ANSES Opinion
Request No. 2022-SA-0155

The Director General

Maisons-Alfort, 19 November 2024

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on characterising and assessing the health impacts of consuming "ultra-processed" foods

On 27 August 2022, ANSES received a formal request from the Directorate General for Food (DGAL) and the Directorate General for Health (DGS) to characterise and assess the health impacts of consuming "ultra-processed" foods.

1. BACKGROUND AND PURPOSE OF THE REQUEST

The results of ANSES's INCA 3 study (2014-2015), published in 2017, documented an increase in French consumption of processed foods, particularly among young people, compared with what had been observed in the INCA 2 study (2006-2007). This has contributed to "the development of a disconnect between individuals and their food, particularly in terms of knowledge of food composition" (ANSES 2017).

The effect of "ultra-processed" foods on health is an emerging research topic, which has led some health agencies to address the issue (AESAN 2020; FAO/WHO 2019; NNR 2023; SACN 2023). Moreover, a growing number of scientific publications have reported an association between the consumption of “ultra-processed” products and the risk of chronic diseases.

While this is now an international concern, shared by both scientists and society as a whole, there is currently no consensus on the definition of “ultra-processed foods”. The Nova classification, which is the most widely used system in epidemiological research, divides foods into four groups according to their degree of processing, with Nova Group 4 corresponding to foods considered to be the most highly processed. In France, although there is no regulatory definition of “ultra-processed” foods, several official recommendations refer to them. For example, the High Council for Public Health's objectives for the National Health and Nutrition Programme (PNNS) are "to halt the growth in consumption of ultra-processed foods", while *Santé publique France* recommends "limiting sweetened beverages, and fatty, sweet, salty and ultra-processed foods". The National Food and Nutrition Programme (PNAN) intends to characterise ultra-processed foods, study the health impact of their consumption and prioritise the actions to be taken. In addition, there have been numerous proposals on ultra-processed foods from parliamentary reports, the Citizens’ Convention on Climate and other citizen initiatives, in connection with labelling, taxation, advertising bans and restrictions on their use in mass catering.

In response to a request from the DGAL and the DGS, ANSES carried out an expert appraisal from the following five angles:

1 – characterising ultra-processed products by identifying the processing methods likely to induce changes in food composition that pose a threat to health;

2 – identifying existing classifications of foods according to their degree of processing and assessing their relevance with regard to the characteristics identified previously;

3 – studying the epidemiological relationships between the consumption of "ultra-processed" foods and the risk of chronic non-communicable diseases (CNCDs);

4 – determining, where appropriate and on the basis of the risks identified following an analysis of the epidemiological studies, the factors responsible for the harmfulness of "ultra-processed" foods with a view to identifying courses of action that could limit the risks associated with the consumption of these foods;

5 – identifying the scientific work that needs to be carried out to better characterise the health impacts of "ultra-processed" foods.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (January 2024)".

This expert appraisal falls within the scope of the Expert Committee (CES) on "Human Nutrition". The work and conclusions of this CES were based on the work carried out by two groups of rapporteurs who met regularly from May 2023 to June 2024:

- a group of four experts in food science and food technology, who were tasked with answering question 1 on the identification of processing methods likely to induce changes in food composition that pose a threat to health;
- a group of five experts in epidemiology and chronic non-communicable diseases, tasked with answering question 3 on the study of epidemiological relationships between the consumption of "ultra-processed" foods and the risk of chronic non-communicable diseases.

A hearing was organised with two experts who, as part of their research activities, have worked and published on the subject of classifying foods according to their degree of processing. This hearing contributed to the drafting of the response to questions 1 and 2 (Annex 3).

The response to questions 2, 4 and 5 was prepared through an internal expert appraisal.

The work for question 1 was monitored and then validated by the Working Group on "Assessment of materials and processing aids in the areas of food and water" (MATAE WG). As the formal request focused solely on the health risks of processing, the benefits in terms of microbiological risk control were not addressed.

All the work was presented to and discussed with the CES on "Human Nutrition" on eight occasions between December 2022 and September 2024. It was adopted by the CES on "Human Nutrition" at its meeting of 6 September 2024.

ANSES analyses interests declared by experts before they are appointed and throughout their work, in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public on the following website: https://dpi.sante.gouv.fr/.

A major personal interest was identified for one of the experts in the CES on "Human Nutrition", who was therefore not present when the opinion was discussed and validated.

3. ANALYSIS AND CONCLUSIONS OF THE CES ON "HUMAN NUTRITION" AND THE MATAE WG

3.1. Identification of processing methods likely to induce changes in food composition that pose a threat to health

3.1.1. Processing methods and biochemical risks

The conventional aim of the food industry is to stabilise, process, extract and blend raw materials and ingredients to arrive at finished products or ingredients (Bimbenet, Duquenoy and Trystram 2007). It is often necessary for agricultural raw materials to undergo processing to make them edible, safe and palatable, and to prolong their shelf lives in order to guarantee a diversified food supply throughout the year. The production of food ingredients and products is achieved through technological sequences involving a series of unit operations. The purpose of these unit operations is to break down, fragment, restructure, transform or assemble raw materials, ingredients and possibly additives. These unit operations, which are fundamental elements of process engineering, involve transfers of heat, mass or momentum. They also include biological or chemical reactions (bioreactions), which are crucial to product processing. It is common practice to combine different unit operations within a production line or sector, and it is sometimes necessary to use processing aids. Raw materials, which are primarily biological matrices, are inherently variable, mainly depending on their geographical origin, variety and season. They are also sensitive to factors such as temperature, mechanical shearing, enzymes and micro-organisms. In addition, the natural changes that occur in the cells and tissues of living organisms make them more vulnerable during processing. These characteristics remain partly valid for the product during processing, although one of the aims of this processing is generally to reduce variability and increase the stability of the material.

Food processing influences the many properties of food (health, organoleptic, functional and nutritional). For example, processing methods using high temperatures (Augustin 2011; Espinosa *et al.* 2020) and high pressures (EFSA Panel on Biological Hazards *et al.* 2022) are essential for controlling microbiological risks or improving digestibility. However, certain unit operations can also have opposite effects (for example, reducing the microbiological risk but increasing the chemical risk (ANSES 2022), heat treatment in the packaging that stabilises the product but reduces the vitamin content). It is conceptually impossible to recommend processing methods able to optimise all of these properties (Prache *et al.* 2020).

In health terms, the chemical risk associated with food is due to the presence of numerous substances in foods (ANSES 2020): to date, 130 chemicals have been identified as relevant hazards[1] for the ranking of chemical risk in foods. They can result from contamination of raw materials in primary production, the production environment, migration from food contact materials, generation of new substances (newly-formed substances) during the processing method and final preparation by the consumer. In the context of the formal request, only newly-formed substances were considered when responding to question 1, as they constitute the main hazard intrinsically linked to manufacturing processes. Section 3.1.1.2 specifies the hazards concerned. It should be noted that the impact of food contact materials was not taken into account in this analysis, but is addressed in the research proposals (Section 3.4).

[1] According to ANSES's 2020 report, "relevant" hazards are those that represent a health concern in metropolitan France

3.1.1.1. Processing methods, food additives and processing aids

In response to societal, industrial and environmental demands, the food and agricultural sectors deploy three levels of innovation: an extensive and adaptable technological offer, diverse and complex food matrices, and specific tailored sequences of unit operations. Industrial food engineering covers all the means that give a food its attributes (functions). It involves implementing and controlling physical, chemical, biochemical and biological mechanisms.

A manufacturing process is characterised by a combination of unit operations, each one providing one or more functions by modulating the potential of the raw materials, ingredients and food additives that make up the food formulation. Implementation of the manufacturing process is based primarily on the concepts of unit operation, transfers (of momentum, energy and mass) and scale of observation (time and space), as well as on the concepts of "reactions" (chemical, biochemical, microbiological), which are of particular importance in the agri-food industry. Unit operations can vary in nature and level of technological complexity (e.g. pumping, drying, heat treatment, distillation, solid-liquid separation, evaporation, etc.). However, they are always based on technological foundations, control of operating conditions and a biochemical and physico-chemical understanding of the effects on matrices. The design of the desired end product, as delivered to the consumer, determines the choice of raw materials, technological sequence and operating conditions for the unit operations.

The main unit operations fall into five categories (mechanical, physical, thermal, chemical, biological) according to the transfer types (Table 1). A unit operation may incorporate technological aspects of varying degrees of complexity and innovation. For example, heat treatment can be carried out either by 1) indirect (parietal) heating using a secondary fluid (plate heat exchanger, tube heat exchanger, scraped surface heat exchanger, treatment of the food in its final sealed packaging, for example in an autoclave) or electrical energy (heating resistor, Joule effect heat exchanger in the channel wall); or 2) direct (volumetric) heating using radiation (infrared, microwave, radiofrequency), injection (direct injection of culinary steam) or electrical energy (direct Ohmic heat exchanger).

Food additives and processing aids are substances subject to authorisation, and are mainly used in the production of foodstuffs on an industrial scale (European Commission 2008). Processing aids differ from food additives, whose presence is permanent, in that they have a transient action in the process and must be absent (except in trace amounts) or inactivated (in the case of enzymes) in the final product. The number of processing aids used reflects production on an industrial scale and is therefore an indicator of processing. However, since processing aids do not appear on the labelling, consumers are unaware of their use in foods. The number of additives is an indicator of the formulation.

More than 300 food additives are authorised in the European Union and have been classified into different categories, the five main ones being colours, sweeteners, preservatives, antioxidants and texturing agents (emulsifiers, stabilisers, thickeners, gelling agents, etc.). These substances are mainly added to processed foods or other foods produced on an industrial scale, for technical purposes (e.g. to improve safety, prolong shelf life or modify organoleptic properties such as taste, odour, texture, colour, etc.). When food additives are intentionally added to foodstuffs, they or their derivatives become, directly or indirectly, a component (co-formulant) of these foodstuffs and must appear in the list of ingredients.

French regulations[2] on processing aids (around 750 authorised) classify them into 17 categories[3] according to their role in the different production stages of food ingredients or products. Other processing aids are regulated by various European Union texts[4], for certain specific sectors (in particular winemaking, dairy proteins, fruit juices, decontamination of animal products).

The same functions conferred on a raw material can also be obtained via various technological means (number and type of unit operations, addition of food additives, use of ingredients, need for processing aids). The attributes created sometimes have antagonistic effects on the matrices: for example, depending on the biological or biochemical reactions, a positive nutritional or sensory role could be created while at the same time generating an undesirable (bio)chemical impact (e.g. a newly-formed substance). Added to this is the complexity of composite foods (e.g. a fruit yoghurt containing fruit, sugar and fermented milk, or a ready meal containing vegetable and meat products accompanied by a sauce), which multiplies the possible technological sequences.

In conclusion, the intrinsic characteristics of the process to be taken into account to estimate the risk of production of newly-formed substances may be:

- the number and diversity of unit operations that illustrate the steps involved in transforming raw materials into finished products;
- the variations in physico-chemical parameters induced by the operating conditions in the unit operation (time, temperature, pressure, pH, oxidation, etc.);

[2] "Decree no. 2011-509 of 10 May 2011, as amended, laying down the conditions for authorising and using processing aids that may be employed in the manufacture of foodstuffs intended for human consumption." *Official Journal of the French Republic* 0110.

[3] Antifoaming agents, catalysts, clarifying agents/filtration aids, bleaching agents, washing and peeling agents, plucking and hair-removal agents, ion exchange resins, contact freezing and cooling agents, desiccants/anti-caking agents, enzymes, acidifying, alkalinising or neutralising agents, mould release agents, flocculants and coagulants, decontamination agents for plant products, anti-scaling agents, extraction solvents and other processing aids

[4] https://entreprises.gouv.fr/fr/echanges-commerciaux-et-reglementation/libre-circulation-des-produits/auxiliaires-technologiques

- the use of processing aids as an indicator/marker of processing[5].

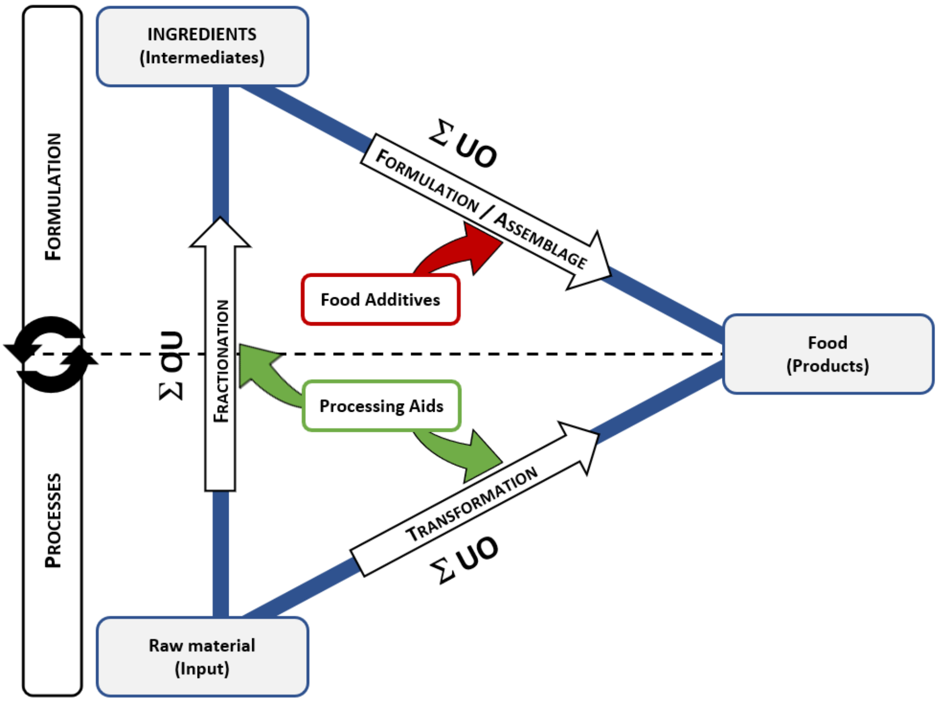


Figure 1.
Technological sequences for food matrices, illustrating the interdependence between all the unit operations used (Σ UO), the formulation (food additives) and the process (processing aids)

Table 1: Main conventional unit operations in food process engineering (Bimbenet *et al.*, 2007)

Classification	Examples of unit operations	Medium[1]

[5] Additives have more to do with formulations than processing methods (

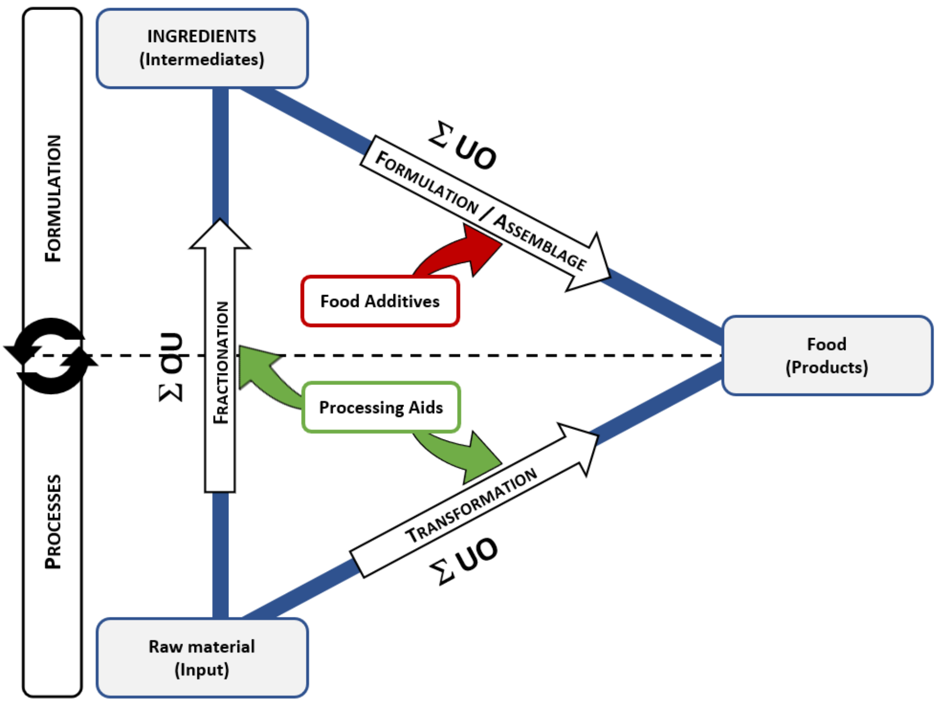


Figure 1).

Mechanical operation		handling, weighing, crushing, sorting	solids particulates powders
Transfer of momentum		shaking, mixing	liquids pastes
		decanting centrifugation filtration	solid – liquid liquid – liquid/particulates solid – gas
		centrifugal spinning pressure extraction	solid – liquid
Transfer of momentum coupled with:	transfer of heat	heating and cooling chilling, freezing, deep-freezing pasteurisation, sterilisation	various
	transfer of heat and mass	evaporation	liquids
		drying	solids, liquids
		distillation	liquids
		biochemical and microbiological reactions	various
	transfer of mass	solvent extraction	solid – liquid liquid – liquid

[1] For the entire column, the dash indicates the two media between which the transfer takes place; the comma indicates different media

3.1.1.2. Processing methods and newly-formed substances

Food technologies can change the chemical composition of foods through the use of processing aids and food additives, or through the application of unit operations. Some of these changes have well-documented health consequences, such as the presence of acrylamide in fried products, bakery products and coffee (Adimas *et al.* 2024). While the impact of food processing on basic nutritional components has been widely studied, its effects on the 26,000 biochemical compounds naturally found in foods is poorly documented (Barabási, Menichetti and Loscalzo 2020). It is equally important to take account of the many substances intentionally added to foods or that inevitably accumulate as a result of the environmental conditions in which they are produced and stored (Barabási, Menichetti and Loscalzo 2020).

Among the substances liable to affect consumer health, newly-formed (or neo-formed) substances are a particular concern (Taş, Kocadağlı and Gökmen 2022). The origin of newly-formed substances in foods is still difficult to determine due to their great chemical diversity. Depending on the processes used in the manufacture of foodstuffs, certain chemically reactive substances found in matrices can lead to the generation of a large number of newly-formed substances, particularly from the fat, protein or carbohydrate components of foodstuffs (Choe and Min 2005; Skog, Eneroth and Svanberg 2003; Stadler and Lineback 2009). Newly-formed substances may be sought after to give a desired characteristic to foods (for example, certain products of the Maillard reaction add colour and flavour to foods) or they may be undesirable due to their potential toxicity and pose a risk to human health. The newly-formed substances relevant to chemical risk assessment[6] include polycyclic aromatic hydrocarbons (PAHs), acrylamide, furan compounds, ethyl carbamates, 3-monochloropropanediol and its esters, glycidol and its esters, biogenic amines (histidine, tyramine), nitrosamines, oxidised triglycerides and heterocyclic aromatic amines (ANSES 2020).

[6] Therefore not considering the risks associated with allergenicity

3.1.2.Ranking method

Given the diversity of chemical reactions that can occur during the various processes used in industrial food manufacturing or preparation, it is very difficult to define the dozens of potential newly-formed substances (ANSES 2018) *a priori* and exhaustively, and to identify among them those that are potentially hazardous and should be selected for risk assessment.

In its 2018 report on the development of a strategy for prioritising newly-formed substances, ANSES proposed using a ranking approach for the processes associated with the matrices or raw materials most likely to induce the occurrence of newly-formed substances, without prejudging their toxicity. The report proposed a step-by-step approach, starting with the ranking of unit operations based on specific criteria, followed by a classification of foods based on these unit operations and on the properties of the raw materials needed to manufacture them[7]. Lastly, the report recommended the use of multi-criteria decision-support methods to combine the criteria for the two rankings.

The current report builds on the findings and recommendations of ANSES's 2018 report. **The rankings proposed in the remainder of this report are not therefore based on chemical hazards as a whole, but on the propensity to generate newly-formed substances**. As in 2018, additives have not been considered in this work because these substances are authorised at European level following a risk assessment that covers, among other aspects, their chemical reactivity with the matrices in which they will be used. Furthermore, as the formal request focused solely on the health risks of processing, the benefits in terms of microbiological risk control have not been addressed.

3.1.2.1. Elements to be ranked

3.1.2.1.1. Unit operations

On the basis of ANSES's earlier report (ANSES 2018), 52 operations were classified (Annex 4). They belong to eight main types of unit operations:

1. heat treatments: these unit operations involve the use of heat to process materials or products. They include operations such as cooking, drying, pasteurisation, sterilisation, extrusion cooking, frying, roasting. These unit operations also involve cold storage operations;
2. chemical and biological processes: these unit operations use chemical reactions or biological processes to modify the chemical composition of substances. This can include fermentation, smoking or hydrolysis reactions;
3. processes using high hydrostatic pressure: these unit operations use high pressure to microbiologically stabilise the products;
4. mechanical processing/shearing: these unit operations involve the use of mechanical forces that modify the physical structure of the foods (e.g. extrusion);
5. electrical (non-thermal) treatments: these methods use electrical fields to process foods (preservation, extraction, etc.) without necessarily producing heat;
6. radiation treatments on the surface or all the way through the product to reduce the microbial load: these involve applying radiation (such as UV rays, high-intensity pulsed light, gamma rays) directly to the food;

7. extractive and refining processes: these unit operations involve the extraction of specific components from complex mixtures, or the purification and refining of substances, such as deodorisation in the food industry, or the extraction of proteins or lipids from plants;
8. miscellaneous processing: this category may include a variety of unit operations that do not fall into the previous categories (e.g. freeze-drying).

3.1.2.1.2. Foods

The group of rapporteurs decided to apply the multi-criteria method to the list of foods shown in Annex 5. These foods were chosen to represent a wide range of raw materials and food processes.

There were several reasons for selecting the sectors analysed:

- to take account of the diversity of technological sequences, reflecting the number of unit operations used between the raw material and the ingredient or product;
- to illustrate the diversity of unit operations in agro-industrial processes;
- to target certain agro-industrial sectors, in line with the probability of occurrence of the newly-formed substances as identified in ANSES's 2018 report.

3.1.2.2. Multi-criteria ranking method

The use of multi-criteria decision-support methods enables different elements or alternatives to be classified objectively on the basis of predefined criteria. One of their advantages is that they can jointly take account of several criteria, potentially of different types (qualitative and quantitative), that are sometimes difficult to consider simultaneously. A complex problem can thus be simplified into unit components, which are then aggregated to obtain a single, optimal solution (Prache *et al.* 2020). Annex 6 explains the rationale behind the choice of the Electre III multi-criteria decision-support method and its main principles. In particular, the method is based on identifying the elements to be ranked (3.1.2.1), then identifying the ranking criteria and determining their weight. These two steps are described below.

3.1.2.2.1. Criteria for ranking unit operations

For this formal request, in order to rank the unit operations according to their capacity to generate newly-formed substances, it was proposed to rely on the criteria for classifying unit operations identified in 2018 (ANSES 2018), i.e. temperature, duration, pressure, expected chemical reactivity[8], ionising radiation and UV rays.

Table 2 defines these ranking criteria for classifying unit operations.

Table 2: Definition of ranking criteria for classifying unit operations (ANSES 2018)

Criterion	Scale	Meaning
Temperature	Ordinal (1 to 5)	The higher the temperature, the more likely it is that the unit operation will generate newly-formed substances. A value of 1 corresponds to unit operations associated with sub-zero temperatures. A value of 5 corresponds to high temperatures (> 150°C).

[8] Defined as the biochemical changes that occur within the food constituents as a direct result of applying the unit operation.

Criterion	Scale	Meaning
Duration	Ordinal (0 or 1)	The criterion is 1 if controlling the duration of the step plays a potential role in the generation of newly-formed substances.
Pressure	Ordinal (0 or 1)	The higher the pressure, the more likely it is that the unit operation will generate newly-formed substances. The value of 1 is assigned to unit operations with pressure levels in excess of 100 bar.
Chemical reactivity	Ordinal (-1, 0, 1)	Three values are available for this criterion. The value of -1 is assigned to unit operations likely to reduce or prevent the generation of newly-formed substances in the food matrix. The value of 1 is assigned to unit operations likely to increase their presence.
Ionising radiation	Ordinal (0 or 1)	If the unit operation uses ionising radiation, it is considered more likely to generate newly-formed substances and is rated 1.
UV	Ordinal (0 or 1)	If the unit operation uses UV rays, it is considered more likely to generate newly-formed substances and is rated 1.

Although studies have attempted to quantify the effect of different manufacturing process characteristics on the occurrence of certain newly-formed substances, there is no information in the scientific literature that can be directly transposed in this report to define the relative importance of these different criteria. Expert knowledge elicitation was used to establish the different scenarios for weighting the criteria for this report (Table 3). The different scenarios propose different distributions of 100 points for the various criteria[9]. Scenario 1 (all criteria equally important) reflects the uncertainty associated with determining the relative importance of the different criteria. Scenarios 2a and 2b were established by the experts and demonstrate the importance they attach to temperature, duration and chemical reactivity (with certain variations). Scenarios 3 and 4 give greater weighting to the temperature criterion and therefore exclude the ionising radiation criterion.

Table 3: Weighting of the six criteria used to classify unit operations for the different scenarios

Scenario	Temperature	Duration	Pressure	Chemical reactivity	UV	Ionising radiation
1	16.7	16.7	16.7	16.7	16.7	16.7
2a	25.0	25.0	8.3	25.0	8.3	8.3
2b	27.8	27.8	5.6	27.8	5.6	5.6
3	40.0	15.0	10.0	25.0	10.0	0
4	40.0	20.0	5.0	25.0	10.0	0

[9] In practice, the experts assigned a relative importance to each criterion on a free scale. The weightings were then standardised on a scale of 100.

3.1.2.2.2. Food ranking criteria

Newly-formed substances occur due to the application of the unit operations and the characteristics of the food constituents (ANSES, 2018). Two groups of criteria were used to rank the foods (according to the recommendations in the 2018 opinion). The first focuses on the characteristics of all the unit operations used to manufacture the food. These characteristics were established on the basis of the ranking of all the unit operations (see the three categories of unit operations described in 3.1.3.1.1). The second focuses on the characteristics of the raw materials (ANSES 2018). Six criteria for characterising raw materials were identified in ANSES's 2018 report: the percentages of unsaturated fats, protein and reducing sugars, the presence of antioxidants, the water activity (a_w)[10] and the difference between the pH of the raw material and pH 7 (noted as Δ pH).

Table 4 defines the ranking criteria used for classifying raw materials.

Table 4: Definition of ranking criteria for classifying foods

Criterion	Unit	Direction
Presence/level of unsaturated fats	%	The higher the percentage, the greater the occurrence of newly-formed substances
Presence/level of protein	%	
Presence/level of reducing sugars	%	
Presence/level of antioxidants	mg	The higher the value, the lower the occurrence of newly-formed substances
Water content	g per 100 g	The lower the value, the greater the occurrence of newly-formed substances
Δ pH / pH 7	pH unit	The higher the value, the greater the occurrence of newly-formed substances
Unit operations <u>most likely</u> to promote the occurrence of newly-formed substances	number of unit operations	The higher the value, the more likely it is that newly-formed substances will occur in the food
Unit operations applied to the food <u>likely</u> to promote the occurrence of newly-formed substances	number of unit operations	
Unit operations applied to the food <u>least likely</u> to promote the occurrence of newly-formed substances	number of unit operations	
Total number of unit operations applied to the food	number of unit operations	

Table 5 presents the different weighting scenarios tested by the group of rapporteurs. The criteria weights were established in two stages. First, the weights of the four criteria relating to unit operations were established. These weights take account of the ranking of unit operations. Next, the same total weight (14 points) was given to the criteria characterising the raw materials (the first six criteria in Table 4). The experts considered that the ranges of variation for the "water content" and "Δ pH" criteria were of less importance than the first four criteria. This led to the first set of weights in Table 5. Two other scenarios were established, giving double weight to the unit operation criteria or criteria relating to the characteristics of the raw materials (2' and 3').

