Identification of hazards in meat products manufactured from cultured animal cells

Area of research interest: Novel and non-traditional foods, additives and processes
Project status: Completed

Identification of hazards in meat products manufactured from cultured animal cells: executive summary

Results available: No results available
Area of research interest: Novel and non-traditional foods, additives and processes
Research topics: Novel foods
DOI: https://doi.org/
Project status: Completed
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Executive summary

Culturing of animal cells was developed in the late 19th and early 20th century, when researchers worked out how to support the growth of cells in media in an ex-vivo environment (footnote 1). The technology has been used commercially in the medical products industry, notably to produce antibodies for use as new medicines and as reagents in diagnostics. Animal cell culturing has expanded into the food industry especially due to its benefit in promoting sustainability for example by freeing up global arable land used for livestock farming, with cultured meat predicted to enter the UK market in the coming year(s) and already on the market in Singapore.

With this in sight, a systematic search protocol was devised to identify hazardous concerns that will help inform the risk assessment for any future applications for authorisation to the FSA. To note, the term ‘cultured’ is now referred to as ‘cultivated’ but the report uses the former term to keep in line with the search string used for the research. This report was limited to meat products manufactured from cultured animal cells. Even though majority of these hazards cross-over to other products such as fish, there is potential to evaluate hazards associated with fish/seafood products separately in the near future.

This hazard identification considers the nature of potential hazards associated with the production of cultured animal cells; a novel technology that uses animal cells and cell culturing to produce a

substance that resembles meat thus avoiding animal rearing for meat products or aquaculture. As cultured animal cells may pose new risks this report aims to ‘scope out’ the technology to gain an understanding of it and to identify the potential risks that this may pose.

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Identification of hazards in meat products manufactured from cultured animal cells: Glossary

Term	Definition
Antibiotics	medications that destroy or slow down the growth of bacteria; used to treat or prevent types of bacterial infection
Aseptic	to prevent infection caused by harmful bacteria, viruses or other microbes; sterilized
Biocompatible material	a material that is not harmful or toxic to living tissue often referred to as a biomaterial. For cell culture, the biomaterial is usually made into a scaffold; a support structure to facilitate cell culture
Biopsey	medical test involving extraction of sample cells/tissue to examine the presence/extent of disease
Bioreactor	device/system facilitating a biologically active environment
Cell bank	facility that stores cells of specific genome for future use in a product or medicinal needs
Cell culturing	process by which cells are grown under controlled conditions mostly outside their natural environment
Cell line	a defined population of cells that can be maintained in culture for an extended period of time
Confluence	when the adherent cells cover the adherent surface of the culture vessel
Cultured meat	also known as cultivated meat or lab grown meat, this is meat (and its products) that is produced by culturing animal cells in vitro (outside of their normal environment)
Differentiate	transition of a cell from an immature state to a mature state with more specialized function
In-vivo	work that is performed within a whole living organism such as clinical trials
In-vitro	work that is performed outside a living organism for example, in a test tube (the opposite of in vitro)
Fungisides	pesticides used to kill or prevent the growth of fungi (and their spores)
Genetically engineered	a lab-based technology to modify or manipulate the genetic make-up of an organism
HACCP	Hazard analysis and critical control points; a global food management system based on 7 principles to control biological, chemical and physical hazards
Identity testing	analytical authenticity verification of food/feed with regard to various aspects such as origin, purity and composition
Immortilized	population of cells from a multicellular organism which have been manipulated to multiply indefinitely enabling culturing over long periods of time
Meat	the flesh of an animal consumed as food

Term	Definition
Microplasma	a bacterium that can infect various part of the body such as lungs and due to their lack of a cell wall, has the ability to be naturally resistant to antibiotics
Novel foods	foods that have not been widely consumed by people in the UK or EU before May 1997
Pluripotent	cells such as a stem cell or immature cell capable of giving rise to several different cell types
Progenitors	an ancestor/parent; from which a person, animal or plant originates from
Satellite cells	predecessors to skeletal muscle cells, responsible for the ability of muscle tissue regeneration
Scaffold	a support structure to facilitate cell culture made using a wide range of techniques including 3D printing
Stem cells	cells from which all other cells with specialized functions are generated
Vial	a small container typically cylindrical in shape and made of glass, used for holding liquid medicines/specimen
Zoonosis	a human infectious disease caused by pathogens such as parasites, viruses or bacteria

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Identification of hazards in meat products manufactured from cultured animal cells: introduction

1.1 Background

The world's population is growing and along with it, the demand for meat and meat products is increasing. This is paving the way for food technology innovations with sustainability in mind. One such emerging innovation is cultured meat which is gaining traction from research stages to commercialization. Originally, cultured meat existed as a fringe science on the edge of the cell culturing space but started to gain popularity in the early 2000s (footnote 1). The first phase of cultured meat development confined itself to the academic landscape between 2000s to 2013 (footnote 2). At this stage, the medical technology traditionally used for growing cells for purposes such as drug testing and making antibodies was applied to generating meat. In this time, there were a series of notable milestones and experiments that ultimately built up to Mark Post's cultured meat burger, a burger made from bovine myosatellite cells in 2013 (footnote 3).

Subsequently, companies were formed to develop cultured meat from a variety of backgrounds including academia, cell culture companies and some government initiatives. As such, 2011 to 2020 saw the arrival of around 32+ start-ups investigating and working in this area (footnote 4) (footnote 5) (footnote 6). As the technology further advanced, it captured the attention of venture capitalists and large food conglomerates such as New Crop Capital, Bell Food Group, Tyson foods and Cargill who have been investing in cultured meat start-ups and placing in sums of money in the range of $2-17 million (footnote 7) (footnote 8) (footnote 9) (footnote 10). This indicates a seismic shift from the proof-of-concept phase to the start-up phase.

