FOOD SAFETY AND STANDARDS AUTHORITY OF INDIA

Inspiring Trust, Assuring Safe & Nutritious Food

Ministry of Health and Family Welfare, Government of India

CHIFSS

CII-HUL Initiative on Food Safety Sciences

GUIDANCE DOCUMENT ON

RISK ASSESSMENT NOVEL FOODS AND FOOD ADDITIVES

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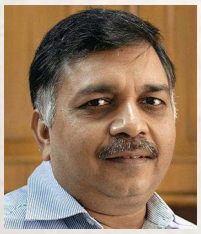

FOREWORD

It gives me immense pleasure to release this guidance document on Risk Assessment of Novel Foods and Food Additives. Given the complexities in the food processing sector, high demand of imported and exotic foods, and rising consumer concerns about food safety, it is important to instill confidence among regulators and trust among consumers by developing objective and transparent mechanisms for setting food safety standards. This is particularly relevant to Novel Foods & Additives therefore I congratulate CHIFSS on this pioneering effort. I am sure this will enable capability building among all relevant stakeholders driving the national food safety agenda.

(Pawan Agarwal)

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Preface

This **Guidance Document on 'Risk Assessment – Novel foods and food additives'** has been prepared with an intent to strengthen application of risk assessment methodology for advancing science-based food safety decision making.

The guidance outlines the four critical steps central to risk assessment - (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and, (iv) risk characterization with the help of case studies, and demystifies risk assessment through relevant case studies, and tools such as a decision tree.

This document is envisaged to be used for orienting the scientific panels to risk based thinking and will be shared with the wider food safety stakeholder communities.

We acknowledge the contribution of the experts from CHIFSS Steering Committee and Scientific Advisory Committee.

And special thanks to following experts for their valuable time and contribution who has helped to prepare this document –

- Dr Indrani Ghose, Strategic Advisor, CII-FACE
- Dr J Lewis, Food Safety Consultant
- Dr Jasvir Singh, Regulatory, Scientific and Government Affairs Leader – South Asia, Dupont Nutrition & Health
- Dr Nimish Shah, Director, Partnerships and Advocacy, Hindustan Unilever Ltd
- Dr Paul Hepburn, Programme Director Food and Refreshment, Safety and Environmental Assurance Centre (SEAC), Unilever, UK
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- Dr Sudarshan Rao, Ex NIN, Chairman-Scientific Panel (Additives), FSSAI
- Ms Surbhi Datta, Counsellor, CII-FACE

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We are also thankful to **CEO-FSSAI, Shri Pawan Kumar Agarwal** for his constant inspiration and encouragement, especially to contribute to food safety matters.

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Glossary

Term	Definitions
Food	Any substance, whether processed, partially processed or unprocessed, which is intended for human consumption and includes primary food, genetically modified or engineered food or food containing such ingredients, infant food, packaged drinking water, alcoholic drink, chewing gum, and any substance, including water used in the food during its manufacture, preparation or treatment, but does not include any animal feed, live animals unless they are prepared or processed for placing on the market for human consumption, plants (prior to harvesting), drugs and medicinal products, cosmetics, narcotic or psychotropic substances.
Food Additive	Any substance not normally consumed as a food by itself and not normally used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result (directly or indirectly), in it or its byproducts becoming a component of or otherwise affecting the characteristics of such foods, but does not include contaminants or substances added to food for maintaining or improving nutritional qualities.
Food contaminant	Any chemical or biological agent, extraneous matter or other substances which may be present in the food as a result of environmental contamination or in raw material and not intentionally added to food, which may compromise food safety or suitability.
Food Control	A mandatory regulatory activity of enforcement by national or local authorities to provide consumer protection and ensure that all foods during production, handling, storage, processing and distribution are safe, wholesome and fit for human consumption; conform to quality and safety requirements; and are honestly and accurately labeled as prescribed by law.

Term	Definitions
Food Hygiene	All conditions and measures necessary to ensure the safety and suitability of food at all stages of the food chain.
Food inspection	An examination, by an agency empowered to perform regulatory and/or enforcement functions of food products or stems for the control of raw materials, processing and distribution. This includes in-process and finished product testing to verify that they conform to regulatory requirements.
Food safety	Assurance that food is acceptable for human consumption according to its intended use.
Food safety management system	The adoption of Good Manufacturing Practices, Good Hygienic Practices, Hazard Analysis and Critical Control Point and such other practices as may be specified by regulation, for the food business.
Functional food	Food having one or more properties beneficial to human health by improving the state of health or reducing health risks in addition to its nutritional value. 'Functional foods' can be produced by either adding, removing, concentrating or modifying one or more components of a food or by modifying its/their bioavailability.
Good Agricultural Practice (GAP)	Practices of primary food producers (such as farmers and fishermen) that are necessary to produce safe and wholesome agricultural food products conforming to food laws and regulations.
Good Manufacturing Practices (GMP)	Conformance with codes of practice, industry standards, regulations and laws concerning production, processing, handling, labelling and sale of foods decreed by industry, local, state, national and international bodies with the intention of protecting the public from health, product adulteration and food fraud.
HACCP	A system which identifies, evaluates and control hazards which are significant for food safety.

Term	Definitions
HACCP Plan	A document prepared in accordance with the principles of HACCP to ensure control of hazards which are significant for food safety in the segments of the food chain under consideration
Hazard	A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.
History of safe use	Quantitatively and Nutritionally significant consumption of food by human species (over several generations and in a large, genetically diverse population) for which there exist adequate toxicological and allergenicity data to provide reasonable certainty that no harm will result from consumption of the food.
Ingredient	Any substance, including a food additive used in the manufacture or preparation of food and present in the final product, possibly in a modified form.
Monitoring	In a HACCP plan, the act of conducting a planned sequence of observations or measurements of control parameters to assess whether a critical control point is under control.
Novel food	Food that: • May not have a history of consumption by humans, or may not have a history of consumption in the region/ country of interest; or • May not have any history of consumption of any ingredient used in it or the source from which it is derived; or • A food or ingredient that is obtained by using new technology and/or innovative engineering process. This procedure may change the size, composition, or structure of the food or its ingredients – which may in turn change its nutritional value, metabolism, properties/ behavior or level of undesirable substances.

Term	Definitions
Primary Food	An article of food, being a produce of agriculture or horticulture or animal husbandry and dairying or aquaculture in its natural form, resulting from the growing, raising, cultivation, picking, harvesting, collection or catching in the hands of a person other than a farmer or fisherman.
Risk	In relation to any article of food, means the probability of an adverse effect on the health of consumers of such food and the severity of that effect, consequential to a food hazard.
Risk Assessment	A scientifically based process consisting of the following steps: (i) hazard identification; (ii) hazard characterization; (iii) exposure assessment; (iv) risk characterization.
Risk communication	The interactive exchange of information and opinions throughout the risk analysis process concerning risks, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.
Risk management	The process, distinct from risk assessment of evaluating policy alternatives, in consultation with all interested parties considering risk assessment and other factors relevant for the protection of health of consumers and for the promotion of fair-trade practices, and, if needed selecting appropriate prevention and control options.
SPS	Sanitary and phytosanitary agreement of the World Trade Organization.
Substantial equivalent	The concept is used to identify similarities and differences between the new food and its conventional counterpart and is useful as a starting point for the nutritional or safety assessment.
TBT	Technical barriers to trade agreement of the World Trade Organization
Traditional food	Foods having an assumed 'history of safe use' in the country in which they are used.

Abbreviations

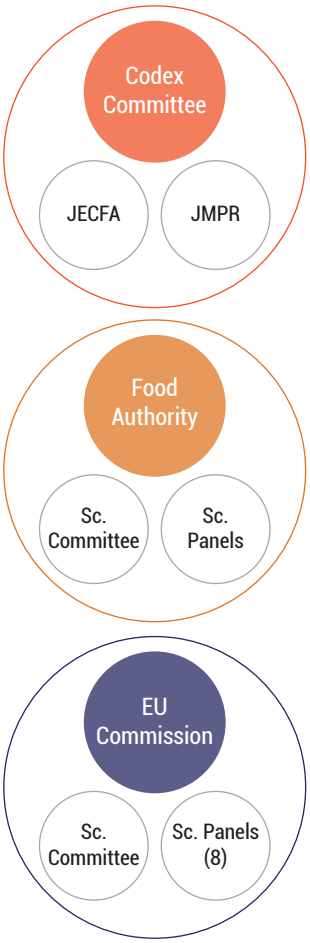
Sl. No.	Abbreviation	Expanded Form
1	ADI	Acceptable Daily Intake
2	ADME	Absorption, Distribution, Metabolism & Excretion
3	AOCS	The American Oil Chemists' Society
4	BMDL	Benchmark Dose (lower confidence limit)
5	CAC	Codex Alimentarius Commission
6	CAS	Chemical Abstracts Service
7	EC	European Commission
8	EFSA	European Food Safety Authority
9	EPA	The Environmental Protection Agency
10	EU	European Union
11	FSSA	The Food Safety and Standards Act'2006
12	FSSAI	The Food Safety and Standards Authority of India
13	GC-MS	Gas chromatography–mass spectrometry
14	GLP	Good Laboratory Practice
15	GM	Genetically Modified
16	GMP	Good Manufacturing Practices
17	HACCP	Hazard Analysis and Critical Control Point
18	HoSU	History of Safe Use
19	HPLC-UV	High-performance liquid chromatography – Ultra Violet
20	INS	International Numbering System
21	IPCS	International Programme on Chemical Safety
22	IR	Infrared
23	ISO	The International Organization for Standardization
24	IUPAC	The International Union of Pure and Applied Chemistry
25	JECFA	Joint FAO/WHO Expert Committee on Food Additives and Contaminants

