Insights on Novel foods Risk Assessment

Nutrition Unit
Risk Assessment of Novel Foods

EFSA Nutrition Unit

Novel Foods Working Group

NDA Panel

Regulation (EU) 2015/2283 on Novel foods
Novel foods (NF) are “foods or ingredients that have not been used for human consumption to a significant degree in the EU before 15 May 1997”.


EFSA has a legal deadline to adopt its scientific opinion within 9 months from the date of receipt of a valid application from the EC.

Data requirements for NF applications are outlined in “EFSA Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283”.
Novel Foods Categories

- New production process
- New or modified molecular structure
- Micro-organisms, fungi, algae
- From plants or their parts
- Of mineral origin
- From animals or their parts
- Cell or tissue cultures derived from animals/plants/fungi/algae
- Engineered nanomaterials
Novel Foods Applications by Category

Diversity & Complexity

### Examples of Novel Foods

<table>
<thead>
<tr>
<th>Newly synthesized/isolated compounds</th>
<th>New Sources</th>
<th>New Processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic Lycopene</td>
<td>Chia seeds</td>
<td>UV-treated milk</td>
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<tr>
<td>Non-sticky chewing gum base</td>
<td>Baobab fruit</td>
<td>Milk products fermented with (B.xylanisolvens)</td>
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<td>Ice-structuring protein</td>
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<td>Noni Juice</td>
<td>Astaxanthin from (H.pluvialis)</td>
<td>UV-treated yeast</td>
</tr>
</tbody>
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EFSA’s Novel Foods Group
Safety Assessment of Alternative Proteins and their Sources as Novel Foods

Ermolaos Ververis, Ruth Roldan Torres

Nutrition Unit
Presentation Outline

Introduction
- Current interest
- The “Novel” status
- General Considerations & Challenges
- Sources and formulations

Animal-derived alternative proteins
- Insects
- Cultured meat

Non-animal alternative proteins
- Plants
- Algae
Alternative Proteins: Current Interest

- New technologies
- Environmental sustainability
- Innovation
- Ethics/Animal welfare
- Health considerations
- Nutrient Composition

European Food Safety Authority
Alternative Proteins: the “Novel” Status

- Newly synthesised compounds
- New Sources
- Traditional Foods from non-EU countries
- New Processes

Regulation (EU) 2015/2283 on Novel Foods
EFSA Novel Food Guidance (2016)

EFSA shall consider the following:

- whether the NF is **safe** under the proposed conditions of use
- whether the normal consumption of the NF would be **nutritionally disadvantageous**
Tiered Toxicity Testing Approach by EFSA

- Tier 1:
  - Absorption
  - Genotoxicity (in vitro)
  - Extended 90-day toxicity study (in vivo)

- Tier 2:
  - ADME: single dose
  - Genotoxicity (in vivo)
  - Chronic toxicity
  - Carcinogenicity
  - Extended One-Generation Reproductive Toxicity Study (EOGRTS)
  - Prenatal developmental toxicity

- Tier 3
  - ADME: repeated dose, volunteer studies
  - Carcinogenicity: Mode of Action
  - Reproductive and Developmental toxicity
  - Specialised studies (immunotoxicity, neurotoxicity, endocrine activity, mode of action)

Triggers Tier 2:
- Systemic availability
- Toxicity in the 90-day study
- Positive in vitro genotoxicity

Triggers Tier 3:
- Bioaccumulation
- Positive in vivo genotoxicity
- Chronic carcinogenicity
- Repro and developmental toxicity
Applicable default uncertainty factor:

- Animal → Humans: 10
- Interindividual differences in humans: 10
- Subchronic → chronic exposure: 2

UF of **200 (10 x 10 x 2)** as a default margin of exposure between the reference point (RP) of a subchronic study (no adverse effect level or benchmark dose lower confidence limit) and the estimated high percentile human exposure.

UF can be lowered depending on other available data (e.g. nature, type and history of use of the NF and/or its source, compositional data, production process, human data on the endpoint used as the RP etc).