Table 5: Weighting of the ten ranking criteria used for classifying foods.

[10] Water content was chosen as the criterion because of the difficulty of providing a_w values.

Six criteria correspond to the characteristics of the raw materials, while three concern the number of unit operations likely to promote the occurrence of newly-formed substances: the unit operations "most likely" (UO_{most}) in red, "moderately likely" ($UO_{moderate}$) in yellow and "least likely" (UO_{least}) in green to promote the appearance of newly-formed substances. The final criterion is the total number of unit operations used.

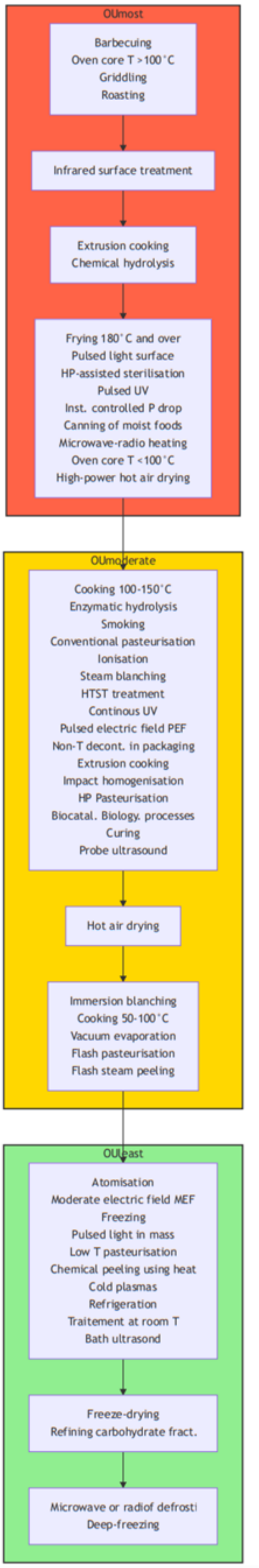
Scenario for criteria weights	% unsaturated fats	% protein	% reducing sugars	antioxidants (mg)	Water content	delta pH (reference pH at 7)	Number of UO_{most}	Number of $UO_{moderate}$	Number of UO_{least}	Total number of unit operations
1'	3	3	3	3	1	1	10	2	1	1
2'	3	3	3	3	1	1	20	4	2	2
3'	6	6	6	6	2	2	10	2	1	1

3.1.3. Classification of unit operations and foods with regard to their capacity to generate newly-formed substances

3.1.3.1. Classification of unit operations likely to give rise to newly-formed substances

3.1.3.1.1. Ranking of unit operations

The values assigned to the various criteria (defined in Table 2) for the 52 unit operations are shown in Annex 4. The Electre III ranking based on these characteristics and on the scenarios



given in Table 3 is shown in

Figure 2. Three categories of unit operations are proposed on the basis of this classification: the unit operations most likely (UO_{most}), moderately likely ($UO_{moderate}$) and least likely (UO_{least}) to promote the occurrence of newly-formed substances (see the colours in

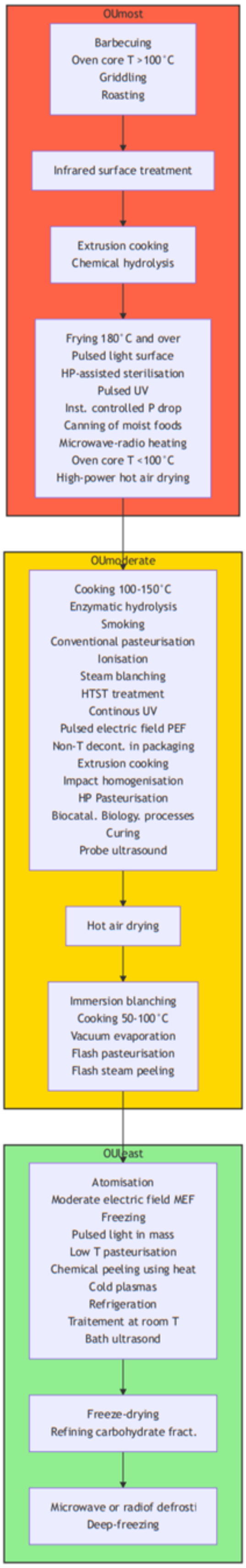


Figure 2). Unit operations that had been excluded from the 2018 report in terms of their capacity to generate newly-formed substances constitute another category (see Table 4 in the 2018 report). A sensitivity analysis was carried out to assess the effect of variations in the criteria weighting scenarios on the classification of the various options. This enabled the robustness of the results obtained to be verified. Annex 7 shows that the rankings are relatively insensitive to the weight scenarios proposed by the experts.

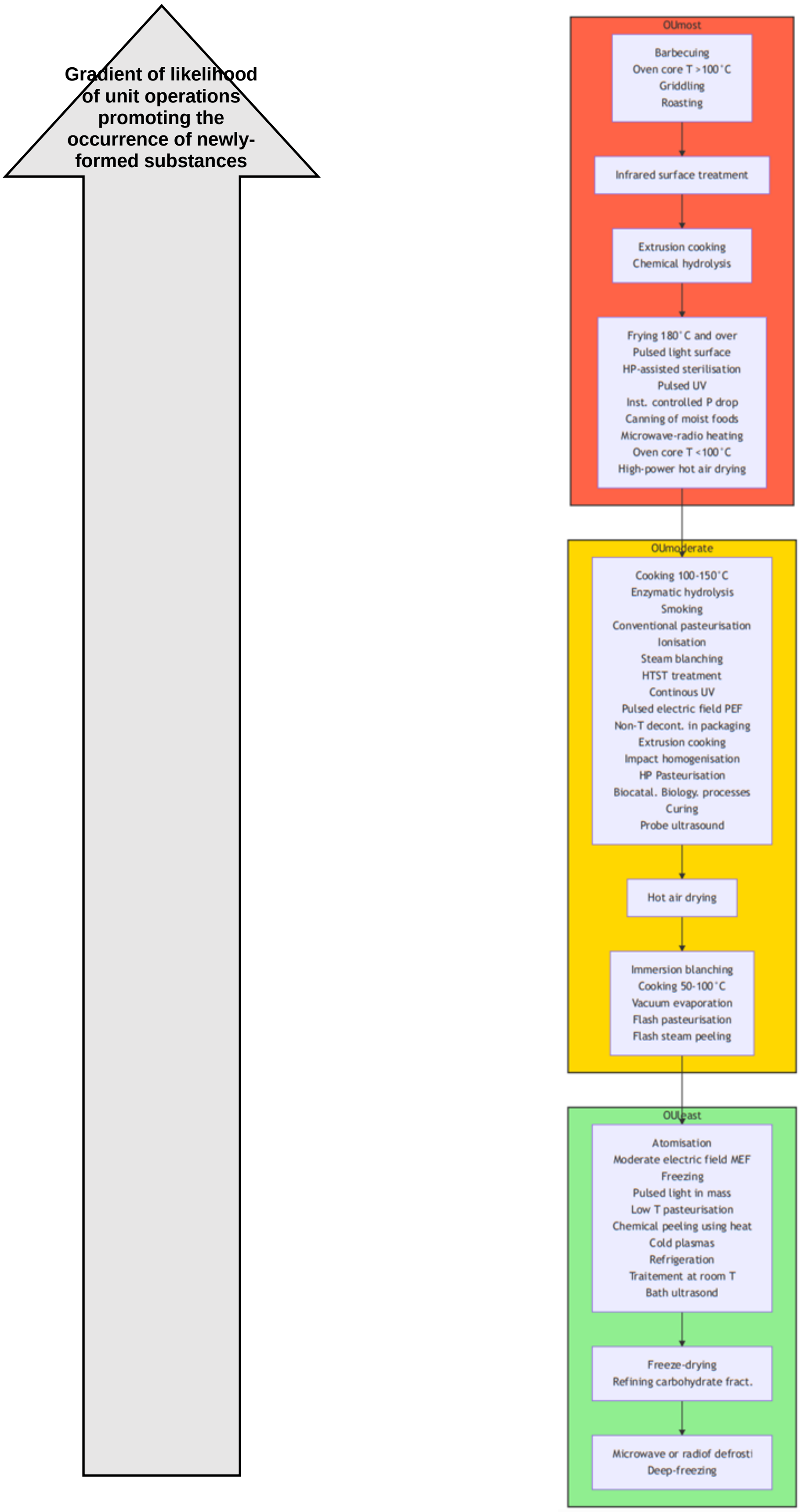


Figure 2. Ranking of unit operations according to their capacity to produce newly-formed substances on the basis of six criteria (weighting scenario 1) and the Electre III method.

Three categories of unit operations are proposed on the basis of this classification: the unit operations "most likely" (UO_{most}), "moderately likely" ($UO_{moderate}$) and "least likely" (UO_{least}) to promote the occurrence of newly-formed substances.

3.1.3.1.2. Discussion on the elements used for ranking unit operations

3.1.3.1.2.1. Unit operations and weight of ranking criteria

The different sets of weights proposed by the experts (Table 3) for the six criteria give particular importance to temperature. This is because studies have shown the importance of temperature in the occurrence of newly-formed substances, particularly acrylamide (Mousavi Khaneghah *et al.* 2022). The second most important criterion identified by the experts was duration. When combined, these two parameters reflect a greater or lesser amount of energy applied to the food. This notion of amount of energy can even be extended to other criteria such as pressure or UV, which are also forms of energy provided by unit operations. This raises the possibility of aggregating the various criteria used in this report into a single criterion, based on the amount of energy applied to the food (Knorr and Augustin 2021).

Regardless of the set of weights studied, the classification of certain unit operations obtained with the ranking method was in line with the conclusions of certain studies. Roasting and grilling are often mentioned as unit operations that are particularly likely to generate newly-formed substances (Nerín, Aznar and Carrizo 2016).

3.1.3.1.2.2. Role of unit operations in the separation, purification and elimination of newly-formed substances

Unit operations, and the associated processing aids, do not systematically promote the occurrence of newly-formed substances. In fact, some unit operations can be neutral with regard to their formation, while a few others can even reduce it (Hee *et al.* 2023). For example, enzymatic treatment with asparaginase, applied prior to heat treatment, can reduce acrylamide levels (Xu, Oruna-Concha and Elmore 2016; de Borba *et al.* 2023). Another example is the use of supercritical CO_2 extraction to reduce acrylamide levels after coffee roasting (Banchero, Pellegrino and Manna 2013).

Unit operations such as separation (liquid-liquid, solid-liquid) and refining (sugar industry), or specific chemical treatments and processing aids – in particular certain enzymes – can also be used to separate or eliminate undesirable constituents newly formed during previous unit operations. Taking the example of the sugar manufacturing process described in Annex 8, there are a large number of unit operations, but the manufacturing process intersperses unit operations potentially associated with the generation of newly-formed substances and unit operations enabling them to be eliminated. For this reason, only the unit operations occurring after the last unit operation to eliminate newly-formed substances have been taken into account for the classification of foods (see 3.1.3.2).

The same is true with certain heat treatments commonly used in the agri-food industry to inactivate the enzymes found in fresh produce that are responsible for the occurrence of newly-formed substances; for example, polyphenol oxidase (PPO), which enables quinones or polyquinones to be synthesised from phenolic compounds (Le Bourvellec *et al.* 2004), oxidases that form pheophytins by oxidising chlorophylls (Paciulli *et al.* 2017), or peroxidases responsible for the degradation of organoleptic properties such as colour or texture. These "blanching" treatments are therefore applied systematically whenever the fresh produce to be processed contains these substrates and enzyme systems. The heat treatments applied are generally of very short duration and carried out at temperatures of between 70 and 90°C.

3.1.3.2. Ranking of foods according to their likelihood of producing newly-formed substances

3.1.3.2.1. Food ranking

The values assigned to the different criteria (defined in Table 4) for the 27 foods are shown in Annex 5. Values are given for the six criteria characteristic of the raw materials and the four criteria associated with the unit operations. To count the number of unit operations relevant to the generation of newly-formed substances, only those occurring after the last unit operation designed to eliminate newly-formed substances were taken into account for the classification of foods (example shown in Annex 8).

The three Electre III rankings derived from these values for each of the three weight scenarios assigned by the experts (Table 5) are shown in Figure 3. The method applied enabled the foods to be classified by taking account of the characteristics of the raw material and the number and sequence of unit operations. As a reminder, the degree of processing should be defined in terms of the thermo-mechanical energy transmitted to the matrix (raw material, ingredient) during the various unit operations. However, this concept is only rarely present and is not quantified in the proposed systems. This approach and its weighting are consistent with the definition of a "Process Score", for ingredients or foods, introduced by Souchon and Braesco (Souchon and Braesco 2022).

The nine classification systems, and the Nova system in particular, rarely consider the objectives, conditions and sequence of unit operations.

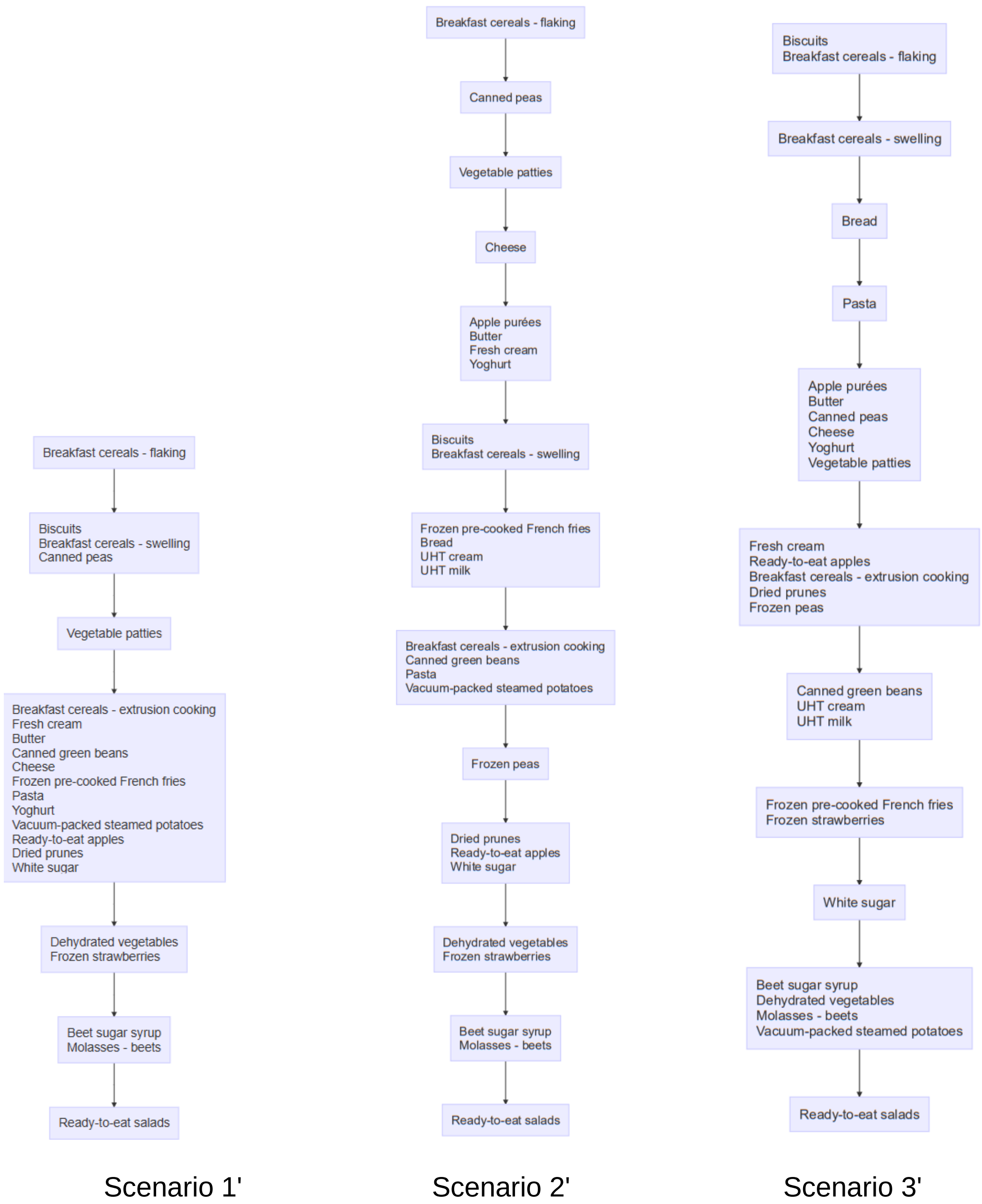


Figure 3. Rankings (obtained according to three weight scenarios) of foods based on criteria linked to the composition of the main ingredient and criteria relating to the unit operations.

The arrow pointing from option A to option B indicates that A outranks B (A is more susceptible to the generation of newly-formed substances) according to the established criteria. Left: scenario 1': overall weight of the ingredient criteria is equivalent to that of the unit operations; centre: scenario 2': weight of the unit operations criteria is twice as high; right: scenario 3': weight of the ingredient criteria is twice as high.

* “Ready-to-eat” salads are generally raw, peeled, cut, washed and packaged.

While breakfast cereals obtained using the flaking process (corn flakes, for example) are at the top of all three rankings, the position of the other foods is very sensitive to the sets of weights used.

3.1.3.2.2. Discussion on the elements used for ranking foods

3.1.3.2.2.1. Food classification criteria and sets of weights

There was a broad consensus among the experts over the criteria proposed by ANSES in 2018 and used in this expert appraisal to classify foods. The scientific literature has confirmed the link between these criteria and the likelihood of producing newly-formed substances (Lee *et al.* 2019; Taş, Kocadağlı and Gökmen 2022). However, few data are available with which to determine the relative importance to be assigned to the criteria relating to the food matrix compared with those relating to the unit operations. At this stage, it seems difficult to propose a robust ranking of foods based on their propensity to generate newly-formed substances. It also seems worth asking whether it is even possible to establish a single weighting system applicable to all food categories. This is because the interactions between the unit operations and the food matrix characteristics could be specific to each food, with opposing, additive or synergistic effects. The WG also found that the number of processing aids could be an additional criterion of interest compared with the 2018 opinion. The number of processing aids for each manufacturing procedure was identified (see Annex 5) but was not taken into account in the ranking because of the difficulty of weighting this criterion.

When validating a food ranking approach, it appears crucial to compare the classifications obtained with studies identifying foods with the highest concentrations of newly-formed substances. For example, the foods with the highest levels of acrylamide are potato crisps and French fries (Abt *et al.* 2019).

Moreover, ranking foods in terms of their capacity to contain newly-formed substances is only an indicator of the presence and hazard level. It does not take product consumption levels into account. Going back to the example of acrylamide, even though concentrations are higher in crisps and French fries, some studies show that breakfast cereals are the main contributors to consumer exposure (Abt *et al.* 2019). In ANSES's second total diet study (TDS2), the food that contributed most to acrylamide exposure was potatoes in the form of French fries or sautéed potatoes. Coffee was the second biggest contributor to acrylamide exposure in adults, while in children it was sweet biscuits (ANSES 2011, 2016).

3.1.3.2.2.2. Complexity of the manufacturing processes

The 27 examples of foods to which the ranking method was applied involve the processing of one main raw material rather than a formulation (

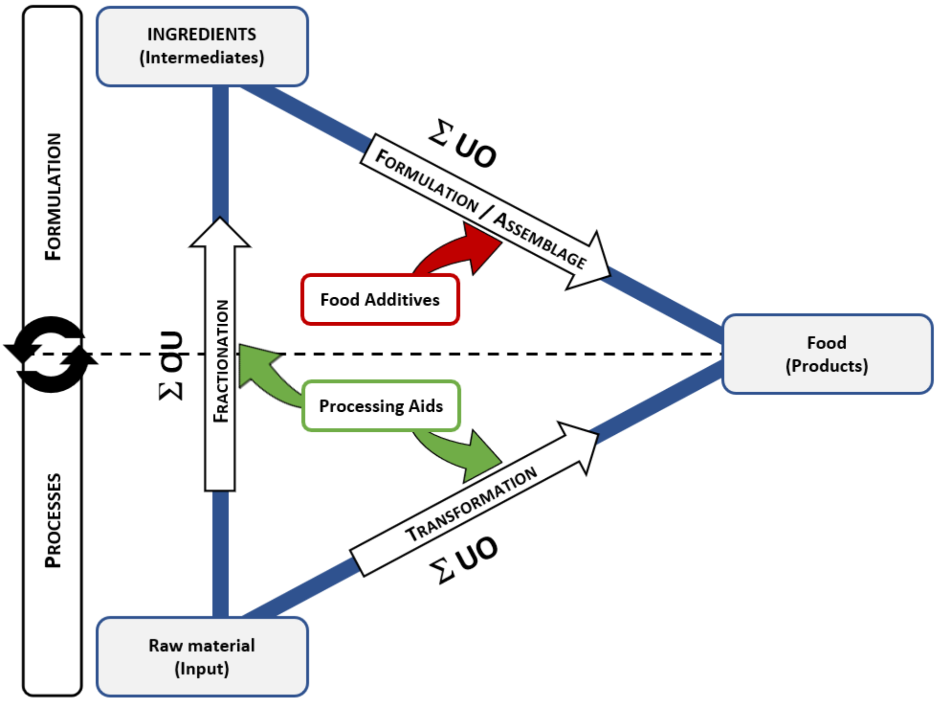
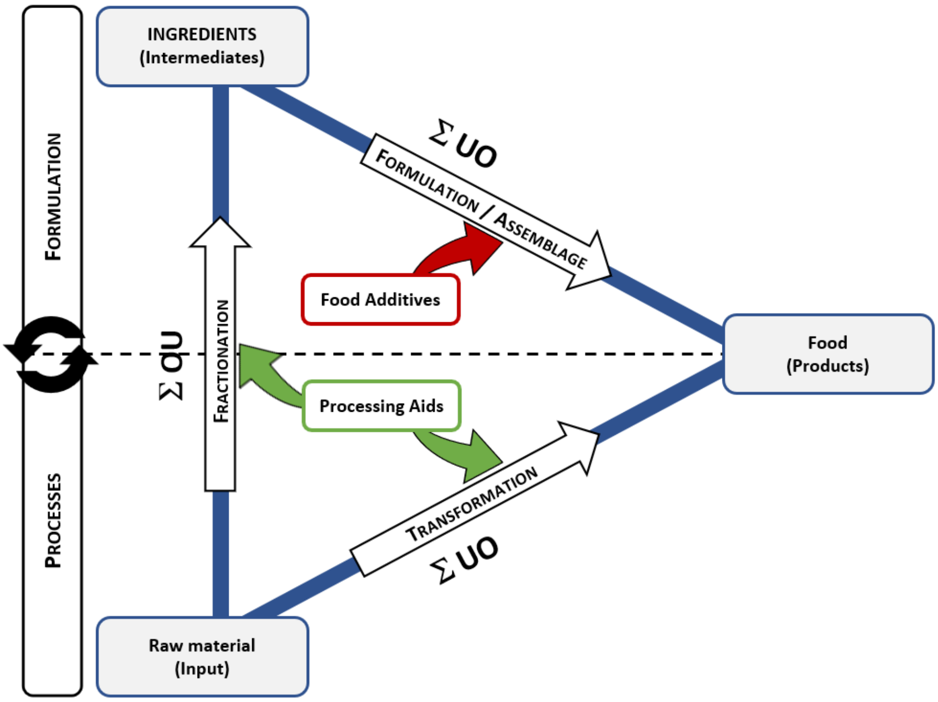


Figure 1). However,



as Figure 1 shows, some technological sequences are complex, involving combinations of ingredients which themselves have undergone manufacturing processes. For example, in Figure 4, which illustrates various yoghurt-making processes, the simplest process comprises only six unit operations in total, including two that are among those least likely to promote the occurrence of newly-formed substances and one that is among those moderately likely to promote their occurrence. The other manufacturing processes are more complex. The milk powder, added to improve the texture of the yoghurt, is itself the result of various unit operations. In the most complex of the three scenarios, the fruit added to the yoghurt may also undergo several unit operations. To manage this complexity and also take account of the processes applied to the ingredients, two approaches are possible: consider the total sum of unit operations regardless of the quantity of foods produced, or take account of the proportions of each ingredient in the final product. Recent research into process quantification (B Maurice 2022) suggests that the latter option is more relevant. It would also be more consistent with risk assessment methods that take account of the quantities consumed.

Figure 4: Examples of manufacturing processes for yoghurts.
In green: unit operations least likely to promote the occurrence of newly-formed substances, in yellow: operations moderately likely to promote the occurrence of newly-formed substances, in grey: other unit operations not classified for their capacity to generate newly-formed substances

3.1.4. Conclusions regarding the question on the identification of processing methods that potentially pose a threat to health

The work on the Electre III multi-criteria method led to a ranking approach being applied to unit operations and foods, specifically with regard to their propensity to generate newly-formed substances, and in line with the criteria established in ANSES's earlier report (ANSES 2018).

The unit operations were classified based on knowledge of their technological basis and operating conditions. Their ranking led to them being classified into three categories. The work carried out on manufacturing procedures for foods and ingredients showed that the order of the unit operations needs to be taken into account when assessing the capacity of a process to promote the occurrence of newly-formed substances. Only unit operations following those[11] that eliminate newly-formed (undesirable) substances should be considered in the ranking.

The ranking was applied to a panel of foods and ingredients with simple manufacturing procedures (involving the processing of a single raw material).

An analysis of the technological sequences for these foods or ingredients then determined the number of unit operations and processing aids used. The experts proposed a ranking for these foods on the basis of the number of unit operations, their propensity to promote or prevent newly-formed substances and the characteristics of the input materials.

[11] Such as separation, purification, bleaching and/or refining operations.

However, this ranking is sensitive to the weighting of the criteria, in particular the comparative importance of those relating to the unit operations and the characteristics of the ingredients used. The ranking of foods is uncertain on the basis of current knowledge, given the uncertainty associated with the relative weights assigned to the criteria by the experts. This reflects the complexity and challenges inherent in the assessment of newly-formed substances. Moreover, the current ranking method is limited to considering the initial characteristics of the raw materials, without taking account of any changes due to the unit operations or the use of processing aids.

Taking account of changes in the characteristics of materials after each process, as well as potential interactions with food additives (formulation), could provide a more comprehensive view of the impact of processes on the occurrence of newly-formed substances, thereby enhancing our ranking approach (Chazelas *et al.* 2020).

The variability of unit operations within food categories potentially complicates their precise classification. The example of cereal products, discussed in detail in Annex 9.1, illustrates this complexity. Differences in cooking processes, whether industrial or domestic, affect the formation of acrylamide and hydroxymethylfurfural (HMF). This formation is influenced by factors such as cereal species and varieties, cooking techniques and product formulation. Precisely managing these variabilities is crucial to reducing the health risks associated with newly-formed substances (Capuano and Fogliano 2011; Halford, Raffan and Oddy 2022; Morales, Mesías and Delgado-Andrade 2020).

Lastly, this study characterised foods "as purchased" rather than "as consumed". It therefore did not take account of any newly-formed substances produced by domestic preparation methods. Processes such as deep-frying and cooking fish and meat are two examples of how domestic practices can differ from industrial processes in terms of temperature and time control, thereby directly affecting the presence of potentially harmful newly-formed substances such as acrylamide and PAHs (Ganesan and Xu 2020; Jakobsen *et al.* 2018; Mahmud *et al.* 2023; Pedreschi and Mariotti 2023). These differences highlight the need to educate consumers about cooking practices that minimise health risks. Annex 9.3 discusses these two examples in more detail.

