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New food sources and production systems: a comparison of international regulations and China's advancements in novel foods with synthetic biology

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ABSTRACT

The global shift towards sustainable food systems has sparked innovations in food sources and production systems, including cell-based meat, plant-based food products, precision fermentation, and 3D food printing. These advancements pose regulatory challenges and opportunities, with China emerging as a critical player in adopting and regulating new food technologies. This review explores the international landscape of new food sources and production systems (NFPS), focusing on China's role and regulatory approaches compared to global practices. Through this comparative analysis, we aim to contribute to the ongoing dialogue on food safety regulation, offering insights and recommendations for policymakers, industry stakeholders, and researchers engaged in the global food system's evolution. This comprehensive overview underscores the dynamic nature of regulatory frameworks governing NFPS, highlighting the international efforts to ensure food safety, consumer protection, and the sustainable evolution of the food industry.

1. Introduction

The escalating global food crisis, accentuated by population growth, rising living standards, and the resultant strain on our finite natural resources, necessitates a paradigm shift in food production methodologies[1]. With the food sector contributing to 34% of total greenhouse gas emissions in 2015[2], the urgency to mitigate environmental impact while securing the food supply is undeniable. Challenges such as environmental degradation, natural resource depletion, and various global dynamics—including climate change, urbanization, and the aftermath of the pandemic—underscore the vulnerability of agri-food systems to shocks and stressors. These circumstances highlight the pressing need to bolster the resilience of agri-food systems and their capacity to anticipate, absorb, and adapt to global disruptions, ensuring access to sufficient, safe, and nutritious food for all. The international community advocates for the transformation of agri-food systems towards greater efficiency, resilience, inclusiveness, and sustainability, aligning with the objectives of the 2030 Agenda for Sustainable Development[3].

This transformation, amid evolving global contexts, requires forward-looking approaches like foresight to navigate the emerging trends and challenges effectively. Among the primary drivers of change is the increasing global population, projecting a higher demand for food production within the limitations of our planetary boundaries. Concurrently, global meat consumption is witnessing an annual increase of 2%, suggesting a rising demand for protein, particularly in middle-income countries, amidst growing awareness

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of climate change and environmental sustainability[4]. This scenario prompts a shift towards diets incorporating a broader diversity of food sources through innovations in food production systems, including the reutilization of food waste into agri-food systems.

In the lead-up to the United Nations Food System Summit scheduled for 23 September 2021, the Scientific Group orchestrated the 'Science Days for the UN Food System Summit 2021', which was facilitated and hosted by the Food and Agriculture Organization (FAO) on 8–9 July 2021[5]. During the event, experts deliberated on the role of agricultural biotechnology, with discussions encompassing a dedicated session on bio-science innovation. This session explored an array of topics including genome editing, bioinformatics, synthetic biology, microbiomes, alternative protein sources, novel sources of essential micronutrients, cell factories, and more.

Scientific and technological advancements are redefining the framework of research and innovation, traditionally centered around material genetic resources and associated information, towards a model increasingly reliant on digital sequence information (DSI)[6]. This shift has precipitated the generation of vast data sets, the establishment of new data-centric organizations, the advancement of breakthrough technologies such as CRISPR Cas-9, and the emergence of novel scientific fields like synthetic biology. Concurrently, there is a global movement towards the democratization of data through open data initiatives and the unencumbered exchange of information worldwide. This segment of the analysis highlights the principal aspects of these technological transformations and examines their implications for key access and benefit-sharing (ABS) principles and the components of the multilateral system (MLS)[7].

Synthetic biology, a field derived from engineering disciplines, integrates various genetic and genomic technologies and techniques. While it has been characterized in numerous ways, consensus on a definitive definition remains elusive, reflecting the rapid evolution of the technological landscape[8]. Common to most definitions, however, is an emphasis on the foundational elements of engineering, applied science, and technology across diverse applications. Nonetheless, products derived from these technologies are subject to premarket approval and rigorous safety assessments[9].

New food sources and production systems (NFPS) are emerging as innovative solutions to meet growing food demands while addressing environmental and food security challenges. This includes a wide range of options from traditional sources like insects, macroalgae, and various plants, to more unconventional ones such as hydrogen-oxidizing bacteria[10], alongside revolutionary approaches like cell-based food production[11], controlled environment agriculture[12], and 3D food printing (3DFP)[13]. Additionally, the rising popularity of plant-based products, aimed at replicating the taste and nutritional benefits of meat using plant ingredients, offers a sustainable alternative to animal-derived foods[14]. These advancements present promising avenues to tackle the challenges of food demand, yet they also bring about regulatory challenges, particularly in ensuring food safety.

The increasing complexity of NFPS underscores the urgency for thorough risk evaluations and the creation of suitable regulatory frameworks[15]. Key global and regional organizations, including the World Health Organization (WHO), and regulatory bodies across Europe, the Americas, and Asia-Pacific, are at the forefront of crafting these crucial regulations. The European Union's Novel Food Regulation (2015/2283), for instance, has established a benchmark for a harmonized safety assessment process for introducing foods to the market, underscoring the importance of consumer safety and the right to informed choice[16]. Concurrently, the United States Food and Drug Administration (FDA) leverages the generally recognized as safe (GRAS) notification program to ensure the safety of novel foods[17]. A groundbreaking development occurred in December 2020 when Singapore made history by approving the sale of cell based meat, marking a significant breakthrough in the global food sector[18]. In support of national and regional initiatives, the Codex Alimentarius Commission (CAC), a collaborative effort between the WHO and FAO, endeavors to establish comprehensive international food standards that promote equitable trade and safeguard global consumer health[19]. This collective and adaptable regulatory approach is indispensable for navigating the complexities of modern food production, fostering innovation, and upholding public confidence in the safety and integrity of an evolving food supply chain.

China, with its burgeoning population and rapidly advancing food industry, is at the vanguard of adopting NFPS. The nation is actively adapting its regulatory framework in response to the rapid advancement of food technologies, including synthetic biology, precision fermentation, and novel food sources, to bolster innovation while ensuring the safety and quality of food products. This regulatory evolution is in alignment with China's strategic objectives for food security and sustainability, crafted to mitigate the challenges introduced by new food sources and stimulate research and development within the food sector. This review critically analyzes China's regulatory measures, policies, and standards in juxtaposition with global practices, offering comprehensive insights into how China's regulatory system is designed to support innovation while adhering to stringent food safety standards. It delineates the challenges, advancements, and prospective directions for enhancing food safety in the age of synthetic biology and food production. Moreover, it emphasizes the crucial role of regulatory agility and international collaboration in achieving the harmonization of safety standards and promoting the worldwide adoption of sustainable and safe food innovations.

2. NFPS

NFPS are areas of increasing focus due to the rising global population and the environmental impacts of traditional agriculture. The CAC, a joint initiative of the WHO and FAO, plays a critical role in defining standards and guidelines for these emerging food technologies and sources[20]. The term "new" food sources refer to those that have not been extensively consumed on a global scale, often due to their historical consumption being confined to specific regions or because they have only recently become available in the global market as a result of technological advances. Similarly, new food production systems denote innovative or enhanced technologies in existing food production methods that facilitate the creation of these emerging foods entering the mainstream market. The recent publication by the FAO has catalogued several of these new food sources and systems, detailing both their potential benefits and the challenges they pose[19,21-22]. Each of these new food sources offers promising alternatives with unique benefits and specific challenges that need to be addressed to achieve wider acceptance and integration into global food systems.

2.1 New food sources

“New” food sources imply those that have not been widely consumed, either because their consumption has been historically restricted to certain regions of the world or they have recently emerged in the global retail space thanks to technological innovations[15]. The topic of innovative food sources and food production systems has recently attracted considerable attention at the Codex level, as evidenced by discussions during the 81st Session of the Executive Committee of the Codex Alimentarius Commission (CCEXEC81) and the 44th Session of the Codex Alimentarius Commission (CAC44). Notable among the new food sources identified by the FAO are edible insects, jellyfish, plant-based substitutes, and seaweeds (or macroalgae) (Fig. 1). Additionally, microalgae (such as spirulina and chlorella) are increasingly recognized as emerging resources. At the same time, microalgae (such as spirulina and chlorella) as sustainable new food resources are also increasingly gaining attention.

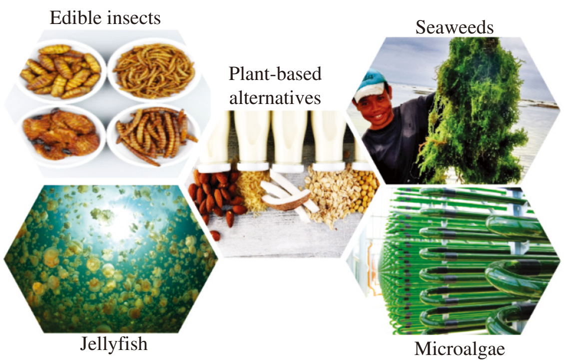

Fig. 1 New Food Sources from the FAO’s perspective[15].

Edible insects: Edible insects represent a sustainable alternative to conventional meat and are praised for their high efficiency in converting feed into protein. They offer significant environmental benefits, requiring far less water and land compared to traditional livestock and emitting fewer greenhouse gases[23]. Popular edible insects include crickets, grasshoppers, and mealworms, which are rich in protein, fats, and micronutrients[24]. Although widely consumed in many parts of the world, the primary challenge for global acceptance is overcoming cultural biases and ensuring safe, scalable production methods.

Jellyfish: Jellyfish are being explored as a novel food source due to their abundance and potential as a protein alternative in an overfished world[25]. They have a low-fat content and are rich in collagen, which might offer health benefits. Jellyfish harvesting could also help manage their populations, which are increasing due to ocean warming and decreased predation. However, challenges include developing appealing culinary techniques, ensuring safe consumption since some species can be toxic, and increasing consumer familiarity with jellyfish as a palatable option[26].

Plant-based alternatives: Plant-based alternatives to meat and dairy products have gained popularity as sustainable dietary options. These products aim to mimic the sensory attributes of animal products while offering environmental and ethical advantages, such as lower carbon footprints and reduced use of natural resources[27]. Ingredients like soy, peas, and various nuts serve as the base for these alternatives, providing high protein content. The primary challenges are improving nutritional profiles, reducing reliance on processed ingredients, and broadening consumer acceptance beyond vegetarians and vegans[28].

Seaweeds/Macroalgae: Seaweeds and macroalgae are highly nutritious, offering a rich source of iodine, vitamins, and minerals[29]. As marine plants, they require no arable land, freshwater, or fertilizers and are capable of mitigating climate change effects by absorbing CO_2. Seaweeds are versatile in culinary applications, from salads to seasonings. However, the challenges lie in scaling up sustainable farming practices, ensuring product safety from marine pollutants, and integrating them into Western diets where they are less traditionally consumed[30].

Microalgae: Microalgae, such as *spirulina* and *chlorella*, are emerging as superfoods due to their dense nutritional profiles, including high levels of proteins, essential fatty acids, and vitamins[31]. They can grow in various water conditions, including wastewater, making them a sustainable choice for food production. The scalability of microalgae cultivation presents opportunities for substantial food production with minimal environmental impact. The main challenges include reducing high production costs, achieving flavors acceptable to mainstream consumers, and overcoming the hurdle of mass consumer education about their benefits.

2.2 New production systems

New food production systems reflect novel innovations or advancements in pre-existing food technologies that are involved in producing some of the new foods that are finding their way into the mainstream. The FAO is increasingly attentive to innovative food production technologies that could play a crucial role in addressing food security, nutrition, and sustainability challenges. Among these innovative approaches, cell-based food production, precision fermentation using synthetic biology, and 3DFP are emerging as transformative technologies (Fig. 2).

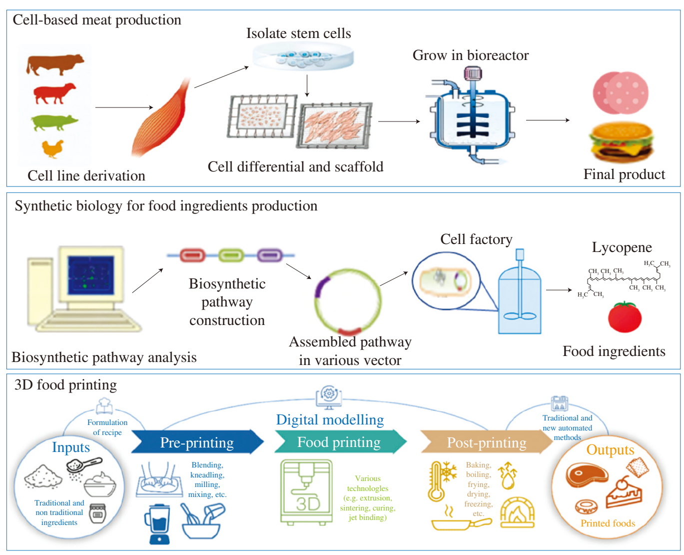

Fig. 2 New food production system on FAO’s discussion[15,51-52].

