Roundtable on Novel Food Regulation 2024

18 Nov 2024, 2 – 5.30 pm (GMT +8)

Marina Bay Sands Expo & Convention Centre (Begonia Ballroom, Level 3)

Executive summary

Introduction

The Singapore Food Agency (SFA) organised the 5th Roundtable on Novel Food Regulations ("Roundtable") on 18 November 2024. The Roundtable is an international platform for regulators, the industry, academics, and key stakeholders in the novel food ecosystem to share best practices and experiences on safety and regulatory aspects of novel foods, as well as to identify opportunities for collaboration. Roundtable 2024 invited participants to discuss the standardisation of novel food safety assessments, best practices in novel food production, and the importance of collaboration in the novel food ecosystem.

Proceedings

The Roundtable started with technical presentations on the development of a Safety Assessed Media Ingredients List (**SAMIL**) and the Production of Fermentation Derived Novel Foods (**FERM**). After the technical presentations, attendees were split into breakout groups to discuss their perspectives on these topics. A total of 12 breakout groups were formed to discuss the development of the **SAMIL** while 7 breakout groups were formed to discuss challenges and best practices for **FERM**. After the breakout group session, attendees convened for a panel discussion.

Key points raised on the development of the SAMIL

- The **SAMIL** was generally viewed as a valuable starting point for standardising cell culture media ingredients, with the potential to streamline safety assessment of these culture media ingredients, particularly benefiting smaller companies and startups. However, some attendees expressed concerns that the list may limit innovations in cell culture media development. Some participants also suggested that the list could first be adapted for regional needs rather than internationally to facilitate adoption.
- While the categorisation framework was broadly seen as reasonable, there were calls for further refinement to address diverse global contexts, including considerations for varying dietary habits, dosage harmonisation, as well as the inclusion of additional factors such as residual levels, production methods, and allergen categorisation.
- Major challenges include the standardisation and validation of assessment methods, the high costs of toxicological testing, the complexity of ingredient interactions, and the need for a collaborative approach involving industry, regulators, and researchers to develop sustainable and efficient safety evaluation protocols.

Key points raised on the challenges and best practices for FERM

- The production of fermentation-derived novel foods presents unique challenges, particularly in managing contamination risks and ensuring consistent quality when using complex feedstocks like side streams or waste inputs.
- Implementing a risk-based approach with standardised procedures, coupled with advanced analytical techniques and proper documentation, was generally deemed to be crucial for ensuring the safety and quality of fermentation-derived novel foods.
- Good Manufacturing Practices (GMPs) and industry guidance are essential for building trust, facilitating industry growth, and providing a common framework for

communication between producers, regulators, and consumers in the emerging field of fermentation-derived novel foods.

Conclusion

As the novel food landscape continues to evolve rapidly, the insights gained from the Roundtable underscore the importance of collaborative efforts among stakeholders to advance the safety and production of novel foods. Consequently, continued dialogue and knowledge through platforms like the Roundtable will be instrumental in fostering a more conducive environment for innovation and fair international trade practices for novel foods.

Full Meeting Report

1 The Singapore Food Agency (SFA) organised the 5th Roundtable on Novel Food Regulations ("Roundtable") on 18 November, 2 – 5.30 pm, at the Marina Bay Sands Expo and Convention Centre. The Roundtable is an international platform for regulators, the industry, academics, and key stakeholders in the novel food ecosystem to share best practices and experiences on safety and regulatory aspects of novel foods, as well as to identify opportunities for collaboration.

2 There were 229 in-person participants. Governmental and intergovernmental agencies, the industry, the research community, and advocacy groups were represented at the Roundtable.

Technical Presentations

3 The Roundtable started with technical presentations on the development of a Safety Assessed Media Ingredients List (**SAMIL**) and the Production of Fermentation Derived Novel Foods (**FERM**). These presentations provided attendees with the context of the breakout topics to facilitate subsequent discussions.

Presentation title	**Presenter**
Safety Assessed Media Ingredient List	Kimberly Ong (Ph.D.) Toxicologist Vireo Advisors, LLC
Production of Fermentation Derived Novel Food Products	Allan Lim (Ph.D.) Chairman of the SFA Advisory Group for Novel Food Production

Breakout group session

4 After the technical presentations, attendees were split into breakout groups, one for **SAMIL**, one for **FERM**. The breakout group session for **SAMIL** involved gathering stakeholder feedback on categorization approach of the **SAMIL**. The discussion aimed to achieve a more efficient risk assessment of the inputs used in cultivated meat and seafood products. On the other hand, the breakout group for **FERM** discussed the unique considerations in the production of fermentation derived novel foods and best practices to overcome them.

5 Prior to the Roundtable, SFA worked with experts from the industry, research community, and advocacy groups to develop the discussion topics. The intent was to foster sharing of knowledge and views during the breakout group session. The discussion questions had been shared with participants ahead of the Roundtable. The facilitators involved in each breakout group are found in **Annex A** and the pre-read materials together with the discussion question sets are found in **Annex B and C**.

6 Participants engaged in lively discussions during the breakout group session. After the breakout session, participants were asked to do a survey with regards to the discussion topic. Participants were able to reach consensus on certain aspects relating to the development of the **SAMIL** as well as the best practices for **FERM**. These are detailed below.

7 Key discussion points from the **SAMIL** breakout group are summarised:

- **76%** of the participants agreed with the methodology used for categorization
- **60%** of the participants agreed with the methodology used to derive the SAMI levels
- **95%** of the participants found the **SAMIL** framework to be beneficial

Views on the Safety Assessed Media Ingredient List

8 The **SAMIL** was generally received as a helpful starting point for industry guidance, with the potential to streamline safety assessments and overcome trade barriers. However, opinions on its usefulness were mixed, particularly regarding Categories 1 (substances with established history of safe consumption and 2 (substances with history of safe consumption and established upper limits or dietary toxicological threshold values), which some viewed as redundant for well-known safe ingredients. Concerns were raised about trade secret protection and the cost burden of implementing the list. There was a recognized need for regulatory support and acceptance to ensure the list's effectiveness. Challenges in harmonization due to dietary differences across countries were noted, highlighting the complexity of creating a globally applicable standard. Differing views were expressed on whether **SAMIL** should serve as a guidance document or be legally binding. Despite these challenges, many stakeholders saw value in the list, particularly for new companies entering the field and for identifying research gaps in academia.

Categories, methodology, and additional considerations

9 While there was general support for the categorization framework, participants noted several areas require further clarification and consideration. A key issue was the need for a clearer definition of "history of safe consumption," which affects how substances are categorized. Applying broad guidelines was seen to be challenging due to population differences in dietary intake and body weight. There were also concerns on how to handle chemically ill-defined ingredients with complex structures or unknown compositions. Some participants proposed using upper limits instead of fixed values to account for methodological variations and differences in portion sizes. There was also a suggestion to allow industry more flexibility in demonstrating product safety. Long-term studies were seen as particularly important for Categories 3 and 4 substances (i.e. substances with limited or no history of safe consumption requiring additional safety data). Additional considerations expressed include the bioavailability of cultivated meat, effects of cooking processes on ingredient safety, and potential ingredient interactions. The variability in meat composition across different cuts and breeds was highlighted as a factor that complicates the establishment of "normal" reference points.

Challenges in assessing safety of Category 3 and 4 substances

10 The assessment of Category 3 and 4 substances presents significant technical, practical and resource-related challenges that requires strategic solutions. Key challenges include the identification and categorization of substances, the need for sensitive and reliable test methods, and gaps in understanding metabolism processes and potential structural changes of these substances in the body. The notable lack of long-term safety data and

concerns about synergistic effects in cell culture media add complexity to the assessment process. From a practical standpoint, the industry faces difficulties in addressing specialized consumer groups who may be more susceptible to adverse effects, while companies' desire to restrict access to proprietary information poses a significant obstacle to comprehensive safety assessments. Resource implications, especially for smaller companies, and ethical considerations regarding animal testing further complicate the situation. While many industry participants have expressed interest and optimism in moving away from traditional toxicology testing towards alternative methods, this transition requires careful consideration and planning.

Strategic focus areas and ongoing initiatives

11 To address these challenges, several key focus areas have emerged. The development of New Approach Methodologies (NAMs) has been identified as one of the alternatives to traditional animal testing. However, the transition to NAMs faces specific challenges including validation requirements for novel food testing, the need for large product quantities for method validation which is particularly difficult for cultivated meat products, and uncertainty about regulatory acceptance of these new methods. International harmonisation through platforms like Codex has been suggested as crucial for establishing globally accepted standards and assessment frameworks. Participants highlighted the need for industry associations to coordinate safety assessments while protecting proprietary information, potentially through shared data repositories and methodologies. There were also calls for government funding to support safety assessments, particularly for Category 3 and 4 substances, and suggestions to involve substance suppliers in safety testing. The development of predictive algorithms for allergenicity assessment, especially for precision fermentation products, was identified as another important area. These initiatives align with current work on establishing international standards while addressing industry concerns about resource constraints and proprietary information protection.