Moreover, the food processing operations undertaken to meet society's demands in terms of cost, sustainability and dietary diversity (Prache *et al.* 2020) sometimes generate complex changes (biochemical, physical) responsible for potential hazards, linked in particular to newly-formed substances. Annex 9.2 provides two examples illustrating these challenges: plant-based substitutes for products of animal origin and gluten-free products (Batista *et al.* 2023; Cao and Miao 2023; Guiné *et al.* 2020). The use of processes such as extrusion to transform plant proteins into meat-like alternatives can potentially generate newly-formed substances due to the high temperatures involved (Sridhar *et al.* 2022; Vallikkadan *et al.* 2023). This contradiction between the benefits of plant-based diets and the health concerns associated with newly-formed substances illustrates the challenges of food innovation in terms of assessing and controlling the benefit/risk ratio. Similarly, gluten-free alternatives often require the addition of numerous food additives to mimic the functional properties of gluten, leading to them being described as "ultra-processed foods". The increased presence of these food additives raises questions about the potential generation of newly-formed substances in these food products (Batista *et al.* 2023).

The recommendations arising from this study are based on five points:

- strengthen knowledge of the different newly-formed substances and their toxicity levels. This identification and characterisation phase is crucial for ranking the risks and ensuring that they are more accurately assessed;
- develop and standardise new models and methodologies capable of precisely quantifying the risk associated with newly-formed substances, taking account of the variability of food processing techniques and consumption models;
- foster a collaborative environment for data sharing between regulatory bodies, research institutions and agri-food industries to improve understanding of food processing operations and their consequences. This should include detailed monitoring of food processing operations and the changes in food composition they bring about throughout the processing chain;
- encourage research into alternative processing technologies that minimise the formation of hazardous substances without compromising food quality or safety;
- create or improve consumer guidelines in order to better convey to the general public the importance of complying with certain practices that can influence the production of newly-formed substances during common domestic processing steps.

In view of the above, it appears that the likelihood of manufacturing processes generating newly-formed substances, regardless of the potential hazard, is linked not so much to the number of transformations carried out during a food manufacturing process as to the types of transformations carried out and the nature of the processed food matrix. It is therefore not possible, on the basis of the processing methods, to rank the foods for which the health risks may specifically be higher.

3.2. Identifying existing classifications of foods according to their degree of processing and assessing their relevance with regard to the characteristics identified previously

3.2.1. Identification of existing classifications

An analysis of the literature identified nine systems for classifying foods according to their degree of processing. These classifications have been examined by several reviews and comparative analyses (de Araujo *et al.* 2022; Crino *et al.* 2017; Souchon and Braesco 2022; Sadler *et al.* 2021).

The main descriptive features of these classifications are given in Table 6.

Table 6: Summary of the different systems for classifying foods according to their degree of processing

Classification name	Country	Publication date	Organisation	General classification principles	Categories
INSP (González-Castell *et al.* 2007)	Mexico	2007	National Institute of Public Health of Mexico (INSP)	According to cultural and social practices.	- Non processed foods; - - Processed traditional foods; - Processed modern foods.
IARC-EPIC (Slimani *et al.* 2009)	Europe	2009	Researchers from the International Agency for Research on Cancer (IARC)	According to the intensity of the processing undergone by the raw material and the place where the food is prepared.	- non-processed foods; - moderately processed foods; - highly processed industrial foods. The three groups were defined with the help of a food scientist. For each food category, examples of unit operations and foods are given.
Nova (C.A. Monteiro *et al.* 2019; C.A. Monteiro *et al.* 2010; D. Monteiro *et al.* 2016)	Brazil	2010, 2016, 2019	Researchers from the University of Sao Paulo – Monteiro	According to how the foods are obtained, but also their formulation (number of ingredients, type and function of ingredients used).	- unprocessed or minimally processed foods (Nova 1); - processed culinary ingredients (Nova 2); - processed foods (Nova 3); - ultra-processed foods (Nova 4).
IFPRI (Asfaw 2011)	Guatemala	2011	International Food Policy Research Institute (IFPRI)	According to practicality and the concept of first and second transformation. List of 94 generic foods	- non-processed foods; - primary processed foods; - highly processed foods (= processed foods that can be consumed without preparation or after simply reheating).
IFIC (Eicher-Miller, Fulgoni and Keast 2012, 2015)	United States		The International Food Information Council (IFIC)	According to their degree of processing, the objectives of the processes applied (longer shelf life, improved nutritional qualities, sensory qualities and/or convenience) and the place where they were carried out.	- minimally processed foods - foods processed for preservation (e.g. frozen vegetables) - mixtures of combined ingredients: • packaged mixes and jarred sauces (e.g. dehydrated soup, spice mixes); • mixtures probably home-prepared (e.g. bread, cakes); - ready-to-eat processed foods:

Classification name	Country	Publication date	Organisation	General classification principles	Categories
					• packaged ready-to-eat foods (e.g. soft drinks, crisps); • mixtures possibly store-prepared (e.g. roast chicken); - prepared foods/meals (e.g. pizza, nuggets).
USP (Louzada *et al.* 2015)	Brazil		Researchers from the University of Sao Paulo	According to the number of ingredients, the place of processing and the presence of industrial ingredients and additives.	- natural, minimally or moderately processed foods; - processed foods; - ultra-processed foods.
FSANZ (*FSANZ* 2014)	Australia and New Zealand		Food Standards Australia & New Zealand	According to the processes applied (by food category, based on 135 foods in the Euromonitor database).	- non-processed foods; - processed foods = foods that have undergone substantial changes in relation to the raw material used
UNC (Poti *et al.* 2015)	USA		University of North Carolina (UNC)	According to rules that take account of the physical, chemical or biological changes brought about by processing, as well as its objectives and the food formulation (number of ingredients and addition of additives or industrial ingredients).	- unprocessed/minimally processed foods; - basic processed foods; - moderately processed foods; - highly processed foods. These levels are then subdivided leading to a total of seven different groups.
SIGA (Davidou *et al.* 2021; Fardet 2018)		2018	Private company (chargeable access)	- According to the characterisation of industrial ingredients known as "markers of ultra-processing" (MUPs) (refined oils, natural flavourings, hydrolysed sugars, synthetic flavourings, starches, etc.). - According to the salt, sugar and fat content of foods using the average nutritional thresholds proposed by the UK Food Standards Agency (FSA). - According to the risks of exposure to certain additives based on the work of health agencies. - According to the levels of loss of structure and composition of the raw agricultural material used ("matrix" effect).	<u>Nine groups:</u> - unprocessed foods; - minimally processed foods; - balanced processed foods; - processed foods high in salt, sugar and/or fat; - balanced UPFs with a single type 1 MUP; - UPFs high in salt, sugar and/or fat with a single type 1 MUP; - UPFs with several type 1 MUPs; - two groups of UPFs with several type 1 and/or type 2 MUPs.

The work by Souchon *et al*. involved a detailed analysis of the classifications (Souchon and Braesco 2022; B Maurice 2022). Table 7 lists the classification systems according to the criteria taken into account by these classification systems.

Table 7: Characteristics of the main systems for classifying foods according to their degree of processing, extracted from Maurice's thesis (B Maurice 2022)

Classification name	consideration of processing methods (e.g. artisanal, homemade, etc.)	consideration of traditional aspect	consideration of unit operations type	consideration of additives	consideration of formulation (industrial ingredients)	consideration of nutritional quality	consideration of usage patterns (ready-to-use)
INSP	✓	✓	✗	✗	✗	✗	✗
IARC-EPIC	✓ (100% industrials)	✗	✓	✗	✗	✗	✓
NOVA	✓	✓	✓	✓	✓	✗	✓
IFPRI	✗	✗	✓	✗	✗	✗	✗
IFIC	✓	✗	✓	✗	✗	✗	✓
FSANZ	✗	✗	✓	✗	✗	✗	✗
USP	✓	✓	✓	✓	✓	✗	✓
UNC	✓ (100% industrials)	✗	✓	✓	✓	✗	✓
SIGA	✓	✓	✓	✓	✓	✓	✗

These systems are based on different criteria: extent/intensity of processing, nature of the changes associated with processing (e.g. modification of properties, addition of ingredients), artisanal or industrial processing methods, or purpose of processing (e.g. longer shelf life).

Other work on food classification is under way, including methods focusing on the manufacturing process (B Maurice 2022; B. Maurice *et al.* 2022). These include the "Process Score", which is a method for assessing the impact of the various unit operations used in food manufacturing. Each operation in the ingredient processing procedure is given a score that reflects the time and intensity of the process, as well as its impact (chemical, physical or biological) on the food product. The more extreme the process conditions (temperature, pressure, time), the higher the score. This assessment is an initial proposal for quantifying the effect of food processing on each ingredient, depending on the specific operations involved in its preparation. At this stage, it has only been proposed for classifying a few food categories (B. Maurice *et al.* 2022).

3.2.2. Agreement between the different classifications

Several studies have sought to compare percentages of the most highly processed foods in the diet and relationships between consumption of these foods and the risk of CNCDs, depending on the classification in question. For example, one study classified the foods in the Greek database (DAFNE) according to five of these systems (IARC, Nova, IFPRI, IFIC and UNC) and compared the distribution of categories for the different food and beverage groups (meat products, seafood, eggs, dairy products, fruit, vegetables, sweetened products, etc.). The breakdown appeared to be similar for the IFPRI, IFIC and UNC classifications. On the other hand, the breakdowns according to the IARC and Nova systems differed considerably from the other three, and also differed from each other. Each of these classifications resulted in different percentages of "ultra" or highly processed foods in the diet: from 10.2% according to Nova to 47.4% according to the IARC (de Araujo *et al.* 2022). The lack of consensus was particularly notable for cereal products (bread, flour, pasta, etc.), milk and dairy products, added fats, sugars/sweetened products and beverages (de Araujo *et al.* 2022). A disparity in estimates of the percentage of the most highly processed foods depending on the classification was also observed in two other studies, one based on Spanish consumption data (Martinez-Perez *et al.* 2021) and the other on US consumption data (Bleiweiss-Sande *et al.* 2019). In the first study, the percentage of the most highly processed foods in the diet varied from 60.7% according to the IARC classification to 27.4% according to Nova (Martinez-Perez *et al.* 2021). In the second study, which classified the 100 most consumed foods according to the Nova, IFIC and UNC classifications, the Nova system resulted in the highest percentage of UPFs (70%) and the IFIC system the lowest (53%). The overall agreement between the three classification systems, as measured by the kappa statistic, was moderate for all comparisons (0.41 < kappa < 0.60) (Bleiweiss-Sande *et al.* 2019).

Another study assessed whether the different classifications led to similar associations between UPF consumption and cardiometabolic risk markers. The comparison was based on four classifications (IARC, IFIC, UNC and Nova), using data on consumption and cardiometabolic risk (BMI, systolic and diastolic blood pressure and HbA1c in particular) from the PREDIMED-Plus study. Higher UPF consumption was associated with higher BMI with the Nova classification only, while it was associated with higher systolic and diastolic blood pressure with the UNC classification only, and with higher HbA1c concentrations with the IARC classification only. For all four classification systems, higher consumption of UPFs was associated with higher body weight and waist circumference (Martinez-Perez *et al.* 2021). The authors concluded that the choice of classification influences the associations between UPF consumption and cardiometabolic risk factors.

These studies highlight disparities in the proportion of UPFs in the diet and in the relationship between their consumption and cardiometabolic risk factors, which could be explained by the different criteria set by these classification systems.

Insofar as the studies included in the systematic review only used the Nova classification (see Section 3.3), this system is the only one described here in detail and analysed.

3.2.3. Description and analysis of the Nova classification

3.2.3.1. Description of the Nova classification

Table 8 contains the description of the classification made by Monteiro's team in 2019, as well as the examples chosen (C.A. Monteiro *et al.* 2019). The four classes are characterised by the following parameters:

- the processing methods;
- the food formulation excluding additives;
- the additives used;
- the purpose of the processes and formulation;
- the packaging.

Table 8: Nova classification ((C.A. Monteiro *et al.* 2019))

Nova group	Definition	Examples
Nova 1: unprocessed or minimally processed foods	Edible parts of plants or animals, fungi, algae, water ± industrial processes such as removal of inedible or unwanted parts, drying, crushing, grinding, fractioning, roasting, boiling, pasteurisation, refrigeration, freezing, placing in containers, vacuum packaging, non-alcoholic fermentation and other methods that do not add salt, sugar, oils or fats or other food substances to the original food. The main aim of these processes is to extend the life of unprocessed foods, enabling their storage for longer use and, often to make their preparation easier or more diverse. Infrequently, contain additives that prolong product duration, protect original properties or prevent proliferation of micro-organisms.	Fresh or pasteurised milk; fresh or pasteurised fruit or vegetable juices (with no added sugar, sweeteners or flavours); fresh or pasteurised plain yoghurt. Also includes foods made up from two or more items in this group and foods with vitamins and minerals added generally to replace nutrients lost during processing.
Nova 2: processed culinary ingredients	Substances obtained directly from Group 1 foods by industrial processes such as pressing, centrifuging, refining or extracting. Used in the preparation, seasoning and cooking of Group 1 foods. These products may contain additives that prolong product duration, protect original properties or prevent proliferation of micro-organisms.	Vegetable oils; butter and lard; sugar and molasses; honey and maple syrup; starches extracted from maize and other plants, and salt mined or from seawater, vegetable oils with added antioxidants and table salt with added drying agents. Includes products consisting of two Group 2 items, such as salted butter, and Group 2 items with added vitamins or minerals, such as iodised salt.
Nova 3: processed foods	Group 2 + 1 products, using preservation methods such as canning and bottling, non-alcoholic fermentation. Processes and ingredients here aim to increase the durability of Group 1 foods and make them more enjoyable by modifying or enhancing their sensory qualities. These products may contain additives that prolong product duration, protect original properties or prevent proliferation of micro-organisms.	Canned or bottled vegetables and legumes in brine; salted or sugared nuts and seeds; salted, dried, cured or smoked meats and fish; canned fish (with or without added preservatives); fruits in syrup (with or without added antioxidants); freshly made unpackaged breads and cheeses.

Nova group	Definition	Examples
Nova 4: ultra-processed foods	Formulations of ingredients, mostly of exclusive industrial use, that result from a series of industrial processes, many requiring sophisticated equipment and technology. Processes enabling the manufacture of Nova Group 4 foods include: the fractioning of whole foods into substances, chemical modifications of these substances, assembly of unmodified and modified food substances using industrial techniques such as extrusion, moulding and pre-frying, frequent application of additives whose function is to make the final product palatable or hyper-palatable ("cosmetic additives"), and sophisticated packaging, usually with synthetic materials. Ingredients often include sugar, oils and fats, and salt, generally in combination; substances that are sources of energy and nutrients but of no or rare culinary use (e.g. high fructose corn syrup, dextrose, lactose, concentrated fruit juices, hydrogenated or interesterified oils, protein isolates or any other source of proteins, fats and carbohydrates not included in the other Nova groups); cosmetic additives (flavours, flavour enhancers, colours, emulsifiers, sweeteners, thickeners and anti-foaming, bulking, carbonating, foaming, gelling and glazing agents); and additives that prolong product duration, protect original properties or prevent proliferation of micro-organisms. Processes and ingredients used to manufacture ultra-processed foods are designed to create highly profitable products (low-cost ingredients, long shelf life, emphatic branding), convenient (ready-to-consume) hyper-palatable snacked products liable to displace all other everyday consumer products.	Carbonated soft drinks; sweet or savoury packaged snacks; chocolate, candies (confectionery); ice cream; mass-produced bread and buns; margarines and other spreads; biscuits, pastries, cakes and cake mixes; breakfast cereals, cereal and energy bars; "energy" drinks; milk drinks, "fruit" yoghurts and "fruit" drinks; "cocoa" drinks; "instant" sauces; infant formulas, follow-on milks, other baby products; "health" and "slimming" products such as meal replacement shakes and powders. Many ready-to-heat products including pre-prepared pies, pasta and pizzas, poultry and fish "nuggets" and "sticks", sausages, burgers, hot dogs and other reconstituted meat products, as well as powdered and packaged "instant" soups, noodles and desserts.

- In red: purpose of the processes and formulation
- In orange: processing methods
- In purple: food composition
- In green: additives used
- In pink: packaging

3.2.3.2. Analysis of the Nova classification

- On the processing methods criterion:

The elements for assessing the link between the manufacturing process and the presence of newly-formed substances set out in the response to question 1 (see Section 3.1) show that there is little congruence between the proposed food classification and the Nova classification. Moreover, some foods in Nova Group 1 may involve the unit operations most likely to generate these newly-formed substances (e.g. coffee roasting).

Similarly, work on processing intensity (Process Score approach) shows that the intensities of processing methods are only weakly correlated with the Nova categories (B Maurice 2022). Current definitions of ultra-processed foods do not adequately reflect the intensity of the technological process. Processes such as pasteurisation, sterilisation or extrusion, as well as processing conditions (temperature, pressure, time, oxygen), are not taken into account in the Nova classification (Capozzi *et al.* 2021; Botelho, Araújo and Pineli 2018). For example, UHT milk is classified in Nova Group 1 even though it undergoes an intense heat process (around 145°C).

Furthermore, for equivalent numbers of unit operations, foods may be classified in different groups. A notable example is chocolate, classified as an ultra-processed product, which undergoes a similar number of unit operations to milk powder, classified as a minimally processed product (Petrus *et al.* 2021).

It should also be pointed out that certain processing methods constitute classification criteria shared between different classes. This is the case with fractionation and non-alcoholic fermentation.

As a result, Nova's concept of ultra-processing is not based on the intensity of the processing methods or the number of unit operations.

Moreover, the Nova classification only reflects processes applied at industrial level. It does not take account of operations carried out during home preparation.

- On the formulation criterion:

The Nova classification, which was initially designed for identifying degrees of food processing, sometimes seems closer to a classification of ultra-formulation than a genuine assessment of ultra-processing. Some studies point to the fact that Nova focuses more on the ingredients used in foods than the unit operations required to process them (Botelho, Araújo and Pineli 2018). For example, plain yoghurt is mentioned among the examples of products in Nova Group 1, while sweetened yoghurt is mentioned in Nova Group 4, even though both undergo the same processing operations (Petrus *et al.* 2021)

In addition, certain "cosmetic" additives (such as flavours, flavour enhancers, colours, emulsifiers, sweeteners, thickeners and various anti-foaming, bulking, carbonating, foaming, gelling and glazing agents), as well as substances not traditionally used in meal preparation (such as high fructose corn syrup, protein isolates or hydrogenated oils), are considered to be indicators of ultra-processing. As a result, foods containing them are automatically classified in Nova Group 4. Lastly, this classification does not take account of their quantity, nor the level of potential threat to health.

As a consequence, this classification essentially reflects the degree of formulation of food products.

- On the criterion relating to the purpose of the processes and formulation:

Besides the two criteria detailed above, the authors added a criterion relating to the purpose of the processes and formulation. This introduces a degree of subjectivity, for example when comparing purpose criteria for Nova Groups 3 and 4. For Nova Group 3, the processes and ingredients used are designed to "make foods more enjoyable by modifying or enhancing their sensory qualities", while for Nova Group 4, they are designed to create "hyper-palatable products liable to displace all other everyday consumer products".

The objective of preserving products is found in all the groups, although it is expressed in different ways ("enabling their storage for longer use" for foods in Nova Group 1, "long shelf life" for foods in Nova Group 4). This criterion is also imprecise, sometimes contradicts the other criteria and is therefore inconsistent with the examples (UHT milk classified as Nova 1 and canned foods classified as Nova 3 have longer shelf lives than certain products classified as Nova 4, such as flavoured yoghurts). As a result, this criterion cannot be used to discriminate between products, and leads to confusion.

- Applicability and reproducibility of the classification:

The Nova criteria are sometimes contradictory and are not precisely described, making the classification subjective. The lists of processes corresponding to each group, as well as the substances not traditionally used in meal preparation and the "cosmetic additives", are not exhaustive (see Table 8).

As seen earlier, the formulation, and in particular the presence of these substances, is key to defining the Nova group to which a food belongs. A very precise knowledge of its composition is therefore required in order to classify it; in other words, access is needed to the list of ingredients and therefore to the product's exact name and brand. However, the data collected on food consumption, including 24-hour recalls, do not provide this degree of precision for all foods. Current databases do not therefore collect the information needed to reliably classify foods according to Nova (Steele *et al.* 2023), and some authors have indicated that it is difficult to apply this classification (Forde, Mars and de Graaf 2020; Adams and White 2015). This difficulty can be seen in studies that have examined the reproducibility of Nova's classification by different people. Using an online survey, Braesco *et al.* asked nutrition specialists to classify around 200 food products for which they did or did not have information on composition (Braesco *et al.* 2022). Overall consistency between assessors was low, even when the list of ingredients was available (kappa coefficient between 0.32 and 0.34)[12]. In another study in which two people classified foods from the USDA Food and Nutrient Database, the kappa coefficient was 0.58, with disagreements mainly concerning mixed dishes (Lorenzoni *et al.* 2021).

To help with classification, the authors of the Nova system suggested some examples (C.A. Monteiro *et al.* 2019). These appear to be key to the classification of foods and may even, in the absence of precise data on composition, replace the classification criteria. However, these examples were defined in a given food context, i.e. that of Brazil in the 2010s. They are not necessarily suited to the foods available in other countries. Consequently, depending on the food supply, these examples could lead to classification errors. For example, sausages are listed by Monteiro's team as Nova Group 4 foods, whereas the French offer is varied and also includes sausages without "cosmetic" additives or "substances not traditionally used in meal preparation", which could therefore be classified as Nova Group 3.

In the absence of sufficiently precise information, implicit rules are sometimes applied, which can lead to classification bias. Thus, plain yoghurts, perceived as healthy, will by default be classified by users as Nova Group 1, whereas some contain added milk proteins in powder form, classifying them as Nova Group 4, and others contain cream, classifying them as Nova Group 3. This classification bias could potentially concern other foods such as non-freeze-dried vegetable soups (some of which contain natural flavourings). Conversely, foods that are perceived as unhealthy – such as certain dark chocolate bars containing no additives – will by default be classified by users as Nova Group 4, when according to their composition they should be in Nova Group 3. These approximations vary in precision depending on the supply available for each food.

In practice, research teams define their own rules to ensure consistency in how they treat different food products. Some describe them in detail in articles on this topic (Steele *et al.* 2023; Sneed *et al.* 2023). For example, an American team classified the foods in the NHANES study, considering breakfast cereals, savoury snacks and industrial bread to be Nova Group 4 foods

[12] It should be noted that the study was carried out online and did not collect data on the participants' characteristics (including any personal interests). Moreover, they were able to respond multiple times.

because the composition of most of these foods corresponds to Nova Group 4 and they are not usually home-made in the United States (Steele *et al.* 2023). Applying these adaptations to the general principles defined by the designers of the Nova classification improved the agreement between coders, which was 0.75 and 0.76 in two studies (Sneed *et al.* 2023; Bleiweiss-Sande *et al.* 2019). However, these decision rules are not always available or sufficiently detailed.

3.2.3.3. Conclusion regarding the analysis of the Nova classification

The name "ultra-processed foods" given to foods in Nova Group 4 is confusing, because this classification is based more on formulation than processing. By only considering formulation, the criteria are not sufficiently precise and are based solely on non-exhaustive lists of substances and additives without any concept of hazard or threshold. The Brazilian authors behind the Nova classification have suggested examples to facilitate its application. However, these are based on generalisations that may not be valid outside Brazil, depending on the foods available. The use of examples makes application of the classification subjective and could lead to classification bias, which is not the case with an algorithm based on precise criteria. Because composition data from epidemiological studies are insufficient for reliably classifying each food according to the Nova criteria, some authors have established classification rules based on an extensive knowledge of the market, according to the food context in their country. For example, the Nova group of a food that predominates on a market can be extrapolated to all foods of the same type.

In view of these factors, it appears that the Nova classification, although widely used in publications studying the health effects of UPFs, does not rigorously reflect the level of food processing. Applying the classification requires a thorough understanding of product composition. Moreover, the key criteria used to classify foods are not based on concepts of potential hazard and are insufficiently precise.

3.3. Study of the epidemiological link between UPF consumption and the risk of chronic non-communicable diseases

In response to the request to study the epidemiological relationships between the consumption of "ultra-processed" foods and CNCDs, a systematic review of the literature was carried out, with an assessment of the weight of evidence.

3.3.1. Systematic review method

3.3.1.1. PECO structure

The Population, Exposure, Comparator and Outcome (PECO) structure formalises the systematic review questions. The population considered in this review is the general population. Exposure is defined as the level of consumption of ultra-processed foods, regardless of the classification used. The comparator is defined as the lowest level of UPF consumption. Confounding factors are also shown in the figure for the PECO structure. Confounding factors for which an adjustment was deemed necessary, and which were therefore regarded as key factors, are shown in bold in the PECO structure. Possible mediating factors were also identified. For each health theme, a specific PECO structure was established. A generic example is shown in Figure 5.

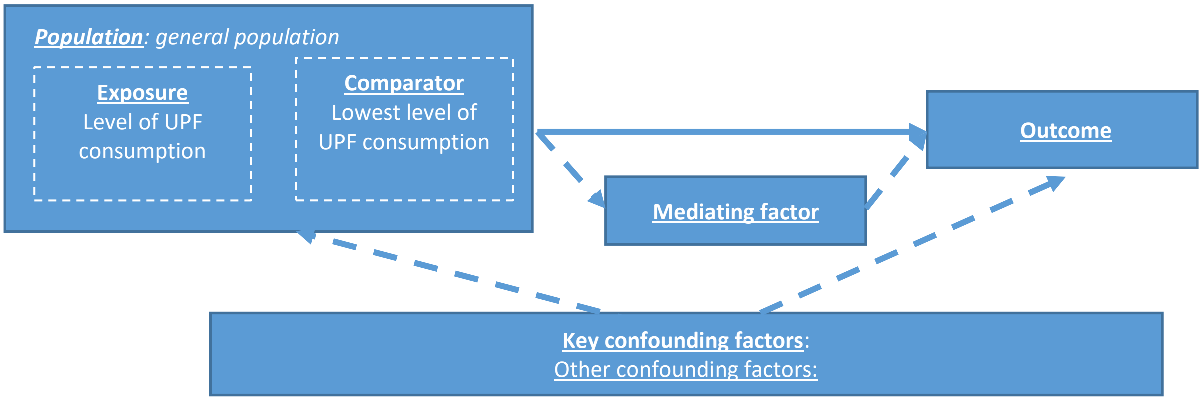


Figure 5: Generic PECO structure illustrating the link between high UPF consumption versus lower consumption and a health outcome

3.3.1.2. Inclusion and exclusion criteria

The group of rapporteurs defined inclusion and exclusion criteria in order to limit the analysis of the scientific literature to the most appropriate articles for addressing the questions asked. These inclusion and exclusion criteria are shown in Table 9. Two exposure-related inclusion criteria should be emphasised: consumption of the most highly processed foods was considered regardless of the classification used, as long as the food consumption data collected were appropriate. This is because classifications based on the degree of processing require a detailed description of the food. Studies where the food consumption data collected were deemed insufficiently precise were excluded: 24-hour recalls or food diaries appear to be essential for describing foods in sufficient detail (in particular describing whether they are home-made, industrial or artisanal) in order to assess their degree of processing. Food frequency questionnaires (FFQs) can also be used if they have been designed to estimate the degree of food processing. However, a method was recently proposed for classifying foods according to the Nova system on the basis of FFQs that had not been developed for this purpose (Martinez-Steele *et al.* 2023). This mainly involves identifying all the foods whose assignment to a Nova group is uncertain, and carrying out a sensitivity analysis by classifying these foods in a different way and then comparing the results. The rapporteurs therefore decided to also include studies in which food consumption data had been collected using an FFQ and for which a sensitivity analysis had been carried out on foods whose classification was deemed uncertain.

