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Analysis of trends and allergenicity risk assessments in novel food approvals within the European Union between 2018 and 2023

Sim Ray Yue [a,*], Kitty C.M. Verhoeckx [b], Geert F. Houben [c,d], Katrine Lindholm Bøgh [a]

[a] National Food Institute, Technical University of Denmark, Henrik Dams Allé, 2800, Kgs. Lyngby, Denmark
[b] Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, the Netherlands
[c] Center for Translational Immunology, University Medical Center Utrecht, Utrecht, the Netherlands
[d] The Netherlands Organisation for Applied Scientific Research TNO, Princetonlaan 6, 3584 CB, Utrecht, the Netherlands

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ABSTRACT

Novel food (NF) approvals in the European Union between 2018 and 2023 (n = 117) were retrieved and analysed. They consist of new NF (52.1%), modification (38.5%), and traditional food (9.4%). The average time taken for new NF applications to be approved was 38 months in 2023, with clock-stops occurring in all approvals since 2020. For new NFs, only 21.3% and 9.8% performed tests by bioinformatics homology and immunological analyses respectively, suggesting that allergenicity assessments remain a challenge. Allergenicity risks were regarded as possible for 47.5% of the new NF approvals, while 52.5% were expected to be low, very low, or unlikely. However, it was not always clear what the decision was based on. While protein intake levels were rarely mentioned in the allergenicity conclusions of approvals, new NFs with allergenicity risks typically had protein intake exceeding 1 mg/day. Establishing a dose that represents a Threshold of Allergological Concern below which a protein is unlikely to cause sensitisation in consumers, could make *de novo* allergenicity assessment of NFs more feasible. This approach might exempt certain proteins from testing, instead focusing on proteins of possible allergenic relevance.

1. Introduction

With the global population estimated to reach 8.5 billion by 2030 (United Nations, 2022), there is a common consensus across scientific organisations and international bodies that increased food production from different sustainable sources is imperative to meet the dietary needs of humans (European Food Safety Authority [EFSA], 2021; Food and Agriculture Organisation of the United Nations, 2021). The introduction of novel foods (NFs) in the European Union (EU) may contribute to the security and sustainability of the EU's food supply (Food and Agriculture Organisation of the United Nations, 2022). Under EU Regulation 2015/2283, a NF is a food that has not been consumed to a significant degree by humans in Member States of the EU prior to 15 May 1997 (European Union, 2015).

Before marketing, safety needs to be assured for NFs and a safety dossier must be approved by the European Commission (EC). NF applications prior to 31 December 2017 were sent to the competent authorities of EU Member States under the old Regulation 258/97 (European Union, 1997). With the introduction of Regulation 2015/2283 regarding NFs and its subsequent implementation from 1 January 2018, NF applications are now sent to the EC under the centralised food system common authorisation procedure platform for safety evaluation (European Union, 2015; European Food Safety Authority, 2020; European Food Safety Authority, 2023a). Applications and approvals are subdivided into three types: 1) new NF, which is food that is newly introduced and has not existed before in that specific form, 2) modification of an already authorised NF, where changes to conditions or additional specifications were made to existing NF approved between 1997 and 2017 under Regulation 258/97 (herein referred to as modifications), and 3) traditional food, which is food that has been widely consumed in at least one non-EU country with minimum 25 years of documented safe consumption (European Union, 2015; EFSA NDA Panel et al., 2021a).

The application procedure for a new NF commences when the applicant submits information about their NF in a dossier to the EC. Relevant information in the dossier includes the description of the NF identity, production processes, compositional data, proposed uses and anticipated intake, and various safety assessments (including

* Corresponding author.
E-mail address: sryu@food.dtu.dk (S.R. Yue).

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allergenicity) with a consideration of any potential risks. When the application is deemed suitable (within 30 working days) and is validated by the EC, the EC then commissions EFSA to perform relevant risk assessments. When completed, the applicable EFSA Panel adopts the scientific output based on the risk assessments performed within nine months (or longer if surplus information is required from the applicants in which case a clock-stop occurs), which is then published in the form of a Scientific Opinion (referred to as opinions) by EFSA. The new NF is then approved to be placed on EU markets through Commission Implementing Regulations (referred to as regulations) by the EC within seven months, acting as official EU approval (European Union, 2015; European Commission, 2021; European Food Safety Authority, 2021b). For traditional foods, the validation, opinion (in the form of a technical report), and approval durations are one, six, and three months respectively (European Union, 2015). This means that the theoretical time taken for a new NF or traditional food to be approved can take up to 17 or 10 months respectively (European Union, 2015), if no clock-stop is initiated.

Under Regulation 2015/2283, the EC has formulated 10 NF categories; 1) food with a modified molecular structure (e.g., 6′-sialyllactose sodium salt, EFSA NDA Panel et al., 2022a); food consisting of, or isolated from, or produced from: 2) microorganisms, fungi, or algae (e.g., vitamin D2 mushroom powder, EFSA NDA Panel et al., 2020), 3) material of mineral origin (e.g., mineral salt containing potassium and magnesium, OpenEFSA, 2019), 4) plants or their parts (e.g., mung bean protein, EFSA NDA Panel et al., 2021b), 5) animals or their parts (e.g., *Tenebrio molitor* - dried yellow mealworm, EFSA NDA Panel et al., 2021c), 6) cell or tissue cultures (e.g., *Antrodia camphorata* mycelia powder, EFSA NDA Panel et al., 2022b); 7) food resulting from production processes not used for food production before 15 May 1997 (e.g., iron hydroxide adipate tartrate, EFSA NDA Panel et al., 2021d); 8) food consisting of engineered nanomaterials (e.g., iron hydroxide adipate tartrate, EFSA NDA Panel et al., 2021d), 9) vitamins, minerals, and other substances produced in a manner not used before 15 May 1997 or that contains/consist of engineered nanomaterials (e.g., iron hydroxide adipate tartrate, EFSA NDA Panel et al., 2021d); and 10) food used exclusively in food supplements within the EU before 15 May 1997, where it is intended to be used in foods other than food supplements. It is possible for a NF to fall under two or more categories, and these are categorised accordingly in the opinions by EFSA (EFSA NDA Panel et al., 2021e; EFSA NDA Panel et al., 2022a).

As with all foods being introduced onto the market, appropriate safety risk assessments, including a microbiological, nutritional, toxicological, and allergenicity risk assessment, must be performed for the NF to ensure that it is safe for human consumption (European Food Safety Authority, 2021b). Concerning allergenicity, the following must be considered: Food allergens typically are proteins and if the NF contain proteins, it is assumed that the food is potentially allergenic (EFSA NDA Panel et al., 2021e; Dall'Asta, 2022). For NFs containing little to no protein, the allergenic potential can be considered low although it cannot be ruled out (Verhoeckx et al., 2020; EFSA NDA Panel et al., 2021e). It is therefore important to analyse the protein content and accurately describe the analytical methods used for determining the protein content. The allergenic potential can be further investigated through assessing taxonomic relationships, production processes, and by performing a comprehensive literature review to retrieve available information on experimental and human data, including information on cross-reactivity, sensitisation, case reports of allergic reactions, and/or allergenicity studies (*in vitro*, in animals, or in humans) of the NF and/or its source(s). Furthermore, the collection of further information such as digestibility, heat, and pH stability, *in silico* homology testing, immunological tests (e.g., immunoblotting), and human testing (e.g., specific IgE, skin prick test, and food challenges), are suggested (EFSA NDA Panel et al., 2021e).

There might be allergenicity information available in the literature especially for proteins derived from known allergenic food sources or sources known to cross-react with existing food allergens, such as in dried yellow mealworms (EFSA NDA Panel et al., 2021c). However, information regarding possible *de novo* sensitisation by new food sources and novel allergens will generally be much more scarce and difficult to obtain (Remington et al., 2018). It has been reported that despite more NF dossiers being submitted to EFSA, allergenicity assessments of NFs can still not be conducted appropriately due to a lack of suitable tools and criteria (Naegeli et al., 2017; European Food Safety Authority et al., 2019; Houben et al., 2019; Verhoeckx et al., 2020). According to these publications, methods to assess cross-reactivity are in place but can be challenging for NFs, with some containing many different proteins. Furthermore, there are no broadly accepted methods available to predict if an NF can induce a new allergy through *de novo* sensitisation with subsequent clinical symptoms (Remington et al., 2018; Verhoeckx et al., 2020; Crevel et al., 2024). Consequently, food producers and risk assessors struggle with the allergenicity assessment for new NFs (Verhoeckx et al., 2020; Dall'Asta, 2022; Precup et al., 2022; Scaffardi and Formici, 2022; López-Pedrouso et al., 2023).

This study on NF approvals provides insight into the current status of NF approvals (type of NF approval, NF categories, duration of approvals including clock-stops), the methods used to determine the potential allergenicity of NFs, and the EFSA conclusions regarding food allergy risks. Specific attention was paid to assess to what extent the level of anticipated NF protein intake was used in the allergenicity assessments. To the best of the authors' knowledge, this is the first deep-dive analysis of NF approvals in the EU since the implementation of Regulation 2015/2283 on 1 January 2018.