Cell-based food production: As global meat consumption rises, particularly in middle-income countries, there’s a growing movement towards alternative protein sources due to environmental and ethical concerns[4]. Cell-based food production involves culturing cells isolated from animals followed by processing to produce food products that are comparable to the corresponding animal versions, such as meat, poultry, aquatic products, dairy products and eggs[32]. Cell-based meat, a pioneering food technology, offers a viable solution by growing meat from animal cells, thus reducing reliance on conventional livestock farming[33]. This process significantly lessens environmental impacts, such as greenhouse gas emissions, land use, and water consumption, while also addressing animal welfare issues. Cell-based meat is produced by cultivating animal cells in a controlled environment, rather than harvesting from slaughtered animals[33]. This technique requires advanced tissue engineering and optimizations in cell culture media, bioreactor configurations, and scaffolding materials to replicate the texture and nutrition of traditional meat[18]. Significant progress has been made in enhancing the efficiency, scalability, and quality of cell-based meat, with efforts now focusing on reducing production costs and improving scaffolding materials[34]. The industry achieved a milestone with regulatory approval in Singapore in 2020, setting a precedent for global market entry. Future developments aim to scale production, lower costs, expand meat variety, and potentially incorporate technologies like 3D bioprinting to customize textures and nutritional content, paving the way for wider consumer acceptance and regulatory approval[34-36].

Precision fermentation with synthetic biology: Synthetic biology is transforming food production by utilizing genetically modified microorganisms (GMMs), such as yeast, bacteria, and fungi, to produce organic molecules like proteins, fats, and flavors (Fig. 3)[37]. This technology enables the production of compounds identical to those in animal products without the need for traditional farming[38]. The process involves genetically engineering microorganisms to produce specific molecules, which are then cultured in bioreactors through fermentation, converting substrates like sugars into desired products. Key process parameters such as temperature, pH, and nutrient supply are tightly controlled to maximize efficiency and product quality. Significant advancements in synthetic biology include its capacity to "facilitate the conceptualization and planning of the engineering of biological components, such as DNA base pairs, codons, amino acids, genes, gene segments, regulatory elements, and the environmental contexts in which they operate"[8]. Therefore, synthetic biology is typically framed within the engineering paradigm known as the design-build-test (DBT) cycle. This cycle outlines a dynamic process wherein the technologies constituting each phase may be subject to modification, replacement, or evolution over time. The automation of the design phase through advanced computer algorithms, software, and machine learning has markedly decreased the duration required to develop new biological components. A critical element of this automation is the utilization of "collections of realizable DNA constructs", which enable researchers not only to design novel genetic functions or traits but also to predict their

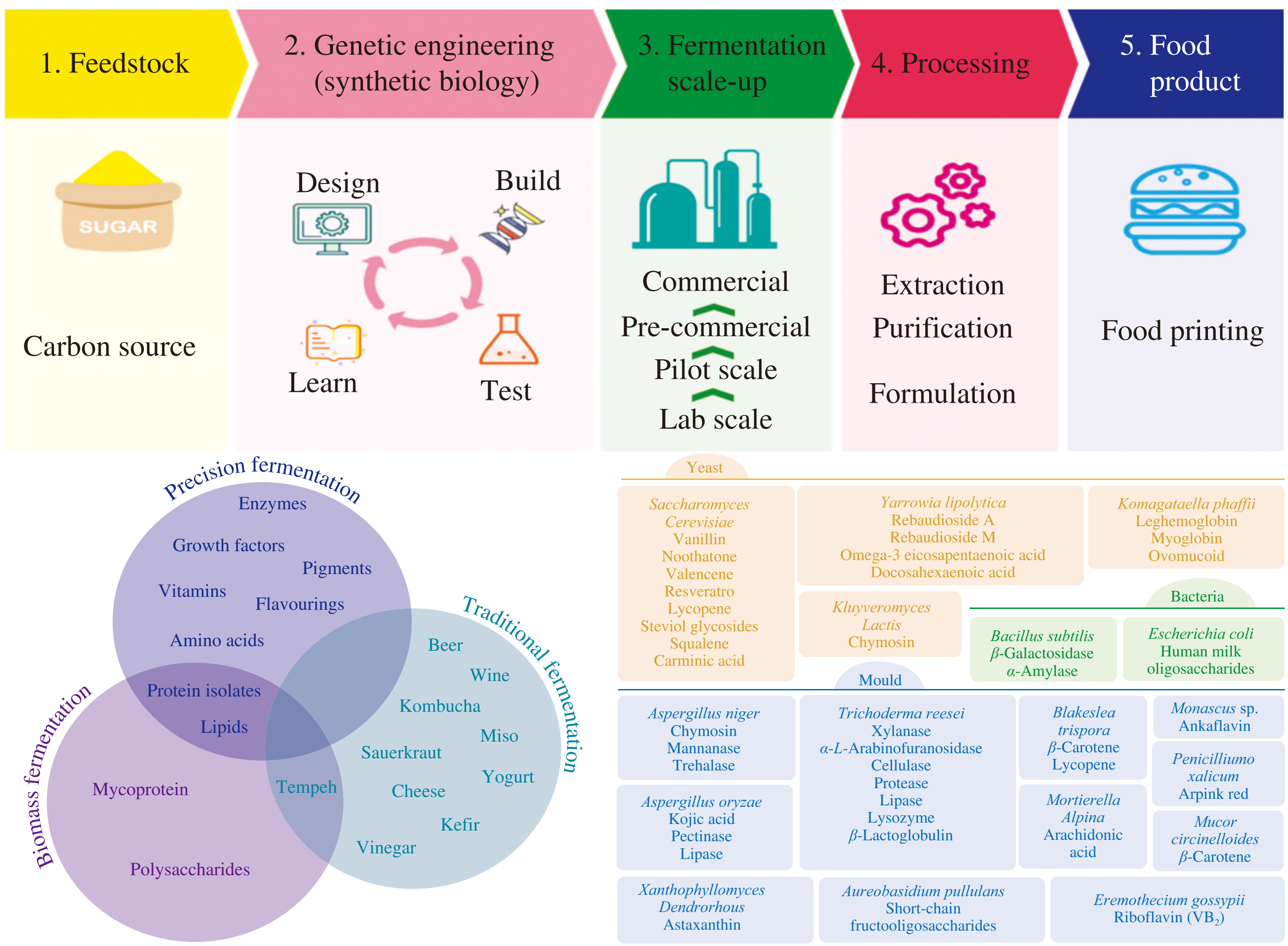

Fig. 3 Precision fermentation powered by synthetic biology for novel food production.

operational dynamics within specific living organisms or systems (e.g., gene expressions)[39]. Recent advances in synthetic biology have enabled the production of alternative proteins and dairy substitutes that closely replicate the sensory and nutritional qualities of their conventional counterparts[40-41]. This method is not only more sustainable but also more ethical compared to traditional animal agriculture[42]. Looking to the future, ongoing research is focused on enhancing the efficiency and reducing the costs associated with these technologies. Innovations in bioreactor design and microbial strain engineering are anticipated to improve the scalability and economic viability of using synthetic biology in food production. Precision fermentation, a core component of this approach, refines the process of selecting and optimizing the growth conditions of these engineered microorganisms to achieve higher yields and better mimic the desired characteristics of food products[37]. Precision fermentation, also known as industrial microbial fermentation or precision biomanufacturing, refers to a controlled production process that utilizes microorganisms such as bacteria, yeast, or fungi to synthesize specific target products. This advanced technique enables the production of a diverse array of products, including enzymes, growth factors, vitamins, flavorings, amino acids, protein isolates, and lipids—essential components for crafting highly specialized and customized food ingredients[37]. Distinct from the general scope of biomass and traditional fermentation, precision fermentation is a refined process, yielding specific components critical for contemporary food technology and broader industrial applications. This technique synthesizes tradition with innovation, marking a leading edge in biotechnological progress in fermentation. Precision fermentation not only underscores the potential of synthetic biology to meet global food demands but also highlights its role in driving the next wave of food technology innovation[42]. The integration of precision fermentation with others, such as 3D printing, promises to further transform food manufacturing by enabling the creation of customizable and nutritionally enhanced food products[43].

As the global demand for proteins and specific nutrients grows, many in the food sector are looking into opportunities to expand the scope of diverse sources of proteins that can be both environmentally sustainable and nutritionally sound. The commercial landscape for cell-based food and precision fermentation is fast expanding with various companies developing assorted products around the world.

3DFP: 3DFP, an advanced additive manufacturing technique, is transforming the culinary and food production sectors by enabling precise customization of food items in terms of shape, texture, and nutrition[44]. This technology uses various food-grade materials, such as purees, doughs, proteins, and carbohydrates, as "inks"[45]. These are layered according to digital models, allowing for the integration of diverse ingredients to customize flavors, colors, and nutrients to meet individual dietary needs[46]. The advancement of 3DFP has broadened its applications across food sectors, enhancing the texture and taste of products to meet consumer expectations[13]. It is especially impactful in creating meat substitutes, aiming to replicate the sensory qualities of animal-derived meats, thus offering sustainable and ethical alternatives[47]. This technology is invaluable for addressing the dietary needs of specific groups, such as the elderly or those with particular health conditions. The future of 3DFP not only focuses on customization for personal health and preference but also emphasizes sustainability by incorporating alternative proteins like insect or plant-based sources[46,48]. Expected developments in more complex forms of printing, such as 4D, 5D, and 6D, promise dynamic flavor changes and interactive culinary experiences, further revolutionizing food perception and consumption to meet global consumer needs more interactively and innovatively[49-50].

3. Knowledge of food safety implications of NFPS

The NFPS introduce both opportunities and challenges within the agri-food landscapes, particularly emphasizing food safety concerns. These concerns are complex, encompassing microbiological, chemical, and physical hazards, each necessitating targeted strategies to safeguard consumer health. Although the principal food safety risks tied to NFPS might not be intrinsically new, the agri-food structures, which include production techniques, stakeholders, and distribution channels developed for these emerging food innovations, are relatively nascent[15]. This novelty presents potential vectors for the introduction of food safety hazards. Among these, cell-based meat, plant-based food products, synthetic biology, and food printing emerge as critical areas. These fields are rapidly gaining traction yet exhibit substantial gaps in food safety knowledge, warranting focused research and regulatory scrutiny.

3.1 Food safety implication for cell-based meat

The production of cell-based meat and seafood involves complex manufacturing methods that may introduce new safety concerns not typically associated with traditional food sources. This section outlines potential hazards identified at each step of the process, highlighting how some hazards are omnipresent while others are specific to particular stages. The hazards linked to specific manufacturing steps and their potential outcomes requiring investigation have been summarized by a review[52].

Microbiological contamination: Microbiological contamination, including bacteria, fungi, and viruses, presents a significant risk throughout cell-based meat production. Mycoplasma, in particular, poses a unique challenge due to its small size, antibiotic resistance, and slow growth, making it difficult to detect and control. Unlike conventional meat, which can be contaminated by microbes in animals and their environments, cell-based meat offers reduced contamination risks[53]. However, the entire manufacturing process, from cell culture to final product processing, must be rigorously controlled to prevent contamination.

Source animal: The health status of the source animal can significantly influence the introduction of biological hazards, such as infectious diseases and prions, into cell-cultured products. The transmission of infectious viral diseases and the propagation of prions responsible for neurodegenerative diseases are of particular concern. Ensuring the health and disease-free status of source animals, along with thorough inspection of biopsied tissues, is crucial for minimizing these risks.

Cell culture medium: The cell culture medium, essential from procuring target tissues/cells through to product collection, may harbor hazards associated with its intended components and potential contaminants. Ingredients of animal origin, such as fetal bovine serum, can introduce viral or prion contamination. Moreover, the novelty and concentration of inputs in the culture medium pose additional safety considerations, including allergenicity and growth factors at levels potentially hazardous to human health.

Antibiotics: The use of antibiotics in cell culture media to control microbial growth raises concerns about the persistence of these substances in the final product and their contribution to antibiotic resistance. Although many producers strive to avoid antibiotics through sterile conditions, their potential use necessitates careful documentation and assessment to ensure they do not risk human health or contribute to broader antibiotic resistance issues.

Cryoprotectants: Cryoprotectants used during cell storage may be toxic if present in the final food product. While many cryoprotectants are already used in food processing and deemed safe at specific concentrations, the potential use of novel cryoprotectants requires evaluation for safe consumption.

Physicochemical transformations: Continual subculturing of cell lines may result in physicochemical transformations affecting the morphology, function, and physiology of cells, potentially yielding a final product with characteristics different from conventional meat. Additionally, the response of cell-based meat to food processing treatments may vary from traditional meats, necessitating further assessment to control potential microbial contaminants.

Genetic modification and novel expression products: Genetic modifications, intentional or unintentional, can introduce changes that may pose food consumption hazards. Genetic engineering techniques leading cells to exhibit new or altered expression of traits require careful evaluation to ensure the safety of the GE cell line and its products.

Adherent surfaces and dissociation reagents: Using scaffolds, microcarriers, and dissociation reagents in cell-based meat production requires safety assessments to ensure these materials and their degradation products are safe for consumption.

The production of cell-based meat and seafood introduce a range of food safety implications that must be carefully managed through rigorous control measures and safety assessments. Addressing these concerns is essential for ensuring the safety of the final product and gaining consumer trust in this innovative food source[54].

3.2 Food safety implication for plant-based food products

The increasing consumption of plant-based food products has raised significant food safety concerns, necessitating rigorous safety assessments throughout their production chain, from growth to processing and retail. The diverse sources of plant-based ingredients introduce multiple points for potential contamination—microbiological, chemical, and physical[55]. Common food safety hazards for these products largely mirror those of traditional foods, but specific processing methods can introduce unique risks, including contaminants from organic matter combustion[55].