Table 9: Summary of the inclusion and exclusion criteria

Category	Sub-categories	Inclusion criteria	Exclusion criteria
Population	Subjects	Studies in humans	Studies in animals, *in vitro*, *in vivo*, *ex vivo*
	Age of subjects	Adults, adolescents, children and infants	
	Health status of subjects	General population	Population made up exclusively of sick subjects or those having undergone bariatric surgery Population made up exclusively of overweight or obese subjects Population made up of subjects following a weight-loss diet
	Countries	Countries listed in the "very high" and "high" human development categories (UNDP 2018)	Other countries
Exposure		High consumption of the most highly processed foods, regardless of the classification used Method suited for collecting food consumption data	Studies exclusively comparing infant formulas (which are processed foods) and breast milk Studies comparing home-made foods with industrial foods Studies on the effects of the degree of processing of a food type Exposure measured only via a food frequency questionnaire (without sensitivity analysis) or a dietary history
Comparator		Lower consumption of the most highly processed foods	-
Health outcomes		Incidence of chronic non-communicable diseases: - all types of cancer, cancer deaths - diabetes - overweight and obesity - cardioneurovascular events: stroke, myocardial infarction, cardioneurovascular deaths, other ischaemic vascular events, heart failure, atrial fibrillation, arterial hypertension (AH) All-cause mortality	Intermediate factors
Study type		Cohort studies with exposure measured prior to measurement of the outcome	Other study types

Category	Sub-categories	Inclusion criteria	Exclusion criteria
		Randomised controlled studies Non-randomised controlled studies	
Publication type		Publication in a peer-reviewed journal	Grey literature, unpublished data, reports, abstracts, conference proceedings
Language		Publication in English or French[1]	Publication in another language
Date			None: no threshold date

[1] This choice can be justified by (Morrison *et al.* 2012; Pieper and Puljak 2021).

3.3.1.3. Selection of articles

After formulating the research questions according to the PECO format (Figure 5), the lexical query developed for the literature search was validated by the group of rapporteurs and the CES on Human Nutrition.

The search equation, which can be found in Annex 10, involved cross-referencing terms relating to ultra-processed foods with terms relating to cardioneurovascular diseases, obesity or overweight, diabetes, cancer and all-cause mortality.

To begin with, the literature search was carried out on the MEDLINE databases using the PubMed and Scopus search engines, and duplicate articles were removed using the Cadima tool. The search did not include criteria relating to the articles' date of publication, thus including articles published up to the date on which it was carried out, i.e. 8 June 2023 for MEDLINE and 7 June 2023 for Scopus. For MEDLINE, the search syntax was based on both MeSH terms and free text.

Subsequently, the group of five rapporteurs defined the inclusion and exclusion criteria (Table 9) for selecting articles. These criteria, determined on the basis of the parameters of the PECO structure, enabled the scientific coordinators to select an initial batch of articles on the basis of their title and abstract (level 1 of the screening) and then to determine their eligibility by reading the full text (level 2 of the screening). These two levels of screening were carried out independently by the two scientific coordinators using the Cadima tool. Where necessary, selection discrepancies were resolved by all the rapporteurs and the scientific coordinators.

In the third and final step, an additional manual search was carried out by the coordinators. This involved checking that all the relevant articles cited in systematic reviews and meta-analyses on this topic had been identified during the systematic literature search phase, and adding them if not. These systematic reviews and meta-analyses had been identified during the first level of screening.

The flow chart in Figure 6 summarises the number of articles included and excluded at each step.

3.3.1.4. Flow chart

After removing duplicates from the two databases consulted and from the manual search, 2745 references were sorted on the basis of their title and abstract. The eligibility of the resulting 91 references was then estimated on the basis of reading the full text, which ultimately led to 10 references being selected.

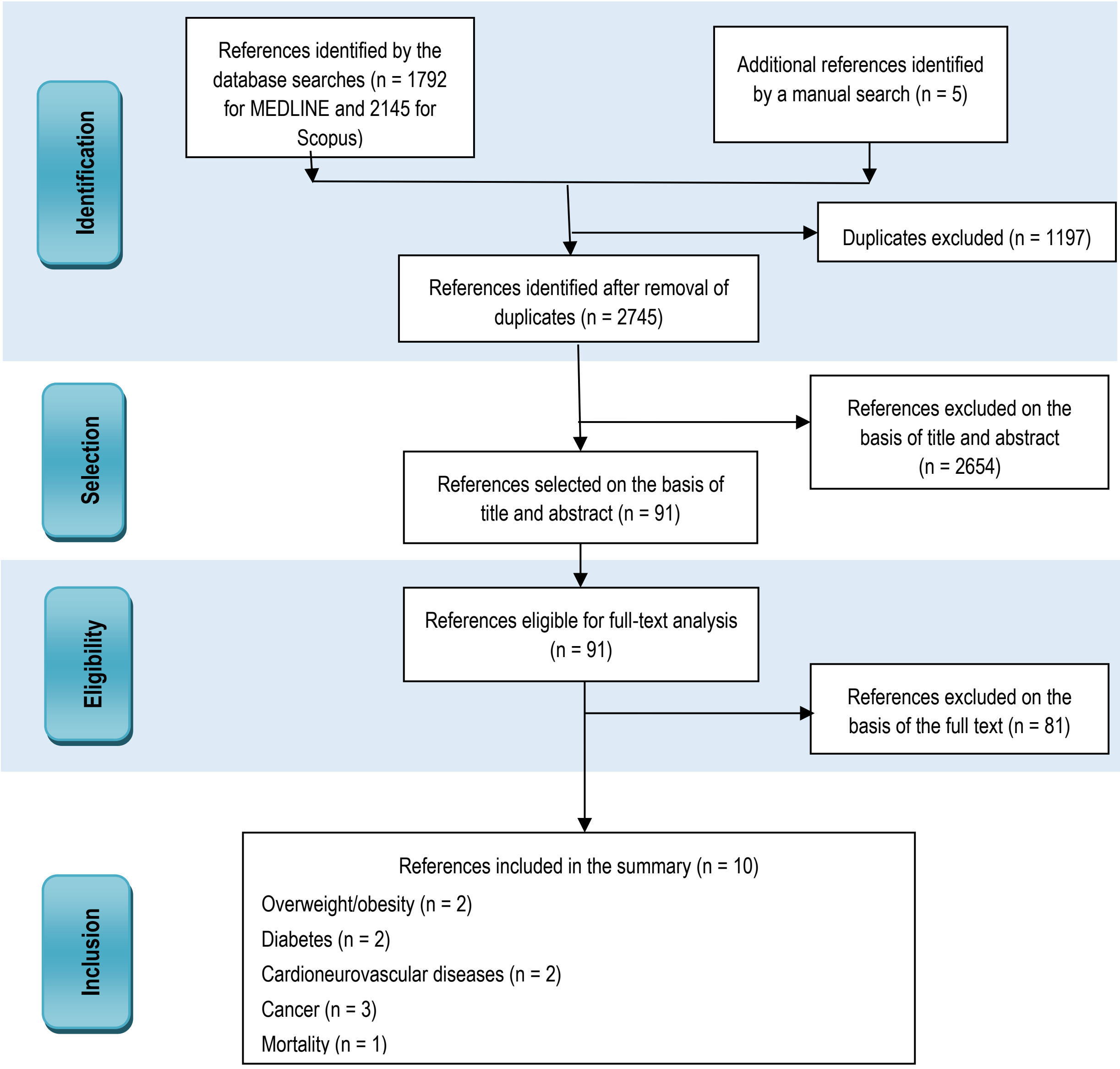


Figure 6: Flow chart of the literature search on the links between UPF consumption and CNCDs

The table listing the studies excluded at the second screening step and the reasons for their exclusion is given in Annex 11.

3.3.2. Extraction of data from selected articles, analysis of the risk of bias and assessment of the weight of evidence

- Data extraction

Once the selection had been made, a member of the coordination team extracted the data from the selected articles. The extraction files (Annex 12) collate for each article:

- the study characteristics (authors, date of publication, journal, type of study, place and period of recruitment);
- the sample characteristics (size, average age, etc.);
- how the UPFs were defined and measured;
- how the outcome was defined and measured;
- the statistical analyses carried out;
- the results;
- an analysis of the risks of bias;

- the sources of funding.

Each extraction was verified by another member of the coordination team.

■ Analysis of the risk of bias

The risk of bias was analysed for each article using the "Risk of Bias for Nutrition Observational Studies" (RoB-NObs) tool developed for observational studies by the Nutrition Evidence Systematic Review (NESR) of the US Department of Agriculture (USDA) (DGAC 2020).

This analysis assessed the extent to which the results reported in the article may have been biased by:

- the randomisation method or the key confounding factors[13];
- the selection of participants[14];
- the classification of exposures[15];
- departures from intended exposures[16];
- missing data[17];
- measurements of outcomes[18];
- selection of reported results[19].

For each type of bias, the risk was qualified according to one of four levels: "low", "moderate", "serious" or "critical" (DGAC 2020). For example, a "low" risk of bias due to confounding factors meant that no residual confounding factor was identified in the study. When the information was unavailable, the extraction file indicated "no information".

The analysis of the risk of bias was carried out independently by each coordinator and then discussed in order to reach a consensus.

The extracted data were presented at working meetings with the group of rapporteurs; clarifications were sometimes provided and the analysis of the risk of bias was discussed and then validated.

Each extraction file, together with the articles, was sent to the rapporteurs to enable a summary to be written and the weight of evidence assessed.

■ Assessment of the weight of evidence

[13] Checks that the statistical models were fitted for all the key confounding factors.
[14] Checks that the start of follow-up of participants included in the study coincided with the start of exposure.
[15] Checks that 1) the diet and the methods used to assess it were clearly defined and concerned the diet of interest; 2) the classification methods were valid, reliable, applied in the same way between the groups and posed a minimal risk of diet misclassification (with a random or systematic error); 3) the type of diet was not affected by the outcome (its presence, knowledge or risk of the outcome).
[16] Checks that there was no change in the status of the diet that could have had an impact on the outcome.
[17] Checks that the data were reasonably complete, or that the proportions of and reasons for missing participants were similar between diets, or that the analysis took account of the missing data and probably eliminated the risk of bias.
[18] Checks that the methods used to assess the outcomes were comparable between diets and that measurement of the results was unlikely to be influenced by knowledge of the diet.
[19] Checks that the reported results corresponded to all the results analysed and all the planned sub-groups.

The weight of evidence was assessed according to the areas of assessment considered by the NESR tool and a scale for expressing the level of confidence, identical for all health themes, with the following possible grades: "strong", "moderate", "limited" and "not assignable".

The areas assessed for each health theme were:

- **Control of the risks of bias**: following the approaches outlined above, the group of rapporteurs assessed how systematic errors resulting from the design and conduct of the studies (e.g. biases related to confounding factors, participant selection, classification of exposures, missing data) could have affected the results reported by all the studies.
- **Consistency of the results**: the group of rapporteurs assessed the degree of similarity between the results of the different studies in terms of their direction and magnitude. They considered whether the lack of agreement in results could be explained by differences in methods.
- **Directness**: the group of rapporteurs assessed whether the studies provided a direct answer to the question posed or whether they only answered it indirectly.
- **Precision**: the group of rapporteurs assessed the level of precision of the results obtained, based in particular on the number of events of interest and the size of the confidence intervals of the estimates.
- **Generalisability**: the group of rapporteurs considered whether the study participants, exposures, comparators and the results examined overall could be generalised to the current French population, with its food consumption habits.

The final grade for the conclusion was then assigned by the group of rapporteurs during working meetings, taking account of the assessment of the different areas and following a decision diagram (Figure 7).

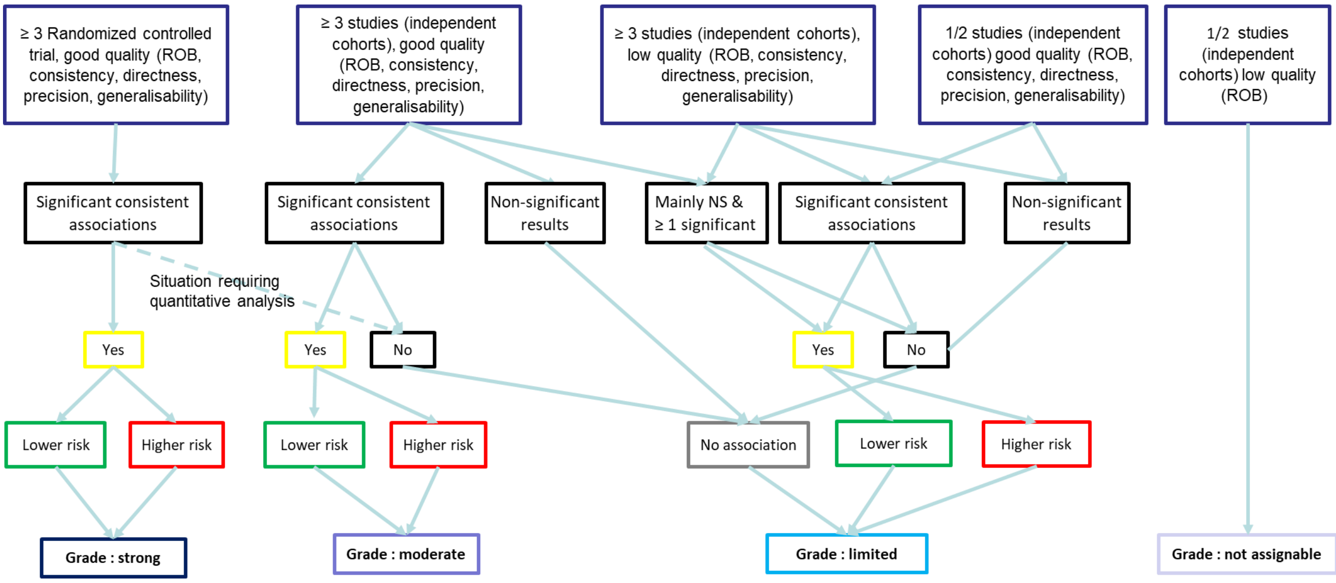


Figure 7: Decision diagram for assigning the weight of evidence

Note for the reader: if there are more than seven independent cohort studies, three of which are of poor quality, then the weight of evidence is moderate. If there are seven studies of which only one or two are of good quality, then the weight of evidence is limited.

A "strong" grade means a high level of confidence in the conclusion, so that it is considered very unlikely that new studies could change this conclusion. This grade corresponds to a body of evidence of very high quality, as assessed in the various areas (low risk of bias, consistency of results, directness, precision, generalisability).

A "moderate" grade means that the conclusion is based on a body of evidence of moderate quality and that it is possible that new studies could lead to a change in this conclusion.

A "limited" grade means that the conclusion is based on a body of evidence that includes few studies or studies of poor quality following assessment of the areas mentioned above, meaning that it is likely that new studies could lead to a change in this conclusion.

A "not assignable" grade means that no conclusion could be drawn either because of a lack of studies of sufficient quality, or because of the absence of a study.

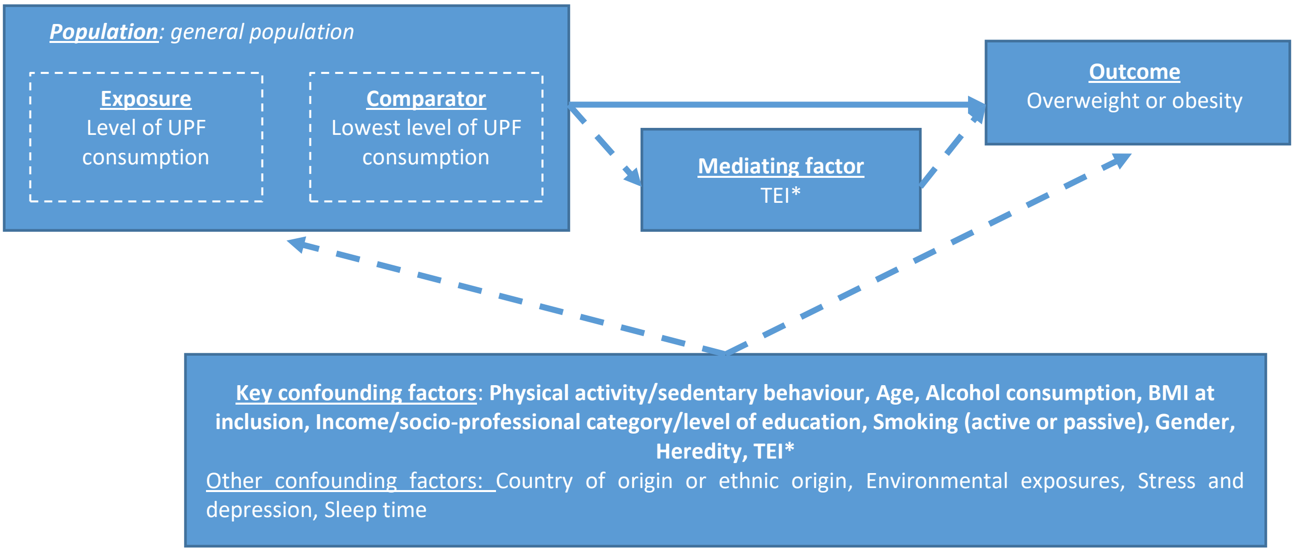
3.3.3. Results

The table extracting the data of interest from the selected publications is given in Annex 12.

3.3.3.1. Incidence of overweight and obesity

The systematic review selected two articles, published in 2020 and 2021, on the relationship between UPF consumption and the risk of overweight or obesity. The two articles were based on prospective cohort studies.

- **PECO**



* Since TEI (total energy intake) is potentially both a confounding factor and a mediating factor, analyses with and without adjustment for TEI are necessary in order to interpret the results correctly

- **Characteristics of the study populations**

The studies were conducted in France (one article) and in Europe[20] (one article). The articles concerned respectively the following cohort studies: the NutriNet-Santé cohort launched in 2009, with a median follow-up of 4 and 5 years, respectively, for overweight and obesity (Beslay *et al.* 2020), and the European EPIC cohort launched in 1991, with a median follow-up of 5.1 years (Cordova *et al.* 2021).

The number of participants was 95,344 in the French study and 348,748 in the European study. The mean age at the start of the study ranged from 43 years in the French study to 52.5 years for the first quintile of UPF consumption in the European study. In the French study, there were 7063 incident cases of overweight and 3066 incident cases of obesity. In the European study, the number of cases of overweight was 16,386 and the number of cases of obesity was 12,708. The ethnic origins of the participants were not reported in either of the two articles.

- **Exposure and comparator: different levels of UPF consumption**

In both studies, the concept of UPF was based on the definition given by the Nova classification. UPFs therefore corresponded to Nova Group 4.

[20] Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom

In the French study, food consumption data were collected by means of a series of three non-consecutive 24-hour recalls (2 weekdays and 1 weekend day) at inclusion and then every six months (an average of 5.7 24-hour recalls during the first 2 years).

In the European study, data collection varied from site to site between FFQs and food diaries, most of which were self-administered. A sensitivity analysis was carried out, comparing the results according to three scenarios: low, intermediate and high. The most likely scenario, given the foods available when collecting food consumption data in the study countries, corresponded to the intermediate scenario. For certain foods, to take account of the variability of supply, a different scenario may have been studied. For example, in countries such as the UK, bread is mainly produced industrially, whereas it used to be produced in artisanal bakeries. As a result, it was assigned to Nova Group 4 in the intermediate scenario, and to Nova Group 3 in the low scenario. In France, on the other hand, bread is mainly produced in artisanal bakeries, but sometimes also industrially. It was therefore assigned to Nova Group 3 in the intermediate scenario and to Nova Group 4 in the high scenario.

UPF consumption was expressed in grams of UPF per day per 100 g of total food (including beverages) and divided into quartiles in the French study. It was expressed in energy-adjusted grams of UPF per day and divided into quintiles in the European study.

In both studies, the comparator group consisted of individuals with low UPF consumption (1st quartile of consumption in the French study and 1st quintile in the European study).

- **Assessment of health outcomes**

The French study analysed the risk of developing overweight, based on a BMI greater than or equal to 25 kg/m^2, or obesity, based on a BMI greater than or equal to 30 kg/m^2. Weight and height were reported by participants using a validated questionnaire.

The European study analysed the risk of developing overweight (BMI greater than or equal to 25 kg/m^2) or obesity (BMI greater than or equal to 30 kg/m^2) in people of normal weight status at inclusion (BMI strictly less than 25 kg/m^2), and the risk of developing obesity in people who were overweight at inclusion (BMI between 25 and 30 kg/m^2). Weight and height were measured at inclusion in most sites and then reported during follow-up. The accuracy of the reported measurements was improved by predictive equations established on subjects for whom both measured and reported data were available.

- **Analysis of results**

The French study showed that higher consumption of UPFs was associated with a higher risk of overweight and a higher risk of obesity.

The European study showed that higher consumption of UPFs among people of normal weight status was associated with a higher risk of overweight or obesity. It also showed that higher consumption of UPFs among overweight people was associated with a higher risk of obesity.

In the French study, the adjustments made included TEI. In the European study, UPF consumption was adjusted for energy using the residual method, but TEI itself was not taken into account in the adjustments. As a result, the residual method was not properly applied (Thiebaut *et al.* 2004).

The French study carried out three additional analyses adjusting, respectively, for nutrients (fibre, sugars, sodium and saturated fatty acids), foods (fruit, vegetables, sweetened beverages) and scores reflecting proximity either to a Western dietary profile (high in fats and sauces, alcohol, meat, starchy foods) or to a healthy diet (high in fruit, vegetables, soups and broths, unsweetened carbonated soft drinks and wholegrain cereals, and low in sweetened carbonated soft drinks), considered by the authors to be associated with an increase or decrease in the risk of overweight or obesity. The associations were similar with these additional adjustments. These data suggest that the association between UPF consumption and the risk of overweight or obesity cannot be explained exclusively by the nutritional composition of the diet.

In the gender-stratified analysis, the association persisted for overweight in both men and women. On the other hand, there was no association for obesity in men, whereas it persisted in women.

- **Assessment of the weight of evidence**

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 11:

- **Bias control** (Table 10): Neither study took family history (heredity) into account as a confounding factor, and the European study did not adjust for TEI. Regarding the classification of exposures, in the European study, consumption was estimated based on FFQs. This data collection method is not very suitable for obtaining sufficient information to classify foods according to the Nova system (see 3.3.1.2). Thus, despite the stability of the results of the sensitivity analysis for the foods whose classification was uncertain, the risk of bias was serious. The risk of bias due to departures from intended exposures was moderate for the European study, as only one exposure measurement was carried out. The other areas were considered to be at low risk of bias in both studies.

Table 10: Grid assessing the risk of bias for the risk of overweight or obesity

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Beslay *et al.*	Serious	Low	Low	Low	Low	Low	Low
Cordova *et al.*	Serious	Low	Serious	Moderate	Low	Low	Low

- **Consistency of the results:** Both studies reported that higher consumption of UPFs was associated with a higher risk of overweight and a higher risk of obesity.
- **Directness:** The populations, exposure, comparator and outcomes were directly related to the systematic review question for both studies.
- **Precision:** Calculations of statistical power were not reported in the studies, but these studies concerned data from a cohort with a high number of cases of overweight and obesity. The precision of the estimates was generally graded as strong, as determined based on the size of the confidence interval.
- **Generalisability:** One of the studies focused on the French population and the other one also included French data. The results could therefore be generalised to the French population.

Table 11: Summary of criteria assessing the weight of evidence for the risk of overweight or obesity

	Bias control	Consistency of the results	Directness	Precision	Generalisability
Overweight or obesity	Limited	Strong	Strong	Strong	Strong

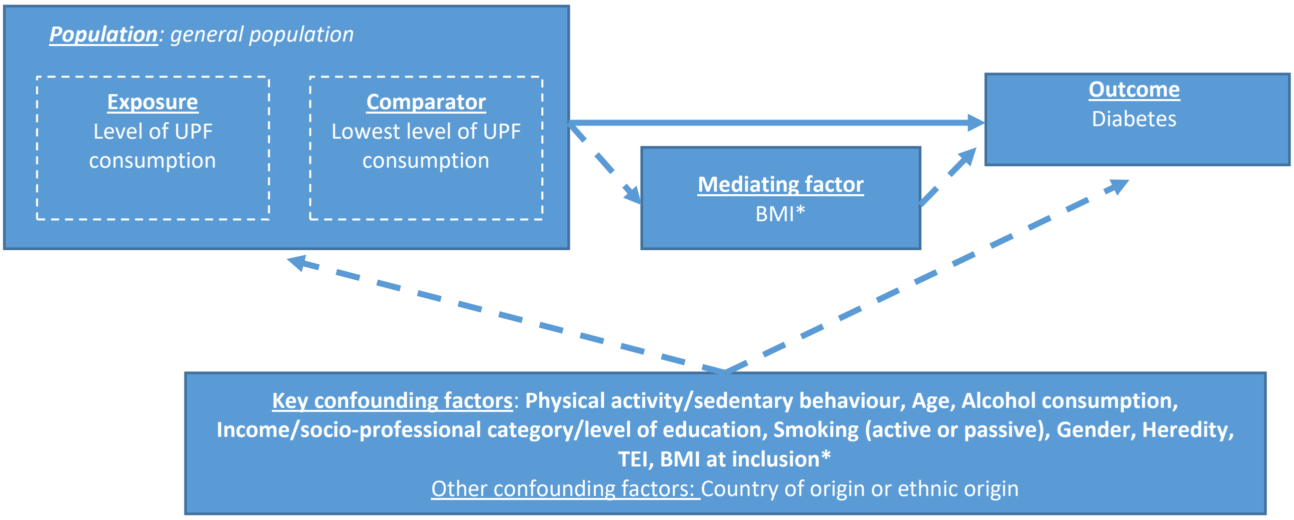
Conclusion

With a limited weight of evidence, the CES concludes that higher consumption of Nova Group 4 foods, compared with lower consumption, is associated with a higher risk of overweight and a higher risk of obesity.

3.3.3.2. Incidence of diabetes

The systematic review selected two articles, published in 2020 and 2023, on the relationship between UPF consumption and the risk of diabetes. The two articles were based on prospective cohort studies.

PECO



* Since BMI is potentially both a confounding factor and a mediating factor, analyses with and without adjustment for BMI are necessary in order to interpret the results correctly

Characteristics of the study populations

The studies were conducted in France (one article) and the United States (one article). The articles concerned, respectively, the NutriNet-Santé cohort launched in 2009, with a median follow-up of 6 years (Srour *et al.* 2020), and three American cohorts: the Nurses Health Study (NHS) I launched in 1984, the NHS II launched in 1991 and the Health Professional Follow up Study (HPFS) launched in 1986 (Chen *et al.* 2023). The median or mean length of follow-up for the three American cohorts was not reported in the article.

The number of participants was 104,707 in the French study and 198,636 in the American study combining all three cohorts. The mean age at the start of the study was 43 years in the French study and was not indicated in the American study. There were 821 incident cases of diabetes in the French study and 19,503 in the American study. The ethnic origins of the participants were not reported in either of the two articles.

■ **Exposure and comparator: different levels of UPF consumption**

In both studies, the concept of UPF was based on the definition given by the Nova classification. UPFs therefore corresponded to Nova Group 4.

Food consumption data were collected using frequency questionnaires completed every two to four years in the American study, whereas they were collected by means of a series of three non-consecutive 24-hour recalls (2 weekdays and 1 weekend day) at inclusion and then every six months (an average of 5.7 24-hour recalls during the first 2 years) in the French study.

In the American study, nine of the 130 foods in the frequency questionnaire had a classification regarded as uncertain by the authors. They initially considered that these foods were not UPFs and then carried out a sensitivity analysis considering them as such.

UPF consumption was expressed in grams of UPF per 100 g of total food (including beverages) and divided into quartiles in the French study, whereas in the American study it was expressed in number of servings of UPF per day and divided into quintiles.

In both studies, the comparator group consisted of individuals with low UPF consumption (1st quartile or 1st quintile of consumption).

■ **Assessment of health outcomes**

In the French study, data on cases of type 2 diabetes and use of diabetes medication were collected by means of health questionnaires every three months. The information was also cross-referenced with the Sniiram database[21] for reimbursement of treatments and consultations, and the CépiDC database[22] for deaths.