2. Methods

2.1. Data collection

The list of EU NF approvals between 1 January 2018 and 31 December 2023 was obtained from the Union list of NFs, which is made publicly available by the EC and provides relevant information on NFs since Regulation 2015/2283 was implemented (European Commission, 2024). For each approval, information was obtained through the respective regulations, opinions, or technical reports (only for traditional food), and individually reviewed for subsequent data extraction. We were not able to access safety dossiers submitted prior to 27 March 2021 before the Transparency Regulation was implemented through Regulation 2019/1381. Information was recorded in Microsoft Excel® to create a database for subsequent data extraction and processing. The relevant information is collated in the Supplementary Database.

2.2. Data extraction and analysis

NF approvals were initially sorted and stratified based on extracted keywords (Table 1) from the regulation documents for each approval to distinguish between the three types of approvals (new NF, modification, and traditional food). These approval types are also reflected in each NF application made under the EFSA Questions interface (European Food Safety Authority, 2023b). For example, the application for

Table 1
Common keywords extracted from the Commission Implementing Regulation approvals to distinguish between the three types of novel food approvals.

Type of Approval	Keywords in Regulation Approvals
New novel food	'authorising the placing on the market … as a novel food'
Modification of an already authorised novel food	'amending Implementing Regulation', 'amended the conditions', 'authorising changes in the specifications', 'authorising the change of the conditions'
Traditional food	'authorising the placing on the market … as a traditional food from a third country'

2′-Fucosyllactose was approved on 26 November 2019 and introduced as a new NF through the keywords "authorising the placing" in the regulations (European Union, 2019). Subsequently, on 22 January 2021, the regulation to "authorise an extension of use and a change in the specifications" was implemented (European Union, 2021). Thus, the initial application was treated as a new NF, while the subsequent application was treated as a modification.

Relevant information extracted from documents includes the names of NF, type of NF approval and category, application and approval dates, protein content, the anticipated maximum daily intake level, and information used to determine the allergenicity as well as conclusions made in the opinions. Data extracted from documents were further processed where required for subsequent analysis. Additional variables were created based on extracted data to determine the duration from when an application was sent to the relevant regulatory body overseeing NF applications until EU approval. The protein intake was calculated using the maximum value of the 95th percentile from the anticipated maximum daily intake. The metadata for the variables are presented in the Supplementary Database. To assess the correlation between the number of clock-stops and the total duration taken, the non-parametric Spearman's ranked correlation test and a linear regression analysis were performed. Results were considered statistically significant when the p-value was less than 0.05. Data was analysed and illustrated with Microsoft Excel® and GraphPad Prism version 10.3.0 (Graphpad, 2024, San Diego, CA, US).

3. Results

3.1. Types of novel food approvals

Between 1 January 2018 and 31 December 2023, 117 NF applications were approved by the EC, with 61 (52.1%) classified as new NF, 45 (38.5%) as modification of already authorised NF, and 11 (9.4%) as traditional food. These were further broken down into yearly trends (Fig. 1).

3.2. Categories in new novel food approvals

From 2018 through 2023 there were 61 new NF approvals spanning seven out of 10 NF categories (Fig. 2). For new NFs falling under more than one category as mentioned in the opinions, the most characteristic category was selected. An example is in the opinion on 6′-sialyllactose sodium salt, which falls under both the categories of NF with a modified molecular structure and NF produced from microorganisms, fungi, or algae, and the first category was selected as the most characteristic category in the database. New NFs from the modified molecular structure category (e.g., 6′-sialyllactose sodium salt, cetylated fatty acids, and cellobiose) had the highest number with 16 (26.2%) approvals. This was followed by the microorganisms, fungi, or algae category (e.g., vitamin D2 mushroom powder, *Yarrowia lipolytica* yeast biomass, and pea and rice protein fermented by *Lentinula edodes* Shiitake mushroom mycelia) with 14 (23.0%) approvals, and the plants or their parts category (e.g., partially defatted rapeseed powder, mung bean protein, and partially hydrolysed protein from spent barley) with 13 (21.3%) approvals, together making up the majority (68.9%) of all new NF approvals. From the category of animals or their parts with 12 (19.7%) approvals, they included bovine milk products (beta-lactoglobulin and osteopontin). Among this category, there were also four edible insect species across six approvals for dried, frozen, and powdered forms; yellow mealworm (*Tenebrio molitor* larvae); migratory locust (*Locusta migratoria*); house cricket (*Acheta domesticus*); and lesser mealworms (*Alphitobius diaperinus* larvae). For the category of vitamin, mineral, and other substances, there were three approvals (iron milk caseinate, nicotinamide riboside chloride, and 1-methylnicotinamide chloride). Two new NFs, *Antrodia camphorata* mycelia powder and apple fruit cell culture biomass, fell under the category "cell culture or tissue culture". Iron hydroxide adipate tartrate was the only approval of a new NF consisting of an engineered nanomaterial.

3.3. Duration of novel food approval processes

For the 117 NF approvals, the average time taken from submission of application to approval for each approval year was calculated (Fig. 3). Across all years, new NF approvals took on average twice as long (35.7

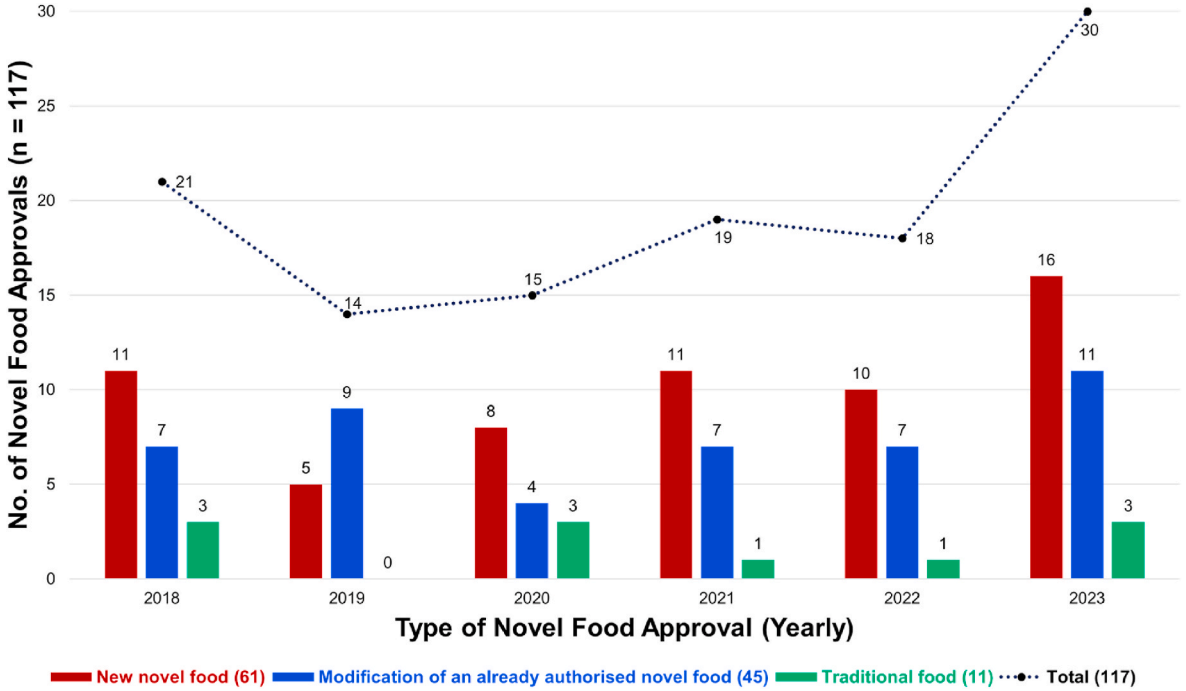

Fig. 1. Type of novel food approvals between 1 January 2018 and 31 December 2023.