Microbiological hazards: Research indicates that microbiological contamination in plant-based foods can occur at multiple points in the production chain. Sources of contamination include animal manure, sewage sludge, or contaminated water used during cultivation[11,57]. For example, plant-based products mimicking meat with their near-neutral pH, high protein, and moisture content are particularly prone to microbial growth[58]. The risk persists through processing, where blending, trimming, extrusion, and other steps can introduce microbiological hazards. Although high temperatures during thermo-extrusion effectively reduce pathogens and spoilage microorganisms, the potential for cross-contamination post-extrusion is a significant concern[59].

Chemical hazards: Chemical hazards in plant-based foods primarily stem from the carryover of mycotoxins from raw ingredients. Rodríguez-Carrasco et al.[60] found up to 10 different mycotoxins in soy-based burgers, highlighting the prevalence and diversity of mycotoxins in plant-based products. The processing of plant-based foods can also lead to the formation of harmful compounds, such as acrylamide, particularly under high-temperature conditions[61-62]. These findings underscore the need to monitor and control chemical contaminants in plant-based food production.

Allergens: The introduction of allergens is a significant concern with plant-based foods. Cross-reactivity among plant proteins can exacerbate allergenic potential, necessitating clear labeling and consumer education on proper handling and cooking[63]. Soy and peanuts, common ingredients in plant-based products, are known allergens, posing risks of allergic reactions among susceptible individuals[64].

Antinutritional factors and plant toxins: Natural toxins and antinutritional factors present in plant ingredients can impact plant-based foods' safety and nutritional quality. Processing techniques can mitigate some effects, but ongoing research is essential for effectively understanding and managing these risks[65-66].

Physical hazards: Physical contaminants, such as metal or wood pieces, have been reported in plant-based food products, highlighting the importance of stringent quality control measures in manufacturing[67].

Generally, ensuring the safety of plant-based food products requires addressing a range of hazards, from microbiological and chemical contaminants to allergens and physical contaminants. Rigorous safety assessments, adherence to good manufacturing practices (GMP), and consumer education are pivotal in mitigating food safety risks associated with plant-based foods. As the demand for these products grows, so does the need for comprehensive research and regulatory oversight to safeguard public health.

3.3 Food safety implication for precision fermentation

Precision fermentation, a process leveraging microbial systems to produce specific food ingredients, demands careful food safety considerations similar to any food production method. This involves evaluating the process, the characteristics of the new substance, and its intended food use. Given that production steps in precision and fermentation are well-established and controlled, with inputs and raw materials adhering to safety and quality standards, the microbial chassis used is generally considered safe for food ingredient production.

Microbiological hazards: An advanced understanding of the microbiology and biochemistry of fermentation processes has enabled the development of rigorous control measures for raw materials, standardized substrate pretreatment, and continuous monitoring of processing conditions. These measures enhance product stability and consistency while ensuring safety and quality. Stringent strain selection, engineering procedures, and adherence to good food safety management guidelines throughout the fermentation process can significantly mitigate microbial contamination risks. Introducing starter cultures during fermentation helps maintain the desired microorganism population, preventing unwanted microbial growth and contamination through competitive exclusion and quorum sensing[68].

The potential presence of GMMs in fermentation products, such as enzymes and flavorings, raises concerns[69]. However, recombinant DNA presence alone is not considered hazardous unless it involves genes related to antimicrobial resistance (AMR), toxigenicity, or pathogenicity[70].

Growth media: The growth or fermentation media used is a critical input during production. Ensuring that contaminants are not introduced into the production system involves proper sourcing and analytical testing of growth media. Raw materials for growth media can be sources of chemical contaminants, like toxic heavy metals, necessitating downstream processing steps to remove or mitigate these contaminants[37].

Chemical hazards: Food safety concerns also extend to potential contamination with lipopolysaccharides from Gram-negative bacteria like *Escherichia coli*, commonly used in precision fermentation. These endotoxins can elicit strong proinflammatory responses, underscoring the need for endotoxin level controls in products expressed in *E. coli*[71]. Additionally, the formation of inclusion bodies due to protein misfolding presents challenges in producing biologically active proteins at industrial scales[72].

Allergenic potential: The allergenic potential produced via precision fermentation must be considered, especially if the protein is a known food allergen in the final product. For example, β-lactoglobulin produced in *Trichoderma reesei*, bio-identical to bovine milk protein, can trigger milk protein allergies[73]. Moreover, fungal production strains introduce post-translational modifications differently from mammals, potentially affecting the allergenic potential of the produced protein[37].

Secondary metabolites: Certain fungal species used in precision fermentation can produce toxic secondary metabolites, such as citrinin from *Monascus purpureus*, alongside desired pigments. Regulations in various jurisdictions limit citrinin content in fermented products to mitigate nephrotoxic and hepatotoxic effects[74].

The food safety implications for precision fermentation underscore the need for comprehensive risk assessments, including microbiological and chemical hazards, allergenic potential, and secondary metabolites. Adhering to stringent safety and quality controls throughout the production process is crucial for ensuring the safety of food ingredients derived from precision fermentation.

3.4 Food safety implication for 3DFP

The advent of 3DFP introduces novel considerations in food safety, paralleling some concerns familiar to conventional food production while presenting unique challenges. Despite the burgeoning interest in 3DFP technology, comprehensive studies on its food safety aspects remain limited. However, rigorous food safety management practices, including good manufacturing and handling practices and appropriate labeling, can mitigate many risks. The hazard analysis and critical control points (HACCP) framework is equally applicable in managing food safety hazards associated with 3DFP.

Microbiological hazards: The potential for microbiological contamination in 3DFP is underscored by the propensity for opportunistic bacteria and biofilm formation on 3D printed surfaces, a concern reported in other 3D printing applications, such as medical devices. The inherent surface roughness and grooves characteristic of extrusion-based printing provide niches for microbial attachment and biofilm development, enhancing the risk of contamination. The microbiological safety of 3D-printed food is influenced by the storage conditions of food inks, printing and processing time, and sanitation practices. The hygienic design of 3D food printers is critical in preventing microbial buildup, yet current printer designs often lack features facilitating thorough cleaning, particularly in components like nozzles and extruders, posing significant food safety challenges.

Chemical hazards: Chemical hazards in 3DFP may arise from substances leaching from food contact surfaces within the printer. Ensuring these components are made from suitable, non-migrating materials is crucial for preventing chemical contamination. Concerns also extend to the potential for contaminant transfer from other uses of multi-purpose 3D printers, including ultra-fine plastic particles. Specific attention has been drawn to the potential for lead transfer from brass nozzles, although the risk is minimal.

Physical hazards: Physical hazards associated with 3DFP include choking risks from hard surfaces in the printed product and the potential detachment of printer particles into the food, particularly when brittle materials are used in printer fabrication. These risks necessitate rigorous quality control and material selection standards to ensure the physical safety of printed food products.

Currently, the potential health risks and concerns in alternative protein food sources due to fraud has not been well studied and is therefore a major knowledge gap. The potential health risks associated with alternative proteins include altered nutritional structure, viruses, diverted complexity of microbiota, insufficient information on all novel species, toxins, heavy metal pollution, genetically modified organisms, potential allergenic effects. Fraud adds further risks in terms of unknown exposure to allergens and chemical adulterants. The two most significant food fraud scandals of the 21st century are the melamine (2008) and horsemeat scandal (2013). Both incidents are known as economical motivated adulterations (EMA) in the undertaking of fraudulent activity in relation to animal proteins (dairy and meat). The consequences of both were catastrophic. Hospitalizations, deaths in the case of melamine and huge economic losses and consumer being lost in both cases. The interruption of global food supply chains by the pandemic and the Ukraine war are also major threat to food security. Low-cost protein ingredient categories (as potential adulterants) are constantly changing accordingly to their price and availability on the global markets. According to a recent survey published by United Kingdom Food Standards Agency (FSA) with regards to alternative proteins, plant-based protein followed by insect protein and algae will be of huge interest in the next 3–5 years, based on the acceptance of consumers and maturity of the production technologies. However, the technology for cell-based meat is in its infancy and may not be widely commercialized for years. The potential for a major food scare due to the adulteration of an alternative protein could put the market back many years.

4. International regulatory frameworks on NFPS

Comprehensive risk assessments focusing on food safety hazards are crucial for establishing fitting control measures and formulating pertinent regulatory frameworks. Identifying hazards is a fundamental initial step in risk assessment. Although most food safety hazards (whether microbiological, chemical, or physical) linked with new food sources might not be novel, they could present in unique combinations or introduce new hazards specific to the food source or production method. For example, a recent FAO/WHO report on cell-based foods elaborated on various food safety hazards specific to such products[75]. While the principles of GMP and HACCP apply to these innovative food sources and systems for managing food safety risks, a more comprehensive dialogue may be necessary to determine if adjustments to these standards and principles are required for the novel foods. Moreover, an initial assessment of the landscape for each area is provided, offering insights into market growth, environmental implications, and nutritional considerations. The narrative also touches upon (but not exhaustively) the current regulatory frameworks overseeing the production and trade of these novel food sources, maintaining a neutral stance on the various regulatory approaches.

4.1 Comparative analysis of regional regulations on new food sources

In recent years, numerous authoritative bodies have implemented regulatory frameworks for emerging food sources across different regions. Although certain current standards, guidelines (e.g., CAC/GL 46/2003, CAC/GL 44/2003), and private certifications apply to these new food sources, there is a lack of specific, internationally harmonized standards for them at the Codex level. This gap has brought the issue of new food sources to the forefront of discussions during the 44th and 45th sessions of the CAC, as highlighted by the FAO and WHO in 2021[20] and 2023[76], respectively. The Commission emphasized the need for Codex to adapt flexibly and promptly to address NFPS, urging member states to propose NFPS-related initiatives through existing Codex processes and inviting members and observers to pinpoint any challenges within the current system that might not encompass NFPS. These deliberations progressed during the 46th session that convened in 2023.

The comparative analysis of new food sources announcements and regulatory management across different countries unveils distinct practices that align with each nation's food safety protocols and legislative requirements. China mandates official announcements on the NHC's website, which comprehensively detail each ingredient's specifics, ranging from nomenclature to dietary recommendations and safety standards, with a noted preference for plant-based and plant-derived extracts[77-79]. The European Union delineates a multistep process leading to official publication on the EUR-Lex website[80], with a unique aspect of a 5-year data protection period for disclosed information, setting it apart from China's approach. The United States does not recognize a separate category for new food ingredients; instead, it operates under the "Generally Recognized as Safe" framework, with announcements featured on the FDA's GRAS notice website, characterized by a unified content structure[81]. Canada's procedure involves an application to Health Canada, followed by detailed public assessment reports that include additional considerations for genetically modified products. In contrast, Australia and New Zealand provide a fully transparent documentation process on the official Food Standards website from application to approval.

A comparative analysis focused on plant-based and plant-extracted ingredients shows that China provides both English and Latin names, when available, while other countries typically standardize on English names alone (Table 1). Commonalities across all regions include essential product information, production processes, labeling requirements, target consumer groups, and food safety standards. In China, "new food sources"—those not historically consumed or only recently available due to technological advances—are at the forefront of this transformation. Recognizing the potential and challenges of these novel foods, China has proactively adapted its regulatory frameworks through the 'three new foods' initiative. This initiative, which categorizes new food ingredients, additives, and related products, is tailored to streamline safety and compliance processes. China's specifications often refer to national standards; however, other countries may not set recommended consumption amounts if usage scope and maximum quantities are defined specifically for unprocessed plant-based ingredients. Quality specifications typically apply to extract-type ingredients with case-by-case determinations for plant-based ones. Consumption methods are predominantly specified in China, particularly for utilizing plant-based ingredients as tea substitutes. The EU is the only region providing data protection for a limited period of time to safeguard technical and experimental data; this provision does not extend to cover plant-based ingredients. In comparison to other nations' regulations, the USA's GRAS announcements include specific bases for determination along with applicant information and address details as additional requirements. Canada oversees genetically modified foods under the new food ingredient category by including safety assessments alongside gene expression studies and comparative analyses in its disclosures. This analysis underscores the necessity of globally harmonized regulatory practices that ensure safety while accommodating technological advancements and protecting proprietary data within the international food industry landscape.

4.2 Overview of global regulatory landscapes on new food production system

International regulatory frameworks on NFPS encompass various approaches across different jurisdictions, emphasizing the importance of ensuring food safety and consumer protection. These frameworks continually evolve to accommodate the rapid advancements in food production technologies, including precision fermentation, cell-based food products, and genetically engineered foods.

4.2.1 Regional regulation comparation on precision fermentation

As novel synthetic biology produced new food materials and ingredients increasingly permeate the consumer market, the imperative for clear policy support and enhanced regulatory frameworks becomes crucial. This comprehensive review delves into the regulatory landscape across various regions, examining how countries like Brazil, Canada, China, the European Union, and the United States manage foods derived from precision fermentation (Table 2). Across various countries, the regulatory approach to managing foods derived from precision fermentation reflects a blend of existing frameworks and new guidelines tailored to the emerging nature of this technology. In Brazil, foods and additives from genetically modified organisms are regulated under general novel foods legislation, with required pre-market approval and specific

Table 1
A comparative analysis on plant-based and plant-extracted ingredients across different countries or regions.