In the American study, cases of type 2 diabetes were reported in self-administered questionnaires every two years, and were confirmed by completing a specific self-questionnaire on symptoms, diagnostic tests and treatments for type 2 diabetes. This self-reporting was then validated or not according to the criteria of the National Diabetes Data Groups before 1998, and then the criteria of the American Diabetes Association.

■ **Analysis of results**

Both studies showed that higher consumption of UPFs was associated with a higher risk of type 2 diabetes.

In the French study, the association persisted after adjustment for an overall diet quality score based on the FSA-Nutrient Profiling System (FSAm-NPS DI), for different nutrients (fibre, sugars, sodium, saturated fatty acids) or different foods (red and processed meats, sweetened beverages, fruit and vegetables, wholegrain cereals, nuts and yoghurt) or for scores reflecting proximity to a Western dietary profile (high in fats and sauces, alcohol, meat, starchy foods) or a healthy nutritional diet (high in fruit, vegetables, soups and broths, unsweetened carbonated soft drinks and wholegrain cereals, and low in sweetened carbonated soft drinks) combined with the overall quality score, considered by the authors to be associated with the diabetes risk. Whether or not an adjustment was made for BMI did not change the association. In the gender-stratified analysis there was no association for men, unlike for women.

In the American study, the association persisted whether or not the nine foods whose classification was uncertain were regarded as UPFs. The way in which the UPF measurement was expressed did not change the association. Whether or not an adjustment was made for BMI did not change the association. The association also persisted when the TEI was replaced in the adjustments by the quantity (in grams) of non-UPF foods (i.e. fruit, vegetables, nuts,

[21] French health insurance scheme's national inter-regime information system
[22] Epidemiology centre on medical causes of death

legumes, tea, coffee, wholegrain cereals, red meat, fish and poultry). Furthermore, a stratified analysis based on a nutritional score (AHEI[23] score) showed no significant interaction.

Assessment of the weight of evidence

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 13:

- **Bias control** (Table 12): The risk of bias due to confounding factors was moderate in both studies because, as these were observational studies, there were potentially residual confounding factors, but both studies took adequate account of all the key confounding factors. With regard to the bias associated with the classification of exposures, consumption was estimated based on FFQs for the American study. This data collection method is not very suitable for obtaining sufficient information to classify foods according to the Nova system (see 3.3.1.2). Thus, despite the stability of the results of the sensitivity analysis for the foods whose classification was uncertain, the risk of bias was serious. In the American study, no information was provided on missing data, so the associated risk of bias was moderate. The risk of bias due to the measurement of outcomes was moderate for the American study because it was based on self-reporting.

Table 12: Grid assessing the risk of bias for the risk of type 2 diabetes

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Srour *et al.*	Moderate	Low	Low	Low	Low	Low	Low
Chen *et al.*	Moderate	Low	Serious	Low	Moderate	Moderate	Low

- **Consistency of the results:** Both studies reported that higher consumption of UPFs was associated with a higher risk of type 2 diabetes.
- **Directness:** The populations, exposure, comparator and outcomes were directly related to the systematic review question.
- **Precision:** Calculations of statistical power were not reported in the studies, but the majority of these studies concerned data from a cohort with a high number of cases of diabetes. The precision of the estimates was generally graded as strong, as determined based on the size of the confidence interval.
- **Generalisability:** The population in the French study was drawn from the population living in France. The population in the American study was less comparable because it was made up exclusively of healthcare professionals. In addition, food consumption was further removed from that in France because the study period was a long time ago and American dietary habits are different. Generalisability was therefore deemed to be moderate.

Table 13: Summary of criteria assessing the weight of evidence for the risk of type 2 diabetes

	Bias control	Consistency of the results	Directness	Precision	Generalisability
Type 2 diabetes	Moderate	Strong	Strong	Strong	Moderate

[23] AHEI: Alternative Healthy Eating Index

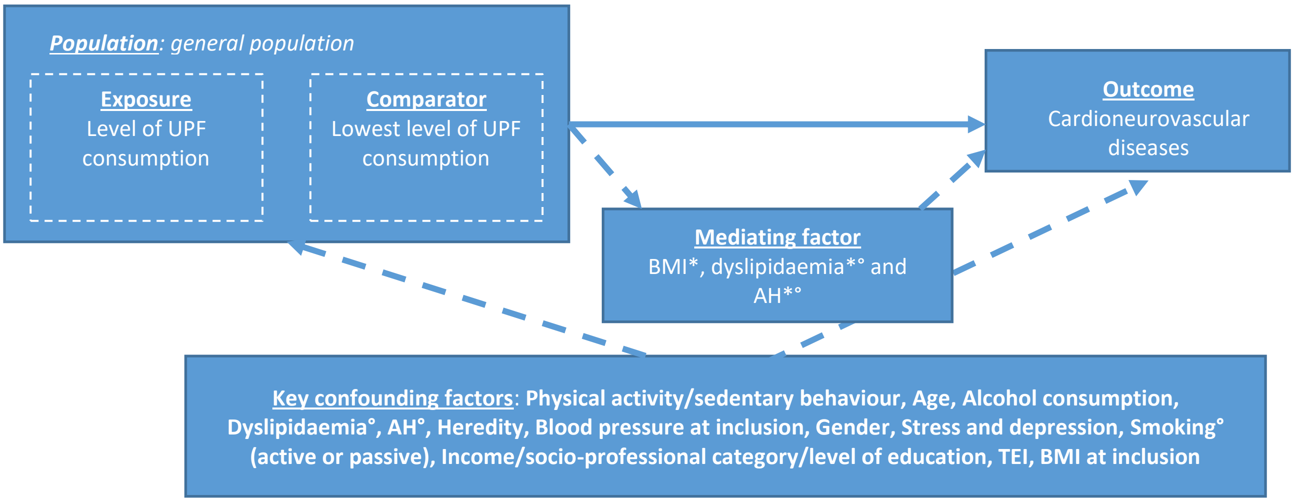
■ Conclusion

With a limited weight of evidence, the CES concludes that higher consumption of Nova Group 4 foods, compared with lower consumption, is associated with a higher risk of type 2 diabetes.

3.3.3.3. Incidence of cardioneurovascular diseases

The systematic review selected two articles, published in 2019 and 2022, on the relationship between UPF consumption and the risk of cardioneurovascular diseases (CNVDs), i.e. the risk of stroke, myocardial infarction, other ischaemic cardiovascular events, heart failure, atrial fibrillation, arterial hypertension (AH) and death due to CNVDs. The two articles were based on prospective cohort studies.

■ PECO



* Since these factors are potentially both confounding and mediating factors, analyses with and without adjustment for these factors are necessary in order to interpret the results correctly

° These factors do not concern the AH outcome.

■ Characteristics of the study populations

The studies were conducted in France (one article) and China (one article). The articles concerned, respectively, the following cohort studies: the NutriNet-Santé cohort launched in 2009, with a median follow-up of 5.2 years (Srour *et al.* 2019), and the China Health and Nutrition Survey cohort launched in 1997 with a median follow-up of 9.5 years (Li and Shi 2022).

The number of participants was 105,159 in the French study and 15,054 in the Chinese study. The mean age at the start of the study was 43 and 40 years, respectively. The total number of incident cases of CNVD or death due to CNVD was 1409 (including 106 cases of myocardial infarction, 155 cases of stroke, 674 cases of transient ischaemic attack, 74 cases of acute coronary syndrome and 485 cases of angioplasty) in the French study. There were 4329 cases of AH in the Chinese study. The ethnic origins of the participants were not reported in either of the two articles.

■ Exposure and comparator: different levels of UPF consumption

In both studies, the concept of UPF was based on the definition given by the Nova classification. UPFs therefore corresponded to Nova Group 4.

In the French study, food consumption data were collected by means of a series of three non-consecutive 24-hour recalls (2 weekdays and 1 weekend day) at inclusion and then every six months (an average of 5.7 24-hour recalls during the first 2 years). In the Chinese study, consumption data were collected by means of a series of 24-hour recalls over three consecutive days, carried out face-to-face during the various follow-ups in 1997, 2000, 2004, 2006 and 2009.

UPF intake was expressed in grams of UPF per 100 g of total food (including beverages) in the French study (average of 24 h recalls available during the first 2 years) and in g/day in the Chinese study (average of 24 h recalls). UPF consumption was divided into quartiles in the French study, whereas in the Chinese study it was divided into consumption categories: non-consumers (0 g/d), then those consuming 1-49 g/d, 50-99 g/d and ≥ 100 g/d.

In the French study, the comparator group consisted of individuals with low UPF consumption (1st quartile of consumption), whereas in the Chinese study, the comparator group consisted of non-UPF consumers.

- **Assessment of health outcomes**

The French study reported the risk of developing CNVD of coronary origin (myocardial infarction, acute coronary syndrome and angioplasty) or cerebrovascular origin (stroke, transient ischaemic attack). Health events and treatments were recorded by means of a health questionnaire every three months and at any time. The participants were asked to provide their medical data (ECGs, diagnoses, radiology reports, etc.) and, if necessary, the team's doctors contacted the participants' doctors to obtain more information. A panel of doctors analysed the participants' medical data to validate the cardiovascular events. In addition, the information was cross-referenced with the Sniiram database (reimbursements, treatments and consultations) and the CépiDC database (deaths).

In the Chinese study, blood pressure was measured by an investigator and AH was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, or having known AH.

- **Analysis of results**

The French study showed that higher consumption of UPFs was associated with a higher risk of coronary and cerebrovascular CNVD (considered separately or together).

The Chinese study showed that high consumption of UPFs (≥ 100 g/d), compared with no consumption, was associated with a higher risk of AH.

In both studies, the adjustments made included TEI. The authors also carried out additional analyses adjusting for nutrients (sodium for both studies and potassium for the Chinese study) and foods that are risk factors for CNVD. The French study also adjusted for a score reflecting proximity to a healthy nutritional diet (high in fruit, vegetables, soups and broths, unsweetened carbonated soft drinks and wholegrain cereals, and low in sweetened carbonated soft drinks). The associations were similar with these additional adjustments. These results suggest that the associations between UPF consumption and the risk of CNVD or AH cannot be explained exclusively by the nutritional composition of the diet. In both studies, the gender-stratified analysis showed that the associations persisted in both men and women.

In the French study, the association remained robust across the various sensitivity analyses, whether the results were considered with or without adjustment for BMI.

- **Assessment of the weight of evidence**

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 15:

- **Bias control** (Table 14): The risk of bias due to confounding factors was serious in both studies, as stress and depression were not included as confounding factors in either study. In addition, the Chinese study examining AH did not adjust for blood pressure at inclusion, nor for heredity. Regarding the other types of bias, there was considered to be a low risk of bias in both studies.

Table 14: Grid assessing the risk of bias for the risk of cardioneurovascular diseases

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Srour *et al.*, 2019	Serious	Low	Low	Low	Low	Low	Low
Li *et al.*, 2022	Serious	Low	Low	Low	Low	Low	Low

- **Consistency of the results:** Both studies reported that higher UPF consumption was associated with a higher risk of CNVDs (coronary and cerebrovascular diseases in one study and AH in the other).
- **Directness:** The populations, exposure, comparator and outcomes were directly related to the systematic review question for both studies.
- **Precision:** Calculations of statistical power were not reported in the studies, but these studies concerned data from a cohort with a high number of cases of coronary and cerebrovascular diseases and AH. The precision of the estimates was generally graded as strong, as determined based on the size of the confidence interval.
- **Generalisability:** the population and exposure (consumption levels and types of UPFs) in the Chinese study were probably not very comparable to those of the population living in France, whereas the population in the French study was taken from the population living in France. Generalisability was deemed to be moderate.

Table 15: Summary of criteria assessing the weight of evidence for the risk of cardioneurovascular diseases

	Bias control	Consistency of the results	Directness	Precision	Generalisability
CNVDs	Limited	Strong	Strong	Strong	Moderate

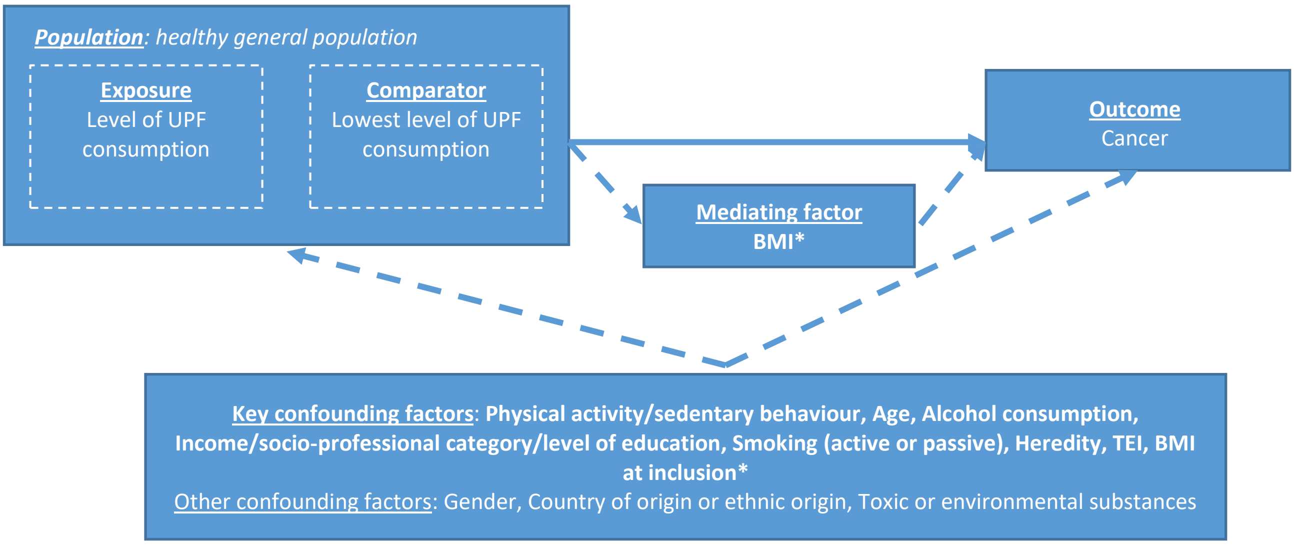
■ **Conclusion**

With a limited weight of evidence, the CES concludes that higher consumption of Nova Group 4 foods, compared with lower consumption, is associated with a higher risk of cardioneurovascular diseases.

3.3.3.4. Incidence of cancer

The systematic review identified three scientific articles, published between 2018 and 2023, on the relationship between UPF consumption and the risk of cancer. All the articles were based on prospective cohort studies.

PECO



* Since BMI is potentially both a confounding factor and a mediating factor, analyses with and without adjustment for BMI are necessary in order to interpret the results correctly

Characteristics of the study populations

The studies were conducted in France (one article), Europe[24] (one article) and the United States (one article). The articles concerned the following cohort studies: the NutriNet-Santé cohort launched in 2009, with a median follow-up of 5 years (Fiolet *et al.* 2018), the EPIC cohort launched in 1991, with a median follow-up of 14 years (Kliemann *et al.* 2023) and three American cohorts: the Nurses Health Study (NHS) I launched in 1984, the NHS II launched in 1991 and the Health Professional Follow up Study (HPFS) launched in 1986 (Wang *et al.* 2022), for which the median or mean length of follow-up is unknown.

The number of participants was 104,980 in the French study, 450,111 in the European study and 206,248 in the American study (the female and male populations were studied separately). The mean age at the start of the study ranged from 43 years in the French study to 55 years for the first quintile of UPF consumption in the American study.

Exposure and comparator: different levels of UPF consumption

In all three studies, the concept of UPF was based on the definition given by the Nova classification. UPFs therefore corresponded to Nova Group 4.

In the French study, food consumption data were collected by means of a series of three non-consecutive 24-hour recalls (2 weekdays and 1 weekend day) at inclusion and then every six months (an average of 5.7 24-hour recalls during the first 2 years). In the American study, consumption data were collected by FFQs. In the European study, data collection varied from site to site between FFQs and food diaries, most of which were self-administered.

In the European study, a sensitivity analysis was carried out, comparing the results according to three scenarios: low, intermediate and high. The most likely scenario, given the foods available when collecting food consumption data in the study countries, corresponded to the intermediate scenario. For certain foods, to take account of the variability of supply, a different scenario may have been studied. For example, in countries such as the UK, bread is mainly produced industrially, whereas it used to be produced in artisanal bakeries. As a result, it was assigned to Nova Group 4 in the intermediate scenario, and to Nova Group 3 in the low

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[24] Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom

scenario. In France, on the other hand, bread is mainly produced in artisanal bakeries, but sometimes also industrially. It was therefore assigned to Nova Group 3 in the intermediate scenario and to Nova Group 4 in the high scenario.

In the American study, nine foods had a classification regarded as uncertain by the authors. They initially considered that these foods were not UPFs and then carried out a sensitivity analysis considering them as such.

In the French and European studies, UPF consumption was expressed in grams of UPF per day per 100g of total food (including beverages). It was divided into quartiles.

In the American study, UPF consumption was expressed in number of servings of UPF per day (cumulative average of exposures during follow-up). It was divided into quintiles.

In all three studies, the comparator group consisted of individuals with low UPF consumption (lower quartiles or quintiles).

- **Assessment of health outcomes**

In the French study, data on the reporting of a cancer were collected by the annual health questionnaire or a questionnaire listing health events every three months. For each reported case, the data were validated against the medical reports and cross-referenced with the Sniiram database[25] for reimbursement of treatments and consultations, and the CépiDC database[26] for deaths.

In the European study, the collection of data on cancer cases was based on the use of cancer registries or, during follow-up, on different sources: cancer and disease centres, health insurance records or the active follow-up of participants.

In the American study, data on cases of colorectal cancer (all sites combined, proximal, distal and rectal) were collected on the basis of self-reported information in follow-up questionnaires every two years and confirmed by medical diagnosis (the doctors analysing the cases were unaware of the exposure data), particularly with regard to location. The data were cross-referenced with the National Death Index and death certificates to add the incidence of colorectal cancer resulting in death and whose diagnosis had not been reported in the follow-up questionnaires.

The cancer sites examined by the selected studies are shown in Table 16.

Table 16: Cancer sites examined by the selected studies

	French study (Fiolet *et al.,* 2018)	European study (Kliemann *et al.,* 2023)*	American study (Wang *et al.,* 2022)
Cancer, all sites combined	x	x	
Colorectal cancer	x	x (colon only)	x
Prostate cancer	x		
Breast cancer	x		
Head and neck cancer		x	
Hepatocellular carcinoma		x	

[25] French health insurance scheme's national inter-regime information system
[26] Epidemiology centre on medical causes of death

* Numerous results were presented in the tables in the article, but only those whose statistical model was valid in the substitution analyses have been included.

3.3.3.4.1. UPFs and cancer risk for all sites

Only the French and European studies analysed the risk of cancer for all sites combined.

■ **Incidence**

The total number of cancer cases was 2228 in the French study (Fiolet *et al.* 2018) and 47,573 in the European study[27] (Kliemann *et al.* 2023). The ethnic origins of the participants were not reported in either of the two articles.

■ **Analysis of results**

The French study showed that higher consumption of UPFs was associated with a higher risk of cancer for all sites combined. The association remained significant after adjustment for sodium, fat and carbohydrate intakes, whether or not combined with a score reflecting proximity to a Western dietary profile (high in fats and sauces, alcohol, meat, starchy foods). The gender-stratified analysis showed that the association persisted in both men and women.

The European study showed that higher consumption of UPFs, when analysed by quartiles, was also associated with a higher risk of cancer for all sites combined (including when a sensitivity analysis was carried out on the food classification), even though this association was not found in the continuous analysis and in the different sensitivity analyses.

■ **Assessment of the weight of evidence**

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 18:

- **Bias control** (Table 17): The risk of bias due to confounding factors was serious in the European study due to the absence of adjustment for family history of cancer. It was moderate in the French study because, as this was an observational study, there were potentially residual confounding factors, but it took adequate account of all the key confounding factors. With regard to the bias associated with the classification of exposures, consumption was estimated based on FFQs for the European study. This data collection method is not very suitable for obtaining sufficient information to classify foods according to the Nova system (see 3.3.1.2). Thus, despite the stability of the results of the sensitivity analysis for the foods whose classification was uncertain, the risk of bias was serious. Furthermore, in the European study, there were probably changes in exposure status (long follow-up) and adjustment measures and techniques were not used to correct this problem, so the risk of bias due to departures from intended exposures was moderate. Lastly, in the European study, the amount of missing data varied according to exposure, but remained low, so the risk of bias due to missing data was moderate.

Table 17: Grid assessing the risk of bias for the cancer risk for all sites combined

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Fiolet	Moderate	Low	Low	Low	Low	Low	Low
Kliemann	Serious	Low	Serious	Moderate	Moderate	Low	Low

[27] Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom

- **Consistency of the results:** Both studies reported that higher consumption of UPFs was associated with a higher risk of cancer for all sites combined.
- **Directness:** The populations, exposure, comparator and outcomes were directly related to the systematic review question for both studies.
- **Precision:** Calculations of statistical power were not reported in the studies, but these studies concerned data from a cohort with a high number of cancer cases. The precision of the estimates was generally graded as strong, as determined based on the size of the confidence interval.
- **Generalisability:** One of the studies focused on the French population and the other one also included French data. The results could therefore be generalised to the French population.

Table 18: Summary of criteria assessing the weight of evidence for the cancer risk, all sites combined

	Bias control	Consistency of the results	Directness	Precision	Generalisability
Cancer, all sites combined	Moderate	Strong	Strong	Strong	Strong

■ Conclusion

With a limited weight of evidence, the CES concludes that higher consumption of Nova Group 4 foods, compared with lower consumption, is associated with a higher risk of cancer for all sites combined.

3.3.3.4.2. UPFs and risk of colorectal cancer

The French (Fiolet *et al.* 2018), European[28] (Kliemann *et al.* 2023) and American (Wang *et al.* 2022) studies analysed the risk of colorectal cancer.

■ Incidence

The total number of cases of colorectal cancer was 153 in the French study and 3216 (1294 in men and 1922 in women) in the American study. The number of cases of colon cancer in the European study was 3993. The participants' ethnic origins were only reported in the American study.

■ Analysis of results

The French study reported no association between UPF consumption and the incidence of colorectal cancer. Sensitivity analyses did not change the main results.

In the European study, the main analysis reported no association between UPF consumption and colon cancer. However, a sensitivity analysis on the "high" scenario reported that higher UPF consumption was associated with a higher risk of colon cancer.

The American study showed that high consumption of UPFs, compared with lower consumption, was associated with a higher risk of colorectal cancer, for all sites combined, in men only. This association did not persist after adjustments for foods and nutrients whose consumption is considered by the authors to be associated with an increased or reduced risk

[28] Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom

of cancer (consumption of processed meats, fruit, vegetables, wholegrain cereals, calcium, vitamin D and folates). On the other hand, it was stable after adjustment for a score reflecting proximity to a Western dietary profile (high in fats and sauces, alcohol, meat, starchy foods) or a healthy diet (high in fruit, vegetables, soups and broths, unsweetened carbonated soft drinks and wholegrain cereals, and low in sweetened carbonated soft drinks). This association was also stable after a further adjustment for BMI. By examining the incidence of colorectal cancer for each site, the study showed that higher consumption of UPFs was associated with a higher risk of distal colon cancer, and this association persisted after adjustments for BMI, dietary profiles or the foods and nutrients mentioned above. However, it reported no association with the incidence of rectal or proximal colon cancer. The associations with colorectal cancer and distal colon cancer persisted in sensitivity analyses on foods whose classification was uncertain and according to the way in which UPF consumption was expressed.

■ **Assessment of the weight of evidence**

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 20:

- **Bias control** (Table 19): The risk of bias due to confounding factors was serious in the European study due to the absence of adjustment for family history (heredity). It was moderate in the French and American studies because, as these were observational studies, there were potentially residual confounding factors, but they took adequate account of all the key confounding factors. With regard to the bias associated with the classification of exposures, consumption was estimated based on FFQs for the American study. This data collection method is not very suitable for obtaining sufficient information to classify foods according to the Nova system (see 3.3.1.2). Thus, despite the stability of the results of the sensitivity analysis for the foods whose classification was uncertain, the risk of bias was serious. On the other hand, in the European study, the risk of bias due to the classification of exposures was considered to be critical, as the sensitivity analysis on the classification of certain foods in the different Nova groups revealed different results in the associations studied. Furthermore, in the European study, there were probably changes in exposure status (long follow-up) and no adjustment measures or techniques were used to correct this problem, so the risk of bias due to departures from intended exposures was moderate. Lastly, in the European study, the amount of missing data varied according to exposure, but remained low, so the risk of bias due to missing data was moderate.

Table 19: Grid assessing the risk of bias for the colorectal cancer risk

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Fiolet	Moderate	Low	Low	Low	Low	Low	Low
Kliemann	Serious	Low	Critical	Moderate	Moderate	Low	Low
Wang	Moderate	Low	Serious	Low	Low	Low	Low

- **Consistency of the results:** The French and European studies did not report any association. In contrast, the American study reported that higher consumption of UPFs was associated, in men only, with a higher risk of colorectal cancer for all sites combined, and of distal colon cancer. The consistency of the results was deemed to be moderate.
- **Directness:** The populations, exposure, comparator and outcomes were directly related to the systematic review question.

- **Precision:** Calculations of statistical power were not reported in the European and American studies, but these studies concerned data from a cohort with a high number of cancer cases. The precision of the estimates was generally graded as strong, as determined based on the size of the confidence interval.
- **Generalisability:** One of the studies focused on the French population and the other one also included French data. On the other hand, the American study population was less similar to the French population because it was made up exclusively of healthcare professionals, and in addition food consumption was further removed (the study period was a long time ago and American dietary habits are different). Generalisability was therefore deemed to be moderate.

Table 20: Summary of criteria assessing the weight of evidence for the colorectal cancer risk

	Bias control	Consistency of the results	Directness	Precision	Generalisability
Colorectal cancer	Limited	Moderate	Strong	Strong	Moderate

Conclusion

With a limited weight of evidence, the CES concludes that higher consumption of Nova Group 4 foods, compared with lower consumption, is associated with a higher risk of colorectal cancer (all sites combined and distal colon) in men only.

3.3.3.4.3. UPFs and risk of prostate cancer

Only the French study analysed the risk of prostate cancer (Fiolet *et al.* 2018).

Incidence

The number of cancer cases was 281. The ethnic origins of the participants were not reported.

Analysis of results

The study reported no association between UPF consumption and the incidence of prostate cancer. This result was stable, regardless of the adjustments made (sodium, fat and carbohydrate intakes, whether or not combined with a score reflecting proximity to a Western dietary profile).

Assessment of the weight of evidence

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 22:

- **Bias control** (Table 21): The risk of bias due to confounding factors was moderate because, as this was an observational study, there were potentially residual confounding factors, but it took adequate account of all the key confounding factors.

Table 21: Grid assessing the risk of bias for the prostate cancer risk

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Fiolet *et al.*	Moderate	Low	Low	Low	Low	Low	Low

- **Consistency of the results:** The assessment was carried out by a single study. The consistency of the results was therefore not assignable.
- **Directness:** The populations, exposure, comparator and outcomes were directly related to the systematic review question.
- **Precision:** Calculations of statistical power were not reported, but the study concerned data from a cohort with a high number of new cases of prostate cancer. The precision of the estimates was graded as strong, as determined based on the size of the confidence interval.
- **Generalisability:** The study population was drawn from the population living in France, so the results could be generalised to the French population.

Table 22: Summary of criteria assessing the weight of evidence for the prostate cancer risk

	Bias control	Consistency of the results	Directness	Precision	Generalisability
Prostate cancer	Moderate	Not assignable	Strong	Strong	Strong

■ **Conclusion**

With a limited weight of evidence, the CES concludes that no association has been demonstrated between the level of consumption of Nova Group 4 foods and prostate cancer.