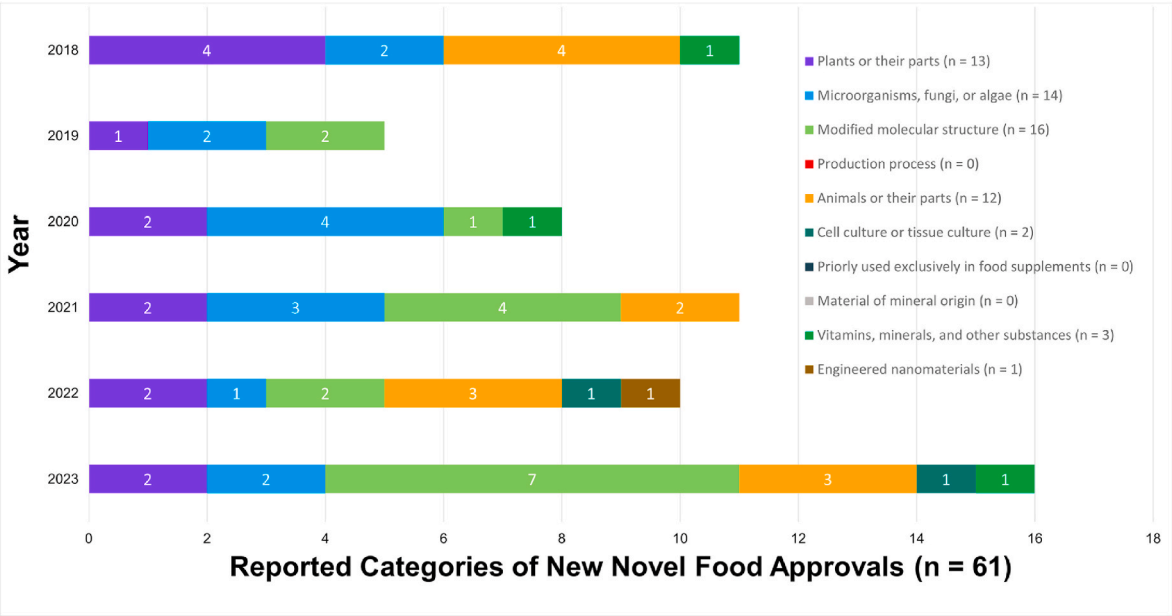

Fig. 2. Number of new novel food approvals reported within each of the 10 categories between 1 January 2018 and 31 December 2023. For new novel foods falling under more than one category as mentioned in the opinions, the most characteristic category was selected. Adapted with permission from Ververis et al. (2020).

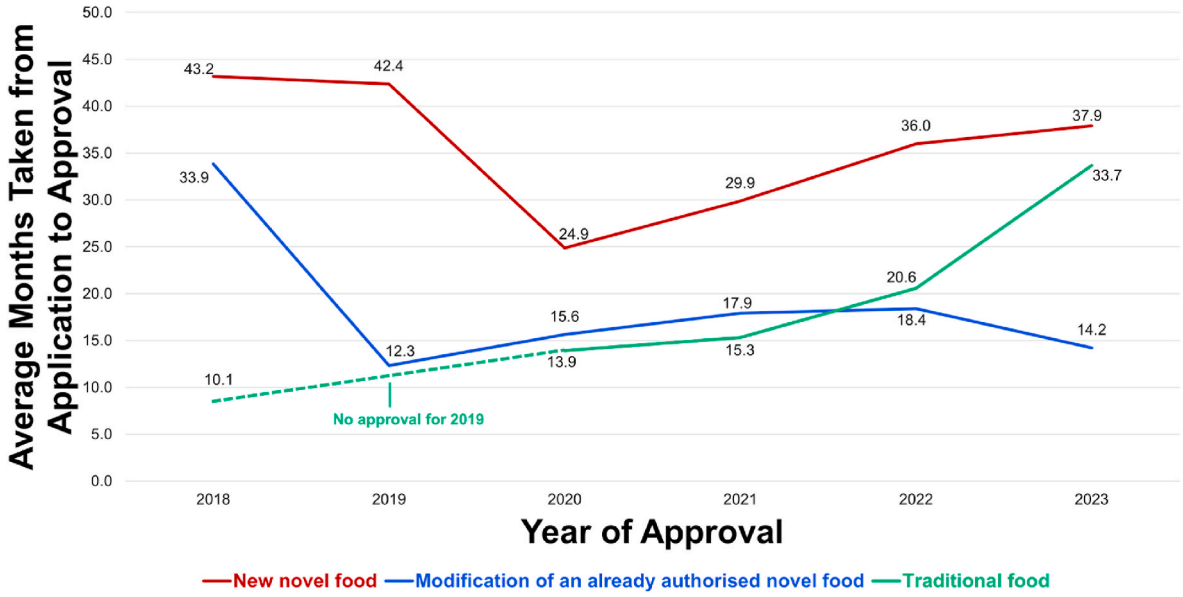

Fig. 3. Average months taken for novel food applications (n = 117) to be approved in the period between 1 January 2018 and 31 December 2023. Approvals are divided into the approval types of new novel food, modifications of an already authorised novel food, and traditional food.

months) as approvals for modifications (18.7 months) or traditional food (18.7 months). For new NF approvals, after Regulation 2015/2283 was implemented, it took more than 40 months on average for 2018 and 2019 for applications to be approved, before dropping to approximately 25 months in 2020. However, the average time taken has since been on an upward trend increasing to an average of 38 months in 2023. No new NF applications submitted after 27 March 2021 (when the Transparency Regulation was implemented) were approved by 31 December 2023. The average time taken for modifications decreased to less than half from 2018 to 2019 and has remained rather constant since, while it increased significantly for traditional food to almost comparable duration as new NF in 2023.

For new NFs with risk assessments performed after 1 January 2018, a clock-stop was initiated when EFSA requested additional information from applicants, putting the assessment process on hold. Once additional information was provided by the applicant, the assessment process resumed. This could occur multiple times throughout the assessment. Seven applications were omitted from the statistics below as their scientific evaluations were performed before Reg. 2015/2283 was implemented, therefore no information on clock-stops was available. For new NF approvals where assessments were performed after 2018 (n = 54/61), 51 (94.4%) had clock-stops (Table 2). Thirty-five applications had publicly available clock-stop letters where EFSA requested additional information, among which additional information on

Table 2
Description of clock-stops for new novel food approvals between 1 January 2018 and 31 December 2023.

Year	Clock-stops	Requests for additional allergenicity information	Average no. of times additional information was requested				Total average duration during clock-stops (total days)			
			Mean	Median	IQR (P75 – P25)	Range (Min to Max)	Mean	Median	IQR (P75 – P25)	Range (Min to Max)
2018	2/4	–	1.4	1.0	2.0	0 to 2	49.3	42.0	105.8	0 to 113
2019	4/5	–	2.4	2.0	2.0	0 to 3	89.6	91.0	104.5	0 to 179
2020	8/8	–	2.0	2.0	1.8	1 to 4	127.1	138.0	111.0	21 to 250
2021	11/11	1	2.9	3.0	2.0	1 to 7	270.6	214.0	318.5	116 to 632
2022	10/10	2	3.3	2.5	3.0	2 to 7	354.0	250.0	350.5	80 to 784
2023	16/16	4	2.5	2.0	2.0	1 to 8	429.9	395.5	260.0	117 to 1110
Total	51/54	7	2.5	2.0	2.0	0 to 8	278.9	215.0	300.3	0 to 1110

allergenicity was requested for seven applications (20.0%). An increase in clock-stops due to the demand for additional information on allergenicity has been seen, especially in recent years, although the specific kind of information requested was not mentioned in the letters. Since 2020, all approvals had at least one clock-stop.

For all new NF applications, the overall median number of times EFSA requested further information from applicants was 2.0 (IQR: 1.0, 2.0), while the median duration of the clock-stop phase was 215 days (IQR: 116.0, 416.3). Using the second approval of *A. domesticus* as an example, according to the supporting documents (OpenEFSA, 2023), EFSA paused the assessment three times, requesting additional information on sections such as compositional data, proposed uses and use levels, allergenicity, and production process. This resulted in a clock-stop duration of 413 days. A Spearman's rank correlation test was conducted to evaluate the relationship between the number of clock-stops and the total duration of clock-stops (days) in Fig. 4. There was a moderate positive correlation between the number of clock-stops and the total duration (rho = 0.37, n = 51, p = 0.0073). A linear regression model showed a moderate positive influence of the number of clock-stops on the total duration (Adj. $R^2 = 0.42$; df = 1, 49; $p < 0.001$), indicating that the number of clock-stops influences the total duration.

3.4. Allergenicity risk assessments for novel food approvals

Assessing the allergenicity of NFs is especially important if proteins, glycoproteins, or lipoproteins (hereafter collectively referred to as proteins) are present in the NF, as food allergens are predominantly proteins. To determine any potential allergenicity risks of a new NF, there were primarily four methods performed by applicants or EFSA; protein quantification; literature review with already available information from immunological tests or bioinformatics analyses; immunological methods; and bioinformatics methods. Information about the methods used was extracted from the opinions, which should be concise summaries of the applications.