Country	Year	New food materials	Category	English name	Latin name	Basic information	Production process	Recommended dietary intake	Quality specifications	Scope of application	Maximum usage amount	Labeling requirements	Not suitable for the crowd	Method of consumption	Food safety standards	Data protection	Basis for GRAS determination	Application	Applicant's address	Safety	Gene expression	Differential comparison
China	2023	Tiger nut	Plants	√		√									GB							
		Yellowhorn leaf	Plants	√		√	√	√	√			√	√	√	√							
		Yellowhorn seed kernel	Plants	√		√	√		√			√	√		GB							
		Rye pollen	Plants	√		√	√	√	√			√	√		√							
	2022	Kanzan flower	Plants	√		√						√	√		GB							
	2021	*Rumexpatientia* L. × *Rumextianshanicus* A. Los	Plants		√	√						√	√		GB							
	2020	Cicada flower seed entity (artificially cultivated)	Plants			√	√	√				√	√		GB							
		Penthorum chinense Pursh.	Plants		√	√	√	√				√	√	√	GB							
	2019	Loquat flower	Plants	√		√	√	√				√	√		GB							
		Ashitaba stem and leaf	Plants	√		√		√				√	√		GB							
	2018	Nostoc sphaeroides	Plants		√	√		√				√	√		GB							
		Aronia melanocarpa (Michx.) Ell.	Plants	√		√		√				√	√		GB							
	2023	Peach gum	Plant extracts	√		√	√	√	√			√	√		√							
		Blueberry anthocyanins	Plant extracts	√		√	√	√	√	√	√	√	√		√							
	2022	Sugarcane polyphenols	Plant extracts	√			√	√	√			√	√		√							
	2021	Dihydroquercetin	Plant extracts	√		√	√	√	√	√	√	√	√		√							
		β-1,3-/*α*-1,3-Glucan	Plant extracts	√		√	√	√	√			√	√		√							
European Union	2023	Roasted gorgon nut	Plants	√		√			√			√			√							
		Philippines' pili nuts (*Canarium ovatum*)	Plants	√		√			√			√			√							
	2023	Aqueous ethanolic extract of *Labisia pumila*	Plant extracts	√		√	√		√	√	√	√	√		√	5 years						
		Cellobiose	Plant extracts	√		√	√		√	√	√	√	√		√	5 years						
United States	2018	Lesser duckweed powder	Plants	√		√	√		√	√	√				√		√	√	√			
	2022	Resistant dextrin (derived from cassava starch)	Plant extracts	√		√	√	√	√	√					√		√	√	√			
Canada	2022	Genetically modified sugarcane CTC75064-3	Plants (genetically modified)	√		√	√													√	√	√
	2022	Rapeseed protein isolate and glucosinolate-rich rapeseed protein isolate	Plant extracts	√		√	√					√	√							√		
	2020	Ahiflower oil (field gromwell seed oil)	Plant extracts	√		√	√			√										√		
Australia and New Zealand	2020	Rapeseed protein isolate	Plant extracts	√		√	√		√	√	√				√							

Note: GB, National Standard of the People's Republic of China.

Table 2
Official definitions and regulations of across different countries and organizations.

A	B	C	D	E	F	G	H	I
Name of the country/ jurisdiction	What is "precision fermentation" to your country/jurisdiction? (If an official definition exists, please indicate the source.) Working definition exists?	Specific regulations/guidelines exist for regulating foods derived from precision fermentation? If not, any other regulation covers precision fermentation. (Please reference the regulations/guidelines)	In case pre-market approval is necessary, is pre-submission consultation available? If yes, how?	In case food safety assessment is required, are there guidelines for conducting the assessment available?	Food products derived from precision fermentation are already on the market (as of 1 March 2024)?	Are precision fermentation derived products considered as additives, ingredients, or any other category?	Is there a labelling requirement for precision fermentation derived products?	Use this column to provide any additional relevant information
Brazil	No official definition	There is no specific legislation for precision fermentation. Food ingredients obtained from GMO are regulated under the same resolution for novel foods ingredients-RDC 839/2023[82]. In case of additives, the legal requirement to be met is RDC 778/23[83]. Also, GMO are regulated by Brazilian Biosecurity Law 11.105/2005	A pre-market approval is necessary for any novel food ingredients or additives. For novel foods a consultation is possible[84]	Yes, the applicant must follow Guide 23/2019[85]	Yes. 2'Fucosyllactose, glucosamine, 6'-sialyllactose sodium salt	Food ingredients produced from GMO can be novel foods (nutritive purpose) or additives/processing aids (technological function)	No specific labelling as precision fermentation derived product	
Canada	No official definition	Any food ingredient for nutritive purposes produced from an organism genetically modified to change the organism's characteristics meets the definition of novel food and is subject to the pre-market provisions under the *Food and Drug Regulations* B.28 (*Novel Food Regulations*)	Petitioners preparing a Novel Food pre-market submission are encouraged to request a pre-submission consultation by contacting the Submission Management Information Unit (smiu-ugdi@hc-sc.gc.ca). The consultation meeting is a voluntary service allows petitioners to ask questions about the pre-market process their intended approach for meeting safety end-points	Yes. See Guidelines for the Safety Assessment of Novel Foods-Canada.ca section 4.2.3 for GM microbes. For products produced using cultured cells other than microbes, please consult submission management and information unit (SMIU)	Yes. 2'Fucosyllactose, soy leghemoglobin, beta-lactoglobulin	Food ingredients produced from GM organism and are for nutritive purposes are novel foods. Products for other food uses could be classified as food additives or processing aids. Consultation with food directorate is recommended for any questions regarding classification	Under federal law, all foods sold in Canada, including any approved product of cellular agriculture such as precision fermentation derived products, must be labelled so that they will not be mistaken for another food. The label must have the food's common name that is specific and accurately identifies or describes the food in clear terms to allow a person to make an informed purchasing decision. All label information must be truthful and not misleading, including any health- or environment-related claims. Other food labelling rules may also apply, such as labelling for health and safety (i.e., allergen labelling) and compositional standards of identity. They would apply on a case-by-case basis	Not applicable
China	No definition of "precision fermentation" in China's relevant national food safety standards, but for some products of precision fermentation, China is allowed to use. For example, some food additives and nutritional fortifiers produced by GM microorganisms have been approved for use	No specific one. However, China Food Safety Law asked National Health Commission (NHC) to carry our pre-market approval of following three new food products, novel foods/new food ingredients, new food additives, new food related products. NHC allow to use new technologies, such as precision fermentation to produce the enzymes and ingredient with GMMs. However, at present, for food additives and nutritional fortifiers produced by GMO and synth-biology technology, the safety of the producing strains is first evaluated by the Ministry of Agriculture and Rural Affairs, mainly based on the relevant management documents of GMO. After issuing the GMO biosafety certificate, NHC take the pre-market approval after the China National Center for Food Safety Risk Assessment (CFSA)'s risk assessment	Yes. In China, three new food products (novel foods/new food ingredients, new food additives, new food related products) using new technologies, such as precision fermentation, need the pre-market approvals	Yes. At present, for food additives and nutritional fortifiers produced by GMMs, the safety of the strains produced is mainly based on the relevant management documents of GMMs of the Ministry of Agriculture and Rural Affairs. Now CFSA is studying the classification and management measures for novel foods, novel foods and new food-related products produced by GMMs or precision fermentation, and establishing the related guideline based on classification	Yes. Some food additives and nutritional fortifiers produced by GMMs have been approved for use. For example: human milk oligosaccharides (HOMs) produced by microbial fermentation. Up to now, China has approved 2-FL and 1 LNnT produced by 4 different strains, which can be used as nutritional fortifiers for children's milk powder, infant formula, etc.	They are usually food additives and nutritional fortifiers. New food ingredients will come soon	Such substances are managed in accordance with food additives in China, and their labeling should comply with the GB 29924 National Food Safety Standards General Principles for the Labeling of Food Additives". If new food ingredients, GB 7718 should be comply with National Food safety standards for food labelling	

Table 2 (*Continued*)

A	B	C	D	E	F	G	H	I
Name of the country/ jurisdiction	What is "precision fermentation" to your country/jurisdiction? (If an official definition exists, please indicate the source.) Working definition exists?	Specific regulations/guidelines exist for regulating foods derived from precision fermentation? If not, any other regulation covers precision fermentation. (Please reference the regulations/guidelines)	In case pre-market approval is necessary, is pre-submission consultation available? If yes, how?	In case food safety assessment is required, are there guidelines for conducting the assessment available?	Food products derived from precision fermentation are already on the market (as of 1 March 2024)?	Are precision fermentation derived products considered as additives, ingredients, or any other category?	Is there a labelling requirement for precision fermentation derived products?	Use this column to provide any additional relevant information
European Union	No legal definition. In the absence of a legal definition and for the purpose of the 27th European Food Safety Authority (EFSA)'s Scientific Colloquium on "Cell culture-derived foods and food ingredients", EFSA defined precision fermentation as the use of engineered microbial cell factories in the production of food ingredients	No specific regulation for precision fermentation-derived foods. In the EU, food ingredients derived from precision fermentation require pre-market authorisation under different regulatory frameworks and are subject to risk assessment by EFSA. Food additives and flavourings fall under the scope of Regulations (EC) No 1331/2008, 1333/2008 and 1334/2008, Food enzymes under Regulation (EU) 1332/2008, Novel foods under Regulation (EU) 2015/2283, GMOs under Regulation (EC) No 1829/2003	For novel foods a consultation is possible in the case that food business operators would be unsure on whether or not a food which they intend to place on the market within the EU falls within the scope of the Novel Foods Regulation. But it is not specific to precision fermentation products, https://food.ec.europa.eu/safety/novel-food/consultation-process-novel-food-status_en In addition, general pre-submission advice by EFSA is available, together with other dedicates services for potential applicants[86]	Yes, EFSA guidance documents for: novel foods[87]. Please kindly note that the EFSA guidance on Novel Foods has been updated and is currently under public consultation (until 14/04/2024)[88] GMMs[89] Food additives[90] Food enzymes[91] EFSA is currently developing a horizontal guidance on the risk assessment of microorganism intentionally added to the food chain, in order to harmonies the scientific requirements for the risk assessment across regulatory sectors. This guidance is relevant for precision fermentation derived products	Yes. This counts, e.g., for common food additives (vitamins, colorants) and enzymes from precision fermentation, that are already on the market for a long time. With regards to novel foods i) Ice-structuring protein (ISP) type III (originally isolated from *Macrozoarces americanus*), produced by precision fermentation, was authorized in 2009[92]. ii) Several human-identical milk oligosaccharides (HiMOs) produced by precision fermentation are already authorised as novel foods (2-FL, 3-fucosyllactose, 2-FL/ difucosyllactose mixture, lacto-N-tetraose, LNnT, 3'-sialyllactose sodium salt and 6'-sialyllactose sodium salt). In addition, a lacto-N-fucopentaose I/2-FL mixture has already been assessed by EFSA with positive outcome	This may depend on the final use of the product and on the regulatory framework under which the applicant decides to apply, see column C. In the case of precision fermentation-derived proteins used as ingredients, these are likely to be assessed under the novel foods or the GMO regulation depending on the specific characteristic of the product	No specific labelling as precision fermentation derived product. If product is free of recombinant DNA also no labelling as GMO. Note: general labelling requirements or restrictions may exist. E.g., food additives need to be mentioned as ingredient on a label. Precision fermentation derived dairy products cannot be named as e.g. milk or cheese	
United States of America	No official definition	Substances produced from precision fermentation are regulated using the same legal provisions to use to regulate the use of other food ingredients. We have tools available to help developers determine the regulatory status of a food ingredient and guidances that can be used to inform safety assessment and how to make a submission to our programs	Yes. We strongly encourage firms wishing to engage in our premarket processes to meet with us prior to making a submission. Presubmission meetings are typically available upon request and are operated virtually	Yes. We have a wide range of tools available to help developers. We have tools available to help developers determine the regulatory status of a food ingredient and guidances that can be used to inform safety assessment and how to make a submission to our programs. We also recognized that the Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms may have useful information. Because precision fermentation can be used to produce a wide range of products, we strong suggest that developers meet with us before making a premarket submission to our programs. During such meetings we can point developers to the guidance most relevant to their product	Yes. Such products have arguably been on the market since the 1990's when chymosin was produced in a genetically engineered microbe	Ordinarily substances derived from precision fermentation (purified substances intended to be added to food for a specific intended use) would be considered ingredients and would be regulated as food additives unless their use is GRAS. Importantly, however, the fact that a product was or was not produced through precision fermentation is not determinative of its regulatory status	Whether labeling indicating that a food contains an ingredient that is "bioengineered" may depend on specific aspects of the product and how it is intended to be used. This program is administered by the Department of Agriculture's Agricultural Marketing Service. Resources for complying with bioengineered labeling requirements can be found at https://www.ams.usda.gov/rules-regulations/be/bioengineered-foods-list	

guides for application processes. Canada categorizes such foods under its Novel Food Regulations, urging pre-submission consultations to ensure compliance with detailed safety assessments. China, lacking a specific definition for precision fermentation, regulates these products under broader genetically modified organisms (GMO) guidelines, requiring pre-market approval from health commissions after initial agricultural safety evaluations. The European Union, using a working definition for precision fermentation, requires these products to pass through stringent pre-market authorizations across various food safety regulations, supported by extensive risk assessment guidelines. Similarly, the United States regulates precision fermentation products under general food ingredient provisions, with an emphasis on pre-submission consultations to assist producers in navigating the regulatory landscape. This global perspective indicates a cautious yet evolving regulatory approach, aiming to balance innovation in food technology with consumer safety and public health.

