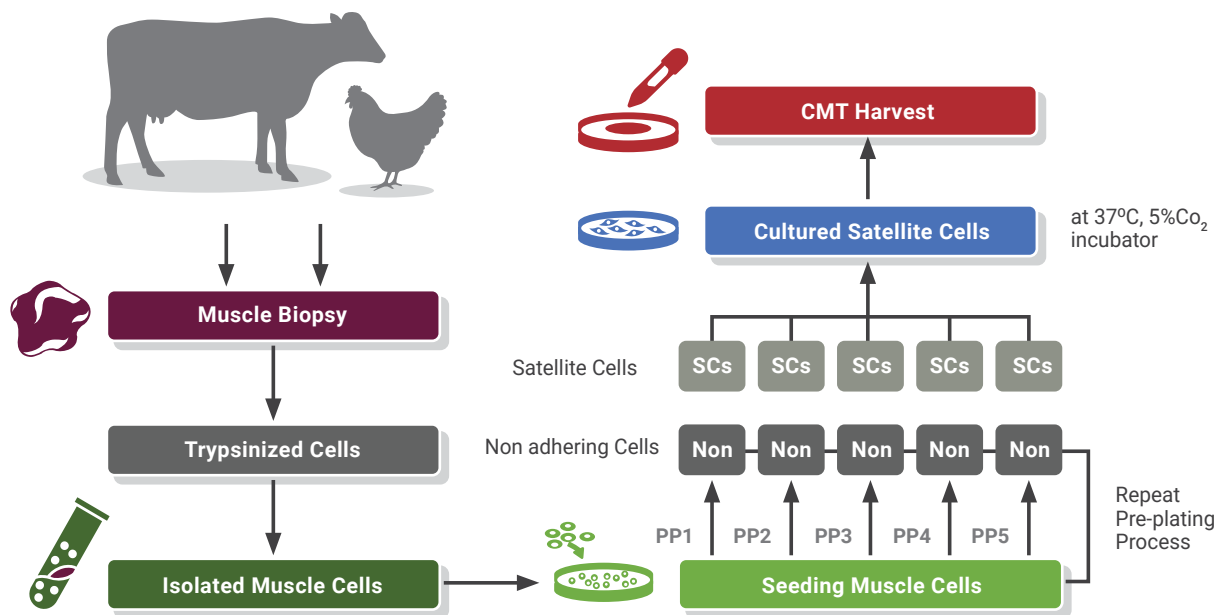
Cell sourcing

Production of cell-based food starts with the selection of the desired cell sources (livestock, poultry, game, fish, seafood) and cell types (e.g. non-differentiated stem cells, muscle precursor cells, fibroblasts or adipose-derived cells) to be used for developing the final product. Small tissue samples can be obtained by taking a biopsy from live or slaughtered animals, after which the desired cell type can be isolated or reprogrammed for *in vitro* cultivation. It is important that, before taking biopsies, the health status of the animal is confirmed. Cells used for cell-based food production can be e.g. embryonic stem cells, which are pluripotent cells that are located within blastocysts and have an unlimited capacity for self-renewal and the ability to differentiate into any somatic cell type, induced pluripotent stem cells (iPSCs) that are derived from reprogrammed adult somatic cell and have regained their capacity to differentiate into any cell type found in the body, mesenchymal stem cells or adult stem cells such as myosatellite cells (Ben-Arye and Levenberg, 2019; Ong *et al.*, 2021; Reiss, Robertson and Suzuki, 2021). For some products, primary cell lines that are freshly isolated from specific organ tissues and maintained for growth *in vitro* might be used, which is the case for most fish cell lines, as they are not readily available from cell culture collections (Rubio *et al.*, 2019). Mesenchymal stem cells can readily be obtained from bone marrow or adipose tissue, while muscle precursor cells are sourced from muscle.

Cell isolation

Tissues obtained from biopsies are either explanted (a method whereby a sample adheres to a plate, which encourages cell migration to the culture surface) or further processed through mechanical and enzymatic steps that liberate the cells. One example is the isolation of muscle cells, where enzymatic digestion uses e.g. trypsin or collagenase to release cells from muscle samples (see **Figure 4** and **Box 2**). In general, the use of digestive enzymes enables the isolation of muscle stem cells from a large piece of muscle without damaging the cells, though some digestion of cell surface antigens may occur. As for all isolation methods, it also carries the risk of contamination with other types of cells. Complementary methods are therefore warranted for further purification of muscle stem cells from these initial extracts. Methods that have been successfully used to this end can be cost-demanding (though negligible in the overall costs for the production process) and include selective plating, differential adhesion, cytochalasin-B-based detachment of myogenic cells from myoblast cultures (Choi *et al.*, 2021), cell capture using magnetic beads with cell-specific antibodies or fluorescence-activated cell sorting (FACS) (Post *et al.*, 2020; Rubio *et al.*, 2019), or Percoll density gradient centrifugation. It may therefore be important to develop alternative pre-plating methods amenable to industrial-scale production (Guan *et al.*, 2021). **Figure 4** shows a general scheme for isolation of muscle satellite cells from livestock and poultry for cultured muscle tissue (CMT) production. Specific cell isolation procedures may apply, depending on the desired cell types; thus two examples for livestock and poultry have been provided in **Box 2** and **Box 3** to illustrate the different cell sourcing and isolation processes. Detailed isolation procedures also exist for other cell types, such as adipose-derived stem cells (Lu *et al.*, 2014; Sampaio *et al.*, 2015), mesenchymal stem cells (Feyen *et al.*, 2016; Vassiliev and Nottle, 2013) or fibroblasts (Park *et al.*, 2022). For cells derived from fish or seafood, protocols are currently not publicly available.

Figure 4. Flow diagram for the sourcing and isolation of cultured muscle satellite cells



Source: Joo, S.T., Choi, J.S., Hur, S.J., Kim, G.D., Kim, C.J., Lee, E.Y., Bakhsh, A. *et al.* 2022. A Comparative Study on the Taste Characteristics of Satellite Cell Cultured Meat Derived from Chicken and Cattle Muscles. *Food Science of Animal Resources*, 42(1): 175–185. 10.5851/kosfa.2021.e72

Box 2. Cell sourcing and isolation of chicken and bovine muscle satellite cells

The flow diagram for the cultured muscle satellite cell isolation is shown in **Figure 4**.

Cell sourcing

Skeletal muscle samples were derived from 4- to 6-week-old broiler chickens or 24- to 27-month-old cattle steers. Animals were euthanized following approved human methods. Several small pieces of the pectoralis major muscle from chickens and the biceps femoris muscle from cattle were removed from the carcasses immediately after slaughter. The collected muscle pieces were sterilized with 70 percent ethanol, placed in Hanks' Balanced Salt Solution containing 3 percent antibiotic-antimycotic (containing penicillin, streptomycin, and amphotericin B), and transported to the cell culture laboratory. On a clean bench, muscle pieces were washed once with 70 percent ethanol and placed in a Petri dish. Each muscle tissue was rinsed 3–5 times with a 4-fold volume of cold phosphate-buffered saline (PBS), followed by the removal of visible adipose and connective tissue. Muscle tissue was cut into very small pieces using scissors after spraying with 0.25 percent trypsin-EDTA. Muscle tissue was minced, and 4 grams of minced muscle were transferred and 5 times the volume of 0.25 percent trypsin-EDTA was added. Muscle tissue was transferred to a tube and incubated in a water bath at 37 °C for 30 minutes while gently inverting every 10 minutes. The digested muscle tissue was collected by low-speed centrifugation, and after removing supernatant, 10 mL of proliferation medium (PM) was added to the pellet and serially filtered through 100, 70, and 40 µm strainers. The filtered cell suspension was centrifuged to collect the cell pellet.

Isolation of muscle satellite cells

Muscle satellite cells (MSCs) were separated by the pre-plating method utilizing the difference between the cell adhesion rate and the growth rate. The cell pellet obtained after sourcing was re-suspended in PM and plated onto a cell culture dish coated with 0.2 percent gelatine. The cell culture dish was incubated at 37 °C in the presence of 5 percent CO₂ for 1 hour (pre-plating 1, PP1). Fibroblasts quickly adhered to the bottom of the cell culture flask, while MSCs remained in the supernatant. The supernatant containing MSCs was collected in a centrifuge tube and centrifuged for 10 minutes at 500×g. The MSC pellet was re-suspended with PM, plated onto a cell culture dish and incubated at 37 °C with 5 percent CO₂ for 2 hours (pre-plating 2, PP2). The supernatant and non-attached cell suspensions were recovered, centrifuged again, and only the cell pellets were cultured for 24 hours (PP3). This pre-plating process was repeated up to PP5 to isolate muscle satellite cells that are as pure as possible in the final PP5 fraction. Cells in all steps from PP1 to PP5 were cultured in PM.

Source: Example protocol from Joo Seon-Tea *et al.* A Comparative Study on the Taste Characteristics of Satellite Cell Cultured Meat Derived from Chicken and Cattle Muscles. *Food Sci Anim Resour.* 2022;42(1):175–185. <https://doi.org/10.5851/kosfa.2021.e72>.

Box 3. Cell sourcing and fluorescence-activated cell sorting to enrich bovine muscle satellite cells

Alternative isolation protocol for bovine muscle satellite cells (not related to [Figure 4](#)).

Cell sourcing

Bovine satellite cells were derived from fresh (within 30 minutes of euthanasia) muscle samples obtained from 1- to 2-year-old male cattle. Freshly harvested bovine muscle was immediately transferred to the lab on ice and washed with 75 percent ethanol for 1 minute, followed by washing 2 times in phosphate-buffered saline (PBS). Tissues were mechanically dissected and dissociated with collagenase II (CLS-2, 0.2 percent) in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 1 percent penicillin-streptomycin at 37 °C for 1.5 hours. The mixture was mixed by vortexing or triturated with a pipette every 10 minutes. After digestion, 20 percent fetal bovine serum (FBS) in DMEM was added and mixed well with a pipette. Muscle fragments were centrifuged at 80 g for 3 minutes and the supernatant was collected as mononuclear cell suspension. The precipitated debris was again triturated with a 20-gauge needle in PBS and centrifuged at 80 g for 3 minutes. The supernatant was collected and mixed with previous mononuclear cell suspensions. After centrifugation at 1,000 g for 5 minutes, the cells were washed twice with PBS followed by DMEM with 20 percent FBS. After that, the cells were filtered through a 100 µm cell strainer followed by a 40 µm cell strainer. The cells were then centrifuged at 1,000 g for 5 minutes at 4 °C and incubated with the erythrocyte lysis buffer (ACK) buffer for 5 minutes on ice. The cells were washed twice with PBS and cell pellet was reconstituted with FACS buffer (1 percent bovine serum albumin [BSA] in PBS) or frozen in FBS supplement with 10 percent dimethyl sulphoxide (DMSO) until further use.

Fluorescence-activated cell sorting

Frozen cells were recovered in a 37 °C water bath and washed with PBS twice before further processing. The cells were resuspended in FACS buffer and stained with selected APC anti-human CD29 Antibody (1:10), PE-CyTM7 anti-human CD56 (1:10), FITC anti-sheep CD31 (1:10), FITC anti-sheep CD45 (1:10) for 30–45 minutes on ice. After antibody incubation, the cells were washed twice with cold PBS and reconstituted in F-10 with 20 percent FBS. The viable CD31–CD45–CD56+CD29+ cells (bovine satellite cells) were isolated by cell sorting. Cell sorting was performed with a BD FACS Aria cell sorter using 405 nm, 488 nm and 640 nm lasers. Unstained cells were routinely used to define FACS gating parameters.

Source: Example protocol from Joo Seon-Tea *et al.* A Comparative Study on the Taste Characteristics of Satellite Cell Cultured Meat Derived from Chicken and Cattle Muscles. *Food Sci Anim Resour.* 2022;42(1):175–185. <https://doi.org/10.5851/kosfa.2021.e72>.

Preparation of robust production cell lines

Many cell lines currently used for cell-based food production are not genetically modified (Hadi and Brightwell, 2021; Post *et al.*, 2020; Zhang *et al.*, 2020). These cell lines therefore may not necessarily possess the exact physiological or genetic characteristics desired for optimized growth and prolonged cultivation in large-scale bioreactors, such as a limited number of cell divisions, or low resistance to shear stress and sub-optimal oxygenation. Developing so-called immortalized cell lines is one of the approaches that could lead to cells with an extended proliferation capacity. This can be achieved by, for example, targeting the telomerase activity through genetic modification and thereby preventing senescence (Soice and Johnston, 2021), but can also be obtained through non-GM methods whereby primary cells are serially sub-cultured until clonal populations of immortalized cells arise from spontaneous genetic variation over time.

Cell storage

The cell type used for cell-based food production has a large impact on the parameters used in the production process, as each cell type has its particular requirements that might be beneficial for or detrimental to efficient production. For consistent production of cell-based food products, it is also vital to use stable cell lines that maintain the same genetic and physiological characteristics and exhibit uniform/consistent production performance over time. This necessitates storage of cells after isolation from animals (primary cells) or storage of cells from specific stages of the production process. To this end, cells are stored as frozen aliquots in master cell banks after the addition of cryopreservation fluid (Ong *et al.*, 2021). Individual vials of the master cell bank can then be used to generate large “working” cell banks from which individual vials are used to initiate cultures for each production run or period of experimentation (Healy *et al.*, 2011) Prior to cryopreservation, cell lines are screened for the presence of microbial contaminants, and may be verified for the species cell line identity to ensure that cell cultures are not contaminated during the seed phase of biomass production (Andriolo *et al.*, 2021). Cell banks for animal cell lines have not been developed yet for many animal species, in particular for fish, and establishing such cell banks is therefore an important factor for future large-scale cell-based food production (Ramani *et al.*, 2021).

2.2.3. Production - cell proliferation and differentiation and large-scale production

Cell proliferation

For large-scale production, isolated cells need to be proliferated on a large scale and to a high cell density and in "many cases differentiated into specific cell types, which will involve several scale-up steps from the seed stage to full scale production in large bioreactors (1 000–10 000 L volumes or higher). The cell source and type used have an important impact on the proliferation and scale-up requirements. Cell types such as skeletal muscle cells, fibroblasts, satellite cells, and iPSCs are in general being favoured, on their own or in combination with adipogenic stem cells, and each have their particular benefits and requirements for proliferation factors such as oxygenation, pH and temperature (Swartz, 2021). While most mammalian cells typically need to be proliferated at a narrow range of temperatures from 36.5 to 37.5 °C (Choi *et al.*, 2021), fish cells can be grown at much lower temperatures in a wider range between 15 and 30 °C. Moreover, fish cells are expected to tolerate lower oxygen levels compared with mammalian cells and to be more adaptable to a wider pH range, based on the physiology of fish and aquatic invertebrates (Fernandez *et al.*, 1993; Rubio *et al.*, 2019). The use of a fresh/non-exhausted medium is also considered important, as it was found that medium exchange was critical in maintaining good cell growth (Hanga *et al.*, 2020).

For creating cell-based fat, mesenchymal stem cells isolated from fat or bone marrow may be an option as these multipotent stem cells have the capability to develop into fat cells (adipocytes) (Fish *et al.*, 2020). iPSCs, for example, can still develop into myotubes, a propensity also exploited in research into human tissue engineering for medical purposes. In addition, adipose tissue-derived stem cells (ADSCs) can also be triggered to develop into various types of cells, such as bone-, muscle-, and fat-cells (Balasubramanian *et al.*, 2021). The tendency of the isolated cells to proliferate and differentiate may differ depending on the tissues from which they are sourced, as shown for muscle satellite cells (Choi *et al.*, 2021). Reiss *et al.* (2021) point out that pluripotent stem cells may be costlier to obtain and to grow, and that more time may be needed to have them differentiate into cells with the desirable phenotype. They also note that primary adult stem cells, for example, may be easier to obtain from e.g. biopsies of animal muscle tissue. For seafood, the fact that fish muscle consists of three different types of muscle (red, white, pink) opens up possibilities when designing cultivation systems (Rubio *et al.*, 2019).

Co-cultures of different types of cells, such as muscle and fat cells, may not only help to mimic the structure and characteristics of meat, poultry or fish closely (e.g. marbling) but different types of cells may also secrete factors and matrices that induce other cell types to proliferate and differentiate (Balasubramanian *et al.*, 2021). Various authors, for example, used a technique to layer alternating sheets of muscle and fat cells on top of each other (Pandurangan and Kim, 2015; Shahin-Shamsabadi and Selvaganapathy, 2021). Co-cultures may also be used for the creation of "self-organizing" methods of cell-based food production, as an alternative to methods employing scaffolds. One challenge in this regard is the transport of nutrients and oxygen throughout the mixed-cell-type tissues being formed, which may be done with the aid of artificial blood-circulation-imitating concepts (Bhat *et al.*, 2015).

Cell differentiation

After cell proliferation, cells need to be induced to differentiate into cell types with the desired characteristics for the cell-based food product. Cell differentiation can be stimulated e.g. by changing to a culture medium with an altered composition of signalling molecules, environmental conditions or by changing scaffolds. Medium composition for cell differentiation can be achieved by addition or removal of growth factors, vitamins, amino acids or trace minerals. The media used are complex, and besides the proper amounts of, e.g. lipids, amino acids, and vitamins, the addition of essential growth factors is also required to stimulate the proliferation and differentiation of those cell types that do not produce such factors themselves in culture (Arshad *et al.*, 2017). The chemical and biochemical compounds that could act as hormones or growth factors for this purpose range widely, including for example steroids, signalling molecules, insulin and insulin-like growth factors (IGFs), fibroblast growth factors (FGFs), transforming growth factor beta-2 (TGF-βs), and interleukins (Choi *et al.*, 2021). As cell differentiation is never 100 percent efficient, further purification might still be required of the target cell type. Whilst plasma and serum from animals, such as foetal calf serum, may be added for cell proliferation and differentiation (up to 20 percent),

this might not align with the strategy directed towards animal-slaughter-free production. Alternatives that can be used include recombinant growth factors, the recycling of growth factors used by cultured cells themselves and adapting cell lines to grow in serum-free media or in alternative media containing plant or microbial components (O'Neill *et al.*, 2021). Besides or as an alternative to growth factors, mechanical stimulation such as contraction, fluid flow, or magnetic particles may be used to stimulate muscle cells in particular.

Process design for large-scale production

Bioreactor configuration and process design takes into account factors such as oxygenation, shear stress, pH through carbon dioxide concentration and temperatures that are optimal for proliferation of the selected mammalian, fish or seafood cell line (Allan *et al.*, 2019; Arshad *et al.*, 2017). Fish and seafood cell lines might be more amenable towards temperature, oxygen and pH ranges than other animal cell lines and might therefore be proliferated using a simpler (and cheaper) reactor design. In contrast, avian cell lines might require optimal growth temperatures higher than 37 °C. Different types of bioreactors might be used for cell-based food production, such as stirred tank bioreactors and rocking bed bioreactors, but also those using fluidized or packed beds, or hollow fibres (Allen, 2013; Choi and Hyun-Jae, 2019; Djisalov *et al.*, 2021; Hanga *et al.*, 2020). It is important that the reactor configuration that is used for a specific cell line is scalable without negative effects on the cell proliferation and differentiation capacities that could, for example, be introduced by increased shear stress or reduced oxygenation. The stirred tank bioreactor is currently preferred for the large-scale and cost-effective growth of animal cells for food production and elsewhere in the biopharmaceutical sector (Eibl *et al.*, 2021). In all reactor set ups it is important to monitor the process carefully, such as for pH (controlled via carbon dioxide), dissolved oxygen, temperature, nutrients (e.g. ammonia, glutamate, glucose), biomass, cell density and proliferation, as well as cell image analysis (Djisalov *et al.*, 2021). Medium exchange is expected to be critical to maintaining good cell growth, as was demonstrated in a lab-scale stirred flask model for growing fat cells (Hanga *et al.*, 2020), and is therefore a key part of the process design.

Cells used for cell-based food production in many cases might need to utilize an adherent surface for proliferation (Ong *et al.*, 2021). These surfaces can be microcarriers (MCs, small beads) or more robust scaffolds that allow the formation of more complex cell structures such as sheets. MCs are often composed of materials such as gelatine, dextran, collagen or polystyrene (Bodiou *et al.*, 2020). Scaffold materials might include natural components such as polysaccharides (cellulose, alginate, chitosan, decellularized plant materials), proteins such as gelatine and collagen (from animal or non-animal sources), textured soy protein or synthetic scaffold materials composed of polymers such as polyethylene glycol (PEG), polylactide (PLA) or polyacrylamide (Ben-Arye and Levenberg, 2019; Ng and Kurisawa, 2021; Seah *et al.*, 2022). Composites of natural and synthetic materials may also be used. In all cases, microcarrier or scaffold materials are preferably biocompatible, biodegradable, edible and safe to use and, in the case of scaffolds, provide the final product with structure and texture (Bomkamp *et al.*, 2022). Matrices may be structured such that the cells are stimulated to grow into fibre-like structures. Acevedo and co-workers (Acevedo *et al.*, 2018; Orellana *et al.*, 2020) employed an edible film with laser-cut microchannels and observed that cells after seeding did start to form muscle-forming (myogenic) structures. Eibl *et al.* (2021) note that the choice of MCs and media to be used in stirred bioreactors are mutually dependent for optimal results and affect the scalability of the process (Bodiou *et al.*, 2020; Eibl *et al.*, 2021). For example, when using an air-lift reactor design, the air bubble size needs to be chosen carefully as the use of MCs requires a smaller bubble size in order to prevent cells from being dislodged from the carrier and harmed (Li *et al.*, 2020).

Biopolymers used as microcarriers or scaffolds can also serve a function as an additional fibrous substance in the final product, or to contain molecules that emulate the action of hormones (Ng and Kurisawa, 2021). Park *et al.* (2021), for example, describe a porous multilayer film containing different polysaccharides with C-phycoerythrin. The latter is an algal protein with proliferation-inducing properties and hence a possible substitute for foetal bovine serum as a media additive. Results showed that muscle cells grown on this substrate displayed increased proliferation (Park *et al.*, 2021). Alternatively, they can also be selected or designed to be biodegradable, with their degradation possibly leading to the release of flavour or nutritional compounds. Edible biopolymers are generally not cell-adhesive and modifications may be needed for this purpose (Ng and Kurisawa, 2021).

2.2.4. Harvesting

Once cells have reached their maximum density during proliferation and have differentiated into the desired cell type, they are harvested in a way that maintains cell/tissue integrity and avoids microbial contamination. Cells can be collected using sedimentation, centrifugation or filtration techniques, and when cells were grown on scaffolds/MCs that are not edible or biodegradable, they must first be dissociated from the scaffold before further processing. Dissociation can be done using enzymatic, chemical or mechanical methods (Allan *et al.*, 2019; Bodiou *et al.*, 2020; Rodrigues *et al.*, 2019). Depending on the production system used, only part of the cells might be harvested, after which fresh (or recycled) media can be added to the remaining cells for further cultivation. The implementation of automated cell harvesting systems instead of manual harvesting could be a development that can greatly reduce the risk of contamination during the harvesting stage (Specht *et al.*, 2018; Tan *et al.*, 2017). The literature review did not find any technical articles describing specific harvesting processes for cell-based food products. However, Bodiou *et al.* (2020) discuss three cell proliferation and harvesting scenarios as described in **Box 4**.

Box 4. Cell harvesting scenarios in cell-based food production

Scenario 1: Temporary microcarriers (MCs) for satellite cells proliferation

MCs that are used as temporary substrates for the proliferation of satellite cells (SCs) need to be removed before further processing, which requires (1) a high detachment (dissociation) yield and (2) easy separation from the cells.

Dissociation of SCs from MCs can be based on (i) chemical, (ii) mechanical or (iii) thermal principles to detach cell from MCs while maintaining cell viability, proliferation and differentiation capacity. (i) Chemical detachment consists of the enzymatic and non-enzymatic dissociation of cells. The enzymatic detachment is based on proteases in combination with chelating agents for Ca²⁺ to reduce cell binding. Non-enzymatic dissociation agents, such as dextran-sulphate, N-acetyl-L-cysteine and dithiothreitol, mimic enzyme activity that cleaves or degrades MCs' coating; (ii) mechanical methods to detach cells from MCs include pipetting, high agitation and vibration and can be used in combination with enzymes and chelators like trypsin-EDTA; and (iii) thermal response materials used for cell detachment from MCs can undergo a phase transition and/or morphological modification in response to a variation of temperature, leading to cell detachment. The advantages of mechanical and thermal techniques over chemical techniques are that they do not require the use of dissociation agents and do not have washing steps before and after dissociation which leads to longer processing times and extensive manipulation of the culture.

Separation systems for separating detached cells from MCs are based on one of the following four principles: filtration, centrifugation, inertia and magnetism. The most common filtration methods use dead-end filtration systems, (alternate) tangential flow filtration or continuous centrifugal separators. Magnetism can be used as a separation method when magnetic particles (made from iron, nickel, cobalt or their alloys) are incorporated into the MCs' core. After dissociation of the cells from the surface of the MCs, the introduction of a magnetic field separates the MCs from the cells.

Scenario 2: Non-edible, degradable microcarriers

MCs that serve as a temporary substrate for cell proliferation are separated at the end of the process through MC degradation instead of dissociation in order to obtain the cells. Diverse natural or synthetic degradable materials have been used for MC production, including polystyrene, cellulose, collagen, gelatine, alginate, chitosan, poly (L-lactic-co-glycolic acid) (PLGA), polylactide (PLA), or poly(+)-caprolactone (PCL). These polymers can be degraded according to five principles: thermal, chemical, mechanical, photo and biological degradation. The degradation of MCs needs to be controlled in order to be robust, fast and prevent damage or interaction of the SCs with the degradation products. In addition, premature degradation of MCs should be prevented during cell proliferation. Up to date, only one MC has been commercialized and developed with the purpose of being totally and rapidly biodegradable for cell harvesting. It is made of cross-linked polygalacturonic acid (PGA) and can be easily dissolved within 10–20 minutes using an EDTA solution in combination with pectinase, which that digests the polymer. Other polymers including dextran, cellulose, collagen, pectin or gelatine could be enzymatically digested in a similar way.

Thermal and photo degradation are likely to be less suited for cell culture, as the high temperatures required to thermally degrade polymers, or the ultraviolet radiation needed to induce photo-degradation are known to cause protein and DNA denaturation and damage. Mechanical forces such as stirring speeds, shaking or fluidization can also be used in combination with chemical degradation (enzymatic or non-enzymatic) to facilitate/accelerate the degradation process and reduce the concentration of enzymes. Finally, slowly degrading materials compatible with SC culture could also be performed. The use of degradable MCs eliminates the need for separation, thereby simplifying the process and resulting in increased cell recovery. The resulting cell suspension can be washed and directly used for downstream processing.

Scenario 3: Edible microcarriers (MCs) embedded in the final product

MCs composed of edible materials can be embedded in the final product. As opposed to scenario 1 and 2 where MCs are considered as a food contact material, in this scenario, MCs should comply with the regulations for use as a food ingredient or additive. Edible polymers that can be used as substrates for cell expansion belong to four categories: polysaccharides (e.g. starch, alginate, carrageenan, chitosan, cellulose, carboxymethylcellulose, pectin), polypeptides (e.g. collagen, gelatine, gluten), lipids (e.g., paraffin, shellac) and composites/synthetics (e.g. PGA, PEG). They have been widely used in the food industry as stabilizers, thickeners, coatings and emulsifiers. Less stringent separation methods through sedimentation or centrifugation are more relevant in this context. Edible MCs with controllable degradation properties can also be used and be partially degraded, remaining in the cell harvest for further processing. The dissociation step can be omitted completely when using edible MCs, and the edible polymer to be used as a cell substrate during cell proliferation can be designed to enhance or introduce desired properties, such as texture, taste or colour.

2.2.5. Food processing and formulation

Harvested cells/tissues are further processed and formulated into a specific type of cell-based food product for commercialization. In most cases, this involves the addition of other food ingredients for flavour and in some cases, it may involve the addition of preservatives. Different cell types may also be combined (e.g. muscle and fat cells) to replicate the structure and texture of conventional meat or meat cells/tissue combined with plant-based components to produce blended products. Common techniques to achieve structure and texture in cell-based food products include shear-cell technology, extrusion or 3D-printing, depending on the desired final product type (Handral *et al.*, 2020). In addition, biopolymers can be used to impart structure to the cell-based meat structure. Ideally, such biopolymers are already used during the cultivation stage as a cost-effective means for triggering myotube formation, for example, in the final stage of cell cultivation within a scaffold in a fixed bed reactor, following passages through stirred and suspension reactors for the multiplication of cells. Alginate (besides many other polysaccharides such as carrageenan, pectin, gellan, xanthan, etc.) appears to be an attractive candidate for this purpose as this biopolymer can accommodate smaller parts of cultured tissue into a kind of reconstituted meat product. Its gelatinization can be induced at low temperatures by the addition or release of calcium ions.

2.2.6. Potential food safety hazards and concerns

Overview

Cell-based food production involves various processes, techniques and steps and in some cases, novel inputs, meaning added steps, materials, technologies or techniques that have not commonly been used in conventional food production (e.g. scaffolds or modified cell properties) can be used. To be able to properly identify potential hazards, a generic mapping of potential hazards and concerns is simplified and presented in **Table 3**.

Table 3. A generic map of potential hazards/concerns in production processes

	Transmission of zoonotic infectious diseases	Residues and by-products	Novel inputs	Biological contamination
1. Cell selection	X	X		X
2. Production	X	X	X	X
3. Harvesting		X	X	X
4. Food processing		X	X	X

Source: FAO. 2022. Thinking about the future of food safety - A foresight report. Rome. <https://www.fao.org/3/cb8667en/cb8667en.pdf>

Potential hazards/concerns during cell selection

The cell sourcing, isolation and storage steps in cell-based food production may introduce microbial contaminations that could be propagated during subsequent production phases. A potential hazard is the transmission of zoonotic infectious diseases and foodborne pathogens from the source animal that is used to obtain biopsies, although the chances are considerably lower compared with conventional livestock breeding (Treich, 2021). Commonly encountered pathogenic bacteria that reside on or in animals and their faeces include *Salmonella*, *Campylobacter*, *Escherichia coli* and *Listeria*, and also of specific importance is the transmission of pathogenic *Mycoplasma* species (spp.) (see 3.6.3). Along with these bacteria other pathogens that might contaminate cell lines are animal-derived viruses and parasites (FAO/WHO, 2014; Ong *et al.*, 2021).

To prevent contamination by microorganisms during cell sourcing, isolation and storage, it is common practice to use antibiotics (see Boxes 1 and 2) and some of these antibiotics might be used further in the initial cell proliferation phase (seed stage). Cryoprotectants are used for cell storage of production cell lines in cell banks. Common cryoprotectants used for the cryopreservation of cell lines include dimethyl sulfoxide, (poly)ethylene glycol, trehalose and sucrose (Choi *et al.*, 2021), where DMSO has been shown to exert negative toxicological effects (Awan *et al.*, 2020). Antibiotics and cryoprotectants are diluted to very low concentrations or washed-out during production scale-up and their levels in the final products will be safe for consumption.

Potential hazards/concerns during production

Cell cultivation is sensitive to microbial contamination and is therefore performed under sterile cultivation conditions. Among the bacteria that commonly infect eukaryotic cell lines, *Mycoplasma* spp. are of chief concern, as several *Mycoplasma* spp. are known human pathogens and they are known to cause crashing of cell culture growth and are difficult to eradicate during biomanufacturing (Nikfarjam and Farzaneh, 2012). During manufacturing, contamination by other bacteria, yeast and fungi from the production environment can also occur, in particular spore-forming bacteria and fungi that are difficult to kill off and can spread easily by air are of concern (Møretrø and Langsrud, 2017; Snyder *et al.*, 2019). The risk of contamination by viruses and infectious prions may also exist when animal-derived serum or animal-derived medium components are used for cell cultivation (Hadi and Brightwell, 2021, Ong *et al.*, 2021). While testing or controlling such viruses and infectious prions is a significant challenge, sufficient heat processing may provide a solution. To limit the occurrence of contaminations, early detection of infections in cell cultures via regular monitoring is critical, as well as following good hygiene practices (GHPs) throughout the whole production process, such as common cleaning and sterilization practices for equipment. Replacing animal-derived components with non-animal derived components from plants or recombinant sources can also reduce the chance of contaminations. As cell cultivation is performed in strictly controlled sterile culture conditions, the use of antibiotics is drastically reduced or can be eliminated. It will thereby reduce the risk of human exposure to antibiotics as well as the development of antimicrobial resistance. Alternatives to antibiotics to prevent microbial contamination could be the use of approved chemical preservatives such as sodium benzoate or other antimicrobial compounds (Zidaric *et al.*, 2020).

At the level of the cell lines used, there is a risk of (epi)genetic drift in cell lines due to constant sub-culturing, where mutations build up over time that may eventually cause changes in phenotypes (Soice and Johnston, 2021). The use of quality-controlled cell banks of cryopreserved cell lines is a way to mitigate the risk of losing cell-line fidelity to genetic drift, as well as protecting against the presence of viruses, bacteria, yeast and *Mycoplasma* spp.

Potential hazards/concerns during harvesting

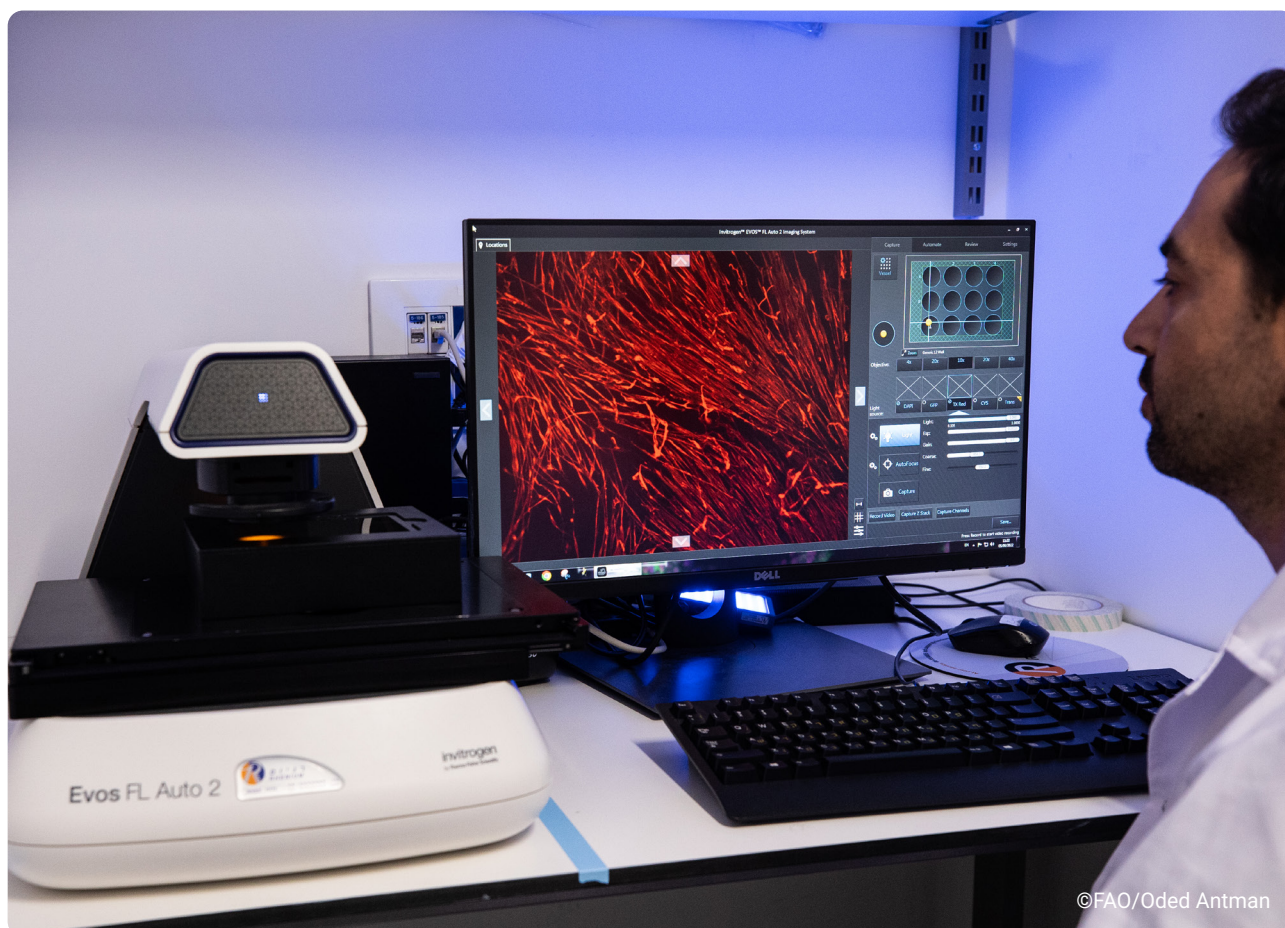
Common media used for cell cultivation are complex mixtures of salts, sugars (glucose), vitamins, amino acids, organic acids, growth factors and hormones (O'Neill *et al.*, 2021). A substantial part of these chemical and biological components and their residues are removed during cell harvesting or destroyed in subsequent processing steps (e.g. due to heating). However, harvesting may also introduce enzymes or chemicals, e.g. those that are required for the dissociation of microcarriers, including enzymes such as proteases, non-enzymatic dissociation agents such as dextran sulphate, N-acetyl-L-cysteine and dithiothreitol, or chelating agents like EDTA (Bodiou *et al.*, 2020;

Ong *et al.*, 2021). Of special attention is the use of biological components such as growth factors and hormones from animal (serum) or non-animal origin, as these biologically active molecules might interfere with the metabolism or have been associated with the development of certain cancers (Ong *et al.*, 2021). Harvesting is also a step that can introduce microbial contamination, and harvesting methods should be designed in a way that minimizes the chance of microbial contamination (Box 4).

Potential hazards/concerns during food processing and formulation

To process cultivated cells or tissues into cell-based food products for consumption, they are formulated with other ingredients and additives to improve e.g. the structure, texture, taste, colour or shelf-life of the end product (Zhang *et al.*, 2020; Zhang *et al.*, 2021). This can be edible and biocompatible microcarrier or scaffolding material that was already included for cell proliferation and differentiation, or e.g. binders, flavour agents and preservatives that are added after harvesting. These ingredients may exert an allergenic effect, and the allergenicity of the components of the cell-based food products is therefore an important factor for assessment. The cell line used might also have allergenic potential by itself, which in particular is the case for cell lines from fish or shellfish (Hallman and Hallman, 2021). Moreover, ingredients added to improve product characteristics, such as wheat gluten/hydrolysates, soy protein or milk components might be the cause of allergic reactions. All additives, ingredients, nutrients and all other substances added will need to be approved for application (e.g. considered to be safe and allowed for the specific cell-based food) and all applicable food labelling requirements will apply (including allergen labelling). As in the other stages of cell-based food production, potential microbiological hazards also exist during food processing, which should be minimized using GHPs.

Oxidation processes (such as lipid oxidation) or unwanted biological degradation through enzymatic or thermal action can also occur during the processing and storage of cell-based food products, and the formation of undesired by-products resulting from such processes therefore should be limited (Fraeye *et al.*, 2020).

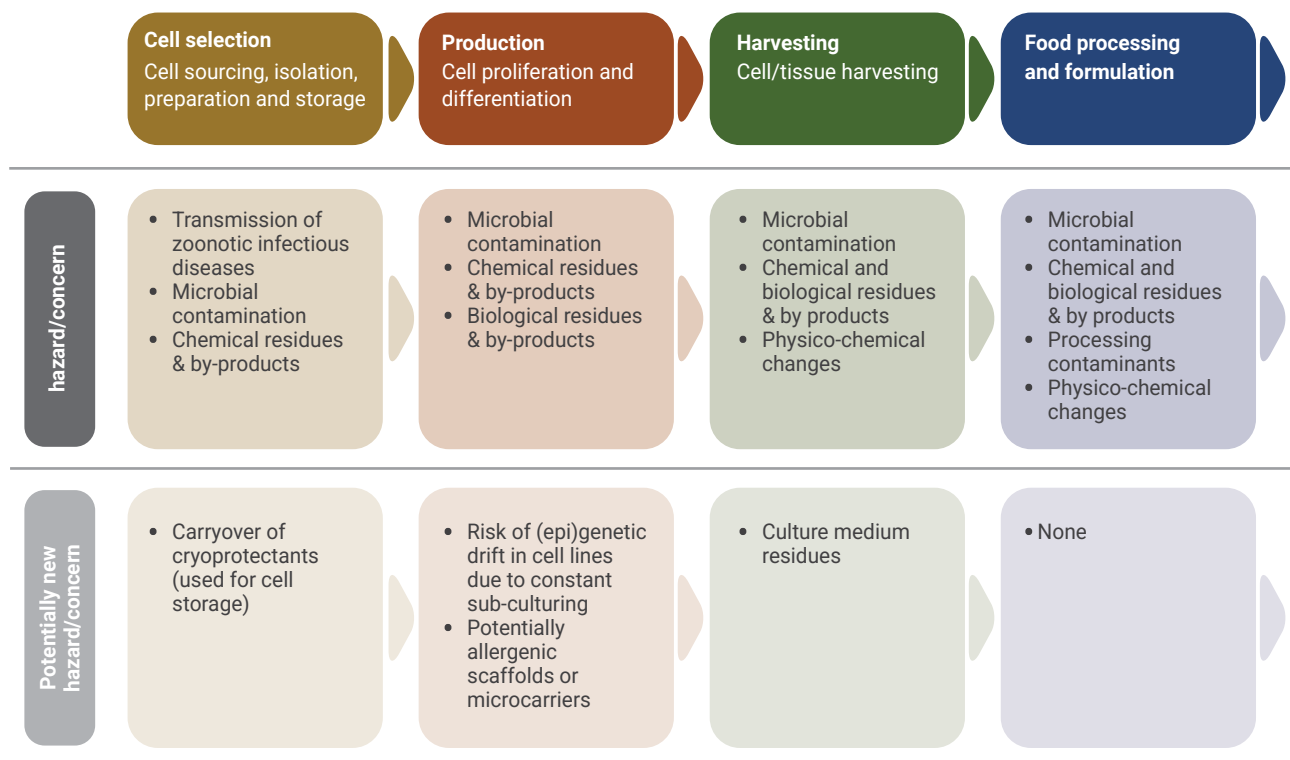


©FAO/Oded Antman

2.3. Discussion

Technological developments for cell-based food products have matured in recent years, but have not yet reached the point of large-scale production or commercialization in most countries. Although the common steps of the production process can be identified in the four major steps (Box 1), each product may employ different cell source, scaffold/microcarrier, culture media composition, cultivation conditions and reactor design. Therefore, it is possible that a case-by-case approach is suitable for the food safety assessment of cell-based food products. While there are many existing tools that can be useful for safety assessment, additional steps may be employed for some particularly novel processes or products. Therefore, with cell-based food products, it is important to focus on the significant differences from existing foods, so that effective methodologies to assess the safety of all elements can be established. Figure 5 shows some potentially new food safety hazards or concerns at different phases of cell-based food production.

Figure 5. Examples of potential food safety hazards and concerns at different phases of cell-based food production



Source: Authors' own elaboration.

Based on the literature review, the majority of the potential food safety hazards in the cell-based food production process, such as microbiological contamination and residue issues, are not new. For such common food safety hazards, there are many risk-mitigating tools available, such as good hygiene, manufacturing, cell-culture, and hazard analysis and critical control points practices (HACCP), as well as the general principles and methodologies for the end-product whole food safety assessment (FAO, 2009). Thus, it is important to learn from various past experiences and consider an effective application of the risk analysis paradigm (Ong *et al.*, 2021). In adopting several established safety assessment methodologies and detection methods from a range of disciplinary fields, such as pharmaceuticals and food biotechnologies including both conventional and modern technologies, various hazards can be systematically identified, and relevant safety assessments can be appropriately conducted. It is important that these methodologies are also validated for the new matrices that are presented by the cell-based food products.

Many countries have not yet experienced an urgent need to conduct food safety assessments of cell-based food products (FAO, 2022). However, it is important for the competent authorities to be prepared and to start dialogues with the various stakeholders including consumers, the private sector, civil society, partner agencies and policy makers. For low- and middle-income countries, it is also important to initiate the assessment of the technical capacity to ensure the safety of cell-based food products as they may benefit from having dialogues with other countries and international organizations to learn from their experiences and to obtain technical assistance. Engaging in the relevant global discussions is recommended for all countries, as shared information and data can only contribute to the global good, with no duplication of efforts.