3.3.3.4.4. UPFs and risk of breast cancer

Only the French study analysed the risk of breast cancer (Fiolet *et al.* 2018).

■ **Incidence**

In the French study, 739 cases of breast cancer of all menopausal statuses were reported, 264 in non-menopausal women and 475 in menopausal women (menopausal status was not stratified at inclusion but over time according to this status).

The ethnic origins of the participants were not reported.

■ **Analysis of results**

The French study showed that higher consumption of UPFs was associated with a higher risk of breast cancer. The association persisted after additional adjustments for sodium, fat and carbohydrate intakes, which the authors consider to be associated with an increased risk of cancer, and a score reflecting proximity to a Western dietary profile (high in fats and sauces, alcohol, meat and starchy foods).

The association persisted in the sub-sample of menopausal women but not in the sub-sample of non-menopausal women.

■ **Assessment of the weight of evidence**

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 24:

- **Bias control (Table 23)**: The risk of bias due to confounding factors was moderate because, as the assessment was based on an observational study, there were potentially residual confounding factors, but it took adequate account of all the key confounding factors.

Table 23: Grid assessing the risk of bias for the breast cancer risk

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Fiolet *et al.*	Moderate	Low	Low	Low	Low	Low	Low

- **Consistency of the results:** The assessment was carried out by a single study, and the consistency was therefore not assignable.
- **Directness:** The populations, exposure, comparator and outcomes were directly related to the systematic review question.
- **Precision:** Calculations of statistical power were not reported, but the study concerned data from a cohort with a high number of new cases of breast cancer. The precision of the estimates was generally graded as strong, as determined based on the size of the confidence interval.
- **Generalisability:** The study population was drawn from the population living in France, so the results could be generalised to the French population.

Table 24: Summary of criteria assessing the weight of evidence for the breast cancer risk

	Bias control	Consistency of the results	Directness	Precision	Generalisability
Breast cancer	Moderate	Not assignable	Strong	Strong	Strong

■ **Conclusion**

With a limited weight of evidence, the CES concludes that higher consumption of Nova Group 4 foods, compared with lower consumption, is associated with a higher risk of breast cancer, both in women overall and in menopausal women.

3.3.3.4.5. UPFs and risk of head and neck cancer

Only the European study[29] analysed the risk of head and neck cancer (Kliemann *et al.* 2023) corresponding to cancers of the ENT sphere (sinuses, pharynx, larynx, salivary glands).

■ **Incidence**

In this study, the number of cases of head and neck cancer was 821.

The ethnic origins of the participants were not reported.

■ **Analysis of results**

The study showed that higher consumption of UPFs was associated with a higher risk of head and neck cancer.

This association persisted in most of the sensitivity analyses, except in the one on the way in which UPF consumption was expressed as a percentage of daily energy intake.

[29] Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom

Assessment of the weight of evidence

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 26:

- **Bias control** (Table 25): The risk of confounding bias was serious due to the absence of adjustment for family history (heredity). With regard to the bias associated with the classification of exposures, consumption was estimated based on FFQs. This data collection method is not very suitable for obtaining sufficient information to classify foods according to the Nova system (see 3.3.1.2). Thus, despite the stability of the results of the sensitivity analysis for the foods whose classification was uncertain, the risk of bias was serious. Furthermore, there were probably changes in exposure status (long follow-up) and no adjustment measures or techniques were used to correct this problem, so the risk of bias due to departures from intended exposures was moderate. Lastly, the amount of missing data varied according to exposure, but remained low, so the risk of bias due to missing data was moderate.

Table 25: Grid assessing the risk of bias for the head and neck cancer risk

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Kliemann *et al.*	Serious	Low	Serious	Moderate	Moderate	Low	Low

- **Consistency of the results:** The assessment was carried out by a single study. The consistency of the results was therefore not assignable.
- **Directness:** The population, exposure, comparator and outcomes were directly related to the systematic review question.
- **Precision:** Calculations of statistical power were not reported, but the study concerned data from a cohort with a high number of cases of head and neck cancer. The precision of the estimates was generally graded as strong, as determined based on the size of the confidence interval.
- **Generalisability:** The European study population was comparable to the population living in France.

Table 26: Summary of criteria assessing the weight of evidence for the head and neck cancer risk

	Bias control	Consistency of the results	Directness	Precision	Generalisability
Head and neck cancer	Limited	Not assignable	Strong	Strong	Strong

Conclusion

The CES concludes that there are not enough good quality studies to assess the link between UPF consumption and the risk of head and neck cancer. The weight of evidence was therefore not assignable.

3.3.3.4.6. UPFs and risk of hepatocellular carcinoma

Only the European study analysed the risk of hepatocellular carcinoma (Kliemann *et al.* 2023).

- **Incidence**

In this study, the number of cases of hepatocellular carcinoma was 215.

The ethnic origins of the participants were not reported.

- **Analysis of results**

The study reported no association between UPF consumption and the incidence of hepatocellular carcinoma. However, a sensitivity analysis that did not take account of alcoholic beverages reported that higher consumption of UPFs was associated with a higher risk of hepatocellular carcinoma.

- **Assessment of the weight of evidence**

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 28:

- **Bias control** (Table 27): The risk of confounding bias was serious in this study due to the absence of adjustment for family history (heredity). The risk of bias due to the classification of exposures was also serious, as consumption was estimated based on FFQs. This data collection method is not very suitable for obtaining sufficient information to classify foods according to the Nova system (see 3.3.1.2). Thus, despite the stability of the results of the sensitivity analysis for the foods whose classification was uncertain, the risk of bias was serious. Furthermore, there were probably changes in exposure status (long follow-up) and no adjustment measures or techniques were used to correct this problem, so the risk of bias due to departures from intended exposures was moderate. Lastly, the amount of missing data varied according to exposure, but remained low, so the risk of bias due to missing data was moderate.

Table 27: Grid assessing the risk of bias for the hepatocellular carcinoma risk

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Kliemann *et al.*	Serious	Low	Serious	Moderate	Moderate	Low	Low

- **Consistency of the results:** The assessment was carried out by a single study. The consistency of the results was therefore not assignable.
- **Directness:** The populations, exposure, comparator and outcomes were directly related to the systematic review question.
- **Precision:** The precision of the estimates was generally moderate, as determined based on the size of the confidence interval.
- **Generalisability:** The European study population was comparable to the population living in France.

Table 28: Summary of criteria assessing the weight of evidence for the hepatocellular carcinoma risk

	Bias control	Consistency of the results	Directness	Precision	Generalisability
Hepatocellular carcinoma	Limited	Not assignable	Strong	Moderate	Strong

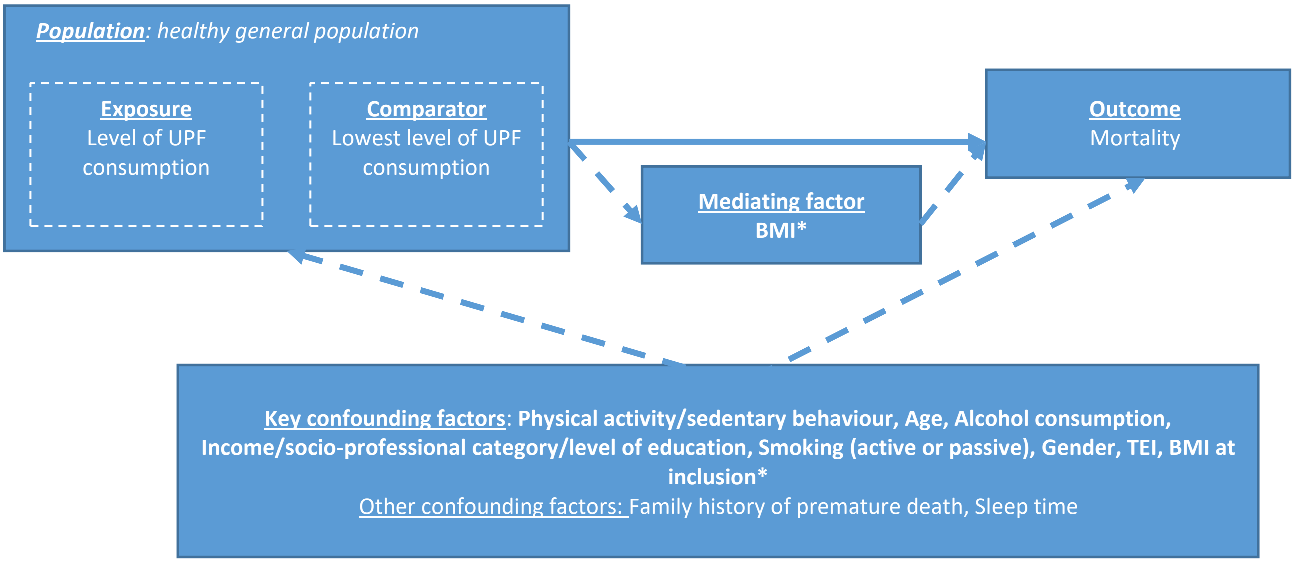
Conclusion

The CES concludes that there are not enough good quality studies to assess the link between UPF consumption and the risk of hepatocellular carcinoma. The weight of evidence was therefore not assignable.

3.3.3.5. Mortality

The systematic review identified one prospective cohort study, published in 2019, on the relationship between UPF consumption and the risk of mortality.

PECO



* Since BMI is potentially both a confounding factor and a mediating factor, analyses with and without adjustment for BMI are necessary in order to interpret the results correctly

Characteristics of the study population

The study was conducted in France using the NutriNet-Santé cohort, which was launched in 2009 and had a median follow-up of 6 to 7 years (Schnabel *et al.* 2019).

The number of participants was 44,551 (only those over 45 years of age were included in the analysis). The mean age at the start of the study was 57 years. The number of deaths was 602. The ethnic origins of the participants were not reported.

Exposure and comparator: high UPF consumption and lower UPF consumption

The concept of UPF was based on the definition given by the Nova classification. UPFs therefore corresponded to Nova Group 4.

Food consumption data were collected by means of a series of three non-consecutive 24-hour recalls (2 weekdays and 1 weekend day) at inclusion and then every six months (an average of 5.7 24-hour recalls during the first 2 years).

UPF consumption was expressed in grams of UPF per 100 g of total food (including beverages) and divided into quartiles.

The comparator group consisted of individuals consuming the least UPF (1st quartile of consumption).

- **Assessment of health outcomes**

The study covered deaths from all causes. It reported the risk of death by cross-referencing with the CépiDC database[30].

- **Analysis of results**

The study showed that higher consumption of UPFs was associated with a higher risk of death from all causes.

With regard to deaths from all causes, the association persisted after adjustment for an overall diet quality score or a score reflecting proximity to a Western dietary profile (high in fats and sauces, alcohol, meat, starchy foods), but this was not the case after excluding cases of cardiovascular disease and cancer at inclusion, and by expressing UPF consumption as a percentage of energy.

- **Assessment of the weight of evidence**

The assessment of the weight of evidence highlighted the following points, which are summarised in Table 30:

- **Bias control**: The risk of bias due to confounding factors was moderate because, as this was an observational study, there were potentially residual confounding factors, but it took adequate account of all the key confounding factors.

Table 29: Grid assessing the risk of bias for the mortality risk

	Confounding factors	Selection of participants	Classification of exposure	Departures from intended exposures	Missing data	Measurement of outcomes	Reported results
Schnabel *et al.*	Moderate	Low	Low	Low	Low	Low	Low

- **Consistency of the results:** The consistency was not assignable because there was only one study.
- **Directness:** The population, exposure, comparator and outcomes were directly related to the systematic review question.
- **Precision:** Calculations of statistical power were not reported, but the study concerned data from a cohort with a high number of deaths. The precision of the estimates was generally graded as strong, as determined based on the size of the confidence interval.
- **Generalisability:** The study population was drawn from the population living in France, so the results could be generalised.

Table 30: Summary of criteria assessing the weight of evidence for the mortality risk

	Bias control	Consistency of the results	Directness	Precision	Generalisabili ty
Mortality	Moderate	Not assignable	Strong	Strong	Strong

[30] Epidemiology centre on medical causes of death

■ Conclusion

With a limited weight of evidence, the CES concludes that higher consumption of Nova Group 4 foods, compared with lower consumption, is associated with a higher risk of all-cause mortality.

3.3.4. Analysis of uncertainty

Table 31 describes and analyses the uncertainties identified during the systematic review.

Table 31. Analysis of uncertainty

Sources of uncertainty				Analysis of uncertainty	
Part of the expert appraisal	Origin (level 1)	Origin (level 2)	Description	How it was taken into account	Consequences on the expert appraisal results
Planning	Context	Revision of the scope of the expert appraisal	The question concerns the impact of UPF consumption on health, with a 2-year time span assigned to the entire formal request	The analysis was limited to the incidence of the most prevalent chronic non-communicable diseases (and not also to intermediate factors)	Non-exhaustive analysis, focusing on the main chronic diseases (in the French context) and mortality
Planning	Context	Selection of input data	The 2-year time span for addressing the formal request made it necessary to stop the literature search in June 2023	Potential articles published after June 2023 were not taken into account	Potential change in conclusions or weight of evidence
Hazard identification	Methodology	Selection of input data	Only two bibliographic databases were used to identify the health effects	A manual search was carried out	Potential non-exhaustiveness of the data available for studying health outcomes
Characterisation of exposure in the studies	Methodology	Selection of input data	Many studies on UPF consumption are carried out around the world	Inclusion of studies carried out in countries with a high or very high human development index	Fewer studies included, but easier to generalise results to the French population
Characterisation of exposure in the studies	Methodology	Selection of input data	The foods available vary from one study to another, and are probably not the same UPFs	Adjustments for key nutrients, foods and nutritional profiles in the development of the disease enable this heterogeneity to be reduced. The heterogeneity of UPFs is discussed in the assessment of the generalisability factor for the level of evidence.	Cannot be estimated
Characterisation of exposure in the studies	Methodology	Selection of input data	Some types of food consumption data collected were too imprecise to be able to classify foods according to Nova (the only classification used in the selected studies)	Selection of studies with relatively more precise consumption data (see Section 4.1.2).	Fewer studies included, but more precise exposure

Sources of uncertainty				Analysis of uncertainty	
Part of the expert appraisal	Origin (level 1)	Origin (level 2)	Description	How it was taken into account	Consequences on the expert appraisal results
Characterisation of exposure	Methodology	Selection of input data	The degree of precision of the consumption data collected in the selected studies is not always known (in particular the brand, food composition, distinction between home-made, industrial and artisanal products)	Taken into account in the analysis of the risk of bias (higher classification bias for exposure measured using FFQs)	Taken into account in the weight of evidence assessment
Characterisation of exposure	Methodology	Selection of input data	During follow-up of the studies, there may be changes in food consumption (particularly linked to supply)	Taken into account in the analysis of the risk of bias	Taken into account in the weight of evidence assessment
Characterisation of exposure/comparator	Methodology	Selection of input data	The populations are sometimes not very similar to the population living in France	Taken into account in the generalisability factor of the articles included	Lower rating for the weight of evidence
Risk characterisation	Method	Quantity and quality of input data	No results for specific populations (e.g. pregnant women, children, etc.)	Not taken into account	General and undifferentiated conclusions
Risk characterisation	Method	Quantity and quality of input data	Only studies using the Nova classification were obtained at the end of the selection process. However, there is no consensual definition of UPFs	Not taken into account	Limitation of conclusions to UPFs as defined by the Nova classification

3.3.5. Summary and conclusion of the review

The aim of this study was to identify and characterise any epidemiological links between the level of UPF consumption and chronic non-communicable diseases (CNCDs), using a systematic review of the literature with an assessment of the weight of evidence. This systematic review identified 10 articles published up to June 2023 that met the inclusion criteria set by the CES on "Human Nutrition".

Although there was no inclusion criterion relating to the type of classification, it appears that the selected studies used only the Nova system. Thus, in the absence of a consensual definition of UPFs, the systematic review can only conclude on the results of associations based on estimates of exposure to UPFs using the Nova classification, i.e. exposure to Nova Group 4 foods.

Furthermore, the selected studies concern four different cohorts (one of which combines three cohorts treated as a single one in the American studies). Of these cohorts, only two used 24-hour recalls to collect food consumption data, while the others used food frequency questionnaires (FFQs). Using the Nova classification is complex because it requires very precise knowledge of the composition of the foods consumed. It is more difficult to classify foods when the cohorts are not recent (the cohorts studied in the European and American studies) and when food consumption data are collected using FFQs, a less detailed method of data collection than 24-hour recalls.

Lastly, none of the selected articles focused on specific populations (children, adolescents, pregnant or breastfeeding women and the elderly). Studies specifically targeting these populations are needed.

For all the outcomes examined, the selected studies used statistical models adjusting the results for total energy intake (TEI), which makes it possible to study the specific effect of foods in Nova Group 4, independently of their contribution to TEI. On the other hand, the potential health effects of an increase in TEI through the consumption of UPFs were not taken into account in this review. This is an important point to emphasise, given that these foods are readily available (ready-to-eat products offered at multiple points of sale), "hyper-palatable" (i.e. designed to be appetising), particularly energy-dense and rapidly ingested.

Four of the 10 articles presented statistical models with and without adjustment for BMI. Adjustment for BMI had little effect on the associations, suggesting that they were not exclusively explained by an increase in BMI.

Similarly, statistical adjustments were made for food or nutritional composition (including dietary profiles, food groups or nutrients) in all the selected studies. In the studies that ran models with and without adjustments for these factors (7 out of 10), these adjustments had little effect on the associations. This suggests that these associations cannot be explained exclusively by the food and nutritional composition of the diets of high consumers of Nova Group 4 foods.

The analysis of all the articles showed, with a limited weight of evidence, that higher consumption of Nova Group 4 foods, compared with lower consumption, was associated with a higher risk of mortality, type 2 diabetes, overweight, obesity, cardioneurovascular diseases, cancer for all sites combined, breast cancer in women overall and in menopausal women, and colorectal cancer in men only.

With a limited weight of evidence, no association was demonstrated between the level of consumption of Nova Group 4 foods and prostate cancer.

The study selected for assessing the link between UPF consumption and the risk of hepatocellular carcinoma and head and neck cancer was not of sufficiently high quality to enable a conclusion to be reached. The weight of evidence was therefore not assignable.

Table 32 summarises the results of the systematic review.

Table 32: Summary of results and levels of evidence on the links between UPF consumption and CNCDs in the general adult population

Outcome		Number of studies selected	Direction of the associations for higher consumption of Nova Group 4 foods	Weight of evidence
Type 2 diabetes		2	↑	Limited
Overweight and obesity		2	↑	Limited
Cardioneurovascular diseases		2	↑	Limited
Cancer	Cancer, all sites	2	↑	Limited
	Prostate cancer	1	=	Limited
	Breast cancer in women overall and in menopausal women	1	↑	Limited
	Colorectal cancer, in men only	1	↑	Limited
	Head and neck cancer	1	n.c.	Not assignable
	Hepatocellular carcinoma	1	n.c.	Not assignable
Mortality		1	↑	Limited

↑: Higher risk

=: No association demonstrated between the level of consumption of Nova Group 4 foods and the outcome studied

n.c.: not conclusive

Given the limited weight of evidence, linked to the limited number of articles selected in total and for each health outcome studied, it is likely that new studies could lead to these conclusions being amended.

3.4. Analysis and conclusions of the MATAE WG and the CES on Human Nutrition

In addition to the composition of the raw materials, the generation of newly-formed substances is intrinsically linked to the processing methods, and the presence of these substances may explain at least part of the link between the processing methods and the health risk. The expert appraisal work therefore consisted in applying a ranking approach to unit operations and foods, according to their propensity to generate or contain newly-formed substances. This ranking led to the creation of three groups of unit operations with, respectively, a low, moderate and high propensity to generate newly-formed substances. The ranking work also showed that the number of unit operations was not the only determinant of the risk of generation of newly-formed substances. Certain operations can prevent or even reduce the presence of these substances. Specific processes, combined with certain food matrix characteristics, are more likely to generate newly-formed substances, but there is little scientific evidence available for assessing the comparative importance of criteria relating to the matrices and to the processes, which leads to a high level of uncertainty when classifying different foods. It is also important to highlight another significant limitation of this method: it considers all the newly-formed substances identified, without taking account of their effect on health.

Comparison of this approach with that of the Nova system, the classification most widely used in epidemiological studies, showed that the processing methods most likely to generate newly-formed substances do not systematically lead to the production of foods that would be classified in Nova Group 4. Analysis of the Nova classification suggests that it is based more on formulation than on processing, since the steps involving the addition of certain additives or "substances not traditionally used in meal preparation" are key to a food's classification in Nova. The term "ultra-processed" used for foods in Nova Group 4 can therefore lead to confusion. The criteria relating to formulation are not sufficiently precise and are based solely on non-exhaustive lists of substances and additives without any concept of hazard or threshold. The Brazilian authors behind the Nova classification have suggested examples of foods for each group to facilitate its application. However, these are based on generalisations that may not be valid outside Brazil, depending on the foods available. The use of examples makes application of the classification subjective and could lead to classification bias, which is not the case with an algorithm based on precise criteria. Because composition data from epidemiological studies are insufficient for reliably classifying each food according to the Nova criteria, some authors have established classification rules based on an extensive knowledge of the market, according to the food context in their country.

The studies selected in the systematic review carried out as part of this expert appraisal only use the Nova classification. This review highlighted certain associations, but the weight of evidence was limited. Thus, higher consumption of Nova Group 4 foods, compared with lower consumption, was associated with a higher risk of overweight, obesity, type 2 diabetes, cardioneurovascular diseases, cancer for all sites combined, breast cancer in women overall and in menopausal women, colorectal cancer in men only, and mortality. Statistical models with and without adjustments for food or nutritional composition (including dietary profiles, food groups and nutrients) were used in the majority of studies. These adjustments had little effect on the associations, suggesting that these associations cannot be explained exclusively by the food and nutritional composition of the diets of high consumers of Nova Group 4 foods. Given the limited weight of evidence, linked to the limited number of articles selected in total and for each health outcome studied, it is likely that new studies could lead to these conclusions being amended. They therefore need to be confirmed or refuted by other studies. In order to clarify the associations between consumption of foods classified as Nova Group 4 and chronic non-communicable diseases (CNCDs), and in particular to distinguish the respective roles of total energy intake (TEI) and the composition of these foods, new studies need to be carried out using statistical models with and without adjustments for TEI and for food and nutritional composition. It would also be worth distinguishing the health effect of high consumption of Nova Group 4 foods from that of low consumption of Nova Group 1 foods. Lastly, the results of the studies selected in the systematic review can be generalised to the general adult population. Nevertheless, further studies should be carried out on specific populations (children, adolescents, pregnant or breastfeeding women and the elderly).

In order to define courses of action in public health, it is necessary to identify the mechanisms explaining these potential associations. Based on existing research, epidemiologists have put forward several hypotheses to explain the associations between Nova Group 4 foods and CNCDs. These concern the generation of newly-formed substances during processes, contamination by food contact materials and the addition of food additives, processing aids or other substances not traditionally used in meal preparation. Some authors mention the possibility that these substances may have an adverse effect, particularly on gut microbiota. The authors also suggest that these substances may also act synergistically (cocktail effect). Another hypothesis is based on the hyper-palatability of Nova Group 4 foods, which may contribute to the increase in total energy intake.

Regarding newly-formed substances, it appears difficult to classify or rank the processing methods likely to produce these substances, and it is therefore more relevant to identify the processes and newly-formed substances posing a health risk. This approach has revealed the hazard posed by frying processes in terms of acrylamide formation and high-temperature meat cooking methods in terms of the formation of polycyclic aromatic hydrocarbons and heterocyclic aromatic amines, and has led to proposed recommendations for good culinary and industrial practices to limit their formation. This approach needs to be continued.

Regarding materials in contact with packaged foods, whether processed or not, only a few data enable contamination of UPFs to be distinguished from that of other foods (by the nature of the materials, the length of contact, the food matrix, heating in the packaging, etc.). Studies should be carried out to clarify this point.

Even though additives and processing aids undergo risk assessments within the regulatory framework, it would be worth conducting more epidemiological studies into the associations between "cosmetic" additives (excluding preservatives) and processing aids, and CNCDs. This would identify additives or processing aids potentially of concern that should then be reassessed as a priority under the regulations.

Similarly, it would be worth conducting epidemiological studies into the associations between substances used exclusively by the agri-food industry and CNCDs. This would identify substances of potential concern that should then be assessed as a priority using conventional toxicology methods.

Lastly, the "cocktail" effect of all these substances should be considered, despite the methodological difficulties of this exercise.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The constant increase in non-communicable diseases in countries with a high development index, along with the increase in intermediate factors (high blood pressure, cholesterol, etc.) whose causes are nutritional, confirms the level of attention that needs to be paid to the role of diet and physical activity in public health policies.

In France, the courses of action that have been implemented, identified and recognised as safeguarding public health include both collective action to control food safety and quality, and individual action. These include the regulation of substances used in preparation or marketing (processing aids, additives, food contact materials), process control requirements, etc. Public policies (PNNS[31], PNAN[32], etc.) include charters of commitments by economic players to better control levels of certain nutrients (salt, sugar, etc.), dietary guidelines, recommendations for physical activity, information and awareness-raising campaigns. All these courses of action are supplemented by observation tools (the Esteban and INCA studies, which have been merged into the Albane study, and the OQALI observatory) that enable the effects of the actions to be monitored.

Despite these efforts, recent results (Esteban study published in February 2020[33]) are less than satisfactory and raise fears that future surveys will reveal results that are just as concerning, if not more so. This observation and this anticipation fuel questions about the lack of leverage in analysing the causes of the public health problem or in actually implementing public policies in this field – or even a combination of the two. In this context, the emergence of the concept of ultra-processed foods (UPFs) can be analysed as a hypothesis of an inadequately understood cause in the prevention of chronic non-communicable diseases, with a view to incorporating it, where appropriate, into the courses of action mentioned above. To be considered as such, it was necessary for ANSES to examine its scientific basis and its relevance for public health purposes.

The purpose of this expert appraisal is to consider this hypothesis, by analysing the proposed classifications and the results of research carried out to date that uses the concept of degree of processing in a scientific approach.

In this context, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) endorses the conclusions of the CES on Human Nutrition and the MATAE WG.

The expert appraisal identified a range of heterogeneous classifications and the absence of a consensual definition of foods to be considered as "ultra-processed". The systematic review of the literature showed that most epidemiological research on this subject is conducted using the Nova classification, the highest group of which, Nova Group 4, is assigned to "ultra-processed foods". For seven of the 10 health outcomes examined, the literature review showed an increased risk of chronic non-communicable diseases (including all-cause mortality) associated with higher consumption of foods classified in Nova Group 4, although the weight of evidence was limited. On the other hand, there was no association for one outcome (prostate cancer), while with two outcomes (head and neck cancer and hepatocellular carcinoma), it was

[31] National Health and Nutrition Programme
[32] National Food and Nutrition Programme
[33] https://www.santepubliquefrance.fr/determinants-de-sante/nutrition-et-activite-physique/documents/rapport-synthese/etude-de-sante-sur-l-environnement-la-biosurveillance-l-activite-physique-et-la-nutrition-esteban-2014-2016.-volet-nutrition

not possible to draw any conclusions. In the factors for obtaining the weight of evidence, the Agency highlights the fact that each of the outcomes was weighed on the basis of only one or two studies (explaining why the weight of evidence was graded as limited).

As this is the classification most commonly used in epidemiological research, the appraisal focused its analysis on the Nova classification. The Agency points out that this classification is not based solely on considerations relating to the degree of processing of the food, but also aggregates diverse concepts such as "cosmetic" additives and certain substances used by the agri-food industry, packaging, as well as objectives of profitability and convenience of consumption. Moreover, from a semantic point of view, various expressions (in particular adverbs of frequency) leave a broad margin of discretion, making it impossible to classify them unequivocally. This imprecision in the classification criteria leads to differences in the way research teams apply them. This assessment is borne out by the low agreement rates between teams, which can only be improved with the help of additional guidelines. This lack of reproducibility in the classification of foods is both a major limitation to the scope of the conclusions that can be drawn from these studies, and a major obstacle to using the classification as it stands as a tool for structuring research.