4.2.2 Regional regulation comparation on cell-based meat

The regulatory frameworks governing cell-based meat vary significantly across key regions, reflecting diverse approaches to managing the introduction and commercialization of this novel food technology. Each region's strategy is shaped by its specific priorities concerning public health, safety standards, technological innovation, and consumer acceptance. Here, we provide a detailed examination of the regulatory environments in the European Union, the United States, Japan, and China, highlighting the distinct approaches each adopts in response to the challenges posed by cultured meat.

Table 3 presents a panoramic view of the contemporary state of safety assessments and regulatory legislation for cell-based food across the globe. This visual compendium synthesizes the progression of policy development, approval processes, and legislative enactments pertaining to alternative protein sources. It serves as a detailed reference point for understanding the varied approaches nations have adopted, delineating the milestones achieved in the regulatory domain of NFPS. This comprehensive portrayal not only charts the advancements in safety evaluation mechanisms but also encapsulates the dynamic and responsive nature of global food governance in the context of cutting-edge food technology paradigms.

The regulatory frameworks underscore the diversity in oversight mechanisms, ranging from stringent pre-market safety assessments to post-market surveillance, reflecting the multifaceted nature of these novel food technologies. Key distinctions are made between countries that have established specific guidelines and those still in the process of developing regulatory pathways that can effectively manage the complexity of NFPS. This comparative analysis highlights the importance of a harmonized regulatory approach to ensure food safety while fostering innovation in the NFPS sector.

4.2.3 Regional regulation comparation on biosynthetic factored foods ingredients

The policy tightening on market regulation of food ingredients and novel foods produced by GMMs has impeded the development of the bio-economy. A comparative analysis of biomanufacturing regulations in the EU, USA, Japan, and China reveals diverse policy approaches despite a universal concern for the regulation of biosynthetic factored foods ingredients (Fig. 4)[93]. The EU approaches with caution, the USA adopts a positive stance, and Japan shows less caution. In recent decades, China has progressively tightened regulations on approving such food ingredients and novel foods. Currently, there is a global push towards managing and facilitating the

Table 3
Safety assessment and regulatory legislation of alternative proteins in major countries and organizations.

Country or region	Critical events and milestones
China	On Dec. 20, 2020: the Institute of Food Science and Technology (IFST) issued China's first plant-based meat standard T/CIFST 001-2020 Between 2004 and 2022, National Health Commission (NHC) sequentially approved eight new algal resources
European Union	In 2015, regulation (EU)-2015/2283 on novel foods: cell cultures can be used as food ingredients In 2021, European Food Safety Authority (EFSA) conducted its first assessment of new food ingredients from insects Until Jan. 2023: approved crickets, mealworms, and locusts
Canada	In 2006: Heath Canada published "Guidelines for the Safety Assessment of Novel Foods" In 2016: announced the launch of "cultured meat" technology In 2018, established safety assessment framework
United States of America	In 2018, The Food and Drug Administration/Department of Agriculture (FDA/USDA) addressed potential hazards and regulatory labeling of cell-cultured meat In July 2018, the FDA issued a generally recognized as safe (GRAS) notice for soy leghemoglobin In October 2021, the FDA issued a GRAS notice for bovine myoglobin In November 2022, the FDA issued a "no objections" letter regarding the consultation on cell-cultured chicken meat (a milestone) In 2023, the USDA oversaw production
Food and Agriculture Organization/ World Health Organization (FAO/WHO)	WHO Western Pacific Region Alternative Protein Working Meeting (2021) FAO established a Cell-Cultured Meat Expert Committee (2022) FAO established an Expert Committee on new food sources and production systems (2023) Stakeholder Meetings (Israel 2022, Shanghai (China) 2023) Standard terminology Safe production Regulation framework National case studies
South Korea	Feb. 22, 2024: Korea Food and Drug Administration (KFDA) established its framework for the regulatory approval of cultivated meat, with startups set to file applications
Japan	Regulation focuses more on standard setting and risk assessment In 2021, Prime Minister of Japan: promotes a white paper on cultured meat
Singapore	In 2020: approved the world's first cultured chicken meat for commercial sale Eat Just, Inc.: Cell-cultured chicken meat was approved for sale

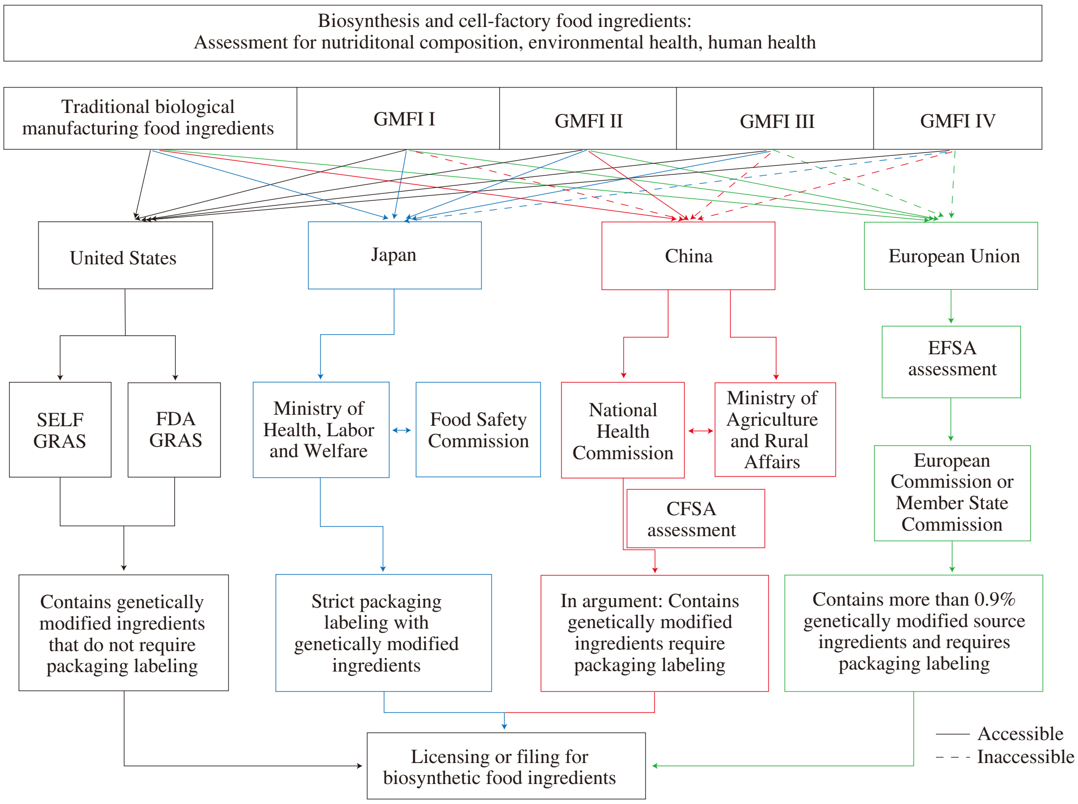

Fig. 4 Comparison of market regulations of biosynthetic factored food ingredients in the USA, EU, Japan, and China[93].

entry of new food products developed through innovative technologies. To enhance the commercialization of new products in China, it is recommended to establish a unified, simplified, and positive path for application and approval.

United States: The regulatory environment in the United States is characterized by a permissive and product-focused approach. The FDA oversees the safety of biomanufactured food ingredients, predominantly through the GRAS designation. Unlike the EU, the USA does not differentiate significantly between traditional and genetically modified ingredients in regulatory practices, focusing instead on the safety of the end product. This orientation facilitates a faster integration of biotechnological innovations into the market. The Bioengineered Food Disclosure Law, effective from 2022, mandates labeling of foods containing genetically modified food ingredients (GMFIs), reflecting an evolving regulatory stance that seeks to balance innovation with consumer transparency.

European Union: The European Union demonstrates a stringent and precautionary regulatory framework for biomanufactured food ingredients, orchestrated by the EFSA. The EU's regulatory regime is bifurcated into two main strategies: one for traditional food ingredients (TFIs) and another for GMFIs. The EFSA employs the qualified presumption of safety (QPS) approach to streamline the approval process for microorganisms used as production tools. Additionally, the Regulation (EU) 2015/2283 outlines strict guidelines for novel foods, demanding comprehensive safety assessments and transparent labeling of all GMFIs, underscoring the EU's cautious stance towards biotechnological integration in food production.

Japan: Japan administers a moderate regulatory approach that emphasizes both innovation and public health safety. The Ministry of Health, Labour and Welfare is responsible for the safety and approval of food additives, which includes both TFIs and GMFIs. The regulatory process is detailed, involving an initial safety evaluation followed by public consultation, demonstrating Japan's commitment to maintaining stringent safety standards while also being open to biotechnological advancements. Furthermore, Japan has established specific regulations for foods and food additives produced using DNA recombination techniques, indicating a careful yet progressive approach to regulating new biotechnologies.

China: China's regulatory policy for biomanufactured food ingredients has grown increasingly stringent, with a significant focus on safety and control, particularly concerning genetically modified organisms. The regulatory oversight, managed by the National Health and Family Planning Commission, mandates thorough safety assessment submissions for novel food ingredients and additives under the Food Safety Law. Despite this rigorous approach, China faces challenges in facilitating the market entry of innovative biomanufactured products, which impacts the overall development of its bio-economy. The cautious and tight regulatory framework reflects broader socio-economic and health safety priorities within the country's governance of food technologies.

These regional frameworks are shaped not only by internal policies and consumer sentiment but also by the influence of international bodies such as the CAC, which provides a set of voluntary international standards. Though not legally binding, Codex standards serve as a reference point for national legislation and aim to harmonize safety standards and facilitate international trade. The comparison highlights the spectrum of regulatory practices, from the USA's focus on product safety to the EU's consumer-centric model with its stringent labeling requirements, and from Japan's comprehensive safety and labeling regime to China's cautious and controlled approach to GM foods. Each region's strategy reflects its own risk assessment methodologies, societal values, public awareness, and government policies concerning the cultivation, distribution, and consumption of GM foods.

4.3 Harmonization efforts and future directions in NFPS regulation

Future directions in NFPS highlight the exploration of underutilized protein sources, blending plant-based ingredients with animal-based products, and the potential of precision fermentation to create functional ingredients. Integrating innovative technologies, such as non-thermal processing methods and 3D printing, promises to enhance plant-based food products' nutritional value and safety. Moreover, the application of side streams as food ingredients and the development of plant molecular farming techniques underscores the industry's shift towards more sustainable and efficient food production systems.

Synthetic biology and precision fermentation represent a significant area of innovation within NFPS, characterized by the controlled cultivation of modified microbial cells to produce specific food products and ingredients. This technology has led to the development of enzymes, flavoring agents, sweeteners, proteins, and other ingredients with broad applications in the food industry. The regulatory landscape for precision fermentation-derived products involves pre-market authorization and risk assessments to ensure food safety. Consumer acceptance of these products varies globally, with ongoing efforts to improve public understanding of genetically modified organisms and their safety. International regulatory frameworks for synthetic biology and precision fermentation are complex and diverse, reflecting the need to balance innovation with food safety and consumer protection. These frameworks include detailed provisions for pre-market approvals, risk assessments, labeling requirements, and consumer education. As NFPS continues to evolve, regulatory bodies worldwide are challenged to adapt their policies and guidelines to ensure that these NFPS meet stringent safety standards while supporting industry growth and innovation.

5. China's advancements in synthetic biology for food production

5.1 Premarket approval on novel food ingredients and additives

China is one of the pioneering nations globally in establishing an innovative food raw material management system, formerly known as new resource food. From 1987 to the present, great changes have taken place in the management of new food raw materials in China, and the regulatory system has been increasingly improved. The Food Hygiene Law (Trial) of 1983 introduced the groundbreaking requirement for health department approval of foods derived from new resources, and in 1987, the former Ministry of Health issued its inaugural supporting regulations. Over the course of more than three decades, significant progress has been made with extensive approval and widespread utilization of numerous novel food raw materials across various culinary applications. The regulations governing the approval of new food raw materials have undergone 4 revisions since 1987, accompanied by substantial transformations in management practices and an increasingly sophisticated regulatory framework (Fig. 5).

At the same time, the regulatory framework for new food resources encompasses key laws such as the "Food Safety Law" of 2015 and the "Administrative Licensing Law" of 2019 (Fig. 6), providing a comprehensive basis for ensuring the safety of novel foods in accordance with China's rigorous food safety standards[94]. Complementing these are departmental regulations like the "Hygiene Administrative License Measures (2017)" and the "Administrative Measures for Safety Review of New Food Materials (2017)", which specifically address licensing intricacies and safety reviews pertaining to novel food ingredients and additives, including synthetic biology food products[61]. Further, the procedural regulations established in 2021, including the "Provisions on the Application of New Food Materials", "Procedures for the Safety Evaluation of New Food Materials", and "Application Materials requirement for the Safety Evaluation Opinion of New Food Materials" delineate the procedures for the submission, assessment, and approval of synthetic biology-derived food products. These regulations ensure a thorough evaluation process aligning with national and international food safety standards.