12 Key discussion points from the **FERM** breakout group are summarised:

- **82%** of the participants agree with the unique safety considerations related to the production of fermentation derived novel food products.
- Among the considerations listed, the participant viewed the use of waste side steam input, contamination of fermentation process, as well as cross-contamination of starting cultures with other production organism are of equal importance.
- **80%** of the participants viewed that it is beneficial to develop Good Manufacturing Practices for producing fermentation derived novel food products.

Unique Considerations for Fermentation-Derived Novel Foods

13 The discussion highlighted several unique considerations for fermentation-derived novel foods:

i. Safety testing emerged as a crucial topic, with participants emphasizing the need for hypothesis-driven testing specific to each production system. For examples, when *Escherichia coli* is used, endotoxin testing would be specifically required. For precision fermentation products, discussion centred on residual DNA and its implications, with varying perspective across groups. Some emphasising the need for specific standards for allowable DNA levels, particularly in non-heat-treated products, which other viewed DNA monitoring as a useful indicator of overall contamination control. The potential

adoption of modern methodologies, such as omics and *in-silico* methods, was also explored.

ii. The regulatory approach was another key area of discussion, with participants advocating for a flexible, risk-based approach rather than universal requirements. They suggested that products using well-characterized safe organisms should face different regulatory scrutiny compared to those using novel organisms. Particular attention was given to products combining precision and biomass fermentation, which might require specific regulatory considerations.

iii. Additional concerns were raised about protein integrity and allergenicity, particularly for proteins derived from GMOs. Previously mentioned issues, including various types of contamination, genetic stability concerns, and process-related challenges like batch inconsistency and waste stream management, remained relevant to the discussion.

Best Practices to Address These Considerations

14 Participants proposed several best practices to address the considerations raised:

i. In terms of safety testing, participants suggested developing a list of host-specific tests and starting with small molecules to identify corresponding impurities. Using the purification process flow as a reference for product purity was also recommended. The potential use of omics methodology as a way of generating data on allergenicity was discussed as a modern approach to safety assessment.

ii. Regarding the regulatory approach, establishing a middle ground for safety testing requirements and adjusting framework flexibility based on organism safety profiles were suggested. Participants emphasized the importance of developing comprehensive standards or guidelines for contaminants under the food safety framework. They also stressed the need to consider risk aspects and necessary tests early in the process to avoid unnecessary requirements later.

iii. Previously mentioned best practices, such as various contamination control measures, genetic and strain management practices, thorough process understanding and documentation, conducting clinical trials, and effective public communication, were reaffirmed as crucial elements in addressing these considerations.

Usefulness of Good Manufacturing Practices in the production of Fermentation-derived Novel Food

15 The discussion on the usefulness of Good Manufacturing Practices (GMP) and guidance for fermentation-derived novel foods covered several aspects:

i. Regarding the impact on industry growth and innovation, participants emphasized the need for a balance between safety requirements and support for innovation. They also noted the potential for adopting modern methodologies in regulations to keep pace with technological advancements.

ii. In terms of operational benefits, clearer guidelines on safety testing and contaminant control were seen as valuable, potentially leading to more efficient and targeted safety assessments.

iii. However, several key challenges were identified. These included addressing the complexity of mixed fermentation products, ensuring that requirements were commensurate with the level of safety concerns, and keeping pace with technological advancements in testing and production methods. Harmonizing regulations across

different jurisdictions and addressing information gaps, such as endotoxin-related matters, were also noted as significant challenges.

iv. Participants reaffirmed the importance of GMP in contamination prevention, the need for clear contamination levels and detection limits, and the significance of process control and documentation.

Panel discussion

16 After a summary presentation of the two breakout groups, the Roundtable proceeded with a panel discussion moderated by Mr Low Teng Yong (*Director, Risk Assessment and Communications, SFA*). The panellists were representatives from governmental and intergovernmental agencies:

Panellist	**Affiliation**
Masami Takeuchi (Ph.D.)	Food and Agriculture Organization of The United Nations (FAO)
Ana Afonso (DVM)	European Food Safety Authority (EFSA)
James Cooper (Ph.D.)	U.K. Food Standards Agency (FSA)
Jason Dietz	U.S. Food and Drug Administration (FDA)
Tracy Hambridge	Food Standards Australia and New Zealand (FSANZ)

17 The theme of the panel discussion was: "**Fostering Collaboration in the Novel Food Ecosystem**". It reflected on the discussions on cultivated meat and precision fermentation held during the breakout rooms and explored international collaboration and cooperation in the novel food ecosystem.

18 The key points raised by the panellists were:

i. With rapid advancements in the novel food sector, regulatory frameworks must be flexible and forward-thinking while still prioritising safety. This requires transparent and two-way communication between regulators, industry, and academic researchers to ensure that novel food regulations are informed and practical.

ii. On an international level, panellists stressed the importance of sharing information, best practices, and scientific methodologies across borders. This collaboration would create more consistent and efficient regulatory processes, reducing duplication of efforts by industry and consequently facilitating international trade.

iii. Future collaboration should focus on harmonising scientific methods for novel food assessments. One area of improvement identified is allergenicity assessments. As novel foods may introduce new allergens or alter the allergenic potential of existing foods, there is a need to re-evaluate allergenicity assessments to protect vulnerable populations.

Acknowledgement

19 SFA thanks all discussion facilitators, panellists, scribes and participants for their support and for sharing their valuable insights and experiences at this Roundtable. SFA looks

forward to continued support from stakeholders for next year's Roundtable. SFA will continue to engage with interested parties and stakeholders to develop standards, guidelines, and recommendations that ensure the safety of novel foods while facilitating fair trade and business practices.

Photos

Opening address by Mr Damian Chan

Technical presentation on Safety Assessed Media Ingredient List by Dr Kimberly Ong

Technical presentation on Production of Fermentation Derived Novel Food Products by Dr Allan Lim

Presentation on the key points from the breakout discussion on Safety Assessed Media Ingredient List by Dr Jo Anne Shatkin

Presentation on the key points from the breakout discussion on Production of Fermentation Derived Novel Food Products by Dr Allan Lim

Breakout group discussion

Panellists with Dr Tan Lee Kim and Mr Low Teng Yong. From left: Dr James Cooper, Ms Tracy Hambridge, Mr Jason Dietz, Dr Tan Lee Kim, Mr Low Teng Yong, Dr Masami Takeuchi, Dr Ana Afonso

Annex A – Facilitators for the breakout group session

Topic	Name	Affiliation
Safety Assessed Media Ingredients List (**SAMIL**)	Dean Powell (Ph.D.)	The Good Food Institute APAC (GFI-APAC)
	Hannah Lester (Ph.D.)	Atova Regulatory Consulting; Cellular Agriculture Europe (CAE); Gourmey
	Karin Ke (Ph.D., DABT, ERT)	Keller and Heckman LLP
	Shigeki Sugii (Ph.D.)	SIFBI
	Wilfred Feng	Dacheng Law Offices (Shanghai) LLP
	Etienne Duthoit	Vital Meat
	Richard Khaw	Nanyang Polytechnic
	Samuel Goh	Good Food Institute
	Calisa Lim	APAC Society for Cellular Agriculture
	Jolieke van der Pols (Ph.D.)	Queensland University of Technology
	Kimberly Ong (Ph.D.)	Vireo Advisors, LLC
	Jun Cheng Er (Ph.D.)	SFA
Production of Fermentation Derived Novel Foods (**FERM**)	Allan Lim (Ph.D.)	Chairman of the SFA Advisory Group for Novel Food Production
	William Chen (Ph.D.)	Nanyang Technological University (NTU)
	Melaine Weingarten (Ph.D.)	A*STAR
	David Ettinger	Keller and Heckman LLP
	Yong Quan Tan (Ph.D.)	SFA
	Jun Wei Yeo	SFA
	Gamaliel Ma (Ph.D.)	SFA

Annex B – Pre-read materials and questions for the breakout discussion on Safety Assessed Media Ingredient (SAMI) List

Safety Assessed Media Ingredient (SAMI) List White Paper

November 2024

Prepared by:

Vireo Advisors, LLC

In Collaboration with:

Good Food Institute APAC

Future Ready Food Safety Hub (FRESH)

Table of Contents

Executive Summary

This project is a collaboration aimed at developing a list of media components commonly used in cultivated meat and seafood production with safety assessed use levels in final cultivated products.