Active and transparent communications through public-private collaboration are crucial, not only to better prepare industries and governments, but to maximize the effectiveness of their safety assurance programmes. If the competent authorities can provide clear food safety guidelines for the private sector, this would enable and promote the Safe-by-Design approach to jointly aim at ensuring the food safety of cell-based food production, where this approach aims to address safety issues as early as the R&D and design phases of new technologies (van de Poel and Robaey, 2017).

3. Regulatory frameworks

3.1. Introduction

In many countries, the commercialization of food produced using innovative technologies may require regulatory authorization before food items enter markets. For this pre-market authorization, various assessments, including a food safety assessment, compliance assessment, environmental assessment and some other socioeconomic assessments, are conducted by the relevant competent authorities. Because food safety is one of the key interests for consumers, food safety competent authorities often play an important role in this process to ensure that their regulatory frameworks are sufficient and appropriate to cover the safety assurance of such innovative food products. The majority of the legislative texts and regulations related to food are based on food safety risks, nutrition and consumer concerns; therefore, if newly identified hazards or concerns exist for novel food technologies, adjustments to such legal documents will be necessary.

In recent years, many innovations in food production have focused on the so-called “protein transition”, where more sustainable ways of producing animal proteins and alternative non-animal proteins are sought, in order to accommodate the increasing demand for animal products and ensure global food security (Aiking and de Boer, 2020; Henchion *et al.*, 2021). Cell-based food production that makes use of *in vitro* cultivation of animal cells is one of the main technological developments for this. In addition, the production of analogues of specific animal proteins, such as milk or egg proteins, can be done using microbial production platforms. The first development of such products was presented to the general public in 2013, when researchers from the Netherlands presented the first cell-based beef burger (so called “lab-grown” beef burger) (BBC News, 2013). In December 2020, chicken nuggets containing cell-based chicken became the first commercialized product of the kind, after market approval in Singapore (Carrington, 2020). On a wider scale, the research and development of analogues of animal products, such as meat, poultry, seafood, dairy, and eggs produced through cell-based technologies has been advancing quickly in recent years and a large number of companies are developing similar products in over 22 different countries (Byrne, 2021).

Considering the rapid development in the area of cell-based food, it is important that national competent authorities are prepared for market entry of these products in their jurisdictions and have adequate regulatory frameworks in place. In addition to the core food safety assessments, regulatory considerations may be necessary for other issues such as labelling, consumer preference/acceptance, ethical or religious aspects of cell-based food products.

One of the key roles of FAO is to provide science-based policy advice to its Members, particularly to the low- and middle-income countries with an expressed need for such technical assistance. This chapter provides an overview of the state of the art in various regulatory frameworks for animal cell-based food, and food safety is the core area of interest of this document. The country examples introduced in the document do not mean they have been endorsed by FAO, but they simply mean that such information has been made available. For other countries, this information was not publicly available or not presented in English, and therefore information from such countries has been excluded for the scope of this chapter. The information provided here was updated until March 2022.

3.2. Literature synthesis results

3.2.1. Regulatory frameworks and authorization for market entry

Market entry of cell-based food products may require authorization on different levels and the authorization may include a food safety assessment of the cell-based food product, approval of planned and implemented quality controls, assurance protocols for the production process and the use of approved labelling of the products. The essential elements for an effective regulatory framework for cell-based food are still a matter for considerations in many countries. In the following sections, the current status of general and specific regulatory frameworks for cell-based food products is discussed for countries and economic zones where this information is available. These cases are listed in alphabetical order and then summarized in [Table 4](#). Available information on regulatory frameworks for the countries presented here does not always cover the same topics, and certain topics are therefore not discussed in some cases, such as regulations for labelling or the use of genetic modification for food production.



©FAO/Oded Antman

Table 4. Developments in different countries relevant for cell-based food products and their safety

Country / economic zone	Competent authority	Legislative/ standard-setting bodies	Cell-based food product on the market? (until 1 March 2022)	Cell-based food-specifically addressed in food safety regulations and/or safety guidelines/instructions? (until 1 March 2022)
Australia and New Zealand	Food Standards Australia New Zealand	Food Standards Australia New Zealand, "Ministry for Primary Industries"	No	No
Canada	Health Canada	Health Canada	No	No
China	National Center for Food Safety Risk Assessment	Food Safety Committee of the State Council	Unknown	No
European Union / European Economic Area / United Kingdom of Great Britain and Northern Ireland	European Food Safety Authority (European Union) / Federal Food Safety and Veterinary Office (Switzerland) / Mattilsynet (Norway) / Matvælastofnun (Iceland) / Food Standards Agency SA (United Kingdom of Great Britain and Northern Ireland)	European Parliament, Council, European Commission, national ministries, Food Standards Agency (United Kingdom of Great Britain and Northern Ireland)	No	Yes
India	Food Safety and Standards Authority of India	Food Safety and Standards Authority of India	No	No
Israel	National Food Service	Ministry of Health	No	No
Japan	Food Safety Committee	Ministry of Health, Labour and Welfare Ministry of Agriculture, Forestry and Fisheries	No	No
Qatar	Ministry of Public Health	Qatar General Organization for Standards and Metrology and Gulf Cooperation Council Standardization Organization	No	No
Singapore	Singapore Food Agency	Singapore Food Agency	Yes Chicken nuggets and processed comminuted poultry products containing cell-based chicken	Yes
United States of America	Food and Drug Administration / United States of America Department of Agriculture Food Safety Inspection Service	Food and Drug Administration / United States of America Department of Agriculture	No	Yes

Source: Authors' own elaboration.

3.2.2. Australia and New Zealand

Food Standards Australia New Zealand (FSANZ) is the agency that draws up the standards for the regulation of the use of food ingredients, additives and processing aids in Australia and New Zealand. Its Food Standards Code also covers the composition of dairy, meat and beverages as well as foods developed by new technologies, such as genetic modification. FSANZ is responsible for some labelling requirements for packaged and unpackaged food, including specific mandatory warnings or advisory labels.

FSANZ also develops Australia-only primary production and processing standards. FSANZ deals with new types of foods, including foods produced by new technologies, but its Food Standards Code does not contain permissions or requirements for cell-based meats (FSANZ, 2021). The Food Standards Code defines a novel food as a non-traditional food that requires an assessment of the public health and safety considerations, whereby non-traditional food means: (a) a food that does not have a history of human consumption in Australia or New Zealand; or (b) a substance derived from a food, where that substance does not have a history of human consumption in Australia or New Zealand other than as a component of that food; or (c) any other substance, where that substance, or the source from which it is derived, does not have a history of human consumption as a food in Australia or New Zealand (FSANZ, 2017).

FSANZ indicates that cell-based meats would be covered by the existing standards in the Food Standards Code and require pre-market approval in the future (FSANZ, 2021). Depending on the composition of cell-based meats, these standards may include those for: (i) novel foods - foods without a history of traditional human consumption in Australia and New Zealand; (ii) processing aids – substances used to produce foods but which serve no technological function in the final food for sale; (iii) food additives – substances that serve a technological function in the final food for sale; (iv) foods produced using gene technology; (v) vitamins and minerals; (vi) labelling that indicates the true nature of the food; (vii) definition of cell based meat and (viii) food safety requirements.

3.2.3. Canada

Health Canada and the Canadian Food Inspection Agency are the federal authorities responsible for the regulations dealing with foods sold in Canada, including novel foods. Health Canada is responsible for establishing the standards and policies governing the safety and nutritional quality of foods and developing labelling policies related to health and nutrition. The Canadian Food Inspection Agency develops standards related to the packaging, labelling and advertising of foods, and handles all inspection and enforcement duties. Health Canada controls the sale of novel foods in Canada via a mandatory pre-market notification requirement, as set out in Division 28 of Part B of Canada's Food and Drug Regulations (Canada, 2021). Health Canada's guidelines for the assessment of novel foods are grounded in the internationally harmonized principles for the comparative safety assessment of foods derived from recombinant DNA organisms as outlined by the Codex Alimentarius Commission, FAO, the World Health Organization (WHO) and the Organisation for Economic Co-operation and Development (OECD) (Health Canada, 2021).

According to the Canadian regulations, a novel food means: (i) a substance, including a microorganism, that does not have a history of safe use as a food; (ii) a food that has been manufactured, prepared, preserved or packaged by a process that has not been previously applied to that food, and causes the food to undergo a major change; and (iii) a food that is derived from a plant, animal or microorganism that has been genetically modified such that the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism, the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism, or one or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism. To the authors' knowledge, no cultured meat product has passed through the Canadian novel food procedure yet, whilst these products appear to fall within three domains of novel food classification: no history of use, novel process, and possibly genetically engineered (Suresh, 2018).

The procedure for authorizing a novel food involves a pre-market notification in writing to the government which should include (amongst other things) the following information regarding the novel food: (i) the common name

under which the novel food will be sold; (ii) a description of the novel food, together with details of the methods for manufacturing, preparation, preservation, packaging and storage, details of the major change (if any), information on its intended use and directions for its preparation, information demonstrating its history of use as a food in a country other than Canada (if applicable), and information that establishes that the novel food is safe for consumption; (iii) information on the estimated levels of consumption by consumers of the novel food; and (iv) the text of all labels to be used in connection with the novel food.

In addition, along with Health Canada oversight, Environment and Climate Change Canada (ECCC) and Fisheries and Oceans Canada (FOC) also have responsibilities for ensuring that novel products respect all environmental responsibilities. Other regulations that could apply to cell-based food products are the New Substances Notification Regulations (NSNR) under the Canadian Environmental Protection Act, 1999 (CEPA) (Cellular Agriculture Canada, 2021). The CEPA sets toxicity criteria to ensure that no new substances are introduced into Canadian commerce before their potential risk to human health and the environment has been assessed. 'Substance' is defined by the CEPA as any distinguishable kind of organic or inorganic matter, whether animate or inanimate, and includes chemicals, biochemicals, polymers, biopolymers, and living organisms. The NSNR is divided into two separate sets of new substances provisions: new living organisms (e.g. bacteria, viruses, cells) are subject to the NSNR (Organisms), while new chemicals and polymers are subject to the NSNR (Chemicals and Polymers). Substances that are not listed on the Domestic Substances List (DSL) are considered new substances and may require notification under the NSNR prior to being imported into or manufactured in Canada. For the cell-based meat industry this means that cultured cells, if not already on the Domestic Substances List, would most likely be subject to the NSNR (Organisms). Tissues that are generated through cell culture, as well as substances used in the cellular agriculture process, would likely be subject to NSNR (Chemicals and Polymers).

3.2.4. China

In China, cell-based food would fall under the definition of "new food raw materials" as defined by the Administrative Measures for the Safety Review of New Food Raw Materials (NHFPC, 2013). As stated in Article 2, the term "new food raw materials" refers to the following items which are not of traditional eating habits in China: (1) animals, plants and microorganisms, (2) ingredients extracted from animals, plants and microorganisms, (3) food ingredients the original composition of which has been changed, and (4) other newly developed food raw materials. The safety of these new food raw materials needs to be reviewed by the National Center for Food Safety Risk Assessment, before approval of their use in food production and trading (CIRS, 2021).

3.2.5. The European Union, the European Economic Area and the United Kingdom of Great Britain and Northern Ireland

The preamble to the Novel Food Regulation (European Union) No. 2015/2283 (European Union, 2015) explicitly mentions that its scope includes food from the culture of cells or tissues from animals, plants, and microorganisms, fungi or algae. This aligns with the notion that cell-based foods and the processes for manufacturing them lack a history of substantive and safe consumption within the European Union. Regulatory approval and inclusion in the Catalogue of approved novel foods will therefore be needed before cell-based foods can be sold within the European Union. The approval procedure requires that companies wishing to market a novel food submit an application dossier containing, amongst other things, a safety dossier (EFSA Panel on Dietetic Products *et al.*, 2016). Besides data from original safety studies, these dossiers may also contain literature and other existing data to support the application. The latter would conceivably apply to product components that are food-grade (e.g. certain natural biopolymers used for scaffolding) or that have a substantial history (25 years) of consumption or traditional use in a country outside the European Union (European Union, 2015; Seehafer and Bartels, 2019).

Moreover, any food should be safe, novel or not, and its labelling should not be misleading, and if it replaces a particular existing product, this replacement should not be nutritionally disadvantageous to the consumer, for which data would need to be provided. The safety of the particular products is then assessed at a centralized European

level by experts in a scientific Panel of the European Food Safety Authority (EFSA), which specifically advises the European Commission on matters of food safety, including that of regulated products such as novel foods. The Commission can then take a decision (or propose it to the regulatory European Union bodies) to approve a product for entry into the European Union market.

Besides novel foods, also other sectors of legislation may also be applicable in the European Union. For example, genetic modification may have been used to produce improved cell lines for cell-based food production. In that case, the products should also comply with legislation on genetically modified products, such as the GM Food and Feed Regulation (European Union) No. 1829/2003 (European Union, 2003) according to which a pre-market safety assessment will be required. In addition to these rules on novel and GM foods, generic rules on food hygiene and safety, also within production environments apply, such as good manufacturing practices (GMP) and hazard analysis and critical control points (HACCP) rules.

Labelling rules apply, but Seehafer and Bartels (2019) note that in the absence of specific European Union provisions, the national legislation of Member States will have to fill this gap for the time being, and labelling rules are delegated to member states (Seehafer and Bartels, 2019). The European Commissioner has in several instances alluded to the possibility of invoking labelling provisions at the European Union level to ensure that consumers are informed about the nature of these products (Parliament, 2018; Parliament, 2019). As for the United Kingdom of Great Britain and Northern Ireland, it has retained European Union legislation on novel foods, including its risk assessment and decision-making procedures, although these take place at the national level as of May 2021 (except for Northern Ireland, which continues to abide by European Union rules and procedures for authorization) (FSA, 2020).

3.2.6. India

In India, according to the Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations (2016), a novel food is defined as a food that: (a) may not have a history of human consumption; or (b) may have any ingredient used in it which or the source from which it is derived, may not have a history of human consumption; or (c) a food or ingredient obtained by using new technology with innovative engineering processes, where the process may give rise to significant change in the composition or structure or size of the food or food ingredients, which may alter the nutritional value, metabolism or level of undesirable substances (FSSAI, 2016). Cell-based foods would fall under these definitions. For novel foods like cell-based foods to be manufactured and sold in India, approval is required from the Food Safety and Standards Authority of India (FSSAI) for which the procedure is laid out in the Food Safety and Standards (Approval of Non-Specified Food and Food Ingredients) Regulations, 2017 (FSSAI, 2017). Other regulations that are likely to play a role include, amongst others, general quality assurance and hazard management systems and good hygiene and manufacturing practices, as well as e.g. laws against animal cruelty (Kamalapuram *et al.*, 2021).

3.2.7. Israel

In Israel, the National Food Service at the Ministry of Health is responsible for assuring the safety, quality, and authenticity of food for consumers. The safety assessment standards and laws are to a great extent harmonized with those of the European Union, and Israel's risk assessors will also take into consideration the assessments of the safety bodies of the European Union, the United States of America, Canada, Japan and the Australian and New Zealand bodies, which can help fast-track the national application (AgroChart, 2016).

Cell-based food is considered to be a novel food under Israeli legislation (Gross, 2021). Novel Food in Israel is defined as food that had not been consumed to a significant degree by humans in Israel before 19 February 2006, when the first Regulation on novel food in Israel came into force. The pre-market authorization process in Israel is outlined in its novel food regulation framework (Israel Ministry of Health, 2015). This framework defines novel food as a food or food ingredient that falls into at least one of the following criteria and which is not classified as a food additive, a food supplement, a processing aid or a food flavouring:

1. Is of a novel primary molecular structure or has undergone an intentional alteration in its primary molecular structure, for which there is insufficient history of safe human consumption before February 2006.
2. It contains a genetically modified organism or a part thereof.
3. It contains a plant, animal, microorganism, fungi or algae, or derived from these, for whom there is insufficient history of safe human consumption.
4. It was manufactured in a process which was not used in Israel for the manufacturing of this specific food or food component, and this process has led to a substantial change in the composition of the food, its structure or components, and has affected its nutritional value, its metabolic qualities or the level of undesired substances in it.

More information on regulatory developments can be found in Israel's case study (see [Section C](#)).

3.2.8. Japan

Cell-based meat marketing in Japan is expected to become operational in late 2022 (Ferrer, 2021), and part of the cell-based meat landscape in Japan has its roots in the do-it-yourself biology (DIY Biology) movement carried out by young scientists, represented in the media wearing futuristic apparel, and guided by “open science” principles (Hanyu, 2021). Japan has not yet communicated any new food regulations or standards that explicitly address a regulatory framework for cell-based meat (Ettinger and Li, 2021).

However, some general basic requirements from the existing food legislation are likely to apply, such as Article 3 of the Japanese Food Sanitation Act that requires that food business operators shall take necessary measures to ensure the safety of the food for sale for human consumption, and Article 7 that states that “when things which have not generally been served for human consumption and have not been proven to be unlikely to cause harm to human health or things including those things have newly come to be sold or are going to be sold as food, the Minister of Health, Labour and Welfare may prohibit the sales of those things as food, by hearing the opinions of the Pharmaceutical Affairs and Food Sanitation Council, when the Ministry of Health, Labour and Welfare finds it necessary to prevent food sanitation hazards” (Japanese Law Translation, 2022).

A technical working group within the Japanese Ministry of Agriculture, Fisheries and Food has recently started developing strategies for various types of alternative protein sources (replacing animal products), such as plant- and insect-based substitutes but also cell-based meat. Besides regulations, these strategies also consider other aspects, such as research policy, public-private partnerships, consumer acceptance, and food security. The establishment of the Food Tech Research Group in April 2020 has been instrumental in gathering the perspectives from government agencies, research institutions, and industrial players.

3.2.9. Qatar

According to recent news reports, Qatar will host a cultured chicken meat production facility which is to become operational shortly, a first of its kind for the Middle East and North African region. Whilst an export licence may have been granted, Qatar's Free Zone Authority and Ministry of Public Health also intend to grant regulatory approval for the new product (Business Wire, 2021). For the regulatory risk assessment of novel foods, the Gulf Standardization Organization, of which Qatar is a member, developed a guideline for novel food products. More information on the regulatory developments can be found in Qatar's case study (see [Section C](#)).

3.2.10. Singapore

In Singapore, chicken nuggets containing cell-based chicken have been granted regulatory approval and marketed since 2020 and a novel food regulatory framework was established by the Singapore Food Agency (SFA) in 2019. The SFA states that alternative proteins generally refer to proteins derived from sources other than animal protein. Some forms of alternative proteins, such as “cultured meat”, are considered to be a novel food as they do not have a history of being consumed by humans as food (SFA, 2020). Cultured meat refers to “meat developed from animal cell culture, where the process to produce cultured meat involves growing the selected cell lines (or stem cells) in a bioreactor. These cells are grown in a suitable growth media, and subsequently onto a ‘scaffold’ to produce products resembling meat muscle”.

Under Singapore’s regulatory framework for novel foods, companies producing novel food products are required to conduct and submit safety assessments of their products for the SFA’s review before they are allowed to be put on sale. In order to facilitate this process, SFA has released a document on the food safety information that would be required for novel food safety assessment (SFA, 2021a). The information should cover potential food safety risks, such as toxicity, allergenicity, the safety of its production method, and dietary exposure arising from consumption. Companies must also provide detailed information on the materials used in their manufacturing processes and how these manufacturing processes are controlled to prevent food safety risks.

In particular, the SFA notes that the science for producing cultured meat is still at an early stage. The specific requirements for information that should be submitted for the safety assessment of cultured meat are included in the SFA guidance (SFA, 2021), but the SFA notes that information required may change based on the developments on the science of producing cultured meat. The SFA may also accept, for its own review, safety assessment reports conducted by food safety authorities in other countries, such as Australia, Canada, New Zealand, Japan, the European Union and the United States of America, provided these assessments have been conducted in conformity with reference documents from the authorities in the United States of America, EFSA or FAO/WHO.

To ensure that the safety assessments provided by applicants are rigorously reviewed, the SFA has established a Novel Food Safety Expert Working Group to provide scientific advice. The expert working group comprises experts specializing in food science, food toxicology, bioinformatics, nutrition, epidemiology, public health, genetics, carcinogenicity, metabolomics, fermentation technology, microbiology and pharmacology.

The SFA also emphasises the importance of engaging companies in the novel food regulatory framework even when the companies are in the early stages of their research, as this will help companies prioritize resources towards productive research directions which will minimize compliance costs and time. To this end, the SFA introduced Novel Food Virtual Clinics in September 2021.

Regarding labelling, SFA requires that cell-based meat products be labelled such that their nature can be clearly conveyed to consumers, with terms such as “cultivated meat”, “cell-based meat” or “cultured meat” (SFA, 2021). More information on regulatory developments can be found in Singapore’s case study (see [Section C](#)).



3.2.11. The United States of America

In the United States of America, jurisdiction over cell-based human food products is dependent on the animal from which developers derive the cultured cells. The FDA will have sole responsibility for the oversight of human foods derived from animals other than livestock, poultry, or siluriformes fish. This includes all foods derived from the cells of seafood (except siluriformes fish). The FDA also has sole jurisdiction over the production of all cell-based foods for animals, such as pet-foods and other animal feeds, regardless of the source of the cells.

The FDA and the United States Department of Agriculture's Food Safety and Inspection Service (USDA-FSIS) have established a joint regulatory framework for the oversight of human food products derived from livestock, poultry, and siluriformes fish (FDA, 2019). Under this agreement, the FDA will oversee the initial stages of production, including the collection, banking, growth and differentiation of cells for livestock, poultry, and siluriformes fish. A transition from FDA to USDA-FSIS oversight will occur at the time of harvest. The USDA-FSIS will then oversee the processing, packaging, and labelling of the resulting meat and poultry products. For foods comprising cultured seafood (other than siluriform fish) or game meat cells, the FDA will oversee processing, packaging and labelling in addition to the culture process.

Developers of cell-based products should complete a pre-market consultation with the FDA, which will typically address the processes used and the resulting products, including the biological materials used. If these consultations on the safety of the cell-based product are successful and once commercialization has begun, the FDA will initiate inspections for the production process of products under its exclusive jurisdiction. However, developers of cell-based food derived from livestock, poultry, and siluriformes fish must take the additional step of applying for a USDA-FSIS grant of inspection. Upon issuance of a USDA-FSIS grant of inspection, FDA will initiate inspections for the production process of cell-based meat or poultry products and the USDA will, at the time of harvest, initiate inspections at a frequency similar to those for traditional meat and poultry. Developers must also ensure that sanitation and quality control procedures (e.g. HACCP) are in place for the production.

The labelling of poultry and meat is within the USDA's remit, whilst that of seafood (siluriformes species not included) is within that of the FDA. Both agencies are jointly pursuing a consistent labelling policy for animal food products derived from cultured cells and both agencies have announced their intention to address the labelling of these products. The FDA published a "Request for Information" in October 2020 in which it requests comments for "the labelling of foods comprising or containing cultured seafood cells." The FDA intends to use the information and data resulting from this notice to determine what type(s) of actions, if any, the agency should take to ensure that these foods are properly labelled (FDA, 2020). The FSIS did so through an "Advance Notice of Proposed Regulation (ANPR)", while noting that the proposed labels for cell-based products comprising livestock or poultry cells will be subject to a pre-market review (FDA, 2020, USDA, 2021). Notably, the FSIS ANPR draws a parallel with two historic cases of advanced meat separation techniques applied to poultry for the production of boneless "separator" meat. In a first case for Mechanically Separated Poultry (MSP), a new standard of identity was established by the USDA-FSIS as physical form, texture, and ingredients (e.g. bone content) of these Mechanically Separated Poultry products were considered materially different from those of other boneless poultry products produced by hand deboning techniques. In a second case for new meat products derived from advanced meat recovery, the USDA-FSIS did not impose a new labelling requirement, as advanced meat recovery meat was considered comparable to meat derived by hand deboning in terms of its composition, appearance, and texture, so long as it was produced in accordance with the regulations. Instead, compositional requirements were set and the legal definition of meat modified so as to clarify that boneless meat products (such as advanced meat recovery meat) were not allowed to contain significant portions of bone or bone components.

The USDA used its ANPR to solicit comments on questions as to whether terms are needed to discern cell-cultured products from others, which terms should be in the product name of a food containing animal cells, which terms could be potentially misleading if names refer to the form of a meat or poultry product (e.g. fillet, steak), and which names might have a negative impact on consumers and industry. It also asked if the legal definitions of meat and poultry products should be amended so as to include or exclude foods derived from cultured animal cells. These issues of regulation and safety in the ANPR thereby also addressed the various aspects identified by the scientific investigations into the impact of naming of these products on acceptance and on interpretation accuracy.

3.2.12. Legislation in relation to religious laws and regulations

As mentioned by Bhat *et al.* (2019), cell-based meat does not involve slaughtering a large number of animals, and could therefore be considered to be free of any ritual link such as halal, kosher or Jhatka. However, the initial source of the cells and biopsies for starting cell cultures will certainly have an impact on the perception and decision of consumers (Bhat *et al.*, 2019). If the culture medium and initial cells were halal (e.g. myoblasts and media taken from animals considered halal or animal-free media), the developed cell-based meat may be allowed by Islamic law, according to some Muslim scholars (Billinghurst, 2013). Likewise, if the initial cells were taken from a kosher animal slaughtered according to Jewish law, the developed product may be considered kosher (foods considered permissible by Jewish dietary laws), according to several rabbis. A recent decision on the kosher status by some rabbis declared that “cultured meat” products derived from embryonic stem cells (ESCs) taken from a bovine blastomere/blastula is considered “Kosher Parve” – e.g. not meat per se – and as such can be eaten together with dairy (Greenwood, 2022). A consensus on these issues does not yet exist, due to the different nature of the religious certifying bodies (JTA 2018; Kenigsberg and Zivotofsky, 2020; Shurpin, 2018).

3.2.13. Other potentially relevant legislation and regulations

Besides food safety-related legislation and regulations, there may be other regulatory elements that could be of concern for cell-based food production. For cell sourcing and isolation, there may be relevant legislation related to taking biopsies from live or dead animals, and this could involve animal welfare issues. In addition, isolated cells might be stored in cell banks for which regulations exist in several countries (EMA, 1998; FDA, 2010). Cell-based food production might also produce new types of biological or chemical by-products and waste, for which specific regulations apply, such as environmental legislation. Furthermore, by-products might also be used in feed applications if they meet the feed safety requirements.

3.3. Discussion

Cell-based food production technologies have matured over the years and commercialization of these products has been initiated in a limited number of countries, while market introduction is expected in other countries in the coming years. Considering the fast global developments in cell-based food production, countries may wish to be well prepared in order to have the necessary regulatory frameworks, bodies and infrastructure in place for assessing the safety of cell-based food products and production processes, as well as legislation developed for accepted terminologies and labelling requirements for marketing these products.

Analysis of the global developments in the regulation and risk assessment of cell-based food products indicates that, in most countries, cell-based foods can be assessed within existing novel food regulations. Singapore has already made amendments to its novel food regulations to specifically include cell-based foods (cultured meat), while the United States of America has drawn up a formal agreement for food made from cultured cells of livestock (including siluriformes fish) and poultry that addresses safety and labelling requirements. In addition, the USDA has stated its intent to draw up regulations on the labelling of meat and poultry products derived from animal cells. This new labelling regulation is being prepared via a public process consistent with United States of America agency practices for rulemaking. Consistent with the USDA/FDA formal agreement, the FDA has also requested information on labelling of foods comprising or containing cultured seafood cells to determine what type(s) of actions, if any, the agency should take to ensure that these foods are properly labelled.

The labelling of cell-based food products in most countries is expected to be clear, understandable and not misleading for consumers and to be distinguishable from related products, such as conventional meat or fish or plant-based meat replacers. No regulations seem to exist worldwide for the designation of the modifier part of “cultured meat”, but there are restrictions in many countries for the “meat” part. In some countries, terms related to conventional meat or meat products will not be allowed, such as in Germany and France, while Singapore has indicated that meat terms will be allowed with suitable qualifying terms, and in the United States of America and other countries this is still a matter of debate.

Other legislative acts that may be of importance include religious food laws, legislation on biopsies, animal welfare legislation, and environmental regulations for the removal of “cultured” meat production waste (Stephens *et al.*, 2018). Opinions from Muslim and Jewish religious scholars indicate that cell-based meat products might be labelled as halal or kosher respectively, and therefore these products adhere to some of the existing religious laws, which is an important factor for manufacturing and marketing cell-based foods in certain countries. However, some others are also stating that such labelling depends on exactly what cells and materials have been used during the entire process of the production; thus a case-by-case approach may be appropriate or the establishment of some standards that could guide regulators.

These developments can serve as examples for other countries to decide whether assessment of cell-based food products is possible within their existing and relevant food regulations, or if specific regulations need to be developed for cell-based food products for which they can provide information on what elements might be important to include in novel food legislation. To set up the regulatory frameworks, it is also important for the competent authorities to do so in a transparent dialogue with various stakeholders, including consumers, the private sector, civil society, partner agencies and policy makers (FAO/WHO, 2016).

At its 44th session in November 2021, the Codex Alimentarius Commission discussed this important topic with the paper prepared by FAO and WHO, entitled “New food sources and production systems: need for Codex attention and guidance?” (Codex Alimentarius, 2021). During the session, while a number of emerging issues relevant to food safety, such as seaweed, microalgae, edible insects, protein alternatives and 3-D printed foods were highlighted, cell-based food was also included as an option to be included in the scope of future discussion. The Codex Executive Commission is currently analysing the submitted information from the Members and observers on the issues so that the future direction of the potential work by the Codex can be determined (Codex Alimentarius, 2022).

There is currently a limited amount of information and data on the food safety aspects of cell-based foods to support regulators in making informed decisions, and therefore active and global data-sharing is desired to employ an evidence-based approach to prepare any necessary regulatory actions. For low- and middle-income countries, it may be of benefit to start dialogues with other countries and international organizations to learn from their experiences and to obtain technical advice and assistance, in order to develop a significant capacity for the safety assurance of cell-based food products. It is also important to discuss these matters on a global scale and to share experiences and good practices, as this can contribute to strengthening appropriate and effective regulatory frameworks with no duplication of efforts.



C. COUNTRY CASE STUDIES

1. Israel – country contexts

1.1. Terminology

In Israel, consumer protection laws require that all product labelling be truthful, accurate and verifiable so that it fully reflects the true nature of the product to the consumer. Having an agreed upon, fixed terminology is critical for regulatory purposes, and especially for labelling. Therefore, a unique term that differentiates traditional meat products from “cell-based” products will be defined by the relevant competent authorities. Though the term in Israel should be set in Hebrew, labelling is also required in Arabic, and in many cases English is also used. As such the defining term in the three languages should have the same meaning and should be as exact a translation as possible.

Currently, Israel does not have a formal or legal definition in place to describe cell-based food products, regardless of their origin: meat, poultry, fish or seafood-based products. Several common terms are used in the media in Hebrew and are to some extent known and are familiar to the public. These terms include: “[modifier] *Meturbat* – מתורבת []” Hebrew for cultivated, cultured, refined or domesticated [meat, poultry, etc.]; “[modifier] *Maabada* – מעבדה []” Hebrew for lab (grown) [meat, poultry, etc.]. Less common terms include “[modifier] *Synteti* – סינטטי []” Hebrew for synthetic [meat, poultry, etc.]; “[modifier] *Naki* – נקי []” Hebrew for clean [meat, poultry, etc.].-

In addition to the Hebrew speaking population, about 20 percent of the Israeli public speak Arabic and consume Arabic speaking media. Common terms known by the Arabic speaking population include: “[modifier] *Masna* – مصنع []” Arabic for processed [meat, poultry, etc.]; “[modifier] *Mazru* – مزروع []” Arabic for cultivated [meat, poultry, etc.]; and “[modifier] *Fi'l Muhtabar* – في المختبر []” Arabic for lab (grown) [meat, poultry, etc.].

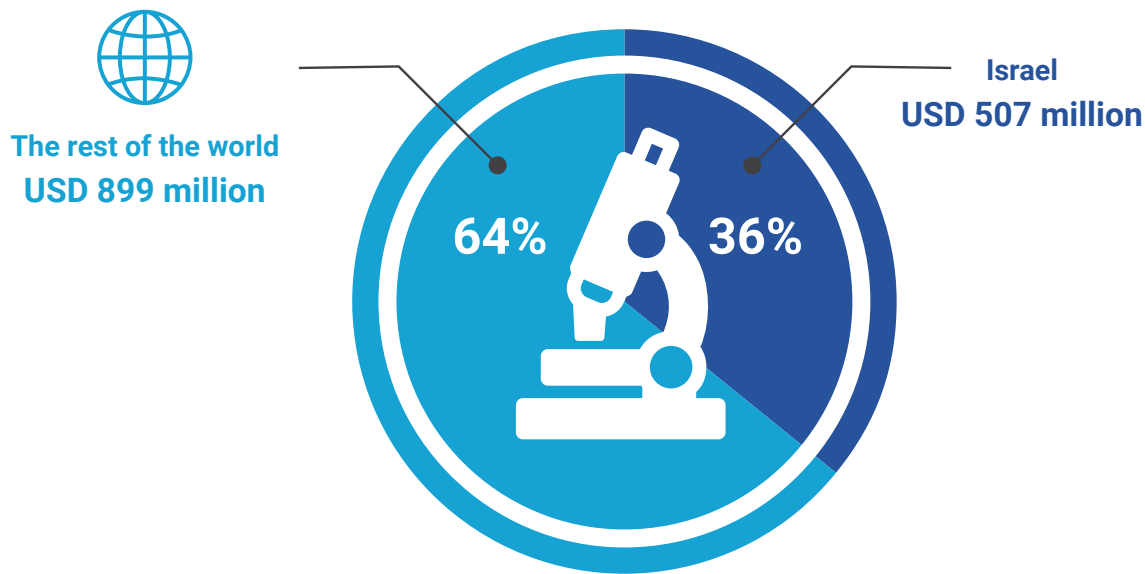
The Israel National Food Service (NFS) within the Ministry of Health (MOH) is in the process of designing public surveys to study the public’s acceptance of cell-based food products and to study the effect labelling has on public perception. Among other things, the possibility of not using the word “meat” at all for labelling cell-based products is also being considered.

1.2. Current status

As of July 2022, no cell-based food products had been approved and none were placed on the market in Israel, despite the fact that Israel is a global hub for research and development (R&D) in the field. Currently, in Israel, there are 13 cell-based food start-up companies in various stages of development and scaling-up. These start-ups produce a variety of cell-based products including various types of meat, poultry, fish and other types of seafood.

The Israeli cell-based food start-up scene saw investments of USD 507 million in 2021, which represents upwards of 36 percent of global investments made during 2021 in cell-based food products. This capital funding comes from both local and foreign investors.

Figure 6. Global investments in cell-based food products in 2021



Note: Thirty-six percent of global investments made in cell-based food businesses during 2021 were in Israeli companies, and particularly in two companies.

Source: GFI (Good Food Institute). 2022. *Israel State of Alternative Protein Innovation Report*. GFI Israel. <https://gfi.org.il/resources/israel-state-of-alternative-protein-innovation-report-march-2022/>

Cell-based food start-ups in Israel are increasingly drawing attention away from established, traditional food manufacturers in Israel and abroad. Several large traditional food manufacturing companies have teamed up with start-ups from both the food and agrotech sectors as well as from the pharma sector, to evaluate and develop technologies to produce cell-based food products. These collaborations and investments are indicative of the booming start-up scene within Israel.

Recently, the industry has been launching more public relations campaigns within various media platforms, through mainly online and on social media. These campaigns emphasize the advantages of cell-based food products, when compared to traditional animal-derived food products, in multiple environmental performance indices. The campaigns focus on the sustainable, ethical and humane aspects of cell-based food production and are directed at environmentally conscious consumers aiming to reach not only vegans and vegetarians, but also flexitarians. The legislation concerning labelling in Israel directly addresses the claims related to environmental advantage, since labelling legislation covers any and all publications related to the food product. These claims, therefore, must be truthful, accurate and verifiable before cell-based food products can be placed on the Israeli market.

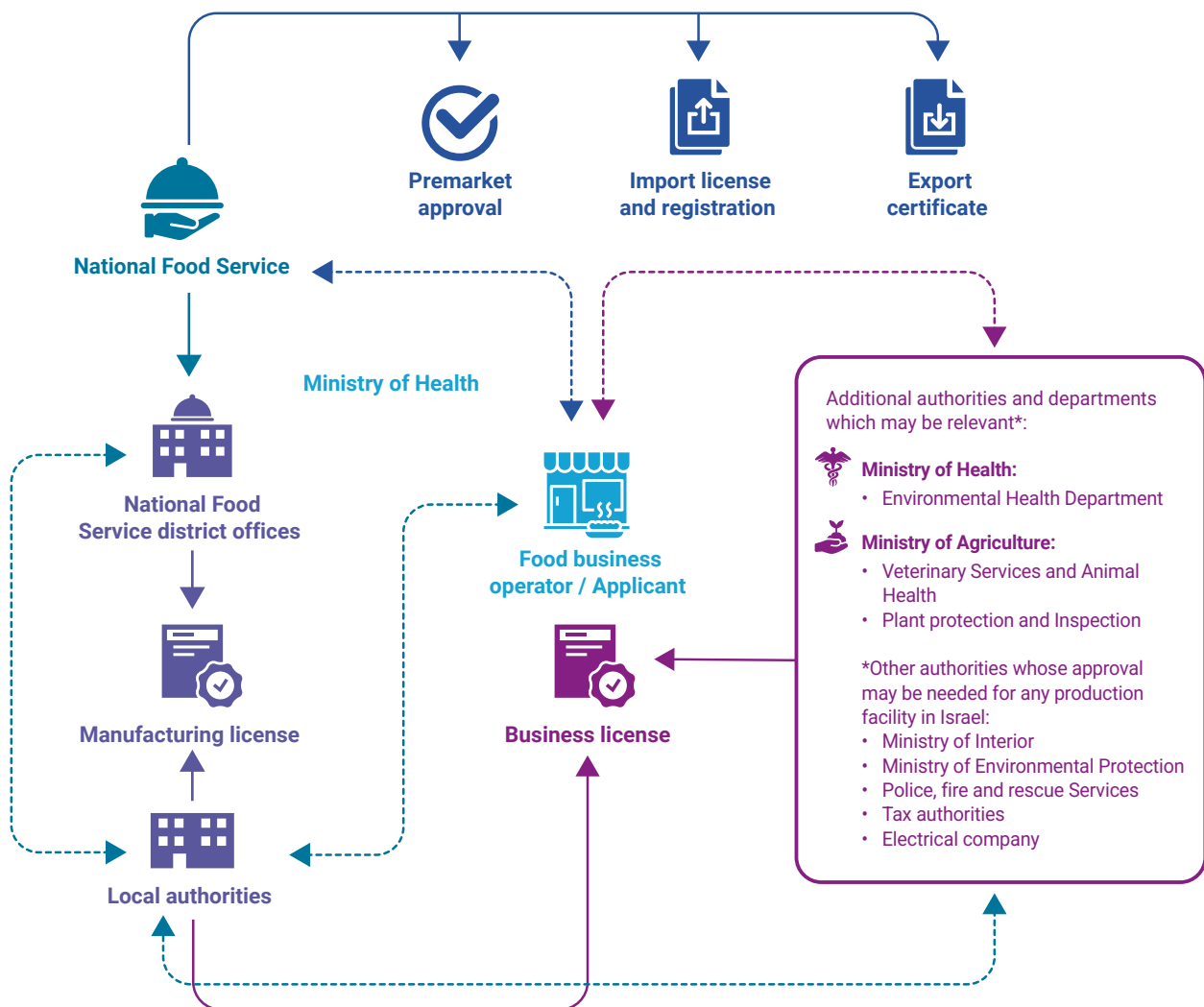
Generally speaking, the Israeli consumer is quite liberal and open to trying innovative technologies and novel foods, yet there is no formal consumer research on the topic of cell-based food. There is a growing need for research in this field that can evaluate the acceptance rates in the general population and in specific sub-populations, and that can allow for estimates of how much the general public might consume. The NFS is in the process of designing a study to offer insight regarding public acceptance of these products. Data driven evaluations of the future exposure of consumers to cell-based food products will help the overall process of risk assessment and pre-marketing approval.

1.3. Regulatory framework

1.3.1. Regulatory/competent authorities

The Israeli Ministry of Health is responsible for ensuring the health of the population. The MOH determines policy on matters of health and medical services, and is in charge of planning, supervision and control, licensing and coordination of the health system's services. The MOH provides health services in hospitalization and preventive medicine, in matters of mental health, geriatrics, rehabilitation and public health. Public health services within the MOH are responsible for preventive medicine perspectives, including food and nutrition.

Figure 7. Regulatory agencies and ministerial offices that may be involved in various stages of a cell-based food start-up company up to and including pre-market approval and issuing the required licences for commercial manufacturing



Note: Additional details are presented in section 2.5.1. Ministry of Health and National Food Service responsibilities include pre-market approval, import licence and export certificate (in dark blue), as well as the manufacturing licence issued by the NFS district offices (in red). Dashed lines indicate communication channels.

Source: Author's own elaboration.

The NFS within the MOH of Israel, is the regulatory agency responsible for developing food standards and regulations related to food placed on the market in Israel. The NFS is mandated to assure the safety, quality and authenticity of food for consumers. All aspects of supply and safety of food designated for human consumption falls under the responsibility of the NFS, which enacts standards, regulations and laws that are to be implemented throughout the different districts nationwide.

The NFS regulates local food manufacturing, food import and export, and issues around importing and manufacturing licences. It also supervises various aspects of food production, marketing and sales. The NFS conducts a risk management assessment to ensure that food is safe for consumption.

The preapproval process of novel foods, including cell-based food products, falls within the mandate of the NFS. The process includes discussions with the novel food committee that considers the different safety aspects (toxicology, nutrition, etc.) of such foods. More broadly, the Israeli Ministry of Agriculture and Rural Development, the Ministry of Environmental Protection and the Ministry of Economy might have to collaborate on specific cell-based food products.

1.3.2. Regulatory category

Cell-based food is considered a novel food under the Israeli legislation. Novel food in Israel is defined as food that was not much consumed in Israel before February 2006 when the first regulation on novel food came into force in the country. Israel's pre-market authorization process is outlined in its novel food regulation framework. This framework defines a novel food as a food or food ingredient that falls into at least one of the following criteria and which is not classified as a food additive, a food supplement, a processing aid or a food flavouring:

1. is of a novel primary molecular structure or has undergone an intentional alteration in its primary molecular structure, for which there is insufficient history of safe human consumption before February 2006 in Israel;
2. contains a genetically modified organism or a part thereof;
3. contains a plant, animal, microorganism, fungi or algae, or is derived from these, for which there is insufficient history of safe human consumption in Israel; and
4. has been manufactured in a process that has not previously been used in Israel for food manufacturing or for manufacturing this specific food category or food component, especially if this process has led to a substantial change in the composition of the food, its structure or components, and has affected its nutritional value, its metabolic qualities or the level of undesired substances.

Cell-based food products may fall under the food category of "meat" or "processed meat products" as defined in The Public Health Protection Law (Food): edible parts of livestock (cattle, sheep, goat, deer, buffalo, camel, horse, mule, donkey, pig and rabbit), poultry (chicken, geese, duck, turkey, pigeon, swan, muscovy duck, mallards, peacock, guineafowl, ostrich, quail and pheasant) and aquatic animals (fish, crustacean and mollusk), with or without bones and with or without skin. The precise nature of cell-based foods still requires regulatory definition in this scope; an internationally agreed upon definition can prove beneficial for harmonization and trade.

All food categories in Israel are divided into two groups, "regular food" and "sensitive food", which determines their regulatory requirements. The sensitive food category is more tightly regulated (for example, good manufacturing practices (GMP) and hazard analysis and critical control points (HACCP) certificates are needed, both for locally produced and imported food. Cell-based food products fall under the sensitive food category, though it is possible that a new category could be created.

The Public Health Protection Law (Food) (Sensitive Food Proclamation) 2019 lists those products that could be considered to be "sensitive food", and currently include:

1. milk and milk products and their analogues, which contain milk components;
2. meat and its products;
3. fish and fish products including shellfish, crustaceans and animals from the echinoderm group;
4. eggs and their products;

5. honey and its products;
6. products containing gelatine or collagen or both;
7. canned foods with low acidity (pH > 4.5);
8. food products that must be stored, held or transported at a controlled temperature or at a defined temperature, as defined by law, provided that the temperature is below 8 °C;
9. foods for special nutritional purposes, other than foods marked “gluten-free”, as specified below:
 - i. foods intended for consumption by infants and toddlers including food compounds and complementary foods marked as such,
 - ii. designated food as defined by law, other than food marked “gluten-free”,
 - iii. foods intended to be a substitute for the daily diet, in whole or in part, including formulas or nutritional supplements for athletes,
 - iv. a dietary supplement as defined by law, and
 - v. vitamins, minerals and amino acids for use as a nutrient in the food industry;
10. mushrooms or mixtures thereof including products of which mushroom is a principal component;
11. microorganisms for use in the food industry or as a finished product;
12. bottled drinking water, mineral water and mineral water-based beverages;
13. food colouring intended for retail marketing; and
14. the leaves of the *Catha edulis* plant in their natural form that are intended for mastication.

