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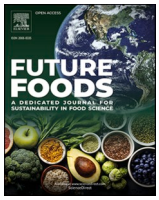

The safety assessment of microalgae-derived products as novel foods by the European Food Safety Authority

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ABSTRACT

Recent advancements in food research alongside the growing interest in new sources with enhanced nutritional value have led to an increasing development of food products derived from microalgae. Some of these products fall under the category of novel foods (NFs) in the European Union (EU) and their safety must be evaluated by the European Food Safety Authority (EFSA) before being authorised on the EU market. By August 2024, EFSA had evaluated eleven NFs derived from microalgae, including oils rich in docosahexaenoic acid (DHA) from *Schizochytrium* spp., whole biomass of the microalga *Euglena gracilis* and its derivative beta-glucan polymer (paramylon), ethanolic extract from *Phaeodactylum tricornutum* and oleoresin rich in astaxanthin from *Haematococcus pluvialis*.

One of the key scientific requirements for the safety assessment of these products is the characterisation of the microalga strain, including its unambiguous taxonomic identification at species level and pathogenicity. The "Qualified Presumption of Safety" (QPS) status of the microalgae also plays a significant role in determining the safety assessment approach to be applied. Other relevant requirements comprise a thorough chemical characterisation (e.g., biotoxins, undesirable substances, heavy metals) together with microbiological and nutritional characterisation of the product, description of the manufacturing process and a toxicological and allergenicity assessment.

By illustrating examples of NF that consist of, are isolated from or are produced by microalgae we highlight the main requirements needed for their safety assessment alongside the challenges encountered. Taking into account the continuous evolution of the microalga sector leading to innovative products, we also extend these requirements to the safety assessment of microalgal proteins, considering potential future mandates to assess algae-derived proteins as NFs by EFSA.

1. Introduction

The continuously rising global population is driving a growing demand for dietary proteins, rendering the current system of animal-based foods unsustainable in the long term. Therefore, it is necessary to search for alternative, environmentally sustainable protein sources that account also for animal health and welfare (United Nations, 2022). Algae could offer a potential solution as an alternative source of proteins and nutrients. Technological advances in the algae food industry have made their production more feasible, fuelling an increased interest in

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algal-based food products and algae-derived food ingredients (Araujo and Peteiro, 2021; Procházka et al., 2023). Algae comprise a diverse group of eukaryotic photosynthetic organisms that are divided into microalgae, which are microscopic and single-celled, and macroalgae, commonly known as seaweed (Procházka et al., 2023; Wu, Tso, Teo, and Haldar, 2023).

Algae can be a source of sustainable and high-value ingredients. Microalgae species such as *Chlorella* and *Arthrospira* can provide up to 50-70 % protein by dry weight, making their dried forms a rich source of essential amino acids (Procházka et al., 2023; Wu et al., 2023). Some algae species contain indigestible carbohydrates (e.g., β-glucans), polyunsaturated fatty acids (PUFAs) (e.g., omega-3 and -6), vitamins (including A, C, D, E, K, and B vitamins), and minerals (e.g., calcium, magnesium, iodine) (Lucakova, Branyikova, and Hayes, 2022; Procházka et al., 2023; Wu et al., 2023).

Over the last decade, an increase of 150 % was noted in the number of companies producing algae derived products, mirroring a surge in the development of innovative food products from algal biomass or its components (e.g., ingredients isolated or produced from algae) (Araújo et al., 2021; Ferreira de Oliveira and Bragotto, 2022). The European Commission, through its proposed action "Towards a Strong and Sustainable Algae Sector" and the EU4Algae Initiative, is at the forefront of driving the development of the EU's algae sector (Bruce F., 2023). This initiative aims to promote sustainable production and innovation in this sector, increasing the need for up-to-date regulatory aspects to support the potential of algae as a prospective food source.

Regarding the regulatory status of novel products in the European Union (EU), the term 'Novel food' (NF) specifically refers to those foods that were not consumed by humans to a significant degree within the Union before 15 May 1997 and fall into one or more categories listed in the NF Regulation (EU) 2015/2283[1]. While some algae species had been used as food in the EU before this date, all those that were not previously consumed to a significant degree fall under the NF regulatory framework and, therefore, require a safety assessment by the European Food Safety Authority (EFSA) before being authorised on the EU market. The safety assessment by EFSA involves an extensive evaluation of the NF, including its identity, production process, composition, nutritional profile, history of use, proposed uses and use levels, and data from toxicological and allergenicity studies (EFSA NDA Panel EFSA Panel on Nutrition, Novel Foods and Food Allergens et al., 2024).

This article provides critical insights into EFSA's experience in assessing, in particular, NFs consisting of, isolated from or produced with microalgae, while highlighting the challenges encountered upon the assessments. Additionally, the relevance of this experience is discussed in relation to microalgae-derived proteins as NFs.