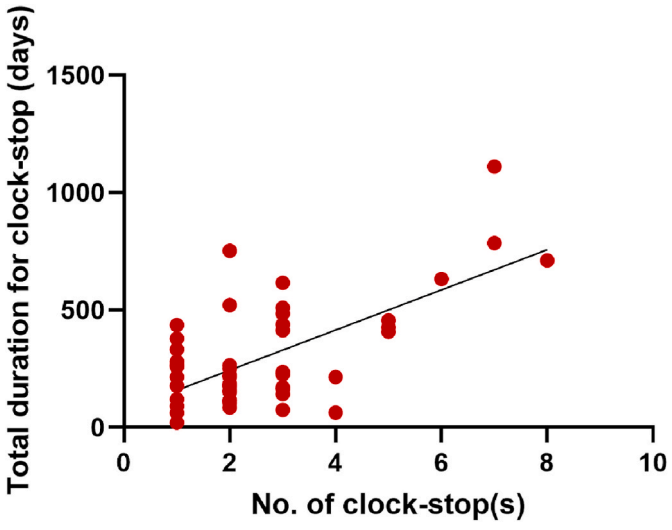

Fig. 4. Correlation between the number of clock-stop(s) and the total duration for clock-stops (total days).

Methods carried out to determine the allergenicity were investigated according to the opinions for new NF and modifications, or technical reports for traditional foods, and summarised (Table 3 and Supplementary Database). A new safety evaluation (opinion) was deemed unnecessary in two-thirds of modification approvals, typically because the changes made were unlikely to impact consumer health more than the un-modified product, and allergenicity was a focus for only a few modifications (e.g. chia seeds). In new NF approvals (n = 61), 55 (90.2%) contained protein quantification data, 27 (44.3%) a literature review, 13 (21.3%) results from bioinformatics tests, and/or 6 (9.8%) immunological tests. This shows that immunological or bioinformatics testing were only performed by applicants in few cases, though for some NFs these tests are well-reported in the scientific literature (e.g., edible insects and bovine milk). Interestingly, 11 out of the 13 new NF applications that performed bioinformatics testing were of low protein content (≤ 0.01%) from oligosaccharide products and were concluded to have a low likelihood of triggering allergic reactions (e.g., fucosyllactose, sialyllactose, and lacto-N-tetraose). The remaining two new NFs were mung bean protein and apple fruit cell culture biomass. There were also hardly any immunological and bioinformatics tests conducted by applicants for modifications and traditional food approvals.

Based on the opinions, different conclusions have been drawn about the allergenicity of new NFs (Table 4). Several conclusions regarding allergenicity can apply to a NF. For instance, possible "sensitisation" and "cross-reactivity" were concluded for insects. In one opinion (dried yellow mealworm) the possibility for sensitisation was mentioned as "may cause *de novo* sensitisation". Although this was also possible for the other insects, it was not mentioned as such. Out of 29 new NFs with possible sensitisation, 11 new NFs contain known allergenic proteins which are reported to induce sensitisation (e.g., milk, egg, and insect-based NFs), 13 new NFs a cross-reaction with known food allergens

Table 3
Information from scientific opinions or technical reports to determine potential allergenicity for novel food approvals between 1 January 2018 and 31 December 2023.

Information provided concerning allergenicity	New novel food (61)	Modifications (45)	Traditional food (11)
New scientific opinion	61 (100%)	15 (33.3%)	N/A
Technical report	N/A[a]	N/A	11 (100%)
Allergenicity information	61 (100%)	8 (17.8%)	7 (63.6%)
Protein quantification methods	55 (90.2%)	7 (15.6%)	9 (81.2%)
Literature reviews	27 (44.3%)	3 (6.7%)	7 (63.6%)
Bioinformatics methods	13 (21.3%)	1 (2.2%)	0 (0%)
Immunologic methods	6 (9.8%)	0 (0%)	1 (9.1%)

[a] N/A – not applicable.

Table 4
Conclusions on allergenicity of new novel foods (NFs) based on European Food Safety Authority Scientific Opinions compared to protein content, maximum daily food intake, and protein intake for new NF approvals (n = 61) between 1 January 2018 and 31 December 2023.

Conclusion of allergenicity[a]	Number of new NF (n = 61)	Approved new NF[b]	Protein content (%)[c]	Anticipated max. daily food intake (mg)[d]	Anticipated max. daily protein intake (mg)[e]	Supplementary Database ID[f]
Possible	**29**					
(*De novo*) sensitisation	11	Hen egg white lysozyme hydrolysate	90.0	1000	900	5
		Bovine milk basic whey protein isolate	90.0	334	300	15
		Refined shrimp peptide concentrate	87.0	1200	1044	16
		Egg membrane hydrolysate	90.0	450	405	17
		Betaine	0.1	184	0.18	30
		Bovine milk beta-lactoglobulin (β-lactoglobulin)	93.6	34,480	32,273	86
		Antrodia camphorata mycelia powder	20.0	990	198	87
		Bovine milk osteopontin	80.5	167	135	96
		Iron milk caseinate	65.0	430	280	103
		Aqueous ethanolic extract of *Labisia pumila*	9.0	750	67.5	107
		Apple fruit cell culture biomass	20.0	0.15	0.03	115
Cross-reactivity[g]	13	Extract of three herbal roots (*Cynanchum wilfordii* Hemsley, *Phlomis umbrosa* Turcz. and *Angelica gigas*)	17.0	514	87.4	4
		Partially defatted chia seed (*Salvia hispanica)* powders	40.0	–	–	41
		Partially defatted rapeseed powder from *Brassica rapa* L. and *Brassica napus* L.	43.0	21,000	9030	55
		Dried *Tenebrio molitor* larva (yellow mealworm)	61.0	23,600	14,414	58
		Synsepalum dulcificum dried fruits	6.0	700	42.0	64
		Frozen, dried and powder forms of *Locusta migratoria* (migratory locust)	60.0	44,730	26,838	65
		Frozen, dried and powder forms of yellow mealworm (*Tenebrio molitor* larva)	60.0	40,600	24,360	72
		Frozen, dried and powder forms of *Acheta domesticus* (house cricket)	65.0	26,960	17,524	74
		Mung bean (*Vigna radiata*) protein	84.0	18,179	15,270	77
		Jatropha curcas L. (edible variety) kernels	32.0	21,000	6720	80
		Acheta domesticus (house cricket) partially defatted powder	78.0	2775	2164	89
		Frozen, paste, dried and powder forms of *Alphitobius diaperinus* larvae (lesser mealworm)	70.0	4000	2800	93
		Partially hydrolysed protein from spent barley (*Hordeum vulgare*) and rice (*Oryza sativa*)	90.0	50,587	45,528	116
No difference from original food[g]	5	Cranberry extract powder	1.16	819	9.5	14
		Vitamin D2 mushroom powder	40.0	23.6	9.4	45
		Vitamin D2 mushroom powder	22.0	34,450	7579	67
		Vitamin D2 mushroom powder	40.0	121.5	48.6	88
		Pea and rice protein fermented by *Lentinula edodes* (Shiitake mushroom) mycelia	75.0	86,700	65,025	90
Expected to be low, very low, or unlikely	**32**					
Low	22	*Ecklonia cava* phlorotannins	2.2	360	7.9	1
		Pyrroloquinoline quinone disodium salt	0	20.0	0	9
		Dried aerial parts of Hoodia parviflora	4.5	400	18.0	12
		Xylo-oligosaccharides	0.2	7700	15.4	18
		d-ribose	0	8061	0	28
		Yarrowia lipolytica yeast biomass	55.0	6000	3300	29
		Nicotinamide riboside chloride	0	300	0	36
		Dried *Euglena gracilis*	20.0	1235	247	47
		Extract from *Panax notoginseng* and *Astragalus membranaceus*	4.5	350	15.8	48
		Chromium-containing yeast (*Yarrowia lipolytica*) biomass	50.0	4000	2000	49
		Selenium-containing yeast (*Yarrowia lipolytica*) biomass	50.0	1000	500	50
		6′-Sialyllactose (6′-SL) sodium salt (microbial source)	0.01	1000	0.1	53
		3′-Sialyllactose (3′-SL) sodium salt (microbial source)	0.01	500	0.05	54
		Calcium fructoborate	0.41	220	0.9	68
		Akkermansia muciniphila (pasteurised)	35.0	2000	700	71
		Tetrahydrocurcuminoids	0.027	300	0.08	79

(*continued on next page*)

Table 4 (*continued*)

Conclusion of allergenicity[a]	Number of new NF (n = 61)	Approved new NF[b]	Protein content (%)[c]	Anticipated max. daily food intake (mg)[d]	Anticipated max. daily protein intake (mg)[e]	Supplementary Database ID[f]
		LactoN-tetraose ('LNT') (produced by derivative strains of *E. coli* BL21(DE3))	0.01	4600	0.46	91
		3-Fucosyllactose ('3-FL') (produced by a derivative strain of *E. coli* BL21(DE3))	0.01	3000	0.3	92
		3′-Sialyllactose ('3′-SL') sodium salt (produced by derivative strains of *E. coli* BL21(DE3))	0.01	700	0.07	94
		'6'-Sialyllactose ('6′-SL') sodium salt (produced by derivative strains of *E. coli* BL21(DE3))	0.01	1800	0.18	102
		3-Fucosyllactose produced by a derivative strain of *Escherichia coli* K-12 DH1	0.01	4000	0.4	112
		6′-Sialyllactose sodium salt produced by derivative strain of *Escherichia coli* W (ATCC 9637)	0.01	1000	0.1	114
Very low	2	2-Fucosyllactose/Difucosyllactose mixture	0.01	4000	0.4	34
		Lacto-N-tetraose ("LNT") (microbial source)	0.01	2000	0.2	40
Unlikely	8	1-Methylnicotinamide chloride	0	58.0	0	10
		Phenylcapsaicin	0	2.5	0	33
		Schizochytrium sp. (WZU477) oil	0.001	1137	0.01	57
		Schizochytrium sp. (FCC-3204) oil	0.6	819	4.9	62
		3-Fucosyllactose (3-FL) (microbial source)	0.01	5000	0.5	66
		Cetylated fatty acids	0	2100	0	73
		Iron hydroxide adipate tartrate	0	100	0	84
		Cellobiose	0.01	3000	0.3	101