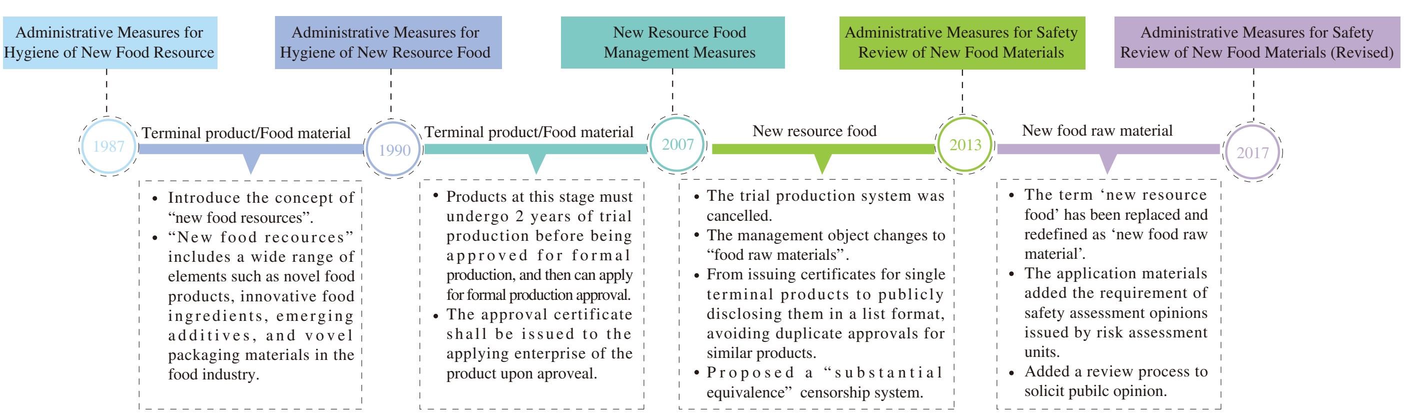

Fig. 5 Development of management policies for new food resources in China.

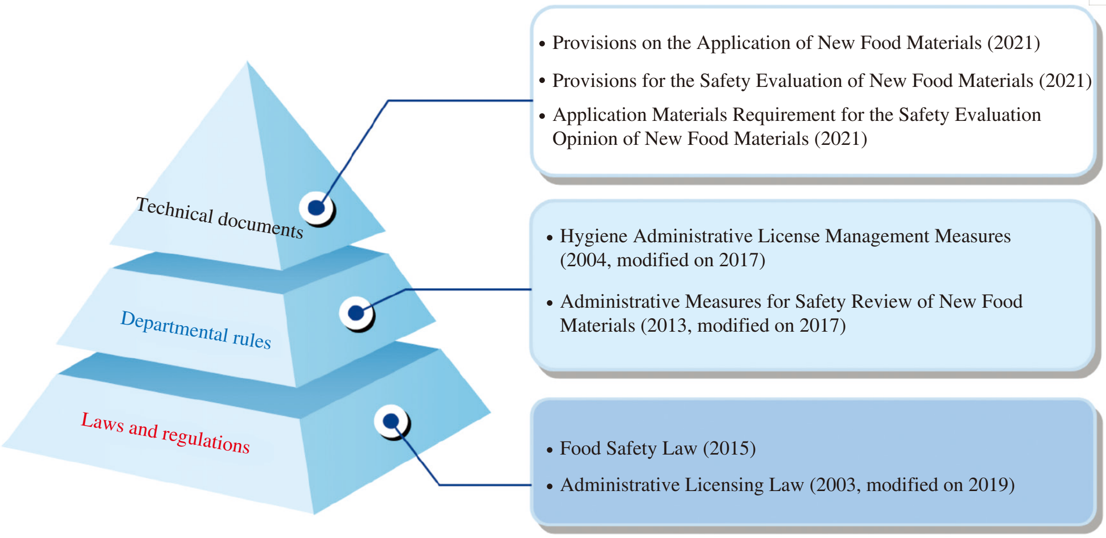

Fig. 6 Key regulations for declaration and management novel food in China.

According to China's current management regulations, food materials are mainly divided into traditional food materials, food additives, nutrient supplements, microorganism used in food processing, medicine and food homology, and new food raw materials (Fig. 7). According to China's current management regulations, food materials are primarily classified into 6 categories: traditional food materials, food additives, nutrient supplements, microorganisms used in food processing, foods with both medicinal and nutritional uses (medicine-food homology), and new food raw materials. Building on this classification, China has introduced the concept of "Three New Foods", which refers to "new food ingredients", "new varieties of food additives", and "new varieties of food-related products".

In China, precision fermentation powered by synthetic biology may require pre-market approval under the "Three New Food" regulatory categories. This regulatory framework, designed to ensure safety, foster innovation, and maintain compliance, is critical for managing foods produced through synthetic biology. It highlights China's commitment to effectively regulating emerging food technologies. The declaration process for "Three New Foods" in China requires applicants to submit comprehensive documentation (Fig. 8)[95]. This documentation must demonstrate safety, efficacy, and compliance with existing food safety standards. The rigorous review process aims to ensure that these innovative products are safe for consumer use and meet the regulatory criteria set by Chinese food safety authorities.

NHC and CFSA are pivotal in administering the safety review process for new food materials. These institutions are responsible for the administrative review, licensing, acceptance, and comprehensive safety assessment of new food ingredients, including those produced through synthetic biology. In alignment with the State Council's directives to streamline administration, delegate powers, and improve regulation and services, the NHC has promulgated regulatory

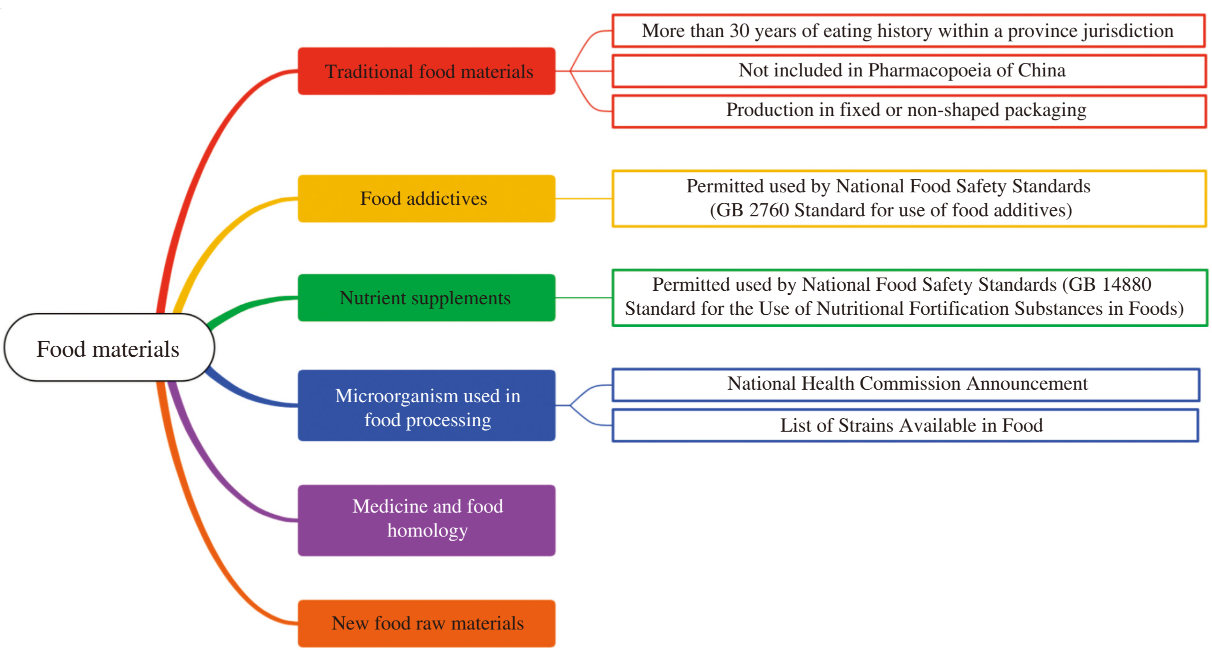

Fig. 7 Classification of food materials under the Chinese Food Safety Management Framework.

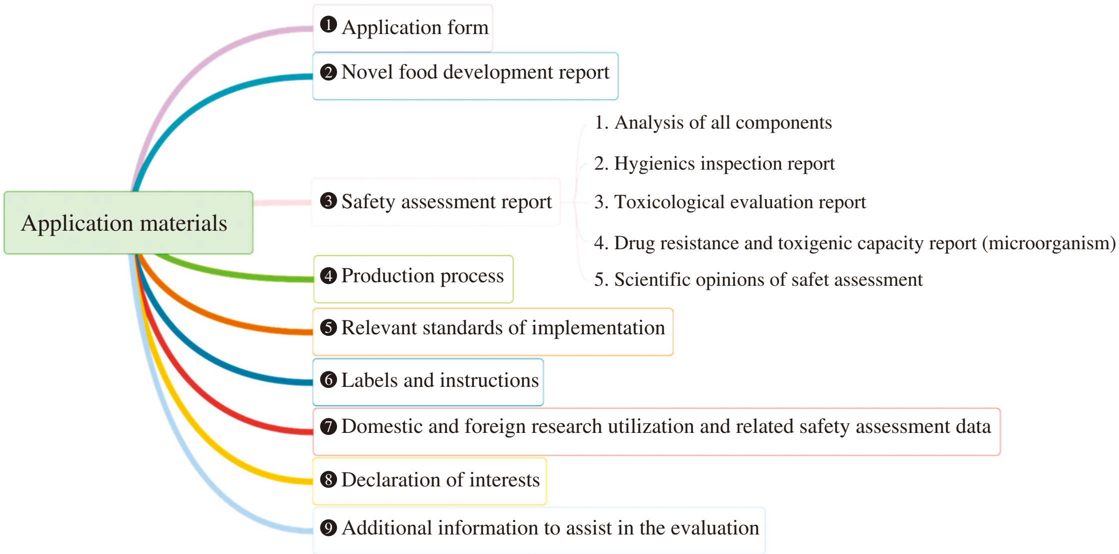

Fig. 8 Application materials for "Three New Foods" materials.

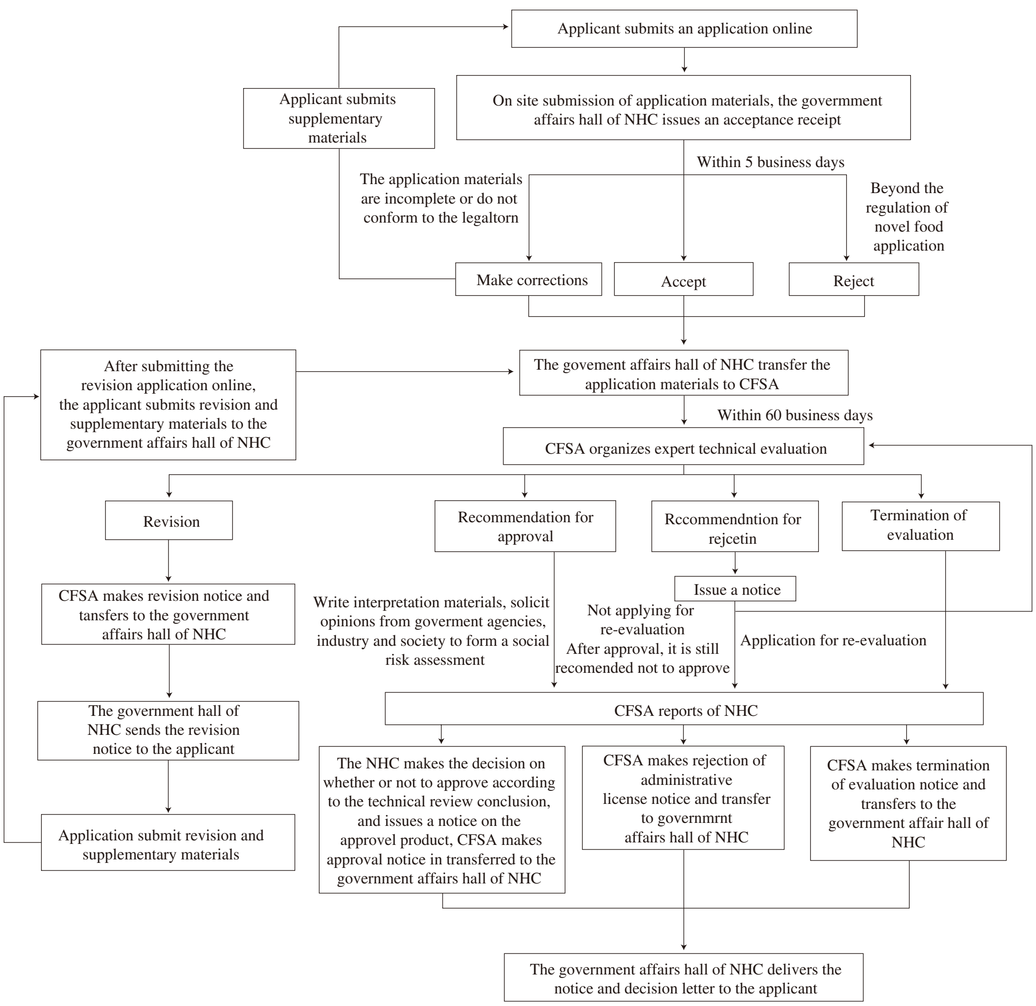

Fig. 9 Novel food administrative licensing workflow in China.

documents such as the "Management Measures for the Safety Review of New Food Ingredients", "Regulations on the Declaration and Acceptance of New Food Ingredients", and "Procedures for the Safety Review of New Food Ingredients". These documents clarify the procedures for the declaration, acceptance, and safety review of new food ingredients, signifying ongoing reforms to the approval system of new food ingredients aimed at simplifying processes and optimizing services.