In addition to this major methodological weakness, the analysis examined how the classification takes account of food processing methods. It should be remembered that the very role of certain processes is to ensure or reinforce – particularly over time – the safety of foods that cannot be consumed directly or that potentially contain pathogens needing to be neutralised. Processing is broken down into unit operations, whose risks vary according to their type, intensity, sequence and the food in question.

The expert appraisal noted that the classification studied does not take account of the risk of occurrence of newly-formed substances, which is one of the basic elements that can be objectively measured. Some of these substances can be harmful and need to be characterised in order to prevent their formation and the associated risks. However, the data available on food processing methods mean that this is not easy to do [ANSES, 2018].

For these various reasons, the limitations of the Nova classification led ANSES to consider that it is not possible to use this classification system, nor any of the others studied, directly as a basis for developing tools to prevent chronic non-communicable diseases, such as recommendations or inclusion in a categorisation mechanism.

However, even though the weight of evidence was limited, ANSES considers that the results of the literature review should be viewed as a reason to explore the avenues associated with the concept of ultra-processing, as these are not currently taken into account in public health actions and should be investigated.

It lists the following possible lines of work:

- the presence of high-energy foods in the food supply, which can upset the energy balance, even more so when energy expenditure is low;
- food formulations that make it easier to consume unsuitable portions;
- consideration of the risk in the broader sense, including the conditions of consumption encouraged by the type of food: fast food, irregular eating rhythms, social environment, etc.

The Agency therefore recommends that studies be undertaken to characterise any causal links between the factors identified and the health effects, and to establish the attributable share of these different factors. In order to identify the most appropriate courses of action, it considers that this work should seek to improve understanding of the respective roles played by food composition and excessive energy intake in the occurrence of effects detrimental to consumer health.

In addition, the hazards potentially associated with food formulation or certain processes, particularly in terms of newly-formed substances, merit further research in order to identify foods whose production methods may pose a health risk.

In the current context of preparing the next PNNS and the next PNAN, and without waiting for the recommended studies to be completed, ANSES reiterates that before considering the deployment of a concept that has not been sufficiently scientifically justified, it would be preferable to review the limitations of the actions taken, with regard to achieving ambitious objectives for improving public health, in order to significantly remedy the findings of the latest population studies.

Pr Benoit Vallet

KEY WORDS

Aliments ultratransformés, AUT, Nova, substances néoformées, transformation, formulation, opérations unitaires, santé, maladies chroniques non transmissibles, diabète, obésité, cancer, maladies cardiovasculaires, mortalité

Ultra-processed foods, UPF, Nova, newly-formed substances, process, formulation, unit operations, health, non-communicable diseases, diabetes, obesity, cancer, cardiovascular diseases, mortality

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ANNEX 1: PRESENTATION OF THE PARTICIPANTS

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP ON "ASSESSMENT OF MATERIALS AND PROCESSING AIDS IN THE AREAS OF FOOD AND WATER" (MATAE WG)

Chair

Mr Nicolas CABATON – INRAE Researcher – Food toxicology, nutrition

Members

Mr Sébastien ANTHERIEU – Doctor of Science – General toxicology, regulatory toxicology, genotoxicity, risk assessment

Mr Claude ATGIE – Professor – Food toxicology, nutrition

Ms Christelle AUTUGELLE (WEBER) – Engineer – Migration tests, analysis methods, knowledge of material formulations and positive lists, EU and international standards and regulations on food/water contact materials

Ms Emilie BAILLY – Technical Manager – Migration testing, analysis methods, knowledge of material formulations and positive lists, EU and international standards and regulations on materials in contact with water

Mr Jean BARON – Doctor of Science – Water quality, water treatment products and processes, materials in contact with water (organic, metallic, mineral and hydraulic binders), EU and international standards and regulations on materials in contact with water

Mr Jalloul BOUAJILA – Lecturer – Analytical chemistry, extraction of value from natural substances

Mr Auguste BRUCHET – Retired – Analytical chemistry, water quality, organic micropollutants, materials in contact with water

Ms Marie-Christine CHAGNON – Professor – Food toxicology, food contact materials

Ms Véronique COMA – Lecturer – Food technology, active and intelligent packaging materials

Mr Pascal DEGRAEVE – Professor – Food chemistry, food manufacturing processes

Mr Luc FILLAUDEAU – INRAE Research Director – Food and biotechnology process engineering

Mr Jean-Baptiste FINI – Doctor of Science at CNRS/French Natural History Museum – Endocrinology, diabetes, metabolic diseases

Mr Michel LINDER – Professor – Industrial processes, lipids and fats, enzymatic processes, nanovectorisation, food quality and safety

Mr Stéphane PEYRON – Teacher-researcher – Food contact materials, migration, exposure assessment, mass transfers

Ms Anne PLATEL – Lecturer – Genetic toxicology

Mr Philippe SAILLARD – Engineer – Chemistry of food contact materials

Ms Claire TENDERO – Teacher-researcher – Chemistry, materials, surface treatments, coatings, microbial adhesion

Mr François ZUBER – Scientific Director – Food processing and preservation processes

"NUTRITION EPIDEMIOLOGIST" RAPPORTEURS

Ms Charlotte BEAUDART – Research Manager (University of Liège) – Specialities: epidemiology, public health, meta-analyses, sarcopenia

Ms Blandine de LAUZON-GUILLAIN – Research Director (INRAE, CRESS) – Specialities: epidemiology, infant nutrition, nutrition of pregnant or breastfeeding women, public health

Ms Emmanuelle KESSE-GUYOT – Research Director (Sorbonne Paris Nord University, INRAE, UMR Inserm U1153/INRA U1125/CNAM) – Specialities: epidemiology, nutrition and pathologies, nutrition and public health, food sustainability

Mr Nathanael LAPIDUS – University Lecturer-Hospital Practitioner (AP-HP Saint-Antoine, Inserm-UPMC, UMR-S1136) – Specialities: epidemiology, clinical research, methodology, meta-analyses, public health, biostatistics

Mr Olivier STEICHEN – University Professor-Hospital Practitioner (Sorbonne University Faculty, Tenon Hospital) – Specialities: nutrition and non-communicable diseases, biological functions, cardiology, endocrinology, systematic reviews and meta-analyses, clinical intervention studies

"FOOD TECHNOLOGY" RAPPORTEURS

Mr Luc FILLAUDEAU – INRAE Research Director – Food and biotechnology process engineering

Mr Michel LINDER – Professor – Industrial processes, lipids and fats, enzymatic processes, nanovectorisation, food quality and safety

Mr Michel BACCAUNAUD – Retired – R&D, technology transfer, industrial processors of plant products (ready-to-eat fresh and cooked produce, preserves, frozen foods), conventional and innovative technologies (ionisation, high hydrostatic pressure treatments, low pressure steam, pulsed light) for processing and maintaining the quality of traditional fresh produce

Mr Luc SAULNIER – INRAE Research Director – Food biochemistry

EXPERT COMMITTEE

- Expert Committee on "Human Nutrition" (2022-2026)

Chair

Ms Clara BENZI-SCHMID – Federal Food Safety and Veterinary Office (FSVO), Switzerland – Specialities: revision and updating of legal bases of foodstuffs

Members

Ms Karine ADEL-PATIENT – Research Director (Paris-Saclay University, CEA, INRAE) – Specialities: food allergy, immunology, perinatal care, metabolomic analyses, allergic risk management

Ms Charlotte BEAUDART – Research Manager (University of Liège) – Specialities: epidemiology, public health, meta-analyses, sarcopenia

Ms Annabelle BEDARD – Research Manager (Inserm UMR 1018, CESP) – Specialities: nutritional epidemiology, nutrition in adults, pregnant women and children, chronic non-communicable diseases, environment, exposure estimation and assessment

Ms Clara BENZI-SCHMID – Federal Food Safety and Veterinary Office (FSVO), Switzerland – Specialities: revision and updating of legal bases of foodstuffs

Ms Cécile BETRY – University Lecturer-Hospital Practitioner (Grenoble Alpes University, Grenoble Alpes University Hospital) – Specialities: clinical nutrition, artificial nutrition, malnutrition, nutrition and diabetes, nutrition and obesity

Mr Patrick BOREL – Research Director (INRAE, UMR C2VN) – Specialities: bioavailability, fat-soluble vitamins, micro-constituents, metabolism of micronutrients, edible insects, nutrigenetics

Ms Blandine de LAUZON-GUILLAIN – Research Director (INRAE, CRESS) – Specialities: epidemiology, infant nutrition, nutrition of pregnant or breastfeeding women, public health

Ms Christine FEILLET-COUDRAY – Research Director (University of Montpellier, INRAE, UMR 866 DMEM – Muscular Dynamics and Metabolism, Mitochondrial Endocrinology & Nutrition Team) – Specialities: mineral metabolism, oxidative stress

Mr Jérôme GAY-QUEHEILLARD – University Professor (University of Picardy Jules Verne, Ineris UMR I-01 INERIS) – Specialities: gastroenterology, nutrition, obesogenic diet, immune system, pesticides, endocrine disruptors

Ms Aurélie GONCALVES – University Lecturer (University of Nîmes, UPR APSY-v) – Specialities: physical activity for health, sedentary behaviour, nutrition, obesity, bioavailability

Ms Tao JIANG – University Lecturer (University of Burgundy, Inserm U1028 – CNRS UMR5292) – Specialities: methodologies of consumer studies, methodologies of clinical studies, food behaviour and consumption, biostatistics

Ms Emmanuelle KESSE-GUYOT – Research Director (Sorbonne Paris Nord University, INRAE, UMR Inserm U1153/INRA U1125/CNAM) – Specialities: epidemiology, nutrition and pathologies, nutrition and public health, food sustainability

Mr Nathanael LAPIDUS – University Lecturer-Hospital Practitioner (AP-HP Saint-Antoine, Inserm-UPMC, UMR-S1136) – Specialities: epidemiology, clinical research, methodology, meta-analyses, public health, biostatistics

Ms Corinne MALPUECH-BRUGERE – University Professor (University of Clermont Auvergne) – Specialities: human nutrition, metabolism of macro- and micronutrients

Ms Christine MORAND – Research Director (INRAE Clermont-Ferrand) – Specialities: prevention of vascular dysfunctions and related diseases, micro-constituents of plants

Mr Thomas MOUILLOT – University Lecturer-Hospital Practitioner (University of Burgundy, François Mitterand University Hospital) – Specialities: nutrition, hepatology, gastroenterology, physiology, food behaviour

Mr Ruddy RICHARD – University Professor-Hospital Practitioner (Clermont-Ferrand University Hospital) – Specialities: clinical research, sports medicine, nutrition, chronic disease, bioenergetics, exercise

Ms Anne-Sophie ROUSSEAU – University Lecturer (University of Côte d'Azur, iBV, UMR 7277 CNRS, UMR 1091 Inserm) – Specialities: nutrition and physical activity, oxidative stress, immunometabolism

Mr Olivier STEICHEN – University Professor-Hospital Practitioner (Sorbonne University Faculty, Tenon Hospital) – Specialities: nutrition and non-communicable diseases, biological functions, cardiology, endocrinology, systematic reviews and meta-analyses, clinical intervention studies

Mr Stéphane WALRAND – University Professor-Hospital Practitioner (University of Clermont Auvergne and Gabriel Montpied University Hospital in Clermont-Ferrand) – Specialities: pathophysiology, protein metabolism, vitamin D, amino acids

ANSES PARTICIPATION

Scientific coordination

Mr Fernando AGUILAR – Scientific Coordinator – Risk Assessment Department – Food Risk Assessment Unit (UERALIM). Until December 2023

Mr Daire GIBBONS – Scientific Coordinator – Risk Assessment Department – UERALIM

Mr Laurent GUILLIER – Scientific Coordinator – Risk Assessment Department – UERALIM

Ms Claire MATHIOT – Scientific Coordinator – Risk Assessment Department – Nutritional Risk Assessment Unit (UERN)

Ms Anne MORISE – Scientific Coordinator – Risk Assessment Department – UERN

Scientific contribution

Mr Fernando AGUILAR – Scientific Coordinator – Risk Assessment Department – Food Risk Assessment Unit (UERALIM). Until December 2023

Ms Estelle CHAIX – Scientific Coordinator – Risk Assessment Department – UERALIM

Mr Aymeric DOPTER – Head of the Nutritional Risk Assessment Unit (UERN) – Risk Assessment Department

Mr Daire GIBBONS – Scientific Coordinator – Risk Assessment Department – UERALIM

Mr Laurent GUILLIER – Scientific Coordinator – Risk Assessment Department – UERALIM

Ms Irène MARGARITIS – Deputy Director for Food, Animal and Plant Health – Risk Assessment Department

Ms Claire MATHIOT – Scientific Coordinator – Risk Assessment Department – Nutritional Risk Assessment Unit (UERN)

Ms Anne MORISE – Scientific Coordinator – Risk Assessment Department – UERN

Ms Perrine NADAUD – Deputy Head of the UERN – Risk Assessment Department

Ms Karine TACK – Head of the Food Risk Assessment Unit (UERA) – Risk Assessment Department

Administrative secretariat

Ms Chakila MOUHAMED – Risk Assessment Department

HEARINGS WITH EXTERNAL PERSONS

INRAE, Department of Sciences for the Engineering of Food, Biobased Products and Residues of Human Activity (UAR1008 TRANSFORM)

Ms Catherine RENARD – Deputy Head of Department

Ms Isabelle SOUCHON – Research Director – Safety and quality of products of plant origin (UMR SQPOV)

ANNEX 2: FORMAL REQUEST LETTER

GOUVERNEMENT
Liberté
Égalité
Fraternité

Courrier arrivé
31 AOUT 2022
DIRECTION GENERALE

Paris, le 27 AOUT 2022

Dossier suivi par : Erwan de Gavelle
DGAL/SPPSI/SDATAA/BPAL
Réf. : SDATAA-BPAL
Tél. : 01 49 55 50 24
Mèl. : erwan.degavelle@agriculture.gouv.fr

Dossier suivi par : Isabelle de Guido
DGS/EA/EA3
Réf. : I-22-004536-29
Tél. : 01 40 56 68 47
Mèl. : Isabelle.DE-GUIDO@sante.gouv.fr

La Directrice générale de l'alimentation
Le Directeur général de la santé

à

Monsieur le Directeur général de l'ANSES
14, rue Pierre et Marie Curie
94701 MAISONS ALFORT CEDEX

Objet : Demande d'avis de l'Anses relatif à la caractérisation et à l'évaluation des impacts sur la santé de la consommation d'aliments ultra-transformés

Contexte

L'étude INCA3 (2014-2015) de l'Anses, publiée en 2017, a souligné l'augmentation de la consommation de produits transformés par les Français. L'étude montre également que les produits agro-alimentaires industriels représentent la majorité de ces aliments transformés consommés par les Français hors restauration, en particulier chez les jeunes (deux tiers chez les enfants et la moitié chez les adultes). L'Anses indique que cette part très importante des aliments transformés chez les plus jeunes contribue à « créer une distance entre les individus et leur alimentation, notamment en termes de connaissance de la composition des aliments ». La perte du lien avec l'agriculture et les procédés industriels complexes dont sont issus les aliments transformés contribuent aux questionnements actuels sur les effets sanitaires de leur consommation régulière.

Les aliments ultra-transformés sont une thématique de recherche émergente, ce qui a notamment permis une synthèse de la littérature par la FAO[1] et une prise de position de l'agence espagnole de nutrition et de sécurité sanitaire des aliments (AESAN) sur le sujet[2]. Un nombre croissant de publications scientifiques ont en effet observé une association entre la consommation de produits ultra-transformés et le risque de maladies chroniques, indépendamment de leur qualité nutritionnelle.

Si la préoccupation est aujourd'hui internationale, et portée tant par la sphère scientifique que par les médias, il n'existe pas à ce jour de définition consensuelle pour les aliments transformés. La classification NOVA, par exemple, différencie les aliments en 4 groupes en fonction de leur degré de transformation et la catégorie « NOVA4 » correspond aux aliments les plus transformés. En France, bien qu'il n'existe

[1] http://www.fao.org/3/ca5644en/ca5644en.pdf
[2] ttps://www.aesan.gob.es/AECOSAN/docs/documentos/seguridad_alimentaria/evaluacion_riesgos/informes_cc_ingles/ULTRA-PROCESSED_FOODS.PDF

pas de définition réglementaire pour les aliments ultra-transformés, plusieurs recommandations officielles y font référence. Ainsi, les objectifs du Haut Conseil de la santé Publique pour le Programme national nutrition santé (PNNS) sont « *d'interrompre la croissance de la consommation des produits ultra-transformés (selon la classification NOVA)* » et Santé Publique France recommande « de limiter les boissons sucrées, les aliments gras, sucrés, salés et ultra-transformés »[3]. Le Programme national de l'alimentation et de la nutrition (PNAN) prévoit la caractérisation des aliments ultra-transformés, l'étude de l'impact pour la santé de la consommation d'aliments ultra-transformés et la priorisation des actions à mener. De plus, de nombreuses propositions issues de rapports parlementaires, de la Convention citoyenne pour le climat ou d'initiatives citoyennes concernent les aliments ultra-transformés, en lien avec l'étiquetage, la taxation, l'interdiction de la publicité ou la limitation en restauration collective.

L'Anses avait prévu dans son programme de travail pour 2021 l'évaluation des risques nutritionnels auxquels sont exposés les forts consommateurs d'aliments ultra-transformés. Il a été indiqué lors du Comité d'orientation thématique "Santé alimentation" du mercredi 19 mai 2021 que les données n'étaient pas suffisantes pour poursuivre les travaux à ce sujet. Le sujet étant récent, une revue de la littérature sur les impacts sanitaires de la consommation régulière d'aliments ultra-transformés permettra d'alimenter les réflexions, notamment sur le choix d'une définition, et sur les hypothèses relatives aux potentiels impacts sur la santé.

Cadre général de la saisine

Au regard des études scientifiques déjà publiées et des travaux précités (FAO, AESAN), il est demandé à l'Anses :

I. de caractériser les produits dits ultra-transformés (procédés industriels impliqués et modifications de la composition associées, ajouts d'additifs, diversité des ingrédients incorporés individuellement ou en combinaison, caractéristiques nutritionnelles de ces produits, modifications des comportements alimentaires liés à leur consommation...) ;
II. d'identifier les caractéristiques des produits dits ultra-transformés qui pourraient être à l'origine de maladies chroniques non transmissibles ;
III. de réaliser un recensement des classements existants des produits ultra-transformés et d'en évaluer la pertinence par rapport aux caractéristiques identifiées précédemment ;
IV. d'étudier les relations entre la consommation d'aliments ultra-transformés et les risques de maladies chroniques non transmissibles ;
V. de déterminer, si les niveaux de preuves paraissent suffisamment élevés, des quantités minimales et/ou maximales d'aliments ultra-transformés à consommer au-delà des recommandations ciblant les caractéristiques nutritionnelles, et si oui, pour quelle population ;
VI. de déterminer, si pertinent et en fonction des risques identifiés, les leviers permettant de limiter les niveaux de consommation des AUT ;
VII. de déterminer les travaux scientifiques devant être conduits pour mieux caractériser les impacts sanitaires des aliments les plus transformés.

Délai de réponse

La remise d'un document est attendu pour **un délai de deux ans après la réception de la demande de saisine.**

Destinataires pour la réponse mail :

DGS : manon.egnell@sante.gouv.fr,isabelle.de-guido@sante.gouv.fr, melanie.picherot@sante.gouv.fr
DGAL : carole.foulon@agriculture.gouv.fr, erwan.degavelle@agriculture.gouv.fr, saisines-anses.dgal@agriculture.gouv.fr

[3] https://www.santepubliquefrance.fr/content/download/35744/683783

Nos services se tiennent à votre disposition pour vous apporter toute information complémentaire. Nous vous remercions de bien vouloir accuser réception de la présente demande.

La Directrice Générale de l'Alimentation

Maud FAIPOUX ID Signature numérique de Maud FAIPOUX ID

Maud FAIPOUX

Le Directeur Général de la Santé

Jérôme SALOMON

ANNEX 3: REPORT OF THE HEARING WITH MS RENARD AND MS SOUCHON

Participants:

- Persons interviewed: Catherine Renard (Deputy Head of Department at INRAE) and Isabelle Souchon (Research Director at INRAE)
- Rapporteurs: Luc Saulnier, Michel Linder and Michel Baccaunaud
- ANSES coordinators: Daire Gibbons, Laurent Guillier and Anne Morise

Date and time: 05/04/2024 2pm-4pm

Location: TEAMs

Presentation of work on UPFs:

Catherine Renard outlined her thoughts on the classification of foods according to their degree of processing, emphasising the challenges associated with these classifications and the resulting research questions. In particular, she highlighted the fact that existing classification systems did not take account of processes carried out in the home. Mechanistic hypotheses were discussed: the presence of harmful substances and destruction of the food matrix.

Isabelle Souchon then presented a critical analysis of the existing classifications, in particular the Nova system, and discussed her own proposal for a classification based on a processing score, known as the Process Score. This was developed for assessing the degree of food processing and was presented as a more suitable alternative to the Nova classification for this purpose. Laurent Guillier then explained the objectives and principle of the work carried out for question 1.

Discussion:

- The finding: public health policy aimed at improving the nutritional quality of foods does not seem to be enough to reduce chronic non-communicable diseases. This has led to the emergence of classification systems based on the degree of food processing. The most widely used is the Nova classification.
- Limitations of this classification: the Nova classification criteria are deemed to be vague and the examples presented sometimes appear to contradict them. A revision is needed to clarify the criteria for this classification.
- Newly-formed substances: it is difficult to distinguish between newly-formed substances and degradation products, and there is uncertainty about their impact on human health. Some newly-formed substances can even have positive effects on health. Furthermore, the generation of newly-formed substances depends on the composition of the raw materials. For example, polyphenols are thought to protect against the generation of newly-formed substances.
- Additives, processing aids and contact materials: it is difficult to assess the health impact of these substances in real-life conditions. The presence of flavourings in foods is a criterion for classifying them as Nova Group 4, yet they are involved in the "satiety cascade". Flavourings therefore play a role in regulating TEI, despite being perceived negatively since they are a marker of Nova Group 4. A further complication comes from the fact that it is not always possible to separate the process from the packaging type.
- Description of the classification: use of the term "ultra-formulated" rather than "ultra-processed" has been suggested in certain cases, even if it is related.

- Applicability of the classification: it is not easy to conduct epidemiological studies on the effects of ultra-processed foods because of:
    - o the difficulty in collecting sufficiently precise food consumption data in order to classify foods according to the Nova system, and the difficulty in taking account of all the other parameters that may influence the relationship between UPF consumption and the risk of disease;
    - o changes in the classification over time;
    - o the variability of ratings produced by different users of the classification.
- How variability is taken into account in the different sectors: it is difficult to have an overall tool for classifying foods according to their processing methods that encompasses all sectors. A tool tailored to each sector would enable their specific features to be taken into account, for greater precision, although such a tool may be difficult to implement. The Nova classification, on the other hand, appears at first glance to be very simple to implement, as it makes extensive use of "processing markers" such as "cosmetic" additives and processing aids.
- Process Score: like the Process Score proposed by Isabelle Souchon, the work currently being conducted by ANSES focuses on food processing methods. The ranking methodology is similar. Although these two approaches differ (the Process Score does not take account of the health aspect of the processing methods), they both highlight the difficulty of proposing a classification based on processing methods.

Ms Souchon offered to provide the different cookie and sandwich bread recipes used in their work on the Process Score, to enable the method used by ANSES's experts to be applied to these two food categories.

ANNEX 4: LIST OF UNIT OPERATIONS AND VALUES SELECTED FOR THE VARIOUS CRITERIA ASSOCIATED WITH RANKING THE CHEMICAL RISK OF GENERATING NEWLY-FORMED SUBSTANCES

Unit operations	Temperature	Time	Pressure	Chemical reactivity	Ionising radiation	UV
Deep-freezing	1	0	0	0	0	0
Freezing	2	0	0	0	0	0
Refrigeration	2	0	0	0	0	0
Microwave or radiofrequency defrosting	1	0	0	0	0	0
Treatment at room temperature	2	1	0	0	0	0
Low-temperature pasteurisation	2	0	0	0	0	0
Conventional pasteurisation	3	1	0	0	0	0
Flash pasteurisation	3	0	0	0	0	0
Cooking between 50 and 100°C	3	0	0	0	0	0
Immersion blanching	3	0	0	-1	0	0
Chemical peeling using heat	2	0	0	0	0	0
Hot air drying	2	1	0	0	0	0
Canning of moist foods	4	1	0	0	0	0
HTST treatment	4	0	0	0	0	0
Microwave or radiofrequency heating	4	1	0	0	0	0
Flash steam peeling	3	0	0	0	0	0
Steam blanching	4	0	0	0	0	0
Atomisation	2	0	0	0	0	0
High-power hot air drying	4	1	0	0	0	0
Oven, core temperature below 100°C	4	1	0	0	0	0
Oven, core temperature above 100°C	5	1	0	1	0	0
Frying 180°C and over	5	0	0	1	0	0
Cooking between 100 and 150°C	3	1	0	0	0	0
Infrared surface treatment	5	1	0	1	0	0
Barbecuing	5	1	0	1	0	0
Griddling	5	1	0	1	0	0
Roasting	5	1	0	1	0	0
Chemical hydrolysis	4	1	0	1	0	0
Enzymatic hydrolysis	3	1	0	0	0	0
Smoking	2	1	0	1	0	0
Curing	2	0	0	1	0	0
Biocatalytic/biological processes	2	0	0	1	0	0
Non-thermal decontamination in packaging	2	0	1	0	0	0
HP-assisted pasteurisation	2	0	1	0	0	0
HP-assisted sterilisation	3	0	2	0	0	0
Probe ultrasound	2	0	0	1	0	0
Bath ultrasound	2	0	0	0	0	0
Impact homogenisation	2	0	1	0	0	0
Extrusion cooking	4	0	2	0	0	0
No-bake extrusion	2	0	1	0	0	0
Instant controlled pressure drop	3	0	1	0	0	0

Moderate electric field (MEF)	1	0	0	1	0	0
Pulsed electric field (PEF)	2	0	0	1	0	0
Pulsed light on the surface	2	0	0	1	0	1
Pulsed UV	2	0	0	1	0	1
Cold plasma	1	0	0	1	0	0
Continuous UV	2	0	0	0	0	1
Pulsed light throughout the product	2	0	0	0	0	0
Ionisation	2	0	0	0	1	0
Extraction with supercritical CO_2	2	1	0	1	0	0
Refining of carbohydrate fractions	2	0	0	-1	0	0
Freeze-drying	2	0	0	-1	0	0

ANNEX 5: LIST OF FOODS/INGREDIENTS AND VALUES SELECTED FOR THE VARIOUS CRITERIA ASSOCIATED WITH THEIR RANKING

Foods	Input materials	% unsaturated fats	% protein	% reducing sugars	antioxidants (mg)	Water content (g per 100 g)	delta pH/pH 7	UO_{most}	$UO_{moderate}$	UO_{least}	Total number of UOs	Processing aids
Vacuum-packed steamed potatoes	potatoes	0.14	0.18	1.18	18.9	80	-0.9	1	1	1	7	1
Canned green beans	green beans	0.14	1.80	2.3	13.6	90	-1	1	1	1	8	0
Canned peas	peas	0.45	5.80	5.7	41	79	-1	1	1	1	8	0
Frozen peas	peas	0.45	5.80	5.7	41	79	-1	0	1	2	8	0
Ready-to-eat salads	lettuce	0.18	1.30	0.7	12	95	-1	0	0	1	6	0
Dried prunes	prunes	0.40	0.90	5.8	4	80	-3	0	1	0	5	0
Apple purées	apples	0.50	0.40	8.5	1.3	85	-3	0	1	1	9	0
Frozen strawberries	red fruits – strawberries	0.50	0.60	5.6	54	90	-3.5	0	0	2	5	0
Vegetable patties	peas	0.45	5.80	5.7	41	79	-1	1	1	1	7	0
Dehydrated vegetables	carrots	0.23	0.60	1.7	1.3	88	-2	0	1	0	7	0
Ready-to-eat apples	apples	0.50	0.40	8.5	1.3	85	-3	0	0	1	6	1
Frozen pre-cooked French fries	potatoes	0.14	0.18	1.18	18.9	80	-0.9	1	1	2	9	0
UHT milk	milk	1.21	3.25	4.2	1.30	90	-0.2	1	0	2	5	0
UHT cream	milk	1.21	3.25	4.2	1.30	90	-0.2	1	0	2	5	0
Fresh cream	milk	1.21	3.25	4.2	1.30	90	-0.2	0	1	2	6	0
Yoghurt	milk	1.21	3.25	4.2	1.30	90	-0.2	0	2	1	7	0
Butter	milk	1.21	3.25	4.2	1.30	90	-0.2	0	2	1	7	0
Cheese	milk	1.21	3.25	4.2	1.30	90	-0.2	0	2	1	8	0

Foods	Input materials	% unsaturated fats	% protein	% reducing sugars	antioxidants (mg)	Water content (g per 100 g)	delta pH/pH 7	UO_{most}	$UO_{moderate}$	UO_{least}	Total number of UOs	Processing aids
Bread	wheat (flour)	0.4	10.00	2	0.12	15	-1	1	0	2	5	0
Breakfast cereals – flaking	wheat	0.4	10.00	2	0.12	15	-1	1	2	0	5	0
Breakfast cereals – extrusion cooking	rice	0.076	7.50	2	0	20	-1	1	1	0	3	0
Breakfast cereals – swelling	wheat (flour)	0.4	10.00	2	0.12	15	-1	1	1	0	4	0
Biscuits	wheat (flour)	0.4	10.00	2	0.12	15	-1	1	1	0	4	0
Pasta	durum wheat flour	0.4	10.00	2	0.12	15	-1	0	2	0	5	0
Beet sugar syrup *	beets	0	0.25	0.15	0	77	-1	0	0	0	15	9
Molasses (beets) *	beets	0	0.25	0.15	0	77	-1	0	0	0	18	11
White sugar *	beet	0	0.25	0.15	0	77	-1	0	1	0	21	11

** For the last three rows, for the number of UOs in the three classes (UOmost, UOmoderate and UOleast), only OUs occurring after the last sanitising step were considered'*

ANNEX 6: CHOICE OF MULTI-CRITERIA METHOD AND PRINCIPLE OF THE METHOD USED

Multi-criteria methods

A wide range of multi-criteria methods are used for analysis and decision-making. Among these, "outranking" methods are approaches used in multi-criteria analysis to establish a preferential classification of several alternatives by conducting a pairwise comparison. These methods seek to identify the alternatives that "dominate" the others on all the criteria, i.e. those that are better or at least as good as the other alternatives for each criterion. These methods therefore provide preferential classifications by assessing the alternatives sequentially, based on predefined criteria, and identifying the dominant ones. They are often used when decision-makers' preferences are focused on key criteria, and when a pairwise comparison of alternatives is deemed more appropriate than the use of aggregate measures (such as score calculation methods).