1.3.3. Relevant laws and regulations

Apart from the Novel Food Regulation 2006, novel foods are required to comply with all relevant Israeli food legislation covering multiple aspects of food safety. The Israeli Public Health Protection Law (Food) 2015 is the main legislation dealing with food safety regulation in Israel. The law has introduced a comprehensive and coherent system of official controls by public bodies in charge of public health surveillance regarding food intended for human consumption. The official controls vertically cover the entirety of the food chain once the food products leave the primary production site and are destined for processing and then to the marketplace and finally to consumers. The law lists both safety and quality criteria as well as the organizational and administrative structure of controls. There are various institutions in charge of official controls with distinct roles.

The current demands, set out in the Public Health Protection Law (Food) 2015, require small and large food manufacturers in Israel to obtain a manufacturer’s licence before they start producing the food product. This licence can be obtained from local municipal authorities along with the authorization of the sanitary plan by the MOH food inspectors located in the facility’s district. The regulatory demands for food production are set out in the law and there are specific procedures and food standards (set out by the Standards Institute of Israel) for several food categories.

Additional regulations covering cell-based food products include those that relate to the levels of various contaminants, chemicals and biological hazards, as well as pesticide residues. These regulations have recently been reformed to align with the European Union Acquis following the adoption of European Commission Regulations No. 1881/2006; 73/2018; 2073/2005 and 396/2005. Additional Codex Alimentarius guidelines on various issues such as food additives also apply in Israel.

1.3.4. Authorization requirements

As previously described, cell-based food products are considered novel foods under the Israeli Novel Food Regulation 2005. As such, cell-based food products require pre-market approval from the NFS before being placed on the market. A complete safety dossier that establishes the safety of the product for human consumption must be submitted by the applicant and is subject to scientific evaluation by the novel food committee and the food risk management unit of the MOH. This process is outlined in **Figure 8**. It can take up to one year after all the information has been submitted to reach a decision.

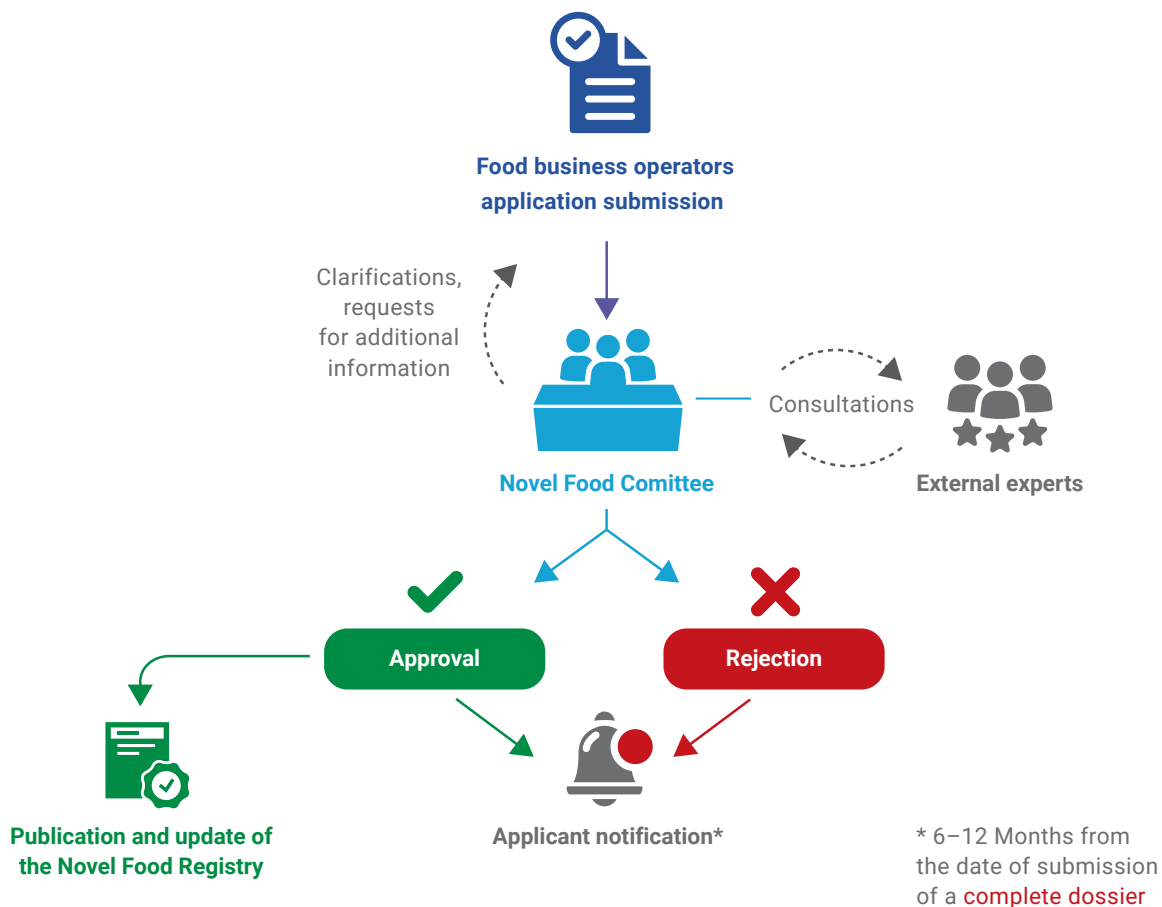
The dossier should include:

- a complete scientific overview with all supporting data establishing the safety of the product for human consumption;
- a detailed description of the manufacturing process including, but not limited to, how to implement HACCP-based food safety plans, information on packaging, labelling and storage of the final product; and
- data supporting the safety of the product, such as a history of safe consumption, toxicological studies, identification of potential allergens, compositional and nutritional data, anticipated intake by food categories together with an overall risk assessment.

Novel foods are assessed on a case-by-case basis and the specific data requirements depend on the type of novel food in question. The novel food committee consists of experts in multiple fields, including: food engineering, biotechnology, toxicology, veterinary medicine, animal sciences, nutritional sciences, environmental health, genetics, cellular and molecular biology, microbiology, developmental biology, and more.

Specific safety requirements regarding cell-based food products are still being formalized alongside the ongoing effort to identify and communicate both existing and novel hazards related to food safety and public health. Additional aspects of cell-based food products that are to be included in the dossier and that do not relate to food safety and public health concerns relate to the sustainability of the production process and the proposed labelling of the final product.

Figure 8. Approval process for novel foods in Israel



Note: The term “competent bodies” relates to authorities listed in the novel food guidelines

Source: Author’s own elaboration.

1.3.5. Steps for production, retail and import/export

Production and retail sale of cell-based food

In general, the commercial production of cell-based food products requires a food manufacturing licence and a business licence. These licences are not specific to cell-based food manufacturers, but are required throughout the food industry in Israel. The licences are issued following the inspections by several competent bodies in both governmental and local authorities, which inspect the manufacturing site to ensure that the relevant regulations are being followed. Food safety regulations are enforced by the NFS and include sanitation, manufacturing layout, contact surfaces, etc. These regulations set general requirements for food manufacturers. Regulations unrelated to food safety cover zoning, fire and chemical hazards, environment, labour, etc., and are covered by various local authorities or other government offices (Figure 7).

As previously noted, cell-based food products are considered novel foods under the Novel Food Regulation 2006. This regulation states that novel foods require approval by the NFS before being placed on the market. An effort is currently underway to define the requirements needed to assure that once cell-based food products are placed on the market, that they will not pose a concern for public health.

In addition to the general requirements, cell-based food products are considered sensitive foods. Sensitive food manufacturing sites require the implementation of HACCP-based food safety plans and some of the categories also require a GMP certificate by the NFS. The GMP standard is an Israeli standard combining ISO 22000 / ISO 9001 with HACCP principles.

Export and import of cell-based foods

With regard to trade in cell-based food products, several discussions with foreign competent bodies have been conducted to understand the export procedures, if and when needed, of future cell-based food products from Israel. All food importers are requested to register the food products with NFS for import into Israel. Cell-based foods will require preapproval before they can be imported into the country under the novel food regulation related to imported food. Overall, the pre-market approval of foreign competent bodies is taken into consideration when an application is submitted.

The following steps could hasten the approval process:

- register importers and foods with NFS;
- apply to the NFS for approval of the declaration for regular food, or preapproval for the import of sensitive food;
- apply for preapproval for novel foods;
- check the food on arrival at the port and obtain a permit that allows food to be released from the port; and
- inspect the food product at the place of storage.

At each stage, the importer is required to act in accordance with procedures and present the required documents according to the type of food it is importing.

1.4. Food safety assessment

1.4.1. Assessment guidelines and steps

Novel food applications can be submitted to the secure NFS portal, which does not require specific formatting. This means the dossier can include safety assessments that have been submitted to other competent authorities as long as the application and all documents submitted are in English.

Assessment guidelines for cell-based products are being drafted based on several pre-submissions of cell-based food products (pilot project). International guidance and harmonized standards and agreements on various aspects of food safety concerning cell-based food products can be of great assistance.

1.4.2. Identify potential food safety related hazards or concerns and risk management

Preliminary assessment guidelines have been drafted based on several local chosen case studies, for which pre-submissions have been received for the regulatory market pre-approval of cell-based food products. Initial safety data requirements have been drafted for this pilot project with the eventual intention of formalizing clear safety guidelines and requirements. This process is currently underway in collaboration with the industry, which intends to promote an open dialogue on emerging issues of concern.

The current requirements of the safety data to be submitted for the approval of cell-based foods includes product specification, manufacturing process, consumer and marketing issues and more. Several key points are listed below:

Cell line identity: Detailed information establishing the identity of the primary cell lines and of the cell lines used in the manufacturing process is to be submitted. This information should include a description of all the steps beginning with the sampling method of the cells, the tissue of origin and the animal from which the cells are derived and refer to its genetic identity and stability throughout the manufacturing process.

Modifying, selecting, expanding and storing cells: Any and all genetic modification or genetic selection of the primary cells taken from the original animal, and any following selection, expansion and storage steps should be outlined and any potential concerns arising from these steps about the safety of the final products should be addressed.

Manufacturing process: A detailed description should be included of the culturing conditions throughout the manufacturing process including media composition, with an emphasis on novel ingredients not previously used in the food industry, identity and purity of various additives, recombinant proteins, growth factors, scaffolding materials, etc. The process should also include the implementation of mandatory GMP and HACCP systems and a description of all steps taken to ensure the sanitation of the manufacturing process and site.

Allergens and toxins: Identify any allergens or toxins that could be included in the final product, whether originating in the cell mass, scaffolding material, processing of final product, etc.

Specification of the final product: This would include specification certificates from a number of lots that demonstrate compliance with the regulatory limits concerning various known food contaminants such as heavy metals, and additional chemical contaminants as well as relevant microorganisms. Consider novel contaminants that may raise health concerns such as residual hormones and growth factors, that should be addressed. Additional information included in the specifications should characterize the final product and include information such as nutritional values, cell biomass ratio within the final product, etc.

Shelf life and labelling: Submit data establishing the shelf life of the product along with the storage instructions. Suggested labelling should include preparation instructions, warnings and nutritional values.

Exposure assessments: Provide information regarding the retailing model of the product such as whether the product is ready to eat, ready to cook and so forth, and information on the expected daily intake with any limitation concerning specific vulnerable populations.

Sustainability: A sustainability assessment of the manufacturing process is requested as energy expenditure per kilogram of product. This requirement is unrelated to the product's safety aspects, but it is intended to validate the different claims arising in the media concerning the sustainability of these products and address the developing perception and acceptance of future consumers of these products. It is clear, however, that given the current production scales and unstable supply chains, life cycle assessment analysis may be inflated and may not perfectly reflect the whole environmental perspective. More broadly, sustainability labelling of food products is currently not required in Israel but may be in the future.

These general requirements are being refined and formalized through the ongoing submission of additional safety data from the participating companies, following requests by the NFS expert staff.

Risk management options are still being considered. Applications are evaluated on a case-by-case basis, with each manufacturer receiving a market preapproval for a specific technology-process-product combination after all safety considerations are satisfactorily addressed and the regulatory demands have been met.

1.5. Other key considerations outside food safety

1.5.1. Labelling

According to Israeli food law, food labelling includes publications on different media regarding the food product. Labelling is required to be truthful, not misleading and verifiable so as to fully reflect the nature of the product to the consumer. The general food labelling requirements set by Israeli law will naturally apply to all foodstuffs placed on the market including novel foods. This general labelling requirement covers issues such as the name of the food product, contents of the food product (weight or volume), ingredients and nutritional values. In addition, warning labels on food products that are categorized as high in saturated fat, sugar or salts are required (red stickers).

In addition to the existing requirements concerning food safety, and for any foodstuff placed on the market including cell-based food products, the MOH emphasizes the value of transparency and of providing relevant information to the final consumer to allow that consumer to make an informed choice. This additional information may include the mandatory terminology to be set by the regulator, the specific animal origin of the cell culture, the percentage of the cells from the total mass of the product, etc.

1.5.2. Technical capacity

The state of Israel is a relatively small-sized country with limited resources. The rapid increase over the past few years in private sector investments in cell-based food products, and the rapidly growing number of Israeli companies developing this category of foods, poses a real challenge for regulators, making it difficult for them to stay informed of the industry's need for policies, guidelines and regulations that will encourage the development of this emerging industry with its broad and heterogeneous variety of products.

Over the last few years, the Israeli Government declared its desire to promote the Israeli food-tech industry, including cell-based food products, and it has increased governmental investments to promote capacity building in both academia and in the public sector. Yet, independent scientific research that can fully cover the safety, nutritional, behavioural and clinical issues arising from the introduction of cell-based food products to the market is still lacking.

Since cell-based products are assessed using the same basic requirements and regulatory framework that apply to the safety evaluation of novel foods, the infrastructure needed to evaluate both existing and emerging food safety hazards and risks related to the industry of cell-based food in Israel already exists. To further enable the regulator to keep up with industry needs and meet the needs of the growing, broad and diverse cell-based food industry in Israel, additional human resources and budgets are necessary. Extending the abilities and capabilities of existing labs in Israel and developing new analytical methods will further support both industry and regulatory needs.

1.5.3. Environmental impact

It is generally assumed that producing cell-based food products is more environmentally friendly and sustainable than producing food from traditional animal farming practices. This assumption has some scientific support in relation to feed conversion, water use, animal waste, land use, veterinary medications, greenhouse gas emissions (GHG), etc., but data is still missing and the impact is still being debated (Santo *et al.*, 2020). The industry must have scientific validation before making such claims to avoid misleading the public.

In addition to the presumed environmental benefits of cell-based food products, developing a local and self-sustained market can produce indirect environmental benefits. Such advantages may be the result of shortened supply chains, especially when considering that Israel currently imports a large percentage of its beef and small ruminants. The expected impact on animal welfare and animal health is also expected to be positive. Reduced traditional farming practices, reduced livestock shipments, and shortened supply chains are expected to reduce greenhouse gas emissions in line with global and national commitments.

1.5.4. Economic growth and sustainability

As previously noted, current R&D capacities in cell-based food production are limited in government and academia, and, to a lesser extent, in the private sector. To address these limited capacities and enable safe, nutritional, sustainable and tasty products to be produced at a competitive price will require novel technologies, improved analytical and interpretive skills.

There are several measures already identified that will enable capacity building in these respects, such as:

- establishing a national food institute to house analytical equipment and the physical infrastructure for manufacturing during the pilot phase;
- establishing a micro industrial zone that will connect infrastructure and know-how to promote the production of new food technologies during the pilot phase;
- encouraging and financing local development and competitive production of both novel components, required at various stages of cell-based food production, and components with local and international demand;
- attracting accomplished academic researchers by raising the awareness of the field, recruiting new researchers and allocating research grants;
- building academic curricula to introduce food technologies in schools beginning at a young age through to post-secondary education;
- establishing a food-tech hub to promote dialogue between stakeholders and to hold meetings between the industry and the regulator from the earliest stages of development; and
- Formulating clear, dynamic guidelines for business in this field at various stages.

1.5.5. Food security

Israel is a small market that relies significantly on imported foods, including food derived from animal origins. Although food security is not an acute problem in Israel, the malnutrition status of certain subpopulations, specifically those at a low socioeconomic level, is an issue of concern.

High quality, nutritional and accessible protein sources may fill nutritional gaps and promote a healthier diet in accordance with MOH recommendations. Theoretically, *in vitro* production of cell-based food products can address specific nutritional requirements through enrichment with specific vitamins and minerals and by reducing unwanted ingredients that have detrimental health effects such as saturated fats.

On the other hand, the effects of cell-based food products on various aspects of human health are still to be determined, including metabolic balance, digestibility, bio accessibility, effect on the microbiome, cognition, eating patterns, etc. In addition, the availability of cell-based products may influence consumer dietary habits (e.g. for vegetarian and vegan consumers as well as for religious reasons).

It is possible that global political instability may change the distribution and limit the availability of certain foodstuffs. The effect on global supply chains may have a more drastic effect on countries that rely heavily on imported foods and could reduce their ability to maintain food security for their populations. In this way, a sustainable independent local industry can contribute to a country's food security.

Good security may also be destabilized because of various natural and/or anthropogenic influences such as climate change. For example, the effects of climate change may reduce national agricultural resilience while also decreasing the trade volume of foodstuffs, which would make it more difficult to meet the nutritional needs of the population.

1.5.6. Kosher/halal status

In Israel, approximately 74 percent of the population is Jewish, 18 percent is Muslim and the rest are affiliated with other minority groups such as Christians, Druze and others (Central Bureau of Statistics, 2021). Both Jewish and Muslim people have religious rules regarding foods of animal origin. Kashrut in Judaism and halal in Islam are collections of religious dietary regulations that prohibit the eating of certain foods and require that other foods be prepared in a specified manner. Several issues related to the kashrut status of foods are still under consideration with respect to cell-based products. Firstly, if products derived from animals prohibited by religious laws and considered Tareif, or forbidden for consumption by Jews, are themselves Tareif. Secondly, it must be determined whether these cell-based products, specifically those derived from mammals, are not considered meat products and should be handled as Parve (not classified as meat or a dairy product) as defined by Kashrut laws allowing them to be handled and consumed with dairy products.

These debates are ongoing and there is no consensus as yet on these issues, especially given the distinct streams within Judaism. One example is a decision by the Tzohar rabbinical organization that has declared cell-based meat products derived from embryonic stem cells taken from a bovine blastocyst to be considered Parve and, as such, it can be eaten with dairy products (Tzohar, 2022). It should be noted that religious rulings like these may substantially alter the dietary intake of religious Jews once these products are placed on the market.

1.6. Discussion

The novel food regulatory framework is defined and in place in Israel. It applies to cell-based products that require a case-by-case assessment and pre-market approval. The NFS is in the process of evaluating several cell-based food products that have been pre-submitted within the framework of a pilot submission process. This process allows for ongoing dialogue between the applicants and the regulators, allowing the applicant to submit the relevant safety data needed for the assessment of any potential existing and emerging hazards to public health from cell-based foods.

The cell-based food industry in Israel is advancing and rapidly developing. This requires that regulators be up to date with the new technologies and novel products in a way that allows them to carry out professional and responsible risk assessments. It also requires the regulators to better manage the risks to protect public health without being a barrier to innovation and economic development.

Cell-based products raise unique challenges and questions beyond food safety considerations, such as nutritional values, labelling requirements, religious certificates, public acceptance and sustainability. Ongoing collaboration and open dialogues between regulators and the global community on food safety requirements will strengthen and improve the emerging cell-based food industry and help the industry to meet all safety demands to protect and promote human health.



2. Qatar – country context

2.1. Terminology

As of May 2022, Qatar, like most countries, did not have official terminology to define what is known as a cell-based food. Qatar recognizes the importance of using the terminology that will offer the consumer a clear understanding of cell-based food products as well as cell-based food production, which fall under the umbrella of cellular agriculture. Any terminology used must also be compliant with the requirements of the relevant standards, technical regulations and specifications.

The first step is to identify a name for a product that makes clear its nature and characteristics, to avoid any confusion or misinformation among consumers. It is important to begin with an understanding of the characterization of these products, to facilitate a clear definition by describing the product and how it has been manufactured. According to Seon-Tea *et al.* (2022), cultured meat refers to meat produced by using artificial cell culture. It is made by growing master cells that are themselves produced from samples collected from livestock through a biopsy of tissue from live or slaughtered animals and/or from embryonic stem cells (Ding *et al.*, 2018). In the context of Islam, cell-based meat can possibly be defined as follows:

Cell-based meat products are products obtained by culturing cells in vitro, where they are manufactured by growing the main cells that have come from livestock either through a biopsy of the animal tissues or by cutting tissues from slaughtered animals and/or from embryonic stem cells, on the condition that each step in the process of slaughtering, cell collection and production in the laboratory comply with the requirements of Islamic Sharia.

There are several related Gulf specifications that deal exclusively with what a name used to describe a food product should convey. The goal of setting such controls is to ensure the clarity of product information provided to consumers. Currently, the most used terminology in the media in Arabic is “اللحوم المستزرعة”, which, translated literally to English is “farmed meat”. Qatar seeks international guidance on the terminologies used for cell-based foods in the interest of international harmonization. It is also worth noting that Qatar’s large English-speaking expat population makes it necessary to have corresponding Arabic and English terminologies for clear labelling.

2.2. Current status

As of July 2022, there were no commercially traded cell-based food products in Qatar. However, approval was given in 2021 to establish a factory for cell-based food production (production only) in the territory of Qatar within the borders of the Qatar Free Zone. The Qatar Free Zone, according to the applicable laws (such as Law No. 36 of 2005), is considered to be outside the administrative borders of the state and has its own laws, and is not subject to all legislation that applies within the state. However, permission to establish a factory in the Qatar Free Zone is not considered to be approval for allowing imports of these products for the local market before regional and local regulations are put in place.

2.3. Regulatory framework

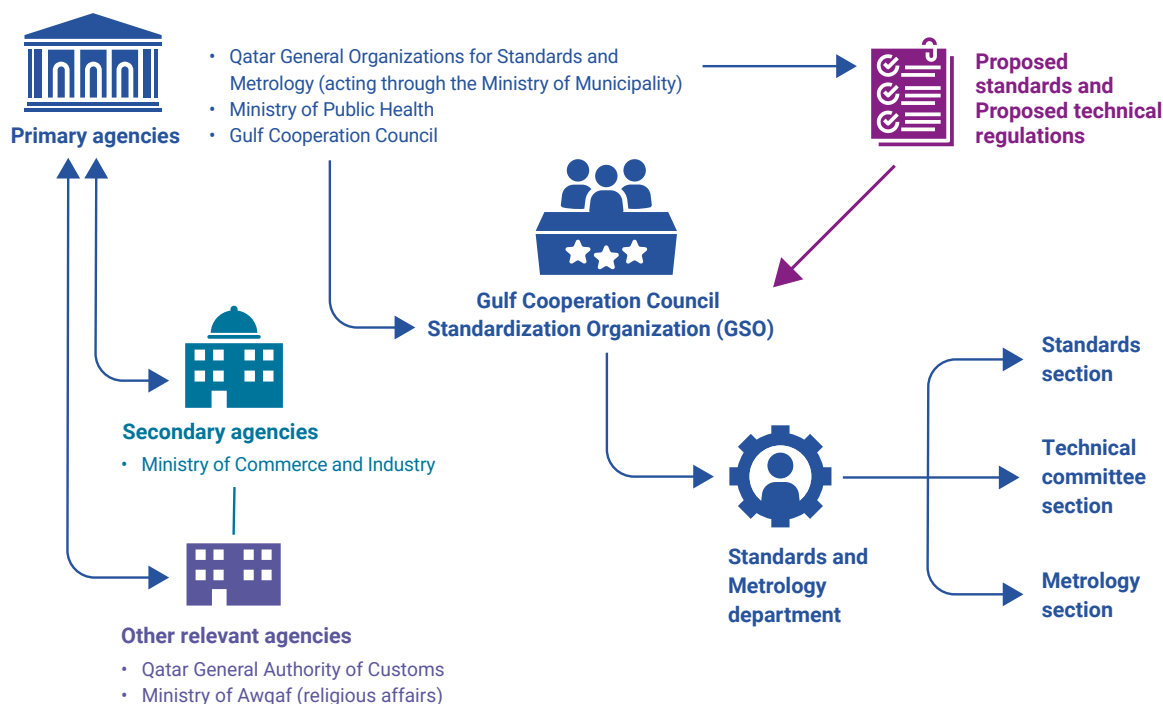
2.3.1. Regulatory/competent authority(-ies)

Overview

The regulatory framework in Qatar for food safety has been managed through many government agencies (Figure 9), since there is no dedicated competent authority to manage food safety and control food exports/imports as well as food handling (from farm to fork) within the country. Two laws, the Emiri decree No 44, for the year 2014 that established

the Qatar General Organization for Standards and Metrology (QS) and Law No. 8 of 1990 regarding regulation and control of food for human consumption and its amendments (Law No. 4 of 2014 and Law No. 20 of 2017) state that the Ministry of Public Health (MOPH), the Ministry of Commerce and Industry (MOCI), the Ministry of Municipality and Environment (MME), and the Gulf Cooperation Council (GCC), including the Standardization Organization (GSO), are to coordinate food safety related issues.

Figure 9. Summary of the food safety regulatory competent authority agencies in Qatar



Source: Author's own elaboration.

While the development of a food safety authority as a single agency, is still being considered, the development of a new food safety law is being evaluated by the supreme council. In the meantime, the current structure of the government authorities for food safety can be divided into three levels.

Primary agencies

1. Qatar General Organization for Standards and Metrology (QS) acting through the Ministry of Municipality and Environment (MME): While the jurisdiction of the MME essentially falls under the control and inspection of food products that circulate in the country such as in the market and restaurants, the only intervention of the MME in the regulations is to attest to the standards issued by the QS that were already implemented by the GSO. The intervention of the MME in QS standards is due to its relation to the law established under the Emiri Decree (44) in 2014, stating that QS is a public organization with a legal entity that is attached to the MME. It is through QS that the MOPH proposes a project to amend an existing food standard or a new food standard project to be sent to the GSO for review by the member states of the GCC. Once agreed upon, the GSO will implement the new food standard or the amendment in the member states through their General Organization for Standards and Metrology as the QS in Qatar.

2. The MOPH, through the Department of Food Safety and Environmental Health (FSEH): The FSEH plays an effective role in implementing health policy in all food safety-related matters and carries out the powers entrusted to the MOPH under Law No. 8 of 1990 regarding the control of food to ensure the safety of the consumer. FSEH conducts food control and inspection in places where food is being handled and traded to ensure its safety and validity. It also prohibits the handling of any food that does not meet the specifications and requirements of the competent authorities. In addition, it responds to emergency cases related to food safety and validity in partnership with more than one entity, and it manages and operates laboratories to examine and analyze food samples. The MOPH also proposes new food standards, makes amendments to existing food standards and proposes amendments or new standards to QS, since MOPH is a member of the national committee (that is created by QS). QS will send all of the information to the GSO based on the proposals of the national committee.
3. GSO: The GSO is a Regional Standardization Organization (RSO) that was established by the resolution of the GCC Supreme Council (22nd Session, Muscat, Oman, 30 to 31 December 2001) and assumed its operation in May 2004 with the membership of the competent authorities in the following countries: Bahrain, the United Arab Emirates, Kuwait, Oman, Qatar, Saudi Arabia and Yemen, which joined in January 2010. The GSO aims to unify the various standardization activities and follow their implementation and commitment in cooperation and coordination with the national standardization bodies in the member states (QS in Qatar). It is done in a way that contributes to the development of production and service sectors, the development of intra-trade, consumer protection, environment and public health, and the promotion of Gulf industries, products and services. Furthermore, all of this is performed in order to support the Gulf economy, preserve the gains of member states, and contribute to reducing technical barriers to trade in line with the objectives of the GCC Customs Union and the Gulf Common Market.

Secondary agencies

The Ministry of Commerce and Industry (MOCI) (referred to as the Ministry of Economy and Commerce in Law No. 8 of 1990). MOCI mainly oversees commercial and industrial activities for Qatar, directing these activities in accordance with national development requirements. Its mandate includes developing business needed to attract investments and supporting and developing exports. MOCI is also responsible for developing methods and procedures for providing public services to the business and investment sector, regulating the trade professions, registering commercial and investment establishments, issuing related and necessary licences, and supervising the regulation and control of markets in its area of competence. It also takes the necessary measures to protect consumers, combat commercial fraud, safeguard competition and prevent monopolistic practices, as well as protecting intellectual property rights. For the regulatory framework, MOCI has the right to present its opinion and make amendments to the QS standards, since it is a focal point for the World Trade Organization (WTO) and other international organizations as well as international governmental entities. This makes MOCI an important stakeholder in the establishment of the regulatory framework of food products.

Other relevant agencies

1. The Qatar General Authority of Customs (referred to as the customs department in Law No. 8 of 1990): This authority has no jurisdiction when it comes to the regulatory framework of food products. It is mainly an executive body following regulations issued by the GSO. It consults with the MOPH for any other related matter with food products as mentioned in Law No. 8 of 1990.
2. The Ministry of Awqaf (religious affairs): This ministry is involved when a food product is categorized as meat or as a meat product, or if there is a related fatwa needed for that product in particular. (A fatwa is a formal ruling or interpretation on a point of Islamic law given by a qualified legal scholar. Fatwas are usually issued in response to questions from individuals or Islamic courts).

2.3.2. Regulatory category

The Codex Alimentarius texts play an important role in new or already adopted regulations in the GCC countries and particularly in Qatar. The FSEH department at the MOPH is the main responsible agency in the regulatory framework and is responsible for executing and implementing the standards and regulations for the control of food products in the country. It is also involved in imports/exports. The FSEH department uses the Codex Alimentarius as a reference for categorizing food products. Food categories in Qatar are classified according to the World Classification by Codex Alimentarius beginning with dairy and ending with uncategorized foods, or group number 16. The document describes the different food categories in tables where every type of food product is classified.

Every food category described in the document has a corresponding standard and technical regulation (QS) to control and monitor a product according to the nature and level of risk associated with the product. In order to categorize any food product, it is necessary to have a clear description of the product that can be related to a specific standard or technical regulation for that type of food product, which includes a definition linked to its nature and related hazards. Since cell-based meat products do not yet have an international or national standard or technical regulation, they cannot as yet be categorized. If a food standard is adopted for this type of product, it will be categorized based on its nature and possible hazards. Therefore, cell-based meat products can be categorized as meat and meat products, including poultry and game (category No. 8) or as fish and fish products, including mollusks, crustaceans and echinoderms (category No. 9) or as prepared foods/composite foods – foods that cannot be placed in categories 01 to 15, but rather category No. 16.

As for the competent authorities for food categorization, they are mainly the MOPH (since the proposal/project of the regulation is written by the experts in the FSEH department), the QS, the GSO, and the MOCI. It is worth noticing that an intervention from the Ministry of Awqaf (religious affairs) could be necessary if the product would be categorized as category No. 8 or if any related fatwa is needed for that product in particular, as noted above. Recently, a new standard of general requirements for novel foods GSO 2696:2022 was implemented in the GCC countries, which might suggest that cell-based meat products will be categorized under novel foods.

There is also a need to determine whether cell-based food is to be included in the Novel Good Catalogue list or to be included in the list of products generally recognized as safe (GRAS).

1. If they were included in the Novel Food Catalogue, which are products of animal and plant origin and other substances subject to the Novel Food Regulation in Qatar, a reference would need to be made to the information provided by the European Union Member States. It is a non-exhaustive list and serves as an orientation on whether a product would need authorization under the Novel Food Regulation. European Union countries may restrict the marketing of a product through specific legislation. For information, businesses should contact their national authorities. In some cases, businesses will be asked to provide information on the history of use of food supplements and ingredients used exclusively in food supplements in European Union countries. If foods and/or food ingredients were used exclusively in food supplements, new uses in other foods would require authorization under the Novel Food Regulation (European Union, 2023).
2. To be included in the list of GRAS products in Qatar, Recently Published GRAS Notices and Food and Drug Administration (FDA) letters (FDA, 2023) and/or Current Animal Food GRAS Notices Inventory (FDA, 2023a) would be required.

2.3.3. Relevant laws and regulations

Relevant definitions

1. Gulf Standard Specification (GCC Standardization Organization, 2023). This is a document approved by the relevant Ministry's Committee for Standardization Affairs that sets for regular and repeated use, the rules, instructions or characteristics of relevant products, processes and production methods, compliance with which is not mandatory. It also may include or specifically examine terms, definitions, configuration, labelling or labelling requirements that applies to products, processes or production methods. The standard specification guarantees the achievement of the specific purpose of the goods or service by setting technical requirements, procedures and quality control systems to fulfil the product or service with the requirements that fulfil the desires of users, and are in line with the capabilities of producers and service providers, considering the safety of the user and protecting him/her from fraud or deception.
2. Gulf Technical Regulations (GCC Standardization Organization, 2023). This is a document approved by the relevant Ministry's Committee for Standardization Affairs that lays down the characteristics of products, related processes and production methods, including the applicable (effective) administrative provisions. It may include or specifically look at terms, definitions, packaging, labelling or labelling requirements that apply to products, processes or production methods.

Regulations relevant to cell-based food products

1. Gulf Technical Regulation Labelling of Pre-packaged Food Stuffs GSO 9:2013: This document deals with the labelling of all pre-packaged foods and with requirements relating to the presentation thereof. It requires that the product name be clear and specific to avoid consumer confusion and to prevent the producer from being misleading.
2. Guidelines for Labelling Food Products GSO 2406:2014: These guidelines cover the definitions and general and special requirements governing the labelling of food products in addition to the provisions laid down in the GSO standards for food and agricultural product labels. Product labelling is subject to the provisions stated in the "labelling" Article of the GSO Standard. The provisions of these guidelines would be applied in accordance with other existing mandatory provisions.
3. General guidelines on claims GSO CAC/GL 1:2008 – CAC/G, 1:1979: The scope and the principles of these guidelines relate to any claims made for a food, regardless of whether or not the food is covered by an individual Codex Standard. These guidelines are also meant to prevent food from being described or presented in a false, misleading, or deceptive manner, or from being described in such a way as to create a false impression regarding its character.
4. Gulf Technical Regulation Processed Meat: Minced chicken meat. GSO 1327:2002: This standard is concerned with minced chicken meat. However, it is not yet determined if this would also cover cell-based minced chicken meat.
5. Gulf Technical Regulation Halal Food - Part 1: General Requirements GSO 2055-1:2015: This standard covers the general steps required for halal food products. Such steps must be followed at all stages of the halal food chain including, receiving, preparing, packaging, labelling, handling, transporting, distributing, storing, displaying and halal food service.

6. Gulf Standard Halal Products – Part 2: General Requirements for halal certification bodies GSO 2055-2:2021: This Gulf standard outlines the requirements that must be met by halal certification bodies. It also specifies the requirements for implementing the procedures for issuing a Halal certificate for products, services or systems.
7. Gulf Standard Halal Products – Part three: General Requirements for halal accreditation bodies accrediting halal certification bodies GSO 2055-3:2021: This standard also includes the activities covered by accreditation such as testing, calibration, inspection, halal certification, people, products, processes, services, provision of proficiency testing, production of reference materials, verification and validation.
8. Gulf Standard Halal Packaging-General Guideline GSO 2652:2021: This Gulf Standard describes the general guidelines for manufacturing and handling halal packaging. It serves as the basic guidance and requirements for halal packaging for halal products.
9. Gulf Technical Regulation Additives Permitted for Use in Food Stuffs GSO 2500:2021.
10. Gulf Technical Regulation Microbiological Criteria for Foodstuffs GSO 1016:2015: This GSO technical regulation is concerned with the microbiological criteria for foodstuffs and for some food ingredients used as raw materials in food processing.
11. Gulf Technical Regulation Expiration Dates for Food Products -Part 1: Mandatory expiration dates GSO 150-1:2013: This Gulf Technical Regulation is concerned with mandatory expiry periods for food products.
12. Gulf Standard Expiration Dates for Food Products - Part 2: Voluntary expiration dates GSO 150-2:2013: This Gulf Standard provides guidance on expiry dates for food products.
13. General Requirements for Novel Food GSO 2696:2022: This newly implemented Gulf Standard is concerned with the general requirements for importing, manufacturing and marketing a new food in the markets of GCC member states.

2.3.4. Authorization requirements

The General Requirements for Novel Food GSO 2696:2022, is concerned with importing, manufacturing and marketing a new food in the markets of GCC member states. Some complementary standards exist, such as 1) GSO 2055-1 halal Products - Part one: general requirements for halal food and 2) GSO 9 – Labels of pre-packaged foodstuffs.

While the official definition and categorization of cell-based foods are still pending in Qatar, it will most likely be considered to be a novel food, as novel food has been defined in the GSO 2696:2022, which includes a clause stating that novel food consists of, is isolated from, or is produced from cell culture or tissue culture derived from animals, plants, microorganisms, fungi or algae. Therefore, there are two possible key authorization requirements for cell-based food: 1) a pre-market evaluation as a novel food, which includes a food safety assessment and other considerations; and 2) compliance with halal standards.

As for the approval system, it is likely that the products will need to be registered in the food registration system of the FSEH department of the MOPH and approved by the department's food experts. It would be necessary to submit the necessary documentation including a proper and scientifically based risk analysis/assessment of the cell-based meat product, a laboratory analysis report of the product issued from an ISO 17025 certified laboratory in the country of origin (including all the analyses required according to the food experts), all relevant related documentation (such as halal certification) and any pictures required by the food experts.

2.3.5. Steps for production, retail and import/export

Currently, Qatar does not produce any cell-based food, nor is any such food approved for sale in the local market. Any food production requiring cell culture will need all the necessary technologies, ministerial pre-market approvals for production and other legal approvals for sales/exports, etc.

Any import of cell-based meat or related raw products must also undergo a pre-market approval. Inspection requirements and methodologies for imported cell-based food products will likely be established and adopted, which may include lab testing at the point of import. A lab testing facility for imported food products may need to be established.

Any company that wants to produce cell-based food products must submit the necessary evidence to the FSEH department of MOPH to prove that all steps of production have been followed from raw materials up to the final product. Since there is no clear international guidance regarding the accreditation of production methodology of cell-based meat products, as of June 2002, MOPH did not approve or permit any kind of production of cell-based meat products.

2.4. Food safety assessment

2.4.1. Assessment guidelines and steps

The guidelines on food safety assessments in Qatar and the GCC countries are mainly built on a risk-based approach, which is an international approach adopted by international organizations such as the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO), the European Food Safety Authority (EFSA), the United States Food and Drug Administration (US FDA), etc. In this regard, the following are factors that should be considered in order to apply a risk-based food control system: classification of imported foods, compliance history of imported foods, evidence of new or emerging hazards, as well as any well-known established food safety hazards, in the food supply, and a whole of food chain approach to food safety.

Imported foods will be classified according to their potential to transmit foodborne disease relative to their intended end use. While this classification will be further developed to apply for many different types of food in general, there may be a necessity to develop a different approach to conduct risk profiles of cell-based food production processes.

Regarding evidence of new or emerging hazards in the food supply, the competent authorities of Qatar will interact with competent authorities in other countries to identify and manage the risk of any new or emerging hazards in the food supply. Since Qatar does not currently have the technical ability to monitor imported foods for new or emerging hazards, it is expected that the competent authority in the exporting country will have applied the same tests and safeguards as they would for food in their domestic market.

Qatar recognizes that the most effective and efficient means of mitigating food safety risks to the consumer are often achieved through prevention, such as the application of good agricultural and manufacturing practices as well as hazard analysis risk-based preventive controls during primary production and processing. For imported food products, port-of-entry inspection is recognized as a very limited means of assuring the safety and suitability of imported food. Special arrangements with competent authorities in exporting countries to assure the safety of food during primary production and across the food chain are encouraged by Qatar. These can include alternative measures based on:

- food certified as being produced in registered or otherwise officially recognized food premises in the exporting country, and subject to audit by the GCC countries or their agents;
- memorandum of understanding between competent authorities;
- equivalency agreements; and
- broader trade agreements, e.g. mutual recognition of inspection and certification systems.

Since there is no clear classification or guidance for risk categories regarding cell-based meat products from international organizations, it is not currently possible for Qatar to make decisions or apply any procedures to control such food. A company that is willing to produce cell-based meat products in Qatar would have to be based in the Qatar Free Zone (QFZ), which is considered to be a completely distinct territory with jurisdiction allowing it to produce and export these food products to other countries as long as these countries approve the importation of such food. In this case, the state of Qatar would be considered as the importing country for any company based in the Qatar Free Zone.

Therefore, it would be very beneficial for Qatar to obtain international guidance regarding the food safety assessment of cell-based foods. In addition, it would help if Qatar could adopt the best practices of competent authorities that have conducted risk-based food safety assessments of cell-based food products.

2.4.2. Identified potential food safety-related hazards/concerns and risk management

Qatar does not currently have an official list of potential food safety hazards for cell-based food products. However, such a list is necessary to conduct risk assessments of cell-based foods. Qatar has undertaken preparatory work for this purpose.

2.4.3. Food safety issues

When the competent authorities have been approached by a cell-based food manufacturer, the following questions and issues are often raised:

- Are there potential hazards (physical, chemical and biological) to consider for biomaterials?
- Chemical residues/contamination issues: What chemicals are being used and what levels of residue can remain in the products?
- Comparative approach issues: While some products are a hybrid of cell-based and other plant- or animal-based proteins, how can we compare them to conventional products to conduct a safety assessment, and how effective is this assessment?
- Short and long-term impact: Are there any studies available on the potential for an acute impact on health? Are there any theoretical studies or modelling available to evaluate the long-term impact of consuming cell-based food?
- Unintended effects: Are there any other potential hazards related to producing cell-based food?

2.4.4. Other technical issues for management considerations

- Nutrient bioavailability issues: Is the bioavailability of proteins from cell-based sources and those from plant- or animal-based proteins different? Some products have added vitamins; are there any differences in the bioavailability of such vitamins as compared to other food items?
- Nutrient composition issues: What is the quantity of protein available from cell-based meat/chicken and why do some have a very large percentage of water?
- Processing issues: Adding saturated fat, deep frying and other processing steps may increase the palatability, but may also decrease the nutritional value. How do we evaluate this?
- Environmental issues: What is the level of water used for the entire production/processing process, and what are the CO₂ emission levels?
- Halal issues: Some production steps may require the use of alcohol. Alcohol residues can be a problem – what is the probability of this occurring and what would be the level of residues?

2.4.5. Regulatory issues

- Control and inspection: Are there any lists of control measures and detailed procedures for inspection available from any countries of the world for cell-based foods?
- Detection: If special regulations apply, the ability to detect/quantify the presence/amount of a cell-based food may be required by regulatory authorities. Are there any effective methodologies to detect/quantify cell-based foods? This can be useful not only for compliance control, but also for fraud prevention.

2.5. Other key considerations outside food safety

2.5.1. Labelling

It will most likely be necessary to clearly label cell-based food products in Qatar. Food labelling in Qatar and in the GCC countries is regulated by several standards and technical regulations since the requirements differ from one type of food product to another. These standards include: 1) GSO 2406/2014: Guidelines on Labelling of Food Products; 2) GSO 9/2013: Labelling of Pre-packaged Food Stuffs; and 3) GSO CAC/GL 76-2011: Compilation of Codex texts relevant to labelling foods derived from modern biotechnology.

There is no specific labelling guidance for novel food in the GSO standards regarding special foodstuff, however, the MOPH has issued several guidelines, including for organic food, and is applying certain requirements for GMO food. Therefore, if cell-based meat products are approved for consumption in Qatar, the MOPH will issue specific requirements for i) labelling these products; ii) guaranteeing the safety and quality in the country and at its points of entry, and iii) disseminating transparent and honest information to help inform the consumer.

2.5.2. Technical capacity

Currently, the central food laboratories have all the chemical, microbiological and other capabilities to test food samples for human consumption (GSO 1016:2015). However, having the specific technical capacity to test cell-based foods for safe consumption is not enough, since there are no international standardized methods for testing these foods, that have never been produced or consumed in most of the world. MOPH is always open to collaboration with local stakeholders such as Qatar University and organizations such as FAO/WHO to conduct research aimed at fully understanding and, therefore, being able to control this kind of novel food and to be able to make the right decision when it comes to assuring the public of its safety for human consumption.