The outcome is a draft Safety-Assessed Media Ingredient (SAMI) List of 56 media components, and their relevant salt forms and isomers, for which safety assessments have been conducted and SAMI List use levels proposed. A framework for categorizing media ingredients in terms of safety is proposed as part of this project, advancing a process to continue growing the number and types of components on the SAMI List. The ultimate aim of this project is for the categorisation framework and SAMI List to be a guide employed by companies and regulatory bodies across jurisdictions to support the development of a harmonised international approach to the safety assessment of media components. Please note that the proposed levels are to allow for screening of culture media ingredient levels in products, however, are not limit values for safe use.

The work is a collaboration between Vireo Advisors, LLC (Vireo), Good Food Institute Asia-Pacific (GFI APAC), and the Future Ready Food Safety Hub (FRESH). Inputs were sought from the Singapore Food Agency (SFA) during the project. Feedback from alternative protein stakeholders is sought to refine the assessment framework and the SAMI list.

Project partners

Vireo Advisors, LLC

Vireo is an expert advising firm working globally on a mission to move the bioeconomy forward with safer and more sustainable products. We bring extensive expertise to our collaborators and clients on market and regulatory requirements for new technologies, advanced materials and novel food ingredients; we advise on and support product testing and validation and provide clarity to ever-changing safety and sustainability standards. We develop strategies, assist technology developers, and create consortia to build safety and market resources supporting commercialization.

GFI APAC

Headquartered in Singapore, the Good Food Institute APAC is Asia's leading alternative protein think tank, accelerating a shift towards a more secure, sustainable, and just food system through open-access food science R&D, corporate engagement, and public policy.

Future Ready Food Safety Hub (FRESH)

Set up as a national research platform under the Singapore Food Story R&D agenda, the Future Ready Food Safety Hub (FRESH) provides expert counsel and food safety research services to public and private organisations working to bring novel foods to Singapore. FRESH is also developing innovations on New Approach Methodologies (NAMs) for safety risk assessment and nutritional benefits of novel foods. Together with our partners in Singapore and beyond, we help ensure that foods, even those without prior history of safe consumption, can be safely consumed.

Background

Industrial animal agriculture is a leading contributor to critical environmental problems such as land degradation and water scarcity and is responsible for up to 18% of all greenhouse gas emissions. This raises concerns about sustainability, food safety and security, worker safety, public health, and the ethical treatment of animals (FAO 2006). Cultivated meat and seafood products may supply animal-based protein while enhancing global food security and providing benefits to human health, the environment, and animal welfare. Safety demonstration is a critical aspect of cultivated meat and seafood commercialization.

Culture media are used throughout the cultivated meat and seafood manufacturing process to support survival, growth, and differentiation. Most culture media are removed from the cells after collection from the bioreactors. However, the inputs have the potential to accumulate in or bind to the cells, remaining as residues in the final cultivated product.

Many companies use a proprietary and customized media formulation. Formulations with different ingredients are developed to reduce production costs or improve scalability. As a result, the safety of each formulation is evaluated on a case-by-case basis. Creating a risk assessment framework and Safety-Assessed Media Ingredient (SAMI) List for cultivated meat and seafood media components streamlines the safety assessment and evaluation of cultivated meat and seafood products. Inputs used in the manufacturing process are assessed during regulatory and safety review to determine whether they are safe for use in food. Conducting an individual assessment of each culture media formulation is inefficient for companies and regulators. Safety is typically evaluated using information demonstrating that the input can be safely consumed at the estimated or measured concentration in the final product, or by confirming that the input is absent from the final product.

The overall goal of the SAMI List and assessment proposed in this white paper is to establish a process for listing media components commonly used in cultivated meat and seafood production and to develop internationally accepted frameworks to conduct safety assessments of certain components with associated SAMI use levels. The list is intended for use by regulatory reviewers, industry, and risk assessors to reduce the level of effort and improve the efficiency of assessing media inputs for cultivated meat and seafood. Note that the use levels are intentionally conservative for screening purposes; exceeding the levels indicates a need for more detailed analysis, not a safety concern.

Approach to Developing the SAMI List

To develop the SAMI List:

1. The list of media components was developed and refined based on industry and regulatory stakeholder feedback.
2. Components were organized in a categorization framework based on their history of safe consumption and the availability of dietary safety information.
3. A safe level for each component was derived from available safety information.

Development of the Initial List

An initial list of media components was developed as a starting point. Components were included if identified in literature or by expert opinion as common to cultivated meat manufacture. Seventeen companies replied to a survey sent with the initial list. Companies were asked to comment on whether the component should remain in, or be removed from, the SAMI List and suggest the inclusion of any additional components. Substances were included if the majority of companies were in favor of having the component on the list.

Companies were also asked to provide optional information on the stage of manufacturing the component is employed, the concentration used, whether any residue is present in harvested cells, and whether the substances are species- or cell line-specific. Most companies declined to provide these data, therefore the list did not consider these attributes. The available information provided insight into whether the substances were anticipated to be present in the final product and confirmed that most substances were not species- or cell line- specific, and therefore widely applicable to many processes.

Categorization framework

A categorization framework can help classify media components that support more efficient risk assessments. Some companies categorize media components according to their regulatory status, history of safe consumption, and/or safety assessment (*e.g.,* UPSIDE Foods U.S Food and Drug Administration [FDA] submission, GOOD Meat FDA submission). The framework for developing the SAMI List is intended to be internationally acceptable; therefore, it focuses on safety information rather than regulatory status.

The categories are developed to organize components according to the available knowledgebase and history of safe consumption. Category 1 represents substances with the most available supporting dietary data, while Category 4 represents substances requiring additional safety data to support safe use. As the category increases from 1 through to 4, more thorough safety demonstration becomes necessary.

For this initial project, only Category 1 and Category 2 components are considered. These substances have a history of safe consumption, and/or experts have concluded that substances may be safely consumed in food. Additional substances and categories are planned for future phases of work.

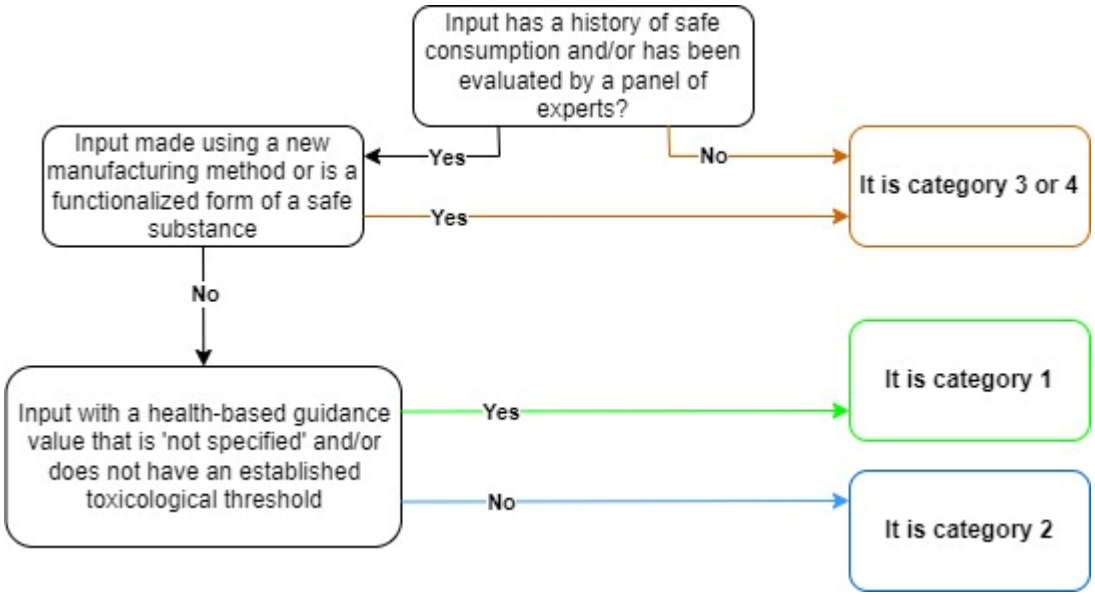

Figure 1. Decision tree for categorizing culture media inputs.