NF consisting largely of macronutrients usually cannot be readily tested at doses 100 or 200 times higher than the intended human intake.

EFSA Guidance on conducting subchronic toxicity study in rodents on whole food/feed
Animal Toxicity Testing

Need for toxicological studies

- Quality & extent of compositional data
- Other starting materials
- Processing e.g. fractionation, enrichment, condensation
- Scarce literature data
- No history of use of the NF and its source

European Food Safety Authority
Alternative Proteins – Examples
Animal-derived Alternative Proteins and their Sources

Insects & Products thereof
Insects as Food around the World

Around 2000 insect species reported to be consumed as food.
Insects & Products thereof as Novel Foods

(NF dossiers received by EFSA)
November 2020

11 EFSA Risk assessment
4 EFSA Suitability check

7 Adults
2+2 Acheta domesticus
1+1 Locusta migratoria
1 Gryllodes sigillatus

8 Larvae
4 Tenebrio molitor
1+1 Alphitobius diaperinus
1 Hermetia illucens
1 Apis mellifera
Processing & Formulations

(in the NF dossiers arrived at EFSA)

Blanching
- Drying (oven, lyophilisation)
  - Whole, dried
    - Grinding (powder)
  - Freezing/refrigeration
    - Whole, “wet”
      - Grinding (paste)

Freezing
- Blanching
- Defatting
  - Grinding (powdered fraction)

Freezing
- Whole (raw)
Safety Assessment: Main Considerations

Production process

**Insect species**
- Physical hazards/risks
- Developmental stage
- Endogenously produced compounds

**Farming**
- Rearing conditions
- Feeding substrate

**Harvest & killing**
- Fasting step
- Intestinal track not removed
- Separation of insects from frass, decayed animals

**Processing**
- Microbiological aspects
- Processing contaminants
- Stability
Characterisation & Specifications

- Whole insects: complex foods
- Qualitative and quantitative characterisation of the main constituents & proximate analysis
- Nutritionally relevant constituents (e.g. vitamins, minerals)
- Inherent substances of possible concern to human health
- Impact of feed (bioaccumulation/cross-contamination)
- Collection & extrapolation of data from literature
- Stability (microbiological & oxidative stability of fats)
- Processing contaminants
- Quantification of protein and interference of chitin
- Analytical accreditations are matrix-related
Safety Assessment: Main Considerations

History of Use

- Precautions and restrictions of use (e.g. removal or parts before preparation and consumption)
- Role in the diet of other populations & non-food uses

Proposed Uses, Use Levels & Intake

- Form of uses & food categories to be used must be clear
- Exposure assessment as appropriate
Safety Assessment: Main Considerations

**Nutritional Information**

- Protein quantification, non-protein nitrogen of chitin, nitrogen-to-protein conversion factor
- Protein quality (e.g. amino acids, digestibility)
- Antinutritional factors (e.g. inhibiting absorption or modifying bioavailability)

**Allergenicity**

- *de novo* sensitization
- Cross-reactivity
- Allergens from the feed (e.g. gluten)
- Chitin
Animal-derived Alternative Proteins and their Sources

Cultured (*in vitro*) Meat
What is cultured (in vitro) Meat?
Safety Assessment: Main Considerations

**Identity**

Foods consisting of, isolated from or produced from cell culture or tissue

- Biological source (International codes of nomenclature)
- Organ and tissue or part of the organism
- Information on the identity of cells
- Type of culture
- Stem cells, laboratory, culture collection
- Cell or tissue substrate used as a novel food

**Characterisation**

- Identities and quantities of impurities, by-products or residues, antimicrobial residues
- Nutritionally relevant constituents
- Biological hazards: BSE/TSE, viruses (source, zoonotic), microbiological contaminants
- Type and spectrum of target analytes depending on sources and production process
Safety Assessment: Main Considerations

Production Process

Detailed description including:

- Treatment, modification, immortalisation of cells
- Raw materials, starting substances, medium/substrate, growth factors/hormones, culture conditions, antimicrobials, hygiene measures, description of the equipment.