Consequently, there is need to have an appropriate regulatory framework to ensure that products from this technology are safe for human consumption. To date, only one authority, the Singapore

Food Agency (SFA), has approved cell-cultured chicken (footnote 11). Also, in 2019 the United States Department of Agriculture's Food Safety and Inspection Services (USDA-FSIS) and the Food and Drug Administration (FDA) took an approach to collaborate in regulating cultured meat. Further to that, UPSIDE Foods successfully completed the FDA's pre-market safety review for a cultivated chicken product moving it one step closer to commercialisation in the U.S. (footnote 12)

At the time of writing (2022) in GB, the FSA mirrors the European Food Standards Agency (EFSA) regulatory framework for Novel Foods regime that oversees the authorisation of new food products that meet the criteria in the regulation. These include genetically engineered (GE) products (newly referred to Products of Genetic Technologies in the UK) where not subject to rules on genetically modified organisms or other specific legislation. The identity of this novel food falls into two classes of the Regulation 2015/2283/EU under article 3: item (vi) food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, micro-organisms, fungi or algae; and item (vii) food resulting from a production process not used for food production within the Union before 15 May 1997, which gives rise to significant changes in the composition or structure of a food, affecting its nutritional value, metabolism or level of undesirable substances. It is for this purpose that this hazard identification report was commissioned (footnote 13).

1.2 Risk question and scope

The question to be addressed in this hazard identification was:

- What are the potential hazards to the consumer in the consumption of cultured meat?

Hazard identification is the identification of biological, chemical and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods. It is one of the first steps in risk assessment. The outcome of hazard identification is a scientific judgement as to whether the initial agents being evaluated could, under certain given exposure, cause an adverse effect in humans. Those hazards identified that have an expected increased exposure due to the consumption of cultured meat will be considered via specific risk assessment.

This work is aimed to highlight potential hazards associated with the production of cultured meat. The hazards identified include the generic hazards of production and composition such as the materials used: chemicals and biological materials used in the process are safe and do not cause harm to the end consumer, and that the product does not contain any microbiological or chemical components of concern. However, there are also more specific hazard considerations centred on the specifics of the bioprocess and the final product composition. For instance, ensuring that the stem cells differentiate correctly so that the product is composed of meat-related cells that have a composition comparable or better than that of meat and having processes for quality control. Another is ensuring that the final product does not lack any key nutritional components or limit the bioavailability of such components. A final example is ensuring that components that are not normally in meat, that are used in cell culturing such as scaffolds, and possibly some media ingredients, are absent or present at levels that do not have any unintended consequences when consumed.

There are many stages of development for producing cultured meat as outlined in section 1.3, from taking a cell line from a small vial (footnote 14) (footnote 15) or biopsy and increasing the culture volume stepwise (footnote 16) in stages (footnote 17) (footnote 18) (footnote 19) (proliferation), until a commercial sized bioreactor can be seeded, to differentiating the cells to final desired cell type (footnote 20) (footnote 21) (footnote 22) (footnote 23) (footnote 24), then maturing them, usually on a scaffold, to increase the protein content (footnote 25) (footnote 26) (footnote 27), and then detaching/grinding the cells with/from their scaffold to produce a final product that can be used to make meat like cells (footnote 28). At each stage, different chemicals (footnote 29) (footnote 30),

biologics, media formulations (footnote 31) (footnote 32) (footnote 33) (footnote 34), additives (footnote 35) and supplements are used to ensure a successful culture.

1.3 Cultured meat production process

1.3.1 Selection of the starting cell lines

Cultured meat is currently defined as a cell-derived meat-like product that is produced for consumption by humans and animals (footnote 36). Cells are that are derived from an animal in an ex vivo environment are grown using a cell culturing processes (footnote 37) (footnote 38). Cultured meat describes the generation of skeletal muscle cells (myocytes) and/or with/or without associated cell types including, fibroblasts, adipocytes, stromal cells, vascular cells and nerve cells. Stem cells are obtained by isolation from an animal (footnote 39), but the cells can also be obtained from a cell bank once a stable cell line has been established and safely stored (footnote 40). Different types of cells can be used for the generation of cultured meat including adult stem cells, adult progenitor cells, embryonic stem cells, induced pluripotent stem cells and immortalised cell lines. Adult stem cells and progenitor cells are currently the most used due to their ease of differentiation, and being most analogous to the natural cell type (footnote 41) (footnote 42) (footnote 43) (footnote 44).

1.3.2 Culture environment

To commence culturing, the obtained cells are placed in an ex vivo environment that is used to maintain their growth (footnote 45). The culturing environment normally comprises three main components: a sterilized container such as a plastic culture flask or bioreactor, a nutrient medium containing nutritional components to support cellular growth by supplying nutrition needed to survive and the growth factors needed to control growth (footnote 46) (footnote 47) (footnote 48), a scaffold which is a biocompatible material used to provide 3D mechanical support to the cells. Additionally, controlling the culture conditions such a temperature, pressure, viscosity etc is necessary (footnote 49) (footnote 50) (footnote 51). The scaffold is important as most cell types associated to muscle are adherent in nature and would naturally die without it (footnote 52). There can be a diffusion limit placed on the cells by a scaffold that needs to be overcome by ensuring the cells have adequate supply of medium (footnote 53). The media is important as it supplies the cells with nutrition needed to survive and the growth factors needed to control growth (footnote 54) (footnote 55) (footnote 56) (footnote 57) (footnote 58) (footnote 59) (footnote 60).

The purpose of this ex vivo environment is to simulate what happens naturally under the conditions of homeostasis and to control growth of the cells (footnote 61). In this, there are many parameters that need to be controlled including the moisture level, dissolved O2 and CO2, temperature, waste removal, pressure, viscosity, hydrodynamic pressure, cell density, viable cells, glucose levels, flow rates, sparging rates, bubble size, waste removal, pH, and the mixing speed (footnote 62) (footnote 63) (footnote 64) (footnote 65). There are numerous ways of managing these, such as having perfusion pumps that continually remove waste and/or by using sensors that check the physio-chemical parameters of the culture that automatically rectify needed changes, such as adding more buffer, adding more O2 or increasing the flow rates.

This environment will ultimately ensure that the cells can be grown to produce a meat like product, and when using satellite cells, ensuring that all the stages of myogenesis are recapitulated (footnote 66). It also allows control over the process, as the parameters of the cell culturing can ultimately be monitored and changed to suit the production requirements (footnote 67). However, this growth environment will be different to the internal workings of the body, meaning there may be differences in the composition of the cells between the bioreactor and nature.