Category 1

Category 1 culture media components have an established history of safe consumption or use in food. These substances have been reviewed by a panel of experts (*e.g.,* Food Chemicals Codex (FCC), Joint FAO/WHO Expert Committee on Food Additives (JECFA), European Food Safety Authority (EFSA), Food and Drug Administration (FDA), or other recognized expert body) and/or are common components of conventional food with a history of safe consumption. These components may have a health-based guidance value (HBGV) of 'not specified', meaning the food substance has very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other), does not represent a hazard to health. These substances have been established to be safe for use without the need to establish Tolerable Upper Intake Levels (ULs) or toxicological thresholds. Category 1 inputs may have Dietary Reference Intake (DRI) values, but do not have an associated UL value.

Category 2

Category 2 culture media ingredients have a history of safe consumption and/or use in food but also have established Tolerable Upper Intake Levels (ULs) or toxicological thresholds in addition to HBGV. These substances have been reviewed by a panel of experts (*e.g.,* FCC, JECFA, EFSA, FDA, or other recognized expert body) and/or are common components of conventional food with a history of safe consumption. Nonetheless, they also have established upper limits for safe dietary exposure. The UL or dietary toxicological threshold values may be established by a recognized expert body or derived from peer-reviewed scientific safety data. Dietary toxicological thresholds include peer-reviewed dietary health base guidance values such as No Observed Adverse Effects Levels (NOAELs), provided

the established NOAEL is not equal to or greater than the maximum dose tested in the study (where the highest dose did not result in any adverse effects) or any other experimentally derived value that is associated with toxicological effects with suitable margin of exposure values.

Category 3

Category 3 substances are media ingredients that may not have a history of safe consumption (*e.g.,* not present in conventional food) and have not been established to be safe by a panel of experts (e.g., FCC, JECFA, EFSA, FDA, or other recognized expert body) to be safe. However, sufficient information is available to conclude that the component does not present a food consumption risk under its conditions of intended use in cultivated meat/seafood production. These substances can be demonstrated to be safe for human consumption using generally accepted principles of food safety evaluation or risk mitigation practices. Generally accepted principles of food safety evaluation include, but are not limited to, comparison to concentrations in conventional food and/or a margin of exposure (MOE) calculation from an established NOAEL. Category 3 substances may include but are not limited to components produced using new manufacturing methods that have not yet been reviewed by a panel of experts.

Category 4

Category 4 components are ingredients with no history of safe use in food, are not present in conventional food, and have not been reviewed by a panel of experts nor concluded to be safe for use in food production. The current available literature does not adequately demonstrate the safety of the component under the intended use. Therefore, additional safety testing and data collection is required. Some components may require conducting standard toxicological testing, developing and validating new approach methods (NAMs) to demonstrate safety, or other efforts to demonstrate substantial equivalence or similarity to substances with a history of safe use in food. The collection of additional safety data may result in the re-evaluation of a substance and reclassification to a Category 3 component. Media components classified into Category 4 may include but are not limited to components that lack dietary safety data, or may have adverse physiological effects, pharmacological action, or therapeutic effects in the human body at the levels present in cultivated meat and seafood.

Derivation of SAMI use levels

The proposed SAMI List culture media components discussed in this report are Category 1 or 2 substances. The use levels in the SAMI List represent final product/residue levels that have been derived from established DRIs, concentrations of the substance in conventional foods, and/or developed from established NOAELs. The SAMI use levels represent conservative safe use levels to streamline risk assessment. The presence of a substance above these levels does not imply that it is not safe for use; rather, further risk assessment is required by the assessor.

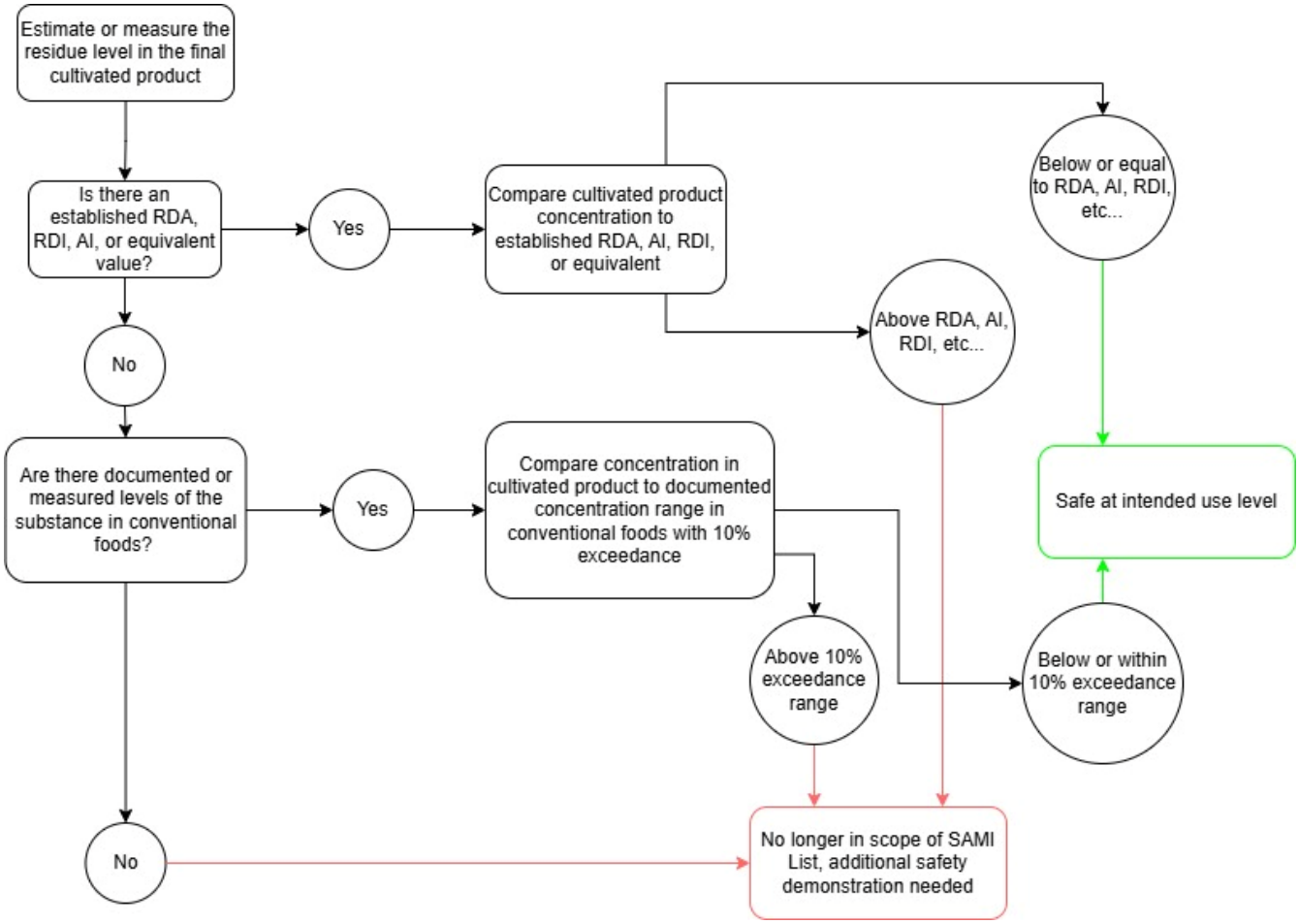

Figure 2. Flowchart for the risk assessment strategy for Category 1 culture media inputs.

Category 1

Category 1 components include substances with a history of safe consumption. This may include some carbohydrates, inorganic salts, water-soluble vitamins, fatty acids, and nucleic acid-related compounds. Category 1 substances may either be either present in conventional food, used in conventional food processing, and/or have been evaluated by a panel of experts that has reached a conclusion of safety for use in food, with "not specified" HBGV or dietary toxicological threshold values. For salts that dissociate in aqueous solution, the assessment is conducted on the constituent compounds.

The SAMI use levels are derived from:

a) Established Dietary Reference Intakes (DRIs); or
b) Levels in conventional meat and seafood; or
c) Levels in other conventional foods with a history of safe consumption.

If a DRI exists, the SAMI use level for Category 1 components is equal to an established DRI (*e.g.,* Acceptable Daily Intake (ADI), Adequate Intake (AI), Recommended Dietary Intake (RDI),

Recommended Dietary Allowance (RDA), or equivalent value), expressed in mg/day. Category 1 components present in final cultivated meat and seafood products at concentrations equal to or below the DRI levels satisfy the SAMI use level criteria and are concluded safe for use in cultivated meat and seafood.