Generic issues related to manufacturing processes using cultured cells:

- Potential by-products, impurities, contamination, stability of cells, consistency of the production process
- Operational limits and key parameters of the production process
Nutritional Information

- Role of the NF in the diet (based on the intended uses)
- Comparative approach with conventional meat
- Quality and quantity of macro & micronutrients

Allergenicity

- Basis: comprehensive compositional data
- Potential use of «omics» tools (genomics, transcriptomics, proteomics, metabolomics)
Plants & Products thereof as Novel Foods
Processing & Formulations

**Input**
- Whole plants
- Grains or seeds, and their derivates (e.g. flours)
- Part of plants (e.g. leaves, roots)

**Output**
- Protein-based powders/extracts
- Protein isolates/concentrates
- Others (e.g. fermented protein mixtures)

**Processing**
Safety Assessment: Main Considerations

Production process

**INPUT**

- Fertilizer composition
- Pesticide residues
- Growth medium
- Primary/secondary metabolites
- Water/ground contamination
- Environmental and transportation conditions

**PROCESSING**

- Heat-treatment
- Reduction of antinutrients
- Off-flavours
- Extraction solvents
- Process enzymes
- Fermentation
- Toxic compounds from Maillard reaction
Characterisation & Specifications

- Contaminants & undesirable substances
  (e.g. primary & secondary metabolites, process enzymes and heavy metals, residues of cultivation conditions)
- Microbiological aspects
  (e.g. pH, water activity, microbial counts & toxins)
- Processing contaminants
  (e.g. thermal processing: lysinoalanine, Maillard reaction products, acrylamide)
- Stability markers
  (e.g. lipid oxidation markers, organoleptic attributes)
- Macro- and micro- nutrients
- Antinutritional factors
- Toxicants/allergens
Safety Assessment: Main Considerations

Characterisation & Specifications

Alfalfa protein concentrate
- 45 - 60 % protein
- L-canavanine
- Phytoestrogens (coumestrol and isoflavones)
- Saponins
- Phytate

Rapeseed powder & protein isolate
- Powder 33–43 % protein, isolate ≥ 90 % protein
- Glucosinolates
- Phytate
- Erucic acid

Chia seeds
- seeds 15-26 % proteins, powder ≥ 40 % protein
- Phenolic acid derivatives and flavonoids
- Process contaminants
Safety Assessment: Main Considerations

Nutritional Information

Protein digestibility

Aminoacid profile

Antinutrients
Safety Assessment: Main Considerations

Allergenicity

- Scarce evidence in the existing literature
- *de novo* sensitization
- Cross reactivity (e.g. rapeseed with mustard)
- Potential impact of the production process
- Mixture of various proteins
Non-animal Alternative Proteins and their Sources

Algae & Products thereof
Algae & Products thereof as Novel Foods

Examples of NF applications

Macroalgae
- *Laminaria digitata*

Microalgae
- *Galdieria sulphuraria*
- *Schizochytrium* sp.
- *Phaeodactylum tricornutum*
- *Tetraselmis chuii*
Safety Assessment: Main Considerations

Identity

- Scientific name & synonyms
- Verification according to internationally recognized databases and methodology
- Deposition in an officially recognized culture collection
- Qualified Presumption of Safety (QPS) status

Production Process

- Fermentation/cultivation conditions (e.g. time, temperature, pH, presence of light, open vs. close systems)
- Culture medium constituents
- Downstream processing
- Absence/ presence of viable cells of the production strain in the NF
Safety Assessment: Main Considerations

**Characterisation**
- Nutritional composition (e.g. iodine)
- Algal toxins and other toxic substances (e.g. accumulation of heavy metals)
- Particle size distribution in case of dried biomass (powder)
- Stability tests in relation to their composition and the intended uses