2. Methodology

All EFSA scientific opinions on NFs derived from microalgae published until August 2024 were retrieved from the EFSA Journal[2] and the OpenEFSA portal[3]. Mandates from the European Commission to EFSA requesting the safety assessment of microalgae-derived NFs, referring both to concluded and to ongoing assessments, and the respective scientific opinions retrieved from this search, are provided in Annex A.

The latest publication from the European Commission on algae was also reviewed to gather information on microalgae groups used as NFs in the European Union (Araújo and Peteiro, 2021).

Requirements for microalgae and protein safety assessment were taken from the updated Scientific Guidance on NFs (EFSA NDA Panel EFSA Panel on Nutrition, Novel Foods and Food Allergens et al., 2024), which outlines the scientific requirements necessary for preparing an application for authorisation of a NF.

3. Results and discussion

In the following sections, NFs derived from microalgae assessed by EFSA will be illustrated, together with the key elements for their safety assessment, which are further extended to the safety assessment requirements for algal protein sources and products thereof.

3.1. Novel Foods derived from microalgae

As of August 2024, a total of eleven EFSA's scientific opinions on microalgae-derived NFs have been published, and six safety assessments are currently ongoing.

Among the published opinions, only one NF consisted of the dried whole biomass of a microalga, *Euglena gracilis* (EFSA NDA Panel, 2020b), whereas the remaining NFs consisted of components or extracts isolated or produced from the microalgal biomass. These include astaxanthin-rich oleoresin from *Haematococcus pluvialis* (EFSA NDA Panel, 2014b, EFSA NDA Panel, 2020a), an ethanolic extract of the dried biomass of *Phaeodactylum tricornutum* (EFSA NDA Panel, 2023a), paramylon (beta-glucan) from *E. gracilis* (EFSA NDA Panel, 2023d), and DHA-rich oils derived from *Schizochytrium* spp. (EFSA NDA Panel, 2014a, EFSA NDA Panel, 2020c, EFSA NDA Panel, 2021a, EFSA NDA Panel, 2021b, 2022, EFSA NDA Panel, 2023b, EFSA NDA Panel, 2023c). Fig. 1 reflects the intended uses of these NFs assessed by EFSA. Among the ongoing safety assessments, the dried biomass from *Galdieria sulphuraria*, dried biomass powder from *Chlamydomonas reinhardtii* and three DHA-rich oils (two derived from *Schizochytrium* spp. and one from *Nannochloropsis oculata*), are included.

3.2. Safety assessment of Novel Foods derived from microalgae

The key elements for the safety assessment of microalgae-derived NFs by EFSA (Fig. 2) are illustrated with examples which are elaborated in the following subsections.

3.2.1. Identity

The scientific requirements for taxonomic and hazard identification of microorganisms intentionally used in the food chain (bacteria, yeasts, filamentous fungi and viruses) generally rely on whole genome sequence (WGS) data analysis (EFSA FEEDAP Panel EFSA Panel on Additives and Products or Substances used in Animal Feed et al., 2018; EFSA BIOHAZ Panel EFSA Panel on Biological Hazards et al., 2024). These requirements depend on (i) the specific role of the microorganism (active agents, biomasses, or production strains) and, when applicable, on (ii) the genetic modification (GM) and (iii) the qualified presumption of safety (QPS) status (EFSA European Food Safety Authority, 2024). For other taxonomic units (TUs), such as microalgae and protists, the same principles would apply on a case-by-case basis (EFSA European Food Safety Authority, 2024; EFSA FEEDAP Panel EFSA Panel on Additives and Products or Substances used in Animal Feed et al., 2018). However, there are currently limitations in the analysis of WGS data for certain microalgae/protists due to incomplete information on reference genomes, highlighting the need for further development of guidance on the microbial characterisation of microalgae/protists (EFSA GMO Panel, 2024).

Regarding aspects (i) and (ii), NFs consisting of (non-GM) microalgal biomasses (non-viable cells and their genetic material are present) (*E. gracilis, G. sulphuraria, C. reinhardtii, Odontella aurita*) or isolated/produced from (non-GM) microalgal strains (*H. pluvialis, P. tricornutum, Schizochytrium* spp., *N. oculata, Tetraselmis chuii, Ulkenia sp.*) have been