For substances with no DRI, the concentration of the substance in conventional meat and seafood or other foods (if they are not present in conventional meat and seafood) forms the basis for the SAMI use level. These concentrations are collected from the following food composition databases: USDA FoodData Central, FSANZ Australian Food Composition Database – Release 2.0, and MEXT – Standard Tables of Food Composition in Japan - 2015 - (Seventh Revised Version). Values from beef, pork, and chicken are used to represent meat and poultry values. Salmon was chosen to represent seafood because of the availability of composition data and because salmon aquaculture is the fastest-growing food production system in the world (WWF, 2024). Values were included only if the concentrations of the substance was measured in conventional meat or seafood, while estimates of concentrations were excluded. If the food composition databases lacked data, a literature search was conducted for any reported concentrations of the substance in meat, seafood, or other conventional foods. The maximum measured concentration of the substance in conventional food was identified. A 10% exceedance of the maximum measured concentration was calculated (see Equation 1). A 10% threshold value is used in the approach taken by the US FDA in assessing whether there is biological significance beyond statistical significance for genetically engineered animals such as the genetically engineered AquAdvantage Salmon (FDA 2008; FDA 2015). The SAMI use level assumes that 90g of cultivated meat and seafood product will be consumed per day (equivalent to one serving of conventional meat) (HealthHub, 2022). When the comparator is derived from other conventional foods, the assumed serving size is aligned with that of the reported conventional food. For example, the concentration of sulphate in brussels sprouts is calculated using a standard serving size of 100 g for vegetables [HealthHub, 2022]. Therefore, the SAMI use level is equal to 10% above the concentration in one serving of the conventional food.

Equation 1. SAMI use level, derived from concentration in conventional foods

$$SAMI\ use\ level\ \left(\frac{mg}{day}\right) =$$

$$Conc.of\ component\ in\ conventional\ food\ \left(\frac{mg}{g}\right) x\ daily\ serving\ size\ \left(\frac{g}{day}\right) x\ 10\%\ exceedance\ level \quad (1.1)$$

If a Category 1 component is estimated or measured in the product above the SAMI use level, additional safety demonstration is required to conclude that it is safe under the conditions of intended use. However, note that exceedance of the SAMI use level in a product does not indicate the level is unsafe, only that further safety demonstration is necessary.

All media components also must meet the listed specifications for food-grade substances (*e.g.,* those established by the Food Chemicals Codex [FCC] or Joint FAO/WHO Expert Committee on Food Additives [JECFA]), or similar, where available.

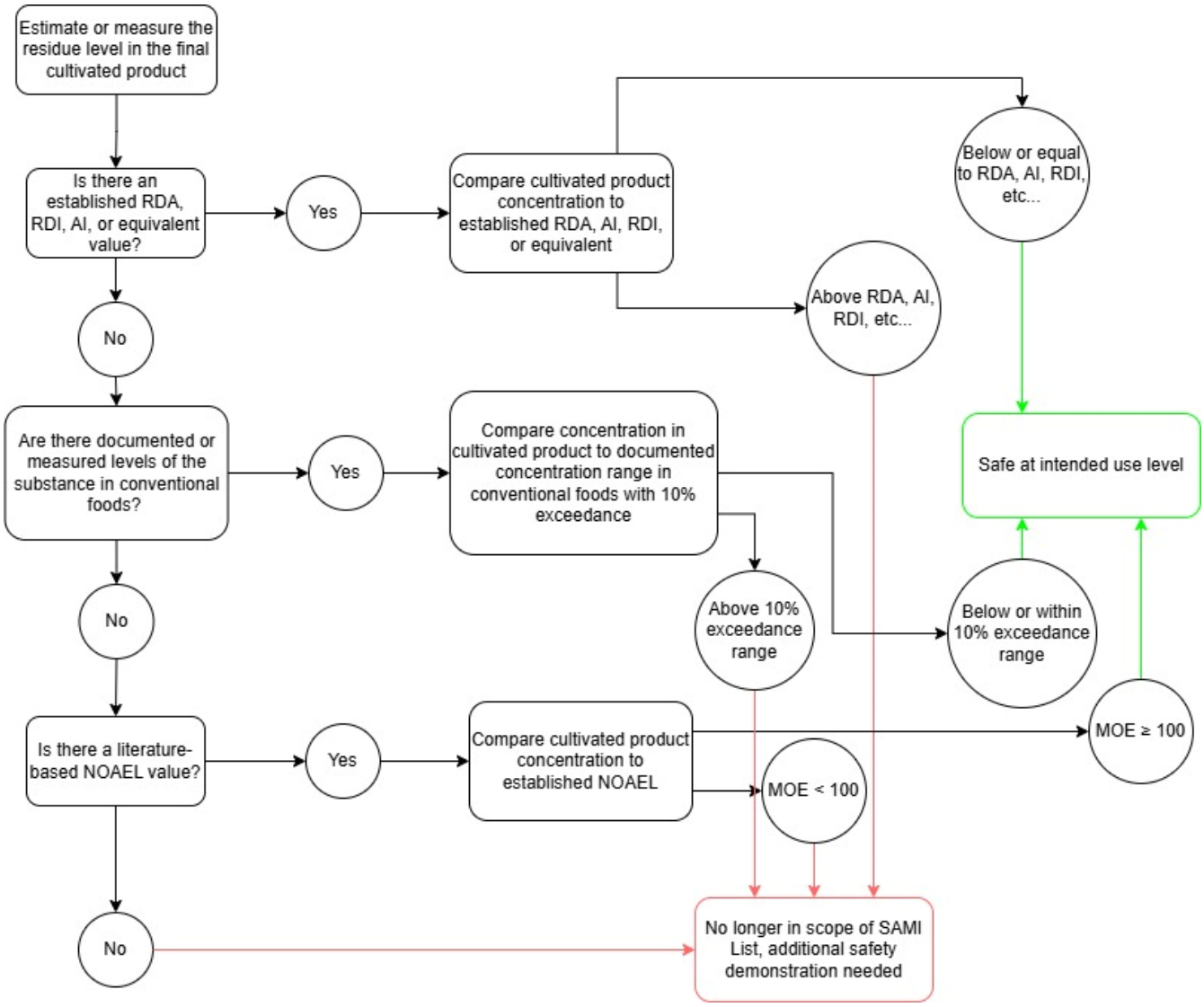

Figure 3. Flowchart for the risk assessment strategy for Category 2 culture media inputs.

Category 2

Category 2 media components include substances with a history of safe consumption, including some amino acids, water-soluble vitamins, fatty acids, inorganic salts, nucleic acid-related compounds, and organic substances with established ULs or dietary toxicological threshold values. Category 2 substances may either be present in conventional food; are used in conventional food processing; and/or an evaluation conducted by a panel of experts has concluded their safe use in food if below ULs, or established dietary toxicological thresholds. For salts that dissociate in aqueous solution, the assessment is conducted on the constituent compounds.

Category 2 SAMI use levels are derived from:

a) Established Dietary Reference Intakes; or
b) Levels in conventional meat and seafood; or
c) Levels in other types of conventional foods with a history of safe consumption; or
d) Peer reviewed published toxicological thresholds.

If a DRI exists, the SAMI use level for Category 2 components is equivalent to an established DRI (*e.g.,* ADI, AI, RDI, RDA, etc.). Recommended or adequate intake values (e.g., ADI, AI, RDI, RDA), were selected as the benchmarks for safety assessment because they provide a more conservative approach than using the Tolerable Upper Intake Level (UL). Category 2 media components present at levels equal to or below the DRI levels satisfy the SAMI use level criteria and are safe for use in cultivated meat and seafood.

For substances with no established DRI, the concentrations of the substance in conventional meat and seafood or other foods (if they are not present in conventional meat and seafood) are used to establish SAMI use levels. The use level is derived by calculating 10% above the reported concentrations in conventional meat and seafood or other conventional foods, as previously described.

For substances without DRIs or reported concentrations in meat, seafood, or other foods, the SAMI use levels for Category 2 components are derived from a Margin of Exposure (MOE) calculation using an established NOAEL value, according to the principles described by FAO/WHO (2009). NOAELs are established from relevant and scientifically sound animal or human dietary studies. Appropriate uncertainty factors are applied to account for interspecies differences, intraspecies variability, and other uncertainties in the data. For example, an uncertainty factor of 100 is used to convert the NOAEL from a study in experimental animals (*e.g.,* repeated dose 90-day oral toxicity study in rats) into a mg/kg SAMI level. The mg/kg SAMI level is then multiplied by a conservative body weight value of 60 kg to reach the mg/day SAMI level. For the initial SAMI List, DRIs or concentrations in meat, seafood, or other foods exist for all components; therefore, derivation of a safe-use level based on a NOAEL was not required.

If a Category 2 component is estimated or measured in the cultivated meat or seafood product at a concentration above the SAMI use level, this is not an indication the level is unsafe, only that additional safety demonstration is required to reach a conclusion of safety under the conditions of intended use.