2.5.3. Halal status

Whether the cultured meat is halal or not is important for religious reasons. Some studies consider cell-based meat to be halal if the cells used to culture the meat were taken from an animal that is considered halal and has been slaughtered according to Islamic rules, and if blood or serum was not used during the production process (Hamdan *et al.*, 2018). However, cell-based meat from animals that are forbidden for consumption by Muslims, such as pigs, dogs, etc., would not be considered halal.

A new food category must comply with ethical rules, regulatory obligations (GSO 2055-1:2015, GSO 2470:2015, GSO 2670:2021, GSO 1016:2015, etc.) and obtain the necessary halal certification from a recognized halal certification body before selling or marketing such products in Qatar (GSO 2055-2:2021). It is noteworthy that the FSEH department of MOPH / Ports Health and Food Control Section has issued guidelines for importing halal food and for Islamic bodies to be authorized and permitted to issue halal slaughtering certificates. The guidelines cover all the requirements for accepting and distributing imported food that needs to have halal certification in Qatar. There is also a List of approved Islamic associations in the countries exporting to Qatar, which is a consideration if the products are being imported from non-Muslim countries.

2.5.4. Nutritional concerns and effects on health

Cell-based foods can be presented as processed food products such as nuggets or hamburgers. For these products to be similar in appearance to products made from traditional meat, food processing with some additional ingredients, such as beetroot juice, saffron or caramel, are often added to mimic the flavour and the colour of traditional meat (Fraeye *et al.*, 2020).

It is not possible to make a straightforward comparison of traditional meat to cell-based meat because cell-based meat does not have an exact counterpart. Thus, it might not be possible to take a simple comparative approach to analyze the nutritional differences.

Poultry and meat are categorized under the “fish, poultry, meat & alternatives,” food group within the Qatar Dietary Guidelines (QDG) (MOPH, 2015). This group is high in protein, iron, zinc and vitamin B12. Regarding proteins, it is still not clear to what extent protein content and composition of cultured cells resembles that of traditional meat.

Over the years, red meat has been scrutinized for its fat content. However, with the advancement of science and with years of longitudinal studies, it has been proven that meat can still be part of a healthy balanced diet. It is crucial to clarify that not all fat is bad, and although the overall fat content has a direct impact on the caloric density of the food product, the fatty acid composition influences the dietary and nutrient value of the product.

Meat provides the human body with a variety of micronutrients and macronutrients especially high-quality protein as it contains essential amino acids (MOPH, 2015). However, it is still uncertain whether the protein content/profile of cell-based meats is the same as traditional meat (Fraeye *et al.*, 2020).

There is much to consider regarding the nutritional value of cell-based meat compared to traditional meat, such as i) macronutrients (fat, carbohydrate, protein); ii) micronutrients (vitamins and minerals); iii) the type and percentage of fat and iv) the absence or low quantity of certain important micronutrients that are naturally found in traditional meat such as iron, zinc and vitamin B12 and how they can be added to cell-based meat.

2.6. Discussion

Qatar has several regulations that can be used as a basic framework for the control of cell-based food products. However, due to their novelty and lack of historical information in terms of human consumption, it is necessary for the Government of Qatar to assure they are safe and suitable for human consumption. Currently, Qatar’s limited technical capacity and expertise are also issues in terms of assessing their safety. Qatar has not implemented specific regulations for the control of novel foods. Internationally and regionally accepted methodologies for cell-based food production would be useful for Qatar to refer to, since this kind of food has never been produced or consumed in most parts of the world. Qatar is open and keen to collaborate with various countries, and seeks guidance from international bodies such as FAO, WHO and Codex Alimentarius to fully understand the relevant food safety issues and other legitimate issues. In this regard, this case study was developed to share the current situation in Qatar in the hope that other countries and the international community may find it useful when collaborating to establish proper and specific methodologies, approaches, regulations and control procedures for safe and sustainable cell-based food products.

3. Singapore – country context

3.1. Terminology

In Singapore, as in many other countries, cell-based food is classified under a subset of food known as alternative proteins. These are proteins derived from sources other than animal proteins such as animal cells, plants, microorganisms (e.g. algae, fungi, bacteria) and insects. Terminology used to describe some of these alternative proteins, such as plant-based proteins and insect proteins, have gained wide acceptance. Interestingly, there has been global debate on the terminology that most accurately describes cell-based meat that has been cultured from animal cells in an *in vitro*, setting or in scaled-up production facilities. Several terms have previously been proposed, including clean, *in vitro*, synthetic, cellular, lab grown, cultivated and cultured among others (Szejda, 2021). In Singapore, the Singapore Food Agency (SFA), which is the leading agency for food-related matters, has adopted the term “cultured meat” to describe products developed from animal cell cultures in bioreactors supplemented by culture media. In order to ensure consistent messaging, SFA uses the term “cultured meat” in its communications about the requirements for safe assessments of these products, as well as in its risk communication initiatives for consumers describing how the safety of these products is ensured. SFA has not received any objections related to the use of this term so far.

3.2. Current status

Alternative proteins such as cultured meat have the potential to contribute towards global food security, but food safety must be considered before all else (SFA, 2021). To be clear about how the safety of novel foods such as cultured meat should be considered, SFA introduced the Novel Food Regulatory Framework in 2019, which requires novel food companies to conduct pre-market safety assessments for their products that do not have a history of being consumed as food. These assessments, which evaluate toxicity and allergenicity, are performed on an acute and chronic risk basis to determine whether the product poses any potential food safety risks. The safety of the production method is also considered, as well as the impact of dietary exposure. SFA’s assessment also requires detailed information on the materials used in the manufacturing processes as well as the details of process controls in place to prevent food safety risks.

At the time of writing, at least one cultured meat company has successfully gone through this safety assessment process, and cultured meat is now available for sale commercially in Singapore at a restaurant and through food delivery service. Several other companies are in discussions with SFA to seek approval for their cultured meat products. SFA does not consider the mode of sale in its safety assessment process. It is purely a commercial decision to be made by companies.

3.3. Regulatory framework

3.3.1. Regulatory/competent authority

SFA is the regulatory agency responsible for developing food standards and regulations related to food placed on the market in Singapore. It is a statutory board formed under Singapore’s Ministry of Sustainability and Environment. Under the governance of SFA, all food-related resources and capabilities are brought together to ensure the holistic management of the food industry from farm to fork. SFA actively works with other agencies across government as required to meet its goals, especially in the domain of cultured meat. For example, SFA works closely with Singapore’s economic agencies (e.g. Economic Development Board (EDB) and Enterprise Singapore) to engage companies and start-ups developing cultured meat, as well as with the Agency for Science, Technology and Research to support the research needs of cultured meat companies to further develop their products. Even in the regulation of cultured meat, SFA may from time-to-time work with other entities where required. For example, if genetically modified organisms (GMO) are present in the finished food product (whether or not it is cultured meat), SFA would work with the Genetic

Modification Advisory Committee of Singapore (GMAC) as part of the safety dossier review, as Genetic Modification Advisory Committee would need to investigate issues related to the use of GMOs that are beyond food safety considerations (e.g. worker safety and accidental release provisions). SFA also works closely with the Ministry of Health (MOH) and Health Promotion Board (HPB) on any health-related matters.

3.3.2. Regulatory category

SFA considers novel foods to be foods and food ingredients that do not have a history of safe use. Substances with a history of safe use are those that have been consumed as an ongoing part of the diet by a significant human population (e.g. the population of a country), for a period of at least 20 years and without reported adverse human health effects. As the history of safe use for cultured meat cannot be established since it is new, it falls within the novel food category and requires pre-market approval before it can be allowed for sale.

3.3.3. Relevant laws and regulations

Under Singapore's regulatory framework for novel foods, food businesses that intend to produce/manufacture, import, distribute and/or sell novel food or food products containing novel food ingredients in Singapore are required to first seek SFA pre-market regulatory approval. To do so, applicants must conduct safety assessments on their novel food products for SFA's review. The assessments must identify potential risks with the product and its production process, and ensure these risks are appropriately managed (e.g. applicants would be required to identify critical control points).

The requirements for the safety assessment are detailed in SFA's requirements document entitled "Requirements for the Safety Assessment of Novel Foods and Novel Food Ingredients", which was last updated on 26 September 2022.

As with all food products that are imported, produced or manufactured for sale in Singapore, novel food products are required to comply with the Singapore Food Regulations. The Singapore Food Regulations include requirements such as microbiological criteria for ready-to-eat foods, maximum limits for chemical contaminants, the usage of food additives and labelling.

3.3.4. Authorization process

Approval from SFA is not required for research on novel food and novel food ingredients. This covers activities that do not involve the consumption of the novel food and novel food ingredient, such as the selection and optimization of appropriate cell-line(s), culture media component(s) and processing aid(s), as well as studies on how to achieve effective production scale-up, among others.

At a high level, the process of seeking SFA pre-market approval can be divided into the following stages. The time taken for each stage varies depending on the complexity of the application.

1. **Initial engagements:** SFA encourages novel food companies to consult SFA early in their product development process to understand the information that it is required to submit to substantiate the safety of the novel food. As such, SFA regularly conducts a Novel Food Virtual Clinic with companies. These virtual clinics serve as a platform for engagement with SFA and are an opportunity for SFA to share more details about the novel food regulatory framework, approval process and document requirements. This platform facilitates SFA's engagement with novel food companies, as many of them are not based in Singapore. Recognizing that novel food companies have questions specific to their companies' inputs and processes, as well as those of a confidential nature, the virtual clinics also feature a one-on-one engagement session with the companies.

2. **Pre-submission consultations:** As novel food companies progress along their research and development journey, they will eventually decide on the inputs required (e.g. cell-line, microbial strain) as well as the nature of the final product (e.g. cell-based meat, fermentation product). At this juncture, close pre-submission consultations occur between the company and SFA to prepare the company to submit their safety dossier. During these consultations, companies may seek SFA's opinion on the adequacy of data generated in addressing food safety concerns. SFA does not prescribe the methodologies that companies should adopt to generate data. It is the responsibility of the submitting company to ensure appropriate validity and sensitivity of the methods used to generate safety data. Where possible, adherence to standardized guidelines such as from the Organisation for Economic Co-operation and Development is recommended. Regulatory consultants, acting on behalf of the submitting company, may join in the pre-submission consultations. In Singapore, one such party offering regulatory consultation services is the Future Ready Food Safety Hub (FRESH). FRESH is a tripartite initiative jointly formed by SFA, Agency for Science, Technology and Research and Nanyang Technological University (NTU) to support Food Safety research and development in Singapore and to assist novel food companies to safely bring their products to market in Singapore (<https://www.ntu.edu.sg/fresh>).
3. **Preliminary review of safety dossier:** The safety dossier submitted to SFA must cover the requirements set out in SFA's requirements document (SFA, 2021a) and is typically presented as a safety assessment report (including supporting documents of any experimental work, literature search and/or calculations performed). Some examples of the information that should be included are (i) the identity and characterization of the novel food, (ii) identities and chemical specifications of process inputs, (iii) manufacturing process, and (iv) the purity, allergenicity and toxicological data, as well as the intended uses of the novel food.

In order to expedite the review process as much as possible, it is acceptable for companies to submit safety information in phases for SFA's review, although this would not count towards the expected timeline of the review process. SFA will also review submissions made by companies based outside Singapore. The submission is made by emailing the safety dossier to SFA-NovelFoods@sfa.gov.sg, and applicants are reminded to ensure that the information is presented in a format that is available for SFA to download as a copy. Information that is not in English should be translated.

4. **Queries and clarification on safety dossier:** During the review process, SFA will contact the company in case queries and clarifications are required. If there are significant scientific issues to be resolved, it may be necessary for SFA to seek the opinions of members of the Novel Food Safety Expert Working Group. This working group was established by SFA to provide scientific advice to ensure that safety assessments are rigorously reviewed. It consists of experts specializing in food science, food toxicology, bioinformatics, nutrition, epidemiology, public health, genetics, carcinogenicity, metabolomics, fermentation technology, microbiology and pharmacology. To prevent the theft of intellectual property and conflicts of interest, members of the expert group must sign an acknowledgement to protect business confidential information and trade secrets, as well as make the necessary declarations prior to joining the expert working group. SFA also shares information with the expert working group on a need-to-know basis, redacting information that is not relevant for discussions.
5. **Issuance of regulatory decision:** After the company has provided a complete set of safety information, and after outstanding queries and clarifications have been addressed, SFA will issue a regulatory decision on the application. SFA estimates that the review of safety assessment dossiers submitted by companies will take about 9–12 months. However, this timeline assumes that the safety assessment dossier is complete with no further need for questions or clarifications from SFA. As this is generally not the case, it is important for companies to engage in pre-submission consultations with SFA and to provide parts of their safety assessment dossier in phases for early discussion and allow for opportunities to seek clarification.

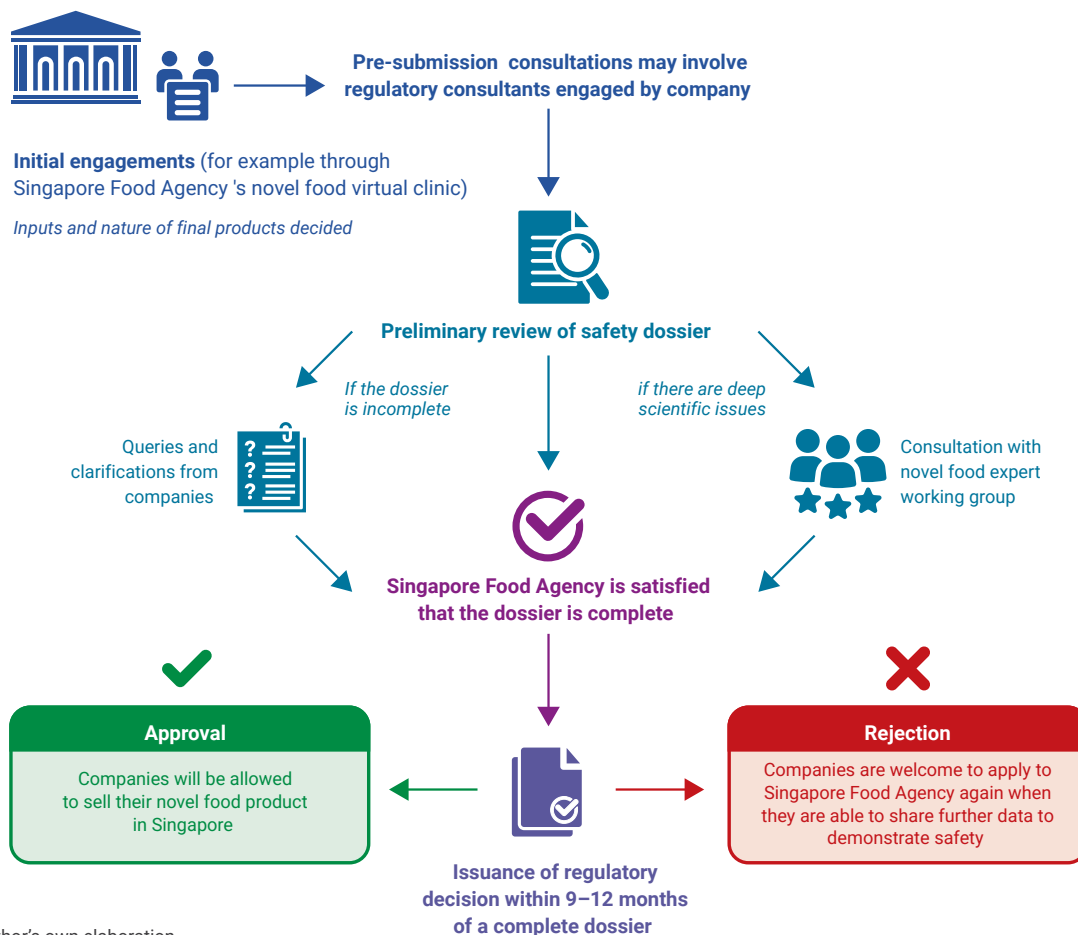
At the time of writing, SFA did not make external audits or visits to the facilities of novel food companies during the process of evaluation. However, after SFA has issued a pre-market approval for the novel food, like any other food establishment, as part of licensing requirements, facilities involved in the production of such novel food based in Singapore will be subject to SFA's inspection programme.

Even after SFA has issued a pre-market approval for a cultured meat product, as with any other food, it would be subject to sampling and testing by SFA under the market monitoring programme. SFA has a sampling and testing programme in place to ensure food safety. So far, no food safety concerns have been detected in the cultured meat products sampled and tested by SFA.

If changes are made to the manufacturing process of novel foods that have received pre-market regulatory approval by SFA and that may affect the validity of the original safety assessment submitted, novel food companies are required to seek approval from SFA before the products made using the updated manufacturing process are imported, distributed, or sold in Singapore. An example of such a change would be modifications in input materials (e.g. cell-lines or culture media components) in the production of cultured meat. It is the responsibility of the company to inform SFA should there be any changes to the inputs and processes used for the production of their cultured meat product(s).

The outcomes of a novel food safety assessment for a company, is not applicable to similar novel foods produced by other companies. This is because novel food safety assessments are specific to the materials and manufacturing processes described within the application. Different companies could be using completely different materials and processes in the production of their novel foods, and should conduct their own safety assessments, even if they are producing a similar novel food. For ease of reference, the flowchart in **Figure 10** summarizes the process of seeking SFA's pre-market approval.

Figure 10. Process of seeking the Singapore Food Agency's pre-market approval for cultured meat



Source: Author's own elaboration.

3.3.5. Steps for production, retail, import/export

Producing cell-based food in Singapore

Following SFA's pre-market approval of the novel food, companies that wish to set up a food processing establishment to produce the novel food product for commercial sale are required to obtain a food processing licence from SFA. To obtain a licence, companies first need to ensure that they have a valid registration with the Accounting and Corporate Regulatory Authority (ACRA) under the Business Registration Act (Cap. 32) of Singapore. Entities that are operating as companies must be incorporated and registered under the Companies Act (Cap. 50).

The process of obtaining a food establishment licence from SFA to produce cell-based food is not significantly different from other non-novel food products. Firstly, applicants should ensure that the premise's location is within a food zone area or an area with compatible industrial uses. Secondly, applicants should submit documents covering the layout plan, process flow chart and particulars of products for SFA's preliminary evaluation and pay an application fee. SFA will then assess the proposed plans to ensure they are designed in compliance with SFA's food safety requirements.

Once SFA has evaluated the submitted proposal, an in principal approval notification will be sent to companies to enable renovations to begin. Thirdly, applicants are required to make an appointment with SFA for a final inspection after renovations are completed. Documentation covering the particulars of the appointed hygiene officer, particulars of food handlers, cleaning and sanitation programme, pest control programme, maintenance programme and leased (tenancy) agreement should be made available for inspection. The final inspection will be carried out at the premises before the licence is issued. A licence will only be issued after all accompanying documents are submitted and SFA has assessed that the licensing requirements have been met satisfactorily. Companies should also seek SFA's prior approval if they intend to carry out future additional business activities beyond what has been allowed in the original licence).

For cultured meat, companies should ensure that all reagents/ingredients used in the manufacturing process have been assessed in the submissions approved by SFA prior to the licence being issued. The process flow diagrams and descriptions should also cover details such as the preparation of inputs, ingredients, and media, as well as processes related to cell banking and those leading to the cell-based food product. Critical control points should also clearly be indicated, justified and validated/verified to ensure that they are effective in minimizing food safety risks. Further information on the licensing process is available online (SFA, 2023a).

Exporting cell-based food from Singapore

The process of exporting food (novel or otherwise) from Singapore can be summarized as follows:

1. ensure that the food product is eligible for entry into the destination country and/or region;
2. apply for a trader's licence from SFA (if applicable);
3. seek pre-approval of the export establishment by the competent authority of the importing country;
4. apply for the relevant export documents required by the importing country; and
5. apply for an export or transshipment permit.

Further information can be found on the SFA website (SFA, 2023b). For cell-based food, it would be prudent for companies to first seek pre-market approval of the novel food (if applicable) from the relevant authorities of the destination country and/or region before companies initiate the process of exporting such food.

3.4. Food safety assessment

3.4.1. Assessment guidelines and steps

As the innovations behind novel foods are constantly evolving, the industry will need to align its safety assessment based on the specific microbiological, chemical or physical hazards related to their novel food products. While there is currently no one-size-fits-all approach for novel food safety assessments, SFA does have general guidance for companies seeking pre-market regulatory approval for their novel food products, which can be found on the SFA website.

SFA firmly believes that food safety is a joint responsibility and that engagement between regulator and industry is key to ensuring an adequate safety assessment for novel foods. SFA encourages early discussions with the industry during the initial stages of their product development. Such engagements allow the industry to consider the regulator's guidance and build safety assurance into their product development process. Regulators will also benefit from early information provided by the industry on upcoming food innovations that can contribute to their regulatory considerations. For companies that require more technical support for safety assessments on their products, SFA can help to refer them to Singapore's FRESH for additional support.

SFA does not impose a specific format for the safety assessment report to be submitted for pre-market regulatory approval. The intention is to facilitate the application process by providing the industry with flexibility and reduce the compliance burden. For instance, safety assessments submitted to other overseas regulatory agencies can be directly submitted to SFA for review if they contain the necessary information required by SFA.

With respect to cell-based food, the general principles and requirements for the safety assessment report typically include the following:

- 1. Information on cell-lines used:** As the major, if not the main, composition of cell-based foods would be the cell lines, SFA is of the opinion that it is essential to provide detailed information on the cell line used. This will include but not be limited to the following:
 - identity and source of cell lines including information on the origin of the host animal (if applicable);
 - information to demonstrate that biopsies (if applicable) comply with Singapore's animal health and food safety requirements and are free from animal disease;
 - methods used for extracting cells from the host animal (if applicable), subsequent selection and screening of cells;
 - methods used for cell line preparation and cell line banking;
 - description of any modifications and adaptations made to the cell lines used, and how these relate to the expression of substances that may result in any food safety risk;
 - risk assessments on any chemicals used in the cell line preparation and banking process;
 - characterization of the cell line (e.g. purity, composition); and
 - tests on relevant infectious agents (e.g. viruses, bacteria, fungi, prions).
- 2. Production Process:** Similar to the production of conventional foods, a good process control during production can be critical for ensuring food safety. For this reason, SFA requires applicants to provide all relevant information pertaining to their food safety management systems. Accepted documentation includes hazard analysis and critical control points (HACCP) plans, good manufacturing practices (GMP) and good cell culture practices (GCCP). The documentation must include a clear description of the risk monitoring and mitigation steps that have been established, including physical parameters and critical control points to address possible inherent risks. A production flow chart should also be provided.

For example, since cell-based foods are at risk of both chemical and biological contamination during the production process, information on the aseptic processing steps established to mitigate the risk of contamination to the culture media and cell lines throughout cell line selection, cell adaptation, cell proliferation, scaffolding, extraction, concentration and washing should be clearly described and highlighted in the safety assessment report.

- 3. Input characterization:** Upstream risk assessment through the control of inputs used in production of cell-based food is an effective food safety risk management strategy. For this, applicants are required to provide the specification characterization (e.g. purity, composition, amount and concentration) and food safety evaluation of all the inputs in the safety assessment report. Inputs would include all biological and chemical substances and contact materials, intended or unintended, introduced into the product during the novel food development and production process.

These can include but not be limited to:

- chemical and biological reagents for cell line manipulation and preparation;
- scaffolding materials, solvents, enzymes and processing aids; and
- culture media, growth promoters, modulating factors and anti-microbials.

In addition to the identity and quantification data, companies need to indicate in the safety assessment report whether specific inputs are intended as ingredients of the novel food product, whether their purities comply with specifications listed on the Singapore Food Regulations, the British Pharmacopoeia, the European Pharmacopoeia, the Joint Food and Agriculture Organization of the United Nations (FAO) / World Health Organization (WHO) Expert Committee on Food Additives (JECFA) Reports or the Food Chemicals Codex.

- 4. Output characterization:** As the final food product outputs represent the food safety endpoint of interest, the safety assessment report requires their detailed characterization and safety evaluation. Information should include but not be limited to:
 - percentages of major components present determined on a dry or wet mass basis (e.g. water content, protein, fat, carbohydrate, fibres, vitamins, minerals, ash);
 - purity of the food components, identities and quantities/concentrations of impurities that are expected to be present (e.g. contaminants, toxins, residual solvents, by-products, or metabolites) whether intended or unintended; and
 - if any of the food components is a potential human health hazard, it must be shown that its presence in the final product is at levels that will not cause any significant food safety concerns, under the proposed intended uses and conditions of consumption.
- 5. Toxicity and allergenicity characterization:** The safety assessment report must include information demonstrating the absence of toxicity risks in the novel food product. This should cover systemic (acute, sub-chronic and chronic) toxicity, carcinogenicity, mutagenicity, reproductive toxicity, developmental toxicity, genotoxicity and other relevant toxicity parameters. A weight of evidence and tiered toxicity testing approach would be applicable for the toxicological assessment.

The risks of allergenicity should also be assessed in the safety assessment report and can be calibrated according to the inherent risks. For example, shellfish is a common food allergen. Companies using cell-lines related to these species might determine the need to better assess this specific allergenicity risk through comparing the levels of the major shellfish associated allergens (e.g. tropomyosin) present in their novel cell-based food product relative to its conventional counterparts.

It is important to appreciate that the development and production processes of cell-based food, as an innovation, can change rapidly together with its associated potential food safety risks. Hence, the use of untargeted screening technologies (e.g. genomics, meta-transcriptomics, proteomics and metabolomics) might have a role for the evaluation of potential unexpected hazards and associated risks through comparison with reference controls.

6. **Exposure assessments:** To support the exposure assessment in the safety assessment report, the intended use, proposed use levels and anticipated intake amounts of the novel food/novel food ingredients should be specified. Deterministic estimates of intake should be derived using proposed use levels/serving sizes and comparative data on actual food consumption for equivalent proteins (e.g. slaughtered meat). Novel foods that are intended for consumption by specific population groups should be indicated. Any potential health hazards that have been identified should be discussed and adequately addressed in the proposed conditions of use to ensure that the consumption of the novel food/food ingredients is safe for the target population.
7. **Food testing methodologies:** To ensure the accuracy and quality of testing results, SFA recommends that, wherever possible, testing is conducted in accordance with principles of good laboratory practices (GLP). The testing methodologies should also be validated to an international standard such as ISO/IEC 17025 or its equivalent and/or published in peer-reviewed scientific literature. References to these methods should be clearly stated in the safety assessment report. Companies that require the use of in-house/novel testing methods will need to send details of the testing method, accreditation status of the testing method (if available) and the validation results to SFA, for evaluation of the scientific robustness, accuracy, precision and sensitivity of the method.

3.4.2. Identified potential food safety-related hazards/concerns and risk management

Cultured meat is a new and varied industry and it is undergoing rapid changes. As such, SFA constantly keeps abreast of the latest innovations in this space through active engagements with industry, academia and overseas regulatory counterparts. In these engagements, several scientific issues related to food safety have emerged, two of which are highlighted below.

1. **Food safety risks arising from genetic drift:** In the production of cultured meat, cells undergo copious amounts of cellular replications in an *in vitro* environment. Consequently, genome instability and genetic drift are posited as potential major contributors to phenotypic variations in cultured meat (Soice and Johnston, 2021). This is emphasized by the need for cells to adapt to *in vitro* selection pressures exerted by the cell culture conditions. It is important that the stability of the cellular output is ensured in cultured meat because the whole cell biomass is consumed. Perceived food safety concerns pertaining to undesirable proteins and/or metabolites (e.g. potential toxins and allergens) need to be addressed, as these could be produced in a deregulated manner as a result of genome instability and genetic drift (Soice and Johnston, 2021).
2. **Safety assessment of biological products used for cell cultivation:** Cell culture requires a carbon-based energy source (e.g. glucose), amino acids, salts, vitamins, water and other components to support cell viability and vitality. To facilitate proliferation of mammalian cells, a basal medium must be supplemented with several factors, which are traditionally provided for by the addition of fetal bovine serum (FBS) into the culture media (van der Valk *et al.*, 2018). However, some cultured meat/seafood companies increasingly seek to use serum-free media for cell cultivation due to various reasons, including cost, sustainability, batch-to-batch variability in serum composition, to eliminate reliance on animal-based products and potential viral or prior contamination of serum. This involves supplementing the basal media with insulin, transferrin, as well as downstream growth factors regulated by hormones found in FBS (Liu *et al.*, 2019). However, these substances have not been previously added to food and so there are no established health-based guidance values. The threshold of toxicological concern approach would also not be suitable for proteins and steroids, as these substances could have structures not adequately represented in the original databases used to derive threshold of toxicological concern values (More *et al.*, 2019) with limited toxicity data for specific chemical-specific assessment. The challenge is to develop an appropriate assessment approach for such substances. It is critical to assess the safety of culture media used in the production of cultured meat and seafood as components of the cell culture medium may potentially become part of the final food product.

SFA is developing regulatory positions on these issues at the time of writing, referencing, where available, relevant regulatory positions adopted by other jurisdictions for both the food and pharmaceutical sectors. SFA regularly consults the Novel Food Expert Working Group and subject matter experts to seek their views on the proposed regulatory position. This will ensure that the regulatory deliberations are backed by rigorous science.

3.5. Other key considerations outside food safety

3.5.1. Labelling

Proper food labelling is among the most important and direct channels for manufacturers to communicate accurate product information to the consumer, thereby allowing the consumer to make informed dietary choices. Therefore, all pre-packed food products for sale in Singapore must be labelled according to the general labelling requirements (name of product, list of ingredients, presence of allergens, etc.) of the Singapore Food Regulations. For information, guidelines on the use of precautional allergen labelling can be found at <https://www.sfa.gov.sg/food-information/food-allergens/food-labels>.

As with all other foods, novel foods are required to be labelled with product names that accurately describe the true nature of the product. In the area of pre-packed alternative proteins such as cultured meat, Singapore requires companies to incorporate suitable qualifying terms such as “cultured” or “cell-based” in naming these products to indicate their true nature. While there are no positive labelling requirements in the Singapore Food Regulations, food businesses are not allowed to label their genetically modified (GM) food products as non-GM food. Similarly, food establishments selling non prepacked foods are required to clearly communicate to their customers the true nature of the food being sold. Misrepresenting cultured meat as conventionally produced meat will not be allowed.

3.5.2. Consumer acceptance of cultured meat

As with most new technologies, consumer acceptance of cultured meat is likely to be mixed. However, there are emerging signs of growing acceptance of cultured meat. With Singapore being the first country to allow the sale of cultured meat to the public, a recent study investigated the acceptance of cultured meat by Singaporeans compared to Americans. The study revealed that Singaporeans are generally more accepting of cultured meat, which was motivated by a fear of losing out or being left behind (Chong *et al.*, 2022). In addition, there was also a desire to project a “trailblazer” trait and to be quick in trying or experiencing novel products such as cultured meat. However, there is also scepticism regarding the cost of producing the cultured meat which was reported to be approximately USD 50 for a single nugget. Serving the chicken nuggets as a dish was also reported to cost SGD 23, which is considered a high-end restaurant price by the local population. It is most likely that the production costs for cultured meat will have to be reduced significantly to make it affordable for ordinary consumers before cultured meat can be more widely accepted by Singaporeans.

3.5.3. Developing the cultured meat industry

As Singapore continues to position itself as a hub to foster innovation and encourage high-potential food tech companies to anchor locally, multiple companies who are interested in obtaining regulatory approval in Singapore have also engaged with SFA to kickstart the safety assessment of cultured meat products. These companies feature a range of products from cultured meat, seafood, milk proteins, fungal proteins, as well as algal and fermentation proteins. Several of these cultured meat companies have also attracted investments or interests from state-backed investment companies such as Temasek Holdings, Singapore Economic Development Board Investments and private venture capital firms such as Big Idea Venture from Singapore. For example, since 2013, Temasek Holdings are reported to have invested USD 8 billion in global agrifood supply chains, which includes companies in the cultured meat and alternative protein space (Ng and Ramli, 2021). The state backed investment firm also launched the Asia Sustainable Foods Platform to provide advisory, pilot facilities and investment support to novel food companies.

To encourage innovation in the ecosystem, FoodInnovate, which is a multi-agency food innovation platform led by Enterprise Singapore, was launched in 2018. The platform provides resources to food companies to drive food tech and innovations, enabling them to develop new and sustainable food products to meet the evolving demands and nutritional needs of consumers. Through FoodInnovate, companies can build capabilities, access shared facilities and co-innovate with other partners.

Recognizing that the science and technologies surrounding novel foods are extremely new, SFA together with the Agency for Science, Technology and Research initiated the Singapore Food Story R&D Programme where SGD 144 million (about USD 100 million) has been dedicated to drive innovation in sustainable urban food solutions, further the production of advanced biotech-based protein (including cultured meats) and develop innovations in food safety science. (The Straits Times, 2020) This will help to push towards Singapore's national agenda of strengthening Singapore's food security. Nonetheless, ensuring public health is still of utmost importance. Therefore, all novel food products including cultured meats will be required to undergo safety assessments based on the novel food regulatory framework to ensure food safety prior to approval for sale in Singapore.

3.6. Discussion

SFA has put in place a regulatory framework for novel foods (including cultured meat), established processes and requirements to facilitate applications for pre-market approvals and laid down labelling requirements for pre-packed alternative proteins (including cultured meat). Recognizing that the cultured meat industry is new and varied, these developments will help to ensure adequate space for the industry and research community to innovate while protecting the health of consumers.

However, the novel food industry (including cultured meat) is still rapidly developing, and it is paramount that SFA continue to keep abreast of the latest innovations in this area. SFA regularly updates its requirements document to ensure that the regulatory framework is robust and relevant. The document was last updated in April 2022.

The challenge of ensuring the safety of cultured meat is not unique to Singapore alone, and Singapore will need to work closely with Singapore's strategic alliances to formulate solutions. Recognizing that collaboration is key, SFA has been keen to encourage international conversations on the safety assessment of novel foods. Since 2019, SFA has held the Roundtable for Novel Foods to provide a platform to raise awareness about new technologies for novel food production, discuss the challenges in safety assessment and explore opportunities to advance the regulatory agenda, while encouraging food innovations. This case study, developed in collaboration with FAO, is another example of SFA's efforts to encourage conversations in the international community regarding the safety of novel foods such as cultured meat.



©CelIX/Ning Xiang

D. FOOD SAFETY HAZARD IDENTIFICATION

1. Overview of the Expert Consultation

For the Expert Consultation held in Singapore from 1 to 4 November 2022 to conduct the first global food safety hazard identification of cell-based food, FAO issued an open and global call for experts from 1 April to 15 June 2022 in order to form a group of experts with multidisciplinary fields of expertise and experience to provide scientific advice to conduct the first step of food safety hazard identification of cell-based food.

A total of 138 experts applied and an independent selection panel, reviewed and ranked the applications based on the pre-set criteria. Considering the overall score, gender, sector, and geographical balance, 33 applicants were short-listed. Among them, 26 completed and signed their Confidentiality Undertaking and Declaration of Interest. After the evaluation of all disclosed interests, candidates with no perceived conflict of interest were listed as experts while candidates with a relevant background on the matter who had declared interests that could be perceived as a potential conflict of interest were listed as resource people. In addition, three have withdrawn their applications due to schedule conflict for the Expert Consultation meeting. As a result, a total of 23 people (13 experts and 10 resource people) formed the Technical Panel for the Expert Consultation.



2. Technical Panel experts and resource people

To assure the highest integrity, all the appointed Technical Panel members were asked to complete the Declaration of Interests form prior to the Expert Consultation. The declared interests of the Technical Panel experts were considered unlikely to impair the individual's objectivity or cause significant influences on the impartiality, neutrality and integrity of the work. On the other hand, the declared interests indicated by the Technical Panel resource people may be potentially considered substantial, however, that is the very reason why they are particularly knowledgeable about the topic to contribute the expertise and experience to the Expert Consultation, therefore they were considered to be fully eligible to be a member of the Technical Panel, but were excluded from the decision-making processes.

Technical Panel experts

1. **Anil Kumar Anal**, Professor, Asian Institute of Technology, Thailand
2. **William Chen**, Endowed Professor and Director of Food Science and Technology, Nanyang Technological University, Singapore (Vice Chair)
3. **Deepak Choudhury**, Senior Scientist, Biomanufacturing Technology, Bioprocessing Technology Institute, Agency for Science, Technology and Research, Singapore
4. **Sghaier Chriki**, Associate Professor, Isara (Institut Supérieur de l'Agriculture Rhône-Alpes), Researcher, INRAE (National Research Institute for Agriculture, Food and Environment), France (Working Group Vice Chair)
5. **Marie-Pierre Ellies-Oury**, Assistant Professor, Institut National de la Recherche Agronomique et de L'Environnement and Bordeaux Sciences Agro, France
6. **Jeremiah Fasano**, Senior Policy Advisor, United States Food and Drug Administration, United States of America (Chair)
7. **Mukunda Goswami**, Principal Scientist, Indian Council of Agricultural Research, India
8. **William Hallman**, Professor and Chair, Rutgers University, United States of America (Vice Chair)
9. **Geoffrey Muriira Karau**, Director Quality Assurance and Inspection, Bureau of Standards, Kenya
10. **Martín Alfredo Lema**, Biotechnologist, National University of Quilmes, Argentina (Vice Chair)
11. **Reza Ovissipour**, Assistant Professor, Virginia Polytechnic Institute and State University, United States of America
12. **Christopher Simuntala**, Senior Biosafety Officer, National Biosafety Authority, Zambia
13. **Yongning Wu**, Chief Scientist, National Center for Food Safety Risk Assessment, China

Technical Panel resource people

1. **Breanna Duffy**, Director of Responsible Research and Innovation, New Harvest, United States of America (Working Group Vice Chair)
2. **Neta Lavon**, Chief Technology Officer, Aleph Farms, Israel
3. **Amanda Leitolis**, Cultivated Meat Scientist, The Good Food Institute, Brazil
4. **Kimberly Ong**, Safety and Regulatory Consultant, Vireo Advisors, Canada (Working Group Vice Chair)
5. **Mark Post**, Professor, Maastricht University, Netherlands
6. **Jo Anne Shatkin**, President, Vireo Advisors, United States of America
7. **Elliot Swartz**, Lead Scientist, The Good Food Institute, United States of America (Working Group Vice Chair)
8. **Keri Szejda**, Principal Research Scientist, North Mountain Consulting Group, United States of America
9. **Mercedes Vila Juarez**, Chief Technical Officer, BioTech Foods, Spain
10. **Peter Yu**, Program Manager and Consultant, Asia Pacific Society for Cellular Agriculture, Singapore

Participation of an expert / resource person in the meeting does not imply that they are endorsed or recommended by FAO, nor does it create a binding relationship between the expert and FAO. An appointed Technical Panel member does not represent the government of country of which they are a citizen, nor the institution or group with which he or she is associated. The selected individuals attended the meeting in their personal capacity as scientific and technical experts with responsibility for providing independent advice to FAO.

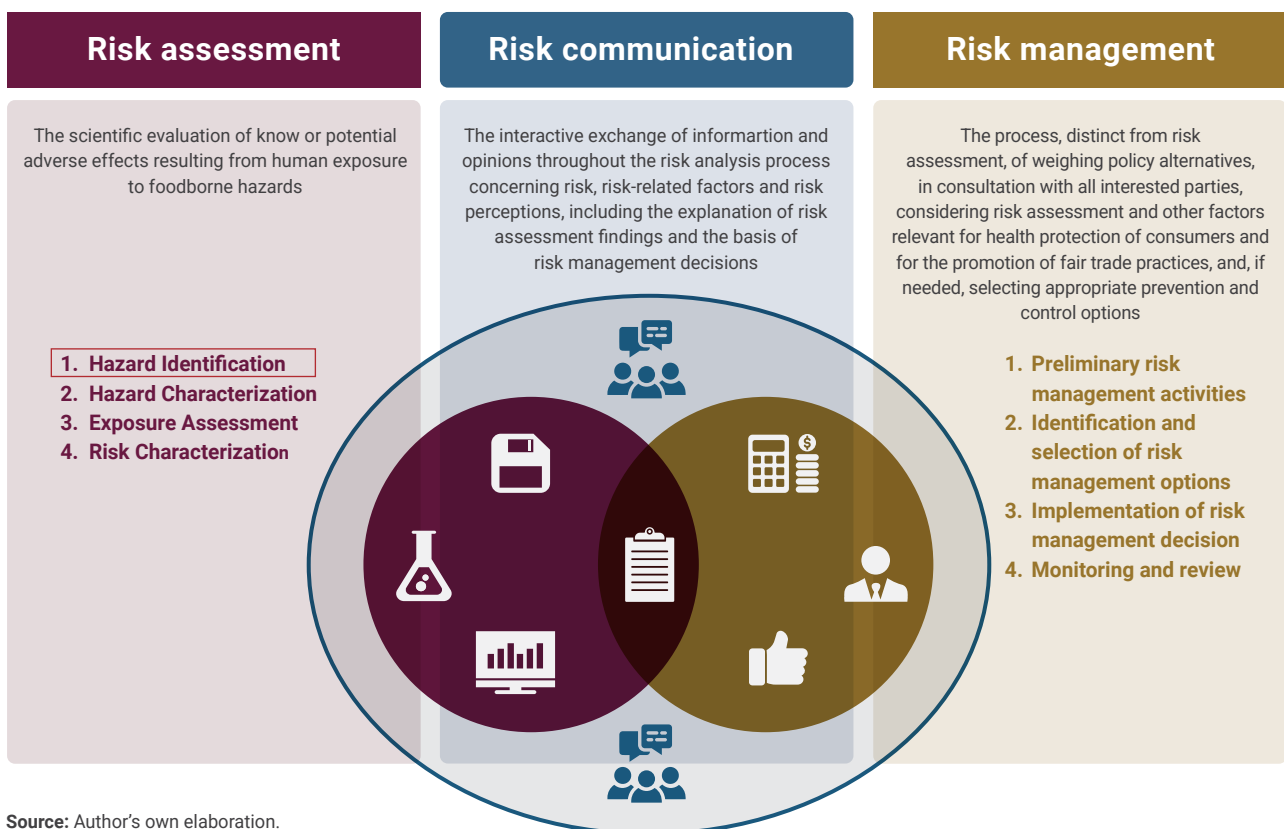
3. Expert Consultation methodologies

3.1. Approach for the hazard identification

In general, scientific advice provided by FAO and WHO follows the food chain approach to cover the entire system from the very first point of the production to the end point with consumers (farm-to-plate or production-to-consumption). However, for the topic of cell-based food, the products have not yet widely reached general retailers and consumers at the time of the Expert Consultation, therefore the focus has been put on the relevant production stages up to the food processing phase. The major food safety issues considered during the Expert Consultation included physical contamination, chemical hazards (including additives, contaminants and residues), biological hazards, allergenicity (including hypersensitivity) and other concerns regarding the use of latest/emerging technologies and new production systems.

FAO and WHO promote the application of risk analysis in all matters involving food safety. Risk analysis represents a structured decision-making process with three distinct but closely connected components: risk management, risk assessment and risk communication (Figure 11).

Figure 11. Generic components of food safety risk analysis paradigm



Source: Author's own elaboration.

The three components are essential and complementary parts of the overall discipline. Risk assessment is the central scientific component of risk analysis and has evolved primarily because of the need to make decisions to protect health in the face of scientific uncertainty. Risk assessment can be generally described as characterizing the potential adverse effects to life and health resulting from exposure to hazards over a specified time period. The risk assessment process is generally represented as consisting of four steps (see Figure 11). Specific identification of the hazard(s) of concern is a key step to be conducted first in the risk assessment process. In other words, without a hazard being clearly identified, the relevant risk cannot be assessed.

To comprehensively identify all the potential food safety hazards for cell-based food production, all 23 Technical Panel members were first asked to submit an individual report on hazard identification to the FAO secretariat. Overall, more than 300 hazards, including overlapping and duplicating hazards among Technical Panel members, were compiled to serve as a basis of the discussions at the Expert Consultation.

During the Expert Consultation, working groups were formed to discuss the following items for each hazard identified:

1. Hazard agent;
2. Problem description / consequence to human health;
3. Hazard type (biological hazard, chemical hazard, physical hazard or allergen);
4. Potential mitigation control measures;
5. Potential testing control measures;
6. Whether or not the hazard can be addressed in the food safety plan such as a HACCP plan;
7. Similar presence of the hazard in other food products / comparators / relevant experiences / gaps; and
8. Causal chain examples.

The Technical Panel agreed to exclude any occupational health hazards of the production process (e.g. injuries, heat and noise, psychosocial hazards). However, it was noted that some issues, such as the possible ingestion of *Mycoplasma* spp., in terms of public health, the science is not definitive (see [Chapter 4.4](#) of this section).