The "Elimination and Choice Translating Reality" (ELECTRE) method is widely used among outranking methods. This family of methods comprises several variants, including ELECTRE I, ELECTRE II and ELECTRE III, and is used to classify alternatives by comparing their concordance (favourable performance) and discordance (unfavourable performance) on each criterion used. Alternatives with high concordance and low discordance are considered the best. There are also other alternative outranking methods (PROMETHEE, TOPSIS, etc.).

The working group selected the ELECTRE III method used in the ranking of risks. However, it should be noted that the results obtained by the different methods may have an influence on the rankings obtained (Kadziński and Ciomek 2016; Garre *et al.* 2020).

Principle of the ELECTRE III method

➊ The first step in a multi-criteria analysis is to identify and define appropriate criteria for the analysis. These criteria must be clearly defined and measurable.

The scale of each criterion, as well as the preference and indifference thresholds, must be defined. In the ELECTRE III method, the p and q values correspond to thresholds used to assess the concordance and discordance indices between the alternatives.

1. p value: the p value is the preference threshold. It represents the level of difference between the values taken by two alternatives (c(I1, I2)) for a criterion from which a strict preference for I1 over I2 can be concluded.

2. q value: the q value is the indifference threshold. It represents the maximum level of acceptable disagreement between two alternatives for them to be considered discordant. Alternatives whose discordance index is less than or equal to the q value are considered to be discordant.

By setting the values of p and q, it is possible to determine the limits at which one alternative is considered superior or inferior to another in terms of concordance or discordance. These thresholds are defined according to expert preference and judgement.

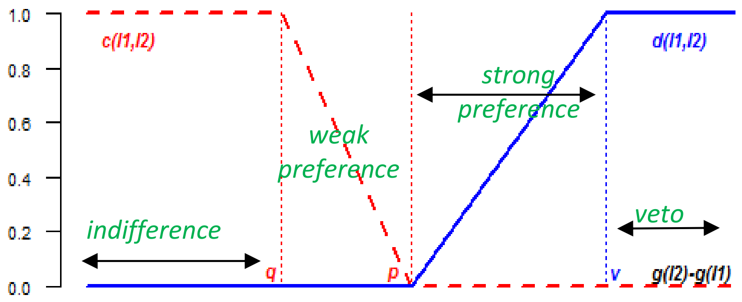


Figure 1. Illustration of the concept of p, q and v values in the ELECTRE III method

❷ The second step involves drawing up a list of the elements to be ranked.

❸ The third step is to complete the performance matrix. These input data are important in the process of assessing and classifying alternatives in the ELECTRE III method. The matrix is constructed with the ordinal or cardinal scales used to assess the alternatives.

❹ The fourth step involves weighting the criteria. Each criterion is weighted to reflect its relative importance to the other criteria. These weightings are generally determined using judgement methods, such as questionnaires or interviews with experts. In the case of this expert appraisal, several sets of weights were tested in order to evaluate the robustness of the rankings according to the uncertainty expressed by the experts about the relative importance of the different criteria.

❺ The fifth step involves classifying the alternatives, using the concordance and discordance indices. Alternatives with high concordance indices and low discordance indices will be considered the best.

ANNEX 7: SENSITIVITY ANALYSIS FOR CLASSIFYING UOS

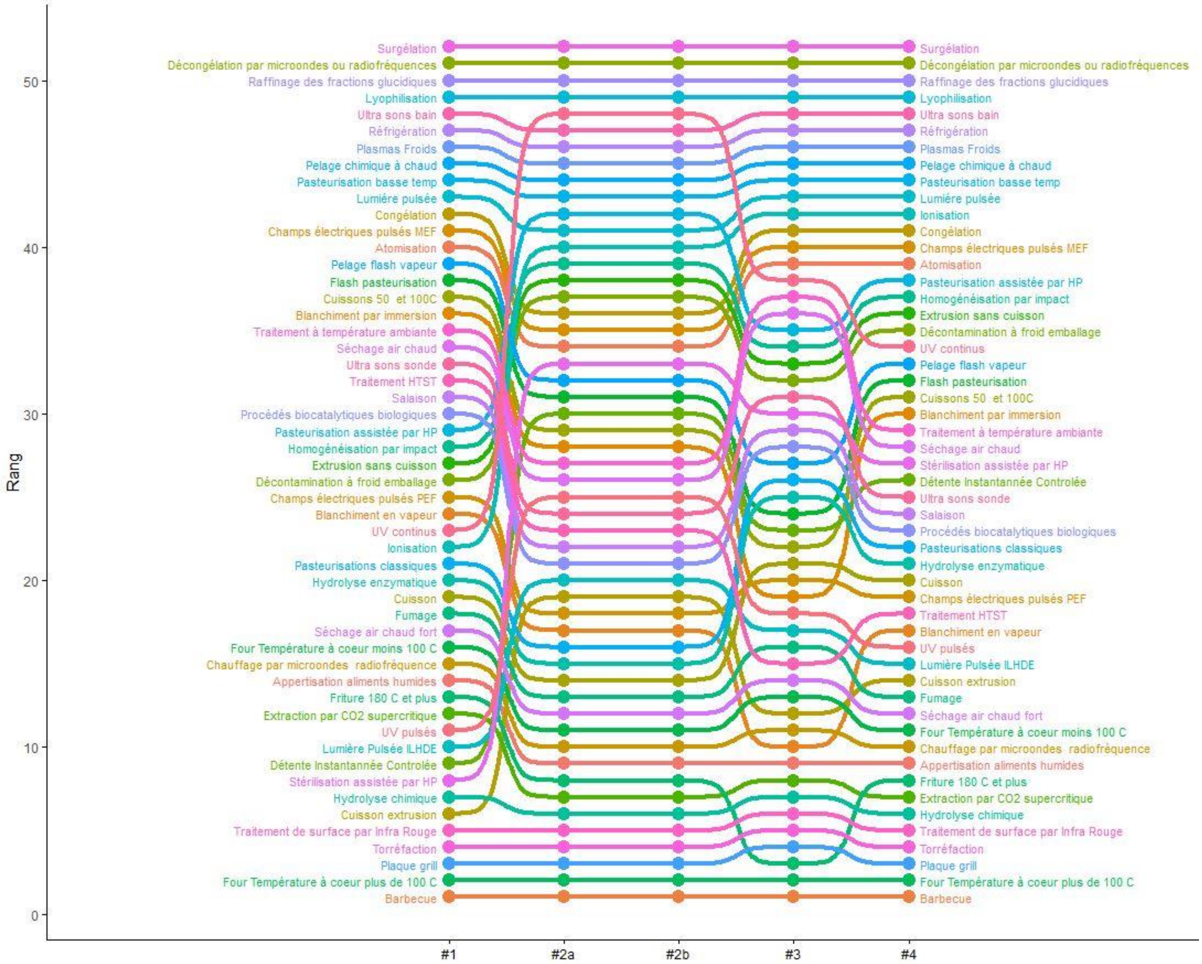
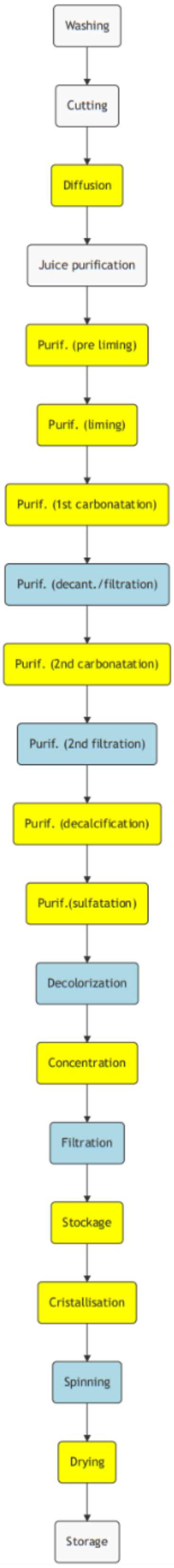


Figure A5.1. Classifications obtained with the different scenarios varying the sets of weights for the different criteria (from left to right: scenario #1, #2a, #2b, #3, #4, see Table 3).

The unit operations most likely to give rise to newly-formed substances are located in the lower part of the figure.

ANNEX 8: CONSIDERATION OF OPERATIONS TO ELIMINATE UNDESIRABLE NEWLY-FORMED SUBSTANCES



The sugar manufacturing process comprises 21 unit operations (UOs), 11 of which are used to eliminate undesirable substances (impurities, processing aids and newly-formed substances).

The UOs shown in yellow are those likely to generate newly-formed substances. The UOs enabling them to be eliminated are shown in blue. In the end, only one UO (drying) was counted for ranking purposes.

Figure A6.1 Sugar manufacturing procedure

ANNEX 9: SUPPLEMENTS TO THE SECTION ON THE AGENCY CONCLUSIONS AND RECOMMENDATIONS FOR FOOD PROCESSING

A9.1 Variability of practices and impact on product categorisation: the example of cereal products

Cooking cereal products generates major newly-formed substances such as acrylamide and 5-hydroxymethylfurfural (HMF) through Maillard reactions that occur during heat treatments (such as baking, toasting and extrusion cooking) used in cereal processing. This formation is promoted by high temperatures and low water content. HMF is closely linked to the formation of colours and flavours, particularly in bread crust, a characteristic appreciated by consumers, whereas acrylamide is strictly undesirable. A wide range of variation in acrylamide and HMF levels in cereal products has been reported in the literature. For example, for acrylamide, the median and mean values (in µg/kg) were, respectively, 169 and 317 for biscuits, 50 and 136 for breads, and 100 and 156 for breakfast cereals (Capuano and Fogliano 2011). In cereals, the amount of asparagine naturally found in the grains and flours controls the acrylamide levels (Halford, Raffan and Oddy 2022). The level of asparagine varies according to the varieties, for example in wheat, and between cereal species (levels: rye > wheat > maize) (Halford, Raffan and Oddy 2022).

The variability of the presence of these newly-formed substances within the main categories of cereal products is examined below, depending on whether they are manufactured domestically or industrially.

- Bakery products

Traditional French bread made artisanally and industrially-produced bread, such as sandwich bread, involve strictly the same processing UOs. They differ essentially in the way their recipes are formulated (added fat and sugars, corrective food additives in the sandwich bread; these additives are totally or partially absent from artisanal breads). The formation of acrylamide and HMF is particularly high in the crust because the surface reaches a higher temperature than the centre of the loaf. It is therefore important to avoid excessive browning of the crust to limit the occurrence of newly-formed substances, for example by choosing a lower temperature and a longer cooking time. In this respect, industrial sliced bread, in particular crustless, which is a typical example of an "ultra-processed" food, presents conditions that are less favourable to the generation of newly-formed substances than artisanal bread with a thick crust. A long fermentation time and an acid pH, conditions that are typical of sourdough fermentation, reduce acrylamide formation by limiting the availability of asparagine. On the other hand, the use of wholemeal flours, which are beneficial from a nutritional point of view, promotes the formation of acrylamide because these flours are richer in asparagine than refined flours.

- Biscuit products

The composition of biscuit products (dry biscuits, soft biscuits, cakes) is extremely diverse and based around the triptych flour, fat (oil or butter) and sugar (sucrose, glucose syrup, honey), amplified by the presence of other ingredients, for example chocolate. This formulation has an impact on the occurrence of newly-formed substances. The use of glucose syrup (reducing sugar) instead of sucrose (non-reducing sugar) in certain industrial recipes is a factor increasing acrylamide levels, as is the use of honey or caramel as a sweetener (Rannou *et al.* 2016). In industrial practice, baking times and temperatures are strictly controlled (typically 180-240°C, 12 to 15 min for dry biscuits), which is important for limiting the occurrence of newly-formed substances, unlike domestic practice where these parameters are less controlled.

- Breakfast cereals

Breakfast cereals encompass products manufactured using a variety of processes, essentially flaking, swelling and extrusion cooking. The resulting petals, flakes and puffed grains may then be coated in sugar, chocolate or honey. Consequently, the level of newly-formed substances is not significantly higher in sweetened breakfast products, whether they contain chocolate, or not (Morales, Mesías and Delgado-Andrade 2020). However, their nutritional composition is very different. Extrusion conditions with a higher water content and a lower die temperature can limit the formation of acrylamide and HMF (Rannou *et al.* 2016).

A9.2 Points requiring attention

Food processing enables society's demands to be met, particularly in terms of cost, sustainability and dietary diversity. These societal demands sometimes conflict with each other (Prache *et al.* 2020). By adapting production techniques, the agri-food industry can not only improve the nutritional quality of food while limiting production costs, but also meet the specific needs of various consumer groups, including those with restricted or special diets. This adaptability is necessary to offer alternatives that respond to growing ethical, environmental and economic concerns (Batista *et al.* 2023; Cao and Miao 2023; Guiné *et al.* 2020). Two relevant examples of this adaptation are the creation of substitutes for cheeses and meat-based products, and the production of gluten-free foods.

Processing methods and substitutes for products of animal origin

The INCA 3 study carried out over the period 2014-2015 revealed that 0.13% of the adult French population excludes animal products (meat, fish and eggs, as well as milk and dairy products) from their diet. Consumer intentions indicate an upward trend in this type of diet (de Gavelle *et al.*, 2019). Industrial production of plant-based foodstuffs for vegetarians and vegans has developed considerably in Europe in recent years (Saari, Herstatt, Tiwari, Dedehayir, & Mäkinen, 2021). New food products imitating products of animal origin are now available on the market.

Plant-based meat substitutes, designed to mimic the texture, taste and appearance of meat, can involve UOs that transform plant proteins into meat-like products. Extrusion is the most commonly used process for manufacturing meat substitutes. Plant proteins of varying purity (extracted from soy, peas or wheat, for example) are mixed with water and other ingredients, heated under high pressure and subjected to high shear (Vallikkadan *et al.* 2023). The mixture is then forced through a die, causing a change in structure that results in a fibrous texture similar to meat. There are alternative technologies not involving heat, such as the use of high pressure and ultrasound for legume proteins (Sridhar *et al.* 2022). However, these processing methods can be associated with the generation of newly-formed substances, which raises health concerns. For example, high-temperature extrusion is one of the UOs most likely to promote the presence of newly-formed substances. This illustrates the potential contradiction between the dietary transition towards more plant-based diets and the health concerns this may generate.

Processing methods and gluten-free products

The development of gluten-free products meets the medical need for people with coeliac disease (0.5 to 1% of the French population[34]) to avoid gluten in the diet. It also responds to growing societal demand to address symptoms grouped under the term "gluten intolerance".

Different cereals such as rice or maize naturally lack the proteins responsible for digestive problems and do not have the functional properties associated with wheat gluten. These properties are essential for the formation of a visco-elastic dough, which is needed for the manufacture of many products (bread, cakes, pizza dough, etc.). To compensate for this absence, the manufacture of gluten-free products requires the addition of numerous food additives and/or processing aids such as thickening hydrocolloids, emulsifiers or enzymes, in order to improve their texture and organoleptic acceptability to consumers.

As a result, gluten-free products can often be described as "ultra-processed", due to the need for multiple technological interventions, particularly relating to the formulation, designed to compensate for the loss of functional properties associated with gluten. It would be useful to investigate the potential impact of these specific production strategies on the probability of occurrence of known newly-formed substances.

A9.3 Consumer practices

Frying process: generation and control of newly-formed substances

Consumption of deep-fried food products accounts for a considerable proportion of the French diet. Among fried foods such as doughnuts, crisps, breaded fish and meat, meat fondue or tempura, French fries remain the most widely consumed food in both domestic and out-of-home catering settings, in line with changing lifestyles.

The deep-frying process involves a cooking UO that dehydrates the product, modifies its internal structure to make it soft (gelatinisation of the starch) and forms a crust on the surface for crispness. Numerous exchanges take place between the heat transfer fluid and the food during the heat treatment, which lasts a few minutes at a temperature of 175 to 190°C. This is the case with water vapour, which draws sugars, water-soluble vitamins and proteins into the oil bath, but also with the absorption of oil by the potatoes (15% for French fries; 40% for crisps), which generally occurs when they come out of the fryer as a result of condensation.

Although relatively short, this heat treatment results in the hydrolysis of triglycerides and the occurrence of newly-formed substances leading to the release of free fatty acids, monoglycerides and diglycerides (Mahmud *et al.* 2023; Ganesan and Xu 2020). Unsaturated fatty acids are susceptible to oxidation at high temperatures, generating oxidised glyceride compounds and polymerisation reactions, leading to the formation of polar compounds (Rani *et al.* 2023; Quek *et al.* 2023). Daily monitoring of this parameter, which must not exceed 23%, using instrumental measurements in out-of-home catering facilities, guarantees the quality of the frying oil (Fatima *et al.* 2023). If this is not the case, the oil in the fryer must be changed.

Other newly-formed substances are generated during the deep-frying process. One such example is acrylamide, classified respectively as a Group 2A substance (probably carcinogenic to humans), according to the International Agency for Research on Cancer (IARC, 1994) (Martínez Steele, Buckley and Monteiro 2023; Verma *et al.* 2023). Acrylamide is

[34] https://www.snfge.org/grand-public/maladies-digestives/maladie-coeliaque

formed at temperatures above 120°C and in conditions of low humidity, when asparagine (an amino acid) reacts with reducing sugars such as glucose in the Maillard reaction (Yassin *et al.* 2022).

Classified in Group 4 of the Nova classification, i.e. considered as ultra-processed foods, deep-fried foods often undergo prior UOs during their industrial preparation (but not in domestic preparation) designed to limit the occurrence of these newly-formed substances during heat treatment.

For example, blanching French fries (in hot water at 90°C for 10 minutes) will inactivate the enzymes that could potentially break down the triglycerides and extract the reducing sugars responsible for acrylamide formation. This step reduces the concentration of this newly-formed substance by 60%. Use of a processing aid such as asparaginase (which hydrolyses L-asparagine into L-aspartate and ammonium) and a temperature below 176°C also limits the occurrence of this substance (Yassin *et al.* 2022).

Specific treatments can also be applied to French fries before the frying step to limit the amount of oil absorbed. Solutions of pectin, methylcellulose, carboxy methylcellulose, hydroxypropyl methylcellulose, maize starch, chitosan, guar gum or sodium caseinate (Liberty, Dehghannya and Ngadi 2019; Dehghannya and Ngadi 2023) or the use of oleogels can reduce oil absorption by French fries (Mahmud *et al.* 2023).

It is also possible to limit oxidation phenomena in fryers by choosing temperature-resistant frying oils and filtering them (Ganesan and Xu 2020; Mahmud *et al.* 2023; Başaran and Turk 2021).

Cooking meat

Cooking meat is an essential process for microbiological safety (Augustin *et al.* 2020) and organoleptic aspects (Kondjoyan *et al.* 2014). It can, however, lead to the generation of newly-formed substances that are undesirable for health (ANSES 2015). These substances, such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic aromatic amines (HAAs), are mainly formed during high-temperature cooking, particularly when using UOs such as grilling or barbecuing. The mechanism by which these substances occur involves pyrolysis reactions of meat fats and proteins, where high temperatures break down amino acids, sugars, fatty acids and creatine into more complex and potentially toxic substances (Gibis 2016).

To prevent these newly-formed substances occurring during the cooking of meat, several strategies can be adopted on both an industrial and domestic scale. Using marinades before cooking can significantly reduce the formation of PAHs and HAAs. Reducing cooking times, lowering cooking temperatures (Duedahl-Olesen and Ionas 2022) and avoiding direct contact between meat and flames are also effective methods. In addition, frequently turning the meat and removing burnt parts can help minimise the health risks associated with these newly-formed substances (Jakobsen *et al.* 2018).

When comparing industrial and domestic cooking methods, it is interesting to note that industrial processes are often better controlled (Pedreschi and Mariotti 2023). The food industry uses equipment that enables precise regulation of temperature and cooking time, thus reducing the formation of undesirable substances. On the other hand, when cooking at home, the lack of precise control and the use of high-temperature methods such as barbecuing can significantly increase the risk of formation of these substances (Jakobsen *et al.* 2018).

ANNEX 10: RESEARCH EQUATIONS DEFINED FOR THE SYSTEMATIC REVIEW

Search equation on PubMed (performed on 8 June 2023)

("food, processed"[MeSH Terms] OR "ultra process*"[Title/Abstract] OR "processed food*"[Title/Abstract] OR "ultraprocess*"[Title/Abstract] OR "food classification"[Title/Abstract]) AND ("neoplasms"[MeSH Terms] OR "cancer*"[Title/Abstract] OR "neoplas*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract] OR "leukemia"[Title/Abstract] OR "lymphoma"[Title/Abstract] OR ("mortality"[MeSH Terms] OR "mortality"[Title/Abstract] OR "death*"[Title/Abstract]) OR ("overweight"[MeSH Terms] OR "obesity"[Title/Abstract] OR "overweight"[Title/Abstract] OR "over weight"[Title/Abstract] OR "high BMI"[Title/Abstract] OR "low BMI"[Title/Abstract] OR "bmi change*"[Title/Abstract] OR "bmi increas*"[Title/Abstract] OR "increased bmi"[Title/Abstract]) OR ("diabetes mellitus"[MeSH Terms] OR "diabet*"[Title/Abstract]) OR ("stroke*"[MeSH Terms] OR "brain infarct*"[Title/Abstract] OR "cerebral accident*"[Title/Abstract] OR "vascular accident"[Title/Abstract] OR "myocardial failure"[Title/Abstract] OR "cardiac failure"[Title/Abstract] OR "cardiac event*"[Title/Abstract] OR "cerebrovascular accident*"[Title/Abstract] OR "cerebral infarct*"[Title/Abstract] OR "myocardial infarct*"[Title/Abstract] OR "myocardial stroke*"[Title/Abstract] OR "myocardial attack"[Title/Abstract] OR "cardiovascular stroke*"[Title/Abstract] OR "cardiovascular attack"[Title/Abstract] OR "cardiovascular infarct*"[Title/Abstract] OR "heart stroke*"[Title/Abstract] OR "heart attack"[Title/Abstract] OR "heart infarct*"[Title/Abstract] OR "heart failure"[Title/Abstract] OR "cardiovascular disease*"[Title/Abstract] OR "cardiovascular event*"[Title/Abstract] OR "cardiovascular diseases"[MeSH Terms] OR "hypertension"[Title/Abstract] OR "blood pressure"[Title/Abstract] OR "arterial pressure"[Title/Abstract] OR "hypertension"[MeSH Terms] OR "aortic tension"[Title/Abstract] OR "aortic pressure"[Title/Abstract] OR "cardiac insufficiency"[Title/Abstract] OR "atrial fibrillation*"[Title/Abstract] OR "coronary heart disease*"[Title/Abstract] OR "cerebrovascular disease*"[Title/Abstract]))

Search equation on Scopus (performed on 7 June 2023)

(TITLE-ABS-KEY ("ultra process*" OR "processed food*" OR "ultraprocess*" OR "food classification")) AND ((TITLE-ABS-KEY ("brain infarct*" OR "cerebral infarct*" OR "myocardial infarct*" OR "myocardial stroke" OR "myocardial attack" OR "myocardial failure" OR "cardiovascular stroke" OR "cardiovascular attack" OR "cardiovascular infarct*" OR "heart stroke" OR "heart attack" OR "heart infarct*" OR "heart failure" OR "cerebral accident*" OR "vascular accident*" OR "cardiac failure" OR "cardiac event*" OR "cerebrovascular accident*" OR "cardiovascular disease*" OR "cardiovascular event*" OR "hypertension" OR "blood pressure" OR "arterial pressure" OR "aortic tension" OR "aortic pressure" OR "cardiac insufficiency" OR "atrial fibrillation*" OR "coronary heart disease*" OR "cerebrovascular disease*")) OR (TITLE-ABS-KEY (obesity OR overweight OR "over weight" OR over-weight OR (bmi) W/2 (chang* OR increas* OR variation OR high OR low OR gain))) OR (TITLE-ABS-KEY ("diabet*")) OR (TITLE-ABS-KEY (cancer* OR neoplas* OR "tumor*" OR "tumour*" OR "leukemia" OR "lymphoma")) OR (TITLE-ABS-KEY (mortalit* OR "death*")))

ANNEX 11: LIST OF ARTICLES EXCLUDED DURING PHASE 2 OF THE SELECTION PROCESS AND REASONS FOR THEIR EXCLUSION

This annex consists of an Excel file available on the website.

ANNEX 12: TABLE EXTRACTING THE DATA OF INTEREST FROM THE SELECTED PUBLICATIONS

This annex consists of an Excel file attached separately.