1.3.3 Main production stages

During the processing, the cells will need to go through three main stages of growth, namely proliferation, differentiation and maturation (footnote 68) (footnote 69). In proliferation the stem cells are stimulated to remain as stem cells by preventing differentiation to increase the cell numbers (footnote 70). In differentiation, the stem cells are triggered to differentiate, commencing conversion from stem cells to the desired cell type (footnote 71). In maturation, the cells are permitted to fully develop in their final form (footnote 72). These stages are managed by controlling the parameters of the culture to direct the growth phases of the cells and the differentiation to the final cell type. There are many ways to control the culture and the growth phases. For instance, use of a high amount of growth factors and/or serum is used to keep satellite cells undifferentiated, a change of culture medium from the proliferation medium to the differentiation medium, where the growth factor/serum level is severely reduced is used to trigger differentiation (footnote 73) (footnote 74). Alternatively, a genetically engineered cell line that contains a genetically inducible switch could be used, such that when one chemical is added the cells remain in a state of proliferation, whilst adding another chemical and removing the first will induce differentiation57.

1.3.4. Large scale production

For the economical production of cultured meat, the cells would need to be scaled up from a small volume in plate culture up to a commercial sized bioreactor. This occurs by making stepwise increases in the size of the culture volume. At first, the cells will be seeded in a small culturing flask and grown for a specified time period or until confluence is reached (footnote 75). This flask is then used to seed another larger flask with more medium. This process is repeated until there are enough cells to seed a bioreactor (footnote 76) (footnote 77). For instance, a small 1L stirred tank reactor could be used to seed 1000L wave bioreactor, which could be used to seed a 10,000L airlift bioreactor (footnote 78). Using this process, a small 1ml vial of cells can be scaled up to a 25m3 tank, with volumes of 1000m3 potential being needed for cultured meat development (footnote 79).

Although many bioreactor designs exist, and sizes of up to 25m3 are used in industry, large industrial bioreactors used for stem cell culturing purposes are not common, and these need to be designed and made operational for cultured purposes (footnote 80). The most common bioreactors used are made of stainless steel. Additionally, as the bioreactor size increases so does everything else, including the media and reagents required, which may pose a challenge of being able to safely and sustainably source materials such as growth factors (footnote 81).

Scaffold materials also need to be produced at scale as the culture size increases. These materials are 3D biocompatible materials, that mimic the extra cellular matrix and provide a structure for the cells to grow on, directing their growth and providing mechanical support (footnote 82) (footnote 83) (footnote 84). They are required as most cultured meat cells are adherent in nature and there is a diffusion limit on growing cultured meat cells. In culture without blood vessels, cultured meat cells can only grow to around 0.5mm thick (footnote 85). Scaffolds can be made from natural or synthetic components, such as collagen, cross-linked pectin, agar, and alginate or poly-lactic-acid, polyacrylamide, poly-glycolic acid (footnote 86). There are number of designs proposed for use in manufacturing cultured meat (footnote 87) (footnote 88) (footnote 89), such as using a mesh network scaffold and perfusing media through the scaffold (footnote 90) (footnote 91), or by using microcarriers or aggregates (footnote 92) (footnote 93) (footnote 94) but these have to be designed in conjunction with the bioreactors (footnote 95) (footnote 96), made suitable for scalable production (footnote 97) (footnote 98), and to accommodate the proliferation, differentiation and maturation of the stem cells (footnote 99) (footnote 100) (footnote 101)35,69,70.

1.3.5 Cell harvest and detachment

Once a sufficient level of culture volume has been obtained and the cells have been differentiated and matured, they are harvested and processed to produce meat like products (footnote 102). Depending on the scaffolding used, the cells may need to be removed from the scaffold or the scaffold may be used along with the cellular biomass to produce a meat product (footnote 103) (footnote 104) (footnote 105). For instance, a collagen/gelatine scaffold could be used and incorporated into the final product (footnote 106), whilst a polystyrene scaffold would not be suitable for edible consumption (footnote 107). Detachment can occur in several ways, such as mechanically removing the cells, enzymically separating the cells from the scaffold, or by using a scaffold material with designed properties such as thermal lift off or pH lift of where a temperature or pH change causes a reversible change in the structure of the scaffold that enables the cells to detach (footnote 108).

1.3.6 Final product formulation

The resulting mass can then be used to produce comminuted products, like burgers and mincemeat. Currently, comminuted products are the first products emerging for cultured meat as these are simple to make and have lower structural requirements (footnote 109) (footnote 110). More complex tissue structures like whole-cut steak cannot currently be produced due to the biological complexity, their diffusion limit on the cells and may require the making of an intricate vascular network which is not yet possible for the formation of tissue or cultured meat. However, there are a few designs proposed to produce more structured tissues, such as using 3D printing technologies where the cells are placed in a hydrogel and cast into shapes (footnote 111). Finally, there will be the packaging and marketing of the product, but this may be preceded by additional product formulation and processing stages, such as using transglutaminase or binding proteins to cross link the meat and adding flavourings or additives to the cellular mixture, and these will depend on the final cell type produced and the components missing from the cells (footnote 112), for the desired nutritional, taste and texture profile of the product.

1.3.7. Good production practices

All culturing is required to be conducted under aseptic conditions to prevent contamination from cells that can outgrow the culture and spoil a batch (footnote 113). This requires that all laboratories, equipment and work surfaces are sterilized and maintained in this state throughout processing steps associated with the culture of the cells. Consequently, there are stringent cleaning/sterilization protocols with strict management practices such as documentation of all the cleaning. At the laboratory scale this means working in sterilized laboratories in laminar airflow cabinets. For production plants it means having regimes to clean and sterilize all the equipment, such as having inlets for hot steam and cleaning chemicals like sodium hydroxide and minimising any human contact with product lines.

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Identification of hazards in meat products manufactured from cultured animal cells: review methodology

2.1 Search protocol

The report followed a scoping literature review methodology. It commenced by generating a search string through a trial-and-error process that comprised of a variety of epithets for cultured meat. These epithets were concatenated together with Boolean operators to complete a Boolean based search for papers using phrases like “Cultured meat” or “Synthetic Meat”, whilst using NOT operators to screen out papers that focused on ethics, perceptions and attitudes. The generated search string was then searched in databases listed in section 2.2, to return results related to the topic.