[a] For possible allergenicity, several conclusions can apply to a new novel food (e.g. sensitisation, and cross-reactivity or no difference to original food).
[b] Names of novel foods are taken directly from the approval documents.
[c] Protein content values are obtained from either the approval documents or scientific opinions.
[d] Anticipated maximum daily food intake of novel foods are taken from the scientific opinions, based on either 1) the population group with the highest 95th percentile intake, or 2) the population group with the highest mg/kg body weight per day.
[e] Anticipated daily protein intake are calculated based on the formula [(Protein content/100) x anticipated maximum daily intake of population group with the highest 95th percentile intake].
[f] Examples of new novel food approvals are arranged in chronological order. References to the respective approved novel foods are found in the Supplementary Database.
[g] Denotes that the novel food also falls under possible sensitisation.

was expected (e.g., insects with shrimp), and in five new NFs it was found that the new product did not pose any more allergenic risk than the original counterpart (e.g., Vitamin D2-enriched mushroom powder). The allergenicity risk also depends on the dose of protein and possibly the frequency of exposure, but it is unclear how this information was taken into account in the allergenicity assessment. The anticipated maximum daily NF intake and the corresponding anticipated maximum daily protein intake for all new NFs are shown (Table 4, detailed information in the Supplementary Database). Interestingly, with the exception of apple fruit cell culture biomass (0.03 mg/day) and betaine (0.18 mg/day), all new NFs for which sensitisation or cross-reactivity was considered possible, have estimated protein intake of >1 mg/day. On the other hand, it was stated in 32 (52.5%) of the opinions that allergenicity risks were low, very low, or unlikely to occur (e.g., 6′-siallylactose, lacto-N-tetraose, and iron hydroxide adipate tartrate, respectively). Estimated protein intake of <1 mg/day were seen in 22 new NF approvals (Table 4). The remaining 10 new NFs had estimated protein intake of >1 mg/day, but they had explanations on why they were still considered having low or unlikely allergenicity (Table 5). Yet, it usually is unclear to what extent the opinion conclusions regarding allergenicity were based on protein intake expected or other considerations.

4. Discussion

While information on the trends in EU NF applications exists (Ververis et al., 2020; Crevel et al., 2024; European Food Safety Authority, 2024), to the best of our knowledge, there has been no in-depth analysis of NF approvals since Regulation 2015/2283 was implemented. According to Art. 10 and 12 in Regulation 2015/2283, the theoretical duration of a new NF approval could be 17 months (European Union, 2015; Heo et al., 2023), however this is rarely met. This study shows that new NF applications currently take on average 38 months for approval. The delay in approvals is mainly caused by clock-stops upon the request of additional information from applicants and has occurred in every new NF approval process since 2020. The types of additional information requested by EFSA include information on the production process, composition, representativeness of the testing material used in toxicity testing, intake estimates, intended uses, history of use, human studies, and allergenicity (Ververis et al., 2020). Ultimately, these additional information requests, coupled with increased workload by EFSA, prolong the approval process (Ververis et al., 2020).

With regards to allergenicity assessment, NF applications must include at least information on protein content and a comprehensive literature review to retrieve available information on sensitisation, allergic reactions and/or allergenicity studies (*in vitro*, in animals, or in humans) of the NF and/or its source under EFSA guidelines (European Food Safety Authority, 2021b; EFSA NDA Panel et al., 2021a). Beyond this, applicants can decide what information they want to provide to characterise allergenicity risks, for instance information regarding protein composition, pH/heat stability and digestion, or homology, immunological and/or human testing. Present study suggests that allergenicity has not been extensively assessed for all NF. For example, protein quantification was performed in 90.2%, and a literature study was described in 44.3% of new NF applications. Bioinformatics and immunological tests were only described in respectively 21.3% and 9.8% of the cases. Based on our findings, information on the potential allergenicity of new NFs typically came from literature searches and/or protein content. Another study that analysed different regulatory bodies for NF allergenicity assessments also concluded that allergenicity

Table 5
Reasons for the conclusion of low or unlikely allergenicity risks that had an estimated protein intake of >1 mg/day in 10 cases for new novel food approvals between 1 January 2018 and 31 December 2023 based on Scientific Opinions.

Example of new novel food	Reason for conclusion on allergenicity	Protein content (%)	Anticipated max. daily food intake (mg)	Anticipated max. daily protein intake (mg)	Supplementary Database ID
Ecklonia cava phlorotannins	"Performed a literature search in databases … information from current commercial consumption of the NF and clinical trials performed … did not identify any evidence of allergenicity to *E. cava*", "have adverse event reporting procedures in place … to date allergic reactions to the NF have not been reported"	2.2	360	7.92	1
Dried aerial parts of *Hoodia parviflora*	"Provided an ELISA screening … did not reveal cross-reactivity with some of the major food allergens", "conducted a literature search … no cases of food allergy were identified", "NF is being marketed in the USA since 2011 … no reports of allergic reactions to the NF"	4.5	400	18.0	12
Xylo-oligosaccharides	"The activity of the xylanase in the NF was also below the limit of detection (10 U/g) of the applied assay.", "likelihood of allergic reactions to the NF is low"	0.2	7700	15.4	18
Yarrowia lipolytica yeast biomass	"Naturally occurring in foods … not known to cause allergic reactions in humans", "not among the yeast species which have been shown to elicit allergic reactions in humans"	55.0	6000	3300	29
Dried *Euglena gracilis*	"Comprehensive literature search … did not reveal any studies or case reports raising potential concerns on the allergenicity of *E. gracilis*", "history of use of *E. gracilis* in Japan and the US and … lack of identified allergenic reactions so far."	20.0	1240	247	47
Extract from *Panax notoginseng* and *Astragalus membranaceus*	"Literature searches … did not retrieve any studies reporting incidents of allergenicity to the NF or to *A. membranaceus*"	4.50	350	15.8	48
Chromium-containing yeast (*Yarrowia lipolytica*) biomass	"In its previous opinion on *Y. lipotytica* biomass … risk of allergic reactions to the biomass of *Y. lipotytica* is low", "previous conclusion … also applies to the NF under assessment"	55.0	4000	2000	49
Selenium-containing yeast (*Yarrowia lipolytica*) biomass	"In its previous opinion on *Y. lipotytica* biomass … risk of allergic reactions to the biomass of *Y. lipotytica* is low", "previous conclusion … also applies to the NF under assessment"	50.0	1000	500	50
Schizochytrium sp. (FCC-3204) oil	"new analysis of five batches of the NF, which indicated that proteins were below the LOQ (0.25%) that the NF is unlikely to trigger adverse allergic reactions"	0.6	819	4.9	62
Akkermansia muciniphila (pasteurised)	"*A. muciniphila* is part of a balanced gut microbiota. No allergies are expected to be elicited from its protein composition"	35.0	2000	700	71

information was generally obtained from literature reviews, with little additional tests performed (Kedar et al., 2024). Food allergic reactions are typically caused by protein-containing food, where food with no or very low protein content has a low risk of inducing allergic reactions (EFSA NDA Panel et al., 2021a). Carrying out an allergenicity assessment may not have been regarded as needed for new NFs with low or only trace amounts of proteins. Thus, the allergenicity risks were probably anticipated as negligible when the protein content, anticipated NF intake, and hence the resulting protein intake were low. However, there is no guidance or clear benchmarking from e.g., EFSA opinions on what can be regarded as a sufficiently low protein content or protein intake to be considered safe. As mentioned above, immunological or bioinformatics tests to determine the potential allergenicity (sensitisation and/or cross-reactivity) have rarely been performed regardless of protein content. In some cases, information was obtained from studies that already performed these tests, such as in the cases for insect approvals (Verhoeckx et al., 2014; Broekman et al., 2015).