[1] Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001

[2] https://efsa.onlinelibrary.wiley.com/journal/18314732

[3] https://open.efsa.europa.eu/

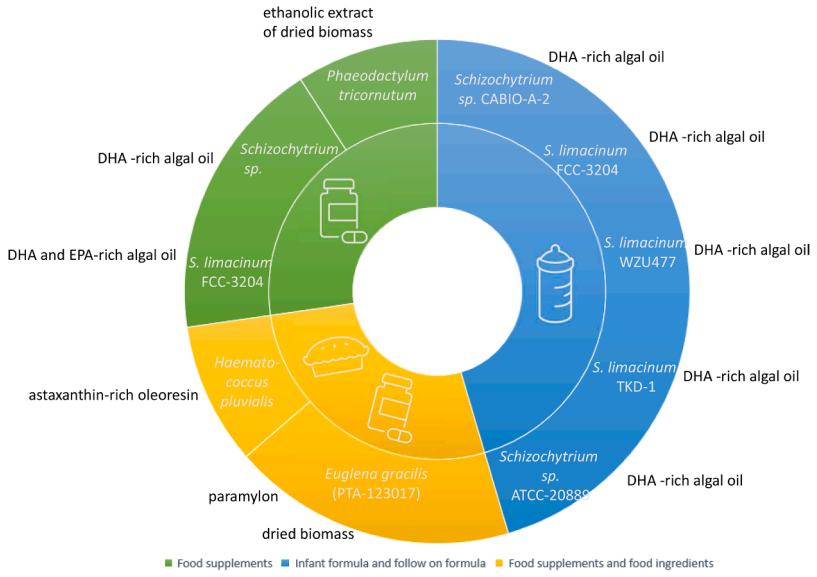


Fig. 1. NF products derived from different microalgae assessed by EFSA together with their intended use (food ingredient, food supplement, infant and follow-on formulae). DHA: docosahexaenoic acid.

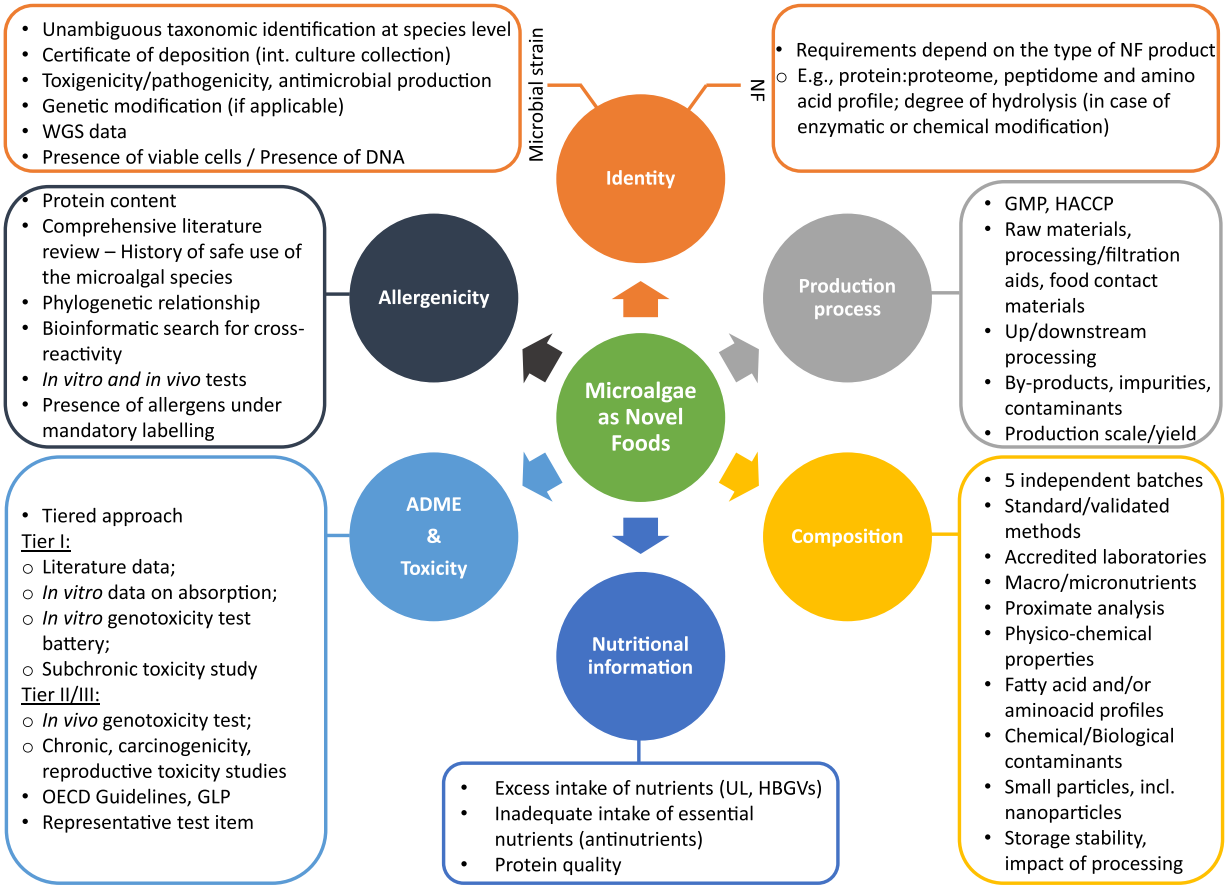


Fig. 2. Key scientific requirements for the safety assessment of microalgae-derived NFs by EFSA (EFSA NDA Panel 2024). GLP: Good Laboratory Practices; GMP: Good Manufacturing Practices; HACCP: Hazard Analysis Critical Control Points; HBGV: Health-Based Guidance Values; NF: Novel Food; QPS: Qualified Presumption of Safety; UL: Upper Levels.