The aim was to keep the search string as identical as possible across all the databases for consistency. However, slight modifications were made to the search string in each database to account for the differences of the respective databases. No screening was applied when completing the searching, and no filters were applied, so all studies were collected for the full time-range. The result from the databases were collected as CSV files and transposed into Microsoft excel for pooling and screening.

The first round of screening occurred by removing all the duplicate titles that were found across the different databases. The Second round of screening occurred by generating eligibly criteria and screening the remaining titles of the papers against this criterion. The criteria contained a list of include words and exclude words. The third round of screening used the judgement of the author by reading the abstracts to only include papers that discussed cultured meat as a technology.

This took the total return of papers from 1348 to a final pool of 154 papers. Due to the low number of final papers, individual papers were not screened, and all papers were read for formulation of the review. Finally, the paper underwent an internal peer review before final editing and publishing. In this process, no metanalysis was conducted, no protocol registration occurred, and all work took place internally within the FSA.

2.2 Databases

Five databases were selected to perform the search:

- EBSCOhost
- Scopus
- Science Direct
- Springer Link
- ProQuest
- PubMed

2.3 Eligibility criteria

The papers selected focused on the technology used to produce cultured meat (e.g. cell lines, production process, scaffolds) and the potential regulatory risks to the consumer (e.g. product

composition, toxicology, regulations, specifications). Papers excluded comprised of those that focussed on the media perception, ethics, attitudes, medical research, tabloid, journalism, sociological aspects, and those that did not pertain to cultured meat. For the abstract screening step, papers were screened at the authors discretion to identify papers that considered the technology of cultured meat or potential risks and implications of using this technology.

2.4 Search string development

The generation of the search string followed a trial-and-error process. It commenced by completing initial reading on the topic to gather a list of different names, concepts and ideas that described cultured meat. Subsequently, a list of the stages involved in the development of cultured meat and the associated words was compiled, then different combinations of the terms and Boolean operators were combined and searched on PubMed to identify if useful results were being returned. Through an iterative process the search string was refined to its final formulation. The final search strings are found in Table 1 below.

Table one: final search strings

Database	Search string	Results
Database used: Scopus	("Cultured Meat" OR "In vitro Meat" OR "Clean Meat" OR "Synthetic Meat" OR "Cultured beef" OR "Artificial Meat" OR "In Vitro Meat Production System" OR “Stem Cell Meat") ANDNOT Ethics ANDNOT Perceptions ANDNOT attitudes	192 returns
Databased used: Science Direct	("Cultured Meat" OR "In vitro Meat" OR "Clean Meat" OR "Synthetic Meat" OR "Cultured beef" OR "Artificial Meat" OR "In Vitro Meat Production System" OR “Stem Cell Meat") NOT Ethics NOT Perceptions NOT attitudes	396 returns
Data base used: PubMed	("Cultured Meat" OR "In vitro Meat" OR "Clean Meat" OR "Synthetic Meat" OR "Cultured beef") NOT Ethics NOT Perceptions NOT attitudes	49 returns
Databased used: EBSCOhost	"Cultured Meat" OR "In vitro Meat" OR "Clean Meat" OR "Synthetic Meat" OR "Cultured beef" OR "Artificial Meat" OR "In Vitro Meat Production System" OR “Stem Cell Meat" NOT Ethics NOT Perceptions NOT attitudes	117 returns
Database used: Springer Link	"Cultured Meat" OR "In vitro Meat" OR "Clean Meat" OR "Synthetic Meat" OR "Cultured Beef" OR "In Vitro Meat Production System" OR "Stem Cell Meat" NOT Ethics NOT Perceptions NOT attitudes	163 returns
Database used: ProQuest	"Cultured Meat" OR "In vitro Meat" OR "Clean Meat" OR "Synthetic Meat" OR "Cultured Beef" OR "In Vitro Meat Production System" OR "Stem Cell Meat" NOT Ethics NOT Perceptions NOT attitudes	431 returns

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Identification of hazards in meat products manufactured from cultured animal cells: Hazards

3.1 Nutritional hazards

One of the key potential hazards highlighted in the literature was the nutritional impact of these products, as the nutrition profile of the product could be different from that it is replacing. This may arise because the meat produced in a bioreactor will not be directly identical to meat grown in an animal. At present it is impossible to fully recreate the in vivo (in life) environment in vitro (in the artificial setting) (footnote 1) (footnote 2) (footnote 3). There will be differences that arise between meat produced from cell lines and meat produced in animals. It is possible that this will lead to nutritional differences between cultured meat and traditional meat. The following are some considerations identified in the literature:

- There may be some vitamins, minerals and other nutritionally relevant components that are present in meat that may not be present in cultured meat. Examples included vitamin B1277, creatin (footnote 4), carnosine, vitamin D3, and iron (footnote 5), which are not created in muscle cells but are transported to the cells from elsewhere in the body or from the diet (footnote 6) (footnote 7).
- The proposed solution for absence of key components would be to add vitamins and minerals to the culture (footnote 8), but it is yet to be evaluated whether this will be taken up into the final product and compared in bioavailability to traditional meat (footnote 9).
- There are other factors relevant to meat that are not produced in the cells themselves but are important to the development/composition of muscle (footnote 10), e.g. myoglobin (footnote 11), haemoglobin (footnote 12), blood, extra/cellular tissue, lymph (footnote 13), and fat cells (footnote 14). These components which contribute nutritionally to meat may not be present in the final product.
- Muscle from an animal is highly complex as it is made up of over 6500 different proteins in different fractions that contain different muscle fibre types (footnote 15). It is yet to be fully evaluated whether growing the cells in the ex vivo culture environment fully replicate the protein composition of the meat it may replace.
- Cells are grown on a media formulation which provides the nutrition when culturing (footnote 16) (footnote 17). This nutrition formulation may directly impact the final composition of the cells and may produce a difference in composition to the traditionally produced meat.
- Cells require stimulation (footnote 18) (footnote 19) and simulation of the natural environment (footnote 20) in a bioreactor to stimulate growth (footnote 21). This stimulation through use of hormones (footnote 22), growth factors (footnote 23) (footnote 24), cytokines (footnote 25), nutrition (footnote 26) (footnote 27), 3D scaffold materials (footnote 28), bioreactor environment (footnote 29) (footnote 30) will not be identical to the environment in the host animal, so differences could arise between the final composition of the products. This is compounded as these signals are often delivered in regulated ways, across gradients and through stem cell niches (footnote 31) (footnote 32), which helps impart their effects and control the cell growth. Whilst in the production of cultured meat these will be delivered in a bioreactor in a homogeneous cultured broth mix or with different concentration gradients, lacking the complexity of biochemical/physical regulation found in the body.
- Maturation is needed to turn nascent muscle fibres into fully formed fibres (footnote 33). This process may not be fully replicated in the ex vivo culture environment (footnote 34), and the quality of the protein may not match that of traditional meat.
- There may be extra components that are required for the bioprocess that are not required for cultured meat that could contribute to the nutrition or the antinutritional properties of the final product (footnote 35).