The introduction of new proteins in our food supply may undoubtedly induce new allergies (i.e. *de novo* allergenicity), as shown by Broekman et al. for yellow mealworm, where the authors reported that individuals were primarily shown to become allergic to mealworm, without being shrimp allergic (Broekman et al., 2017). Most assessments do not specifically address *de novo* sensitisation, while consumers may be exposed to proteins that humans have not previously been exposed to. From the opinions, it became clear that virtually no assessment was performed to determine the possibility of *de novo* sensitisation. This undoubtedly is due to the fact that there are no adequate tools for assessing *de novo* sensitisation (EFSA NDA Panel et al., 2024; Fernandez et al., 2024; Mills et al., 2024). Several initiatives like ALLPreT and GiantLEAPS are currently underway to develop new allergenicity prediction tools to aid the allergenicity assessment of NFs, with specific attention to the assessment of *de novo* sensitisation (ALLPreT, 2024; GiantLEAPS, 2024). New NFs are nowadays typically approved based on other criteria such as composition of the NF, production processes, foreign contaminants, microbiological and oxidative stability during storage, and toxicity studies (EFSA NDA Panel et al., 2021c). The allergenic risk of a new NF was until now not a reason to reject a NF from the market (e.g. insects, chia seed), provided appropriate measures such as proper labelling to inform at-risk consumers of the risk and post-launch monitoring are implemented. There were seven approvals where additional information on allergenicity was requested by EFSA. Given that information such as production process and proposed uses were requested multiple times for the same approvals, it was likely that the lack of allergenicity assessments did not prolong the duration of the assessment stage for the new NFs. In the evaluation of new NFs since 2018, the attention given to the protein intake levels varied (i.e. protein intake was mentioned for apple fruit cell culture biomass in the allergenicity section, but not for other NFs with higher protein content or intake levels). Furthermore, the type of protein present in the total protein fraction can differ between NFs, contributing to the complexity of protein intake and allergenicity assessments. For example, the predominant protein present in the new NF beta-lactoglobulin is a single protein (EFSA NDA Panel et al., 2022c), while in complex foods like edible insects, the presence of multiple proteins belonging to allergen

superfamilies (e.g., tropomyosin, arginine kinase, and chitin) contribute to the total protein content (EFSA NDA Panel et al., 2021c; Liguori et al., 2022). The abundance of each protein belonging to allergenic superfamilies, coupled with the amount consumed by consumers, may also result in different sensitisation and elicitation probabilities.

This study also assessed how the anticipated protein intake of new NFs across different allergenicity conclusions (Table 4) was considered in allergenicity assessments. The results revealed that although protein intake was rarely mentioned as the reason for allergenicity conclusions, except for apple fruit cell culture biomass and betaine, all new NFs with possible allergenicity risks had a protein intake exceeding 1 mg/day. Most new NFs with low, very low, or unlikely allergenicity had protein intake levels below 1 mg/day, with 10 exceptions exceeding 1 mg/day and thus deviating from this trend. However, their low or unlikely allergenicity risk conclusions were based on factors other than protein intake as outlined in Table 5. Interestingly, the Food and Agriculture Organisation of the United Nations and World Health Organisation [FAO/WHO] Expert Committee considered protein intake of low-protein derivatives of priority allergenic foods < RfD/30 (i.e. per meal) as substantiation of safety. Except for crustaceans, this is in the 0.03–0.3 mg range per meal, or potentially 2 to 3 times higher per day, up to about maximally 1 mg/day or likely below 1 mg/day for priority allergenic foods (Food and Agriculture Organisation of the United Nations/World Health Organisation, 2024). It is important to emphasise that a 1 mg/day threshold was to our knowledge by no means a deliberately used cut-off by EFSA. Also, the dossiers assessed often concerned NFs derived from known allergenic sources. Current data are insufficient to judge whether a similar threshold would appear if more sources of unknown allergenicity would be included. Therefore, selection of <1 mg/day as a criterion for low or negligible allergenicity seems still arbitrary based on today's scientific assessment capabilities. However, this observation presents an interesting point that could serve as a bridge in exploring a threshold of concern.

The correlation between the need for information required for decision-making regarding the allergenicity of NFs and protein intake levels is not clearly substantiated. While elicitation thresholds (minimal amounts of ingested protein that cause a reaction) for known allergenic foods have been discussed extensively in the framework of developing guidance for precautionary allergen labelling (Remington et al., 2020; Houben et al., 2020; Food and Agriculture Organisation of the United Nations, 2022), there is currently no information regarding the *de novo* sensitising capacity of individual proteins nor a threshold of sensitisation for known allergenic proteins. The establishment of a dose representing a Threshold of Allergological Concern (TAC) below which a protein is unlikely to cause sensitisation in consumers could possibly make the *de novo* allergenicity assessment of NFs more feasible. It could be helpful to identify proteins that could be exempted from being tested, enabling a focus on proteins of possible allergenic relevance (Houben et al., 2019). Recently, an expert panel from ILSI Europe suggested that a combination of a TAC concept and bioinformatics approaches could aid in the feasibility of evaluating *de novo* allergenicity risk in NFs in the short term (<5 years). The development of a TAC was considered realistic by Crevel et al. and may be a priority focus of future allergenicity assessment research (Crevel et al., 2024).

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CRediT authorship contribution statement

Sim Ray Yue: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kitty C.M. Verhoeckx:** Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Conceptualization. **Geert F. Houben:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Katrine Lindholm Bøgh:** Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Conceptualization.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2025.115249.

Data availability

The database containing extracted information is included. It will also be uploaded to DTU repository in .csv and.txt (README file for metadata).

References

ALLPreT, 2024. ALLPret: allergenicity prediction toolbox for novel foods. https://www.allpret.eu/en. (Accessed 20 March 2024).

Broekman, H.C.H.P., Knulst, A.C., de Jong, G., Gaspari, M., den Hartog Jager, C.F., Houben, G.F., Verhoeckx, K.C.M., 2017. Is mealworm or shrimp allergy indicative for food allergy to insects? Mol. Nutr. Food Res. 61 (9), 1601061. https://doi.org/10.1002/mnfr.201601061.

Broekman, H., Knulst, A., den Hartog Jager, S., Monteleone, F., Gaspari, M., de Jong, G., Houben, G., Verhoeckx, K., 2015. Effect of thermal processing on mealworm allergenicity. Mol. Nutr. Food Res. 59 (9), 1855–1864. https://doi.org/10.1002/mnfr.201500138.

European Food Safety Authority, Bronzwaer, S., Kass, G., Robinson, T., Tarazona, J., Verhagen, H., Verloo, D., Vrbos, D., Hugas, M., 2019. Food safety regulatory research needs 2030. EFSA J 17 (7), e170622. https://doi.org/10.2903/j.efsa.2019.e170622.

Crevel, R.W.R., Verhoeckx, K., Bøgh, K.L., Buck, N., Chentouf, A., Flanagan, S., Galano, M., Garthoff, J.A., Hazebrouck, S., Yarham, R., Borja, G., Houben, G., 2024. Allergenicity assessment of new or modified protein-containing food sources and ingredients. Food Chem. Toxicol. 189, 114766. https://doi.org/10.1016/j.fct.2024.114766.

Dall'Asta, C., 2022. Why 'new' foods are safe and how they can Be assessed. In: Scaffardi, L., Formici, G. (Eds.), Novel Foods and Edible Insects in the European Union: an Interdisciplinary Analysis. Springer International Publishing, pp. 81–95. https://doi.org/10.1007/978-3-031-13494-4_5.

EFSA NDA Panel, Turck, D., Bohn, T., Castenmiller, J., De Henauw, S., Hirsch-Ernst, K.I., Maciuk, A., Mangelsdorf, I., McArdle, H.J., Naska, A., Pelaez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Cubadda, F., Frenzel, T., Heinonen, M., Maradona, M.P., Marchelli, R., Neuhäuser-Berthold, M., Poulsen, M., Schlatter, J.R., van Loveren, H., Fernandez, A., Knutsen, H.K., 2021b. Safety of mung bean protein as a novel food pursuant to Regulation (EU) 2015/2283. EFSA J. 19 (10), e06846. https://doi.org/10.2903/j.efsa.2021.6846.

EFSA NDA Panel, Turck, D., Bohn, T., Castenmiller, J., De Henauw, S., Hirsch-Ernst, K.I., Maciuk, A., Mangelsdorf, I., McArdle, H.J., Naska, A., Pelaez, C., Pentieva, K.,

Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Cubadda, F., Frenzel, T., Heinonen, M., Marchelli, R., Neuhäuser-Berthold, M., Poulsen, M., Prieto Maradona, M., Schlatter, J.R., van Loveren, H., Turla, E., Knutsen, H.K., 2022b. Safety of freeze-dried mycelia of *Antrodia camphorata* as a novel food pursuant to regulation (EU) 2015/2283. EFSA J. 20 (6), e07380. https://doi.org/10.2903/j.efsa.2022.7380.