authorised, already assessed by EFSA with negative outcome (EFSA NDA Panel EFSA Panel on Nutrition, Novel Foods and Food Allergens et al., 2022, EFSA NDA Panel, 2023a) or are currently under safety assessment. *T. chuii* (AESAN 2013; AECOSAN 2017), *Odontella Aurita*[4], *Ulkenia* sp. and some of the NFs derived from *Schizochytrium* spp. were assessed by Member States. Additionally, GM microalgal strains could be used in the production of NFs, provided that viable cells and DNA from the GM production strain are not detectable in the NF (EFSA FEEDAP Panel EFSA Panel on Additives and Products or Substances used in Animal Feed et al., 2018), following the provisions in Regulation (EU) 2015/2283.[1]

Scientific requirements for microalgal strain characterisation include the unambiguous taxonomic identification at species level, typically using molecular techniques using the complete, or a large portion of, the 18S or 25S rRNA genes and housekeeping gene markers (homology of >98 %) or WGS analysis (ANI > 98.89 %). It is noteworthy that the production strain *Schizochytrium* sp. CABIO-A-2 (EFSA NDA Panel, 2023c) was not unambiguously identified at species level, but the evidence provided demonstrated that it was phylogenetically closely related to *Schizochytrium* sp. ATCC 20888 (18S rRNA showing 99.88 % percentage of identity), which had been previously considered as a reference strain for the assessment of some already authorised *Schizochytrium* sp. oils.

Moreover, a valid certificate of deposition (including accession number) should be provided for the microalgal strain under assessment in an internationally recognised culture collection. Finally, the potential pathogenicity or ability of the microalgal strain to produce metabolites of safety concern should be assessed (e.g., via literature search, chemical/quantitative analyses or toxicological studies).

When the microalgae strain under assessment meets the criteria for the QPS approach to safety assessment (namely, (i) unambiguous taxonomic identification as belonging to a species included in the QPS list, (ii) any QPS qualification is met and (iii) for productions strains, no concerns are raised by genetic modification(s)), toxicological studies with the NF will only be required in relation to possible safety concerns identified elsewhere in the assessment process, e.g., production process. This was the case of paramylon derived from *E. gracilis* (EFSA NDA Panel, 2023d), dried biomass of *E. gracilis* (EFSA NDA Panel, 2020b) and DHA-rich oils derived from *Schizochytrium* (EFSA NDA Panel, 2014a, EFSA NDA Panel, 2020c, EFSA NDA Panel, 2021a, EFSA NDA Panel, 2021b, 2022, EFSA NDA Panel, 2023b, EFSA NDA Panel, 2023c). Interestingly, EFSA concluded that the safety of the oil from *Schizochytrium* sp. ATCC 20889 was not established since the production strain was not unambiguously identified at species level, therefore it did not qualify for the QPS approach (*S. limacinum*), and concerns on the ability of the strain to produce toxins remained, also due to the lack of toxicological studies with the NF.

Furthermore, the presence of viable cells of the microalgal strain under assessment in the NF has to be analysed (EFSA FEEDAP Panel EFSA Panel on Additives and Products or Substances used in Animal Feed et al., 2018) for (i) biomasses and non-QPS TUs as NFs, (ii) QPS TUs with the qualification 'for production purposes only' (currently, *C. reinhardtii, E. gracilis, H. pluvialis, S. limacinum* and *T. chuii*)), and (iii) non-QPS or GM production strains. In addition, the presence of DNA from the microalgal production strain in the NF has to be analysed for GM production strains (EFSA FEEDAP Panel EFSA Panel on Additives and Products or Substances used in Animal Feed et al., 2018).

In case of NFs isolated or produced from microalgae, the requirements to characterize their identity depend on whether it is a chemical substance, a polymer, or mixed substances (e.g., oil rich in certain PUFAs, dried biomass).

For single substances, such as the carotenoid astaxanthin (EFSA NDA Panel, 2014b), the chemical name, CAS number, and molecular weight are required. However, further experiments may be needed to demonstrate the chemical identity of the NF, such as degree of polymerisation, purity, data from the Nuclear Magnetic Resonance spectroscopy, and absence of branching in the case of paramylon (an unbranched β-1, 3-D-glucano polymer synthetised by the microalga *E. gracilis)* (EFSA NDA Panel, 2023d).

Additional considerations for the characterisation of microalgae-derived proteins as NF may include proteome, peptidome and amino acid profiling and degree of hydrolysis in case of enzymatic or chemical modification. In case of proteins derived from GM microalgae strains, post-translational modifications should be characterised, as well as the potential impact on physico-chemical properties (e.g., thermal stability).