According to the Regulations on Declaration and Acceptance of New Food Raw Materials, the submission requirements for new food raw material registration include application form, research report, safety evaluation report, production technology, etc. (Fig. 8). The application process for novel food ingredients is characterized by stringent and intricate requirements as well as comprehensive review procedures. It entails a considerable amount of time from initial acceptance to final approval due to factors such as ingredient nature, historical usage, safety assessment, among others (Fig. 9).

The scope of new food materials in China extends beyond plant-based substances and plant extracts to include animal-based products and their derivatives, as well as microbial products (Table 4). This expansion recognizes the growing complexity and diversity of food ingredients derived from biotechnological innovations and natural sources, catering to a broader range of nutritional and functional food needs in the market.

Table 4
Examples of new resource food categories approved in China.

Category	English name/Latin name	Protein content (%)
Plants	Yellowhorn leaf	≥ 15
	Yellowhorn seed kernel	≥ 20
	Lepidium meyenii Walp	≥ 10
	Tissue culture of *Saussurea involucrata*	≥ 1
Microorganisms (microalgae)	*Chlamydomonas reinhardtii*	≥ 30
	Chlorella pyrenoidesa	≥ 58
	Haematococcus pluvialis	≥ 15
Plant extracts	Wheat oligopeptides	≥ 90
	Tissue culture of *S. involucrata*	≥ 80
Animal extracts	Earthworm protein	≥ 65
	Milk basic protein	≥ 90
	Colostrum basic protein	≥ 80
	Bonepet	≥ 60

Between 1987 and 2007, the former Ministry of Health approved 76 novel food resources. The approval process accelerated after the terminology shifted from ‘new food resources’ to ‘new food materials’ in 2008. From 2008 to 2023, a total of 128 new food raw materials received approval, comprising 105 animal and plant-derived materials and 23 microorganism-derived materials. A pivotal enhancement in China’s regulatory approach to microbial strains utilized in the food industry was evidenced by the revision of the “List of Bacteria Used in Foods” and “List of Bacteria Used in Foods for Infants and Toddlers” by the NHC on August 25, 2022[96]. This revision is noteworthy as it consolidates all bacterial cultures previously approved through official notices into these updated lists (Table 5). It also meticulously aligns the nomenclature and classification of bacterial cultures with international standards and recent scientific findings. For the first time, the updated lists specify bacterial cultures down to the subspecies level, providing greater specificity and clarity. Furthermore, for those bacterial cultures whose classification or names have been altered, a 2-year grace period is instituted to facilitate a smooth transition to the new standards. This systematic update reflects a significant stride towards harmonizing China’s microbial regulatory framework with global practices, thereby enhancing the transparency and scientific basis of its food safety regulations.

The NHC is currently revising National Food Safety Standards, such as the “General Rules for the Labeling of Prepackaged Foods (GB 7718-2011)”, “General Rules for Nutrition Labeling of Prepackaged Foods (GB 28050-2011)”, “Standards for the Use of Nutritional Fortification Substances in Foods (GB 14880-2012)”, and “Labeling of Prepackaged Foods for Special Dietary Uses (GB 13432-2013)”. These revisions aim to regulate the food industry’s development further and better meet the diverse health needs related to food and nutrition among different populations.

An illustrative case is the proposal to include edible insects in the national food catalog[97]. This proposal, though innovative, highlighted several challenges, including market access, dietary perceptions, public opinion, educational gaps, and the lack of an industrial scale for production. In response, the national health authorities undertook a thorough safety review as part of the approval process. This involved receiving the application through the Government Affairs Hall of the National Health Commission and delegating the technical evaluation to specialized institutions to assess the safety and compliance of the proposed food ingredients.

The evolution of China’s management policies for new food resources—encompassing final products, new food raw materials, food additives, and new varieties of food-related products (“Three New” permissions)—illustrates a progressive and adaptive approach. This involves connecting past and future, adapting to contemporary times, and daring to break new ground. The current policy interconnectivity suggests that the biosecurity and safety issues related to synthetic biology and cell factory technologies are essentially similar to those associated with genetic engineering (with the current management norms being largely “adequate”). Adjustments and supplements to existing policies should closely track the developmental trends of synthetic biology and cell factory technologies, investigate new characteristics and changes, and review existing management policies for any issues or inadequacies.

5.2 Research on multiple identity problems of food materials

In food safety and regulation, China’s meticulous approach to the classification of food materials is particularly significant given the multifaceted nature of such substances. The complexity arises when a single ingredient serves multiple functions, potentially qualifying it as a traditional food material, food additive, nutrient supplement, or a component with both medicinal and food properties (Fig. 3). This multifunctionality necessitates a sophisticated regulatory system that can accommodate the varied attributes and corresponding safety standards.

Traditional food materials are identified based on longstanding regional consumption and are produced following specific packaging regulations, ensuring consistency with historical use. Food additives are subject to National Food Safety Standards (GB 2760), which delineate permissible uses, while nutrient supplements are governed by standards (GB 14880) that oversee nutritional fortification in foods. The categorization extends to strains listed by the National Health Commission, recognizing their safe application in food, and new food raw materials, which mark the frontier of food innovation.

This detailed classification system not only addresses the multiple identity problems but also streamlines the regulatory oversight. It ensures that each category—from raw materials to food additives—is regulated under appropriate safety assessments, reflecting the substance’s specific characteristics and intended use. This nuanced

Table 5

New version of "List of Bacteria Used in Foods" and "List of Bacteria Used in Foods for Infants and Toddlers".

No.	Updated Latin name	Original Latin name	No.	Updated Latin name	Original Latin name
List of Bacteria Used in Foods (*n* = 40)					
Ⅰ	*Bifidobacterium*	*Bifidobacterium*	Ⅶ	*Latilactobacillus*	*Lactobacillus*
1	*Bifidobacterium adolescentis*	*Bifidobacterium adolescentis*	1	*Latilactobacillus curvatus*	*Lactobacillus curvatus*
2	*Bifidobacterium animalis animalis* subsp.	*Bifidobacterium animalis* (*Bifidobacterium lactis*)	2	*Latilactobacillus sakei*	*Lactobacillus sakei*
3	*Bifidobacterium lactis animalis* subsp.		Ⅷ	*Streptococcus*	*Streptococcus*
4	*Bifidobacterium bifidum*	*Bifidobacterium bifidum*	1	*Streptococcus salivarius* subsp. *thermophilus*	*Streptococcus thermophilus*
5	*Bifidobacterium breve*	*Bifidobacterium breve*	Ⅸ	*Lactococcus*	*Lactococcus*
6	*Bifidobacterium longum* subsp. *longum*	*Bifidobacterium longum*	1	*Lactococcus lactis* subsp. *lactis*	*Lactococcus lactis* subsp. *lactis*
7	*Bifidobacterium infantis longum* subsp.	*Bifidobacterium infantis*	2	*Lactococcus lactis* subsp. *lactis* biovar diacetylactis	*Lactococcus lactis* subsp. diacetylactis
Ⅱ	*Lactobacillus*	*Lactobacillus*	3	*Lactococcus cremoris*	*Lactococcus lactis* subsp. *cremoris*
1	*Lactobacillus acidophilus*	*Lactobacillus acidophilus*	Ⅹ	*Propionibacterium*	*Propionibacterium*
2	*Lactobacillus crispatus*	*Lactobacillus crispatus*	1	*Propionibacterium freudenreichii* subsp. *shermanii*	*Propionibacterium freudenreichii* subsp. *shermanii*
3	*Lactobacillus bulgaricus delbrueckii* subsp.	*Lactobacillus bulgaricus delbrueckii* subsp.	Ⅺ	*Acidipropionibacterium*	*Propionibacterium*
4	*Lactobacillus lactis delbrueckii* subsp.	*Lactobacillus lactis delbrueckii* subsp.	1	*Acidipropionibacterium acidipropionici*	*Propionibacterium acidipropionici*
5	*Lactobacillus gasseri*	*Lactobacillus gasseri*	Ⅻ	*Leuconostoc*	*Leuconostoc*
6	*Lactobacillus helveticus*	*Lactobacillus helveticus*	1	*Leuconostoc mesenteroides* subsp. *mesenteroides*	*Leuconostoc mesenteroides* subsp. *mesenteroides*
7	*Lactobacillus johnsonii*	*Lactobacillus johnsonii*	XIII	*Pediococcus*	*Pediococcus*
8	*Lactobacillus kefiranofaciens* subsp. *kefiranofaciens*	*Lactobacillus kefiranofaciens* subsp. *kefiranofaciens*	1	*Pediococcus acidilactici*	*Pediococcus acidilactici*
Ⅲ	*Lacticaseibacillus*	*Lactobacillus*	2	*Pediococcus pentosaceus*	*Pediococcus pentosaceus*
1	*Lacticaseibacillus casei*	*Lactobacillus casei*	XIV	*Weizmannia*	*Bacillus*
2	*Lacticaseibacillus paracasei*	*Lactobacillus paracasei*	1	*Weizmannia coagulans*	*Bacillus coagulans*
3	*Lacticaseibacillus rhamnosus*	*Lactobacillus rhamnosus*	XV	*Mammaliicoccus*	*Staphylococcus*
Ⅳ	*Limosilactobacillus*	*Lactobacillus*	1	*Mammaliicoccus vitulinus*	*Staphylococcus vitulinus*
1	*Limosilactobacillus fermentum*	*Lactobacillus fermentum*	XVI	*Staphylococcus*	*Staphylococcus*
2	*Limosilactobacillus reuteri*	*Lactobacillus reuteri*	1	*Staphylococcus xylosus*	*Staphylococcus xylosus*
Ⅴ	*Lactiplantibacillus*	*Lactobacillus*	2	*Staphylococcus carnosus*	*Staphylococcus carnosus*
1	*Lactiplantibacillus plantarum*	*Lactobacillus plantarum*	XVII	*Kluyveromyces*	*Kluyveromyces*
Ⅵ	*Ligilactobacillus*	*Lactobacillus*	1	*Kluyveromyces marxianus*	*Kluyveromyces marxianus*
1	*Ligilactobacillus salivarius*	*Lactobacillus salivarius*			
List of Bacteria Used in Foods for Infants and Toddlers (*n* = 14)					
1	*Lactobacillus acidophilus* NCFM	*Lactobacillus acidophilus* NCFM	8	*Limosilactobacillus reuteri* DSM 17938	*Lactobacillus reuteri* DSM 17938
2	*Bifidobacterium animalis* subsp. *lactis* Bb-12	*Bifidobacterium animalis* Bb-12	9	*Limosilactobacillus fermentum* CECT 5716	*Lactobacillus fermentum* CECT 5716
3	*Bifidobacterium animalis* subsp. *lactis* HNO1C	*Bifidobacterium lactis* HNO1S	10	*Bifidobacterium breve* M-16V	*Bifidobacterium breve* M-16V
4	*Bifidobacterium animalis* subsp. *lactis* Bi-07	*Bifidobacterium lactis* Bi-07	11	*Lactobacillus helveticus* R0052	*Lactobacillus helveticus* R0052
5	*Lacticaseibacillus rhamnosus* GC	*Lactobacillus rhamnosus* LGG	12	*Bifidobacterium longum* subsp. *infantis* R0033	*Bifidobacterium infantis* R0033
6	*Lacticaseibacillus* HN001 *rhamnosus*	*Lactobacillus rhamnosus* HNO01	13	*Bifidobacterium bifidum* R0071	*Bifidobacterium bifidum* R007
7	*Lacticaseibacillus rhamnosus* MP10S	*Lactobacillus rhamnosus* MP108	14	*Bifidobacterium longum* subsp. *longum* BB536	*Bifidobacterium longum* subsp. *longum* BB536

approach is crucial for safeguarding public health while fostering the development and introduction of new, innovative food products.

The versatility of certain ingredients, which can be classified under multiple regulatory categories, creates a challenge for food safety governance. For instance, an ingredient could simultaneously be considered a traditional food material, a food additive, a nutrient supplement, a strain for food use, or part of the category of medicine and food homology. This necessitates a regulatory framework that is both flexible and rigorous to effectively manage these substances' safety and ensure they meet the standards set forth for their respective categories. To navigate the complexities inherent in regulating food raw materials with multiple identities, CFSA has embarked on a meticulous process of evaluation and categorization. This endeavor, aimed at addressing the regulatory challenges presented by food additives, food raw materials, and healthy food raw materials that cross multiple categories, has resulted in significant strides toward the refinement of China's food safety regulatory framework. A pivotal component of this initiative was the development of a comprehensive comparison of the status across various countries concerning declaring food additives as novel food ingredients (Tables 6 and 7). This international overview provides a crucial benchmark for aligning China's regulatory approach with global standards and practices, facilitating a more harmonized international food trade environment. Building upon this foundation, CFSA further delineated the specific quantities of raw materials across two or more of the identified categories. This classification, detailed in Table 6, underscores the complexity of modern food production technologies and the need for a regulatory framework that is both flexible and robust, capable of addressing the nuances of multi-attribute food raw materials.

Table 6
Comparison of multiple attribute quantities and whether food additives can be declared as novel foods in different countries.

Country	Multiple attribute quantity	Can food additives be declared as novel foods
China	116	No
United States	39	Yes
Canada	95	No
South Korea	72	Yes
Australia and New Zealand	108	Yes
Japan	138	Yes
European Union	238	No

Table 7
Specific quantities of multi-attribute food raw materials.