Sl. No.	Abbreviation	Expanded Form
26	JMPR	Joint FAO/WHO Meeting on Pesticide Residue
27	LC-MS	Liquid chromatography–mass spectrometry
28	LOAEL	Lowest observed adverse effect level
29	NAS	National Academy of Sciences
30	NMR	Nuclear Magnetic Resonance
31	NOAEL	No Observed Adverse Effect Level
32	NOEL	No Observed Effect Level
33	OECD	Organisation for Economic Co-operation and Development
34	PBI	Protein Bound Iodine
35	PE	Phytosterol-esters
36	SCF	Scientific Committee of Food
37	TDS	Total Diet Study
38	TOR	Terms of Reference
39	TTC	The Threshold of Toxicological Concern
40	USFDA	US Food and Drug Administration
41	UV	Ultra Violet
42	UV -VIS	Ultraviolet–Visible Spectrophotometry

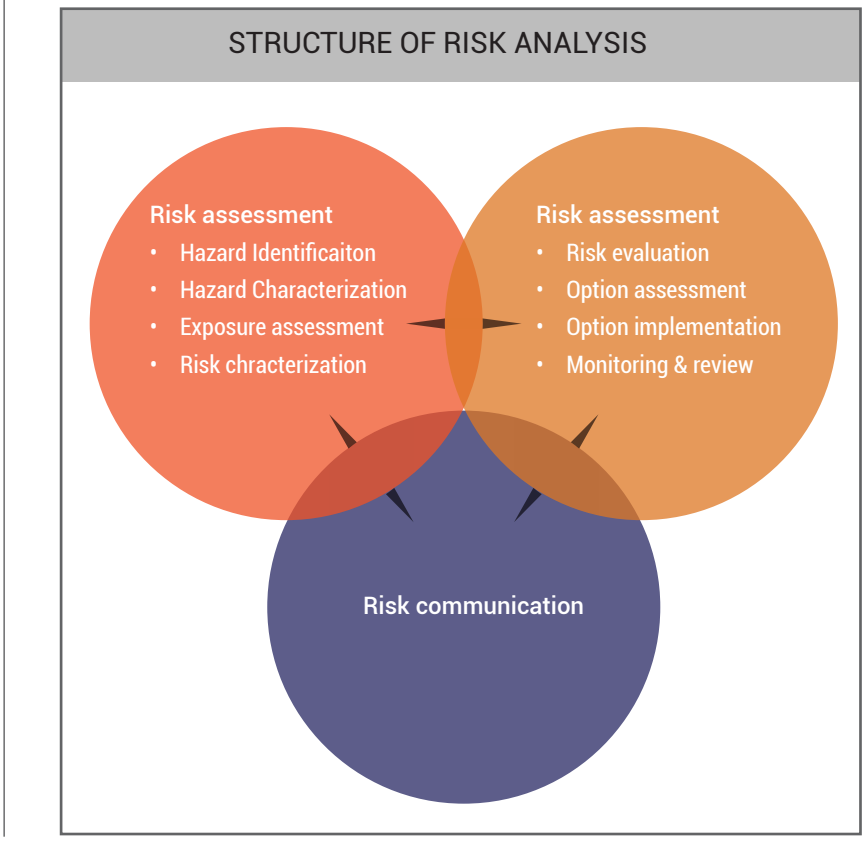
1. Introduction

The Food Safety and Standards Act, 2006 (FSSA), implemented from August 2011, is a science-based act replacing the erstwhile Prevention of Food Adulteration Act, 1954 *(1)*. Under the Act a major shift is required to a risk-based approach to food safety during rulemaking as well as in food control. A risk-based approach to food safety considers both the hazard characterization and exposure scenarios when arriving at whether a risk exists or is imminent or not. In this respect, because risk assessment opens a predictive window, preventive actions can be taken to protect the consumer.

The first risk analysis paradigm for public health was proposed by the United States National Academy of Sciences (NAS) (NRC, 1983) and focused on assessing the risk of cancer from chemicals in food. The decision-making process was divided into three major steps: research, risk assessment and risk management. *(2)*



Codex schematic framework for risk analysis



The risk analysis paradigm is a formal representation of the three interactives but functionally separate components and performed by those who are tasked with responsibility for each of the three components. Food law that rests on a risk-based framework detail out statutory performance of the separate roles - in an independent and transparent manner - through well-defined structural organization. These roles underpin harmonization of rulemaking decision. *(2)*

Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) and Joint FAO/WHO Meeting on Pesticide Residues (JMPR) make evaluations on scientific principles and ensure necessary consistency in their risk assessment determinations, Codex Alimentarius Commission (CAC) and its respective committees (WHO) are responsible, as risk managers, to take final decisions on establishing maximum limits for e.g. contaminants or additives in food. The use of risk analysis methodology facilitates consistent and orderly decision-making. *(3)*

Food Safety and Standards Authority of India (FSSAI) established its Risk Assessment Cell to support risk assessment work required under the functional roles of the Scientific Panels/Committee; and risk management by the Food Authority during the making of standards or specifications. Under the Act, the Food Authority shall while framing the regulations or specifying standards take into account – among other things – risk assessment based on the available scientific evidence.

FSSAI has notified final regulations on Food Safety and Standards (Approval of non-specified food and food ingredients) Regulations, 2017*(5)*. This regulation lays down the rules and procedure for grant of prior approval of non-specified food and food ingredients.

The regulation covers the following articles of food and food ingredients:

1. Novel food and novel food ingredients or processed with the use of novel technology
2. New Additives
3. New processing aids including enzymes
4. Articles of food and food ingredients consisting of or isolated from microorganisms, bacteria, yeast, fungi or algae.

To create awareness, understanding and capabilities in applying the process of risk assessment with all stakeholders engaged with rulemaking, FSSAI, under several initiatives is actively promoting the use of food safety sciences. Broadly, risk assessment may be applied to products, processes that may increase a health risk through an agent or condition in food.

2. Role of risk assessment in risk analysis

Risk analysis is a conceptual framework in food safety that provides a mechanism or platform for a structured review of the information relevant to estimating a health outcome. Risk assessment generally includes a key component in which the probability of harm is estimated. As a probability calculation, a risk assessment will include both a statement of the nature of the harm (severity) and the basis for the assertion that the harm may occur (probability). *(2, 3)*

Although it is desirable to separate the functional activities of risk assessment from those of risk management and risk communication in order to ensure scientific independence, it is acknowledged that risk managers should communicate and interact with risk assessors during the process to establish the scope of the analysis, particularly during problem formulation (Terms of Reference). Thus, the relationship between risk assessment, risk management, and risk communication is an interactive, often iterative, process. *(2, 3)*

Risk Assessment considers all available relevant scientific data and identifies any uncertainties in the knowledge base. It means a scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and, (iv) risk characterization. *(2, 3)*

FSSA define the meaning of terms and processes that is used in risk analysis and requires thorough understanding in order to provide well-reasoned outputs and ultimately public health outcomes.

Hazard identification

Hazard Identification is the first of four steps in risk assessment and is defined as:

- Codex (CAC, 2006); "The identification of biological, chemical and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods". *(2)*
- International Programme on Chemical Safety, (IPCS), 2004): "The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub) population." *(3)*

The purpose of hazard identification is to focus the evaluation and assessment of the weight of evidence for an adverse health effect and mode of action. It is primarily designed to address two questions*(2)*:

1) the nature of any health hazard to humans that an agent may pose, and
2) the circumstances under which an identified hazard may be expressed.

Hazard identification may also arise from analyses of a variety of data, ranging from observations in humans or domestic animals, studies in laboratory animals and in vitro laboratory studies, or through analysis of structure–activity relationships. From the range of studies and observations available, the nature of any toxicity or adverse health effect occurring and the affected (target) organ(s)/tissue(s) is identified. *(2)*

The outcome of hazard identification is a scientific judgement as to whether the chemical being evaluated could, under given exposure conditions, cause an adverse effect in humans. *(2)*

Hazard characterization

Hazard characterization is the second of four steps in risk assessment. Also known as dose–response assessment) is defined as follows:

- CAC, 2006: "The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents which may be present in food. For chemical agents, a dose–response assessment should be performed. For biological or physical agents, a dose-response–assessment should be performed if the data are available" *(2)*
- IPCS, (2004): "The qualitative and, wherever possible, quantitative description of the inherent properties of an agent or situation having the potential to cause adverse effects. This should, where possible, include a dose–response assessment and its attendant uncertainties." *(3)*

Hazard characterization describes the relationship between the administered dose of, or exposure to, a biological or chemical (agent) and the incidence of an adverse health effect. For most types of toxic effects, it is generally considered that there is a dose below, which an adverse effect will not occur (i.e. a threshold). Such a dose is described as the no-observed-adverse-effect level (NOAEL) or no-observed-effect level (NOEL) and can be considered as a first approximation of the threshold for that particular chemical for that particular effect. The NOAEL or NOEL for the critical effect is usually a starting or reference point for the risk characterization. The critical effect, that is, the first or lowest observed adverse effect level (LOAEL) is determined as the dose/exposure is increased. *(2,3)*

In contrast to threshold-type effects, for some other types of toxic effect it is assumed that there is some probability of harm at any level of exposure (i.e. that no biological threshold exists). At the present time, this assumption is primarily applied in the case of mutagenicity and genotoxic carcinogenicity. In the case of genotoxic carcinogenicity, the Benchmark dose (lower confidence limit) (BMDL) derived from animal studies may be used as a point of departure for risk characterization. *(2)*

Exposure assessment

Intake/exposure assessment is the third step in risk assessment, in which the extent of human exposure to the chemical (actual or anticipated) is determined *(2,3,4)*.

Exposure assessment is defined as:

- CAC (2006) as follows - "The qualitative and/or quantitative evaluation of the likely intake of biological, chemical and physical agents via food as well as exposure from other sources if relevant".*(2)*
- IPCS (2004) as follows: "Evaluation of the exposure of an organism, system, or (sub) population to an agent (and its derivatives). *(3)*

In the case of food chemicals, exposure assessment takes into consideration the occurrence and concentrations of the chemical in the diet, the consumption patterns of the foods containing the chemical and the likelihood of consumers eating large amounts of the foods in question (high consumers) and of the chemical being present in these foods at high levels. Usually a range of intake/exposure estimates will be provided (e.g. for average consumers and for high consumers) and may be broken down by subgroup of the population (e.g. infants, children, adults).