3.2.2. Production process

Microalgae-derived NFs should be produced following Good Manufacturing Practices and Hazard Analysis Critical Control Point principles, and typically in compliance with the Food Safety System Certification 22000, in line with Regulation (EC) No 852/2004[5] on the hygiene of foodstuffs. The main steps of the manufacturing process of microalgae-derived NFs include the cultivation/growing of the cells, harvesting (by e.g. filtration, centrifugation), drying, extraction (for oils)/ milling, packaging and storage.

Regarding algal protein, the main conventional steps reported in literature (Bleakley and Hayes, 2017; Mosibo, Ferrentino, and Udenigwe, 2024; Sathya, MubarakAli, MohamedSaalis, and Kim, 2021) for its extraction include aqueous, acidic, and alkaline methods, followed by several rounds of centrifugation and recovery techniques (e.g., ultrafiltration, precipitation, chromatography). Cell disruption methods are also applied to increase the availability of proteins.

Safety related aspects such as potential presence of by-products, impurities, or contaminants should be quantitatively documented. Inconsistencies in those parameters can lead to safety concerns in the production process, as it was the case for the ethanolic extract derived from *P. tricornutum* (EFSA NDA Panel, 2023a).

Specific requirements for microalgae-derived NFs refer to information on the culture conditions, including temperature, water quality, length of growth, composition of fertilisers used, etc. For instance, for the production of oil from *S. limacinum* (EFSA NDA Panel, 2020c), the applicant provided information on the steps taken to ensure that the water did not contain any marine biotoxins or other compounds of concern and compliance with the requirements set out by EU Directive (EU) 2020/2184[6].

Applicants should also inform on the use of extraction solvents, reagents, additives and their residues in the NF, and provide a list of the culture media with their respective certificates of analysis. Only permitted organic solvents can be used, in compliance with Directive 2009/32/EC[7].

Furthermore, when food enzymes of microbial origin are used in the production of microalgae-derived NFs, the steps and conditions to inactivate or remove the enzymes from the final NF need to be provided, along with experimental data showing their presence/absence and (remaining) enzymatic activity (EFSA CEP Panel EFSA Panel on Food Contact Materials, Enzymes and Processing Aids et al., 2021). For

[4] https://www.anses.fr/fr/system/files/AAAT2001sa0082.pdf

[5] Regulation (EC) No 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of foodstuffs. OJL 139, 30.4.2004, pp. 54

[6] Directive (EU) 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the quality of water intended for human consumption (recast) OJ L 435, 23.12.2020, p. 1–62.

[7] Directive 2009/32/EC of the European Parliament and of the Council of 23 April 2009 on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients. OJ L 141, 6.6.2009, p. 3–11.

instance, for the production of oil from *Schizochytrium* sp. (strains CABIO-A-2; TKD-1), the applicants used an alkaline protease derived from a non-GM *Bacillus licheniformis,* for which absence in the final NF was demonstrated (EFSA NDA Panel, 2023b, EFSA NDA Panel, 2023c).

Additional data on the microorganisms used to produce the food enzymes could be requested following relevant EFSA guidance documents (EFSA CEP Panel EFSA Panel on Food Contact Materials, Enzymes and Processing Aids et al., 2021; EFSA FEEDAP Panel EFSA Panel on Additives and Products or Substances used in Animal Feed et al., 2018). For example, in the manufacturing process of oil from *Schizochytrium* sp. (strain CABIO-A-2) (EFSA NDA Panel, 2023c) and *S. limacinum* (strain TKD-1) (EFSA NDA Panel, 2023b), an enzyme derived from the non-GM *B. licheniformis* was used, for which a QPS status with the qualification of 'absence of bacitracin production ability' was given (EFSA European Food Safety Authority, 2024). The applicant demonstrated that the level of bacitracins in the NF was below the detection limit. Additionally, the applicant certified that the microorganism was not present in the enzyme preparation and provided data which confirmed the absence of acquired antimicrobial resistance genes.

3.2.3. Compositional characterisation

Comprehensive compositional characterisation of NFs, including microalgae-derived foods and food ingredients, is essential, as compositional data form the "backbone" of both NF application dossiers and the safety assessment process. Such characterisation covers chemical, physicochemical, microbiological, and nutritional profile, enabling the evaluation of safety, nutrition-related implications, and regulatory compliance (Ververis et al., 2020; EFSA NDA Panel EFSA Panel on Nutrition, Novel Foods and Food Allergens et al., 2024).

For microalgae-derived NFs, compositional characterisation typically encompass a thorough assessment of various components, including macronutrients (proteins, lipids, carbohydrates), micronutrients (vitamins, minerals), and bioactive compounds (antioxidants, pigments such as chlorophylls and carotenoids, and polysaccharides). Additionally, the fatty acid and amino acid profiles, antinutrients, chemical and biological contaminants (e.g., heavy metals, pesticides, pathogens, marine biotoxins, mycotoxins), processing contaminants (e.g., polycyclic aromatic hydrocarbons, total dioxin and dioxin-like polychlorinated biphenyls, glycidol and 3-monochloro-propanol-1,2-diol) and substances of potential concern (e.g., phycotoxins) are critically examined. These potential hazards could be intrinsic of the microalgae, or arise from components present during cultivation, harvest and post-harvest processing (Ferreira de Oliveira and Bragotto, 2022; Hadi and Brightwell, 2021). Microplastics constitutes an emerging risk due their potential incorporation into certain microalgal species.