The genus *Mycoplasma* contains more than 100 species, some of which can cause chronic diseases in animals and humans. *Mycoplasma* spp. (except for *M. pneumoniae*) are usually commensal respiratory and urogenital tract inhabitants, but they can become pathogenic. Around 16 species are known to colonize humans, with *M. pneumoniae* being the best known and most intensely studied human mycoplasmosis. It is the primary cause of many upper respiratory tract infections in humans, including primary atypical pneumonia and tracheobronchitis.

M. pneumoniae infections are most common in young adults and school-aged children, but can affect anyone, including i) those individuals who work in crowded in-door settings, including long-term care facilities and hospitals, and ii) high-risk individuals such as those recovering from a respiratory illness or those with a weakened immune system.

In terms of transmission, *M. pneumoniae* is primarily transmitted by large droplets from person-to-person and can also be transmitted by fomites to those in close contact with an infected person. Thus, like many respiratory pathogens, *M. pneumoniae* is most commonly spread by coughing and sneezing. To the authors' knowledge, there have been no reported foodborne outbreaks caused by *M. pneumoniae*, and transmission of the organism by the oral and fecal/oral route has not been documented. In addition, gastro-intestinal symptoms, such as diarrhea, are rare or have not been reported. Therefore, for the time-being, the issues around *Mycoplasma* spp., have been considered out of scope of food safety hazard identification.

The results of hazard identification are illustrated in four tables within [Chapter 4.2](#) of this section. In addition, each hazard has been further explained in narratives in [Chapter 4.3](#) of this section.

3.2. Approach for developing practical guide for relevant communication

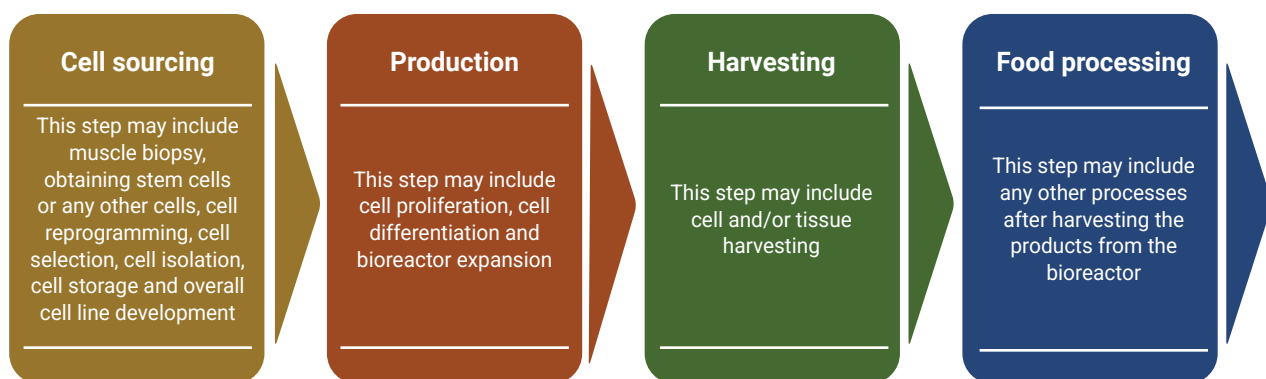
During the Expert Consultation, one working group was assigned to develop an evidence-based practical guide for food safety competent authorities to engage stakeholders in communication regarding the food safety aspects of cell-based food. For this purpose, prior to the Expert Consultation, the Technical Panel members with expertise in social science were asked to provide relevant texts and peer-reviewed evidence that can identify important elements on food safety communication to build consumer trust. Based on the individual contributions, the working group developed the text in [Chapter 4.5](#). In addition, as the issue of terminologies was recognized as critical in communication, special consideration texts on terminologies (see [Chapter 4.6](#)) were also developed by the working group.

4. Results of the Expert Consultation

4.1. Overview

To conduct the comprehensive food safety hazard identification with available information and knowledge, the Technical Panel considered all potential hazards to develop an exhaustive list based on the four stages of the cell-based food production, namely: 1) cell-sourcing; 2) cell growth and production; 3) cell harvesting; and 4) food processing and formulation (Figure 12). The cell sourcing step includes muscle biopsy, obtaining stem cells, cell reprogramming, cell isolation, cell storage and overall cell line development. The cell growth and production step include cell proliferation, cell differentiation and bioreactor expansion, while the cell harvesting step includes cell and tissue harvesting. The food processing step includes any other process after harvesting the products from the bioreactor.

Figure 12. Four stages of the cell-based food production



Source: Author's own elaboration.

The experts found that for cell-based food, many hazards are already well-known, and they exist in conventionally produced food. For example, microbiological contamination can occur at any stages of any food production process, including those involved in producing cell-based food. The experts concluded, however, that most cases of microbial contamination during the cell growth and production stages would inhibit cell growth. If the cells have grown and reached product expectations for harvest, then occurrence of such contamination would be extremely rare during the production process but it could occur post-harvest, as is the case with many other food products. Various existing prerequisite programmes such as good manufacturing and hygiene practices, as well as food safety management systems such as Hazard Identification and Critical Control Points (HACCP), are applicable to ensure food safety for cell-based food.

Food safety plans would also need to focus on the materials, inputs, ingredients, and equipment that can be specific to cell food production, including the use of new substances needed to nourish the cells, and the possibility of allergic reactions to them. However, while such inputs and materials may be novel, the Technical Panel noted that there are existing preventative measures and controls available to address these potential hazards.

4.2. Hazard tables by four production stages

It is important to note that there is a significant difference between the terms "hazard" and "risk". According to Codex Alimentarius, a food safety "hazard" is explained as "a biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect" and a food safety "risk" is described as "a function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food". In this chapter, four tables (Tables 5-8) are presented with a list of potential hazards associated with cell-based food production. It is critical for the readers have a full understanding on the respective terms and not to confuse the list hazards with the list of risks.

4.2.1. Potential hazards during cell-sourcing

Table 5. Hazards identified by the Technical Panel for the cell sourcing stage

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
1.	Cell sourcing (biopsy step)	Veterinary drugs (including antimicrobials)	Veterinary drugs may be present in biopsied tissues and be present in the final food product, causing negative human health effects, which include allergenicity to antimicrobials	C, A	Access to animal health records (e.g. information related to withdrawal periods)	Quantification of the levels of veterinary drugs in the final product	The same hazard is also present in the production processes for conventional livestock production and aquaculture	The drug is present in the sampled tissue and the cells brought into culture > the cell culture is not disrupted > the drug is not degraded or washed away, and the drug goes undetected throughout the cell sourcing, production and harvesting, and food processing stages > the drug survives food preparation > the drug reaches the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for drugs that can elicit allergic responses)
2.	Cell sourcing (biopsy step)	Pathogens (bacteria, virus, fungi, parasites, protozoa), including antimicrobial resistant strains	Pathogens may be present in the biopsied tissues and eventually carried to the end product where they could be pathogenic if handled or consumed	B	Access to herd (for terrestrial livestock) or lot (for aquaculture) health certification Health inspection (pre- or post-slaughter) by certified professional of source animals and biopsied tissues for signs of infection Antimicrobials can be added at the moment of sampling Sample can be kept cold to reduce growth or metabolism of pathogens	Testing can be performed prior to cell banking Testing for viruses, including species-specific viruses Testing for prions in the case of limited health information on source animals Testing for other pathogens	This same hazard is present in conventional meat products Health certification and veterinary inspections are rare or non-existent for seafood or other wild-caught species	The pathogen is present in "the biopsied sample or enters the sample during the biopsy process > the pathogen survives antibiotic or antimycotic treatment (e.g. for bacteria and fungi) > the pathogen survives and replicates in cell culture > the cell culture is not disrupted throughout the cell sourcing, production and harvesting, and food processing stages > the pathogen is not detected through macroscopic or analytical inspection > the pathogen survives food preparation > the pathogen is present in final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
3.	Cell sourcing (biopsy step)	Prions	Prions may be present in the biopsied tissues and eventually carried to the end product where they could be pathogenic if handled or consumed	B	<p>Healthy inspection (pre- or post-slaughter) by certified professionals of source animals and biopsied tissues for signs of infection</p> <p>Access to herd health certification</p> <p>Avoiding procuring tissues that are known to harbour prions (e.g. central nervous system tissues)</p> <p>Obtaining tissues from phenotypically healthy animals and animal populations with no history of prion disease</p>	<p>Testing for prions can be performed prior to cell banking if appropriate (e.g. if there is limited health information on source animals, especially for bovine source animals)</p>	<p>This same hazard is also present in certain conventional meat products</p> <p>Regulations to control prions in food animal populations exist in several countries or regions</p>	<p>Prions are present in the biopsied tissue and enter the cell culture > prions propagate and spread in cell culture > the cell culture is not degraded or detected throughout the cell sourcing, production and harvesting, and food processing stages > prions survive food preparation > prions are present in final product (any amount would be expected to be hazardous)</p>
4.	Cell sourcing (biopsy step)	Microbial toxins	Microbial toxins could be sourced from particular animal tissues and eventually carried to the end product where they could be harmful if consumed	C	<p>Depending on the species, access to authorized health information can guide animal sourcing</p> <p>Obtaining tissues from regions known not to harbour toxicant-producing bacteria or sequester toxins</p>	<p>Testing for toxins in cases where limited health information on source animal is available</p> <p>Calculating dilution factor of the toxin prior to banking</p>	<p>This same hazard is also present in some conventional seafood</p>	<p>The toxin is present in the biopsy sample and the cells brought into culture > the cell culture is not disrupted > the toxin is not degraded or washed away > the toxin goes undetected throughout the cell sourcing, production, harvesting, and food processing stages > toxin survives food preparation > toxin is present in high enough level to pose a health risk</p>

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
5.	Cell sourcing (biopsy step)	Novel substances (with allergenic or toxic properties) from genetic modification	The source animal has been intentionally genetically modified, leading to novel substances such as new bioactive molecules or proteins that may be toxic if consumed or allergenic if consumed or handled when present in the final product	B, A	Safety assessment of genetically modified animals ^c	Testing is not applicable as safety assessment has already been performed in these instances	This same hazard is present in other genetically modified foods	The substances resulting from the genetic modification are present in the cells that are biopsied > the substances expressed by the cells persist in the cell culture > the cell culture is not disrupted and the substances are not ^d degraded or washed away throughout the cell sourcing, production and harvesting, and food processing stages > the substances survive food preparation > the substances reach the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for substances that can elicit allergic responses)
6.	Cell sourcing (biopsy step)	Food allergens	The source animal has a history of use in food and is known to produce allergens; or is species without a history of use in food Some consumers may have an allergic cross-reaction to the end product when handled or consumed	A	Labelling for known allergen	Testing is not applicable as safety considerations have already been accounted for in these instances	The same hazard is present in conventional meat, seafood, and other foods	Food allergens are present in the cells because they were sourced from an animal known to produce allergens > the food allergens are not degraded or washed away throughout the cell sourcing, production and harvesting, and food processing stages > the allergens survive food preparation > the allergen reaches the final product at a concentration that exceeds a tolerable threshold
7.	Cell sourcing (cell culturing)	Pathogens (bacteria, viruses, fungi, parasites, protozoa) and pathogenic agents (prions)	Pathogens in cell culture media components or other reagents may be present in the end product and could be pathogenic if handled or consumed	B	Following relevant good practices ^d Sterilization methods (heat, irradiation, filtration) can be applied depending on the composition of the media Avoiding the use of animal-derived components	Testing for viruses, including species-specific viruses Testing for prions in the case of limited health information on source animals Testing for other pathogens	This same kind of hazard may be present in fermented food products, fermented food ingredients, and recombinant enzymes used in food production	Pathogen / pathogenic agent present in intentional input (e.g. medium / serum) > Input is not sterilized > the pathogen is transferred into the cell culture or cell line > the pathogen survives antibiotic or antimycotic treatment (if used) > the pathogen survives and replicates in cell culture > the pathogen survives and replicates in the bioreactor > the cell culture is not disrupted > pathogens are not detected by any testing or process monitoring throughout the cell sourcing, production and harvesting, and food processing stages > the pathogen survives food > the pathogen is present in final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
					<p>Healthy inspection (pre- or post-slaughter) of source animals</p> <p>Access to herd / lot health certification</p> <p>Source reagents from pathogen free regions or herds (e.g. bovine spongiform encephalopathy [BSE]-free)</p> <p>Antimicrobials can be used to prevent bacterial and fungal contamination</p>			
8.	Cell sourcing (cell culturing)	Pathogens (bacteria, viruses, fungi, parasites)	Pathogenic contaminants (bacteria, viruses, fungi, parasites) due to unhygienic operators, environment or equipment could be carried to the end product and be hazardous when handled or consumed	B	<p>Following relevant good practices^d</p> <p>Aseptic handling of cells and inputs</p> <p>Process monitoring</p> <p>Antimicrobials can be used to prevent bacterial and fungal contamination</p> <p>Sterilization methods (heat, irradiation, filtration), if appropriate</p> <p>Storage of cells in the vapor phase of liquid nitrogen</p>	Testing for pathogenic contaminants during the process or in the final product	The same kind of hazard is present in conventional meat products and in common food processes	The pathogen is introduced to cells culture through equipment / environment / personnel > the pathogen is transferred into the cell culture or cell line > the pathogen survives antibiotic or antimycotic treatment (if used) > the pathogen survives and replicates in cell culture > the cell culture is not disrupted > pathogens are not detected by any testing or process monitoring throughout the cell sourcing, production, harvesting, and food processing stages > the pathogen survives food processing > the pathogen survives food preparation > the pathogen is present in final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
9.	Cell sourcing (cell culturing)	Hazardous chemical / food additive residues (culture medium stabilizers, modulators of cell function, nutrients, etc.)	Residues or metabolites of hazardous chemicals (e.g. steroids, small molecular entities, surfactants, antifoaming agents, pH buffers, etc.) used during cryopreservation and / or cell culture could remain in the end product and be toxic or allergenic at anticipated exposure levels for consumption	C, A	<p>Following relevant good practices^d</p> <p>Use of chemicals or modulators that have established food safety history</p> <p>Use of the minimal levels for effective action</p> <p>Washing procedures to remove chemicals or reduce their concentration can be used</p> <p>Use of substances that are non-allergenic and safe for consumption</p> <p>Evaluation of potential hazard and exposure, perform safety assessment</p> <p>Development of specifications</p>	<p>If using chemicals that do not have a safe history of use in food, quantify the levels of the hazardous chemical residues in the final product</p> <p>Quantification of the levels of the food additive in the final product</p> <p>If a proteinaceous modulator is modified in some way, allergenicity testing on the new substance can be performed</p>	<p>The same or similar kind of residues may be present in products of fermentation and precision fermentation, in fortified foods, in assisted reproduction techniques used for terrestrial and aquatic species, novel and conventional protein and other processed foodstuffs</p> <p>Databases that document the safety of chemicals in foods or levels known to be safe for foods can be referenced^e</p> <p>For some of these substances, there are no reference values regarding safe levels in food</p>	<p>Hazardous chemicals or additives are used and enter the cell culture > the cell culture is not disrupted > the chemicals or additives are not degraded, metabolized, or washed away, and the chemicals or additives remain throughout the cell sourcing, production, harvesting, and food processing stages > the chemicals or additives survive food preparation > the chemicals or additives reach the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for chemicals that can elicit allergic responses)</p>
10.	Cell sourcing (cell culturing)	Food allergens	Certain media ingredients or compounds added to the cell culture could contain allergens or be derived from allergenic sources that are present in the end product, which could elicit an allergic reaction when handled or consumed	A	<p>Labelling for known allergen</p> <p>Use of ingredients not known to contain allergens</p> <p>Hydrolysis or other processes to reduce or eliminate allergic epitopes of specifications</p>	<p>Residue testing on the end product at downstream process stages to determine if allergens are present at levels known to be unsafe</p>	<p>The same hazard is present in conventional meat, seafood, and other foods</p>	<p>Food allergens / immunogenic substances are used in the media and enter the cell culture > the food allergens are not degraded or washed away throughout the cell sourcing, production, harvesting, and food processing stages > the allergens survive food preparation > the allergen reaches the final product at a concentration that exceeds a tolerable threshold > allergenic / immunogenic ingredient is not properly labelled or disclosed on final product</p>

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
11.	Cell sourcing (cell culturing)	Antimicrobials	Antimicrobials are added to the media as a preventative measure during cell culture and may be present in the end product and be a health hazard or elicit an allergic reaction	C, A	Following relevant good practices ^d Testing for residues of antimicrobials prior to banking Use of the minimal levels for an effective action	Quantification of the levels of antimicrobial residues in the final product	A similar type of hazard is present in conventional meat and aquatic animal products Antimycotics are used in food preservatives and food preparation services	Antimicrobials are used and enter the cell culture > the cell culture is not disrupted > the antimicrobials are not degraded, metabolized, or washed away, and the antimicrobials persist throughout the cell sourcing, production and harvesting, and food processing stages > the antimicrobials survive food preparation > the antimicrobials reach the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for antimicrobials that can elicit allergic responses)
12.	Cell sourcing (cell culturing)	Novel allergenic or hazardous substances due to intentional genetic modification, including those involving transgenes and resultant changes in endogenous genes	A genetic modification is implemented in the cell line development stage, leading to the expression of novel substances These new proteins or bioactive molecules may be toxic or allergenic if present in the end product Additionally, changes in endogenous genes may increase the levels of endogenous allergens or toxicants	B, A	The method of genetic modification may vary and may introduce different hazards that may need to be examined on a case-by-case basis Avoiding modifications that encode allergenic sequences	Allergenicity testing for the new protein Toxicity testing for the new protein Compositional analysis of the whole food (performed at a later process stage) Analyzing level of expression of molecules related to the modification and correlate to expected exposure from the food product Validation that the modification is as intended without further changes in the genome	The same hazard is present in other genetically modified foods	Novel substances in the genetically modified cells are hazardous or allergenic > these substances are undetected in the safety assessment of the cells > the substances expressed by the cells persist in the cell culture > the cell culture is not disrupted and the substances are not degraded, metabolized, or washed away throughout the cell sourcing, production and harvesting, and food processing stages > the substances survive food preparation > the substances reach the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for substances that can elicit allergic responses)

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
13.	Cell sourcing (cell culturing)	Food allergen	There is limited information about the potential allergenicity of the source animal A new or broader set of consumers are exposed to the proteins of this species, which may elicit allergic reactions when handled or consumed	A	Labelling to refer to an unconventional species	Allergenicity testing for the new protein, including bioinformatic comparison with known allergens	A similar type of hazard exists when considering insects entering the food chain	Comparative bioinformatics fail to detect possible food allergens in cells sourced from animals that may produce allergens > the food allergens are not degraded or washed away throughout the cell sourcing, production and harvesting, and food processing stages > the allergens survive food preparation > the allergen reaches the final product at a concentration that exceeds a tolerable threshold
14.	Cell sourcing (cell culturing)	Novel toxins or allergens or an increase in endogenous toxicants or allergens	Expression of novel toxins, toxic metabolites, or allergens or a change in expression of toxins, toxic metabolites, or allergens as a result of genomic instability (e.g. large rearrangements), genetic or phenotypic instability (e.g. variability due to cell division, <i>mycoplasma</i> contamination), and / or induced through physical or biochemical stimuli during cell culture that are present in the end product, which becomes (more) toxic or allergenic when handled or consumed	B, A	Following relevant good practices ^d Listing of relevant components that could impact food safety depending on species or cells being used so that monitoring can be effective Monitoring of cells Use of a washing procedure to remove substances	Evaluation of genetic and phenotypic stability by molecular techniques (e.g. karyotyping) Allergenicity and toxicity testing Analyzing level of expression of molecules related to the change and correlate to expected exposure from the food product	This hazard is also possible due to genetic variation in conventional breeding or cloning processes This hazard is also a concern in the cellular therapeutics and biosimilars industry	Genetic, genomic, or phenotypic instability affects a relevant gene or phenotype in the cell line > the endogenous toxicant or allergen is increased or a novel toxicant or allergen is expressed during cell culturing or during cell proliferation > there is no detection of this change and no compensatory mechanism occurs in the cell to control these levels > the change does not disrupt the cell culture > the toxicant or allergen is not degraded, metabolized, or washed away throughout the cell sourcing, production, harvesting, and food processing stages > the toxicant or allergen survives food preparation > the toxicant or allergen reaches the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for substances that can elicit allergic responses)
15.	Cell sourcing (cell culturing)	Foreign object contamination	Foreign materials or objects (e.g. plastic, metal, hair, jewellery, glass, etc.) originating from personnel, equipment, packaging materials, or elsewhere in the environment enter and are present in the final product, resulting in physical harm to the consumer	P	Following relevant good practices ^d Visual inspection of equipment, accessories, components Continuous monitoring of cells	Inspection of the cells	This same hazard is also present in most processed foodstuffs	A foreign object enters the cell culture > there is no detection of the contaminating object throughout the cell sourcing, production, harvesting, and food processing stages > the object is present in the final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
16.	Cell sourcing (cell culturing)	Allergens, pathogens or pathogenic agents (e.g. prions)	Cross contamination between cell lines of different origins or species may lead to the unexpected presence of allergens, pathogens, or pathogenic agents originating from the contaminating cell line	B, A	Following relevant good practices ^d Storage in the vapor phase of liquid nitrogen Maintaining of a data log for cell vials taken from cryostorage Regular quality checks under microscope for presence of other cells or contaminants	Confirmation of cell line identity of cell banks and of final product Testing for pathogens and allergens in cell banks and in final product	A similar type of hazard is also present in production of conventional foods and cell culture for therapeutics	A cross contamination event occurs during cell sourcing, culturing, or storage > the contaminating cells remain viable or propagate in the cell culture > there is no detection of the cross contamination event > the cell culture is not disrupted and contaminating cells persist throughout the cell sourcing, production and harvesting, and food processing stages > the contaminating cells reach the final product at a concentration that exceeds a tolerable threshold (e.g. for cells that can elicit allergic responses) or at levels that could be hazardous to consumers
17.	Cell sourcing (cell culturing)	Chemical contaminants	Chemical contaminants can be introduced from equipment, cleaning products, ingredients, air, water, or packaging materials and may be present in the final product at levels that cause adverse human health effects	C	Following relevant good practices ^d Raw material quality control Use of food grade equipment, cleaning products, packaging materials	Quantification of the levels of chemicals in the final product	The same hazard is present in conventional foods	Equipment / cleaning products / ingredients / air / water / packaging contains chemical contaminants the cell culture is not disrupted > the chemical contaminants are not degraded, metabolized, or washed away, and the chemicals remain throughout cell culturing, production, harvesting, and food processing stages > the chemicals or reach the final product at a concentration that exceeds a minimum contaminant level or tolerable threshold (e.g. for chemicals that can elicit allergic responses)
18.	Cell sourcing	Microplastics (including nanoplastics)	Microplastics are introduced from water, air, equipment, ingredients, packaging materials, or elsewhere from the environment and accumulate in the final product at levels harmful to a consumers Microplastics are themselves a potential hazard or can interact with other ingredient to change their properties	P	Following relevant good practices ^d Filtration, raw material quality control Reduce use of plastics	N/A	The same hazard is present in conventional food production	Microplastics (MPs) are introduced during cell sourcing or cell culturing from water, air, equipment, ingredients, packaging materials, or elsewhere from the environment > MPs do not affect cell growth > MPs go undetected and remain throughout cell culturing, production, harvesting, and food processing stages > MPs are present in the final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
19.	Cell sourcing	Heavy metals	Heavy metals (e.g. lead, arsenic, cadmium, mercury) can be introduced from source animal (particularly aquatic animal), water, air, materials, equipment, ingredients, packaging materials and may be present in the final product at levels that cause toxicity	C	Following relevant good practices ^d Raw material quality control Use of food grade equipment and packaging materials, reduce use of food-contact metals in processing	Quantification of the levels of heavy metals in the final product Testing source animal for heavy metals prior to biopsy	The same hazard is present in conventional foods	Heavy metals are present in source animal / water / air / ingredient / equipment / cleaning products / packaging > water / air / ingredient / equipment purification is insufficient to remove the heavy metals > heavy metals are introduced to the cell culture > heavy metals may accumulate throughout cell culturing, production, harvesting, and food processing stages > manufacturer does not detect the presence of heavy metals in the product > heavy metals are present in the final product at levels hazardous to consumers

Notes: a) Cell-sourcing step includes muscle biopsy, obtaining stem cells, cell reprogramming, cell isolation, cell-storage, overall cell-line development. Production step includes cell proliferation, cell differentiation, bioreactor expansion. Harvesting step includes cell/tissue harvesting. Food processing step includes any other processes after harvesting the products from the bioreactor. b) Hazard type is categorized into 4 types – B: Biological hazard; C: Chemical hazard; P: Physical hazard; and A: Allergen. c) Existing Codex guideline for the conduct of food safety assessment of foods derived from recombinant-DNA animals (https://www.who.int/docs/default-source/food-safety/food-genetically-modified/cxg-068e.pdf?sfvrsn=c9de948e_2) can be followed/considered. d) Good practices may include good agricultural practices (GAP); good manufacturing practices (GMPs); good hygiene practices (GHPs); and good cell culture practice (GCCP). Hazard analysis and critical control point (HACCP) often integrates such good practices in its plan while specifying essential control points for each potential hazard. e) Joint FAO / WHO Expert Committee on Food Additives (JECFA) like approach for recombinant proteins could be applied.

Source: Author's own elaboration.

4.2.2. Potential hazards during cell growth and production

Table 6. Hazards identified by the Technical Panel for the production stage

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
20.	Production	Potentially hazardous structural materials and related substances	Structural materials (integral or non-integral) or the substances used to manufacture structural materials are hazardous and remain in the final product and cause an adverse impact on human health	A, C	Use of substances that are non-allergenic and safe for consumption Meeting material specifications Use of a washing procedure to remove substances Labelling of any allergenic substance in final product	Quantification of the levels of integral structural materials and related substances in the final product	Similar to qualifying new substances and materials as new food ingredients and additives	Structural materials used contain hazardous or allergenic substances > Materials not properly rinsed > Materials have no observable adverse effect on cell growth > Materials have no observable effect on differentiation > (for non-integral structural materials) materials are not properly rinsed away after cell harvesting > Materials present in final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
21.	Production	Chemical contaminants	Chemical contaminants can be introduced from equipment, cleaning products, ingredients, air, water, or packaging materials and may be present in the final product at levels that cause adverse human health effects (e.g. toxicity)	C	Following relevant good practices ^d Raw material quality control Use of food grade equipment, cleaning products, packaging materials	Quantification of levels of impurities in inputs Quantification of the levels of chemicals in the final product	The same hazard is present in conventional foods	Equipment / cleaning products / ingredients / air / water / packaging contains chemical contaminants > the cell culture is not disrupted > the chemical contaminants are not degraded, metabolized, or washed away, and the chemicals remain throughout production, harvesting, and food processing stages > the chemicals reach the final product at a concentration that exceeds a minimum contaminant level or tolerable threshold (e.g. for chemicals that can elicit allergic responses)
22.	Production	Microplastics (including nanoplastics)	Microplastics are introduced from water, air, equipment, ingredients, packaging materials, or elsewhere from the environment and accumulate in the final product at levels harmful to a consumer Microplastics are themselves a potential hazard or can interact with other ingredient to change their properties	P	Following relevant good practices ^d Filtration, raw material quality control Reduce use of plastics	N/A	The same hazard is present in conventional food production	Microplastics (MPs) are introduced during cell sourcing or cell culturing from water, air, equipment, ingredients, packaging materials, or elsewhere from the environment > MPs do not affect cell growth > MPs go undetected and remain throughout production, harvesting, and food processing stages > MPs are present in the final product at levels hazardous to consumers
23.	Production	Heavy metals	Heavy metals (e.g. lead, arsenic, cadmium, mercury) can be introduced from water, air, materials, equipment, ingredients, packaging materials and may be present in the final product at levels that cause toxicity	C	Following relevant good practices ^d Raw material quality control Use of food grade equipment and packaging materials, reduce use of food-contact metals in processing	Quantification of the levels of heavy metals in the final product	The same hazard is present in conventional foods	Heavy metals are present in water / air / ingredient / bioreactor equipment / cleaning products / packaging > water / air / ingredient / equipment purification is insufficient to remove the heavy metals > heavy metals are introduced to the cell culture > heavy metals may accumulate throughout production, harvesting, and food processing stages > manufacturer does not detect the presence of heavy metals in the product > heavy metals are present in the final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
24.	Production	Microbial toxins	Microbial toxins produced by certain microbes (bacteria / fungi) under certain conditions can be introduced into the product during processing from equipment, ingredients, air, water, human operator; and if toxins are present in the final product they may lead to food-borne disease	B	Following relevant good practices ^d Responsible use of antimicrobials Raw material quality control	Testing and quantification of the levels of toxins in the final product	The same hazard is present in conventional meat and seafood production	During cell production toxins or microbes capable of producing toxins are present in equipment / ingredients / air / water / human operator > manufacturer fails to control for microbes/toxins > microbes/toxins enter the product > microbes are present in correct conditions to produce the toxin > toxin may accumulate during cell proliferation in bioreactor > toxin may accumulate in the harvested product > toxins are not detected in final food product > toxin is present in high enough levels to pose a health risk > toxin survive heat treatment / food processing (or the product is presented raw to consumer)
25.	Production	Pathogens (bacteria, viruses, fungi, parasites, protozoa) and pathogenic agents (prions)	Pathogens in cell culture media components or other reagents may be present in the end product and could be pathogenic if handled or consumed	B	Following relevant good practices ^d Sterilization methods (heat, irradiation, filtration) can be applied depending on the component(s) Avoiding the use of animal-derived components Source reagents from pathogen free regions or herds (e.g. bovine spongiform encephalopathy [BSE]-free), or with health certification Responsible use of antimicrobials Cooking of end products can reduce or eliminate some pathogens	Testing for viruses, including species-specific viruses Testing for prions in the case of limited health information on source animals Testing for other pathogens	This same kind of hazard may be present in fermented food products, fermented food ingredients, and recombinant enzymes used in food production	Pathogen / pathogenic agent present in intentional input (e.g. medium / serum / scaffold) > Input is not sterilized > the pathogen is transferred into the cell culture or cell line > the pathogen survives antibiotic or antimycotic treatment (if used) > the pathogen survives and replicates in cell culture > the pathogen survives and replicates in the bioreactor > the cell culture is not disrupted > pathogens are not detected by any testing or process monitoring throughout the cell sourcing, production, harvesting, and food processing stages > the pathogen survives food processing > the pathogen survives food preparation > the pathogen is present in final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
26.	Production	Pathogens (bacteria, viruses, fungi, parasites)	Pathogenic contaminants (bacteria, viruses, fungi, parasites) due to unhygienic operators or equipment could be carried to the end product and be hazardous when handled or consumed	B	Following relevant good practices ^d Aseptic handling of cells and inputs Process monitoring Responsible use of antimicrobials Sterilization methods (heat, irradiation, filtration), if appropriate	Testing for pathogenic contaminants during the process or in the final product	The same kind of hazard is present in conventional meat products and in common food processes	The pathogen is introduced to cells culture through equipment / environment / personnel > the pathogen is transferred into the cell line > the pathogen survives and replicates in cell culture > the cell culture is not disrupted > pathogens are not detected by any testing or process monitoring throughout the production, harvesting, and food processing stages > the pathogen survives food processing > the pathogen survives food preparation > the pathogen is present in final product at levels hazardous to consumers
27.	Production	Hazardous chemical / food additive residues (culture medium stabilizers, modulators of cell function, nutrients, etc.)	Residues or metabolites of hazardous chemicals (e.g. steroids, small molecular entities, surfactants, antifoaming agents, pH buffers, etc.) or food additives (e.g. colours, flavours, nutrients, vitamins) used during production could remain in the end product and be toxic or allergenic at anticipated exposure levels for consumption	C, A	Following relevant good practices ^d Use of chemicals or modulators that have established food safety history Use of the minimal levels for effective action Washing procedures to remove chemicals or reduce their concentration can be used Evaluation of potential hazard and exposure, perform safety assessment Development of specifications	Quantification of the levels of the hazardous chemical residues in the final product If a proteinaceous modulator is modified in some way, allergenicity testing on the new substance can be performed	The same or similar kind of residues may be present in products of fermentation and precision fermentation, in fortified foods, in assisted reproduction techniques used for terrestrial and aquatic species, and other processed foodstuffs Databases that document the safety of chemicals in foods or levels known to be safe for foods can be referenced ^e For some of these substances, there are no reference values regarding safe levels in food Certain modulators of cell function are naturally present in conventional meat and seafood	Hazardous chemicals or additives are used and enter into the bioreactor during cell proliferation > the cell culture is not disrupted > the chemicals or additives are not degraded, metabolized, or washed away, and the chemicals or additives remain throughout the production, harvesting, and food processing stages > the chemicals or additives reach the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for chemicals that can elicit allergic responses)

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
28.	Production	Food allergens	Certain media ingredients or food additives added to the cell culture could contain allergens or be derived from allergenic sources that are present in the end product, which could elicit an allergic reaction when handled or consumed	A	<p>Labelling for known allergen</p> <p>Use of ingredients not known to contain allergens</p> <p>Hydrolysis or other processes to reduce or eliminate allergic epitopes</p>	Residue testing on the end product at downstream process stages to determine if allergens are present at levels known to be unsafe	The same hazard is present in conventional meat, seafood, and other foods	Food allergens / immunogenic substances are used in the media and enter into the bioreactor during cell proliferation > the food allergens are not degraded or washed away throughout the production, harvesting, and food processing stages > the allergens survive food preparation > the allergen reaches the final product at a concentration that exceeds a tolerable threshold > allergenic / immunogenic ingredient is not properly labelled or disclosed on final product
29.	Production	Antimicrobials	Antimicrobials are added to the media as a preventative measure during cell culture and may be present in the end product and be a health hazard or elicit an allergic reaction	C, A	<p>Following relevant good practices^d</p> <p>Testing for residues of antimicrobials prior to banking</p> <p>Use of the minimal levels for an effective action</p>	Quantification of the levels of antimicrobial residues in the final product	<p>The same hazard is also present in the production processes for conventional livestock production and aquaculture</p> <p>Antimycotics are used in food preservatives and food preparation services</p>	Antimicrobials are used and enter the into the bioreactor during cell proliferation > the cell culture is not disrupted > the antimicrobials are not degraded, metabolized, or washed away, and the antimicrobials persist throughout the cell harvesting > the antimicrobials survive food preparation > the antimicrobials reach the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for antimicrobials that can elicit allergic responses)
30.	Production	Novel toxins or allergens or an increase in endogenous toxicants or allergens	Expression of novel toxins, toxic metabolites, or allergens or a change in expression of toxins, toxic metabolites, or allergens as a result of genomic instability (e.g. large rearrangements), genetic or phenotypic instability (e.g. variability due to cell division, <i>mycoplasma</i> contamination), and / or induced through physical or biochemical stimuli during cell culture that are present in the end product, which becomes (more) toxic or allergenic when handled or consumed	B, A	<p>Following relevant good practices^d</p> <p>Listing of components that could impact food safety depending on species or cells being used</p> <p>Monitoring of cells</p> <p>Use of a washing procedure to remove substances</p>	<p>Evaluation of genetic and phenotypic stability by molecular techniques (e.g. karyotyping)</p> <p>Allergenicity and toxicity testing</p> <p>Analyzing level of expression of molecules related to the change and correlate to expected exposure from the food product</p>	<p>This hazard is also possible due to genetic variation in conventional breeding or cloning processes</p> <p>This hazard is also a concern in the cellular therapeutics and biosimilars industry</p>	Genetic, genomic, or phenotypic instability affects a relevant gene or phenotype in the cell line> the endogenous toxicant or allergen is increased or a novel toxicant or allergen is expressed during cell proliferation > there is no detection of this change and no compensatory mechanism occurs in the cell to control these levels > the change does not disrupt the cell culture > the toxicant or allergen is not degraded, metabolized, or washed away throughout the production, harvesting, and food processing stages > the toxicant or allergen reaches the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for substances that can elicit allergic responses)

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
31.	Production	Foreign object contamination	Foreign materials or objects (e.g. plastic, metal, hair, jewellery, glass, etc.) originating from personnel, equipment, packaging materials, or elsewhere in the environment enter and are present in the final product, resulting in physical harm to the consumer	P	Following relevant good practices ^d Visual inspection of equipment, accessories, components Continuous monitoring of cells Implementation of controls and detectors	Inspection of the cells	This same hazard is also present in most processed foodstuffs	A foreign object enters the bioreactor during cell proliferation > there is no detection of the contaminating object throughout the production, harvesting, and food processing stages > the object is present in the harvested cells > the object is present in the final product at levels hazardous to consumers
32.	Production	Allergens, pathogens or pathogenic agents (e.g. prions)	Cross contamination between cell lines of different origins or species may lead to the unexpected presence of allergens, pathogens, or pathogenic agents originating from the contaminating cell line	B, A	Following relevant good practices ^d Storage in the vapor phase of liquid nitrogen Maintaining of a data log for cell vials taken from cryostorage Regular quality checks under microscope for presence of other cells or contaminants	Confirmation of cell line identity of cell banks and of final product Testing for pathogens and allergens in cell banks and in final product	A similar type of hazard is also present in production of conventional foods and cell culture for therapeutics	A cross contamination event occurs during cell propagation into bioreactor > the contaminating cells remain viable or propagate in the cell culture > there is no detection of the cross contamination event > the cell culture is not disrupted and contaminating cells persist throughout the production, harvesting, and food processing stages > the contaminating cells reach the final product at a concentration that exceeds a tolerable threshold (e.g. for cells that can elicit allergic responses) or at levels that could be hazardous to consumers

Notes: a) Cell-sourcing step includes muscle biopsy, obtaining stem cells, cell reprogramming, cell isolation, cell-storage, overall cell-line development. Production step includes cell proliferation, cell differentiation, bioreactor expansion. Harvesting step includes cell/tissue harvesting. Food processing step includes any other processes after harvesting the products from the bioreactor. b) Hazard type is categorized into 4 types – B: Biological hazard; C: Chemical hazard; P: Physical hazard; and A: Allergen. c) Existing Codex guideline for the conduct of food safety assessment of foods derived from recombinant-DNA animals (https://www.who.int/docs/defaultsource/food-safety/food-genetically-modified/cxg-068e.pdf?sfvrsn=c9de948e_2) can be followed/considered. d) Good practices may include good agricultural practices (GAP); good manufacturing practices (GMPs); good hygiene practices (GHPs); and good cell culture practice (GCCP). Hazard analysis and critical control point (HACCP) often integrates such good practices in its plan while specifying essential control points for each potential hazard. e) Joint FAO / WHO Expert Committee on Food Additives (JECFA) like approach for recombinant proteins could be applied.

Source: Author's own elaboration.

4.2.3. Potential hazards during cell harvesting

Table 7. Hazards identified by the Technical Panel for the harvesting stage

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
33.	Harvesting	Chemical contaminants	Chemical contaminants can be introduced from equipment, cleaning products, ingredients, air, water, or packaging materials and may be present in the final product at levels that cause adverse human health effects (toxicity)	C	Following relevant good practices ^d Raw material quality control Use of food grade equipment, cleaning products, packaging materials	Quantification of the levels of chemicals in the final product	The same hazard is present in conventional foods	Equipment / cleaning products / ingredients / air / water / packaging contains chemical contaminants > the chemical contaminants are not degraded or washed away, and the chemicals remain throughout the harvesting and food processing stages > the chemicals reach the final product at a concentration that exceeds a minimum contaminant level or tolerable threshold (e.g. for chemicals that can elicit allergic responses)
34.	Harvesting	Microplastics (including nanoplastics)	Microplastics are introduced from water, air, equipment, packaging materials, or elsewhere from the environment and accumulate in the final product at levels harmful to a consumer Microplastics are themselves a potential hazard or can interact with other ingredient to change their properties	P	Following relevant good practices ^d Filtration, raw material quality control Reducing / limited use of plastics	N/A	The same hazard is present in conventional food production	Microplastics (MPs) are introduced during harvesting from water, air, equipment, packaging materials, or elsewhere from the environment > MPs go undetected and remain throughout harvesting and food processing stages > MPs are present in the final product at levels hazardous to consumers
35.	Harvesting	Heavy metals	Heavy metals (e.g. lead, arsenic, cadmium, mercury) can be introduced from water, air, materials, equipment, packaging materials and may be present in the final product at levels that cause toxicity	P	Following relevant good practices ^d Raw material quality control Use of food grade equipment and packaging materials, reduce use of food-contact metals in processing	Quantification of the levels of heavy metals in the final product	The same hazard is present in conventional foods	Heavy metals are present in water / air / ingredient / equipment / cleaning products / packaging > water / air / ingredient / equipment purification is insufficient to remove the heavy metals > heavy metals are introduced to the harvested cells > heavy metals may accumulate throughout harvesting and food processing stages > manufacturer does not detect the presence of heavy metals in the product > heavy metals are present in the final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
36.	Harvesting	Microbial toxins	Microbial toxins produced by certain microbes (bacteria/fungi) under certain conditions can be introduced into the product during processing from equipment, ingredients, air, water, human operator can affect human health	B	Following relevant good practices ^d Responsible use of antimicrobials Raw material quality control	Testing and quantification of the levels of toxins in the final product	The same hazard is present in conventional meat and seafood production	Toxins or microbes capable of producing toxins are present in equipment / ingredients / air / water / human operator > manufacturer fails to control for microbes/toxins > microbes/toxins enter the product > microbes are present in correct conditions to produce the toxin > Toxin may accumulate in the harvested product > toxins are not detected in final food product > toxin is present in high enough levels to pose a health risk > toxin survive heat treatment / food processing (or the product is presented raw to consumer)
37.	Harvesting	Pathogens (bacteria, viruses, fungi, parasites, protozoa) and pathogenic agents (prions)	Pathogens in reagents or washing media may be present in the end product and could be pathogenic if handled or consumed	B	Following relevant good practices ^d Sterilization methods (heat, irradiation, filtration) can be applied depending on the composition of the media Avoiding the use of animal-derived components Source reagents from pathogen free regions or herds (e.g. bovine spongiform encephalopathy [BSE]-free), or with health certification Responsible use of antimicrobials Cooking of end products can reduce or eliminate some pathogens	Testing for viruses, including species-specific viruses Testing for prions in the case of limited health information on source animals Testing for other pathogens	This same kind of hazard may be present in fermented food products, fermented food ingredients, and recombinant enzymes used in food production	Pathogen / pathogenic agent present in intentional input (e.g. washing buffer) > Input is not sterilized ^e > Pathogen is present at high enough level to contaminate cells > pathogens are not detected by any testing or process monitoring throughout the cell harvesting > the pathogen survives food processing > the pathogen survives food preparation > the pathogen is present in final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
38.	Harvesting	Pathogens (bacteria, viruses, fungi, parasites)	Pathogenic contaminants (bacteria, viruses, fungi, parasites) due to unhygienic operators or equipment could be carried to the end product and be hazardous when handled or consumed	B	Following relevant good practices ^d Process monitoring Responsible use of antimicrobials Sterilization methods (heat, irradiation, filtration), if appropriate	Testing for pathogenic contaminants during the process or in the final product	The same kind of hazard is present in conventional meat products and in common food processes	The pathogen is present on equipment / environment / personnel > the pathogen is transferred into the harvested cells at high enough levels to contaminate cells > pathogens are not detected by any testing > the pathogen survives food processing > the pathogen survives food preparation > the pathogen is present in final product at levels hazardous to consumers
39.	Harvesting	Hazardous chemical / food additive residues	Residues or metabolites of hazardous chemicals (e.g. pH buffers, washing media, etc.) used during harvest could remain in the end product and be toxic or allergenic at anticipated exposure levels for consumption	C, A	Following relevant good practices ^d Use of chemicals or modulators that have established food safety history Use of the minimal levels for effective action Washing procedures to remove chemicals or reduce their concentration can be used Evaluation of potential hazard and exposure, perform safety assessment Development of specifications	Quantification of the levels of the hazardous chemical residues in the final product If a proteinaceous modulator is modified in some way, allergenicity testing on the new substance can be performed	The same or similar kind of residues may be present in products of fermentation and precision fermentation, in fortified foods, in assisted reproduction techniques used for terrestrial and aquatic species, and other processed foodstuffs Databases that document the safety of chemicals in foods or levels known to be safe for foods can be referenced ^e For some of these substances, there are no reference values regarding safe levels in food Certain modulators of cell function are naturally present in conventional meat and seafood	Hazardous chemicals or additives are used and enter during cell harvest > the chemicals or additives reach the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for chemicals that can elicit allergic responses)

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
40.	Harvesting	Food allergens	Certain ingredients or food additives (e.g. pH buffers, washing media, etc.) used during harvest could contain allergens or be derived from allergenic sources that may be present in the end product, which could elicit an allergic reaction when handled or consumed	A	<p>Labelling for known allergen</p> <p>Use ingredients not known to contain allergens</p> <p>Hydrolysis or other processes to reduce or eliminate allergic epitopes</p>	Residue testing on the end product at downstream process stages to determine if allergens are present at levels known to be unsafe	The same hazard is present in conventional meat, seafood, and other foods	The food allergens are not degraded or washed away during cell harvesting or food processing stages > the allergens survive food preparation > the allergen reaches the final product at a concentration that exceeds a tolerable threshold > allergenic / immunogenic ingredient is not properly labelled or disclosed on final product
41.	Harvesting	Antimicrobials	Antimicrobials are added as a preventative measure during harvesting and may be present in the end product and be a health hazard or elicit an allergic reaction	C, A	<p>Following relevant good practices^d</p> <p>Testing for residues of antimicrobials prior to banking</p> <p>Use of the minimal levels for an effective action</p>	Quantification of the levels of antimicrobial residues in the final product	<p>This same hazard is also present in the production processes for conventional livestock production and aquaculture</p> <p>Antimycotics are used in food preservatives and food preparation services</p>	Antimicrobials are not degraded, metabolized, or washed away, and persist throughout the cell harvesting, > the antimicrobials survive food preparation > the antimicrobials reach the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for antimicrobials that can elicit allergic responses)
42.	Harvesting	Foreign object contamination	Foreign materials or objects (e.g. plastic, metal, hair, jewellery, glass, etc.) originating from personnel, equipment, packaging materials, or elsewhere in the environment enter and may be present in the final product, resulting in "physical harm to the consumer	P	<p>Following relevant good practices^d</p> <p>Visual inspection of equipment, accessories, components</p> <p>Continuous monitoring of cells</p> <p>Implementation of controls and detectors</p>	Inspection of the harvested material	This same hazard is also present in most processed foodstuffs	A foreign object enters into the harvested product > there is no detection of the contaminating object throughout the harvesting, and food processing stages > the object is present in the ≠final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
43.	Harvesting	Allergens, pathogens or pathogenic agents (e.g. prions) depending on the case	Cross contamination between cell lines of different origins or species may lead to the unexpected presence of allergens, pathogens, or pathogenic agents originating from the contaminating cell line may be harmful to the consumers	B, A	Following relevant good practices ^d Storage in the vapor phase of liquid nitrogen Maintaining of a data log for cell vials taken from cryostorage Regular quality checks under microscope for presence of other cells or contaminants	Confirmation of cell line identity of cell banks and of final product Testing for pathogens and allergens in cell banks and in final product	A similar type of hazard is also present in production of conventional foods	A cross contamination event occurs during harvest > there is no detection of the cross-contamination event > the contaminating cells are present in the final product at a concentration that exceeds a tolerable threshold (e.g. for cells that can elicit allergic responses) or at levels that could be hazardous to consumers

Notes: a) Cell-sourcing step includes muscle biopsy, obtaining stem cells, cell reprogramming, cell isolation, cell-storage, overall cell-line development. Production step includes cell proliferation, cell differentiation, bioreactor expansion. Harvesting step includes cell/tissue harvesting. Food processing step includes any other processes after harvesting the products from the bioreactor. b) Hazard type is categorized into 4 types – B: Biological hazard; C: Chemical hazard; P: Physical hazard; and A: Allergen. c) Existing Codex guideline for the conduct of food safety assessment of foods derived from recombinant-DNA animals (https://www.who.int/docs/defaultsource/food-safety/food-genetically-modified/cxg-068e.pdf?sfvrsn=c9de948e_2) can be followed/considered. d) Good practices may include good agricultural practices (GAP); good manufacturing practices (GMPs); good hygiene practices (GHPs); and good cell culture practice (GCCP). Hazard analysis and critical control point (HACCP) often integrates such good practices in its plan while specifying essential control points for each potential hazard. e) Joint FAO / WHO Expert Committee on Food Additives (JECFA) like approach for recombinant proteins could be applied.