EFSA NDA Panel, Turck, D., Bohn, T., Castenmiller, J., De Henauw, S., Ildico Hirsch-Ernst, K., Maciuk, A., Mangelsdorf, I., McArdle, H.J., Naska, A., Pelaez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Cubadda, F., Frenzel, T., Heinonen, M., Prieto Maradona, M., Marchelli, R., Neuhäuser-Berthold, M., Poulsen, M., Rudolf Schlatter, J., van Loveren, H., Germini, A., Knutsen, H.K., 2021d. Safety of iron hydroxide adipate tartrate as a novel food pursuant to Regulation (EU) 2015/2283 and as a source of iron in the context of Directive 2002/46/EC. EFSA J. 19 (12), e06935. https://doi.org/10.2903/j.efsa.2021.6935.

EFSA NDA Panel, Turck, D., Bohn, T., Castenmiller, J., De Henauw, S., Hirsch-Ernst, K.I., Maciuk, A., Mangelsdorf, I., McArdle, H.J., Naska, A., Pelaez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Cubadda, F., Frenzel, T., Heinonen, M., Marchelli, R., Neuhäuser-Berthold, M., Poulsen, M., Prieto Maradona, M., Schlatter, J.R., van Loveren, H., Colombo, P., Noriega Fernández, E., Knutsen, H.K., 2022a. Safety of 6′-sialyllactose (6′-SL) sodium salt produced by derivative strains of *Escherichia coli* BL21 (DE3) as a novel food pursuant to Regulation (EU) 2015/2283. EFSA J. 20 (12), e07645. https://doi.org/10.2903/j.efsa.2022.7645.

EFSA NDA Panel, Turck, D., Bohn, T., Castenmiller, J., De Henauw, S., Hirsch-Ernst, K.I., Maciuk, A., Mangelsdorf, I., McArdle, H.J., Naska, A., Pelaez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Cubadda, F., Frenzel, T., Heinonen, M., Marchelli, R., Neuhäuser-Berthold, M., Poulsen, M., Prieto Maradona, M., Schlatter, J.R., van Loveren, H., Fernández Dumont, A., Noriega Fernández, E., Knutsen, H.K., 2022c. Safety of beta-lactoglobulin as a novel food pursuant to regulation (EU) 2015/2283. EFSA J. 20 (4), e07204. https://doi.org/10.2903/j.efsa.2022.7204.

EFSA NDA Panel, Turck, D., Bohn, T., Castenmiller, J., de Henauw, S., Hirsch-Ernst, K.I., Maciuk, A., Mangelsdorf, I., McArdle, H.J., Naska, A., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Aguilera Gómez, M., Cubadda, F., Frenzel, T., Heinonen, M., Neuhäuser-Berthold, M., Peláez, C., Poulsen, M., Prieto Maradona, M., Schlatter, J.R., Siskos, A., van Loveren, H., Ackerl, R., Albert, O., Azzollini, D., Fernández Dumont, A., Gelbmann, W., Germini, A., Glymenaki, M., Kass, G.E.N., Kouloura, E., Laganaro, M., Matijevic, L., Mendes, V., Noriega Fernández, E., Nuin Garciarena, I., Precup, G., Roldán Torres, R., Rossi, A., Turla, E., Valtueña Martinez, S., Ververis, E., Knutsen, H.K., 2024. Guidance on the scientific requirements for an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. EFSA J. 22 (9), e8961. https://doi.org/10.2903/j.efsa.2024.8961.

EFSA NDA Panel, Turck, D., Bresson, J.-L., Burlingame, B., Dean, T., Fairweather-Tait, S., Heinonen, M., Hirsch-Ernst, K.I., Mangelsdorf, I., McArdle, H.J., Naska, A., Neuhäuser-Berthold, M., Nowicka, G., Pentieva, K., Sanz, Y., Siani, A., Sjödin, A., Stern, M., Tomé, D., Vinceti, M., Willatts, P., Engel, K.-H., Marchelli, R., Pöting, A., Poulsen, M., Salminen, S., Schlatter, J., Arcella, D., Gelbmann, W., de Sesmaisons-Lecarré, A., Verhagen, H., van Loveren, H., 2021e. Guidance on the preparation and submission of an application for authorisation of a novel food in the context of Regulation (EU) 2015/22831 (Revision 1)2. EFSA J. 19 (3), e06555. https://doi.org/10.2903/j.efsa.2021.6555.

EFSA NDA Panel, Turck, D., Bresson, J.-L., Burlingame, B., Dean, T., Fairweather-Tait, S., Heinonen, M., Hirsch-Ernst, K.I., Mangelsdorf, I., McArdle, H.J., Naska, A., Neuhäuser-Berthold, M., Nowicka, G., Pentieva, K., Sanz, Y., Siani, A., Sjödin, A., Stern, M., Tomé, D., Vinceti, M., Willatts, P., Engel, K.-H., Marchelli, R., Pöting, A., Poulsen, M., Schlatter, J., Gelbmann, W., de Sesmaisons-Lecarré, A., Verhagen, H., van Loveren, H., 2021a. Guidance on the preparation and submission of the notification and application for authorisation of traditional foods from third countries in the context of Regulation (EU) 2015/2283 (Revision 1)1. EFSA J. 19 (3), e06557. https://doi.org/10.2903/j.efsa.2021.6557.

EFSA NDA Panel, Turck, D., Castenmiller, J., de Henauw, S., Hirsch-Ernst, K.-I., Kearney, J., Maciuk, A., Mangelsdorf, I., McArdle, H.J., Naska, A., Pelaez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Cubadda, F., Engel, K.-H., Frenzel, T., Heinonen, M., Marchelli, R., Neuhäuser-Berthold, M., Poulsen, M., Sanz, Y., Schlatter, J.R., van Loveren, H., Roldán-Torres, R., Steinkellner, H., Knutsen, H.K., 2020. Safety of vitamin D2 mushroom powder as a novel food pursuant to Regulation (EU) 2015/2283. EFSA J. 18 (1), e05948. https://doi.org/10.2903/j.efsa.2020.5948.

EFSA NDA Panel, Turck, D., Castenmiller, J., De Henauw, S., Hirsch-Ernst, K.I., Kearney, J., Maciuk, A., Mangelsdorf, I., McArdle, H.J., Naska, A., Pelaez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Cubadda, F., Frenzel, T., Heinonen, M., Marchelli, R., Neuhäuser-Berthold, M., Poulsen, M., Prieto Maradona, M., Schlatter, J.R., van Loveren, H., Ververis, E., Knutsen, H.K., 2021c. Safety of dried yellow mealworm (*Tenebrio molitor* larva) as a novel food pursuant to Regulation (EU) 2015/2283. EFSA J. 19 (1), e06343. https://doi.org/10.2903/j.efsa.2021.6343.

European Commission, 2021. Application procedure for novel foods. https://www.efsa.europa.eu/sites/default/files/applications/apdeskapplworkflownutrinovel2018.pdf. (Accessed 1 June 2023).

European Commission, 2024. Union list of novel foods. https://food.ec.europa.eu/safety/novel-food/authorisations/union-list-novel-foods_en. (Accessed 9 February 2024).

European Food Safety Authority, 2020. Programming document 2020-2022. Trusted Science for Safe Food - Protecting Consumers' Health with Independent Scientific Advice on the Food Chain. https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/amp2022.pdf. (Accessed 1 June 2023).

European Food Safety Authority, 2021b. Administrative guidance for the preparation of applications on novel foods pursuant to Article 10 of Regulation (EU) 2015/2283. EFSA Support. Public. 18 (3), 6488E. https://doi.org/10.2903/sp.efsa.2021.EN-6488.

European Food Safety Authority, 2021. EFSA strategy 2027 – Science, safe food, sustainability. Publications Office of the European Union. https://doi.org/10.2805/886006.

European Food Safety Authority, 2023a. Programming document 2023-2025. Trusted Science for Safe Food - Protecting Consumers' Health with Independent Scientific Advice on the Food Chain. https://www.efsa.europa.eu/sites/default/files/2022-01/amp2325.pdf. (Accessed 1 June 2023).

European Food Safety Authority, 2023b. EFSA open: Questions. https://open.efsa.europa.eu/questions. (Accessed 13 July 2023).

European Food Safety Authority, 2024. EFSA's stakeholder webinar on the novel food guidance update. https://www.efsa.europa.eu/sites/default/files/2024-04/ppt-stakeholder-webinar-novel-food-guidance.pdf. (Accessed 1 October 2024).

European Union, 1997. REGULATION (EC) No 258/97 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 January 1991 concerning novel foods and novel food ingredients. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31997R0258. (Accessed 1 June 2023).

European Union, 2015. Regulation (EU) 2015/2283 of the European parliament and of the council of 25 november 2015 on novel foods, amending regulation (EU) No 1169/2011 of the European parliament and of the council and repealing regulation (EC) No 258/97 of the European parliament and of the council and commission regulation (EC) No 1852/2001 (text with EEA relevance). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015R2283. (Accessed 1 June 2023).