The nature of the NF dictates the specific components that require analysis to complement its compositional profile. Standardized protocols are essential to provide reliable and reproducible data. Fig. 3 illustrates key components assessed in the safety assessment of the NFs derived from microalgal strains assessed by EFSA together with common analytical techniques encountered in the microalgae-derived NFs dossiers.

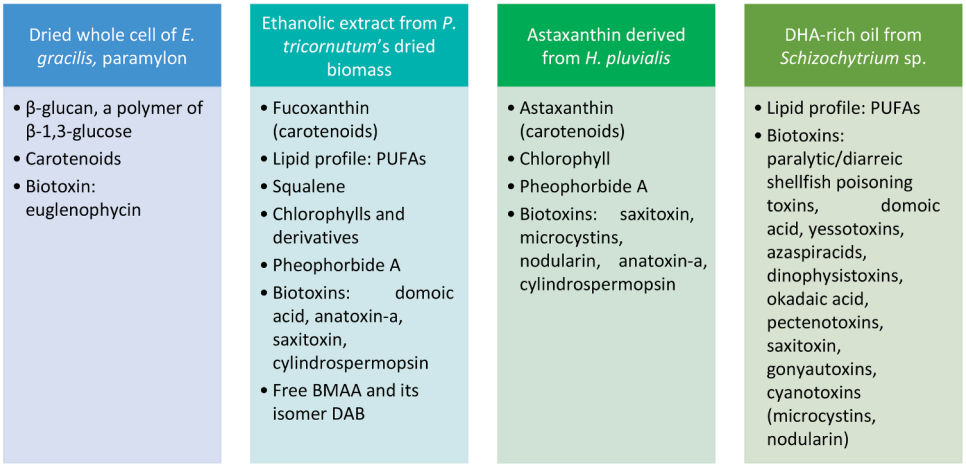
In the ethanolic extract from the dried biomass of *P. tricornutum* (EFSA NDA Panel, 2023a), particular focus was placed to pheophorbide A (PHA), a breakdown product of chlorophyll with documented phototoxicity (Endo, Hosoya, Koyama, and Ichioka, 1982; Hwang et al., 2005). Moreover, the applicant was requested to analyse pyropheophorbide A (PPHA) alongside PHA, as it was quantified in higher concentrations than PHA in the dried purple laver production (Hwang et al., 2005) and it was reported to induce phototoxicity at lower doses compared to PHA (Endo, Hosoya, Koyama, and Ichioka, 1982). In the case of *H. pluvialis,* the low chlorophyll levels suggested correspondingly low PHA levels in the NF ingredient (EFSA NDA Panel, 2014b).

Marine biotoxins also warrant particular attention due to their potential presence in microalgae-based NFs, either as metabolic products or as contaminants from the surrounding aquatic environment. This consideration is further elaborated in the Toxicological Information section (3.2.5).

The complexity of microalgae matrices poses significant challenges, necessitating tailored method development and validation. High levels of pigments in certain microalgae species can interfere with analytical techniques, requiring additional steps to isolate or account for these compounds. The composition of NF batches can vary due to factors such as species, cultivation conditions, and harvesting methods, rendering product standardization and comparison of results challenging. Analysing the variability between batches helps assess the producer's ability to maintain consistency and reproducibility, forming the basis for hazard identification and establishing specification parameters (EFSA NDA Panel, 2014a).

3.2.4. Nutritional information

The nutritional information requirements for microalgae-derived NFs depend on their identity and composition. These are needed to evaluate whether the NF can be nutritionally disadvantageous for the



PUFAs: long-chain polyunsaturated fatty acids; BMAA: Beta-N-Methylamino-L-alanine; DAB: Diaminobutyric Acid

Fig. 3. Relevant components assessed for the biomass of *E. gracilis* and paramylon derived from it (EFSA NDA Panel, 2023d), ethanolic extract from *P. tricornutum* (EFSA NDA Panel, 2023a), astaxanthin derived from *H. pluvialis* (EFSA NDA Panel, 2014b) and oils derived from *Schizochitrium* sp. (EFSA NDA Panel, 2014a, EFSA NDA Panel, 2020c, EFSA NDA Panel, 2021a, EFSA NDA Panel, 2021b, 2022, EFSA NDA Panel, 2023b, EFSA NDA Panel, 2023c) and some of the techniques applied for their determination.

consumers under the intended conditions of use (Ververis et al., 2020: EFSA NDA Panel EFSA Panel on Nutrition, Novel Foods and Food Allergens et al., 2024). The overall intake of nutrients is calculated and compared with health-based guidance values (HBGVs) (e.g., tolerable upper intake levels (UL)), if available.