Under section 16 (3)(b) of the FSSA, the Food Authority is required to search, collect, collate, analyze and summarize relevant scientific and technical data particularly relating to –

(i) Food consumption and the exposure of individuals to risks related to the consumption of food;

(ii) Incidence and prevalence of biological risk;

(iii) Contaminants in food;

(iv) Residues of various contaminants.

Undertaking dietary exposure assessments(4):

The CAC's procedural manual (CAC 2006) provides a description of how exposure assessments are done based on the objective and purpose of the assessment.

The general equation for both acute and chronic dietary exposure is:

$$\text{Dietary exposure} = \frac{\Sigma\,(\text{Concentration of chemical in food} \times \text{food consumption})}{\text{Body weight (kg)}}$$

However, for allergens, as reactions are rapid, the amount of allergenic protein ingested per eating occasion or portion of food is typically calculated.

The use of standard terminology is recommended to ensure consistent application of understanding. Consumption should refer to the amount of food consumed and 'dietary

exposure' to the amount of chemical ingested via food. The term food includes beverages, drinking water and supplements.

Prior to conducting a dietary exposure assessment, the objective must be clearly stated before the appropriate food consumption data and chemical concentration of the substance of interest in foods are selected. For example, if the intent is to evaluate the regulatory impact of specific measure (e.g. revision of max limits) the pre- and post-regulation dietary exposure assessments may have different data sources and default assumptions.

It is recommended that national authorities that wish to perform dietary exposure assessments should use national food consumption data.

Exposure assessments should cover the general population, as well as groups that are vulnerable or are expected to have exposures that are significantly different from those of the general population (e.g. infants, children, pregnant women, or the elderly) and also demographic characteristics.

When collecting consumption information, individual record data will generally provide the most precise estimates of food consumption. Broad surveys, covering the food consumption patterns of the whole population, may not necessarily be needed if the food chemical of interest is consumed by only a subset of the population. If resources are limited, small-scale studies are appropriate and may cover specific foods or target population subgroups (e.g. children, nursing women, ethnic minorities, vegetarians). This approach can improve the precision of estimates of dietary exposure for specific population subgroups of food chemicals.

Collecting data for Exposure Assessment (Few examples)*(4)*:

Poundage

Estimates of the amount of a chemical substance available – though both domestic and import stocks - per capita for use in food manufacturing in a country during a period of time, usually over 1 year. The estimated dietary exposure that is provided with such a calculation is based neither on observed consumption patterns nor on data on the actual concentration of the chemical substance in foods. They may also include non-food uses. Surveys of poundage data are usually performed by producer associations that ask single producers to report their volumes of production. A very large year-to-year variability in poundage data may occur, especially for substances produced in low quantities. This limits the usefulness of poundage data surveyed on a single year basis.

Household Survey

Information regarding food availability or consumption at the household level may be collected by a variety of methods, including data on foodstuffs purchased by a household, follow-up of consumed foods or changes in food stocks. Such data are useful for comparing food availability among different communities, geographic areas and socioeconomic groups and for tracking dietary changes in the total population and within population subgroups. However,

these data do not provide information on the distribution of food consumption among individual members of the household.

Model Diets

Model diets are constructed from available information on food consumption and are designed to represent a typical diet – of the general or a subpopulation whose exposure is to be considered. For example, it may be of interest to evaluate the population subgroup that has the highest consumption of foods of interest (e.g. savory snacks, or fish) in relation to body weight. Although model diets can be extremely useful, the models are only as good as the underlying data and assumptions, which should be stated for each model.

Individual Data

Data collected by individual-based methods provide detailed information on food consumption patterns; however, as with other food consumption surveys, they may be prone to bias. For instance, several studies have found that nutrient intakes derived from 24-h recalls tend to underestimate true intakes of some macronutrients for some subjects (Madden et al., 1976; Carter et al., 1981; Karvetti&Knutts, 1985). Regression analyses between recall and actual intakes exhibited the "flat-slope syndrome", whereby individuals tend to overestimate food amounts when consumption is low and to underestimate food amounts when consumption is high. In some cases, individuals may overestimate consumption of foods perceived as "good foods" and underestimate consumption of foods perceived as "bad foods".

Total Diet Study (TDS)

In principle provide the most accurate measure of the average concentrations of pesticide residues, contaminants, nutrients and/or other chemicals actually ingested in foods by the population living in a country and, if possible, population subgroups. However, the accuracy of some TDSs is lowered by using limited sample sizes and survey durations. Therefore, when using a TDS in a dietary exposure assessment, it should be checked if it is fit for purpose.

Risk characterization

Risk characterization is the final step in the risk assessment process in which the information from the intake/exposure assessment and the hazard characterization are integrated into advice suitable for decision-making in risk management. It provides estimates of the potential risk to human health under different exposure scenarios. It should include all key assumptions and describe the nature, relevance and magnitude of any risks to human health. The advice to risk managers may be qualitative or quantitative.*(2)*

Risk characterization is defined as:

- CAC (2006) as follows: "The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment". *(2)*

- IPCS (2004) as follows: The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions. *(3)*

Qualitative advice may include*(2)*:

- Statements/evidence that the chemical is of no toxicological concern owing to the absence of
  - Toxicity even at high exposure levels;
  - Statements/evidence that the chemical is safe in the context of specified use(s); and
  - Recommendations to avoid minimize or reduce exposure.
- Quantitative advice may include:
  - Health-based guidance values;
  - Estimates of risks at different levels of exposure; and
  - Risks at minimum and maximum intakes (e.g. nutrients)

The risk characterization statement should include a clear explanation of any uncertainties in the risk assessment resulting from gaps in the science base. It should also include, where relevant, information on susceptible subpopulations, including those with greater potential exposure and/or specific predisposing physiological conditions or genetic factors. The advice to risk managers can be in the form of a comparison of the relative risks among risk management options*(2)*.

The risk assessment can either be the basis for provisional risk management decision or a request for a more comprehensive risk assessment further analysis, which may influence any further scientific research that is conducted. The record produced by a risk assessment stands as a scientific basis for any risk management decision at that time. However, the risk assessment/analysis may be reopened—for example, if additional information becomes available. *(1,2)*

3. Risk Assessment – Novel Foods

Safety assessment of any novel material intended as a food or food material is an indispensable prerequisite for the assurance of human health. The primary goal of the management of risks associated with food has been defined as the protection of public health by controlling such risks as effectively as possible through the selection and implementation of appropriate measures *(6)*.

An appropriate safety assessment programme should incorporate the following considerations *(7)*:

- the analytical/compositional and nutritional characteristics of the novel food
- previous history of human exposure;
- the expected applications as a novel food and the predicted exposure;
- the necessity, appropriateness and outcome of animal studies;
- the necessity, appropriateness and outcome of studies in humans; and
- the necessity and outcome of post-launch monitoring.

Novel foods

Novel foods are being introduced into the market at a very fast pace. They are a real challenge for science, industry and regulatory bodies. According to FSSAI, 'Food Safety and Standards (Approval for Non-Specified Food and Food Ingredients) Regulations, 2017 (5), novel food is a food that

(a) may not have a history of human consumption; or

(b) may have any ingredient used in it which or the source from which it is derived, may not have a history of human consumption; or

(c) a food or ingredient obtained by new technology with innovative engineering process, where the process may give rise to significant change in the composition or structure or size of the food of food ingredients which may alter the nutritional value, metabolism or level of undesirable substances.

There are ten categories of 'novel foods' covered by the European Commission (EC) Novel Food Regulation 2015/2283 *(8)*:

- Food with a new or intentionally modified molecular structure;
- Foods consisting of, isolated from or produced from micro-organisms, fungi or algae;
- Foods consisting of, isolated from or produced from material of mineral origin;
- Foods consisting of, isolated from or produced from plants or their parts, except when the food has a history of safe use within the Union and is consisting of, isolated from or produced from a plant or a variety of the same species obtained by:
  - Traditional propagating practices which have been used for food production within the Union before 15 May 1997; or
  - Non-traditional propagating practices which have not been used for food production within the Union before 15 May 1997, where those practices do not give rise significant changes in the composition or structure of the food affecting its nutritional value, metabolism or level of undesirable substances;
- Food consisting of or isolated from or produced from animals or their parts, except for animals obtained by traditional breeding practices which have been used for food production within the Union before 15 May 1997 and the food from those animals has a history of safe food use within the Union;
- Food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, microorganisms, fungi or algae;
- Food resulting from a production process not used for food production within the Union before 15 May 1997, which gives rise to significant changes in the composition or structure of the food, affecting its nutritional value, metabolism or level of undesirable substances;
- Food consisting of engineered nanomaterials;
- Vitamins mineral and other substances where a production process not used for food production within the Union before 15 May 1997 has been applied
- Food used exclusively in food supplements within the Union before 15 May 1997, where it is intended to be used in foods other than food supplements.

As per Canada's Novel food regulation, foods that meet any of these 3 definitions would require a pre-market notification *(9)*.

- no history of safe use as a food
- process that has not been previously applied to food and causes the food to undergo a major change
- food derived from a genetically modified plant, animal or microorganism.

In India FSSAI has notified final regulations on Food Safety and Standards (Approval of non-specified food and food ingredients) Regulations, 2017, that specifies the information/ conditions to be considered for novel foods ingredients or food processed with the use of novel technology. *(5)*

History of safe use

The 'history of safe use' of a food is the body of knowledge accumulated from the use and experience of that food within its cultural context and conditions of use, which describes its established safety profile. This profile also describes known limitations and restrictions for sensitive populations, e.g. known anti-nutrients, toxicants, and allergens. It is assumed that traditional foods have 'history of safe use' in the country of origin. However, some foods that have a 'history of safe use' in one country may be considered to be novel foods when introduced into another country *(8)*.