**Allergenicity**
- Potential risk from algal proteins
- Potential use of proteomic analysis
Novel Carbohydrates as Novel Foods

Reinhard Ackerl, Gabriela Precup, Océane Albert

Nutrition Unit
Outline

- Novel fibre
- Human identical milk oligosaccharides
- Novel Foods intended to replace sugars
Novel Carbohydrates as Novel Foods

Novel Fibre
Manifold Sources and Production Processes

Sources:
- Plants
- Fungi
- Bacteria
- Yeast
- Algae
- Animals

Production processes:
- Chemical
- Enzymatic
- Fermentation
  etc.
## Adequate Intake for Dietary Fibre set by EFSA

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Dietary fibre (g/d)</th>
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<tbody>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2–3</td>
<td>10</td>
</tr>
<tr>
<td>4–6</td>
<td>14</td>
</tr>
<tr>
<td>7–10</td>
<td>16</td>
</tr>
<tr>
<td>11–14</td>
<td>19</td>
</tr>
<tr>
<td>15–17</td>
<td>21</td>
</tr>
<tr>
<td>≥ 18</td>
<td>25</td>
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</tbody>
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Mean dietary fibre intake in g/day in the EU:

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT</td>
<td>19.5</td>
<td>20.1</td>
</tr>
<tr>
<td>DK</td>
<td>21.0</td>
<td>19.0</td>
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<tr>
<td>FI</td>
<td>24.0</td>
<td>21.0</td>
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<tr>
<td>FR</td>
<td>18.7</td>
<td>15.7</td>
</tr>
<tr>
<td>HU</td>
<td>24.2</td>
<td>21.7</td>
</tr>
<tr>
<td>IE</td>
<td>23.2</td>
<td>17.4</td>
</tr>
<tr>
<td>IT</td>
<td>21.8</td>
<td>18.9</td>
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<tr>
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<td>20.9</td>
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<tr>
<td>SE</td>
<td>18.0</td>
<td>16.9</td>
</tr>
<tr>
<td>ES</td>
<td>19.2</td>
<td></td>
</tr>
</tbody>
</table>

|                |          |         |
| Males          | 15.0    | 14.3    |
| DE             | 17.5    | 16.8    |
| DK             | 18.0    | 17.0    |
| FR             | 13.5    | 12.2    |
| NL             | 17.0    | 15.2    |
| NO             | 16.0    | 15.0    |
| PL             | 19.6    | 14.0    |
| PT             | 20.2    | 17.4    |
| SE             | 14.0    | 19.4    |
| ES             |         | 13.0    |

- **Starting material**: starch, i.e. polymeric carbohydrate of numerous glucose units
- **Converted enzymatically** into a molecule with circular structure
- Six glucose subunits linked end to end via α-1,4 linkages
- cannot be hydrolysed by human amylases (salivary, pancreatic) anymore
Resistant Starch – chemically modified

- **Source**: high amylose maize starch
- **Chemically modified** (starch chains cross-linked and esterified with phosphate groups)
  - Creation of phosphated distarch phosphate = resistant starch (Type IV)
  - Digestibility is decreased
Chitin-glucan from *Aspergillus niger*

- Derived from the cell wall of the mycelium of *Aspergillus niger*
- Contains 90% chitin glucan
- Obtained by fermentation
- Non-toxic non-pathogenic strain (used for citric acid production)
Dried biomass

- History of use as feed not food, but it can be found in many types of cheese/dairy products
- ~25% fibre (beta-glucan)
- Yeast species received qualified presumption of safety (QPS) (based on extensive literature search)
- Yeast cells are heat-killed during the manufacturing process

Selenium-enriched *Yarrowia lipolytica*

Chromium-enriched *Yarrowia lipolytica*
Fibre-rich NF from Algae - *Euglena gracilis*

- Single-cell alga extensively used in laboratory as model organism
- History of food outside EU (Japan)
- Received **qualified presumption of safety** (QPS)
- >50% fibre (beta-glucan) in the NF, i.e. dried biomass.
Combination of 3 non-starch Polysaccharides