Source: Author's own elaboration.

4.2.4. Potential hazards during processing

Table 8. Hazards identified by the Technical Panel for the processing stage

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
44.	Food Processing	Physicochemical transformation of food components	Structural and chemical changes (e.g. altered protein structure or sequence, reactive species formation / oxidation), due to food processing (e.g. extrusion, smoking, freeze-drying) or storage may cause adverse health effects	C	Following relevant good practices ^d	New ingredients without a history of safe use must be tested for physico-chemical transformation prior to use in food Sequence analysis Evaluation of ingredients for reactivity (e.g. <i>in silico</i> , <i>in vitro</i>) Toxicity testing of products	The same hazard is present in conventionally produced food production, however cell-based foods may contain new inputs (e.g. scaffolds, residues) and food processing ingredients that must be tested	Physicochemical transformation occurs during food processing > physicochemical transformation is not detected in food product > physicochemical transformation poses a health risk > physicochemical transformation is present in high enough level to pose a health risk

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
45.	Food Processing	Structural and chemical changes of genetic material from cells	Physicochemical transformation of genetic material (e.g. release or modification of synthetic biology products), due to food processing (e.g. extrusion, smoking, freeze-drying) could cause adverse health effects	C	Following relevant good practices ^d	Sequence analysis, toxicity testing of products	The same hazard is present in any food derived through modern biotechnology	Physicochemical transformation occurs during food processing > physicochemical transformation is not detected in food product > physicochemical transformation poses a health risk* > physicochemical transformation is present in high enough level to pose a health risk
46.	Food Processing	Microbial toxins	Microbial toxins produced by certain microbes (bacteria / fungi) under certain conditions can be introduced into the product during processing from equipment, ingredients, air, water, human operator If toxins are present in the final product they may lead to food-borne disease	B	Following relevant good practices ^d Responsible use of antimicrobials Raw material quality control	Testing and quantification of the levels of toxins in the final product	The same hazard is present in conventional meat and seafood production	Toxins or microbes capable of producing toxins are present in equipment / ingredients / air / water / human operator > manufacturer fails to control for microbes/toxins > microbes are present in correct conditions to produce the toxin > food product comes in contact with the microbe and / or toxin > toxin may accumulate in the harvested product > toxins are not detected in final food product > toxin is present in high enough levels to pose a health risk > toxin survive heat treatment / food processing (or the product is presented raw to consumer)
47.	Food Processing	Pathogens (bacteria, viruses, fungi, parasites)	Pathogenic contaminants (bacteria, viruses, fungi, parasites) due to unhygienic operators, ingredients, or equipment could be carried to the end product and be hazardous when handled or consumed	B	Following relevant good practices ^d Process monitoring Responsible use of antimicrobials Sterilization methods (heat, irradiation, filtration), if appropriate	Testing and quantification of the levels of toxins in the final product	The same hazard is present in conventional meat and seafood production	Toxins or microbes capable of producing toxins are present in equipment / ingredients / air / water / human operator > manufacturer fails to control for microbes/toxins > microbes are present in correct conditions to produce the toxin > food product comes in contact with the microbe and / or toxin > toxin may accumulate in the harvested product > toxins are not detected in final food product > toxin is present in high enough levels to pose a health risk > toxin survive heat treatment / food processing (or the product is presented raw to consumer)

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
48.	Food Processing	Hazardous chemical / food additive residues	Residues or metabolites of food additives (e.g. colours, flavours, nutrients, vitamins) could remain in the end product and be toxic or allergenic at anticipated exposure levels for consumption	C, A	<p>Following relevant good practices^d</p> <p>Use of chemicals that have established food safety history</p> <p>Use of the minimal levels for effective action</p> <p>Washing procedures to remove chemicals or reduce their concentration can be used</p> <p>Evaluation of potential hazard and exposure, perform safety assessment</p> <p>Development of specifications</p>	<p>Quantification of the levels of the hazardous chemical residues in the final product</p> <p>If a proteinaceous modulator is modified in some way, allergenicity testing on the new substance can be performed</p>	<p>The same or similar kind of residues may be present in products of fermentation and precision fermentation, in fortified foods, in assisted reproduction techniques used for terrestrial and aquatic species, and other processed foodstuffs</p> <p>Databases that document the safety of chemicals in foods or levels known to be safe for foods can be referenced^e</p> <p>For some of these substances, there are no reference values regarding safe levels in food</p>	Hazardous chemicals or additives are used and enter during food processing > the chemicals or additives reach the final product at a concentration that exceeds a minimum residue level or tolerable threshold (e.g. for chemicals that can elicit allergic responses)
49.	Food Processing	Food allergens	Certain food additives added to the cell culture could contain allergens or be derived from allergenic sources that are present in the end product, which could elicit an allergic reaction when handled or consumed	A	<p>Labelling for known allergen</p> <p>Use of ingredients not known to contain allergens</p> <p>Hydrolysis or other processes to reduce or eliminate allergic epitopes</p>	Residue testing on the end product at downstream process stages to determine if allergens are present at levels known to be unsafe	The same hazard is present in conventional meat, seafood, and other foods	Food allergens / immunogenic substances are used in food processing > the allergens survive food preparation > the allergen reaches the final product at a concentration that exceeds a tolerable threshold > allergenic / immunogenic substances are not properly labelled or disclosed on final product
50.	Food Processing	Foreign object contamination	Foreign materials or objects (e.g. plastic, metal, hair, jewellery, glass, etc.) originating from personnel, equipment, packaging materials, or elsewhere in the environment enter and are present in the final product, resulting in physical harm to the consumer	P	<p>Following relevant good practices^d</p> <p>Visual inspection of equipment, accessories, components</p> <p>Continuous monitoring of cells</p> <p>Implementation of controls and detectors</p>	Inspection of the packaged product (e.g. metal detector, magnet)	This same hazard is also present in most processed foodstuffs	A foreign object enters into the final product > there is no detection of the contaminating object throughout the food processing stages > the object is present in the final product at levels hazardous to consumers

	Production step(s) ^a	Hazard agent	Problem description / consequence to human health	Hazard type(s) ^b	Potential mitigation control measures	Potential testing control measures	Similar presence of the hazard in other food products / comparators / gaps / relevant experience	Causal chain examples
51.	Food Processing	Chemical contaminants	Chemical contaminants can be introduced from equipment, cleaning products, ingredients, air, water, or packaging materials and may be present in the final product at levels that cause adverse human health effects (e.g. toxicity)	C	Following relevant good practices ^d Raw material quality control Use food grade equipment, cleaning products, packaging materials	Quantification of the levels of chemicals in the final product	The same hazard is present in conventional foods	Equipment / cleaning products / ingredients / air / water / packaging contains chemical contaminants > the chemical contaminants are not degraded or washed away, and the chemicals remain throughout the food processing stages > the chemicals reach the final product at a concentration that exceeds a minimum contaminant level or tolerable threshold (e.g. for chemicals that can elicit allergic responses)
52.	Food Processing	Microplastics (including nanoplastics)	Microplastics are introduced from water, air, equipment, ingredients, packaging materials, or elsewhere from the environment and accumulate in the final product at levels harmful to a consumer Microplastics are themselves a potential hazard or can interact with other ingredient to change their properties	P	Following relevant good practices ^d Filtration, raw material quality control Reduce use of plastics	N/A	The same hazard is present in conventional food production	Microplastics (MPs) are introduced during food processing from water, air, equipment, packaging materials, or elsewhere from the environment > MPs go undetected and remain throughout food processing stages > MPs are present in the final product at levels hazardous to consumers
53.	Food Processing	Heavy metals	Heavy metals (e.g. lead, arsenic, cadmium, mercury) can be introduced from water, air, materials, equipment, ingredients, packaging materials and may be present in the final product at levels that cause toxicity	C	Following relevant good practices ^d Raw material quality control Use of food grade equipment and packaging materials, reduce use of food-contact metals in processing	Quantification of the levels of heavy metals in the final product	The same hazard is present in conventional food products	Heavy metals are present in water / air / ingredient / equipment / cleaning products / packaging > water / air / ingredient / equipment purification is insufficient to remove the heavy metals > heavy metals are introduced to the final product > manufacturer does not detect the presence of heavy metals in the product > heavy metals are present in the final product at levels hazardous to consumers

Notes: a) Cell-sourcing step includes muscle biopsy, obtaining stem cells, cell reprogramming, cell isolation, cell-storage, overall cell-line development. Production step includes cell proliferation, cell differentiation, bioreactor expansion. Harvesting step includes cell/tissue harvesting. Food processing step includes any other processes after harvesting the products from the bioreactor. b) Hazard type is categorized into 4 types – B: Biological hazard; C: Chemical hazard; P: Physical hazard; and A: Allergen. c) Existing Codex guideline for the conduct of food safety assessment of foods derived from recombinant-DNA animals (https://www.who.int/docs/defaultsource/food-safety/food-genetically-modified/cxg-068e.pdf?sfvrsn=c9de948e_2) can be followed/considered. d) Good practices may include good agricultural practices (GAP); good manufacturing practices (GMPs); good hygiene practices (GHPs); and good cell culture practice (GCCP). Hazard analysis and critical control point (HACCP) often integrates such good practices in its plan while specifying essential control points for each potential hazard. e) Joint FAO / WHO Expert Committee on Food Additives (JECFA) like approach for recombinant proteins could be applied.

Source: Author's own elaboration.

4.3. Explanations about the identified hazards

4.3.1. Physical hazards – foreign object contamination

Foreign matter includes undesirable physical contaminants that can be introduced during processing from human operators, water, air, equipment, ingredients, or packaging materials. These can enter the product at any point in the production process and, if not controlled, can result in physical harm (e.g. injuries to the mouth, teeth or gums) when consumed.

For this to occur, a foreign object would need to enter the cell culture or product, followed by failure to detect the contaminating object. Depending on the stage in which the contaminating object entered, it would need to persist throughout the cell line development, production, and food processing stages and be present in the final product at levels that are hazardous to consumers.

4.3.2. Chemical hazards

4.3.2.1. Contaminants

For the purpose of this document, chemical contaminants are considered to be chemical substances which are unintentionally introduced during production.

Veterinary drugs

Veterinary drugs are used in many livestock production and aquaculture operations. These drugs may be present in tissues that are used as a source of cells for cell-based food production. Therefore, veterinary drugs, including antibiotics, may be present as contaminants in biopsied tissues and potentially be present in the final food product, causing negative effects on human health.

For this to occur, the drug would first need to be present in the sampled tissue. Then, cell culturing process continues without being disrupted by the presence of the drug itself, the drug is not degraded, diluted or washed away during the process, and the drug goes undetected in the cell line development and banking stages. Finally, the drug would need to persist throughout the cell line development, production, and food processing stages without detection, reaching the final product at a concentration that exceeds a maximum safe level.

This hazard can be controlled by having access to health records of source animals, which can be used to guide the safe sourcing of cells. There are controls upstream of the cell-based food production process for the withdrawal of veterinary drugs. Additionally, testing can be used to quantify the levels of veterinary drugs in the cell line and in the final product. This hazard is not unique to cell-based foods since it is also present in conventional livestock production and aquaculture. A difference is that in cell-based foods, veterinary drugs are considered a chemical contaminant whereas in animal husbandry they are considered as a residue (it is referred to as Residues of Veterinary Drugs in Foods, or RVDF, by the Codex Alimentarius Commission). In the case of cell-based foods, veterinary drugs are not an intentional part of the production process and are instead considered a contaminant that is unintentionally introduced from the cell source.

Microbial toxins

Microbial toxins are toxic compounds that are naturally produced by some microbes under certain conditions. Microbial toxins may be present as a result of microbiological contamination during any production step. In addition, microbial toxins can be present in the host animal used for cell sourcing. For example, some fish, including barracuda, black grouper, dog snapper, and king mackerel, are known to harbour symbiotic microorganisms capable of producing toxins. These toxins are not harmful to the host fish themselves, but they may be toxic to other creatures, including humans, when eaten.

For this hazard to occur, microbes capable of producing a toxin, or in some cases the toxins themselves, must be present in or on the biopsy sample, human operators, water, air, equipment, ingredients, or packaging materials that come into contact with the cell culture or food product. The microbes must also be under the correct conditions to produce the toxin. In order for such toxins to pose a feasible risk to humans, they must not be degraded, washed away, or detected during production and food processing, survive food preparation, and be present in the final product at a level that is hazardous to consumers.

Controls include following relevant good practices,² specifically responsible use of antimicrobials and raw material quality control. For cell-sourcing, this hazard can be controlled by having access to authorized health information, depending on the species, which can guide cell sourcing. For cell-sourcing, cells can be obtained from tissues not known to produce the toxin or from tissues that do not harbour toxin-producing symbiotic microorganisms. In addition, toxin detection tests may be warranted in case of limited health information on the source animal. When toxins are detected, their dilution factor could be calculated and compared to known acceptable safe levels, if applicable. This hazard and the controls are not unique to cell-based foods and are also present in conventional foods.

Physicochemical transformation of food components

Physicochemical transformation in food occurs when components present in the product have interactions with other substances that lead to modifications in the compound's structure and/or sequence. Such transformations can lead to the undesirable occurrence of reactive species and other compounds with deleterious health effects. These transformations can be induced by processing of the food items after harvest (e.g. smoking, heat treatment, chemical treatment), or during sterilization of inputs during production (e.g. irradiation).

For this hazard to occur, substances in the product must be sensitive to the food processing method used, and the physicochemical transformations must pose a health risk. The transformed compounds must then not be detected in the food product and be present in the final product at a level that is hazardous to consumers.

This hazard can be controlled by conducting a safety assessment of the final product, including the analysis of chemical transformation of key food components. New ingredients without a history of safe use can be tested for physicochemical transformations prior to use in food. *In silico* and *in vitro* evaluation of ingredients can be used to screen for reactivity. If transformations pose a risk to health, specifications can be put in place to control the hazardous transformations. Physicochemical transformations are not unique to cell-based food products and are considered for every food product and food production process. However, cell-based foods may include ingredients and inputs not commonly found in conventional meat (e.g. scaffolds, residues) which could result in novel physicochemical transformations that should be considered in the risk assessment of food processing techniques for cell-based foods.

Other chemical contaminants

Substances and materials used in, or put in contact with, the cell-based food production process can contain chemical contaminants. Potential sources of contaminants include air, water, ingredients, equipment, cleaning products, and packaging materials. These contaminants may include, *inter alia*, toxic heavy metals, pesticides, herbicides, fungicides, persistent organic pollutants (e.g. Per- and Polyfluoroalkyl Substances or PFAS, Polycyclic Aromatic Hydrocarbons or PAH, dioxins), residual presence of substances that can migrate food contact material production processes such as unreacted monomers or crosslinkers, or breakdown products of additives such as integral structural materials. A potential food safety concern could result if any of these contaminants are present in the final food product at levels that would be harmful for the consumers.

For this to occur, the contaminant would need to be introduced in an input or from the environment, equipment, cleaning products, ingredients, or packing materials and become incorporated into the product either directly through cell uptake or as a constituent of an integral scaffold material. For the contaminant to persist, it must not produce detectable effects on the energy metabolism, growth characteristics, or any other phenotype of the cultured cells, not degrade or be washed out, and be present in the final product at levels that are sufficient to cause harm.

² Good practices may include good agricultural practices (GAP); good manufacturing practices (GMPs); good hygiene practices (GHPs); and good cell culture practice (GCCP). Hazard analysis and critical control point (HACCP) often integrates such good practices in its plan while specifying essential control points for each potential hazard.

Controls available to mitigate this risk include following relevant good practices,² specifically raw material quality control and the use of food grade equipment, cleaning products, and packaging materials. Analytical testing can be used to detect contaminants in harvested cell material or the final food product. This type of hazard is common in many foods and food production processes, and the control measures described above are commonly used to manage potential food safety risks.

4.3.2.2. Additives

For the purpose of this document, chemical additives are considered to be chemical substances that are intentionally introduced during production and are intended to be present in the final product.

The sequence of events that could result in hypothetical harm to the consumer is clear and direct given that the substance will always be present and thus substantive exposure will occur. Thus, the primary strategy used to control hazards associated with additives involves the use only of substances for which the toxicity profile is well understood and there is evidence to show that the anticipated level of exposure resulting from the use is safe. While this strategy may manifest in a number of different ways (e.g. authorizations, listings, approvals, notifications) the general principles of food additive safety assessment are broadly accepted and are applied to all uses of substances added to food. For new additives or new uses of an existing additives, it may be necessary to first generate data and then obtain acceptance of the information that establishes the safety of the use.

Integral structural materials

Scaffolds, microcarriers, bioinks, and other adherent surfaces provide the structural support for cell attachment, proliferation, and in some cases, differentiation, maturation, and/or subsequent tissue development. These structures are typically made of polymeric materials that are animal or plant origin such as celluloses and alginic acid, inorganic biomaterials, synthetic materials, or potential mixtures of two or more of them (Seah *et al.*, 2022). These structures may be conformed into porous shapes, templates or hydrogels using different synthesis, enzymatic reactions or biofabrication strategies. These structures may also impart organoleptic properties to food such as texture. A potential food safety concern is that structural materials that are intended to remain in the final product are composed of materials that could be harmful at a certain level of exposure.

Other food additives

In many cases, substances will be added during the culture process or during conventional food processing. These substances are not necessary for the cell culture itself but are intended to improve organoleptic properties or alter specific nutritional aspects of the cell-based food. These may include binders, texturizers, plant protein sources, flavours, and colours. A potential food safety concern would result if any substance was present at a level that could result in harm to the consumers.

4.3.2.3. Residues

For the purpose of this document, chemical residues are considered to be chemical substances which are intentionally introduced during production but are not intended to be present in the final product. These substances are expected to be removed or diluted significantly before consumption.

Antimicrobials

Antimicrobials may be used in cell culture to prevent contamination and maintain aseptic conditions. The use of antibiotics such as penicillin, streptomycin, or gentamicin, or antimycotics can minimize loss of cell lines and cell cultures, saving time and conserving resources. Nevertheless, when used in cell-based food production, these substances may be present as residues in the final product and can be a health hazard.

For this to occur, antimicrobials must be used during cell culture or food processing without disrupting the cell culture. In addition, the antimicrobials are not degraded, metabolized, or washed away throughout cell sourcing, production and harvesting, food processing, and food preparation and reach the final product at a concentration that exceeds a safe residue level.

Approaches to control for this hazard include limiting use of antimicrobials at all stages of production and eliminating or reducing the need for antimicrobial agents during culture by using aseptic practices. Washing procedures to remove antimicrobials can be used to reduce their concentration in the final product. Compositional analysis, specifications set by the manufacturer or regulator that establish a maximum residual level expected or permitted in the harvested cell material, and other safety and quality control measures can be used. This hazard is not unique to cell-based foods as similar considerations arise when antimicrobials are used in conventional food production, including integration into packaging materials, direct addition to food, and use as a feed additive or veterinary medicine in livestock and aquaculture.

Culture medium nutrients

Cell culture often includes a supply of nutrients to support cell viability and growth, including carbohydrates, lipids, and proteins as well as vitamins, minerals, and micronutrients. Often, these substances are commonly found in food. However, a potential food safety concern would result if in a particular media formulation, one or more of these substances were present in the final product at levels that would be hazardous to the consumer.

For this to occur, the nutrient needs to be accumulated in some way, such as cell internalization or aggregation onto structural materials. Then the cells do not fully metabolize the substance, the accumulated substance does not disrupt the energy metabolism or growth of the cells, does not interfere with any differentiation steps used, and is present in the cell material or in the final product at a level that is hazardous to consumers.

Controls available for this hazard include use of minimum levels of nutrients sufficient to achieve desired growth in culture and monitoring of cell parameters during culture (e.g. growth) as an indicator of harm to the cells. Composition analysis of the cell material helps to identify nutrients that are present at a level that is harmful. Safety assessment of the final product, with compositional analysis where appropriate, for specific exposure scenarios, as well as specifications for safety control measures can be effective. In general, many of the nutrients used are present in a wide variety of conventional foods, and there is widely available information about safe levels of consumption for these substances.

Culture medium stabilizers

The cell culture process requires the use of substances to balance the culture medium, including control of pH and foaming. Examples of these substances include antifoamers, surfactants, pH buffers, and pH indicators. Such substances can be used throughout all phases of culture and are typically not metabolized by cells. A potential food safety concern could result if residues of these substances were present in the harvested cell material or final food products had such substances at levels that were hazardous to the consumer.

For this to occur, a hazardous chemical or additive is used during production. The cell culture is not disrupted, and the substance is not degraded, metabolized, or washed away throughout the cell sourcing, production and harvesting, food processing, and food preparation stages. The substance needs to reach the final product at a concentration that exceeds a safe maximum residue level.

Controls available for this hazard include use of minimal levels of substances necessary to achieve the desired technical effect in culture, use of validated wash steps at harvest, as well as specifications and other safety and quality control measures. In addition, assessment of potential consumer exposure based on process analysis or analytical data can inform the selection of substances with appropriate safety profiles relative to anticipated consumer exposure. Many of these substances are commonly used in conventional food processing applications and information about safe use levels are available (e.g. sodium hydroxide, phosphoric acid, stearic acid, polyethylene glycol, ascorbic acid, lecithin).

Modulators of cell function

Cell culture typically involves the use of one or more substances that can provide appropriate signals to the cells to support continued cell viability, replication, and differentiation. There are a wide variety of potential substances that could be used, including animal-derived serum (Lee *et al.*, 2022), proteins, and peptides (generally recombinant), steroid hormones, nucleic acids (e.g. Micro ribonucleic acid (RNA) or miRNA, Messenger RNA or mRNA) and small molecular entities (O'Neill *et al.*, 2021). A potential food safety concern could result if one or more of the substances was present in the final product at levels sufficient to cause an adverse health effect in the consumer related to their mode of action.

For this to occur, the substance would need to resist degradation or assimilation during culture, remain after washing at harvest, resist degradation during conventional food processing and food preparation, exhibit activity following oral exposure (e.g. continue to be capable of eliciting a physiological response after ingestion), and be present in the final product at levels sufficient to cause harm to consumers.

Strategies available to control for this hazard include selection of substances that do not demonstrate oral activity, use of minimum levels of the substance sufficient to achieve the desired technical effect, the use of validated wash steps at harvest, as well as specifications and other safety and quality control measures. In addition, assessment of potential consumer exposure based on process analysis or analytical data can inform the selection of substances with appropriate safety profiles relative to anticipated consumer exposure. These substances have generally not been used in conventional food production to date, and it may be necessary to generate data to support a particular safety assessment. However, a number of them are present in conventional animal production, such as assisted reproduction techniques in terrestrial and aquatic species, and this information provides a point of reference in considering the safety of a particular consumer exposure scenario. When recombinant versions of endogenous proteins are used, the potential for deliberate or inadvertent changes in stability or activity relative to this point of reference may arise.

Non-integral structural materials

Some scaffolds, microcarriers, sacrificial biinks, and other adherent surfaces used to provide structural support for cultured cells may be used with the intent to remove the material at or after harvest. A food safety concern would be if residues of the material remained in the final product at levels sufficient to cause harm to the consumer.

For this to occur, the structural material is not properly sequestered after cell harvesting, and the material is present in the final product at levels hazardous to consumers.

Controls available for this hazard include selection of materials with a safety profile appropriate to the intended use, compositional assessment of the harvested cell material or final product to evaluate potential residues, assessment of consumer exposure based on analytical data, and safety assessment based on the predicted consumer exposure. These considerations are routine in conventional food manufacturing.

Other chemical residues

A number of other chemical substances may be used in the culture process for various technical purposes, particularly during cell isolation and cell line establishment, such as cryoprotectants (Best, 2015). A potential food safety concern would be that such a substance was present in the final product at levels sufficient to harm the consumers.

For this to occur, the concentration of the substance could not adversely affect the viability of the cells during culture. The substance would then have to remain at a high enough concentration that sufficient levels remain after very large increases in the volume of the cells, multiple fluid exchanges, and washing steps. The chemical residues would have to be present in the final product at levels sufficient to cause harm to consumers.

Strategies available to control for this hazard include use of minimal levels of substances necessary to achieve the desired technical effect in culture, restricting use to early stages where possible, use of validated wash steps at harvest, quantification of potential residues in the final product, and specifications and other safety and quality control measures. In addition, assessment of potential consumer exposure based on process analysis or analytical data can inform assessment of the safety of the substance given the estimated consumer exposure and selection of substances with appropriate safety profiles relative to anticipated consumer exposure. This hazard is not unique to cell-based foods. For example, a similar hazard is also present in assisted reproduction techniques used in terrestrial and aquatic species meant for human consumption.

4.3.2.4. Allergens

Some chemical substances added to food are capable of eliciting an allergic response³ in some individuals. Common food sources of allergens include soy, wheat, eggs, shrimp, and peanuts. Substances capable of eliciting an allergic response may be introduced as ingredients during the culture process (e.g. structural materials, antimicrobials, medium nutrients, medium stabilizers, modulators of cell function), in the final product (e.g. binders, protein sources), or through cross-contamination from other food products or components being produced in the same production plant.

For an allergenic response to occur, the substance would need to be an allergen, not be degraded or metabolized in culture, not be removed by any wash steps, not be degraded by conventional food processing and food preparation; and remain present in the final product in sufficient concentrations and with sufficient intact epitopes to be able to elicit an allergic response to those who are vulnerable to such allergens.

Controls for this hazard include selection of substances from non-allergenic sources, use of minimal levels of substances necessary to achieve the desired technical effect in culture, restricting use of potential allergens to early stages of production, and use of validated wash steps at harvest. Quantification of potential residues in the final product, assessment of potential consumer exposure based on process analysis or analytical data, specifications, safety and quality control measures, and advisory product labelling can also be used. Specifically for use as medium nutrients derived from known allergenic sources, protein hydrolysis to reduce or eliminate allergenic epitopes is a possible control. Where the substance under consideration is a recombinant protein, any modifications relative to the endogenous sequence may be considered with respect to their impact on the allergenicity of the protein. The concerns and risk management strategies are the same as for conventional foods.

4.3.3. Biological hazards

4.3.3.1. Pathogenic agents

Pathogens or pathogenic agents include microbial agents such as certain bacteria, including antibiotic-resistant strains, viruses, prions, parasites, protozoa, and fungi that can cause human disease either through infection or production of toxins. These may be present in the final product, and if not controlled, may be hazardous if present at high enough levels.

Pathogens from animal-derived cells

Pathogens or pathogenic agents may be present in the biopsied tissue samples used to generate cell lines and could be carried to the end product.

³ Discussions of allergens also includes other substances that can elicit hypersensitivity response. While hypersensitivities are possible with any food, the considerations within cell-based foods are the same as should be considered for any novel ingredients. Reference can be made to the series of FAO/WHO publications on the topic of allergens whose Part 1 is available at <https://www.fao.org/3/cb9070en/cb9070en.pdf>.

For this to occur, the pathogens must go undetected in health inspections, remain present in the sample, or enter the sample during the biopsy process. The pathogens then must survive antimicrobial treatment, if applicable. Then, the pathogens survive and propagate in the cell culture, the cell culture is not disrupted, the pathogens go undetected through the cell line development, production, and food processing stages. The pathogen is not detected through macroscopic or analytical inspection, survives food preparation, and is present in the final product at levels hazardous to consumers.

This hazard can be controlled by having access to herd (terrestrial livestock) or lot (aquaculture) health certification (if available), health inspection (pre- or post-slaughter) of source animals and biopsied tissues for signs of infection by a certified professional, application of antibiotics and/or antimycotics added at the moment of sampling and keeping the sample cold to reduce growth or metabolism of pathogens. However, it must be noted that health certification and veterinary inspections are rare or non-existent for seafood or other wild-caught species. To reduce the risk of prions, tissues that are known to harbour prions (e.g. central nervous system tissues) can be avoided. Testing for prions can be used when limited health information is available for the source animal. Testing for pathogens can be performed prior to cell banking, including species-specific viruses, where appropriate. This hazard is not unique to cell-based foods since it is also present in conventional meat production. The concerns are similar for cell-based foods and conventional foods.

Pathogens from pre-harvest inputs

Pathogens may be introduced from inputs used during production, especially animal-derived inputs which also carry a risk of pathogenic agents. If pathogens and/or pathogenic agents are introduced during production, they might persist in the end product and cause disease if consumed.

For this to occur, the pathogen or pathogenic agent needs to be present in an intentional input (e.g. medium, scaffold) and goes undetected in the quality control, including access to health information for animal-derived inputs. Then, the pathogen is still present and viable after sterilization of ingredients, if applicable. Then, the pathogens should persist in the cell culture, surviving antimicrobial treatment, if applicable, and the cell culture is not disrupted or overgrown. Finally, the pathogen or pathogenic agent goes undetected in any testing or process monitoring, persist throughout the cell line development, production, food processing, and food preparation stages, and is present in the final product at levels hazardous to consumers.

This hazard can be controlled by sterilization methods (e.g. thermal, ultrasound, irradiation, filtration-processing), which can be applied depending on the input and through the use of appropriate antimicrobials. When possible, animal-derived components (a common source of pathogens) can be avoided. When animal-derived inputs are used, health inspection of source animal (pre- or post-slaughter) for signs of infection by certified professionals and access to herd/lot health certification (if available) can inform safe sourcing of animal-derived ingredients. However, it must be noted that health certification and veterinary inspections are rare or non-existent for seafood or other wild-caught species. Antibiotics and antimycotics can be used to prevent bacterial and fungal contamination. Testing for viruses, including species-specific viruses, can be implemented when appropriate. Testing for prions can be implemented in the case of limited health information on source animals (such as ingredients sourced from bovine) when appropriate. Testing for other pathogens can also be implemented when appropriate. Process monitoring is a tool that can be implemented to aid in detection of contaminating pathogens. Biosensors, and authorized rapid detection methods, could be also implemented. This hazard is not unique to cell-based foods, since the same kind of hazard may be present in the production of fermented food products, fermented food ingredients, and recombinant enzymes.

Pathogens from post-harvest inputs

As with conventional foods, pathogens may be introduced from water or ingredients added during food processing. (e.g. binders, texturizers, nutrients, flavours, colours). If pathogens and/or pathogenic agents are introduced during food processing, they might persist in the end product and possibly cause disease if consumed.

For this to occur, the pathogen needs to be present in an ingredient, a food additive or any other element used during the food processing step, colonize on the product, and is under the right conditions for growth. The pathogen then needs to survive further food processing, goes undetected in any testing or process monitoring, and is present in the final product at levels hazardous to consumers.

Pathogens can be controlled through following relevant good practices,² specifically preventative controls such as specifications and standard safety testing procedures. In addition, the use of effective cold chains can reduce pathogen growth. This hazard is not unique to cell-based foods since it is also present in conventional food production and processing. However, it is important to recognize that the nutrient content and innate microbiota present on cell-based foods may be different from their conventional counterparts, which could lead to differences in how readily the product is colonized by foodborne pathogens during food processing.

Pathogens from operators or environment

Pathogens may be introduced from the air, equipment (e.g. sampling tools, culture vessels), packaging materials, or operators in the food production or processing environment, particularly from asymptomatic infected operators and a lack of hygienic practices throughout the production facility and processes.

For this to occur, the pathogen is introduced to the product through equipment, the environment, or operators. The pathogen survives antimicrobial treatment (if applicable), survives and replicates in culture, and the cell culture is not disrupted throughout the cell sourcing, production, harvesting, and food processing stages. The pathogen is not detected through macroscopic or analytical inspection, survives food preparation, and is present in final product at levels hazardous to consumers.

This hazard can be controlled by following relevant good practices.² Specifically, aseptic handling of cells and inputs and process monitoring can be used to prevent pathogens from entering the product. In addition, antimicrobials can be used to prevent bacterial and fungal contamination and sterilization methods, if appropriate, can be used to remove contamination. For cell storage, storage in the vapor phase of liquid nitrogen can help to prevent contamination. Testing for pathogenic contaminants can be used during the process or in the final product. This hazard is not unique to cell-based foods since it is also present in conventional production and in common food processing.

4.3.3.2. Cell lines from species with limited history of safe food use

It is possible that species with limited history of being consumed as food are used as a source for cells. In such cases, there would be limited information about the potential cell products, transformations or endogenous toxins produced by the source animal.

For this hazard to occur, the toxins from the species with a limited history of safe food use must be expressed in the cells used, not be degraded, and persist throughout the cell line development, production, food processing, and food preparation stages. The toxin must be present in the final product at levels hazardous to consumers.

This hazard can be controlled by referring to the end product originating from an unconventional species and bioinformatic comparisons with known toxins in existing databases and further conduct risk assessment if appropriate. However, it should be noted that all animals do not have fully annotated genomes and therefore this data may need to be generated to make comparisons. This hazard is not unique to cell-based foods, as similar concerns arise with introduction of non-traditional, unfamiliar or new foodstuff (e.g. insects, seaweeds) entering the food chain.

4.3.3.3. Genetic instability

The expression of novel toxins or a change in expression of toxins can occur as a result of genomic instability (e.g. large rearrangements), genetic or phenotypic instability (e.g. variability due to cell division, *mycoplasma* contamination), or can be induced through physical or biochemical stimuli during cell culture (Attwood and Edel, 2019; Li *et al.*, 2019, Ong *et al.*, 2021). These would have to be substances that are hazardous to the consumer but not to the cells. Currently, only very specific examples of these substances are known, such as certain vitamins (Olson *et al.*, 2021).

For this hazard to occur, genetic or phenotypic instability would need to affect a relevant gene causing new or increased expression of the endogenous toxin. The change would not be detected or disrupt the cell culture. The toxin is not degraded, metabolized, or washed away during cell sourcing, production, harvesting, food processing, and food preparation and is present in the final product at levels hazardous to consumers.

This hazard can be managed by first developing a scientific understanding of genetic components that are relevant to food safety, considering the differences and varieties of species and/or cells being used. Risk assessment of such components needs to be conducted to establish the safe level of the components remaining in the final food product, considering the exposure levels compared to a relevant reference counterpart to determine whether the levels would affect food safety. Additionally, evaluation of genetic and phenotypic stability by molecular techniques (e.g. karyotyping) may indicate low rates of spontaneous genetic changes in general, including those that could be of food safety relevance. This hazard is not unique to cell-based foods, as it is also present in conventional breeding or cloning procedures. In addition, a similar hazard is present in cellular therapeutics and biosimilars industries, where controls and best practices can be referred to and possibly adopted for cell-based foods.

4.3.3.4. Allergens

Many species used for food production, such as seafood species, are known to have allergens. Therefore, allergens from the cells derived from such sources are a possible hazard. This could occur if the species of the animal used to source cells produces allergens, if cross contamination of cell lines occurs during production, or if genetic drift results in new or increased production of allergens. In any of these cases, an allergen may be present in the cell-based food and some consumers may have an allergic reaction to the end product when consumed. If cell lines are derived from species with limited history of being consumed as food, there is usually limited information about the potential allergens. A new or broader set of consumers may be exposed to the proteins of this species and potentially develop allergies.

For this to occur, a substance with an ability to elicit an allergic reaction (e.g. properties usually present in food allergens, such as thermal stability, stability to protease digestion, glycosylation) must be present in the cells because they were sourced from an animal known to produce allergens or production of an allergen was induced due to genetic drift. The food allergen is not detected, degraded, or washed away throughout the cell sourcing, production and harvesting, and food processing stages. For cross-contamination, the contaminating cell line must remain viable in culture. The allergens survive food preparation and reaches the final product at a concentration that exceeds a tolerable threshold.

This hazard can be controlled by labelling the final food product for the known allergens or when cells are sourced from an unconventional species. Bioinformatic comparisons with known allergens in existing databases can be used to identify novel allergens. However, it should be noted that not all animals have fully annotated genomes and therefore this data may need to be generated to make comparisons. Cross-contamination between cell lines can be controlled by following relevant good practices,² specifically proper storage and handling, separation of production lines, regular safety and quality control checks, personnel training, and a proper record keeping programme.

This hazard is not unique to cell-based foods, as it is the same hazard present in the conventional foods industries; and similar concerns may arise with introduction of non-traditional, unfamiliar or new foodstuff entering the food chain. For cross-contamination of allergens, another point of comparison is the production of biologics, where cell line contamination can compromise the product.

4.3.4. Other hazards

4.3.4.1. Microplastics (including nanoplastics)

Microplastics are small (micro or nano scale) foreign matter particles derived from the degradation of plastics which are found ubiquitously such as in food, water and/or air (WHO, 2022). Microplastics are themselves a potential hazard or can interact with other ingredients to change their properties. It is currently not fully understood whether and if so, to what extent, toxicity occurs from exposure to microplastics. In addition, microplastics might lead to a change in the availability of intentionally or unintentionally present substances in the final food product.

For this to occur, microplastics are present in air, water, or ingredients, followed by insufficient purification. Alternatively, they can be transferred from plastic equipment, processing materials, and packaging materials that come into contact with the final product. To pose a health hazard, the microplastic need to be introduced into the cell-culture process or final product, go undetected, do not affect cell growth, and be present in the final product at levels hazardous to consumers.

Controls for microplastics include following relevant good practices,² specifically filtration of source materials and reduced use of food-contact plastics. Analytical methods are emerging, and possible remediation techniques are still in the research stage (Kwon *et al.*, 2020). This hazard is not unique to cell-based foods as the presence of microplastic particles remains a potential concern for most food products.

4.3.4.2. Intentional genetic modification

Cells sourced from genetically modified (GM) animals

Several genetically modified (GM or recombinant-DNA) animals for food production have been developed during the last decades. There are a few cases of such animals approved for food consumption and there is a Codex Guideline for the Food Safety Assessment of Foods derived from recombinant-DNA animals (Codex Alimentarius, 2008). Therefore, in the foreseeable future, source animals for cell line development could include genetically modified species, which may lead to novel substances being present in the collected tissue. Safety of such new proteins or bioactive molecules needs to be assured.

For the final product from such cell lines to be hazardous, the novel substances in the genetically modified animal must be toxic. Then the toxicity will need to be undetected in the safety assessment of the animal. The genetic modification must be expressed in the cells that are biopsied. Novel substances expressed by the cells must persist in the cell culture, not disrupt the cell culture, and not be degraded or washed away during cell sourcing, production, harvesting, and food processing. The substance must go undetected and be present at levels hazardous to consumers.

This hazard can be controlled by food safety assessments following the relevant Codex guidelines prior to allowing GM animals to be used for cell sourcing. This hazard is not unique to cell-based foods, since it is also present in any food products (other than cell-based foods) derived from genetically modified organisms.

Genetically modified (GM) cell lines

In some cases, cell lines may be genetically modified during the cell line development stage to improve their ability to be cultivated for cell-based food production. Genetic modification can also cause changes in genes regulating the levels of endogenous bioactive substances or toxins. In addition, when genetic modification involves transgenesis, new proteins may be produced; and their safety needs to be assured.

For the final product from such cell lines to be hazardous, genetic modification must introduce or increase expression of substances which are hazardous and go undetected in the safety assessment of the cells. The substance must not disrupt the cell culture; and not be degraded, metabolized, or washed away throughout the cell sourcing, production, harvesting, food processing, and food preparation stages. The substance goes undetected and reaches the final product at levels hazardous to consumers.

This hazard can be controlled by testing for new protein expression when applicable, an analysis of the level of expression of molecules related to the modification and correlation to expected exposure from the food product, and toxicity testing for the new protein. Validation that the modification is as intended without further changes in the genome may also be performed. The method of genetic modification may vary and may introduce different hazards that may need to be examined on a case-by-case basis. This hazard is not unique to cell-based food, as the same potential hazard can be considered for any other genetically modified foods. Relevant Codex guideline (Codex Alimentarius, 2008) can be considered to assure safety of genetic modification to cell lines for cell-based food production.

Additionally, during food processing, physicochemical transformation of food may cause changes to the genetic material. Most foods contain genetic material, which is largely degraded during food processing and passage through the gastrointestinal tract. Within existing food, it is well known that genetic material and its degradation products are not hazardous. However, extra care must be applied to ensure that genes produced from development of modern biotechnology do not result in any additional health concerns.

4.3.4.3. Allergens

Intentional genetic modification of the source animal or cell line can result in the new or increased expression of allergens.

For this hazard to occur, genetic modification must introduce or increase expression of substances with an ability to elicit an allergic reaction. The allergen must be expressed, persist in the cell culture, go undetected, and be present in the final product at levels sufficient to cause harm to consumers.

This hazard can be controlled by allergenicity testing for the new protein when applicable, an analysis of the level of expression of molecules related to the modification and correlation to expected exposure from the food product, and toxicity testing for the new protein. Validation that the modification is as intended without further changes in the genome may also be performed. If an allergen is present, labelling should be used on the final product. This hazard is not unique to cell-based food, as the same allergenicity concerns exist in other genetically modified foods.