The concept of 'history of safe use' is thus used to determine the regulatory status of a food, whether a safety evaluation is required and/or to direct any safety evaluation. Various databases can be used to establish whether a particular product has a 'history of safe use' as a food or food source. These include national food survey reports and global, regional and national surveys of plants with food uses. The data that is used to describe a 'history of safe use' should preferably be robust and reliable (e.g. peer reviewed scientific publications, governmental documents, and scientific expert opinions) and be taken from referenced sources where possible. However, non-scientific and anecdotal evidence is also important, although is given less weight than peer reviewed data.

History of safe use: Key issues

History:	Correct identification Biology (origin, genetic diversity) Length of use Geographic/demographic distribution of use Details of use Evidence of adverse effects Reliability of data
Safe:	Composition (especially toxic, allergenic, metabolic, nutritional and antinutritional components as well as health compromising compounds) In silico tests (e.g. structural homology to known allergens or known toxins) In vitro tests (e.g. serum screening, digestibility tests) Animal studies (toxicology and nutrition studies) Experience from human exposure Clinical studies Epidemiological evidence
Use:	Type/purpose (e.g. as a food, ingredient, supplement or pharmaceutical)

Concept of Substantial Equivalence:

Novel foods are evaluated using the guiding principle of substantial equivalence. This is a starting point, not an end point, and it is designed to highlight the differences between the new food and its traditional counterpart if one exists. These differences then become the focus of further safety assessment, the purpose of which is to determine that the new food or derivative(s) is at least as safe as its traditional counterpart. As the degree of novelty increases so does the requirement for information, but the additional information and subsequent assessment are directed to those aspects of the product which diverge from those of its traditional counterpart. Where the novel product has no relation to a traditional counterpart, extensive information including toxicology and data to establish nutritional characteristics and dietary impact may be required.

Some examples of novel foods and the comparators

Novel food	Novel food
High pressure pasteurised fruit preparations	Corresponding thermal pasteurised fruit preparations.
Phytosterols	Traditional plant sources rich in oil Phytosterols used as medicinal products.

The concept of Substantial Equivalence was originally introduced for Genetically Modified (GM) foods, however, it is now being applied for the safety assessment of foods from novel sources and produced by novel processes. A classification of products is proposed based on equivalence - substantially equivalent, partially equivalent, non-equivalent ***(10)***. Application of the concept of substantial equivalence focusses on toxicological and analytical comparisons, avoids unnecessary duplication of animal experiments and exploits the historical data. It also encourages a comprehensive/holistic approach to safety evaluation based on mechanistic insights, nutritional safety and toxicology where necessary.

The first and foremost step for the safety assessment of a novel food is to determine what (if any) existing food should be used as a comparator (or material reference). If no comparator is present with an acceptable 'history of safe use', it does not imply that the novel food is unsafe; rather it indicates that a more extensive safety assessment programme may be required. On the other hand, if a comparator exists, the novel food is compared with the traditional counterpart in order to gather the maximum of information relative to safety and the safety assessment would focus on where there may be differences. The comparison usually includes:

- chemical composition
- methods of production and use
- intake patterns, nutritional value and target groups

Information should be presented concerning all potential hazards. Depending on the nature of the food this may include:

- Toxicology data including details of known natural toxicants
- Nutritional data including details of known natural antinutritional factors.
- Allergenicity.
- Pathogenicity (for micro-organisms).
- Known health compromising contaminants (nature and level of, for example, mycotoxins, heavy metals or residues of agrochemicals).
- Bioactive substances (e.g. phytoestrogens/androgens).
- Metabolic and/or gastrointestinal effects in humans.

Sometimes, use of more than one comparator is found suitable to address different safety issues. These points are presented below:

1. Exotic products from different countries

   When a food with 'history of safe use' in some parts of the world is introduced into new parts of the world, it is considered novel and the 'history of safe use' in the tradition region is assumed to be the starting point for the safety assessment. Besides, foods that are traditionally consumed in the receiving country that pose some degree of similarity with the novel food can also be taken into account for the safety assessment issues. For example Ngali nuts (an exotic nut proposed for importation from Melanesia) versus other nuts consumed in the receiving country for assessing the allergenicity risk).

2. Plant extracts (or single substances isolated from plant sources)

   Many a times, novel foods are obtained from plant sources that are considered a traditional food or food source having a 'history of safe use'. In such cases, the plant source becomes the comparator. Although the plant source cannot be treated as a food in a traditional sense, it might hold a 'history of safe use' in a different perspective. This is the case for many of the herbal products used in food supplements. Their use has been traditional and information on their safety in the use with respect to traditional consumption is a key element for the purpose of a food safety assessment.

Examples of novel foods

Novel foods

1. Food itself

   Noni juice: Scientific committee of food (SCF) in 2002 reviewed the safety of an exotic fruit juice based on noni (Morindacitrifola L.) from a consumer's health point of view. The committee concluded that the noni juice was acceptable at the observed level of intake of 30 mL/person/day. SCF also noted that the noni juice had been marketed for

several years in a number of countries and that few untoward reactions had been reported. However, SCF also concluded that there was no indication of adverse effects from lab studies on subacute and subchronic toxicity, genotoxicity and allergenicity. This decision of safe use is limited to noni juice as other noni-derived products (e.g. jam, dried whole fruit, spray dried juice, etc.) would require a separate application for approval under Regulation (EC) No. 258/97. Moreover, the approval of noni juice is specific to the applicant as competitors' noni juice cannot be marketed unless evidence of substantial equivalence to the approved juice is demonstrated.

2. Change of use (extract, increased concentration of certain components)

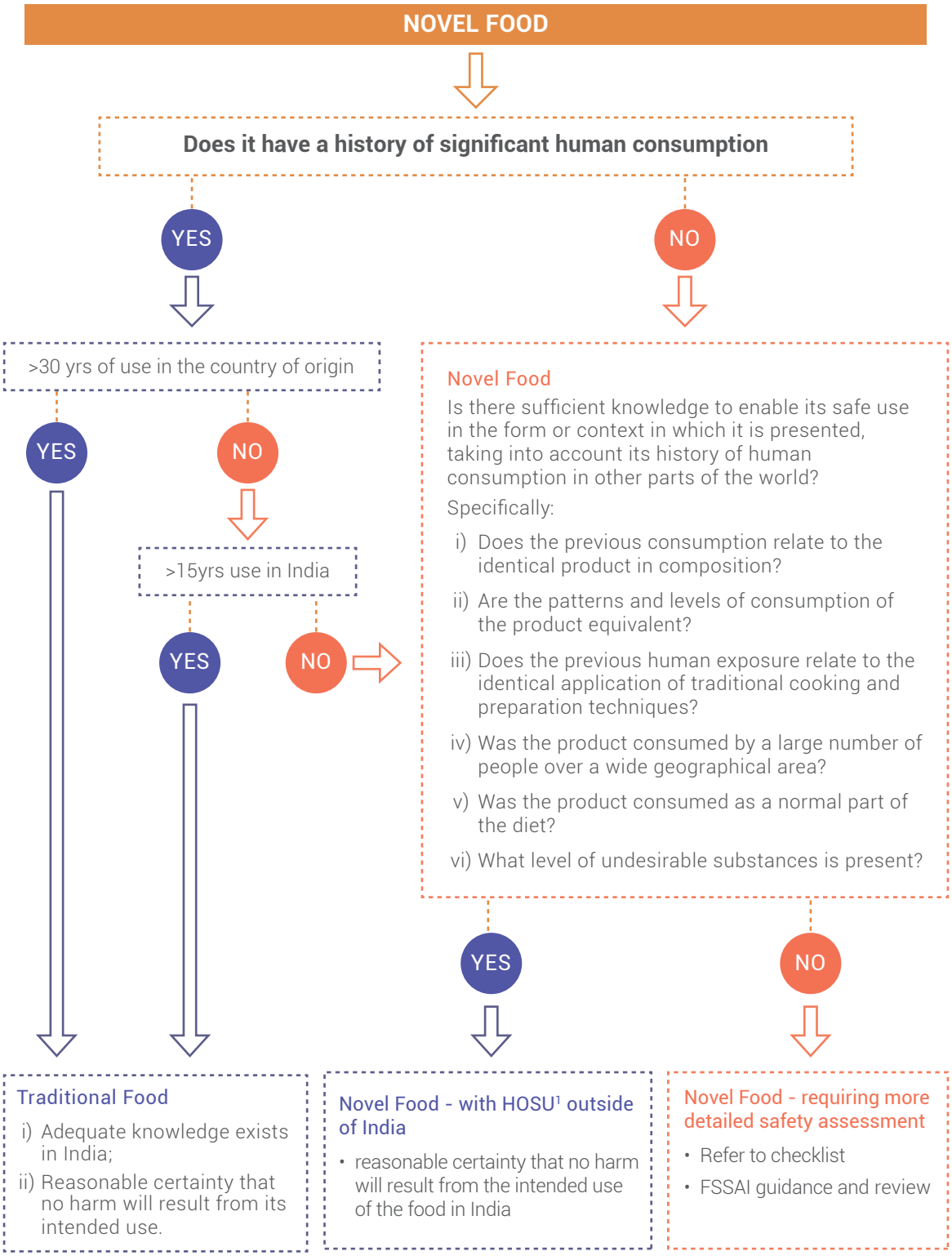
   Phytosterols: Phytosterols are naturally found in food as free alcohol, esterified with long chain fatty acids or conjugated as glucosides. They are extracted from edible oils and esterified with sunflower oil fatty acids. A number of phytosterol-based products have been introduced into the European Union (EU) market with the aim to reducing consumer's serum cholesterol levels. One of the earliest of these, a mixture of phytosterol esters, was reviewed by the SCF in 2000 (SCF, 2000b) following an application for approval as a Novel Food under Regulation (EC) No.258/97 of phytosterol esters in yellow fat spreads. The application proposed a use of up to 12% or 8% on average in yellow fat spread. Even though naturally occurring in foods and thereby presumed to have a history of safe use, the use of phytosterols in yellow fat spreads was deemed to be novel because of the significant (8- to 12-fold) increase in consumption would occur from their use.