In the case of paramylon isolated from *E. gracilis* (EFSA NDA Panel, 2023d) and dried whole cell *E. gracilis* (EFSA NDA Panel, 2020b), the main constituent is beta-glucan, and it was proposed to be used in food supplements, as an ingredient in different food categories and in total diet replacements for weight control. The nutritional analysis, including proximates, vitamins or mineral concentrations, did not raise concerns that the consumption of the NF could be nutritionally disadvantageous.

In 2014, EFSA assessed the safety of a novel astaxanthin-rich ingredient derived from the microalgae *H. pluvialis* under Regulation (EC) No 258/1997[8], which resulted in the determination of an acceptable daily intake (ADI) for the carotenoid astaxanthin (EFSA NDA Panel, 2014b). Concerns about the absorption and metabolism of fat-soluble vitamins after a prolonged administration were raised but the NDA Panel considered the consumption of the NF not to be nutritionally disadvantageous.

EFSA has assessed several NF applications on oils rich in DHA, isolated from the microalgae *Schizochytrium* sp. These oils are mainly used in infant formulae and follow-on formulae, (EFSA NDA Panel, 2020c, EFSA NDA Panel, 2021b, 2022, EFSA NDA Panel, 2023b, EFSA NDA Panel, 2023c) or food supplements (EFSA NDA Panel, 2014a, EFSA NDA Panel, 2021a) for enrichment of the diet with DHA, for instance as set by Regulation (EU) 2016/127[9]. The content of total lipid and fatty acids in those microalgae are affected by different abiotic stress conditions (e.g., light, temperature, nutrients, UV radiation, pH) (Paliwal et al., 2017). Overall, EFSA's conclusion was that the consumption of these oils under the proposed uses was not considered nutritionally disadvantageous.

The protein quality of microalgae as NFs needs to be evaluated under specific circumstances i.e., whenever the total contribution of the NF to the total protein intake is at or above 15 % of the protein average requirement for any population group (EFSA NDA Panel, 2012; 2024). The protein quality should be assessed using the method recommended by the Food and Agriculture Organization (FAO) using the digestible indispensable amino acid score method (FAO, 2013). The digestibility of proteins found in microalgae has not been widely examined in the literature. In general, it has been reported that digestibility of microalgal proteins is inferior to that of conventional sources of food proteins due to the presence of polysaccharides within cell walls (Mosibo et al., 2024; Parodi et al., 2018). This also affects their bioavailability. In this regard, the potential impact of antinutrients (e.g., phytic acid, tannins, and protease inhibitors) present in the NF should also be explored (EFSA NDA Panel EFSA Panel on Nutrition, Novel Foods and Food Allergens et al., 2024; Mosibo et al., 2024). Amino acid profile of microalgae is also affected by environmental conditions (Mosibo et al., 2024).

3.2.5. Absorption, distribution, metabolism, and excretion (ADME) & Toxicological information

ADME and toxicological information are required as an integral part for the safety assessment of NFs, including microalgae-derived NFs, which relies on a tiered approach (EFSA NDA Panel EFSA Panel on Nutrition, Novel Foods and Food Allergens et al., 2024). This generally includes *in vitro* data on gastrointestinal absorption and the study of toxicokinetics (if available), a battery of two genotoxicity *in vitro* tests (i.e., bacterial reverse mutation test and *in vitro* micronucleus assay) and a subchronic 90-day oral toxicity study (conducted by the applicant and/or retrieved from literature) as a first step. All studies should be conducted following international guidelines (e.g., OECD) and Good Laboratory Practices.

Indications of toxicity in a 90-day study and/or a positive outcome in the *in vitro* genotoxicity tests may trigger the need for further studies, in order to investigate aspects of genotoxicity/carcinogenicity, reproductive and developmental toxicity, or other specific endpoints. Human studies are generally not required, but they can provide supportive evidence. Additionally, in cases where strain identity is not unequivocally demonstrated, toxicological studies are required due to the unknown potential of the strain to produce toxins (EFSA NDA Panel EFSA Panel on Nutrition, Novel Foods and Food Allergens et al., 2022).

For NFs that are complex mixtures, and if the mixture cannot be "fully characterised", its unidentified fractions should be tested, or, if not feasible, the experimental testing of the whole mixture should be conducted (EFSA Scientific Committee, 2011, 2019). This was the case for the ethanolic extract from *P. tricornutum* (EFSA NDA Panel, 2023a), for which the whole product was tested for genotoxicity. The tested compound needs to be representative of the NF to allow drawing conclusions from the studies on the safety of the final product.