- Mixed in a specific (proprietary) ratio to produce the Novel Food (“PGX”)

- Konjac glucomannan
  - *Amorphophallus konjak*

- Xanthan gum
  - *Xanthomonas campestris*

- Sodium alginate
  - [Brown seaweed]
Ongoing Assessments

- Rhamnogalacturonan I - enriched carrot fibre (from carrot pomace)
- Chitosan - from exoskeletons of crustaceans
- Bacterial cellulose aqueous suspension (obtained by fermentation with *Komagataeibacter sucrofermentans*)
How Novel Foods enter the Food Chain

- Breads
- Biscuits/cookies
- Cereals/cereal bars
- Pasta
- Milk shakes
- Yoghurts
- Fruit and vegetable juices
- Non-alcoholic beverages
- Dairy desserts
- Meal replacement for weight control
- Infant and follow-on formula
- Food supplements

intention to increase fibre intake
## Implications for the Risk Assessment

- Live microorganism/heat-killed/pasteurised?
- History of use?
- Qualified presumption of safety (QPS)?
- Reagents of production process/residuals?
- Chemical contamination?
- Hygiene/microbiological risk (waste used as source)?
- Secondary metabolites/anti-nutrients of concern?
- Species (or closely related ones) toxin producer (e.g. aflatoxin)?
- Tolerable Upper Intake Levels (ULs) exceeded (e.g. Se-enriched Yarrowia)?
Novel Carbohydrates as Novel Foods

Human identical Milk Oligosaccharides (HiMOs)
Human Milk Oligosaccharides: Interest

- **HMOs**: 3rd largest solid component (after lipids and lactose) of the breast milk
- More than 150 HMOs identified
- **HiMOs**: main components of the NF-identical to HMOs
- Applications in food products and for infant nutrition (IF, FOF)
Human identical Milk Oligosaccharides as Novel Foods in the EU

- 2'-O-fucosyllactose (2'-FL) (EFSA, 2015)
- lacto-N-neotetraose (LNnT) (EFSA, 2015)
- LNnT and 2'-FL in food supplements for children (EFSA, 2015)
- N-acetyl-D-neuraminic acid (NANA) (EFSA, 2017)
- 2'-FL/difucosyllactose mixture (EFSA, 2019)
- lacto-N-tetraose (LNT) (EFSA, 2019)
- 6′-Sialyllactose (6′-SL) sodium salt (EFSA, 2020)
- 3′-Sialyllactose (3′-SL) sodium salt (EFSA, 2020)
- Lacto-N-neotetraose (EFSA, 2020)
- 3-fucosyllactose (3-FL)(2) (EFSA, 202X)
- 2'-FL (EFSA, 202X)
- 3′-Sialyllactose (3′-SL) (EFSA, 202X)
- 6′-Sialyllactose (6′-SL) (EFSA, 202X)
- Lacto-N-tetraose (LNT) (EFSA, 202X)
Main Considerations for Safety Assessment

Identity

- Food with a new or intentionally modified molecular structure*
- Food consisting of, isolated from or produced from microorganisms, fungi or algae *
- Information on the NF source
- Chemical & structural characterization of the NF vs natural HMOs

Production Process

- Chemical synthesis or fermentation by genetically modified microorganisms (GMM, e.g. *E.coli*)
  - check for absence of DNA, byproducts and antimicrobial resistance genes
  - impurities and solvents

*Regulation (EU) 2015/2283
Characterisation & Specifications

- Qualitative and quantitative characterisation of the main constituents & proximate analysis
- Substances of possible concern to human health (residual endotoxins)
Main Considerations for Safety Assessment

Proposed uses, use levels and anticipated intake

- Uses for infant and follow-on formulae, variety of food and food supplements as proposed
- Appropriate exposure assessment from different foods in various population categories
**Anticipated intake:**