   However, the committee also paid attention to the fact that a very small population with inborn error of phytosterol metabolism should be brought to the attention of higher levels of phytosterols in these products, and that patients receiving cholesterol-lowering medication should consume these products under medical supervision.

3. Products of novel processes

   High pressure processing: In 2001, some fruit preparations processed using high pressure processing were approved for food use in the EU. High pressure is an alternative approach to heat pasteurization fruit preparations which have a 'history of safe use' in the EU and elsewhere in the world. No differences of safety significance were observed between the composition prepared heat pressure and heat pasteurized fruit preparations. Although the sensitivity of viruses and micro-organisms to heat and high pressure vary, any potential food safety risks can be managed (for both processes) through the application of a suitable Hazard Analysis and Critical Control Point (HACCP) plan.

Characterization of Novel Foods for India *(10)*: Novel Food Decision Tree For India



[1]HoSU = History of Safe Use

Checklist: Risk Assessment of Novel Foods for India

Risk assessment considers all available relevant scientific data and identifies any uncertainties. The process consists of the following steps: i) hazard identification, ii) hazard characterisation, iii) exposure assessment, and iv) risk characterization. The following Table outlines the specific data required under a series of characteristics of a novel food, whether it is a chemical, plant/animal or derived from cell/tissue culture.

<table>
<tr><th rowspan="2">RISK ASSESSMENT STEP</th><th rowspan="2">CHARACTERISTIC</th><th colspan="3">SPECIFIC DATA REQUIRED</th></tr>
<tr><th>Chemical</th><th>Plant or Animal</th><th>Cell or tissue Culture</th></tr>
<tr><td>Hazard Identification</td><td>Identity</td><td>- CAS name according to IUPAC and other names (e.g. trade name, common name)
- Structural formula, stereochemistry, molecular mass
- Polymers & engineered nanomaterials: particle size, shape and distribution</td><td>- taxonomic name (latin name-family, genus, species, strain)
- Common name
- Parts used
- Geographical origin (country, region)</td><td>- Biological source and taxonomical information
- Organ, tissue sourced
- Laboratory or culture collection
- Identity of cells</td></tr>
<tr><td>Hazard Identification</td><td>Production Process</td><td>- Description of chemical synthesis - reaction sequence, side reactions and purification steps
- Reaction conditions e.g. reagents, temperature, duration, catalysts
- Purification methods, e.g. solvent extraction, crystallisation</td><td>- Plants/fungi: Propagation, growth and harvesting conditions (e.g. wild or cultivated, time of harvest)
- Animals: Breeding, rearing, feeding conditions for farmed animals or hunting collecting for wild animals
- use of pesticides and antimicrobials
- Post harvest handing e.g. transport, drying, storage conditions. Raw materials for further processing
- the process whereby it is converted into an ingredient e.g. heat treatment, fractionation, squeezing, fractionation</td><td>- cell culture conditions</td></tr>
<tr><td></td><td></td><td colspan="3">- Potential for by products, impurities and contaminants
- Measures for quality and safety assurance (E.g. HACCP, GMP, ISO); standardisation criteria</td></tr>
<tr><td>Hazard Identification</td><td>Composition</td><td colspan="3">- National or international methods should be used and described
- Analytes of toxicological concern should include limits of detection and quantification
- Certificates of analysis and accreditation laboratories should be supplied
- In house methods should be fully described including validation procedures
- Compositional data should provide the basis for the specification
- Impurities, by-products, residues, chemical and microbiological contaminants (e.g. heavy metals, mycotoxins, pesticides)
- The source and production process should be a consideration when determining what is analysed for.
- Stability should be established to identify hazards which might arise during storage and transport, including when added as an ingredient to other foods.</td></tr>
<tr><td></td><td></td><td colspan="3">Single substances/ simple mixtures:
- A mass balance should be provided
- Identity tests (e.g. UV-VIS, IR, NMR, GC-MS, LC-MS)
- Physicochemical properties (appearance, melting point, boiling point)
- Solubility data
- Particle size, shape, distribution
- Minimum purity value
- Density and/or viscosity

Complex mixtures/ whole foods
- by definition can't be fully chemically characterised
- qualitative and quantitative characterisation of main constituents e.g. proximate analysis (ash, moisture, protein, fat, carbohydrate); mass balance
- there should be comprehensive qualitative and quantitative data
on components i) which characterise the food (e.g. plant sterols), ii) nutritionally relevant components (e.g. vitamins) and iii) substances of concern (e.g. toxic, mutagenic/carcinogenic, allergenic, addictive)</td></tr>
</table>

RISK ASSESSMENT STEP	CHARACTERISTIC	SPECIFIC DATA REQUIRED		
		Chemical	Plant or Animal	Cell or tissue Culture
Hazard Identification	Specification	- Key parameters that characterise and define the identity of the novel food, including limits. This should include safety parameters e.g. contaminants, microorganisms. - Specification should include limits and reference to analytical methods		
Hazard Identification	Nutrition	- Nutrient composition and bioavailability, considering production process, storage, and processing before consumption. Presence of any anti-nutrients (components which reduce or modify bioavailability of micronutrients) - Importance of cooking where relevant to the removal or inactivation of anti-nutritional substances - If replacing another food, does the replacement cause any nutritional disadvantage? - Should demonstrate that the consumer is not at a nutritional disadvantage from consuming the novel food		
Hazard Identification	Allergenicity	- Food allergens are generally proteins - The allergenic potential of the novel food should be explored by considering its source (including taxonomic relationships) and composition - A novel protein should be assessed for allergenicity by building a Weight of Evidence determining: • Protein content • Molecular weight of the proteins, heat stability, pH sensitivity, digestibility by gastrointestinal proteases. If all protiens are broken down quickly and to small enough peptides gastrointestinal tract then there is a lower risk of it being allergenic • Degree of sequence homology with known allergens • Immunological tests (e.g. western blotting) - Human testing e.g. detection of specific IgE antibodies, skin prick testing, double-blind placebo-controlled food challenge studies, antibody responses to ingestion etc.		
Hazard Identification	Toxicology	- Studies should be conducted to international guidelines e.g. OECD and according to the principles of Good Laboratory Practice (GLP) - Toxicological data on structurally related substances ("read-across") should be considered. - A structured scientific risk-based approach should be used to develop the toxicity testing, which should be based on an understanding of the source and composition of the novel food. Alternatives to the use of animals should be considered where scientifically appropriate and justifiable. - The Threshold of Toxicological Concern (TTC) approach may be helpful when considering the risk of low exposure to substances such as impurities and degradation products for which toxicity data may not be available. - Human studies may be conducted for various purposes (e.g. nutrition) and may also provide valuable information for safety assessment e.g. blood samples and clinical chemistry/haematology measurements, blood pressure, physical examinations.		
Hazard Identification	Absorption, Distribution, Metabolism & Excretion (ADME)	- ADME considerations should be made as part of the nutritional and toxicological assessment, e.g. negligible absorption may be a justification for not undertaking toxicological studies.		
Hazard Characterisation		- Description of the relationship between the administered dose and the occurrence of the adverse event in the experimental system. Typically for toxic effects this will be the determination of the NOAEL or NOEL. - For allergy comparing intake of total protein per eating occasion/portion with Reference Doses for common food allergens can also be useful		

RISK ASSESSMENT STEP	CHARACTERISTIC	SPECIFIC DATA REQUIRED		
		Chemical	Plant or Animal	Cell or tissue Culture
Exposure Assessment	History of Use		- Data on the composition, production and use of products from the source organism may provide relevant information. - For allergy, data on exposure to the source organism and/or derivatives thereof may also be useful, including via non-oral rotes e.g. inhalation - Data may be available on the use of the novel food outside of India, including: • Extent of use (including sales, import/export information) • Population group, • Role in diet, • Handling and preparation, and precautions of use • Human studies reporting safety outcomes - Should also consider similar foods data from the same or closely related sources	
Exposure Assessment	Proposed Use and Anticipated Intake	- The intended target population should be identified e.g. general population, adults, infants - Proposed use/ use level • As a whole food or ingredient • Food categories to be used in e.g. beverages • Is it intended to replace another food • Proposed maximum amounts to be used in food • Proposed average and maximum daily intakes for different age/gender groups - Estimates of anticipated daily (and high 95th percentile) intake of the novel food (per kg body weight and as absolute amounts) for target population as well as vulnerable groups (e.g. pregnant women, children) - Also estimates of anticipated intakes of total protein per eating occasion/ portion - Uncertainties related to this assessment should be made explicit - Other potential sources of intake of the novel food should be considered (e.g. natural occurrence in other foods). In these cases, estimates of intake should be made. - Estimates of exposure to any identified undesirable substances from the compositional analysis should be made - Any precautions or restrictions for use should be specified		
Risk Characterisation	Risk Assessment	Evaluation of all the data in a scientific risk based assessment applying Codex principles of Risk = f (Hazard x Exposure). This may or may not include the derivation of ADI (acceptable Daily Intake).		