4.4. Concerns not included in the scope of hazard identification

During the process of identifying the hazards and discussing the respective sequence of events that would need to occur to result in harm to consumers in each case, the Technical Panel noted that there are additional issues that people may encounter in popular press and social media alleging certain concerns in connection with the cell-based food production process and its potential products. Given the attention they have received, these concerns have been considered by the Technical Panel, even if it was not possible to describe a sequence of events consistent with the current understanding of relevant science that could result in harm to consumers.

One purported concern involves the potential survival of cells after consumption. In the process of cell-based food production, living cells are used as source material and propagated to large numbers to eventually form a product. The possibility was considered that living cells with the capability of extended or immortalized replication could enter the body and survive, leading to harm through some type of tumour formation.

For this to happen, all of the following events would need to occur. First, the cells would need to be capable of remaining alive for an extended period after being removed from the environment of the bioreactor that provides a steady supply of nutrients, dissolved oxygen, and a fixed temperature. The cells would also need to survive actively adverse conditions during a series of steps following harvest. These would typically include conventional food processing, handling and storage at cold or freezing temperatures, and consumer preparation including thermal cooking. A hypothetical cell that survived these steps and remained alive in the final food product would then need to survive gastrointestinal digestion, cross the gastrointestinal barrier layer intact, enter into the blood circulation, evade immune surveillance and attack in the body in spite of being from a non-human species, and finally proliferate in the body.

The probability of even one of these events is extremely low, and their occurrence is not consistent with current scientific understanding. Isolated animal cells, unlike single bacteria or yeast cells, do not have adaptations that protect them from the external environment or allow them to survive without the support of the organism; this consideration is a significant factor in the technical challenges of building bioreactors. More over, based on the current understanding of the relevant science, the capability for extended or sustained cell replication in the environment of the bioreactor does not confer any increased capacity for cell survival outside the controlled environment of the bioreactor. Neither does it convey capabilities that would be useful for establishing residence in tissues, such as immune evasion or tissue invasion. Furthermore, current scientific knowledge does not support the plausibility of human cancer contagion via introduction of cells even from other humans.

Empirical evidence from consumption of conventional meat that, like many animal tissues, may contain microtumours or precancerous lesions, also indicate that oral exposure to cells with enhanced proliferative capacity subsequently subjected to conventional food processing has not resulted in any reported instance of cross-species cell survival and growth. Thus, each of the steps described is at best extremely unlikely to occur, and none that requires active intervention by the manufacturer. The probability of all these events occurring concurrently is such that it was not possible to identify a credible pathway to harm.

Another alleged concern involves the possibility that cell lines from species that are currently not consumed could harbour novel microorganisms that propagate during cell culture, and that their DNA, present in the food, might recombine with that of the human microbiome, leading to adverse effects on the consumer.

For this to happen, all of the following events would need to occur. The microorganism would have to survive use of antibiotics during cell isolation, not be detected by manufacturer during establishment of the cell bank, not impair the growth of the animal cells during culture such that perturbation of growth would alter monitored culture parameters, not be identified by visual inspection during harvest, not be detected by any testing or quality measures used by the manufacturer. Sufficient DNA (either from a living microorganisms or as a residue) would need to be present in the finished food, would need to survive to enter the gut followed by an uptake by a gut-residing microorganism, a recombination event would need to occur, the recombination would need to convey a functional trait or expression product, that trait or expression product would need to allow the recipient gut microorganism to thrive sufficiently to change the overall microbiome, and that trait or expression product would need to be absent from all microorganisms associated with animal species with a history of food use.

Setting aside any estimate of the low probability that all these events would occur concurrently, it was not possible to identify any basis for concluding that microorganisms associated with species with or without a history of food use would be different in this regard.

Another purported concern involves the presence of genetic material present as a potential contaminant or residue, either through use of recombinant proteins which could have some remnant genetic material from the production organism or through use of genetically modified animal cell lines. In either case, the concern is that genetic material could be taken up by the gut microbiome or by human intestinal cells and result in an expression product that would be toxic or otherwise harmful to the consumer.

For this to happen, the genetic material would need to resist degradation from all food processing methods applied to the harvested cell material or through digestion and remain present in the gut as a sufficiently intact sequence encoding some fragment of the expression product, be taken up into a gut microbe or human intestinal cell, become integrated into the genome in such a way that active expression would occur. The integrated genetic material would need to be capable of producing a protein, that protein would need to be capable of causing harm either through direct toxicity or otherwise impairing the gut microbiome, and this uptake and expression would need to occur on a large enough scale for a meaningful quantity of the protein to be produced. When considering the specific scenario of modified animal cells, the expressed protein would need to be harmful to the consumer in some way but not to the animal cells expressing that protein in culture.

When considering the specific scenario of remnant genetic material as a contaminant in a recombinant protein introduced into the medium, in order to even be present in the harvested cell material the recombinant protein product would need to contain DNA from the production organism as a contaminant, the DNA would include remnants of the expression vector, these remnants would still be capable of effective transfection into another organism, and the remnants would be introduced into the culture medium. Following the hypothetical introduction of the remnants, they would need to retain transformation ability, resist degradation by culture conditions, and remain after any washing of the harvested cells.

When considering this general concern regarding genetic material that may be used in the production of cultured animal cells either directly or indirectly, the Technical Panel has acknowledged that there is clear evidence that food-derived DNA fragments of up to several hundred base pairs have been detected in the gut and can be taken up into microbial or gut cells or even enter circulation. However, the current understanding of mechanisms of transfection events in animal and microbial cells and the ecology of the gut microbiome, including the constant presence in the gut of a very wide range of food-derived DNA from animal, plant, fungal, and microbial sources without any documented evidence of clinical significance, is inconsistent with a credible pathway to harm through the general sequence of events described above.

A final speculative concern involves the potential presence of *Mycoplasma* spp. contamination in the cell culture process. Such contamination is relatively common in research settings and possibly in cell culture facilities. It can be difficult to detect through passive measures because this class of microorganisms is relatively slow-growing and causes less disruption to the culture. An expressed concern is that *Mycoplasma* spp. present in the food could behave as human pathogens when consumed.

For this to happen, the *Mycoplasma* spp. would have to be present in culture, not disrupt the culture process sufficiently to be detected by monitoring of environmental parameters, not be detected by active surveillance or testing measures, be present as live microorganisms in the finished food, and be capable of actively infecting or causing pathogenesis via the oral route. There are no reported instances in the clinical literature of human infection or pathogenesis via the oral route. Respiratory infections are observed after extended contact with an infected individual. Urogenital infections require direct contact with an infected individual. It was not possible to identify a credible pathway to harm based on the current understanding of the relevant science.

4.5. Food safety communication and building consumer trusts

4.5.1. A pivotal moment for introducing cell-based food

Cell-based food products are not yet available in most parts of the world; therefore, most consumers are unlikely to be familiar with them or the processes used to make them. Therefore, this is an opportune time for regulatory authorities to communicate about the relevant food safety questions associated with these products and processes, and to establish themselves as useful, authoritative, and transparent sources of information, necessary to the establishment of trust in the food safety regulatory system that will govern these products. There is ample evidence from the communication failures associated with the introduction of other new food technologies, including biotechnology (Mohorčich and Reese 2019) and food irradiation (Bord and O'Connor, 1990; Henson, 1995), about the importance of strategic, proactive communication strategies on the part of food regulators. Once the new products make it to market, the focus of marketers, consumers, and the media will likely be on the product, not on the regulatory process designed to ensure their safety.

4.5.2. Engagement before opinion formation

After the widescale introduction of cell-based food products to the marketplace, and the accompanying marketing campaigns designed to sell (or oppose) them, consumers, policy makers, and other stakeholders may already hold rigid opinions. Studies show that humans have a tendency to assign meaning to incoming information based on their current beliefs and attitudes and what they already believe to be true (Craik and Lockhart, 1972; Shanks, 2010), especially when presented with information they don't understand (Posner and Rothbart, 2002). Once people create a mental model (Johnson-Laird, 2001) of the technology and its products and have established their feelings about it, they engage in motivated reasoning to maintain consistency in their beliefs, attitudes, and actions toward it (Kunda, 1990). To do so, they look for confirming information (including misinformation), discount or ignore disconfirming information, and when they cannot ignore information that is inconsistent with their beliefs, attitudes, or actions, they tend to look for reasons it doesn't apply (Epley and Gilovich 2016; Kahan, 2012).

4.5.3. Current efforts to communicate about cell-based food

Some regulatory authorities have identified a key contact within the organization for information and questions about cell-based food. Some have also created websites devoted to cell-based food. These are designed to both provide basic public-facing information in anticipation of stakeholder questions and as a mechanism for collecting their key concerns. Some regulatory authorities have also contracted with experienced social scientists to conduct research to better understand the key questions of a variety of stakeholders, including consumers, the cell-based and conventional food industries, advocacy organizations, journalists, and science writers. In engaging in these activities, they have established themselves as useful and authoritative sources of information and have created an essential starting point for public understanding of the food safety aspects of cell-based food.

4.5.4. Risk perceptions vary between consumer segments

The type and degree of risk perceptions are likely to vary considerably within any one population (Szejda and Dillard, 2020). Many consumers are likely unfamiliar with cell-based food and their production methods. This unfamiliarity may significantly influence perceptions of risks associated with these new products (Fischer and Frewer, 2009). In addition, some consumers have expressed a tendency to fill in gaps in their knowledge with worst-case scenarios (Szejda and Dillard, 2020).

The degree of interest in the novelty, or the potential personal and altruistic benefits of cell-based food, could either downplay or accentuate risk concerns (Rogers, 2003; Szejda *et al.*, 2019). For example, segmentation studies have found that consumers who are most enthusiastic about the potential of cell-based food have fewer concerns and questions about safety than those consumers who are skeptical or rejecters of this biotechnology (Szejda *et al.*, 2019). Skeptical segments have expressed concerns about (a) what additives and chemicals might be in cell-based food as well as (b) what long-term safety issues might later be discovered (Szejda and Dillard, 2020). Those who have a trait reluctance to try new foods (“neophobia”; Pliner and Hobden, 1992) are less likely to accept new food such as cell-based food (Bryant *et al.*, 2019; Hamlin *et al.*, 2022; Siegrist and Hartmann, 2020). Beyond the uncertainties surrounding these new products, rejecters of cell-based food often explain their reasoning on the basis of moral (Mancini and Antonioli, 2020) or religious grounds (Boerboom *et al.*, 2022; Szejda *et al.*, 2019). Implementation of vigilant hazard/risk assessments, control measures, transparency, and effective risk communication are important strategies for mitigating these risk perceptions.

4.5.5. Not all concerns are based on evidence, yet should still be addressed

Beyond the hazards identified in this document, consumers may have other concerns. Although some of these issues may not be scientifically considered to be a hazard, they may nevertheless strongly influence safety perceptions of cell-based food. There are new and unfamiliar aspects to the production of cell-based food that pose concerns for certain consumer segments, such as “unnaturalness” (Gomez-Luciano *et al.*, 2019; Wilks *et al.*, 2021). Indeed, some consumers do not desire to consume any “unnatural” foods including technological innovations (Bugnagel, 2022). In this regard, consumers may consider three aspects a) the way the food has been grown (food origin), b) how the food has been produced (what technology and ingredients have been used), and c) the properties of the final product (Román *et al.*, 2017). Another challenge is emotional resistance to cell-based food, resulting from perceptions of “absurdity and/or disgust” and subsequently result in an unwillingness to eat “cell-based-food” regularly (Chriki *et al.*, 2021; Liu *et al.*, 2021; Hocquette *et al.*, 2022; Quevedo-Silva and Pereira, 2022).

4.5.6. Conflating hazard and risk

Most consumers are unfamiliar with formal hazard and risk analysis, and therefore tend to conflate hazard and risk (Wiedemann, 2022). For example, the exhaustive list of hazards in this (or any) document could be perceived as risks, rather than controllable hazards with variance in probability and degree of threat. To address these perceptions, regulators may wish to develop and implement communication strategies to contextualize potential hazards and the probability or degree of threat each risk might represent. The causal chains identified in this document provide an opportunity to convey both the probability and ability to control these potential hazards.

4.5.7. Hazard invisibility

Detection of hazards in foods often requires relevant knowledge and tools, and such hazards are usually invisible for consumers, so consumers cannot always judge for themselves whether food is safe (Böcker and Hanf, 2000; Green *et al.*, 2003). Consumers therefore rely on and trust regulators to ensure food safety (Lobb, 2005). Therefore, effective risk management and communication practices are important factors in the development and maintenance of consumer confidence in the area of food safety (Frewer *et al.*, 1996). A single food safety scare related to cell-based food, especially early on, could easily shake consumer confidence, and in the regulatory process/authority itself (Böcker and Hanf 2000; Tonkin *et al.*, 2020).

4.5.8. Ineffective methods

Cell-based products, which are new to consumers and use unfamiliar technologies, will legitimately elicit a number of scientific questions from public audiences. However, communicating about scientific issues, especially in relation to food, is more complex than simply supplying new information or translating scientific findings to lay audiences. The “deficit model”⁴ approach has typically been an unsuccessful method for communicating about new technologies. For example, if a householder living near the site of a new chemical factory is told about high-tech safety precautions, or if a consumer opposed to genetic modification is told about the low probability of gene transfer between species, it is quite likely that neither will change their opposition (Brown, 2009).

4.5.9. Communication skill sets for key personnel

Ensuring that key personnel within the regulatory authority have a good understanding of the technologies, inputs, processes, potential hazards and control methods involved with producing cell-based food is an essential starting point for engaging with and addressing stakeholder concerns. However, competence in understanding the processes and science-related aspects associated with the production and safety of cell-based food is only a prerequisite for effective communication. Communicators with the ability to be “active listeners” (Weger *et al.*, 2014), to express empathy (McMakin and Lundgren, 2018), and to engender trust (Slovic, 1999), tend to be more successful in their interactions with others.

4.5.10. Prerequisites for consumer trust

Although sharing scientific information is one aspect of science communication, communication skills and a set of evidence-based approaches to engage audiences and contextualize information (Howell *et al.*, 2018) are more likely to garner trust in regulators and to help consumers feel comfortable with making personal decisions about cell-based food consumption (de Bruin and Bostrom, 2013). Trust influences whether consumers will want to learn from experts (Lupia, 2013; National Academies of Sciences, Engineering, and Medicine, 2016; Renn and Levine, 1991). Moreover, consumers tend to want to learn from sources who share goals and interests with them (Lupia, 2013; Martinez-Conde and Macknik 2017; Renn and Levine, 1991) and who have expertise in their field (Lupia, 2013; Renn and Levine, 1991). Communicators who are perceived as competent and honest, are also perceived as being more trustworthy (FAO/WHO, 2016). Transparent communication is also critical to build trust (Rawlins, 2008; Jiang and Luo, 2018). Acknowledgement of scientific uncertainties also increases audience’s perceived trust in a communicator (Frewer *et al.*, 2002; Johnson and Slovic, 1995; National Research Council, 2012).

4.5.11. Transparency, openness and public engagement

Transparency in communicating how regulatory decisions are being made is perhaps the most important pillar of a good communication strategy for competent authorities (FAO/WHO, 2016). The public must be able to ascertain that decisions are being made competently and in the interests of protecting public health. To facilitate this, regulatory authorities may consider making health and safety research and data easily accessible to interested stakeholders (Siddiqui *et al.*, 2022). Consistency in safety assessments across regulatory agencies will increase consumer confidence in food safety, so collaboration across agencies may be a useful approach. Openness is also critical to the process. Openness refers to the opportunity for engagement with all food safety stakeholders, including those affected by the risk and those potentially responsible for it (FAO/WHO, 2016). Communication should also be considered an integral aspect of content development, beginning with engagement of relevant stakeholders (Covello, 2003).

4 The original purpose of the ‘deficit model’, coined by social scientists studying the public communication of science in the 1980s, was to characterize a widely held belief that has two aspects. The first is the idea that public skepticism towards modern science and technology is caused primarily by a lack of adequate knowledge about science. Related to this is the idea that, by providing sufficient information about modern science and technology to overcome this lack of knowledge – or ‘knowledge deficit’ – the public will change its mind and decide that both science and the technology that emerges from it are ‘good things’ (Dickson, 2005; Weigold, 2001).

Understanding that food safety communication is iterative and requires continuous improvement, regulatory authorities may also consider how they will create the capacity for ongoing engagement of key stakeholders. They may also want to consider how they will continuously monitor public understanding of and concerns about these new products, the production methods involved, and how they will effectively respond to misinformation or disinformation regarding them (OECD, 2022). This may be of particular importance with respect to traditional and social media (Vosoughi *et al.*, 2018).

4.5.12. Begin with what stakeholders want to know

A key principle of effective communications is to begin by addressing the questions that people want to have answered, rather than with what experts believe they need to know. Stakeholders are more likely to listen to and comprehend the messages that experts wish to communicate if those experts first address their key concerns. To learn consumer questions, regulators may wish to develop public forums, so that regulators and consumers have opportunities to share perspectives. Focus groups might be another way to learn from audiences (Webb and Kevern, 2001). Focus group data offer considerable potential for exploring the co-construction of meaning through an analysis of interactive processes. They could allow regulators to ascertain underlying concerns hidden in consumers' and other stakeholders' questions. Mental modeling interviews can also help surface how consumers think about the technology itself (Morgan *et al.*, 2002).

4.5.13. Framing and message design

Food safety communication strategies, such as communicating using examples and analogies to production of familiar food products and methods for controlling hazards may be helpful for contextualizing risk (Duit, 1981). Moreover, framing scientific information in ways with which people are already familiar renders the learning process easier. Framing new scientific information in narrative form, including visual storytelling (such as comics; Sundin *et al.*, 2018), both engages audiences and makes it easier for them to learn. Individuals can more easily process and remember information that they learned in story form (Graesser *et al.*, 2002; Greenhalgh, 2001) because the cognitive process when engaged with a narrative is uniquely heuristic and low-energy-intensive (Bruner, 1985; Kahneman, 2013). Overall, stories are easier to understand than statistical, informative information (Dahlstrom, 2014) and lead to greater understanding and remembering than traditionally presented science information. Effective food safety messages are (a) evidence-based, (b) helpful for consumers to make decisions, and (c) applicable and useful for consumers (Fischhoff, Brewer, and Downs, 2011). Communication strategies should be continually tested to ensure their effectiveness (Kahan, 2013; Maynard and Scheufele, 2016).



©Steakholder/Shlomi Arbiv

4.6.1 Special considerations on terminologies

4.6.1. Consistent and accurate terminology helps consumers understand and find information

Appropriate nomenclature that is truthful and not misleading facilitates informed decision-making by consumers, helping them understand what they are purchasing or not purchasing (Hastak and Mazis, 2011). Most consumers are currently unfamiliar with cell-based food products and the processes made to use them. Regulatory authorities have the opportunity to communicate about these in advance of consumers' initial encounters with the products on a menu or in a store, increasing familiarity and avoiding surprises in the marketplace. Adoption and consistent use of consistent nomenclature across commodities/ species and used by all stakeholders can help consumers better understand the products and processes and can create a common search term that may be used to find more information about them (Hallman and Hallman, 2020, 2021).

4.6.2. Balancing terminology issues

Because consumers may be unfamiliar with cell-based products prior to encountering them on a menu or in a store, choosing names that balance regulatory requirements with marketing needs is important (Hallman and Hallman, 2021). Appropriate terminology will help consumers who know little or nothing about cell-based food understand their basic characteristics and how they are different from their conventional counterparts, helping them make purchasing decisions. It can also help fulfill consumer desires for transparency in food labeling (FMI and Label Insight, 2020).

4.6.3. Using the term “meat”

Cultural meanings and current regulatory names for the commodity name “meat” vary by region (Ong *et al.*, 2020), so use of the term “meat” to refer to a cell-based food product might not be acceptable in all regions (Hansen *et al.*, 2021). Calling the product “meat” may also complicate halal (Boereboom *et al.*, 2022) or kosher (Krone, 2022) labeling, as the religious status of this new product might depend mostly on its production methods (e.g., cell sourcing, other inputs) (Chriki and Hocquette, 2020; Hamdan *et al.*, 2021). Other stakeholders, such as some conventional meat producers, may also object to using the term “meat” in connection with cell-based food (Faustman *et al.*, 2020). Hybrid products, which include plant-based or other ingredients in varying percentages, also complicate using the term “meat”, and in fact some countries already do not allow using this term for them.

4.6.4. Labelling for allergies

The definition issue of “meat” may further complicate the need to label species names for allergen disclosure. Disclosing the species name as well as the ingredient composition is needed to inform consumers with allergies and/or hypersensitivities (Hallman and Hallman, 2020).

4.6.5. Terminology shapes perceptions

For consumers, the product name creates a cognitive framing that influences their initial understanding of what the product is and guides their consideration of new information about the products and processes used to create them (Charette *et al.*, 2015). What the product is called also creates an affective/emotional framing that influences a consumer's initial positive or negative perception of the product and serves as an important starting point for their future evaluations (Siegrist and Hartmann 2020). Avoiding names that may be derogatory of either cell-based products (e.g., fake meat) or of conventional products (e.g., slaughter-free meat; clean meat; victimless meat) can prevent misperceptions of cell-based food or of conventional products (Chriki *et al.*, 2022; Possidónio *et al.*, 2021).



4.6.6. Stakeholder engagement in decision-making about terminology

Finally, different stakeholders, including industry and advocacy groups, are likely to have preferences and objections regarding terminology. Creating an open and transparent decision-making process based on objective criteria, clear assumptions, and empirical evidence will be important. These can be refined through organized engagements with stakeholders from the cell-based food industry, the conventional meat industry, advocacy groups, and consumers.

4.6.7. Evaluation criteria for determining whether existing terminology will apply in a local context

Where possible, consistent terminology can facilitate international trade. Yet, when determining appropriate terminology in a new market, differences in meaning across languages and cultures may create unintended consequences (CAIC, 2021; Janat *et al.*, 2020). Regulators might first assess whether existing terminology is feasible in their market. In addition to considering the potential overlap of proposed nomenclature with existing trademarks, regulators may team with qualified social-science researchers to generate empirical evidence to evaluate: (a) whether the terminology conveys the intended meaning, (b) enables consumers to distinguish the cell-based food from their conventional counterparts, (c) whether there are potential meanings already associated with other food products, (d) positive or negative connotations associated with the terminology, (e) potential for confusion with other words that look or sound similar, and (f) language that could be easily associated or modified to derogate the products.

4.6.8. Assessment of these criteria

Open discussion, engagement of stakeholders (including industry and advocacy groups), and a transparent decision-making process will contribute to both buy-in and understanding of the issue (Scolobig and Lilliestam, 2016). Beginning terminology discussions by determining what the appropriate terminology needs to achieve, the evaluation criteria necessary to demonstrate that these objectives are met, and how they can be measured can facilitate decision-making and consensus building (Munda, 2008). Using empirical evidence to assess each criterion will help to ensure the validity and reliability of the results. Vetting the research methods proposed to provide empirical evidence regarding these topics prior to implementation will help to ensure the validity and reliability of the results. Appropriate peer-review of these studies will lend additional credibility to their results.

E. CONCLUSIONS AND A WAY FORWARD

Hazard identification is only the first step of the formal risk assessment process. In order to conduct a proper risk assessment for cell-based food, it is essential to collect a sufficient amount of scientific data/information that is required for exposure assessment and risk characterization. To this aim, food safety competent authorities may wish to collaborate with other food safety competent authorities in the region or trade partner countries to share the experience so that the data and insights required for safety assessment of cell-based food can be complemented. Also, active engagement of stakeholders is useful to maintain the transparency in their own food safety assessment data and results.

Many of the Technical Panel members – who have gained knowledge of cell-based food in the public and private sectors, academia, research and non-government organizations – noted that although no perfect terminology currently exists, terminology is such an important issue that it should not be underestimated. Competent authorities may wish to refer to [Chapter 4.6](#) of this section to carefully consider appropriate terminologies that effectively integrate into the national context and language, while balancing with the international harmonization of the relevant terms.



©FAO/Oded Antman

Animal-based meat production has evolved over thousands of years to meet the demand for safe and affordable sources of protein. Global production and consumption of products with animal proteins continues to increase with the demand being driven by population growth, economics and urbanization. With a rapidly rising global population, it is important to carefully assess if cell-based foods would help to provide healthy, nutritious, and sustainable food for future generations, while at the same time reducing environmental impacts by, e.g. using significantly less land and water, emitting fewer greenhouse gases, reducing agriculture-related pollution, improving farm animal welfare and reducing the risk of zoonotic diseases that can spread from animals to humans. Furthermore, even before discussing the sustainability of the technology, it is important to establish the system to assure safety of cell-based food products.

As an initial step towards a thorough assurance of the safety of cell-based foods, the Technical Panel identified the potential hazards that could be introduced during cell sourcing/culturing, production, harvesting and processing, as well as importantly discussed, in each case, the sequence of events that would need to take place in order for harm to occur to consumers.

This hazard identification piece that was conducted by Technical Panel members is an extremely important first step in brain-storming all the potential food safety issues that could arise with the consumption of cell-based foods. In addition, the feedback and comments to be received by the international scientific communities on this publication will be invaluable in helping to move the field forward.

Besides food safety, the other subject areas touched upon by the Technical Panel, such as terminology, regulatory frameworks, nutrition aspects, consumer perception and acceptance (including taste and affordability) are just as important, and possibly even more important in terms of introducing this technology into the marketplace and seeking the sustainability of the production process as well as finding various end products' acceptance by consumers.

Solving the many challenges and hurdles that still exist with cell-based foods such as high production costs, scale-up hurdles, and gaps in fundamental knowledge will require a significant level of both technical and financial commitments from all stakeholders. While private funding and research efforts will further move forward the development, it is important to consider the skewed balance in terms of technical capacity, research opportunities between several advanced countries and low- and middle-income countries. The way forward will consist of continuing to invest in research and development in order to understand whether the alleged benefits in increased sustainability can be realized. In this regard it will be important to closely observe as to what extent, if any, cell-based foods result in differences from conventionally produced foods.



REFERENCES

- Acevedo, C.A., Orellana, N., Avarias, K., Ortiz, R., Benavente, D. & Prieto, P.** 2018. Micropatterning technology to design an edible film for in vitro meat production. *Food and Bioprocess Technology*, 11(7): 1267–1273. [dx.doi.org/10.1007/s11947-018-2095-4](https://doi.org/10.1007/s11947-018-2095-4).
- AgroChart.** 2016. Israel. Agricultural Biotechnology (September 15th, 2016). Montreux: AgroChart. <https://www.agrochart.com/en/news/5806/israel-agricultural-biotechnology.html>
- Aiking, H. & de Boer, J.** 2020. The next protein transition. *Trends in Food Science & Technology*, 105: 515–522. [10.1016/j.tifs.2018.07.008](https://doi.org/10.1016/j.tifs.2018.07.008).
- Allan, S.J., De Bank, P.A. & Ellis, M.J.** 2019. Bioprocess Design Considerations for Cultured Meat Production With a Focus on the Expansion Bioreactor. *Frontiers in Sustainable Food Systems*, 3. [10.3389/fsufs.2019.00044](https://doi.org/10.3389/fsufs.2019.00044).
- Allen, D.** 2013. Upstream chemistry analysis in cell-based process development: Advantages of minimization. *BioProcess International*, 11(8): 62–65.
- AMPS (Association for Meat, Poultry and Seafood Innovation).** 2022. *A Guide to Terminology* [Online]. Alliance For Meat Poultry And Seafood Innovation. Cited 2022. <https://ampsinnovation.org/resources/a-guide-to-terminology>
- Andriolo, G., Provasi, E., Brambilla, A., Lo Cicero, V., Soncin, S., Barile, L., Turchetto, L. et al.** 2021. GMP-Grade Methods for Cardiac Progenitor Cells: Cell Bank Production and Quality Control. In Turksen, K., ed. *Stem Cells and Good Manufacturing Practices: Methods, Protocols, and Regulations*, pp. 131–166. New York, NY, Springer US. Available: https://doi.org/10.1007/7651_2020_286
- Arshad, M. S., Javed, M., Sohaib, M., Saeed, F., Imran, A. & Amjad, Z.** 2017. Tissue engineering approaches to develop cultured meat from cells: A mini review. *Cogent Food & Agriculture*, 3(1). [10.1080/23311932.2017.1320814](https://doi.org/10.1080/23311932.2017.1320814).
- Attwood, S.W., & Edel, M.J.** 2019. iPS-cell technology and the problem of genetic instability—Can it ever be safe for clinical use?. *Journal of clinical medicine*, 8(3), 288. [10.3390/jcm8030288](https://doi.org/10.3390/jcm8030288).
- Awan, M., Buriak, I., Fleck, R., Fuller, B., Goltsev, A., Kerby, J., Lowdell et al.** 2020. Dimethyl sulfoxide: a central player since the dawn of cryobiology, is efficacy balanced by toxicity? *Regenerative Medicine*, 15(3): 1463-1491. [10.2217/rme-2019-0145](https://doi.org/10.2217/rme-2019-0145).
- Balasubramanian, B., Liu, W., Karthika, P. & Park, S.** 2021. The epic of in vitro meat production - a fiction into reality. *Foods*, 10(6). [dx.doi.org/10.3390/foods10061395](https://doi.org/10.3390/foods10061395).
- BBC News.** 2013. *World's first lab-grown burger is eaten in London*. www.bbc.com/news/science-environment-23576143
- Ben-Arye, T. & Levenberg, S.** 2019. Tissue Engineering for Clean Meat Production. *Frontiers in Sustainable Food Systems*, 3. [10.3389/fsufs.2019.00046](https://doi.org/10.3389/fsufs.2019.00046).
- Best, B.P.** 2015. Cryoprotectant toxicity: facts, issues, and questions. *Rejuvenation research*, 18(5), 422-436. [10.1089/rej.2014.1656](https://doi.org/10.1089/rej.2014.1656).
- Bhat, Z.F., Morton, J. D., Mason, S.L., Bekhit, A.E. A. & Bhat, H.F.** 2019. Technological, regulatory, and ethical aspects of in vitro meat: a future slaughter-free harvest. *Comprehensive Reviews in Food Science and Food Safety*, 18(4): 1192-1208. [dx.doi.org/10.1111/1541-4337.12473](https://doi.org/10.1111/1541-4337.12473).
- Bhat, Z.F., Sunil, K. & Hina, F.** 2015. In vitro meat production: challenges and benefits over conventional meat production. (Special Focus: Discussions on artificial meat.). *Journal of Integrative Agriculture*, 14(2): 241–248. [dx.doi.org/10.1016/S2095-3119\(14\)60887-X](https://doi.org/10.1016/S2095-3119(14)60887-X).
- Billingham, T.** 2013. Is 'shmeat' the answer? In vitro meat could be the future of food. *Gulf News*. <https://gulfnews.com/going-out/is-shmeat-the-answer-in-vitro-meat-could-be-the-future-of-food-1.1176127>

- Böcker, A., & Hanf, C.H.** 2000. "Confidence lost and - partially - regained: consumer response to food scares", *Journal of Economic Behavior & Organization*, 43, 471-85. [https://doi.org/10.1016/S2095-3119\(19\)62589-X](https://doi.org/10.1016/S2095-3119(19)62589-X)
- Bodiou, V., Moutsatsou, P. & Post, M.J.** 2020. Microcarriers for Upscaling Cultured Meat Production. *Frontiers in Nutrition*, 7. 10.3389/fnut.2020.00010.
- Boereboom, A., Sheikh, M., Islam, T., Achirimbi, E., & F. Vriesekoop.** 2022. Brits and British Muslims and their perceptions of cultured meat: How big is their willingness to purchase? *Food Frontiers*. n/a:1–12. 10.1002/fft2.165.
- Bomkamp, C., Skaalure, S.C., Fernando, G. F., Ben-Arye, T., Swartz, E. W. & Specht, E.A.** 2022. Scaffolding Biomaterials for 3D Cultivated Meat: Prospects and Challenges. *Advanced Science*, 9(3): 2102908. <https://doi.org/10.1002/advs.202102908>
- Bord, R.J., & O'Connor, R.E.,** 1990. Risk communication, knowledge, and attitudes: Explaining reactions to a technology perceived as risky. *Risk analysis*, 10(4), 499-506. <https://doi.org/10.1111/j.1539-6924.1990.tb00535.x>
- Brown S.** 2009. The new deficit model. *Nature nanotechnology*, 4, 609-611. <https://doi.org/10.1038/nnano.2009.278>
- Bruner, J.** 1985. Chapter VI: Narrative and Paradigmatic Modes of Thought. *Teachers College Record*, 86(6), 97-115. <https://doi.org/10.1177/0161468185086006>
- Bryant, C.J. & Barnett, J. C.** 2019. What's in a name? Consumer perceptions of in vitro meat under different names. *Appetite*, 137: 104-113. [dx.doi.org/10.1016/j.appet.2019.02.021](https://doi.org/10.1016/j.appet.2019.02.021).
- Bryant, C. & Krelling, F.** 2021. Alternative Proteins in Brazil: Nomenclature for Plant Based & Cultured Meat. Sao Paulo: Good Food Institute Brazil. <https://gfi.org.br/wp-content/uploads/2021/03/Nomenclature-Report.pdf>
- Bryant, C., Szejda, K., Parekh, N., Deshpande, V. & Tse B.** 2019. A Survey of Consumer Perceptions of Plant-Based and Clean Meat in the USA, India, and China. *Frontiers in Sustainable Food Systems*, 3: 11. <https://dx.doi.org/10.3389/fsufs.2019.00011>
- Bugnagel, E.** 2022. *Impacts of Perceived Food Naturalness on Consumer Behavior and Acceptance of Eco-Innovations*. Available from: <https://opus.hs-furtwangen.de/frontdoor/index/index/docId/8526>
- Byrne, B.** 2021. *State of the Industry Report: Cultivated Meat and Seafood*. Washington DC: The Good Food Institute. <https://gfi.org/resource/cultivated-meat-eggs-and-dairy-state-of-the-industry-report>
- CAIC (Cellular Agriculture Institute of the Commons).** 2021. *The Results of the Survey on Japanese Attitudes toward Cellular Agriculture and Cell-Cultured Meat in 2020*. Tokyo: Cellular Agriculture Institute of the Commons. www.cellagri.org/english/survey-result
- Canada Food and Drug Administration.** 2021. Food and Drug Regulations. In: Justice, M. o. (ed.). C.R.C., c. 870
- Carrington, D.P.** 2020. No-kill, lab-grown meat to go on sale for first time. *The Guardian*. Cited 23 August 2022. www.theguardian.com/environment/2020/dec/02/no-kill-lab-grown-meat-to-go-on-sale-for-first-time
- Cellular Agriculture Canada.** 2021. Cellular agriculture & the Canadian regulatory framework. <https://static1.squarespace.com/static/5d2bab7b430eb50001e6b381/t/61a8cd9afdda0b5d24805fe0/1638452642351/Cellular+Agriculture+%26+The+Canadian+Regulatory+Framework.pdf>
- Central Bureau of Statistics.** 2021. Population by Religion. *Population, Statistical Abstract of Israel*, No.72. Israel. https://www.cbs.gov.il/he/publications/doclib/2021/2.shnatonpopulation/st02_02.pdf
- Charette, P., Hooker, N.H., & Stanton, J.L.** 2015. Framing and naming: A process to define a novel food category. *Food Quality and Preference*, 40, 147-151.
- Chriki, S., Ellies-Oury, M.P., Fournier, D., Liu, J., & Hocquette, J.F.** 2020. Analysis of scientific and press articles related to cultured meat for a better understanding of its perception. *Frontiers in Psychology*, 11, 1845. <https://doi.org/10.3389/fpsyg.2020.01845>
- Chriki, S., & Hocquette, J.F.** 2020. The myth of cultured meat: a review. *Frontiers in nutrition*, 7. 10.3389/fnut.2020.00007. <https://doi.org/10.3389/fnut.2020.00007>
- Chriki, S., Payet, V., Pflanzner, S.B., Ellies-Oury, M.P., Liu, J., Hocquette, E., Rezende-de-Souza, J.H. and Hocquette, J.F.** 2021. Brazilian Consumers' Attitudes towards So-Called "Cell-Based Meat." *Foods*. 10:2588. 10.3390/foods10112588.

- Choi, K.H., Yoon, J.W., Kim, M., Lee, H.J., Jeong, J., Ryu, M., Jo, C. et al.** 2021. Muscle stem cell isolation and in vitro culture for meat production: A methodological review. *Comprehensive Reviews in Food Science and Food Safety*, 20(1): 10.1111/1541-4337.12661
- Chong, M., Leung, A.K.Y. & Lua, V.** 2022. A cross-country investigation of social image motivation and acceptance of lab-grown meat in Singapore and the United States. *Appetite*, 173, 105990. doi.org/10.1016/J.APPET.2022.105990
- CIRS.** 2021. *The Similarities between the Registration of New Food Raw Materials (Novel Foods) and New Food Additives in China (12 November 2021)*. Huangzhou: CIRS. <https://www.cirs-group.com/en/food/the-similarities-between-the-registration-of-new-food-raw-materials-novel-foods-and-new-food-additives-in-china>
- Codex Alimentarius.** 2008. Guideline for the Conduct of Food Safety Assessment of Foods derived from Recombinant-DNA Animals (CAC/GL 68-2008). Codex Alimentarius Commission, Joint FAO/WHO Food Standards Program, Food and Agriculture Organization, World Health Organization, Rome and Geneva. http://www.codexalimentarius.net/download/standards/11023/CXG_068e.pdf
- Codex Alimentarius** 2018. *General Standard for The Labelling of Prepackaged Foods*. Rome: Food and Agriculture Organization of the United Nations. www.fao.org/fao-who-codexalimentarius/sh-proxy/es/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252Fstandards%252FCXS%2B1-1985%252FCXS_001e.pdf
- Costa, M.** 2022. Carne de laboratório é igual à carne real? Pesquisadora do Cefet-MG explica. *Estado do Minas*, 19 January 2022 www.em.com.br/app/noticia/tecnologia/2022/01/19/interna_tecnologia,1338760/carne-de-laboratorio-e-igual-a-carne-real-pesquisadora-do-cefet-mg-explica.shtml
- Covello, V.T.** 2003. Best practices in public health risk and crisis communication. *J Health Commun* 8(sup1):5-8. <https://doi.org/10.1080/713851971>
- Craik F.I.M & Lockhart R.S.** 1972. Levels of processing: *A framework for memory research*. *Journal of Verbal Learning and Verbal Behavior*, Volume 11, Issue 6, Pages 671-684, ISSN 0022-5371, [https://doi.org/10.1016/S0022-5371\(72\)80001-X](https://doi.org/10.1016/S0022-5371(72)80001-X).
- Dahlstrom, M.F.** 2014. Using narratives and storytelling to communicate science with nonexpert audiences. *Proceedings of the National Academy of Sciences*. 111:13614-20. 10.1073/pnas.1320645111
- Davies, M.** 2016. *Corpus of News on the Web (NOW)*. <https://www.english-corpora.org/now>
- de Bruin, B.W. & Bostrom A.** 2013. Assessing what to address in science communication. *Proceedings of the National Academy of Sciences*. 10.1073/pnas.1212729110.
- Di Bella, C., Traina, A., Giosuè, C., Carpintieri, D., Lo Dico, G.M., Bellante, A., Del Core, M., Falco, F., Gherardi, S., Uccello, M.M., Ferrantelli, V.** 2020. Heavy Metals and PAHs in Meat, Milk, and Seafood From Augusta Area (Southern Italy): Contamination Levels, Dietary Intake, and Human Exposure Assessment. *Front Public Health*. 10.3389/fpubh.2020.00273. PMID: 32733834; PMCID: PMC7359620.
- Dickson, D.C.M.** 2005. *Insurance Risk and Ruin*. Cambridge University Press (CUP). ISBN 0-521-846404. *ASTIN Bulletin: The Journal of the IAA*, 35(2), 487-488. Cambridge University Press.
- Ding, S., Swennen, G.N.M., Messmer, T., Gagliardi, M., Molin, D.G.M., Li, C., Zhou, G. & Post, M.J.** 2018. Maintaining bovine satellite cells stemness through p38 pathway. *Scientific Reports*, 8, 10808. <https://doi.org/10.1038/s41598-018-28746-7>
- Djialov, M., Knezic, T., Podunavac, I., Zivojevic, K., Radonic, V., Knezevic, N. Z., Bobrinetskiy, I. et al.** 2021. Cultivating multidisciplinary: manufacturing and sensing challenges in cultured meat production. *Biology*, 10(3). dx.doi.org/10.3390/biology10030204.
- Duit, R.** 1991. On the role of analogies and metaphors in learning science. *Science education*, 75(6), 649-672.
- Eibl, R., Senn, Y., Gubser, G., Jossen, V., van den Bos, C. & Eibl, D.** 2021. Cellular Agriculture: Opportunities and Challenges. In Doyle, M. & McClements, D. J., eds. *Annual Review of Food Science and Technology*, Vol 12, 2021, pp. 51-73. Available: <Go to ISI>://WOS:000637940300005 <https://www.annualreviews.org/doi/pdf/10.1146/annurev-food-063020-123940>.
- Epley, N., & Gilovich, T.** 2016. The mechanics of motivated reasoning. *Journal of Economic perspectives*, 30(3), 133-40.
- Ettinger, D.J. and Li, J.** 2021. Japan is Contemplating the Future of Cell-based Meats. *Martindale*. (3 September 2021). https://www.martindale.com/legal-news/article_keller-and-heckman-llp_2550214.htm

- European Food Safety Authority (EFSA) Panel on Dietetic Products and Allergies. Turck, D., Bresson, J.-L., Burlingame, B., Dean, T., Fairweather-Tait, S., Heinonen, M., Hirsch-Ernst, K. I., et al.** 2016. Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (European Union) 2015/2283. *EFSA Journal*, 14(11): e04594. <https://doi.org/10.2903/j.efsa.2016.4594>.
- European Medicines Agency (EMA).** 1998. Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products.: CPMP/ICH/294/95 https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-d-derivation-characterisation-cell-substrates-used-production-biotechnological/biological-products-step-5_en.pdf
- European Parliament.** 2018. Answer given by Mr Andriukaitis on behalf of the European Commission. Question reference: E-004200/2018. Brussels and Strasbourg: European Parliament https://www.europarl.europa.eu/doceo/document/E-8-2018-004200-ASW_EN.html
- European Parliament.** 2019. Answer given by Mr Andriukaitis on behalf of the European Commission. Question reference: E-001992/2019. Brussels and Strasbourg: European Parliament https://www.europarl.europa.eu/doceo/document/E-8-2019-001992-ASW_EN.html
- European Union.** 2003. Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed. *In: Union, E. P. a. t. C. o. t. E. (ed.). 1829/2003* <https://eur-lex.europa.eu/eli/reg/2003/1829/oj>
- European Union.** 2015. Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 (Text with EEA relevance). *In: Union, E. P. a. t. C. o. t. E. (ed.). 1-22.2015/2283* <https://eur-lex.europa.eu/eli/reg/2015/2283/oj>
- European Union.** 2023. Novel food catalogue. 09 March 2023. https://food.ec.europa.eu/safety/novel-food/novel-food-catalogue_en
- FAO (Food and Agriculture Organization of the United Nations).** 2009. *GM food safety assessment tools for trainers*. Rome: <https://www.fao.org/3/i0110e/i0110e.pdf>
- FAO.** 2018. *World Livestock: Transforming the Livestock Sector through the Sustainable Development Goals*. Rome: Food and Agriculture Organization of the United Nations. www.fao.org/3/CA1201EN/ca1201en.pdf
- FAO.** 2019. *In brief. Five Practical Actions towards Resilient, Low-Carbon Livestock Systems*. Rome: Food and Agriculture Organization of the United Nations. www.fao.org/3/ca7089en/ca7089en.pdf
- FAO.** 2021. *Food Labelling*. Rome: Food and Agriculture Organization of the United Nations. www.fao.org/food-labelling/en
- FAO.** 2022. *Thinking about the future of food safety - A foresight report*. Rome: <https://www.fao.org/3/cb8667en/cb8667en.pdf>
- FAO (Food and Agriculture Organization of the United Nations)/WHO (World Health Organization).** 2014. Multicriteria-based ranking for risk management of food-borne parasites. Rome.302.No. 23.
- FAO/WHO.** 2016. Risk Communication Applied to Food Safety Handbook. (Food Safety and Quality Series, Volume 2). Rome: Food and Agriculture Organization of the United Nations. ISBN 978 92 4 154944 8 (WHO); ISBN 978-92-5-109313-9 (FAO). <https://www.fao.org/publications/card/en/c/15863E/>
- FAO/WHO.** 2021. Codex Alimentarius 2021. https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-701-44%252FWorking%252BDocuments%252Fcac44_15.Add.1e.pdf
- FAO/WHO.** 2022. Codex Alimentarius 2022. https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-702-82%252FWD%252FEx82_04e.pdf
- Faustman, C.D., Hamernik, D., Looper, M. & Zinn, A.** 2020. Cell-based meat: the need to assess holistically. *Journal of Animal Science*. 10.1093/jas/skaa177