Number	Food additives (including food nutritional enhancers)	Food raw materials	Health food ingredients	Quantity
1	✓	✓	×	17
2	×	✓	✓	18
3	✓	×	✓	79
4	✓	✓	✓	2

In 2023, CFSA advanced its regulatory efforts by disseminating a research survey questionnaire aimed at soliciting insights from industry stakeholders regarding the development status of multi-attribute food raw materials. The responses to this questionnaire were instrumental in compiling a focused list of 12 food additives with the potential for declaration as novel foods. This list includes a diverse array of substances, from amino acids and xanthophylls to more specialized compounds like *D*-ribose (spice), xylitol, Isomaltulose, alginate, steviol glycoside, glucose-based stevia glycosides, tamarind polysaccharide gum, phospholipid, and guarana extract.

The progress made in this area underscores the importance of continuous regulatory adaptation and innovation. By addressing the multiple identity problem of food materials, China is paving the way for more effective food safety management, ensuring that novel food ingredients are thoroughly evaluated for their safety and suitability for consumption. This approach enhances food safety and supports the development of the food industry by providing clear guidelines for incorporating innovative ingredients into food products.

5.3 Current regulation of novel foods produced by precision fermentation in China

Fermentation is a well-established practice, encompassing traditional, mass, and precision fermentation techniques. Recently, precision fermentation, when integrated with synthetic biology, has emerged as a novel focus within food safety policy in China. Currently, China lacks a formal definition of "precision fermentation" within its national food safety regulations. However, the country permits the utilization of certain precision fermentation products. Specifically, GMMs are approved for producing food additives and nutritional enhancers. For instance, human milk oligosaccharides (HMOs) generated through microbial fermentation processes have been sanctioned. To date, China has authorized four distinct strains to produce 2′-fucosyllactose (2-FL) and Lacto-N-neotetraose (LNnT), which can be incorporated as nutritional fortifiers in children's milk powder and infant formulas. These compounds are regulated as food additives under the "GB 29924 National Food Safety Standards General Principles for the Labeling of Food Additives". Several key research areas and developments underscore China's advancements in synthetic biology for food production, demonstrating the country's commitment to harnessing biotechnological innovations to enhance agricultural productivity and sustainability. China has prioritized plant molecular farming and precision fermentation as two pivotal domains within synthetic biology aimed at augmenting food production efficiency and quality. Plant molecular farming involves utilizing genetically engineered plants such as *Nicotiana tabacum* and *Nicotiana benthamiana* as platforms for synthesizing animal-based proteins like lactoferrin, casein, and myosin. This approach offers cost reduction advantages over microbial cell-based systems due to lower operational expenses and scalability facilitated by open-field cultivation of plants.

In China, the management of new food materials produced through precision fermentation technologies, which involve GMMs, requires a nuanced regulatory approach to ensure food safety and public health. The Chinese regulatory framework classifies genetically modified food materials based on the presence of microbial residues and newly introduced genetic fragments (Tables 8 and 9). This classification system is critical as it guides the regulatory oversight and approval processes. For materials that involve genetic modifications, the existing "Regulation on Genetically Modified Organisms" mandates a safety certificate as a prerequisite. This legal requirement underscores the importance of a thorough safety assessment before such products can enter the market.

Under the existing regulatory framework, the safety of genetically modified strains employed as food additives undergoes preliminary evaluation by the Ministry of Agriculture and Rural Affairs. Following approval, applicants must submit documentation detailing the necessity and safety of the employed processes, in alignment with the "Measures for the Management of New Varieties of Food Additives" as delineated by the NHC. Nonetheless, there currently exists no established regulatory pathway for the production of novel foods and food-related products via GMMs. The exploration of management pathways and procedures for such innovations is ongoing. CFSA is in the process of developing classification and regulatory measures for novel foods and new food-related products derived from GMMs or through precision fermentation. This includes

Table 8
Classification of genetically modified foods (GMFs).

Category	Definition	Products
I	Purified products: Purified compounds and their mixtures with clear chemical structures produced by GMMs, in which GMMs and newly introduced genes have been removed	Amino acids, vitamins, breast milk oligosaccharides, etc.
II	Composite products: Composite products produced using GMMs but without living GMMs and newly introduced genes	Most enzyme preparations
III	Dead Bacteria: Using GMMs to produce products without live GMMs, but there are still newly introduced genes	Heat-inactivated starter cultures, recombinant yeast expressing soy hemoglobin, etc.
VI	Live bacteria: GMMs capable of multiplying or transferring genes	Live starter cultures for fermented food and feed

Table 9
Characteristics of GMFs.

Characteristics	GMF I	GMF II	GMF III	GMF IV
Genetic or phenotypic traits, all new traits, and feature descriptions	X	X	X	X
Structure and quantity of vectors and/or insertion sequence information in the genome	X	X	X	X
Identification and testing of technical data	X	X	X	X
Stability of genetic traits		X	X	X
Human and animal safety		X	X	X
The expression level of inserted genes and the activity of expressed proteins			X	X
Can genes be transferred to other organisms			X	X
Application history or environmental release information			X	X

Note: X, not contain.

the formulation of guidelines based on classification, drawing upon international regulatory practices for insights and guidance.

China's approach also highlights the need for dynamic regulatory policies that can adapt to technological advancements. The timely updating of the list of food materials and components is crucial to accommodate new developments in food production technologies, ensuring that regulatory frameworks remain relevant and effective in overseeing the safety and integrity of emerging food products.

5.4 CFSA's ongoing work related to cell-based food

Synthetic biology, precision fermentation, and cell-based food production are interconnected technologies that revolutionize food production by leveraging biotechnological innovations to enhance sustainability and efficiency. Synthetic biology provides the essential tools and genetic designs, enabling precision fermentation to produce specific food components efficiently, and supports cell-based food production by optimizing the growth and differentiation of cultured cells. The rapid development of the cell-based meat market has garnered global attention, as this innovative technology promises to revolutionize the meat industry by offering sustainable and ethical alternatives to conventional meat production. China is actively monitoring both domestic and international progress and safety evaluations of cell-based meats, assessing the development status of domestic enterprises, and is in the process of crafting "Safety Assessment Data Requirements for Novel Foods Concerning Cell-Based Meat".

During the 2020 session of the National Committee of the Chinese People's Political Consultative Conference (CPPCC), a significant proposal was put forward to accelerate the strategic deployment of cultured meat development in China. The proposal highlighted the urgency to invest in this innovative technology as a response to multiple challenges, including food security, environmental sustainability, and public health concerns. In China, cell-based meat is considered a new food material and must undergo a declaration process and regulatory oversight. This regulation ensures that this innovative product adheres to specific safety and quality standards before market release. The government's oversight aims to safeguard public health while fostering technological innovation in the food industry. NHC's response to Proposal No. 3471 during the Third Session of the 13th National Committee of the Chinese People's Political Consultative Conference sheds light on the regulatory framework for managing novel food resources in China[98]. This framework is meticulously outlined to accelerate the strategic deployment of cell-based meat development, demonstrating the NHC's commitment to food safety and innovation. According to Article 37 of the "Food Safety Law", any production of food using new food ingredients must submit safety assessment materials to the Health Administrative Department of the State Council. This department must organize a review within 60 days of receiving the application; if the product meets food safety requirements, it is granted permission and publicly announced, whereas products failing to meet these standards are denied permission with an explanation in writing.

6. Perspective and challenges

The burgeoning field of synthetic biology in food production (novel food production systems) has introduced transformative potential alongside significant regulatory challenges. One major concern is the lack of established international conventions and legislation specifically tailored for synthetic foods, which currently fall under broader genetically modified food regulations[99]. Furthermore, discussions under the United Nations Convention on Biological Diversity highlight the pressing need for a cohesive framework on synthetic biology risk monitoring[100]. Despite the focus on safety, a clear international consensus on regulatory standards remains elusive, complicating the enforcement of uniform safety and quality measures.

In response to the challenges posed by synthetic biology, China is implementing an innovative management model aimed at setting a potential reference for global standards. This model adopts a multidisciplinary approach to enhance scientific oversight and increase participation from the public and professionals, specifically

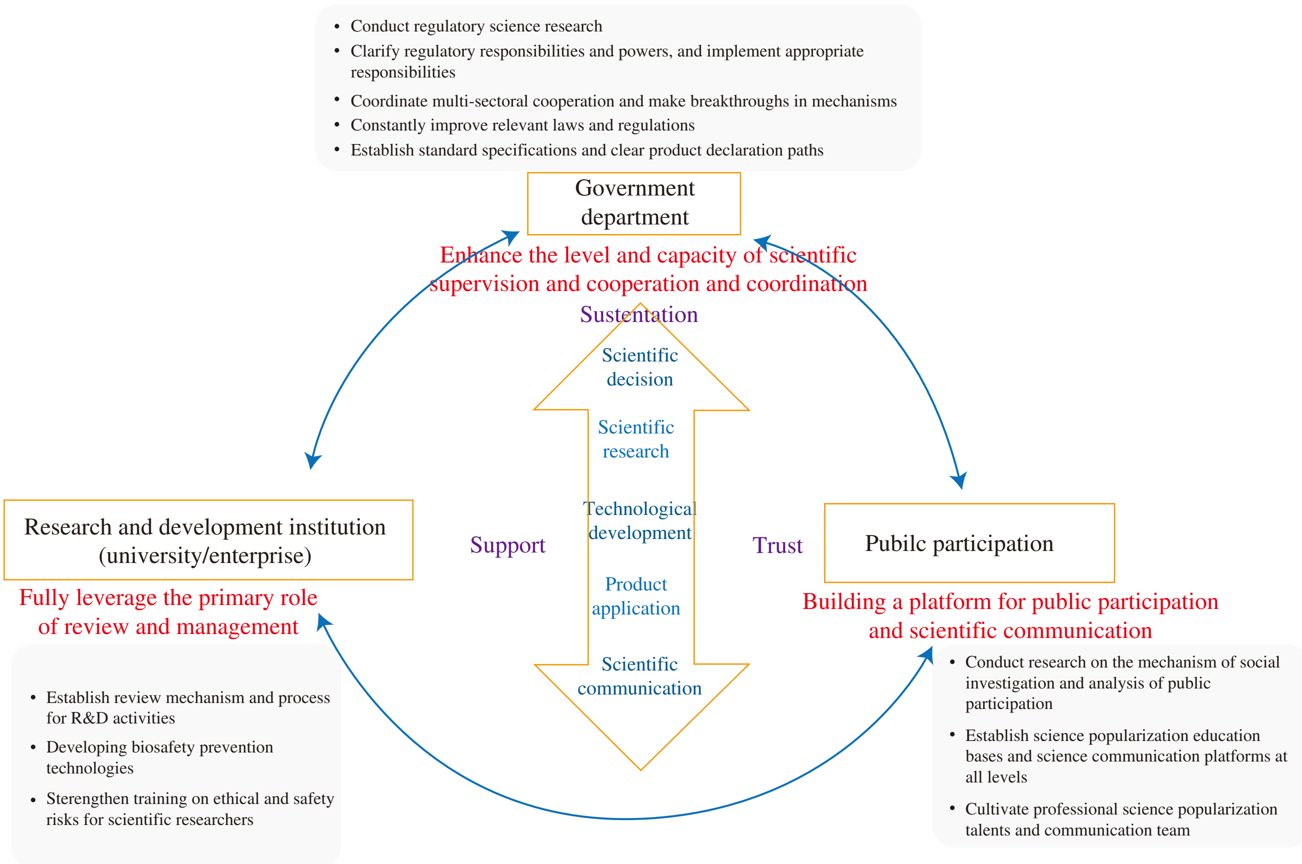

Fig. 10 China is committed to building a new comprehensive food safety management system for NFPS.

focusing on the safety management of synthetic biology-derived food products (Fig. 10). By improving regulatory frameworks and emphasizing biosecurity research, China strives to create a regulatory environment that not only fosters technological innovation but also ensures the safety of these new technologies. This management strategy is designed not only to safeguard the development of synthetic biology and other NFPS technologies but also to serve as a benchmark for global regulatory norms. Emphasizing transparency, inclusiveness, and adaptability, China aims for its management model to support sustainable development and play a significant role in the global management of NFPS.

As the global landscape of food production evolves with synthetic biology innovations, it is essential for regulatory bodies worldwide to adopt robust frameworks, such as the WHO's proposed food risk assessment framework[101], which emphasizes clear processes for scope establishment, information gathering, risk categorization, and inspection frequency determination. Adapting the framework to address the unique challenges of novel synthetic foods will enable nuanced regulatory responses that align with both international standards and local needs. Concurrently, it is crucial for researchers to enhance scientific endeavors in developing more sophisticated detection and processing technologies for synthetic foods. This will ensure their safety, nutritional adequacy, and palatability, thereby safeguarding public health over both the short and long term. Integrating these regulatory and technological advancements will provide a comprehensive approach to safely incorporating synthetic biology into the global food supply, fostering innovation while maintaining rigorous safety and health standards. As part of the build up to the UN Food Systems Summit on 23 September 2021, the Scientific Group of the UN Food Systems Summit organized the "Science Days for the UN Food Systems Summit 2021", facilitated and hosted by FAO on 8−9 July 2021, where more than 2 000 participants from research, policy, civil society and industry came together to examine how to unlock the full potential of science, technology and innovation to transform food systems[5]. The role of agricultural biotechnologies was discussed at the Science Days, including during a session dedicated to 'bio-science innovation', encompassing genome editing, bioinformatics, synthetic biology, microbiomes, alternative protein sources, alternative sources for essential micronutrients, cell factories and more.

Declaration of competing interest

Yongning Wu is an editorial board member for *Food Science and Human Wellness* and was not involved in the editorial review or the decision to publish this article. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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