This has been compiled mainly from considerations of the following documents (11,13,14,15)

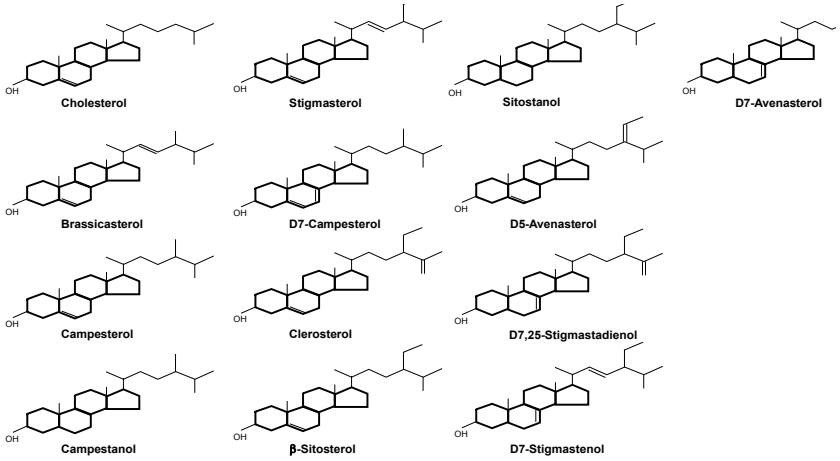
Case Studies

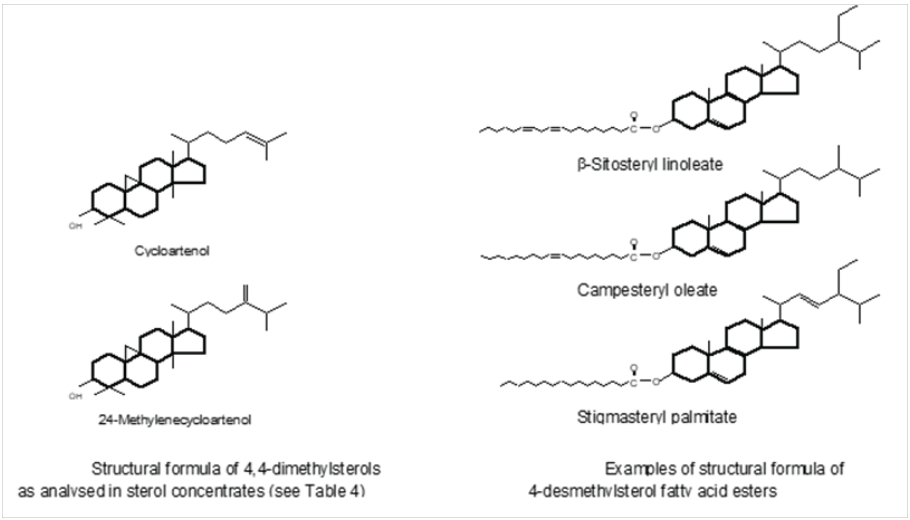
Case Study 1: Phytosterol-esters

Specific application was for "Yellow fat spreads with added phytosterol-esters as a novel food", which was approved by the European Commission in July 2000.

The information provided below is given for illustrative purposes of the type of information that may be considered in developing the risk assessment on a novel food. It is not complete and may be out of date and/or incorrect.

RISK ASSESSMENT STEP	CHARACTERISTIC	INFORMATION AVAILABLE
Hazard Identification	Identity	There are two raw materials for phytosterol-esters (PE): i) free phytosterols, minor constituents of edible vegetable oils present in the unsaponifiable fraction, available as vegetable oil distillates, and ii) edible vegetable oils, such as soybean or sunflower oil.





Structural formula of 4,4-dimethylsterols as analysed in sterol concentrates (see Table 4)

Examples of structural formula of 4-desmethylsterol fatty acid esters

RISK ASSESSMENT STEP	CHARACTERISTIC	INFORMATION AVAILABLE
Hazard Identification	Production Process	Phytosterols (from vegetable oil distillates) are re-esterified with fatty acids from sunflower oil by one of two routes: i) Trans-esterification of phytosterols and fatty acid methylesters; ii) Direct esterification of phytosterols and free fatty acids. Explanation of how PE was incorporated into the margarine.
Hazard Identification	Composition	There are essentially two major constituents to the Novel Ingredient (fatty acid esters of phytosterols): the phytosterols which are sourced from vegetable oil distillates (mainly soya bean oil) and the vegetable oil as the source of the fatty acid. It is expected that there will be some variation in the phytosterol composition due to differences in processing, season and the variety of the crop used. **Description of analytical methods, e.g.** Free sterols Unilever methods Trans fatty acids Unilever methods Iron, Copper AOCS PAH (ppb, total/heavy) Unilever methods Solvents EPA Pesticides EPA Analytical data to indicate the variability in the major sterols content, based on x production batches Phytosterol ester and vegetable oil mixture fulfil the requirements for vegetable oils as described in Codex Standards for Edible Fats and Oils (1982).
Hazard Identification	Specification	The phytosterol specification was published in the Official Journal of the European Commission and specified as: **Component** / **Min.** / **Max.** Campesterol 10% 40% Stigmasterol 6% 30% B-Sitosterol 30% 65% Other 0% 5%
Hazard Identification	Nutrition	Explanation of the mechanism by which phytosterols lower blood cholesterol, and a summary of the large number of studies in experimental animals and humans that have been done. Effect of phytosterols on the absorption of fat soluble nutrients and drugs. In particular, the effect on the absorption of carotenoids and the implications that may have on human health. Consequences of phytosterol consumption on individuals with sitosterolaemia, a very rare genetic disease in which phytosterols are absorbed (normally they are very poorly absorbed from the small intestine).
Hazard Identification	Allergenicity	The protein content is negligible and no new proteins were being introduced. Therefore, investigations into allergenicity were not considered necessary.
Hazard Identification	Toxicology	Full literature review of toxicological studies as well as the specific studies commissioned by Unilever, addressing: • Genotoxicity • Sub-chronic toxicity • Reproductive toxicity • Carcinogenicity Human studies

RISK ASSESSMENT STEP	CHARACTERISTIC	INFORMATION AVAILABLE
Hazard Identification	Absorption, Distribution, Metabolism & Excretion (ADME)	The absorption of phytosterols is very low in both man and experimental animals, typically 4-5% for sitosterol and stigmasterol. Phytosterol-esters are digested in the small intestine to produce phytosterols and fatty acids. Literature review. Description of the studies conducted by the applicant to investigate the metabolism and fate of phytosterols following oral ingestion.
Hazard Characterisation		In a sub-chronic rat feeding study no adverse effects were seen and this was used to establish a NOAEL (3900mg/kg BW/day) from which an ADI (130mg/kg BW/day) was determined after applying a safety factor (30).
Exposure Assessment	History of Use	Phytosterols and the esters are natural components of fruits and vegetables, with people typically consuming 100-300mg/day. The main sources of phytosterols in the diet are cooking oils and margarines and health margarines typically contain between 300-400mg/100g. The average intake of phytosterols in the UK, determined from food samples collected in 1991 was 186mg/day (Morton et al., 1995). The main phytosterols were sitosterol 56%, campesterol 26% and stigmasterol 5%. The intake of phytosterols (expressed per kg body weight) by formula-fed infants is higher than the average intake by adults. Vegetarians typically consume more plant sterols. Use of phytosterols as a cholesterol lowering medication (Cytellin). Summary of the large number of clinical studies studying the cholesterol lowering effects of phytosterols.
Exposure Assessment	Proposed Use and Anticipated Intake	Initially was considered for use solely as an ingredient in margarine. Subsequently, phytosterol-esters have been approved in a wide variety of food types. Food intake data from government surveys e.g. UK National Diet and Nutrition Survey. The applicants own market research data on regular margarine intake as well as what is anticipated from a PE-containing margarine from comparisons with competitors (i.e. Raisio).
Risk Characterisation	Risk Assessment	Phytosterols are natural components of the human diet, they are poorly absorbed, they are not genotoxic/carcinogenic, the potential reproductive effects can be dismissed (don't bind to human oestrogen receptor) and there are no reports of adverse effects in humans. In a sub-chronic rat feeding study no adverse effects were seen and this was used to establish a NOAEL from which an ADI (130mg/kg BW/day) was determined. This gave an adequate safety margin for use in margarine (and subsequently other foods).

Outcome:

- The EU Scientific Committee on Food (SCF) under the EU Novel Foods Regulation (Regulation (EC) No 25 8/97) concluded that the use of phytosterol-esters in yellow fat spreads (maximum level of 8% free phytosterols) is safe for human use.
- Yellow fat spreads with added phytosterol-esters were allowed to be placed on the market in Europe following the Commission decision on 24th July 2000.
- The approval also required that the applicant should establish a surveillance program accompanying the marketing of the product to obtain data on consumption and for further investigation of possible health effects, including among others the effects on plasma β-carotene levels.
- Following subsequent applications it was considered prudent to avoid phytosterol intakes exceeding 3 g/day. This was in consideration of the dose found to be effective for cholesterol lowering, without evidence of additional benefit at higher intakes.

Case Study 2: Noni Juice (Morindacitrofolia extract)

"Morindacitrofolia (noni) fruit – juice, puree and concentrate".

The information provided below is given for illustrative purposes of the type of information that may be considered in developing the risk assessment on a novel food. It is not complete and may be out of date and/or incorrect.