1. The cells are adherent in nature and need to be grown on a scaffold (footnote 36) (footnote 37) (footnote 38). This scaffold could be part of the final structure of the product. The additional nutrition that a scaffold may provide or take away from the meat needs to be accounted for (footnote 39).
2. The scaffold material may not be present in a proportion similar to traditional meat, with one paper stating that it may account for 25% of the total product (footnote 40). Therefore, the scaffold may contribute more significantly to the nutrition of the meat than the extra cellular matrix would for traditional meat, changing the final composition of the cultured meat.

3. If there is a nutritional deficit or antinutritional factors in the scaffold, then this may be passed on to the consumer. One author noted that collagen is often used for the generation of cultured meat scaffolds, and this is high in the amino acid glycine (footnote 41) that may result in side effects to the consumer.
4. In some cases, the scaffold material does not form part of the final product, however the cells are detached from the scaffold (footnote 42). It is possible that during this process e.g. mechanical, physical, biological, separations, could damage the cells/protein, lowering the quality of the final product (footnote 43).
5. The chemical components used in the scaffolds may transfer into the final product. For instance, calcium and sodium have been used in casting methods (footnote 44) (footnote 45), and this may transfer into the product, increasing the presence of these components.
6. Currently, cultured meat lacks the sensory and nutritional properties of traditional meat. Therefore, additives, such as flavourings, colourings, myoglobin, vitamins, and minerals may be added to the culture. Their impact on the final nutrition of the product will need consideration (footnote 46) (footnote 47) (footnote 48)).

- A risk may be generated around the promissory narrative of cultured meat (footnote 49), with proponents purporting it to be healthier through design e.g. controlling the amount of polyunsaturated fatty acids (footnote 50) (footnote 51) (footnote 52) when it may not be healthier depending on the exact specification of the final product formulation. This may lead to consumers over consuming or consuming it when it is not much healthier, and this could have a negative nutritional impact.
- Further to the previous point, there will be limits to how far the meat can be designed to have specific properties, because there will be sensory limitations on what can be added, and saturated fats are those associated with increased flavour versus polyunsaturated fats (footnote 53).

3.2 Contamination from components used in cell culturing

There are several separate stages of development for producing cultured meat and at each stage, different chemicals, biologics, media formulations, additives and supplements are used to ensure a successful culture. The contamination risk of each input needs to be assessed, as any undesirable components that remain in the final product need to be at an acceptable exposure level or need to be food-grade/food safe. Below are some considerations that were found in the literature:

- Different components can/are used throughout cell culturing (see Table 2). These compounds could be absorbed by the cell or become associated with the cell wall and could be transferred into the final product (footnote 54) (footnote 55) (footnote 56). An understanding of how these compounds could bioaccumulate/be present in the final product and how they are removed or are at an acceptable exposure level needs consideration.
- Scaffold materials are used to produce cultured meat (footnote 57) (footnote 58) (footnote 59). Under the conditions of culturing, it is possible for the scaffolds to fracture/break, degrade, leave residuals (footnote 60) (footnote 61)potentially contaminating the final product with undesirable fragments, or leaving trace amounts that need to be accounted for (i.e. how does the scaffold degrade, are these degradation products safe, does detachment from the scaffold leave any residuals, how are these removed/accounted for).
- Antibiotics and fungicides (footnote 62), such as penicillin, streptomycin and gentamicin are commonly used in cell cultures to prevent infection (footnote 63). Although culturing can occur without the use of antibiotics/fungicides (footnote 64), it is likely that they will be used to prevent infection of the culture at some stage in the manufacturing process. The risk of exposure to antibiotics and fungicides residues needs to be understood.
- Some cell isolation, proliferation and differentiation protocols use toxic/non-edible/dangerous chemicals that would be toxic to humans. One example, is the chemicals

that are used to differentiate pre-adipocytes into adipocytes, dexamethasone (steroid), indomethacin, toxic xanthine and IBMX (footnote 65), which would not be allowed in food products (footnote 66).

- Culturing occurs under sterile/aseptic conditions to prevent contamination of the culture (footnote 67). Many plastic components are used, e.g. plastic flasks, pipettes, sterile wrapping, cleaning spray bottles, and single use bioreactors (footnote 68). Plastics can produce toxic leachables and inhibitory chemicals into cell lines (footnote 69). It needs to be understood if any toxic or inhibitory leachables are present in the final product at an unacceptable exposure level. Bioreactors and all equipment are stringently sterilised and cleaned e.g. with heated steam, using chemicals like sodium hydroxide and 70% ethanol solution (footnote 70). Residual chemicals left over from cleaning could transfer into the final product if not properly managed.
- Throughout the cell culturing process, the cells may come into contact with metal components, namely the bioreactor, pipes, pump etc (footnote 71). The possibility that heavy metals could leach into the final product needs consideration.
- Biological components derived from animals and bacteria can transfer disease into the culture. Serum (e.g. foetal bovine serum) traditionally added to cell cultures poses a zoonosis risk through virus transfer (footnote 72). Animal derived collagen is often used as the scaffold material (footnote 73). Most cultured meat companies are now using serum free mediums and working on non-animal derived scaffold components (footnote 74). However, components derived from bacterial cultures e.g. growth factors and scaffold materials may also pose a risk of bacterial contamination (footnote 75). The risk of disease transfer from components derived from animals or bacterial sources needs to be understood.
- Chemical contaminants could still potentially be present in the cell culture due to a lack of quality control process, such as using non-deionized or filtered water, or not using filtered air of CO2, but this would likely result in a spoiled culture medium rather than posing a risk to the consumer. HACCP and quality control processes will be needed to demonstrate safety.
- The cells used in culturing are metabolically active and it could be possible for them to produce metabolites or other components that could contribute negatively to the final product (footnote 76). An understanding of the cell metabolism and a production and removal of unwanted compounds should be demonstrated.
- There may be chemical/physical/biologics components that are intentionally added to the culture that may need to be removed from the final product. Examples include non-biodegraded and non-edible scaffold materials, such as polystyrene, polyacrylamide, polyethylene-glycol, cross-linked dextran etc, and enzymes that are added during the detachment process (footnote 77).