European Union, 2019. COMMISSION IMPLEMENTING REGULATION (EU) 2019/1979 of 26 November 2019 authorising the placing on the market of 2'-Fucosyllactose/Difucosyllactose mixture as a novel food under Regulation (EU) 2015/2283 of the European Parliament and of the Council and amending Commission Implementing Regulation (EU) 2017/2470 (Text with EEA relevance). https://eur-lex.europa.eu/eli/reg_impl/2019/1979/oj. (Accessed 12 October 2023).

European Union, 2021. COMMISSION IMPLEMENTING REGULATION (EU) 2021/50 of 22 January 2021 authorising an extension of use and a change in the specifications of the novel food '2′- fucosyllactose/difucosyllactose mixture' and amending Implementing Regulation (EU) 2017/2470 (Text with EEA relevance). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32021R0050. (Accessed 12 October 2023).

Fernandez, A., Danisman, E., Taheri Boroujerdi, M., Kazemi, S., Moreno, F.J., Epstein, M. M., 2024. Research gaps and future needs for allergen prediction in food safety [Mini Review]. Front. Allergy 5. https://doi.org/10.3389/falgy.2024.1297547.

Food and Agriculture Organisation of the United Nations/World Health Organisation, 2024. Risk assessment of food allergens: part 4: establishing exemptions from mandatory declaration for priority food allergens: meeting report. https://www.who.int/publications/i/item/9789240088924. (Accessed 1 October 2024).

Food and Agriculture Organisation of the United Nations, 2021. Strategic framework: 2022-31. https://www.fao.org/3/cb7099en/cb7099en.pdf. (Accessed 10 May 2023).

Food and Agriculture Organisation of the United Nations, 2022. Thinking about the future of food safety – a foresight report. https://www.fao.org/3/cb8667en/cb8667en.pdf. (Accessed 23 December 2023).

GiantLEAPS, 2024. Reshaping nutrition across Europe: accelerating the dietary shift from animal-based to alternative dietary proteins. https://giant-leaps.eu/. (Accessed 20 March 2024).

Graphpad, 2024. GraphPad prism version 10.3.0. https://www.graphpad.com/.

Heo, S., Lee, G., Na, H.-E., Park, J.-H., Kim, T., Oh, S.-E., Jeong, D.-W., 2023. Current status of the novel food ingredient safety evaluation system. Food Sci. Biotechnol. https://doi.org/10.1007/s10068-023-01396-w.

Houben, G.F., Baumert, J.L., Blom, W.M., Kruizinga, A.G., Meima, M.Y., Remington, B. C., Wheeler, M.W., Westerhout, J., Taylor, S.L., 2020. Full range of population Eliciting Dose values for 14 priority allergenic foods and recommendations for use in risk characterization. Food Chem. Toxicol. 146 (111831). https://doi.org/10.1016/j.fct.2020.111831.

Houben, G., Blom, M., Alvito, P., Assunção, R., Crevel, R., Fæste, C.K., Le, T.-M., Madsen, C.B., Remington, B., Stroheker, T., Vassilopoulou, E., Verhoeckx, K., Žiarovská, J., Constable, A., 2019. Defining the targets for the assessment of IgE-mediated allergenicity of new or modified food proteins. Food Chem. Toxicol. 127, 61–69. https://doi.org/10.1016/j.fct.2019.02.036.

Kedar, O., Golberg, A., Obolski, U., Confino-Cohen, R., 2024. Allergic to bureaucracy? Regulatory allergenicity assessments of novel food: motivations, challenges, compromises, and possibilities. Compr. Rev. Food Sci. Food Saf. 23 (2), e13300. https://doi.org/10.1111/1541-4337.13300.

Liguori, B., Sancho, A.I., Poulsen, M., Lindholm Bøgh, K., 2022. Novel foods: allergenicity assessment of insect proteins. EFSA J. 20 (S2), e200910. https://doi.org/10.2903/j.efsa.2022.e200910.

López-Pedrouso, M., Lorenzo, J.M., Alché, J.d.D., Moreira, R., Franco, D., 2023. Advanced proteomic and bioinformatic tools for predictive analysis of allergens in novel foods. Biology 12 (5), 714. https://www.mdpi.com/2079-7737/12/5/714.

Mills, E.N.C., Orsenigo, F., Salgado, D., Finglas, P.M., Astley, S., 2024. Novel strategies for predicting allergenicity: development of a ranking method and screening tools to assess the allergy risk of innovative proteins. EFSA Support. Public. 21 (6), 8840E. https://doi.org/10.2903/sp.efsa.2024.EN-8840.

Naegeli, H., Birch, A.N., Casacuberta, J., De Schrijver, A., Gralak, Mikolaj A., Guerche, P., Jones, H., Manachini, B., Messéan, A., Nielsen, E.E., Nogué, F., Robaglia, C., Rostoks, N., Sweet, J., Tebbe, C., Visioli, F., Wal, J.-M., Eigenmann, P., Epstein, M., Hoffmann-Sommergruber, K., Koning, F., Lovik, M., Mills, C., Moreno, F.J., van

Loveren, H., Selb, R., Fernandez Dumont, A., EFSA GMO Panel, 2017. Guidance on allergenicity assessment of genetically modified plants. EFSA J. 15 (6), e04862. https://doi.org/10.2903/j.efsa.2017.4862.

OpenEFSA, 2019. Request for a scientific opinion on mineral salt containing potassium and magnesium (NF 2018/0798). https://open.efsa.europa.eu/questions/EFSA-Q-2019-00230. (Accessed 1 February 2024).

OpenEFSA, 2023. Request for a scientific opinion on Whole and ground crickets (Acheta domesticus) as a novel food (NF 2018/0804). https://open.efsa.europa.eu/questions/EFSA-Q-2019-00121.

Precup, G., Ververis, E., Azzollini, D., Rivero-Pino, F., Zakidou, P., Germini, A., 2022. The safety assessment of insects and products thereof as novel foods in the European union. In: Scaffardi, L., Formici, G. (Eds.), Novel Foods and Edible Insects in the European Union: an Interdisciplinary Analysis. Springer International Publishing, pp. 123–146. https://doi.org/10.1007/978-3-031-13494-4_7.

Remington, B.C., Westerhout, J., Meima, M.Y., Blom, W.M., Kruizinga, A.G., Wheeler, M. W., Taylor, S.L., Houben, G.F., Baumert, J.L., 2020. Updated population minimal eliciting dose distributions for use in risk assessment of 14 priority food allergens. Food Chem. Toxicol. 139, 111259. https://doi.org/10.1016/j.fct.2020.111259.

Remington, B., Broekman, H.C.H., Blom, W.M., Capt, A., Crevel, R.W.R., Dimitrov, I., Faeste, C.K., Fernandez-Canton, R., Giavi, S., Houben, G.F., Glenn, K.C., Madsen, C. B., Kruizinga, A.K., Constable, A., 2018. Approaches to assess IgE mediated allergy risks (sensitization and cross-reactivity) from new or modified dietary proteins. Food Chem. Toxicol. 112, 97–107. https://doi.org/10.1016/j.fct.2017.12.025.

Scaffardi, L., Formici, G., 2022. Introduction: feeding the future sustainably—what role for novel foods and edible insects? In: Scaffardi, L., Formici, G. (Eds.), Novel Foods and Edible Insects in the European Union: an Interdisciplinary Analysis. Springer International Publishing, pp. 1–11. https://doi.org/10.1007/978-3-031-13494-4_1.

United Nations, 2022. World population prospects 2022: summary of results. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/wpp2022_summary_of_results.pdf. (Accessed 10 May 2023).

Verhoeckx, K.C., van Broekhoven, S., den Hartog-Jager, C.F., Gaspari, M., de Jong, G.A., Wichers, H.J., van Hoffen, E., Houben, G.F., Knulst, A.C., 2014. House dust mite (Der p 10) and crustacean allergic patients may react to food containing Yellow mealworm proteins. Food Chem. Toxicol. 65, 364–373. https://doi.org/10.1016/j.fct.2013.12.049.

Verhoeckx, K., Lindholm Bøgh, K., Constable, A., Epstein, M.M., Hoffmann Sommergruber, K., Holzhauser, T., Houben, G., Kuehn, A., Roggen, E., O'Mahony, L., Remington, B., Crevel, R., 2020. COST Action 'ImpARAS': what have we learnt to improve food allergy risk assessment. A summary of a 4 year networking consortium. Clin. Transl. Allergy 10 (1), 13. https://doi.org/10.1186/s13601-020-00318-x.

Ververis, E., Ackerl, R., Azzollini, D., Colombo, P.A., de Sesmaisons, A., Dumas, C., Fernandez-Dumont, A., Ferreira da Costa, L., Germini, A., Goumperis, T., Kouloura, E., Matijevic, L., Precup, G., Roldan-Torres, R., Rossi, A., Svejstil, R., Turla, E., Gelbmann, W., 2020. Novel foods in the European Union: scientific requirements and challenges of the risk assessment process by the European Food Safety Authority. Food Res. Int. 137, 109515. https://doi.org/10.1016/j.foodres.2020.109515.