RISK ASSESSMENT STEP	CHARACTERISTIC	INFORMATION AVAILABLE
Hazard Identification	Identity	Morindacitrifolia (Noni) fruit puree and concentrate. Morindacitrofolia (common name "Noni") is a fruit bearing tree in the coffee family (Rubiaceae), which is native to South East Asia, Australasia and Polynesia.
Hazard Identification	Production Process	The fruits are harvested by hand. Seeds and skin are separated mechanically from the pureed fruits. After pasteurisation, the puree is packaged in aseptic containers and stored under cold conditions. The M.citrofolia puree is the starting material to prepare M.citrofolia concentrate. The puree is treated with food grade pectinolytic enzymes (50-60o C for 1-2 hours) to break down the pectin and aid the separation of the juice from the pulp. The puree is heated to inactivate the pectinase and then cooled. The juice is then separated from the pulp in a centrifuge. After the juice is collected, it is heated to 93oC for at least 1 sec, as a pasteurisation step, prior to being concentrated in a double effect vacuum evaporator. These steps are standard procedures commonly applied in the manufacture of fruit juices.
Hazard Identification	Composition	Table 1 Compositional data on M. citrifolio puree, M. citrifolio concentrate and Tahitian Noni Juice (TNJ)

	"M. Citrifolio PUREE"		"M. Citrifolio CONCENTRATE"		"Tahitian Noni JUICE"
	Mean	SD	Mean	SD	Range
Proximate					
Moisture (g/100g)	91.6	2	50.5	2.3	89-90
Protein (g/100g)	0.55	0.1	3.3	0.2	0.2-0.5
Fat (g/100g)	0.1	0.1	0.02	0.01	0.1-0.2
Ash (g/100g)	0.54	0.2	4.7	0.2	0.2-0.3
Total carbohydrates (g/100g)	7.2	1.9	41.5	2.2	9.0-11.0
Fructose (g/100g)	1.1	0.4	10	0.2	3.0-4.0
Glucose (g/100g)	1.3	0.4	10.2	0.6	3.0-4.0
Surcose (g/100g)	<0.1		<0.1		<0.1
Dietary Fiber (g/100g)	2.1	0.3	2.9	1	0.5-0.1
Energy (kJ/100g)	136	32	762	40	163-197
Vitamins					
Vitamin A (IU/g)	<1		<1		<1
β-Carotene (µg/g)	19.1	12.1	124	50	18-22 IU/ 100g
Thiamin (mg/g)	<0.02		<0.02		0.003-0.01 mg/100g
Riboflavin (mg/g)	<0.02		<0.02		0.003-0.01 mg/100g
Niacin (mg/g)	0.03	0.01	0.2	0.05	0.1-0.5 mg/100g
Vitamin B6 (mg/g)	<0.02		<0.02		0.04-0.13 mg/100g
Vitamin B12 (µg/g)	<0.001		<0.002		0.1-0.3 µg/100g
Vitamin C (mg/g)	1.1	0.8	1.3	0.5	3.0-25.0 mg/100g
Vitamin E (µg/g)	11	6.6	52.4	34.1	0.25-1.0IU/g
Folic Acid (µg/g)	<0.06		0.45	0.2	7.0-25.0 µg/100g
Biotin (µg/g)	0.02		0.14	0.01	1.5-5.0 µg/100g
Pantothenic acid (mg/g)	<0.02		0.1	0.2	0.15-0.5 mg/100g

RISK ASSESSMENT STEP	CHARACTERISTIC	INFORMATION AVAILABLE

Hazard Identification

Composition

Table 1 Compositional data on M. citrifolio puree, M. citrifolio concentrate and Tahitian Noni Juice (TNJ)

	"M. Citrifolio PUREE"		"M. Citrifolio CONCENTRATE"		"Tahitian Noni JUICE"
	Mean	SD	Mean	SD	Range
Minerals					
ca (mg/100g)	48.2	16	114	34	20-25
K (mg/100g)	214.3	56.9	2026	144	30-150
Na (mg/100g)	17	6	121	41	15-40
Mg (mg/100g)	26.1	8.3	152	20	3.0-12
P (mg/100g)	20.4	6.8	139	20	2.0-7.0
Fe (mg/100g)	0.7	0.06	26.1	7.5	0.1-0.3
M (mg/100g)	<0.0004	-	<0.0004	-	0.3-1.0
Amino acids					
Alanine (mg/100g)	45	4	259	11	17-33
Arginine (mg/100g)	32	4	148	12	30-44
Aspartic acid (mg/100g)	80	8	409	26	30-77
Cystine (mg/100g)	23	3	138	78	7-11
Glumatic acid (mg/100g)	64	5	331	21	25-44
Glycine (mg/100g)	36	4	150	15	10-22
Histidine (mg/100g)	<10	-	31	5	4-6
Isoleucine (mg/100g)	29	1	136	12	7-11
Leucine (mg/100g)	38	2	173	17	10-22
Lysine (mg/100g)	25	3	79	13	7-11
Methionine (mg/100g)	< 10	-	40	3	1-4
Phenylalanine (mg/100g)	21	5	99	9	5-8
Proline (mg/100g)	26	3	138	7	24-33
Serine (mg/100g)	27	2	107	13	9-12
Threonine (mg/100g)	27	3	104	0.1	8-11
Tryptophan (mg/100g)	< 10	-	31	6	1-3
Tyrosine (mg/100g)	25	3	123	1	6-11
Valine (mg/100g)	36	3	165	12	10-22

Value from SCF Opinion on Tahitian Noni Juice, 2002; SD - standard deviation

For heavy metals the following contents were reported as typical:

Arsenic<0.10mg/kg; Cadmium <0.05mg.kg; lead<0.05mg/kg; mercury<0.025mg/kg

Pesticide screen (USFDA Pesticide Analytical Method 302): organophosphate compounds <0.05mg/kg; organonitrogen compounds<0.5mg/kg; organochlorine compounds <0.2mg/kg; N-methylcarbamate compounds <0.1mg/kg.

Mycotoxin analysis revealed no detectable presence of aflatoxin B1, B2, G1 and G2 (DL=1.0µg/kg), ochratoxin A(DL=5(DL=1.0µg/kg).0µg/kg), T-2 toxin(DL=0.5mg/kg), HT-2 toxin(DL=0.5mg/kg), diacetoxyscirpenol (DL=1.2µm/kg), neosolaniol (DL=0.5mg/kg), fusarenon X(DL=0.5mg/kg), deoxynivalenol (DL=0.1mg/kg), 15 acetyl DON(DL=0.1mg/kg), 3-acetyl DON(DL=0.1mg/kg), nivalenol(DL=0.5mg/kg), zearalenone(DL=100µg/kg), fumonisin B1(DL=0.1mg/kg), fumonisin B2(DL=0.1mg/kg) , fumonisin B3(DL=0.1mg/kg) or patulin (DL=40µg/kg).

The applicant developed and validated an HPLC-UV method for the analysis of anthraquinones. The limits of detection determined for 5,15-dimethylmorindol, lucidin, alizarin and rubiadin were 2.5, 50.0, 6.3 and 62.5ng/ml respectively. The amounts of 5,15-dimethylmorindol detected in 5 batches of M.citrofolia puree ranged from 0.19 to 0.20µg/ml, those in 5 batches of M.citrofolia concentrate from 0.11 to 0.77µg/ml. Lucidin, alizarin and rubiadin were not detected in the samples analysed.

RISK ASSESSMENT STEP	CHARACTERISTIC	INFORMATION AVAILABLE
Hazard Identification	Specification	Composition of Morinda citrifolia fruit puree and concentrate

Moisture	89 - 93%	48 - 53%
Protein	< 0.6g/ 100g	3 - 3.5 g/ 100g
Fat	< 0.2g/ 100g	<0.04 g/ 100g
Ash	< 1g/ 100g	4.5 - 5 g/ 100g
Total carbohydrates	5-10g/ 100g	37 - 45 g/ 100g
Fructose	0.5-2g/ 100g	9 - 11 g/ 100g
Glucose	0.5-2g/ 100g	9 - 11 g/ 100g
Dietary fibre	1.5-3g/ 100g	1.5 -5 g/ 100g
5.15-dimethylmorindol(*)	0.19-20 µg/ml.	0.11 - 0.77 µg/ml.
Lucidin(*)	Not detectable	Not detectable
Alizarin (*)	Not detectable	Not detectable
Rubiadin (*)	Not detectable	Not detectable

(*) By an HPLC-UV method developed and validated by the applicant for the analysis of anthraquinones in Morinda citrifolio puree and concentrate.

Limit of detection: 2.5ng/ml. (5.15 dimethylmorindol); 50.0 ng/ml. (lucidin); 6.3 ng/ml (alizarin) and 62.5 ng/ml. (rubiadin)

Hazard Identification	Nutrition	The composition in terms of macronutrients, vitamins and minerals is comparable to the ranges known for other fruit juices. There were some deviations from normal ranges, but was not considered to be nutritionally relevant.
Hazard Identification	Toxicology	Details of the studies conducted to assess: Human safety study – no clear evidence of treatment-related effects
Hazard Identification	Allergenicity	Guinea pig sensitisation tests were conducted. (Note: animal models are considered not validated and inconclusive for the assessment of the sensitising potential of a novel protein and alternative investigations such as those mentioned in the checklist table, should be undertaken to build the Weight of Evidence).
Hazard Identification	Absorption, Distribution, Metabolism & Excretion (ADME)	Not relevant.
Exposure Assessment	History of Use	It has a long tradition as a dye plant and has been traditionally used throughout Polynesia as a medicinal plant. Several ethnobotanical studies from tropical regions refer to raw or cooked Morindacitrofolia fruit as part of the diet of the aboriginal populations of Polynesia and Australia. According to some references, the consumption was limited to famine due to the rather unpleasant taste and odour of the ripe fruits. Has been marked for several years in a number of countries including USA. US sales data e.g. 4 month period in 2002, an average of 300,000 one litre bottles were sold per month. In 2001 in USA an average number of 46,603 people purchased the product. US complaint data and post market surveillance from the USFDA was also presented. Four case studies of possible association with hepatoxic effects.

RISK ASSESSMENT STEP	CHARACTERISTIC	INFORMATION AVAILABLE
Exposure Assessment	Proposed Use and Anticipated Intake	Proposed to be used in the following products: candy/confectionary, nutritional bars, powdered nutritional drink mixes, fruit concentrates blended with other ingredients, jams, syrups. The total anticipated intake of concentrated noni juice and noni puree is equivalent to 313ml Morindacitrofolia. According to the applicant the quantity of noni fruit puree or concentrate to be included in products will be equivalent to 30ml of Morindacitrofolia fruit juice per serving. Consumer survey data was also presented. The estimated daily intake of Morindacitrofolia fruit juice equivalents based on UK National Diet and Nutrition Surveys was also presented. – mean and 97.5th percentiles for a range of age groups.
Risk Characterisation	Risk Assessment	Long history of use in a number of countries. No adverse effects from toxicology studies and human studies. Marketed for several years in other countries, with only a few reports of adverse health effects which could not be attributed to Morindacitrofolia. Small number of post-marketing surveillance reports of hepatoxic effects were considered to be not relevant – a causal relationship could not be established. Considered to be safe for consumption like other fruit juices.