Table 2: Potential components that may be used in cultured meat production (footnote 78)

Component type	Potential Components
Components to control the proliferation, differentiation, maturation of the cells	Growth Additives, Growth Hormones, Steroids, Sodium Benzoate, Collagen powder, Xanthan gum, Mannitol, Cochineal, Omega-3-fatty acids, Bone Morphogenic Proteins, transforming growth factor ?, Zinc-finger protein Zfp423 Transcription Factors, Myokines, Adipokines, cytokines, interleukin-1, interleukin-6, interleukin-10, hepatocyte growth factor, and tumour necrosis factor alpha, MYOD, MRF4, TGF1, Testosterone, Progesterone, MYOD, muscle specific regulatory factors,
Growth Media components and components added to keep the cells alive/provide nutrition	Glucose, Amino Acids, Vitamins, Minerals, Buffers, Serum Medium, Serum Free Media, Growth Factors, Binding Proteins, Adhesion Factors, Vitamins, Hormones, Mineral Trace Elements, Oxygen Carriers, Modified Haemoglobin, Artificially produced perfluorochemicals, Perfluorochemicals, FBS, HS, L-glutamine, High Glucose, E2, TBA, TBA-E2, amino acids, inorganic salts, buffer systems, carbohydrates, antibiotics, supplements, basal medium, of Dulbecco's Modified Eagle Medium (DMEM), GlutaMAXc, inhibitors and activators of cellular pathways e.g. p38 inhibitor SB203580, poloxamers,

Component type	Potential Components
Scaffolds Materials used to support the growth of the cells by providing material to grow on	Collagen, Collagen Balls, Collagen Mesh, Coating materials, Extra Cellular Matrix Proteins, Laminin, Cellulose, Chitosan, Collagen, polyethylene, polystyrene and epoxy, poly(glycolic acid), poly(lactic-co-glycolic acid), polylactic-acid and poly(N-isopropyl acrylamide), gelatine, fibrin, Matrigel and elastin as hyaluronic acid, chitosan, agar, dextran, or alginate, Cytodex, RGD Biding groups, RHO-associated protein kinase inhibitors, fibronectin,
Bioreactor Components/Cleaning Chemicals	Anti-foaming agents, anti-coagulation agents, thinning agents, thickening agents, cleaning chemicals, sterilisation chemicals, NaOH, Defoamers, Emulsifiers, surfactants, the material of the bioreactor itself e.g. metal, plastic.

3.3 Cell Culture Infections

Cell lines can become infected with adventitious agents (i.e. microorganisms that may have been unintentionally introduced into the culture system product) that can impact the performance of the culture or spoil the culture. These include contamination with other cells, bacteria, yeasts, fungus, viruses, and mycoplasmas, as well as contamination/cross contamination with other cell lines (footnote 79).

3.3.1. Bacterial, yeast and fungal infections

- Infection (sometimes referred to as contamination) can be caused when a fast-growing microbe dominates by using up the resources and outgrowing the selected cell line (footnote 80). Infection is visible by microscope or by eye due to turbidity and a rancid smell. The contamination may arise from contaminated reagents, contaminated air, the water bath, poorly cleaned/maintained equipment, the cell culturist, not following cleaning protocols and not following good laboratory practices (GLP) and good manufacturing practices (GMP) (footnote 81). In cell culture, these infections are generally controlled with the growth antibiotics, fungicides, etc (footnote 82).
- Rapid action must be taken to protect neighbouring culture flasks/bioreactors and prevent the infection from spreading (footnote 83). Strict quality control and critical control measures must be enacted to destroy all infected cells by ensuring clean and sterile worksurfaces. Corrective action e.g. retraining of operators, cleaning of equipment, better monitoring must be put in place. As this infection is rapid an infected batch should be discarded to reduce the risk to consumer (footnote 84).

3.3.2. Mycoplasma infections

- Mycoplasma are small, gram-negative bacteria that do not possess cell walls and are not affected by many antibiotics (footnote 85). Around 20 different species have been identified from cell culture (footnote 86). They can evade the filtering processes, such as filtering the cells over 0.22µm filters. These cells do not cause turbidity in the culture but impact the culture by slowing cellular growth/changing growth rates (footnote 87), altering the cell metabolism (footnote 88), physiology and causing chromosomal aberrations (footnote 89). Data from the literature suggest that somewhere between 5%-35% of cell lines are infected with some form of mycoplasma infection, either with a single species of mycoplasma or more than one species (footnote 90) (footnote 91).
- Contamination from Mycoplasma could arise from contaminated reagents, air, poorly cleaned/maintained equipment, not following good laboratory and manufacturing practices (footnote 92). Cell lines should be regularly screened to check for mycoplasma infections (footnote 93).
- Mycoplasmas are not visible by eye or microscope and are harder to detect. Infections can be detected using testing methods such as DNA staining, fluorescent staining and PCR detection (footnote 94).
- The most common practices (if mycoplasma infection is found) is to discard the cells using autoclaving, incineration or disinfecting and discarding following protocols (footnote 95). In rare cases, the infected cell line can be decontaminated, but this is a difficult and

uncommon practice and should only be completed by an experienced operator (footnote 96) .