- Define an **appropriate natural level** (representative concentration of a given HMO) in breast milk, based on literature data
- Estimate a **possible maximal natural intake** of the HMO per kg bodyweight of infants
- Estimate a **possible maximal intake** of the HiMO per kg bodyweight of infants further to NF intake
- Compare the **intake of HiMO** per kg bodyweight to the **natural intake** of HMOs from breast milk

- **A possible consumption that does not exceed a natural intake** is considered **safe**
Toxicological information

- Limited toxicological studies (Tier I) as per guidance
- Genotoxicity studies to rule-out specific concerns (e.g. for impurities)
- Sub-chronic studies (e.g. 90-day) provide insight on the behaviour of the NF
- Sometimes limited margin of exposure in comparison with the anticipated intake

Nutritional information

- Non-digestible oligosaccharides, negligible nutritional impact
- Demonstration that they are not nutritionally disadvantageous
Novel Carbohydrates as Novel Foods

Intended to replace Sugars
Food Additives or Novel Foods?


  "monosaccharides, disaccharides or oligosaccharides and foods containing these substances used for their sweetening properties are not considered to be food additives"

- Therefore, all mono-, di- and oligo-saccharides with new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997 are considered NOVEL FOOD
NF intended to replace sugars are often obtained by enzymatic reactions

**Food enzymes** covered by Regulation (EC) No 1332/2008, not by the Novel food Regulation (EC) 2015/2283

**However:**
- Evaluation of food enzymes **ongoing** at EFSA
- No **Union List** of authorized enzymes established by the EC yet

Request for information according to the Guidance on the characterisation of microorganisms used as feed additives or as production organisms (EFSA, 2018) and Characterisation of microorganisms used for the production of food enzymes (EFSA, 2019)
If a NF consists, contains or is produced:

- with a microorganism
  - evaluation for **Qualified Presumption of Safety (QPS)** by the Biohazard Panel
- with a microorganism *which has been granted QPS*
  - the NDA Panel would not question the safety of that microorganism
  - other safety aspects of a Novel Food will have to be assessed and additional data may be requested

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**QPS is granted at the taxonomic species level**

**QPS is generally not applied to genetically modified microorganisms**
Challenges in Toxicity Testing

- Default tiered toxicological approach (including Tier 1 absorption, genotoxicity and subchronic toxicity studies) not always optimal/possible

- Possible alternatives/solutions:
  - Good compositional characterisation of the NF
  - Control group(s)
  - Human studies

- Mixtures
- Macronutrients
- Low- & non-digestible carbohydrates

Genotoxicity testing?
Limited margin of exposure
Difficult discrimination between toxicological and metabolic/adaptive effects in rodents
Human clinical trials may provide supportive evidence to investigate potential adverse effects provided they are:

- Absence of adverse effects in human clinical trials is not necessarily evidence of safety
- History of use (human consumption) outside the EU can also prove useful
Outline

- Plant extracts
- (Synthetic) cannabidiol
- Engineered nanomaterials

Focus on Food Supplements
- Vitamin and mineral substances in Annex I + II
- Art 4(6): EFSA assessed about 280 vitamin and mineral substances the majority until 2009

<table>
<thead>
<tr>
<th>No harmonised EU approach</th>
<th>No EU harmonised minimum or maximum levels for vitamins and minerals</th>
<th>No EU harmonised use of “other substances” (incl. botanicals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notification to the EU member state(s) may be required</td>
<td>UL, DRV and background intake to be considered (but subject to manufacturers &amp; national limits)</td>
<td>National provisions</td>
</tr>
</tbody>
</table>

If safety concerns are raised – risk managers, on its own initiative, EFSA could be tasked

- Novel Foods intended for FS may be also a new “nutrient sources”
FS in the EU – Role of the EFSA NDA Panel

- Vitamins and minerals: DRV\s including UL\s
- “Other substances” (safety – only upon request or own initiative)
- Health Claims (efficacy) – *botanicals on hold*
- New nutrient sources (safety and bioavailability)
- Novel Foods (safety)

- Other EFSA Panels for additives (e.g. food colour), GMO etc.
- **Specific target and restrictions of target population** possible, e.g. adults only. This is not applicable for NF intended to be added to foods like breakfast cereals, beverages, dairy products, breads, etc.... - Art 5 (6) of Implementing rules for Art 10 NF applications - Regulation (EU) 2017/2469. **Reasoning for restrictions**

- **Exposure assessment** = proposed maximum intake (possibly background intake) for the proposed target population

- **History of use (HoU) in food supplements** in third countries does not qualify for traditional foods from third countries.