Compounds raising a potential toxicological concern should also be sufficiently characterised. It should be demonstrated that marine biotoxins are i) not produced by the source organism, ii) not present in the NF, and iii) cannot arise from external contamination, as it was requested for DHA-rich oils derived from *Schizochytrium* sp. (EFSA NDA Panel, 2014a, EFSA NDA Panel, 2020c, EFSA NDA Panel, 2021a, EFSA NDA Panel, 2021b, 2022, EFSA NDA Panel, 2023b, EFSA NDA Panel, 2023c). Intakes resulting from the occurrence of biotoxins should remain below their respective acute reference dose, if available (EFSA CONTAM Panel, 2009). For instance, in the case of *P. tricornutum* (EFSA NDA Panel, 2023a), the insufficient characterisation of phototoxic compounds together with a low margin of exposure calculated for these substances at the proposed use levels, lead to the conclusion by EFSA that the safety of the NF could not be established.

Overall, the compositional characterisation of the NF, production process, QPS status, and available data retrieved from literature should be considered together with the results from the toxicological studies.

3.2.6. Allergenicity

Following the EFSA Guidance on the scientific requirements for an application for authorisation of a NF (EFSA NDA Panel EFSA Panel on Nutrition, Novel Foods and Food Allergens et al., 2024), the tiered approach for allergenicity testing of single proteins and simple protein mixtures derived from microalgae includes: tier I) comprehensive literature search and phylogenetic relationships; tier II) bioinformatic search for cross-reactivity; tier III) human-serum specific IgE binding assay; tier IV) human studies.

Microalgae have been reported to cause allergenic reactions (Hadi and Brightwell, 2021). The body of evidence for the allergenicity assessment of NFs consisting of (non-GM) microalgal biomasses or isolated/produced from (non-GM) microalgal strains may typically include: (i) protein content; (ii) comprehensive literature review (e.g., prevalence, clinical relevance, dose, severity, potency, cross-reactivity, *de novo* sensitisation) and references to prior EFSA assessments; (iii) history of safe use of the microalgal species under assessment in third countries or of closely related microalgal species in the EU; (iv) bioinformatics analysis (protein identification by LC-MS/MS) to predict cross-reactivity (e.g., triosephosphate isomerase in *P. tricornutum* biomass (EFSA NDA Panel, 2023a)); (v) presence of allergens under mandatory labelling (e.g., traces of soybean proteins in *S. limacinum* TKD-1 (EFSA NDA Panel, 2023b)); (vi) *in vivo* tests (e.g., prick and patch tests).

Although the allergenicity risk of the assessed NFs was considered to be low by EFSA in most cases, as it has also been reported in literature

[8] Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients.

[9] Commission delegated regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding

(Diaz-Bustamante, Keppler, Reyes, and Alvarez Solano, 2023), for *P. tricornutum* biomass (10 % w/w protein and cross-reactivity with shrimps), EFSA concluded that "allergic reactions may occur upon consumption of the NF, especially in shrimp-allergic individuals" (EFSA NDA Panel, 2023a).

4. Conclusions

The interest in microalgae as alternative food sources, particularly as protein source, continues to grow. For microalgae-derived products that qualify as NF under EU regulation, a safety assessment by EFSA is mandatory before they can be marketed within the EU. EFSA has concluded safety assessments for several microalgae-derived NFs, proposed as ingredients in a variety of products, including in foods intended for the general population, infant and follow-on formula, and food supplements. EFSA's safety assessment of microalgae-derived NFs relies on multiple scientific criteria established in the Scientific Guidance on NFs. These include unambiguous taxonomic identification at species level of the microalgae strain and its QPS status, a thorough chemical characterisation of the NFs, alongside nutritional analysis, description of the production process, and data on potential toxicity and allergenicity. As new technologies for extracting and processing microalgal proteins emerge, EFSA must review and update its safety assessment protocols and requirements, to keep abreast of advances in the field, safeguarding public health.

CRediT authorship contribution statement

Irene Nuin Garciarena: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Reinhard Ackerl:** Writing – review & editing, Data curation. **Esther García Ruiz:** Writing – original draft, Data curation. **Maria Glymenaki:** Writing – review & editing, Writing – original draft, Data curation. **Vânia Mendes:** Writing – original draft, Data curation. **Alejandra Muñoz-González:** Writing – original draft, Data curation. **Estefanía Noriega Fernández:** Writing – original draft, Data curation. **Gabriela Precup:** Writing – original draft, Data curation. **Pablo Rodríguez-Fernández:** Writing – original draft, Visualization, Data curation. **Ruth Roldán-Torres:** Writing – original draft, Data curation. **Annamaria Rossi:** Writing – review & editing. **Emanuela Turla:** Writing – review & editing. **Ermolaos Ververis:** Writing – review & editing, Writing – original draft, Data curation. **Andrea Germini:** Writing – review & editing, Supervision. **George E.N. Kass:** Writing – review & editing, Supervision.

Declaration of competing interest

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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Ethical statement

Studies in human or animal were not carried out by the authors for the purpose of this manuscript.

Supplementary materials

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Data availability

No data was used for the research described in the article.

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