- The significance of mycoplasma infection to cultured meat is still to be evaluated, as mycoplasma infections impact the performance of biomedical research and analysis, but it has not been assessed whether this poses any risk to the consumer. It is known that there are over 200 different types of mycoplasma infections, with the majority being harmless, but there are a few that can cause infections in humans (footnote 97). These include:

1. Mycoplasma pneumoniae
2. Mycoplasma genitalium
3. Mycoplasma hominis
4. Urea plasma urealyticum
5. Urea plasma parvum

3.3.3 Viral contamination

- Viruses are small biological entities that can infect a culture. Due to their small sizes, viruses cannot be spotted with the naked eye or standard laboratory microscopes (footnote 98). This makes them hard to spot and a challenge to remove from reagents and the cells they originate from (footnote 99). However, if they are only Cytopathic (morphological), they may have no impact on the cell culture (footnote 100). There are different more costly tactics to remove/inactivate viruses such as retention in an acidic or basic environment, or through using small nano/micro filters (footnote 101).
- Viral contamination can originate from the donor organisms originally used to extract the cell source or can originate from animal sourced components like serum media, feeder cells and other derived components (footnote 102). They can also arise through other routes of contamination common to cell culture e.g. poor adherence to GMP processes and lack of/not following the proper aseptic techniques (footnote 103).
- It is not evident or considered in the literature whether viruses will pose a significant health hazard to humans or animals through consumption of cell cultured meat products, but some literature sources suggest that the risk will be less or tantamount to that already posed by eating meat (footnote 104).
- With regards to the spreading of viruses to humans from cultured meat, most viruses are host specific, limiting their ability to cross contaminate cell lines, although they can mutate and infect different hosts (footnote 105). However, if exotic animals become more common place in the diet through the cultured meat process, there may be a risk that an unknown virus harboured in a host species could transfer from the cell culture to humans.

3.3.4. Endotoxin infections

Endotoxins are hydrophobic, heat-stable lipopolysaccharides that can contaminate laboratory equipment and become present in the cell culture. Due to their hydrophobic nature they can become stuck to contaminated laboratory equipment such as plastic stirrers and transfer into cellular culture, with sources of contamination coming from impurified water, laboratory equipment, from media, reagents, serum components and recombinant proteins made in E. coli. Due to their heat-stable nature, they cannot be destroyed using heat sterilization processes (footnote 106) (footnote 107). There is evidence that endotoxins can produce variability in cell culturing results (footnote 108). Whether endotoxins need to be considered as a risk for cultured meat is an uncertainty, as they were not considered in the literature empirically (footnote 109) (footnote 110) (footnote 111) (footnote 112) (footnote 113) (footnote 114) (footnote 115).

3.3.5. Cross-contamination/misidentification issues

- There may be a risk of cross contamination of one cell line into another cell due to the use of multiple cell lines. This is a problem that came to fore in the 1960’s when HeLa cells

were identified in a number of cell lines. This is currently still present 18% to above 36% of cell lines showing some contamination, with a number of studies still showing varying results for the percentage of cells that have become cross contaminated/misidentified. One cell culturing bank/company reported that up to 18% of their cell lines were cross contaminated with another reporting 25% of cross contamination. The problem is quite widespread with one report stating that there were 32,755 articles reporting on cross-contaminated cell lines (footnote 116) (footnote 117) (footnote 118) (footnote 119) (footnote 120).

- The cross-contamination of cell lines has had a negative impact in terms of biomedical research and other cell culture applications (footnote 121). This has often led to many results being invalidated due falsification of results, incorrect research being completed and inaccurate results, but the real impact cannot be known.
- The cross-contamination of cell lines can come from many sources, primarily due to failure to follow good manufacturing and laboratory practices. This can include poor maintenance of equipment, poor cleaning regimes, incorrect storage of cells, poor use/cleaning of equipment, working with multiple cell lines in one area, using the wrong cells, incorrect labelling of cells, a drop of cells accidently transferring from one flask to the next, etc. (footnote 122) (footnote 123). Good manufacturing practices therefore need to be followed to ensure that cell lines do not become mixed and miss-identified.
- Furthermore, identity testing should be part of the process to ensure that any cell lines used are authenticated. There are many methods available for authenticating cells and these include PCR based methods, karyotyping the cell line, genetic sequencing by short tandem repeat and isoenzyme analysis. Cell culture operators should be working to ensure that any cell lines purchased should come from reputable cell banks that can supply certificates of authenticity of the cell line (footnote 124) (footnote 125) (footnote 126) (footnote 127).

3.4. Cell line associated risks

The stem cells and progenitors' cells that can be used to produce cultured meat are very complex and nuanced. Forecasting specific potential hazards that may arise due to use of different cell lines or cell line specific risks are hard to make, as each company is likely to be working with their own cell line, which will have its own specific risk considerations (footnote 128). There are a few generalities and considerations that are associated with using cell lines:

- One potential hazard, or perhaps a quality control issue, is whether there is enough control over the process to correctly differentiate and mature cells into a final product comparable to traditional meat (footnote 129).

1. The cells need to be proliferated, differentiated and matured into the final product, such as a muscle fibre, but due to the differences between ex vivo processing and the in vivo growth of muscle in an animal, the final composition of the cultured meat could be different when compared to its in vivo counterpart (footnote 130).
2. Meat undergoes a number of processing stages before it reaches the shop, including being slaughtered, bled and aged, but for cultured meat there are no slaughtering process (footnote 131) and may be no aging process (will be producer-specific choice), which impact the composition and quality of the meat, and will likely create differences between cultured meat and traditional meat (footnote 132).
3. Even if the cells may have correctly differentiated, the maturation of the cells may be incomplete, and the cells may not have the composition that would be expected for an in vivo muscle fibre (footnote 133). This may not be an issue, depending on the target nutritional profile, but this information needs to be readily available, and no false claims made in marketing the final product.

- Another potential hazard is that of cells not properly differentiating, either producing cells of inadequate quality, or producing cells that are of a different cell type, in some cases forming of carcinomas/cancer cells (footnote 134). This could lead to undesired cells being

in the final product.