- **HoU in food supplements within the EU**

- **HoU as drug**

- **HoU**: limited weight in establishing the safety of the NF, especially for plant extract given their diversity of their sources, processing, composition, historical conditions of use. However, data may be important.
Other Trends in Novel Foods

Plant Extracts
Plant Extracts – Diversity of Sources

With or without history of use of the source, its parts, for food, drug or other uses.
Diversity of the Production Process

- Plant part
- Production process
- Extraction solvent
- Fractions
- Isolated compounds from plant materials
- Mixtures of plant extracts
Available knowledge (botanicals & naturally-occurring substances)

- Identity of the plant source
- Chemical composition of the plant/plant part used
- Impact of manufacturing process to chemical composition

Available knowledge on reported toxicity/ adverse effects

- Toxicity of plants/plant preparation
- Toxicity of naturally occurring chemical substances (follow-up)
- Case reports

Literature search

EFSA Compendium of Botanicals*

*Database of naturally occurring substances of possible concern for human health when present in food
Other Aspects – Plant Extracts

- **Safety perspective** on presumed beneficial effects, mode of action
- **Toxicological aspects:** usually mixtures and uncharacterised fraction
  - Representativeness of the test material
  - Tiered toxicological approach (default UF of 200 on subchronic studies)
  - Genotoxicity assessment – usually a mixture
Genotoxicity Assessment of Novel Food
SCIENTIFIC OPINION

Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment

EFSA Scientific Committee

European Food Safety Authority (EFSA), Parma, Italy

This Scientific Opinion, published on 3 October 2012, replaces the earlier version published on 30 September 2011.
Tier 1

In vitro genotoxicity testing recommended test battery:
- Bacterial reverse mutation (Ames) assay (OECD TG 471)
- In vitro mammalian cell micronucleus test (OECD TG 487)

Tier 2 (follow-up of in vitro positives, to be selected case-by-case based on in vitro test results, SAR, metabolic and toxicokinetic considerations, etc.)

In vivo genotoxicity testing recommended tests:
- In vivo micronucleus test (OECD TG 474)
- In vivo comet assay (OECD TG 489)
- Transgenic rodent mutagenicity (TGR) assay (OECD TG 488)

The guidance continues considering examples of different scenarios for the in vivo follow up
Genotoxicity of mixtures

- **Chemically fully defined mixtures**: assessment of all the components, *i.e.* component-based approach

- **Mixtures containing substantial fraction of unidentified components**: identified components assessed individually, *i.e.* component-based approach

- **Unidentified fraction** should be tested as first option. If not feasible, testing of the whole mixture should be undertaken, *i.e.* whole-mixture approach

**Fully Chemically Defined Mixtures—Component Based Approach**

**FULLY CHEMICALLY DEFINED MIXTURE**

- WITH «known» *in vivo* genotoxic substances via a relevant route of administration
  - SAFETY CONCERN FOR GENOTOXICITY
  - Mixture WITH «potential» genotoxic components, e.g. positive results *in vitro* only
    - Additional data needed, e.g. appropriate *in vivo* testing
  - WITHOUT «known» *in vivo* genotoxic substances
    - NO SAFETY CONCERN FOR GENOTOXICITY

- For unavoidable «known» genotoxic contaminants or constituents risk assessment considerations apply

- If no carcinogenicity data, consider TTC approach (exposure < 0.0025 ug/kg bw/day) (SC, 2019)