All media components must also meet specifications for food-grade substances (*e.g.,* those established by the FCC or JECFA), where available.

SAMI List Use Levels

The proposed SAMI use levels are expressed in milligrams (mg) per day, facilitating an exposure-based allowance for final cultivated meat and seafood products. For cultivated meat and seafood products that are consumed in smaller volumes, a higher concentration of the component may be acceptable, and conversely, lower concentrations may be warranted for cultivated products consumed in larger quantities.

Risk assessors may use the SAMI use level as follows: The concentration of a specific culture media component is estimated or measured in the final cultivated meat and seafood product (mg/kg) and multiplied by a daily serving size (kg/day), resulting in a daily intake value (mg/day). This is compared to the SAMI use level. Culture media components lower than the reported SAMI use level are concluded to be safe for their intended use in cultivated meat and seafood products. Conversely, higher concentrations do not signify that the final product is unsafe; rather, they indicate that further safety assessment is necessary to conclude safety of the component under the intended usage conditions.

Equation 2: Calculation of daily intake

$$Daily\ intake\ \left(\frac{mg}{day}\right) = Concentration\ of\ component\ in\ cultivated\ food\ \left(\frac{mg}{kg}\right)\ x\ daily\ serving\ size\ \left(\frac{kg}{day}\right)$$

The DRI values were obtained from those established by the Food and Agriculture Organization/World Health Organization (FAO/WHO) or other authoritative expert groups). SAMI use levels are equivalent to the established DRI value in mg/day.

Concentrations of components in conventional meat and seafood (beef, pork, chicken, and salmon), or other foods were obtained from government food composition databases and/or peer-reviewed literature. SAMI use levels are established at a 10% increase over the maximum concentration of the component in conventional food, as previously described.

The Chemical Abstract Service (CAS) registry numbers for the components originate from the specifications of relevant salt forms and isomers as listed in the Food Chemicals Codex (FCC) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). CAS numbers are provided for each component with an FCC or JECFA specification. Future versions of SAMI List may include additional salt derivatives or isomers that currently lack specifications.

Table 1 summarizes the proposed SAMI Use Levels.

Table 1. SAMI List Components with Use levels

Component	CAS Number	Type of Component	Category	FCC/ JECFA Spec	Derivation of SAMI Use level	SAMI use level (mg/day)
Glycine	56-40-6	Amino Acid	2	Yes	Concentration in meat and seafood	1584
L-Alanine	56-41-7 302-72-7	Amino Acid	1	Yes	Concentration in meat and seafood	1376
L-Arginine hydrochloride	74-79-3 1119-34-2	Amino Acid	1	Yes	Concentration in meat and seafood	1445
L-Asparagine monohydrate	70-47-3 5794-13-8	Amino Acid	2	Yes	Concentration in meat and seafood	3287
L-Aspartic Acid	56-84-8 617-45-8	Amino Acid	2	Yes	Concentration in meat and seafood	2554
L-Cysteine	52-89-1 7048-04-6	Amino Acid	2	Yes	Concentration in meat and seafood	271
L-Glutamic Acid	56-86-0 138-15-8	Amino Acid	1	Yes	Concentration in meat and seafood	3505
L-Glutamine	56-85-9	Amino Acid	2	Yes	Concentration in meat and seafood	3505
L-Histidine hydrochloride monohydrate	5934-29-2 71-00-1	Amino Acid	2	Yes	Concentration in meat and seafood	1089
L-Isoleucine	73-32-5 443-79-8	Amino Acid	2	Yes	Concentration in meat and seafood	1059
L-Leucine	61-90-5 328-39-2	Amino Acid	1	Yes	Concentration in meat and seafood	1822
L-Lysine hydrochloride	657-27-2	Amino Acid	1	Yes	Concentration in meat and seafood	2138
L-Methionine	63-68-3 59-51-8	Amino Acid	2	Yes	Concentration in meat and seafood	714
L-Phenylalanine	63-91-2 150-30-1	Amino Acid	2	Yes	Concentration in meat and seafood	904
L-Proline	147-85-3	Amino Acid	1	Yes	Concentration in meat and seafood	1089
L-Serine	56-45-1 302-84-1	Amino Acid	1	Yes	Concentration in meat and seafood	896
L-Threonine	72-19-5	Amino Acid	1	Yes	Concentration in meat and seafood	1059
L-Tryptophan	73-22-3 54-12-6	Amino Acid	2	Yes	Concentration in meat and seafood	279

Component	CAS Number	Type of Component	Category	FCC/ JECFA Spec	Derivation of SAMI Use level	SAMI use level (mg/day)
L-Tyrosine sodium salt dihydrate	60-18-4	Amino Acid	2	Yes	Concentration in meat and seafood	1000
L-Valine	72-18-4	Amino Acid	1	Yes	Concentration in meat and seafood	1218
Linoleic acid	60-33-3	Fatty acid	1	Yes	DRI	2200
Lipoic acid	1077-28-7	Fatty acid	2	No	Concentration in meat and seafood	0.099
Myristic acid	544-63-8	Fatty acid	1	Yes	Concentration in meat and seafood	2643
Oleic acid	112-80-1 143-19-1	Fatty acid	1	Yes	Concentration in meat and seafood	25740
Palmitic acid	57-10-3	Fatty acid	1	Yes	Concentration in meat and seafood	14543
Stearic acid	57-11-4 1592-23-0	Fatty acid	1	Yes	DRI	5700
Calcium chloride	10043-52-4 10035-04-8	Inorganic salt	2	Yes	DRI	Calcium - 1000
					DRI	Chloride - 3100
Cupric Sulphate	7758-98-7 7758-99-8	Inorganic salt	2	Yes	DRI	Copper – 0.9
					Concentration in conventional food	Sulphate - 102
Ferric Ammonium Citrate	1185-57-5	Inorganic salt	2	Yes	DRI	Iron - 8
					Concentration in meat and seafood	Ammonium - 18
					Concentration in conventional food	Citrate - 3040
Ferric Nitrate	7782-61-8	Inorganic salt	2	No	DRI	Iron - 8
					DRI	Nitrate - 223
Ferric Sulphate	7782-63-0 7720-78-7	Inorganic salt	2	Yes	DRI	Iron - 8
					Concentration in conventional food	Sulphate - 102
Magnesium Chloride	7791-18-6	Inorganic salt	2	Yes	DRI	Magnesium - 320
					DRI	Chloride - 3100
Magnesium Sulphate	14168-73-1 10034-99-8 15244-36-7	Inorganic salt	2	Yes	DRI	Magnesium - 320
					Concentration in conventional food	Sulphate - 102
	7447-40-7	Inorganic salt	1	Yes	DRI	Potassium - 2600

Component	CAS Number	Type of Component	Category	FCC/ JECFA Spec	Derivation of SAMI Use level	SAMI use level (mg/day)
Potassium Chloride					DRI	Chloride - 3100
Sodium Bicarbonate	144-55-8	Inorganic salt	1	Yes	DRI	Sodium - 2000
					Concentration in conventional food	Carbonate - 6600
Sodium Chloride	7647-14-5	Inorganic salt	1	Yes	DRI	Sodium - 2000
					DRI	Chloride - 3100
Sodium Phosphate Dibasic	7558-79-4 10028-24-7	Inorganic salt	2	Yes	DRI	Sodium - 2000
					DRI	Phosphorus - 800
Sodium Phosphate Monobasic	7558-80-7 10049-21-5	Inorganic salt	2	Yes	DRI	Sodium - 2000
					DRI	Phosphorus - 800
Sodium pyruvate	113-24-6	Inorganic salt	1	No	DRI	Sodium - 2000
					Concentration in conventional food	Pyruvate – 4.25
Sodium Selenite	10102-18-8 13410-01-0	Inorganic salt	2	Partial (selenate)	DRI	Sodium - 2000
					DRI	Selenium – 0.055
Zinc Sulphate	7446-20-0 7446-19-7	Inorganic salt	2	Yes	DRI	Zinc - 8
					Concentration in conventional food	Sulphate - 120
Biotin (Vitamin B7)	58-85-5	Vitamin	1	Yes	DRI	0.03
Cobalamin (Vitamin B12)	68-19-9	Vitamin	1	Yes	DRI	2.4
Choline Chloride (Vitamin B4)	67-48-1	Vitamin	2	Yes	DRI	425
D-Calcium pantothenate (Vitamin B5)	137-08-6 6381-63-1 6363-38-8	Vitamin	1	Yes	DRI	5
Folic Acid (Vitamin B9)	59-30-3	Vitamin	2	Yes	DRI	0.4
Niacinamide (Vitamin B3)	98-92-0	Vitamin	2	Yes	DRI	14
Pyridoxine hydrochloride (Vitamin B6)	58-56-0	Vitamin	2	Yes	DRI	1.3