- There needs to be some form of quality check, to ensure that desired differentiation and maturation occurs and that the cells that make up the final product are authenticated/checked, such as using biomarkers to track differentiation, or using genetic techniques (footnote 135) (footnote 136) (footnote 137).
- When using cell lines, but with special regards to immortalized cell lines, induced pluripotent stem cell lines and embryonic cell lines, the cells will mutate over time and be subject to genetic and phenotypic drift (footnote 138) (footnote 139). After several subculturing/passaging the cell lines may be divergent from the original cell line sequence, and the cells may express a different cellular morphology and behaviour. This may pose a risk, and a quality control for the number of times cells can be passaged/doubled may be needed.
- One other area is the potential to use cell lines of animals not commonly eaten in the diets of those countries (footnote 140) (footnote 141). The chance to eat exotic animals may be appealing to the consumer, but as the cell lines could be generated for a range of animals there may be risks of eating new types of meat, such as transfer of new diseases and viruses (if cell lines are not properly vetted and authentic), as well as potential allergenic reactions to new proteins.

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Identification of hazards in meat products manufactured from cultured animal cells: research gaps identified from the review

The research is based on a review of the scientific literature in 2020 and therefore only represents a snapshot of the evidence available at this time in the public domain. All relevant papers were included, regardless of funding source, and therefore any biases or speculations of the underlying papers may be present in the review.

There were considerable gaps in the type of knowledge that is required by other regimes within UK novel foods regulations available in the public domain. For instance, there was little or no empirical data found on the final analytical composition of products, key toxicology data, nutrition profiles, product stability, allergy risk, and any recorded adverse effects when consumed by animals or humans. Safety aspects were more commonly found in the literature on aspects of the environment or impact of the product, with inconsistent results with some reporting negative environmental impact and others positive outcomes.

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Identification of hazards in meat products manufactured from cultured animal cells: conclusion

There are several areas where the data is lacking or more information is needed to truly understand the risk or hazard that these new products may pose. Largely in the scientific

literature, data is missing on how this new product compares to meat that it may replace. Overall, more work is needed from both the cultured meat industry and from regulators to bridge the gap in understanding the hazards that individual products may pose. This could further inform the types of information needed from manufacturers to assess the safety of products before they reach the market.

Furthermore, to reassure the public, it is important to emphasise that we currently anticipate that these new products will come under novel foods regulations in the UK. Therefore, each individual product will need pre-market approval and will need to be assessed by a panel of independent experts for potential risks in: allergy, toxicity, reduced nutrition etc (please refer to FSA web-site for more details) as well as Annex A below.

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Identification of hazards in meat products manufactured from cultured animal cells: Annex A

Criteria for novel food suitability assessment

Any food that meets the definition of ‘novel food’ is subject to the assessment process and requirements of the Novel Foods Regulation (EU Regulation number 2015/2283) and meat products manufactured from cultured animal cells would be regulated as such. The following discusses the key criteria for novel food suitability assessment to ensure that the product under application for authorisation is safe for consumption.

Production process concerns

- The main concerns with the production process include chemicals or biological contaminants that could occur during the cell culturing process. Demonstration of adequate control of the process, correct differentiation and maturation and end-to-end safety management is required with an understanding of how the chemicals used interact with the product and whether any of these are toxic, non-food grade and safe for consumers. Although there is a general sequence of events that will be followed to produce the final cultured meat, there might be great variety across all the cell culture production. It might therefore be necessary for risk assessors to broaden their horizons in understanding how robust these production processes are for consistency in a safe product.

Compositional concerns

- Differences in the final composition of the product can arise through the production process (footnote 1) (footnote 2) resulting in a different final composition compared to meat. This can be from changes induced from not having all the extra material that is found in muscle e.g. no vascularate/stromal cells, not veins, no fat, as well as having a nutritional contribution from the scaffold material (footnote 3) (footnote 4).
- When considering this product, the composition will not just focus on one end product, but on how a cell line develops into the final product, whether it matures correctly, as well as

considering the safety of the scaffold material used to support the cells, the chemicals included in the process, and the medium that the cells have also been grown in. Therefore, depending on the product type and the process involved, the assessment will need to consider this.

Stability/microbiological safety

- There are claims made in the literature that the product will have a better stability profile than that of conventional meat due to the sterile conditions in production resulting in lower microbiological load in the product at its inception, consequently leading to a lower spoilage risk (footnote 5) (footnote 6). Whilst this is a logical hypothesis, without undertaking a stability assessment on the cultured meat at production scale, the actual microbiological safety of the product is not understood. At present, there was not data returned in the literature pool that gave any indication to the final stability/shelf-life of the product.

Allergenicity, toxicology, ADME (and protein analysis)

- One of the main issues with the scientific literature with the reference to understanding the risk profile and potential hazards of culture meet is that there is a very limited amount or product focus or product specific data, especially with regards to the final composition, allergenicity, toxicology and ADME of the product. Only a few papers provided some useful data on these factors, such as the paper on insect cultured meat completing a proximate analysis, but in general most papers review cultured meat conceptually, from the perspective of cell culture, or from improving a specific aspect of cultured meat such as improving the scaffold material There are many quantitative and qualitative measures used to check the extent of proliferation and differentiation e.g. use of genetic biomarkers, florescent imaging, genetic analysis, as well as studies on the impact of stretch and strain. However, the literature on risk assessment on cultured meat is lacking.
- One area that could be of concern is the change to the protein structure and protein sequences off the cells, which could be more dependent on the media formulation (footnote 7) and production process, which could change the protein quality of the final product potentially lowering the product and presenting a nutritional risk to the consumer through being a source lower quality protein (footnote 8) (footnote 9). It is also possible with that changes may lead to unintended consequences such as inducing an allergic reaction or changing the digestibility of the protein due to changes in the structure and composition of the final product (footnote 10).
- When a new product comes to market and it is a food that meets the definition of a novel food all the sections of a novel food should be completed however as the nature of the product may mean, toxicology studies and ADME studies do not provide much information in understanding how these react in the body. However, a detailed composition and protein analysis such as understanding the protein sequences, the protein quality and fractions of this product may be needed to alleviate any concerns alongside allergy studies to ensure that any changes in protein structures from this novel production process does not have any unintended consequences for consumer.

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