- FDA (Food and Drug Administration).** 2010. Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications: FDA-2006-D-0223 <https://www.fda.gov/food/domestic-interagency-agreements-food/formal-agreement-between-fda-and-usda-regarding-oversight-human-food-produced-using-animal-cell>
- FDA.** 2019. Formal Agreement Between FDA and USDA Regarding Oversight of Human Food Produced Using Animal Cell Technology Derived from Cell Lines of USDA-amenable Species. *In*: FDA (ed.). <https://www.fda.gov/food/domestic-interagency-agreements-food/formal-agreement-between-fda-and-usda-regarding-oversight-human-food-produced-using-animal-cell>
- FDA.** 2020. Labeling of foods comprised of or containing cultured seafood cells; Request for information. *Federal Register*, 85(195): 63277-63280.
- FDA.** 2020. FDA Seeks Input on Labeling of Food Made with Cultured Seafood Cells. <https://www.fda.gov/food/cfsan-constituent-updates/fda-seeks-input-labeling-food-made-cultured-seafood-cells>
- FDA.** 2023. Recently Published GRAS Notices and FDA Letters. 9 March 2023. <https://www.fda.gov/food/gras-notice-inventory/recently-published-gras-notices-and-fda-letters>
- FDA.** 2023a. Current Animal Food GRAS Notices Inventory. 17 February 2023. <https://www.fda.gov/animal-veterinary/generally-recognized-safe-gras-notification-program/current-animal-food-gras-notices-inventory>
- Fernandez, R.D., Yoshimizu, M., Ezura, Y. & Takahisa, K.** 1993. Comparative Growth Response of Fish Cell Lines in Different Media, Temperatures, and Sodium Chloride Concentrations. *Fish Pathology*, 28(1): 27–34. 10.3147/jsfp.28.27.
- Ferrer, B.** 2021. Asian and US consumers are prepared to ride the next wave of alternative seafood, GFI highlights. Food Ingredients Global Insights (30 August 2022). <https://www.foodingredientsfirst.com/news/asian-and-us-consumers-are-prepared-to-ride-the-next-wave-of-alternative-seafood-gfi-highlights.html>
- Feyen, D. A. M., van den Akker, F., Noort, W., Chamuleau, S. A. J., Doevendans, P. A. & Sluijter, J. P. G.** 2016. Isolation of Pig Bone Marrow-Derived Mesenchymal Stem Cells. *In* Gneccchi, M., ed. *Mesenchymal Stem Cells: Methods and Protocols*, pp. 225–232. New York, NY, Springer New York. https://doi.org/10.1007/978-1-4939-3584-0_12
- Fischer, A.R., & Frewer, L.J.** 2009. Consumer familiarity with foods and the perception of risks and benefits. *Food Quality and Preference*, 20(8), 576-585. <https://doi.org/10.1016/j.foodqual.2009.06.008>
- Fischhoff, B., Brewer, N.T., Downs J.S., & United States.** 2011. Communicating risks and benefits : an evidence-based user's guide. U.S. Dept. of Health and Human Services Food and Drug Administration. Retrieved February 2, 2023, from <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm268078.htm>.
- Fish, K.D., Rubio, N. R., Stout, A.J., Yuen, J. S. K. & Kaplan, D.L.** 2020. Prospects and challenges for cell-cultured fat as a novel food ingredient. *Trends in Food Science & Technology*, 98: 53–67. [dx.doi.org/10.1016/j.tifs.2020.02.005](https://doi.org/10.1016/j.tifs.2020.02.005).
- FMI and Label Insight.** 2020. Transparency trends: Omnichannel grocery shopping from the consumer perspective. 39 pgs. Available from: <https://www.fmi.org/forms/store/ProductFormPublic/transparency-trends-omnichannel-grocery-shopping-from-the-consumer-perspective>
- Forte Maiolino Molento, C., de Paula Soares Valente, J., Sucha Heidemann, M. & Glufke Reis, G.** 2021. Intenção de consumo de carne celular no Brasil e por que isto é importante (Chapter 9). *In*: Palhares, J.C.P. (Ed.), *Produção Animal e Recursos Hídricos*. Brasília: EMBRAPA, pp. 297-323. www.embrapa.br/busca-de-publicacoes/-/publicacao/1048070/producao-animal-e-recursos-hidricos
- FSANZ (Food Standards Australia New Zealand).** 2017. Australia New Zealand Food Standards Code – Standard 1.5.1 – Novel foods. F2017C00324 <https://www.legislation.gov.au/Details/F2017C00324>
- FSANZ.** 2021. *Cell based meat*. FSANZ. <https://www.foodstandards.gov.au/consumer/generalissues/Pages/Cell-based-meat.aspx>.
- FSSAI (Food Safety and Standards Authority India).** 2016. Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations, 2016. *In*: India, F. S. a. S. A. o. (ed.). New Delhi: REGD. NO. D. L.-33004/99. https://www.fssai.gov.in/upload/uploadfiles/files/Nutraceuticals_Regulations.pdf

- FSSAI.** 2017. Food Safety and Standards (Approval for Non-Specified Food and Food Ingredients) Regulations, 2017. In: India, F. S. a. S. A. o. (ed.). New Delhi: F. No. 12/PA Regulation/Dir (PA)/FSSAI-2016 https://fssai.gov.in/upload/uploadfiles/files/Gazette_Notification_NonSpecified_Food_Ingredients_15_09_2017.pdf
- Fraeye, I., Kratka, M., Vandeburgh, H. & Thorrez, L.** 2020. Sensorial and Nutritional Aspects of Cultured Meat in Comparison to Traditional Meat: Much to Be Inferred. *Frontiers In Nutrition*, 7(35). <https://doi.org/10.3389/fnut.2020.00035>
- Frewer, L.J., Howard, C., Hedderley, D., Shepherd, R.** 1996, "What determines trust in information about food-related risks? Underlying psychological constructs". *Risk Analysis*, 16, 4, 473-85.
- Frewer L., Miles S., Brennan M., Kuznesof S., Ness M., Ritson C.** 2002. Public preferences for informed choice under conditions of risk uncertainty. *Public Underst Sci.* 21;11(4):363-372. 10.1088/0963-6625/11/4/304.
- Friedrich, B.** 2021. *Cultivated meat: A Growing Nomenclature Consensus*. Washington DC: Good Food Institute. <https://gfi.org/blog/cultivated-meat-a-growing-nomenclature-consensus>
- Gulf Cooperation Council and Yemen (GCC) Standardization Organization.** 2023. Standards. <https://www.gso.org.sa/en/standards/>
- GFI (Good Food Institute).** 2022. Israel State of Alternative Protein Innovation Report. Israel. <https://gfi.org.il/resources/israel-state-of-alternative-protein-innovation-report-march-2022/>
- Gomez-Luciano, C.A., de Aguiar, L.K., Vriesekoop, F. & Urbano, B.** 2019. Consumers' willingness to purchase three alternatives to meat proteins in the United Kingdom, Spain, Brazil and the Dominican Republic. *Food Quality and Preference*. 78:103732. 10.1016/j.foodqual.2019.103732.
- Graesser, A.C., León, J.A., & Otero, J.** 2002. Introduction to the Psychology of Science Text Comprehension. In J. Otero, J. A. Leon, & A. C. Graesser (Eds.), *The Psychology of Science Text Comprehension* (pp. 1-15). Mahwah, NJ: Erlbaum.
- Green, J.M., Draper, A.K. & Dowler, E.A.** 2003, "Short cuts to safety: risk and 'rules of thumb' in accounts of food choice". *Health, Risk and Society*, 5, 1, 33-52. <https://doi.org/10.1080/1369857031000065998>
- Greenhalgh T.** 2001. Storytelling should be targeted where it is known to have greatest added value. *Med Educ*. Sep;35(9):818-9. 10.1046/j.1365-2923.2001.01027.x. PMID: 11555216
- Greenwood, H.** 2022. Kosher cheeseburgers? Rabbis say lab-grown meat can be eaten with dairy. *Israel Hayom*. <https://www.israelhayom.com/2022/03/13/kosher-cheeseburgers-rabbis-say-lab-grown-meat-can-be-eaten-with-dairy/>
- Gross, T.** 2021. Novel Food Regulation in Israel – From Directive to Regulation. *GSAP* <https://www.gsap.co.il/novel-food-regulation-in-israel-from-directive-to-regulation/>
- Guan, X., Zhou, J., Du, G. & Chen, J.** 2021. Bioprocessing technology of muscle stem cells: implications for cultured meat. *Trends in Biotechnology*. 10.1016/j.tibtech.2021.11.004.
- Hadi, J. & Brightwell, G.** 2021. Safety of alternative proteins: technological, environmental and regulatory aspects of cultured meat, plant-based meat, insect protein and single-cell protein. *Foods*, 10(6). [dx.doi.org/10.3390/foods10061226](https://doi.org/10.3390/foods10061226).
- Hallman, W.K., & W.K. Hallman, II.** 2020. An empirical assessment of common or usual names to label cell-based seafood products. *Journal of Food Science*. 85:2267–2277. 10.1111/1750-3841.15351.
- Hallman, W.K. & Hallman, W. K., II.** 2021. A comparison of cell-based and cell-cultured as appropriate common or usual names to label products made from the cells of fish. *Journal of Food Science*, 86(9): 3798-3809. [dx.doi.org/10.1111/1750-3841.15860](https://doi.org/10.1111/1750-3841.15860)
- Hamdan, M.N., Post, M. J., Ramli, M.A. & Mustafa, A.R.** 2018. Cultured meat in Islamic perspective. *Journal of Religion and Health*, 57:2193–2206. <https://doi.org/10.1007/s10943-017-0403-3>
- Hamdan, M.N., Post, M., Ramli, M.A., Kamarudin, M.K., Ariffin, M.F.M. & Huri, N.M.F.Z.** 2021. Cultured Meat: Islamic and Other Religious Perspectives. *UMRAN - International Journal of Islamic and Civilizational Studies*. 8:11–19. 10.11113/umran2021.8n2.475
- Hamlin, R.P., McNeill, L. S. & Sim, J.** 2022. Food neophobia, food choice and the details of cultured meat acceptance. *Meat Science*. 194:108964. 10.1016/j.meatsci.2022.108964.

- Henchion, M., Moloney, A. P., Hyland, J., Zimmermann, J. & McCarthy, S.** 2021. Review: Trends for meat, milk and egg consumption for the next decades and the role played by livestock systems in the global production of proteins. *Animal*: 100287. 10.1016/j.animal.2021.100287
- Handral, H.K., Tay, S.H., Chan, W.W. & Choudhury, D.** 2020. 3D Printing of cultured meat products. *Critical Reviews in Food Science and Nutrition*. 10.1080/10408398.2020.1815172.
- Hanga, M.P., Ali, J., Moutsatsou, P., de la Raga, F.A., Hewitt, C. J., Nienow, A. & Wall, I.** 2020. Bioprocess development for scalable production of cultivated meat. *Biotechnology and Bioengineering*, 117(10): 3029–3039. 10.1002/bit.27469.
- Hansen, J., Sparleanu, C., Liang, Y., Büchi, J., Bansal, S., Caro, M.Á., & Staedtler, F.** 2021. Exploring cultural concepts of meat and future predictions on the timeline of cultured meat. *Future Foods*, 4, 100041. <https://doi.org/10.1016/j.fufo.2021.100041>
- Hanyu,** 2021. Commercial launch of food grade basal medium-Serum-free culture of chicken and duck liver-derived cells by CulNet. *Integrative news* (1 April 2022). <https://integrative.com/en/news/5509/>
- Harvard.** 2022. Iron. In: *Harvard T.H. Chan School of Public Health*. The Nutrition Source. Cited 17 May 2022. <https://www.hsph.harvard.edu/nutritionsource/iron/>
- Hastak, M., & Mazis, M.B., 2011.** Deception by Implication: A Typology of Truthful but Misleading Advertising and Labeling Claims. *Journal of Public Policy & Marketing*, 30(2), 157–167. <https://doi.org/10.1509/jppm.30.2.157>
- Health Canada.** 2021. Guidelines for the Safety Assessment of Novel Foods. In: Food Directorate, H. P. a. F. B., Health Canada (ed.). <https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/guidelines-safety-assessment-novel-foods-derived-plants-microorganisms/guidelines-safety-assessment-novel-foods-2006.html#shr-pg0>
- Healy, L., Young, L. & Stacey, G.N.** 2011. Stem Cell Banks: Preserving Cell Lines, Maintaining Genetic Integrity, and Advancing Research. In Schwartz, P. H. & Wesselschmidt, R. L., eds. *Human Pluripotent Stem Cells: Methods and Protocols*, pp. 15-27. Totowa, NJ, Humana Press. https://doi.org/10.1007/978-1-61779-201-4_2
- Henchion, M., Moloney, A.P., Hyland, J., Zimmermann, J. & McCarthy, S.** 2021. Review: Trends for meat, milk and egg consumption for the next decades and the role played by livestock systems in the global production of proteins. *Animal*: 100287. 10.1016/j.animal.2021.100287.
- Henson, S.** 1995. Demand-side constraints on the introduction of new food technologies: The case of food irradiation. *Food Policy*, 20(2), 111-127. [https://doi.org/10.1016/0306-9192\(95\)00020-F](https://doi.org/10.1016/0306-9192(95)00020-F)
- Hocquette, É., Liu, J., Ellies-Oury, M.P., Chriki, S. & Hocquette, J. F.** 2022. Does the future of meat in France depend on cultured muscle cells? Answers from different consumer segments. *Meat Science*. 188:108776. 10.1016/j.meatsci.2022.108776.
- Hong, T., Shin, D., Choi, J., Do, J. & Han, S.** 2021. Current issues and technical advances in cultured meat production: a review. *Food Science of Animal Resources*, 41(3): 355–372. [dx.doi.org/10.5851/kosfa.2021.e14](https://doi.org/10.5851/kosfa.2021.e14).
- Howell, E.L., Wirz, C.D., Brossard, D., Jamieson, K.H., Scheufele, D.A., Winneg, K.M., & Xenos, M.A.** 2018. National Academies of Sciences, Engineering, and Medicine report on genetically engineered crops influences public discourse. *Politics and the Life Sciences*, 37(2), 250–261. Cambridge University Press.
- Israel Ministry of Health.** 2015. Article 18 Public Health (Food) Protection Law 2015. In: Israel, Ministry of Health (ed.). Article 18 Public Health (Food) Protection Law 2015 <https://www.health.gov.il/LegislationLibrary/health-mazon01A.pdf>
- Janat, C. & Bryant, C.** 2020. *Cultured Meat in Germany: Consumer Acceptance and a Nomenclature Experiment*. Miami: Cellular Agriculture Society. <https://osf.io/dj9qx/download>
- Jewish Telegraphic Agency (JTA).** 2018. Rabbi: Lab-grown pork could be kosher for Jews to eat - with milk. *Times of Israel*. Available: <https://www.timesofisrael.com/rabbi-meat-from-cloned-pig-could-be-eaten-by-jews-with-milk/>
- Jiang H. & Luo Y.** 2018. Crafting employee trust: From authenticity, transparency to engagement. *Journal of Communication Management*, 22 (2), pp. 138-160. 10.1108/JCOM-07-2016-0055
- Johnson, B.B., & Slovic, P.** 1995. Presenting uncertainty in health risk assessment: Initial studies of its effects on risk perception and trust. *Risk Analysis*, 15(4), 485–494. <https://doi.org/10.1111/j.1539-6924.1995.tb00341.x>

- Johnson-Laird, P.N.** 2001. Mental models and deduction. *Trends in cognitive sciences*, 5(10), 434-442. [https://doi.org/10.1016/S1364-6613\(00\)01751-4](https://doi.org/10.1016/S1364-6613(00)01751-4)
- Jonas, D.A., Elmadfa, I., Engel, K.H., Heller, K.J., Kozianowski, G., König, A., Müller, D., Narbonne, J.F., Wackernagel, W., Kleiner, J.** 2001. Safety considerations of DNA in food. *Annals of Nutrition and Metabolism*. 2001;45(6):235-54. 10.1159/000046734. PMID: 11786646.
- Jones, P.W.** 1998. Testing health status ("quality of life") questionnaires for asthma and COPD. *European Respiratory Journal*, Jan. 1998, 11 (1) 5-6; DOI: 10.1183/09031936.98.11010005.
- Joo, S.T., Choi, J.S., Hur, S.J., Kim, G.D., Kim, C.J., Lee, E.Y., Bakhsh, A. et al.** 2022. A Comparative Study on the Taste Characteristics of Satellite Cell Cultured Meat Derived from Chicken and Cattle Muscles. *Food Science of Animal Resources*, 42(1): 175–185. 10.5851/kosfa.2021.e72.
- Kahan, D.M.** 2012. Ideology, motivated reasoning, and cognitive reflection: An experimental study. *Judgment and Decision making*, 8, 407-24.
- Kahneman, D.** 2013. The marvels and the flaws of intuitive thinking. *Thinking: The new science of decision-making, problem-solving, and prediction*. New York: Harper Collins.
- Kamalapuram, S.K., Handral, H. & Choudhury, D.** 2021. Cultured Meat Prospects for a Billion! *Foods* (Basel, Switzerland), 10(12): 2922. 10.3390/foods10122922.
- Kenigsberg, J.A. & Zivotofsky, A.Z.** 2020. A Jewish Religious Perspective on Cellular Agriculture. *Frontiers in Sustainable Food Systems*, 3(128). 10.3389/fsufs.2019.00128.
- Krings, V. C., Dhont, K. & Hodson, G.** 2022. Food technology neophobia as a psychological barrier to clean meat acceptance. *Food Quality and Preference*, 96. 10.1016/j.foodqual.2021.104409.
- Krone, A.** 2022. Religion, Animals, and Technology. *Religions*. 13. doi:10.3390/rel13050456. Available from: <https://dspace.allegheeny.edu/handle/10456/55395>
- Kunda, Z.** 1990. The case for motivated reasoning. *Psychological bulletin*, 108(3), 480.
- Kwon, J.H., Kim, J.W., Pham, T.D., Tarafdar, A., Hong, S., Chun, S.H., Lee, S.H., Kang, D.Y., Kim, J.Y., Kim, S.B. & Jung, J.** 2020. Microplastics in food: a review on analytical methods and challenges. *International Journal of Environmental Research and Public Health*, 17(18), 6710. 10.3390/ijerph17186710
- Lamb, C.** 2018. Allergy fears and transparency among issues at latest USDA/FDA meat-ing. *The Spoon* (25 October 2018). <https://thespoon.tech/allergy-fears-and-transparency-among-issues-at-latest-usda-fda-meat-ing>
- Lee, D.Y., Lee, S.Y., Yun, S.H., Jeong, J.W., Kim, J.H., Kim, H.W., Choi, J.S., Kim, G.D., Joo, S.T., Choi, I., Hur, S.J.** 2022. Review of the current research on fetal bovine serum and the development of cultured meat. *Food Science of Animal Resources*, 42(5), 775-799. 10.5851/kosfa.2022.e46.
- Li, J., Settivari, R.S., & LeBaron, M.J.** 2019. Genetic instability of in vitro cell lines: Implications for genetic toxicity testing. *Environmental and Molecular Mutagenesis*, 60(6), 559-562. 10.1002/em.22280.
- Li, X., Zhang, G., Zhao, X., Zhou, J., Du, G. & Chen, J.** 2020. A conceptual air-lift reactor design for large scale animal cell cultivation in the context of in vitro meat production. *Chemical Engineering Science*, 211. 10.1016/j.ces.2019.115269.
- Liu, J., Hocquette, É., Ellies-Oury, M.P., Chriki, S. & Hocquette, J.F.** 2021. Chinese Consumers' Attitudes and Potential Acceptance toward Artificial Meat. *Foods*. 10:353. 10.3390/foods10020353.
- Liu, X., Zhang, T., Wang, R., Shi, P., Pan, B. & Pang, X.** 2019. Insulin-Transferrin-Selenium as a Novel Serum-free Media Supplement for the Culture of Human Amnion Mesenchymal Stem Cells. *Annals of Clinical and Laboratory Science*, 49(1), 63–71.
- Lobb, A.** 2005. Consumer trust, risk and food safety: A review. *Food Economics-Acta Agriculturae Scandinavica*, Section C, 2(1), 3-12.
- Lu, T., Xiong, H., Wang, K., Wang, S., Ma, Y. & Guan, W.** 2014. Isolation and characterization of adipose-derived mesenchymal stem cells (ADSCs) from cattle. *Appl Biochem Biotechnol*, 174(2): 719–28. 10.1007/s12010-014-1128-3.
- Lupia A.** 2013. Communicating science in politicized environments. *Proc Natl Acad Sci U S A*. Aug 20;110 Suppl 3(Suppl 3):14048-54. 10.1073/pnas.1212726110.

- Mancini, M.C., & Antonioli, F.** 2020. To What Extent Are Consumers' Perception and Acceptance of Alternative Meat Production Systems Affected by Information? The Case of Cultured Meat. *Animals (Basel)*, 10. doi:10.3390/ani10040656. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7223365/>
- Martinez-Conde, S., & Macknik, S.L.** 2017. Finding the plot in science storytelling in hopes of enhancing science communication. *Proceedings of the National Academy of Sciences*, 114(31), 8127-8129. <https://doi.org/10.1073/pnas.1711790114>
- Mattick, C.S.** 2018. Cellular agriculture: The coming revolution in food production. *Bulletin of the Atomic Scientists*, 74(1): 32-35. 10.1080/00963402.2017.1413059.
- Maynard, A. & Scheufele, D.A.** 2016. What does research say about how to effectively communicate about science? The Conversation; <http://theconversation.com/what-does-research-say-about-how-to-effectively-communicate-about-science-70244>.
- McMakin, A.H., & Lundgren, R.E.** 2018. Risk communication: A handbook for communicating environmental, safety, and health risks. John Wiley & Sons.
- Ministry of Public Health (MOPH).** 2015. *Qatar Dietary Guidelines* [Ebook] (1st ed., pp. 8-26). Doha. Cited 22 May 2022. <https://hukoomi.gov.qa/en/service/qatar-dietary-guidelines-portal>
- Mohorčič, J., & Reese, J.** 2019. Cell-cultured meat: Lessons from GMO adoption and resistance. *Appetite*, 143, 104408.
- More, S.J., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T.I., Hernández-Jerez, Bennekou, S.H., Koutsoumanis, K.P. et al.** 2019. Guidance on the use of the Threshold of Toxicological Concern Approach in Food Safety Assessment. *EFSA Journal*, 17(6), e05708. doi.org/10.2903/J.EFSA.2019.5708
- Morgan, M.G., Fischhoff, B., Bostrom, A. & Atman, C.J.** 2002. *Risk communication: A mental models approach*. Cambridge University Press.
- Møretrø, T. & Langsrud, S.** 2017. Residential Bacteria on Surfaces in the Food Industry and Their Implications for Food Safety and Quality. *Comprehensive Reviews in Food Science and Food Safety*, 16(5): 1022-1041. <https://doi.org/10.1111/1541-4337.12283>
- Miller, R.K.** 2020. A 2020 synopsis of the cell-cultured animal industry. *Animal Frontiers*, 10(4): 64–72. dx.doi.org/10.1093/af/vfaa031.
- Munda, G.** 2008. Social Multi-Criteria Evaluation for a Sustainable Economy. Springer Berlin, Heidelberg Ed., <https://doi.org/10.1007/978-3-540-73703-2>.
- National Academies of Sciences, Engineering, and Medicine.** 2016. Genetically engineered crops: experiences and prospects. National Academies Press.
- National Health and Family Planning Commission of China (NHFPC).** 2013. Administrative Measures for Safety Review of New Food Materials. In: Commission, NHFPC (ed.). <http://www.lawinfochina.com/display.aspx?lib=law&id=15358&CGid>
- National Research Council, Singer, S.R., Nielsen, N.R., & Schweingruber, H.A.** 2012. Discipline-based education research: Understanding and improving learning in undergraduate science and engineering (pp. 6-11). Washington, DC: National Academies Press.
- Ng, J. & Ramli, D.** 2021. Temasek defends faux-meat valuations in US\$1 trillion market space. *Yahoo*. Retrieved from <https://sg.finance.yahoo.com/news/temasek-defends-faux-meat-valuations-in-us-1-trillion-market-space-020346375.html>
- Ng, S. & Kurisawa, M.** 2021. Integrating biomaterials and food biopolymers for cultured meat production. *Acta Biomaterialia*, 124: 108–129. 10.1016/j.actbio.2021.01.017.
- Nikfarjam, L. & Farzaneh, P.** 2012. Prevention and detection of Mycoplasma contamination in cell culture. *Cell journal*, 13(4): 203–212.
- OECD (Organization for Economic Co-operation and Development) & FAO.** 2021. *OECD-FAO Agricultural Outlook 2021-2030*. Paris: Organisation for Economic Cooperation and Development. https://www.oecd-ilibrary.org/agriculture-and-food/oecd-fao-agricultural-outlook-2021-2030_19428846-en

- OECD.** 2022. Draft Principles of Good Practice for Public Communication Responses to Mis- and Disinformation. Available at <https://www.oecd.org/gov/open-government/public-consultation-draft-principles-good-practice-public-communication-responses-to-mis-disinformation.pdf>
- Olson, J. M., Ameer, M. A., & Goyal, A.** 2021. Vitamin A toxicity. In *StatPearls* [Internet]. StatPearls Publishing.
- O'Neill, E. N., Cosenza, Z. A., Baar, K. & Block, D.E.** 2021. Considerations for the development of cost-effective cell culture media for cultivated meat production. *Comprehensive Reviews in Food Science and Food Safety*, 20(1): 686–709. 10.1111/1541-4337.12678.
- Ong, K.J., Johnston, J., Datar, I., Sewalt, V., Holmes, D. & Shatkin, J.A.** 2021. Food safety considerations and research priorities for the cultured meat and seafood industry. *Comprehensive Reviews in Food Science and Food Safety*, 20(6): 5421–5448. <https://doi.org/10.1111/1541-4337.12853>.
- Ong, S., Choudhury, D. & Naing, M.W.** 2020. Cell-based meat: Current ambiguities with nomenclature. *Trends in Food Science and Technology*, 102: 223-231. 10.1016/j.tifs.2020.02.010.
- Onwezen, M., Bouwman, E., Reinders, M. & Dagevos, H.** 2021. A systematic review on consumer acceptance of alternative proteins: Pulses, algae, insects, plant-based meat alternatives, and cultured meat. *Appetite*, 159, 105058. <https://doi.org/10.1016/j.appet.2020.105058>
- Orellana, N., Sanchez, E., Benavente, D., Prieto, P., Enrione, J. & Acevedo, C.A.** 2020. A new edible film to produce in vitro meat. *Foods*, 9(2). [dx.doi.org/10.3390/foods9020185](https://doi.org/10.3390/foods9020185).
- Pandurangan, M. & Kim, D.** 2015. A novel approach for in vitro meat production. *Applied Microbiology and Biotechnology*, 99(13): 5391–5395. [dx.doi.org/10.1007/s00253-015-6671-5](https://doi.org/10.1007/s00253-015-6671-5).
- Park, J., Choi, J.K., Choi, D.H., Lee, K.E. & Park, Y.S.** 2022. Optimization of skeletal muscle-derived fibroblast isolation and purification without the preplating method. *Cell and Tissue Banking*. 10.1007/s10561-021-09989-7.
- Park, S., Jung, S., Heo, J., Koh, W.G., Lee, S. & Hong, J.** 2021. Chitosan/Cellulose-Based Porous Nanofilm Delivering C-Phycocyanin: A Novel Platform for the Production of Cost-Effective Cultured Meat. *ACS Applied Materials and Interfaces*, 13(27): 32193–32204. 10.1021/acsami.1c07385.
- Pliner, P. & Hobden, K.** 1992. Development of a scale to measure the trait of food neophobia in humans. *Appetite*. 19:105–120. [doi:10.1016/0195-6663\(92\)90014-W](https://doi.org/10.1016/0195-6663(92)90014-W).
- Possidonio, C., Prada, M., Graca, J. & Piazza, J.** 2021. Consumer perceptions of conventional and alternative protein sources: a mixed-methods approach with meal and product framing. *Appetite*, 156(44). [dx.doi.org/10.1016/j.appet.2020.104860](https://doi.org/10.1016/j.appet.2020.104860).
- Post, M.J., Levenberg, S., Kaplan, D.L., Genovese, N., Fu, J., Bryant, C.J., Negowetti, N. et al.** 2020. Scientific, sustainability and regulatory challenges of cultured meat. *Nature Food*, 1(7): 403–415. 10.1038/s43016-020-0112-z.
- Quevedo-Silva, F., & Pereira J.B.** 2022. Factors Affecting Consumers' Cultivated Meat Purchase Intentions. *Sustainability*. 14:12501. 10.3390/su141912501.
- Ramani, S., Ko, D., Kim, B., Cho, C., Kim, W., Jo, C., Lee, C. et al.** 2021. Technical requirements for cultured meat production: a review. *Journal of Animal Science and Technology*, 63(4): 681–692. [dx.doi.org/10.5187/jast.2021.e45](https://doi.org/10.5187/jast.2021.e45).
- Rawlins B.** 2008. Measuring the relationship between organizational transparency and employee trust. *Public Relations Journal*, 2 (2), pp. 1-21
- Reiss, J., Robertson, S. & Suzuki, M.** 2021. Cell sources for cultivated meat: applications and considerations throughout the production workflow. *International Journal of Molecular Sciences*, 22(14). [dx.doi.org/10.3390/ijms22147513](https://doi.org/10.3390/ijms22147513).
- Renn, O. & Levine, D.** 1991. Credibility and trust in risk communication. In: Kasperson, R.E., Stallen, P.J.M. (eds) *Communicating Risks to the Public. Technology, Risk, and Society*, vol 4. Springer, Dordrecht. https://doi.org/10.1007/978-94-009-1952-5_10
- Rischer, H., Szilvay, G.R. & Oksman-Caldentey, K.M.** 2020. Cellular agriculture – industrial biotechnology for food and materials. *Current Opinion in Biotechnology*, 61: 128-134. <https://doi.org/10.1016/j.copbio.2019.12.003>.

- Rodrigues, A.L., Rodrigues, C.A.V., Gomes, A.R., Vieira, S.F., Badenes, S.M., Diogo, M.M. & Cabral, J.M.S.** 2019. Dissolvable Microcarriers Allow Scalable Expansion And Harvesting Of Human Induced Pluripotent Stem Cells Under Xeno-Free Conditions. *Biotechnology Journal*, 14(4): 1800461. <https://doi.org/10.1002/biot.201800461>.
- Rogers, E.M.** 2003. Diffusion of innovations (5th ed.). New York: Free Press.
- Román, S., Sánchez-Siles, L.M., and Siegrist, M.** 2017. The importance of food naturalness for consumers: Results of a systematic review. *Trends in Food Science & Technology*. 67:44–57. 10.1016/j.tifs.2017.06.010.
- Rubio, N., Datar, I., Stachura, D., Kaplan, D. & Krueger, K.** 2019. Cell-Based Fish: A Novel Approach to Seafood Production and an Opportunity for Cellular Agriculture. *Frontiers in Sustainable Food Systems*, 3. 10.3389/fsufs.2019.00043.
- Sampaio, R.V., Chiaratti, M.R., Santos, D.C.N., Bressan, F.F., Sangalli, J. R., Sá, A.L.A., Silva, T.V.G. et al.** 2015. Generation of bovine (*Bos indicus*) and buffalo (*Bubalus bubalis*) adipose tissue derived stem cells: isolation, characterization, and multipotentiality. *Genetics and Molecular Research*, 14(1). <https://doi.org/10.4238/2015.January.15.7>.
- Santo, R.E., Kim, B.F., Goldman, S.E., Dutkiewicz, J., Biehl, E.M.B., Bloem, M.W., Neff, R.A., Nachman, K.E.** 2020. Considering Plant-Based Meat Substitutes and Cell-Based Meats: A Public Health and Food Systems Perspective. *Frontiers in Sustainable Food Systems*. DOI=10.3389/fsufs.2020.00134
- Scolobig A. & Lilliestam, J.**, 2016. Comparing Approaches for the Integration of Stakeholder Perspectives in Environmental Decision Making. *Resources*, 5(4), 37; <https://doi.org/10.3390/resources5040037>
- Seah, J.S.H., Singh, S., Tan, L.P. & Choudhury, D.** 2022. Scaffolds for the manufacture of cultured meat. *Critical Reviews in Biotechnology*. 10.1080/07388551.2021.1931803.
- Seehafer, A. & Bartels, M.** 2019. Meat 2.0 - the regulatory environment of plant-based and cultured meat. *European Food and Feed Law Review*, 4: 323-331.
- Seon-Tea, J., Choi, J-S., Hur, S.J., Kim, G.D., Kim, C.J., Lee, E.Y., Bakhsh, A. & Hwang, Y.H.** 2022. A Comparative Study on the Taste Characteristics of Satellite Cell Cultured Meat Derived from Chicken and Cattle Muscles. *Food Science of Animal Resources*, 42(1): 175–185. <https://doi.org/10.5851/kosfa.2021.e72>
- SFA (Singapore Food Agency).** 2020. Requirements for the Safety Assessment of Novel Foods. In: Agency, S. F. (ed.).
- SFA.** 2021. Safety of Alternative Protein. In: *SFA Food Information*. Risk at a Glance. Cited 15 July 2022. www.sfa.gov.sg/food-information/risk-at-a-glance/safety-of-alternative-protein
- SFA.** 2021a. *Requirements for the Safety Assessment of Novel Foods and Novel Food Ingredients*. Singapore: Singapore Food Agency. https://www.sfa.gov.sg/docs/default-source/food-import-and-export/Requirements-on-safety-assessment-of-novel-foods_26Sep.pdf
- SFA.** 2021b. *A Growing Culture of Safe, Sustainable Meat*. Singapore: Singapore Food Agency. <https://www.sfa.gov.sg/food-for-thought/article/detail/a-growing-culture-of-safe-sustainable-meat>
- SFA.** 2023a. SFA. In: *Food Manufacturers. Setting Up Food Establishments* [online]. Singapore. [Cited 08 February 2023]. <https://www.sfa.gov.sg/food-manufacturers/setting-up-food-establishments>
- SFA.** 2023b. SFA. In: *Food Import & Export. Commercial Food Exports* [online]. Singapore. [Cited 08 February 2023]. <https://www.sfa.gov.sg/food-import-export/commercial-food-exports>
- Shahin-Shamsabadi, A. & Selvaganapathy, P.R.** 2021. Engineering Murine Adipocytes and Skeletal Muscle Cells in Meat-like Constructs Using Self-Assembled Layer-by-Layer Biofabrication: A Platform for Development of Cultivated Meat. *Cells Tissues Organs*. 10.1159/000511764.
- Shanks, D.R.** 2010. Learning: From association to cognition. *Annual review of psychology*, 61, 273-301.
- Shurpin, Y.** 2018. Is the lab-created burger kosher? *Chabad.org*. https://www.chabad.org/library/article_cdo/aid/2293219/jewish/Is-the-Lab-Created-Burger-Kosher.htm
- Siddiqui, S. A., Khan, S., Murid, M., Asif, Z., Oboturova, N.P., Nagdalian, A.A., Blinov, A.V., Ibrahim, S.A., & Jafari, S.M.** 2022. Marketing Strategies for Cultured Meat: A Review. *Applied Sciences*. 12:8795. 10.3390/app12178795.
- Siegrist, M., & Hartmann, C.** 2020a. Consumer acceptance of novel food technologies. *Nature Food*, 1(6), 343-350.
- Siegrist, M., & Hartmann, C.** 2020b. Perceived naturalness, disgust, trust and food neophobia as predictors of cultured meat acceptance in ten countries. *Appetite*. 155:104814. 10.1016/j.appet.2020.104814.

- Slovic, P.** 1999. Trust, emotion, sex, politics, and science: Surveying the risk-assessment battlefield. *Risk analysis*, 19(4), 689-701.
- Snyder, A.B., Churey, J. J. & Worobo, R.W.** 2019. Association of fungal genera from spoiled processed foods with physicochemical food properties and processing conditions. *Food Microbiology*, 83: 211–218. <https://doi.org/10.1016/j.fm.2019.05.012>.
- Soice, E. & Johnston, J.** 2021. Immortalizing Cells for Human Consumption. *International Journal of Molecular Sciences*, 22(21): 11660.
- Southey, F.** 2021. *Cultivated, cultured, or other? Making alt meat terminology appealing and transparent*. *Food Navigator*. www.foodnavigator.com/Article/2021/10/27/The-best-terminology-for-cell-based-meat-Experts-weigh-in
- Specht, E.A., Welch, D.R., Clayton, E.M.R. & Lagally, C.D.** 2018. Opportunities for applying biomedical production and manufacturing methods to the development of the clean meat industry. (Special section on scale-up and manufacturing of cell-based therapies V). *Biochemical Engineering Journal*, 132: 161–168. [dx.doi.org/10.1016/j.bej.2018.01.015](https://doi.org/10.1016/j.bej.2018.01.015).
- Stephens, N., Di Silvio, L., Dunsford, I., Ellis, M., Glencross, A. & Sexton, A.** 2018. Bringing cultured meat to market: Technical, socio-political, and regulatory challenges in cellular agriculture. *Trends in Food Science and Technology*, 78: 155-166. [10.1016/j.tifs.2018.04.010](https://doi.org/10.1016/j.tifs.2018.04.010).
- The Straits Times.** 2020. Strengthening food security with R&D. *The Straits Times*, 13 August 2020, Singapore. www.straitstimes.com/singapore/strengthening-food-security-with-rd
- Sundin, A., Andersson, K. & Watt, R.** 2018. Rethinking communication: integrating storytelling for increased stakeholder engagement in environmental evidence synthesis. *Environ Evid* 7. <https://doi.org/10.1186/s13750-018-0116-4>
- Suresh, S., & Student, C.S.I.** 2018. Friend” or “Fiend”: in vitro lab meat and how Canada might regulate its production and sale. Ottawa, ON: The Canadian Agri-Food Policy Institute. https://capi-icpa.ca/wp-content/uploads/2019/06/2018-10-23-CAPI-in-vitro-meat-technology_Paper_SureshShishira_WEB.pdf
- Swartz, E.** 2021. Cell culture media and growth factor trends in the cultivated meat industry. The Good Food Institute <https://gfi.org/wp-content/uploads/2021/11/Cultivated-meat-media-and-growth-factor-trends-2020.pdf>
- Szejda, K., Allen, M., Cull, A., Banisch, A., Stuckey, B., & Dillard, C., & Urbanovich, T.** 2019. *Meat cultivation: Embracing the science of nature*. Washington, DC: The Good Food Institute.
- Szejda, K., Bryant, C.J., Urbanovich T.** 2021. US and UK consumer adoption of cultivated meat: A segmentation study. *Foods*, 10(5): 1050. [10.3390/foods10051050](https://doi.org/10.3390/foods10051050).
- Szejda, K., & Dillard, C.** 2020. Antecedents of alternative protein adoption: A US focus group study. Research Report. Washington, DC: The Good Food Institute. <https://gfi.org/images/uploads/2020/04/April-2020-Alt-Protein-Focus-Groups-Report.pdf>
- Tan, Y., Salkhordeh, M., Schlinker, A. C., Lazarovitz, G., Wang, J., Khan, S., McIntyre, L., et al.** 2017. Utilization of a closed, automatic LOVO cell processing system to wash and concentrate large volume of mesenchymal stem cell harvest. *Cytotherapy*, 19(5): S120–S121. [10.1016/j.jcyt.2017.02.195](https://doi.org/10.1016/j.jcyt.2017.02.195).
- Tonkin, E., Henderson, J., Meyer, S.B., Coveney, J., Ward, P.R., McCullum, D., Webb, T. & Wilson, A.M.** 2020. Expectations and everyday opportunities for building trust in the food system. *British Food Journal*. <https://www.emerald.com/insight/content/doi/10.1108/BFJ-05-2020-0394/full/html>
- Treich, N.** 2021. Cultured Meat: Promises and Challenges. *Environmental and Resource Economics*, 79(1): 33-61. [10.1007/s10640-021-00551-3](https://doi.org/10.1007/s10640-021-00551-3).
- Tzohar.** 2022. *Meat produced in a laboratory from a non-meat cell*. Position Paper. Israel. <https://www.tzohar.org.il/wp-content/uploads/basar.pdf>
- USDA-FSIS (United States Department of Agriculture’s Food Safety and Inspection Service).** 2021. *Labeling of Meat or Poultry Products Comprised of or Containing Cultured Animal Cells*. 49491-49496.86
- van de Poel, I. & Robaey, Z.** 2017. Safe-by-Design: from Safety to Responsibility. *Nanoethics*, 11(3): 297–306. [10.1007/s11569-017-0301-x](https://doi.org/10.1007/s11569-017-0301-x).

- van der Valk, J., Bieback, K., Buta, C., Cochrane, B., Dirks, W.G., Fu, J., Hickman, J.J., Hohensee, C., Kolar, R., Liebsch, M., Pistollato, F., Schulz, M., Thieme, D., Weber, T., Wiest, J., Winkler, S., Gstraunthaler, G. 2018. Fetal Bovine Serum (FBS): Past - Present - Future. *ALTEX*. 2018;35(1):99-118. 10.14573/altex.1705101. Epub 2017 Aug 9. PMID: 28800376.
- Vassiliev, I. & Nottle, M. B. 2013. Isolation and Culture of Porcine Embryonic Stem Cells. In Alberio, R., ed. *Epiblast Stem Cells: Methods and Protocols*, pp. 85-95. Totowa, NJ, Humana Press. Available: https://doi.org/10.1007/978-1-62703-628-3_7
- Verzijden, K. 2021. *Singapore Cultured Meat Regulatory Approval Process Compared to EU (Food Health Legal Blog)*. Amsterdam: Axon Lawyers. <http://foodhealthlegal.eu/?p=1081>
- Vosoughi, S., Roy, D., & Aral, S. 2018. The spread of true and false news online. *Science*, 359(6380), 1146-1151.
- Webb, C., Kevern, J. 2001. Focus groups as a research method: a critique of some aspects of their use in nursing research. *Journal of Advanced Nursing* 33 (6), 798e805.
- Weger Jr, H., Castle Bell, G., Minei, E. M., & Robinson, M. C. 2014. The relative effectiveness of active listening in initial interactions. *International Journal of Listening*, 28(1), 13-31.
- Weigold, M.F. 2001. Communicating science: A review of the literature. *Science communication*, 23(2), 164-193.
- WHO (World Health Organization). 2022. Dietary and inhalation exposure to nano-and microplastic particles and potential implications for human health.
- Wiedemann, P.M., Kirsch, F., Lohmann, M., Boel, G.F., Freudenstein, F. 2022. Effects of as-if risk framing of hazards on risk perception and its rebuttal. *Regulatory Toxicology and Pharmacology*, <https://doi.org/10.1016/j.yrtph.2022.105282>.
- Wilks, M., M. Hornsey, and P. Bloom. 2021. What does it mean to say that cultured meat is unnatural? *Appetite*. 156:104960. <https://doi.org/10.1016/j.appet.2020.104960>
- Zhang, G., Zhao, X., Li, X., Du, G., Zhou, J. & Chen, J. 2020. Challenges and possibilities for bio-manufacturing cultured meat. *Trends in Food Science & Technology*, 97: 443–450. [dx.doi.org/10.1016/j.tifs.2020.01.026](https://doi.org/10.1016/j.tifs.2020.01.026).
- Zhang, L., Hu, Y., Badar, I.H., Xia, X., Kong, B. & Chen, Q. 2021. Prospects of artificial meat: Opportunities and challenges around consumer acceptance. *Trends in Food Science and Technology*, 116: 434–444. 10.1016/j.tifs.2021.07.010.
- Zidaric, T., Milojevic, M., Vajda, J., Vihar, B. & Maver, U. 2020. Cultured meat: meat industry hand in hand with biomedical production methods. *Food Engineering Reviews*, 12(4): 498–519. [dx.doi.org/10.1007/s12393-020-09253-w](https://doi.org/10.1007/s12393-020-09253-w).

Food Systems and Food Safety - Economic and Social Development
fao.org/food-safety
Food and Agriculture Organization of the United Nations
Rome, Italy

Department Of Nutrition And Food Safety
who.int/health-topics/food-safety
World Health Organization
Geneva, Switzerland