- For genotoxic carcinogens, consider MoE approach (SC, 2005)

**NOT APPLICABLE TO NOVEL FOODS**
Mixture with Unidentified Components

**MIXTURE WITH UNIDENTIFIED COMPONENTS**

- **CHARACTERISED PART OF THE MIXTURE**
  - WITHOUT «known» *in vivo* genotoxic substances
  - WITH «known» *in vivo* genotoxic substances via a relevant route of administration

- **UNCHARACTERISED PART OF THE MIXTURE**
  - Test FRACTION
    - *In vitro* testing with *in vivo* follow-up testing in case of positive results *in vitro* (EFSA SC, 2011)
    - If not possible to isolate fraction, test WHOLE MIXTURE
      - IF POSITIVE
        - SAFETY CONCERN FOR GENOTOXICITY
      - IF NEGATIVE
        - Consider possible limitations of *in vivo* testing
          - NO SAFETY CONCERN FOR GENOTOXICITY

- Mixture WITH «potential» genotoxic components, e.g. positive results *in vitro* only
  - Additional data needed, e.g. appropriate *in vivo* testing

**EFSA SC, 2011**
Other Trends in Novel Foods

Synthetic Cannabidiol
Cultivation of *Cannabis sativa* L. is permitted provided they are registered in the EU’s ‘Common Catalogue of Varieties of Agricultural Plant Species’ and THC content does not exceed 0.2 % (w/w).

Extracts of *Cannabis sativa* L. and derived products containing cannabinoids are considered novel foods.

Synthetically obtained cannabinoids are considered as novel.

3 CBD under EFSA RISK ASSESSMENT
EMA has recently approved Epidyolex which active substance is CBD from the milled botanical raw material (Cannabis sativa L.). Epsydioplex is an adjunctive therapy for seizures associated with Lennox Gastaut syndrome (LGS) or Dravet syndrome (intractable childhood epilepsy) for patients 2 years of age and older.

EFSA assessment will perform an independent RA:
- Assessment is NOT based on risk-benefit
- EFSA target general population, not patients
- Different production process

Evaluation of CBD will follow the approach from EFSA NDA Guidance for NF
Other Trends in Novel Foods

Engineered Nanomaterials
Nanomaterials and Novel foods

**REGULATION (EU) 2015/2283**

**Article 3**

**Definitions**

(3) An *engineered nanomaterial* means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale.

Properties that are characteristic of the nanoscale include:

(i) those related to the large specific surface area of the materials considered; and/or

(ii) specific physico-chemical properties that are different from those of the non-nanoform of the same material.
Engineered nanomaterials

EFSA Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health (2018)

- 1 NF application as source of iron

Nanoparticles

Draft EFSA Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles (under finalisation)

- 7 NF applications under evaluation
Ongoing works and mandates of NDA Panel
## Ongoing Works and Mandates

| Novel foods / Nutrient sources | Art 10 NF applications: **74** in progress (of which 54 stop-clock for supplementary data)  
|                             | NS applications: **1** stop-clock for supplementary data |
| Foods for special groups     | Safety & suitability of Protein-hydrolysate formula: **4** stop-clock for supplementary data  
|                             | Efficacy in reducing risk of developing allergy: **1** stop-clock for supplementary data  
|                             | Total Diet Replacement for weight control: due **02/2021** |
| Health claims               | Art 13(5) new science/proprietary data: **2** in progress, **3** under validation |
| Tolerable Upper Levels      | Dietary sugars: due **12/2021** (Public consultation Summer 2021, Technical meeting with stakeholders September 2021)  
|                             | Selenium: due **03/2022** |
| Other mandates              | Safety of Alpha lipoic acid and insulin autoimmune syndrome (Art 8): due **04/2021**  
|                             | Dietary Folate Equivalent_CaLMF_5LTHF glucosamine salt: due **08/2022** |
| Transparency Regulation     | Updating eight Guidance documents: due **12/2020 / 01/2021** |
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