Component	CAS Number	Type of Component	Category	FCC/ JECFA Spec	Derivation of SAMI Use level	SAMI use level (mg/day)
Riboflavin (Vitamin B2)	83-88-5 130-40-5	Vitamin	1	Yes	DRI	1.1
Thiamine Hydrochloride (Vitamin B1)	67-03-8 532-43-4	Vitamin	1	Yes	DRI	1.1
Vitamin A Acetate (Retinyl acetate)	68-26-8	Vitamin	2	Yes	DRI	0.7
Vitamin C (Ascorbic Acid)	50-81-7 134-03-2	Vitamin	2	Yes	DRI	75
D-Glucose	50-99-7|58367-01-4|50-99-7	Organic compound	1	Yes	DRI	50000
Hypoxanthine sodium salt	45738-97-4	Organic compound	1	No	Concentration in meat and seafood	128
i-inositol	87-89-8	Organic compound	1	Yes	Concentration in meat and seafood	41.6
Putrescine dihydrochloride	333-93-7	Organic compound	2	No	Concentration in meat and seafood	37.9

Derivation of SAMI Use Levels for Category 1 Components

This section explains the approaches employed in establishing SAMI use levels for the subcategories within Category 1 components.

Amino Acids

Category 1 amino acids include L-glutamic acid, L-leucine, L-lysine hydrochloride, L-threonine, L-valine, L-alanine, L-arginine hydrochloride, L-proline, L-serine. These amino acids have a history of safe consumption, have been reviewed as ingredients by panels of experts, and do not have established upper toxicity thresholds. None of these amino acids have established internationally recognized DRIs. There are reported concentrations in conventional meat and seafood. Therefore, the SAMI use level was derived from a 10% exceedance of the reported amino acid concentration in conventional meat and seafood.

Fatty Acids

All listed fatty acids (except lipoic acid) are classified as Category 1 components. These fatty acids have a history of safe consumption as a component of food, and do not have established upper toxicity thresholds. Stearic acid and linoleic acid have established ADIs or RDIs which were used to derive the SAMI use level. The remaining fatty acids (myristic acid, oleic acid, and palmitic acid) have reported concentrations in conventional meat and seafood, and SAMI use levels were derived using a 10% exceedance of the reported fatty acid concentration in conventional meat and seafood.

Inorganic Salts

Potassium chloride, sodium bicarbonate, and sodium chloride are classified as Category 1. These inorganic salts have a history of safe consumption, have been reviewed for safety by experts, and their respective dissociated ions do not have established upper toxicity thresholds. The SAMI use level for each inorganic salt was derived from the established DRI for the dissociated compounds of the inorganic salt.

Vitamins

Biotin, D-calcium pantothenate, riboflavin, thiamine hydrochloride, and cobalamin are classified as Category 1 components. These vitamins have a history of safe consumption, have been reviewed by expert panels, and do not have established upper toxicity thresholds. The SAMI use level for each vitamin was derived from an established DRI.

Organic Substances

Five other organic substances are included on the SAMI List: D-glucose, i-inositol, hypoxanthine

sodium salt, and putrescine dihydrochloride. Except for putrescine dihydrochloride, these substances were classified as Category 1 components. These organic substances have a history of safe consumption as components of food, and do not have established upper toxicity thresholds. The SAMI use level for D-glucose was derived from the established daily upper intake recommendation level. None of the other organic substances had a DRI value. I-inositol and hypoxanthine sodium salt have reported concentrations in conventional meat and seafood, therefore the established SAMI use level for these components was derived from a 10% exceedance of the reported concentration of the substance in conventional meat and seafood.

Category 1 Case Study – L-alanine

L-alanine is an amino acid with a long history of safe consumption and has been reviewed by several expert panels and concluded to be safe (FAO/WHO 2005, EFSA 2010). Oral toxicity studies were conducted for L-alanine. A four-week oral toxicity study in Sprague-Dawley rats observed that a repeated oral dose of 2000 mg/kg bw/day of L-alanine did not result in any adverse effects (Aoki *et al.*, 2014). The highest concentration administered in the study was 2000 mg/kg. Therefore, a NOAEL could not be established for L-alanine. Additionally, no established DRIs exist for L-alanine or any of the other amino acids. The concentration of L-alanine in conventional meat and seafood is reported in government food composition databases. The concentrations of L-alanine in beef, pork, chicken, and salmon were obtained from USDA FoodData Central, FSANZ Australian Food Composition Database - Release 2.0, and MEXT - Standard Tables of Food Composition in Japan - 2015 - (Seventh Revised Version). Values from beef, pork, and chicken are used to represent meat and poultry values. Salmon was chosen to represent seafood because of the availability of composition data and because salmon aquaculture is the fastest-growing food production system in the world (WWF 2024).

The L-alanine concentration ranges for beef, pork, chicken, and salmon were 620-1290 mg/100 g, 750-1200 mg/100 g, 984-1300 mg/100 g, and 1200-1390 mg/100 g, respectively. This results in a range of 620-1390 mg/100 g for L-alanine in conventional meat and seafood. The calculated 10% exceedance for that range is 558-1529 mg/100 g. The 10% exceedance of the maximum concentration of L-alanine in conventional meat and seafood was adjusted from a recommended single serving size of 90 g of conventional meat and seafood to result in the derived SAMI safety limit of 1376 mg/day for L-alanine for one serving of cultivated meat and seafood. Final cultivated meat and seafood products containing L-alanine in concentrations equal to or less than 1376 mg/day are similar to levels in conventional food and do not pose a food safety concern. Cultivated meat and seafood products containing concentrations of L-alanine that result in consumption of greater than 1376 mg per day of L-alanine

fall outside of the scope of the SAMI List and require additional effort to demonstrate safety at the intended use levels. Note than an exceedance of the SAMI use level indicates only that additional analysis is required, not that the product is not safe for consumption.

Derivation of SAMI Use Levels for Category 2 Components

This section describes the approach used in establishing SAMI use levels for the subcategories within Category 2 components.

Amino Acids

The Category 2 amino acids include glycine, L-cysteine, L-isoleucine, L-methionine, L-phenylalanine, L-tryptophan, L-asparagine monohydrate, L-aspartic acid, L-glutamine, L-histidine monohydrate, and L-tyrosine sodium salt dihydrate. These amino acids: have a history of safe consumption; have been reviewed by expert panels; and have established NOAEL values. These amino acids do not have internationally recognized established DRI values. However, they did have reported concentrations in conventional meat and seafood. Therefore, the established SAMI use level was derived from a 10% exceedance of the reported amino acid concentration in conventional meat and seafood.

Fatty Acids

Lipoic acid is classified as a Category 2 component. Lipoic acid has a history of safe consumption as a component of food and has an established toxicological threshold (a NOAEL value). There is not an established DRI value for lipoic acid. However, there are reported concentrations of lipoic acid in conventional meat and seafood. Therefore, the established SAMI use level for lipoic acid was derived from a 10% exceedance of the reported concentration of the fatty acid in conventional meat and seafood.

Inorganic Salts

Calcium chloride, cupric sulphate, ferric ammonium citrate, ferric nitrate, ferric sulphate, magnesium chloride, magnesium sulphate, sodium phosphate dibasic, sodium phosphate monobasic, sodium pyruvate, sodium selenite, and zinc sulphate are classified as Category 2 components. Their respective dissociated ions have a history of safe consumption and have been reviewed by expert panels, but also have established UL values. The SAMI use level for each inorganic salt was calculated from the established DRI value for the dissociated compounds of each inorganic salt.

Vitamins

Choline chloride, folic acid, niacinamide, pyridoxine hydrochloride, retinyl acetate, and ascorbic acid are classified as Category 2 components. The vitamins have a history of safe consumption and have been reviewed by expert panels, with have established UL values. The SAMI use level for each vitamin was calculated using the established DRI value.

Other Organic Substances

Putrescine dihydrochloride is classified as Category 2 due to a history of safe consumption as a component of food and has an established toxicological threshold (a NOAEL value). Putrescine does not have an established DRI value. However, there are reports of putrescine concentrations in conventional meat and seafood available in the literature. Therefore, the established SAMI use level for putrescine dihydrochloride was derived from a 10% exceedance of the reported concentration in conventional meat and seafood.

Category 2 Case Study - Sodium phosphate dibasic

Sodium phosphate dibasic is an inorganic salt that dissociates into sodium and phosphate ions in aqueous solution. Sodium and phosphorus have long histories of safe consumption as they are present in conventional foods. In addition, sodium phosphate dibasic has a long history of use in food processing. The FAO/WHO recommends a maximum of 2000 mg/day sodium in adults (FAO/WHO 2014). No ULs have been established for sodium. The FAO/WHO established an RDA of 800 mg/day and a UL of 4000 mg/day for phosphorus (FAO/WHO 2019). Due to the establishment of a UL for the dissociated component of phosphorus, sodium phosphate dibasic is classified as a Category 2 substance. Sodium and phosphorus have established DRI values, and these were used to derive the SAMI use levels. The SAMI use levels for the dissociated components of sodium and phosphorus are equal to their established DRI values, 2000 mg/day and 800 mg/day, respectively. Final cultivated meat and seafood products containing sodium in concentrations equal to or less than 2000 mg per day and phosphorus in concentrations equal to or less than 800 mg per day are within the scope of the SAMI List and do not pose a food safety concern at the intended use levels. Cultivated meat and seafood products containing concentrations of sodium greater than 2000 mg/day or concentrations of phosphorus greater than 800 mg/day are outside of the scope of the SAMI List, however, are not unsafe; additional arguments of safety are needed to demonstrate safety at the intended use levels,

Next steps

This project is intended to serve as a starting point for discussion toward a more efficient safety assessment of the inputs to cultivated meat and seafood products. Feedback from stakeholders plays a vital role in enhancing the risk assessment framework and the SAMI List, as we aim to ensure that the methods used align with international food risk assessment standards, providing value to the industry, regulators, and other involved parties.

The next step is to gather stakeholder feedback on the categorization approach and SAMI List. The vision is to expand the list further to other Category 1 and 2 components commonly used in cultivated meat and seafood production and, as more data is developed, eventually include Category 3 substances.

Questions for discussion

- Share your views on the categories and the methodology to derive the categories. What are the other considerations that should be taken into account?
- What would be the major challenges to assessing the safety substances with little to no history of safe use (i.e. category 3 and 4 substances)?
- Share your views on the concept of the SAMI list, considering your role (e.g academia, industry, regulators).

Survey Questions

- Do you agree with the methodology to derive the categories? (Yes/No/Not sure)
- Do you agree with the methodology to derive the safety assessed media ingredient list use level? (Yes/No/Not sure)
- Is the safety assessed media ingredient list framework and list beneficial? (Yes/No/Not sure)
- Do you think the list should be expanded? (Yes/No/Not sure)
- If you selected no to any of the above questions, why? (optional)

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Annex C – Pre-read materials and questions for the breakout discussion on Production of Fermentation derived Novel Food Products

Background

Fermentation is one of the oldest food processing technologies that utilises microorganisms, such as bacteria, yeasts, and fungi, to break down complex molecules into simpler ones. While traditional fermentation methods have long been used to create staples like bread, cheese, and yogurt, recent technological advancements have given rise to a new category of food: fermentation-derived novel foods.

In recent years, there are two emerging categories of fermentation-derived novel foods:

1. Foods from biomass fermentation
    a. Biomass fermentation involves the cultivation of microorganisms to produce a biomass that is harvested and used directly in food. This method of production relies on the natural growth of the microorganisms to convert organic substrates into biomass.
2. Foods from precision fermentation
    a. Precision fermentation involves the cultivation of microorganisms (typically genetically modified organisms) to produce specific compounds. At the end of the fermentation process, the food ingredients to be consumed undergo a purification process to isolate them from the starting culture.

Unique considerations of Fermentation-Derived Novel Foods

Fermentation-derived novel foods can differ from their traditional counterparts in their production methods and applications. While traditional fermentation often involves spontaneous microbial action on food substrates, biomass and precision fermentation techniques requires a rigorously controlled environment to produce targeted products. This shift from natural to engineered processes introduces a series of unique safety considerations, including:

- Contamination of fermentation process
- Cross-contamination of starting cultures with other production organisms
- Genetic stability of production organisms
- Use of waste side stream inputs
- The use of genetically modified production organisms (applicable to precision fermentation only)
- Purity of precision-fermentation derived products (applicable to precision fermentation only)

Production of Fermentation-Derived Novel Foods

Currently, manufacturers of fermentation-derived novel foods can apply Codex General Principles of Food Hygiene or local Good Manufacturing Practices to guide the design and operation of their production process. However, these documents are intended for wide application across the production of different food types and may not fully address the unique considerations associated with the production of fermentation-derived novel foods.

To evaluate the necessity and potential benefits of developing a guidance for the production of fermentation-derived novel foods, we invite participants to discuss the aforementioned considerations and their corresponding best practices. A table briefly discussing the rationale and best practices for these additional considerations has been prepared to serve as a starting point for the discussion.

Additional considerations and rationale	**Measures**	**Examples of best practices**
Contamination of fermentation process Exposure to foreign microorganisms or other contaminants may result in the formation of undesirable substances and/or fermentation failures.	Sterilisation of media components and equipment	• Sterilisation of all media components and equipment should destroy or remove foreign organisms that might come into contact with the process fluids. • The sterilisation processes applied should be suitable having regard to the specific characteristics of the product. • In particular, where the sterilisation of the starting and raw materials is required, it should be ensured that the sterilisation process applied (e.g. heat, irradiation, filtration, or chemical inactivation) is effective in terms of removing the contaminants while preserving the activity of starting or raw materials and excipients.
	Aseptic operations	• Operations should be conducted in an aseptic environment to minimise the risks of contaminating organisms entering the fermentation process after initial sterilisation.

<u>Cross-contamination of starting cultures with other production organisms</u> Inadvertent mixing of production organisms within a shared facility handling multiple strains may result in the formation of undesirable substances and/or fermentation failure.	Storage of materials	• All materials and products should be stored under appropriate conditions to ensure their quality and in an orderly fashion to permit batch segregation and stock rotation. • Personnel should be adequately trained to properly label and store materials to prevent mix up and consequent cross-contamination.
	Documentation	• A system that enables the tracking of production organisms from the point of acquisition to its disposal should be created. • Records should be made for all appropriate action to enable the entire history of a batch to be traced.
<u>Genetic stability of production organism</u> Shifts in genetic expression of production organisms may not be detected and may result in the formation of undesirable substances which are not removed during downstream processing	Controllability and reliability of fermentation conditions	• Controlling fermentation conditions ensures that the production organisms are not subjected to environmental, medium, or other conditions outside the range in which it is known to yield product meeting acceptable specifications. • Fermentation parameters should be validated and monitored to ensure fermentation occurs within pre-determined growth conditions and ensure culture purity. • Validation of proposed design of facilities, systems, and equipment should be conducted to ensure consistency in fermentation products.

		• Personnel handling genetically modified organisms should be given specific training relevant to their tasks including the basic aspects of microbiology, hygiene, gowning practices, cleanroom practices, contamination control and aseptic techniques.
<u>Use of waste side stream inputs</u> The use of waste side stream inputs may introduce additional contaminants to the fermentation process, potentially leading to the formation of undesirable products and/or fermentation failure.	Documentation	• Comprehensive descriptions of all raw and starting materials should be recorded to ensure quality and safety of fermentation inputs.
	Pre-processing of side stream inputs	• Where waste side stream inputs are used, it should be processed to remove potential contaminants before being added into the fermentation process.
<u>The use of genetically modified production organisms (applicable to precision fermentation only)</u> Genetically modified organisms may pose a risk to biodiversity and public health if released outside of the production facility.	Containment	• Containment measures should be established to ensure that genetically modified organisms are not transported to any area inside or outside the plant before they have been rendered harmless. • Appropriate decontamination measures should be implemented when personnel, equipment or materials move between areas where different GMOs are handled and areas where non-GMOs are handled. Unidirectional flows should be considered where possible.
<u>Purity of precision-fermentation derived products (applicable to precision fermentation only)</u> The presence of production organisms and/or media components could lead to downstream food safety concerns, namely allergenicity.	Purification of fermentation product	• Purification processes should be established, validated, and monitored to effectively isolate the intended product and remove or inactivate the production organism, cellular debris, and media components while minimising the loss of quality.

Discussion Questions

- Share your views on the unique considerations associated with the fermentation derived novel foods listed above. Are there additional considerations specific to precision fermentation and/or biomass fermentation?
- What are some of the best practices to address these considerations?
- Discuss the usefulness of having good manufacturing practices/guidance for the production of fermentation derived novel foods:
    - How will the guidance document impact the industry's growth and innovation?
    - Would having a guidance document have any benefits on operations?
    - What are some of the key challenges you foresee?