Adapted from:

EFSA (European Food Safety Authority) (2006). Opinion on a request from the Commission related to the safety of noni juice (juice of the fruits from Morindacitrofolia). The EFSA Journal 376, 1-12.

EFSA (European Food Safety Authority) (2009). Opinion on the safety of Noni 'Morindacitrofolia (noni) fruit puree and concentrate' as a novel food ingredient. The EFSA Journal 998 1-16.

SCF (Scientific Committee on Food) (2002). Opinion of the Scientific Committee on Food on Tahitian Noni juice expressed on 4 December 2002. http://ec.europa.eu/food/fs/sc/scf/out151_en.pdf

4. Risk Assessment– Additives

The starting point for determining whether a food additive can be used without having harmful effects is to establish its acceptable daily intake (ADI). The ADI is an estimate of the amount of an additive in food or drinking water that can be safely consumed daily over a lifetime without adverse health effects.

Food additives that have undergone safety assessment either by JECFA or national risk assessment authorities are considered to be safe. Safety evaluations are based on scientific reviews of available biochemical, toxicological, and other relevant data on a given additive – mandatory tests in animals, research studies and observations in humans are considered. The toxicological test includes acute, short-term, and long-term studies that determine how the food additive is absorbed, distributed, and excreted, and possible harmful effects of the additive or its by-products at certain exposure levels.

After the safety assessment of food additive is completed either by JECFA or other national risk assessment bodies, the standard setting body for e.g. CAC or national governments, determine the maximum level of use of the additives in food and drink. Codex standards for consumer protection, and international trade in food, serve as a reference point.

Following risk assessment, the competent authority undertakes standard setting using risk management principles. The following regulations relate to the use of food additives:

- Food Safety and Standards (Food Products Standards and Food Additives) Regulations' 2011 *(17)*
- Food Safety and Standards (Approval of non-specified food and food ingredients) Regulations, 2017 *(5)*

The use of food additives should be done in accordance with the conditions as provided in the above mentioned regulations.

Case Studies

Case Study 1: Erythrosine

Terms of Reference (TOR): Erythrosine (INS127) used as a Food Coloring Substances has an ADI of 0.1mg/kg bw/day. Erythrosine has been permitted in several foods at prescribed levels. Determine if there is a risk of exceeding ADI's at the current exposure levels. (16,17,18)

RISK ASSESSMENT

Hazard Identification

Introduction

Erythrosine (INS 127) is an authorized food additive for several foods at prescribed levels as per Food Safety and Standards Regulations (FSSR). It is also used in many countries around the world in medicines for oral use and for dentistry to stain and visualize plaque.

Technical Data

- It is a Xanthene Dye and has a molecular weight of 879.84g/mol and CAS Registry Number 16423-68-0
- Chemical Name: disodium 2-(2,4,5,7-tetraiodo-6-oxido-3oxoxanthen-9-yl) benzoate
- It is a red odorless powder or granules with a calculated Log P (octanol-water) of 4.95 at 25°C (Molinspiration, 2007) which is soluble in water (<9% w/w) and ethanol.

It was previously evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1990 and the EU Scientific Committee for Food (SCF) in 1989 and recently reevaluated by JECFA in 2018.

The toxicological database for erythrosine is extensive and adequate to establish a suitable health standard for regulatory purposes. The database covered metabolism, reproduction and developmental toxicity and genotoxicity.

It was considered that the weight of evidence still showed that the tumorigenic effects of Erythrosine in the thyroid gland of rats are secondary to its effects on thyroid function and not related to any genotoxic activity. Also, Erythrosine induced rodent thyroid tumors may be considered of limited relevance to Humans based on previous and recent evaluations of Erythrosine.

Further, In the study in rat and a study in man, increased level of Protein Bound Iodine (PBI) (in rat and man) and iodine (in man)were measured in the blood. Erythrosine has a minimal effect in humans at a clinical oral dose of 200mg daily for 14 days, while a dose of 60 mg daily was without effect (Gardner et al., 1987).

Also, studies conducted by Ingbar and collegues (1983, 1984b) provide supporting data that only a very small fraction of the ingested Erythrosine, approximately 1.0%, is absorbed from the Gastro Intestinal tract.

Hazard Characterization

Based on the above studies, 60mg dose was taken to be the equivalent of 1mg/kg bw/day and is considered as NOAEL or NOEL. However, LOAEL is 200mg oral dose/14days in humans had increased thyroid secretions (Hyperthyroidism).

By applying the safety factor of 10 to the NOAEL to allow for the small number of subjects used in the study and its relatively short duration, an ADI of 0-0.1mg/kg bw/day was derived.

Hence, as a weight of evidence, in terms of toxicological database for erythrosine, an ADI of 0.1mg/kg bw/day is considered appropriate for dietary risk assessment purposes, subject to exposure assessment.

Exposure Assessment

The purpose of the dietary exposure assessment was to estimate dietary intake to the food coloring erythrosine for the Indian population, if use of Erythrosine is extended as proposed. Dietary Exposure was estimated for the addition of erythrosine in the specified foods according to the recommended maximum levels.

Below are the commodities mentioned under Food Safety and Standards (Food Product Standards and Food Additives) Regulations along with the prescribed limits. Overall quantity of Erythrosine (mg/day) calculation shown in the below table:

Sl. No.	Commodity Name	Standard	Remarks	How many times we consume (in a week/month)	Annual Consumption per day	g/mg/ml	Quantity of Erythrosine (mg/day)
			I. Dairy Products and Analogues, excluding products of category 2.0				
1	Dairy Based Drinks – flavoured milk and/ or fermented	50mg/kg	Summer Season (120 Days)- Avg 200ml	Twice in a week	18.00	ml	0.88
2	Fermented milk (plains) not heat treated after fermentation	50mg/kg	Summer Season (120 Days)- Avg 200ml	Twice in a week	18.00	ml	0.88
3	Dairy Based Desserts	50mg/kg	Industry Consumption Data - 4000ml/year (Ice Cream) (120 Days)		11.00	ml	0.55
			II. Edible ices, including sorbet				
4	Edible ices, including sorbet	50mg/kg	Summer Season (120 Days)- Avg 100g	Once in a week	4.00	g	0.22
			III. Fruits and Vegetables				
5	Canned and Bottled (pasteurized) fruit	100mg/kg	**NA** (Unlikely to consume)		0.00		0.00

Sl. No.	Commodity Name	Standard	Remarks	How many times we consume (in a week/month)	Annual Consumption per day	g/mg/ml	Quantity of Erythrosine (mg/day)
6	Jam, Jellies and marmalades	100mg/kg	Likely to take every alternate days. Considering avg 4 person in each household. Pack size- 500g	Almost daily	4.00	g	0.42
7	Candid/glazed/ crystallized fruit including murabba	100mg/kg	Avg twice in a week (app 15g) All the year	Twice in a week	4.00	g	0.43
8	Fermented vegetable (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera) and seawood products, excluding fermented soybean products of food categories 6.8.6, 6.8.7, 12.9.1, 12.9.2.1, 12.9.2.3)	30mg/kg	**NA** (Unlikely to consume)		0.00		0.00
			IV. Confectionary				
9	Cocoa and Chocolate Products	50mg/kg	Once in a week (app 30g). All the year	Once in a week	4.00	g	0.21
10	Confectionary including hard and soft candy, nougats etc other than food categories 5.1, 5.3 and 5.4	50mg/kg	One Candy (5g)	Thrice in a week	2.00	g	0.11
11	Chewing Gum	25mg/kg	One Chewing Gum (3 g)	Thrice in a week	2.00	g	0.05
12	Decorations (e.g for fine bakery wares), toppings (non-fruit) and sweet sauces	50mg/kg	Decorations (30ml)	Twice in a month	2.00	ml	0.10
			V. Cereal and Cereal Products				
13	Cereals/ Pulses and starch-based desserts	50mg/kg	**NA** (Unlikely to consume)		0.00		0.00
			VI. Bakery Products				
14	Cakes, Cookies, Biscuits, Cracker and pies	50mg/kg	Twice in a week (app 30g). All the year	Twice in a week	8.00	g	0.43
			VII. Meat and Meat Products including Poultry				
15	Processed meat and poultry products in whole pieces and cuts	30mg/kg	**NA** (Unlikely to consume)		0.00		0.00
16	Processed Comminuted meat and poultry products	30mg/kg	**NA** (Unlikely to consume)		0.00		0.00

Sl. No.	Commodity Name	Standard	Remarks	How many times we consume (in a week/month)	Annual Consumption per day	g/mg/ml	Quantity of Erythrosine (mg/day)
			VIII. Beverages excluding Dairy Products				
17	Water Based Flavoured drinks, including sport, energy or electrolyte, drinks and particulated drinks, includes carbonated fruit beverages, carbonated beverages with fruit	50mg/kg	Summer Season (120 Days) - Avg 250ml	Twice in a week	22.00	ml	1.10
18	Non-carbonated water based flavoured drinks including punches and ades, ginger cocktail (ginger beer and gingerale), thermally processed fruit beverages/ fruit drinks/ ready to serve fruit beverages	100mg/kg	Summer Season (120 Days) - Avg 200ml	Twice in a week	18.00	ml	1.75
19	Concentrates (liquid or solid) for water based flavoured drinks (Synthetic syrups for dispensers, sharbat) (Synthetic syrups), squashes, crushes, fruit syrup, cordials and barley water.	100mg/kg	Summer Season (120 Days) - Avg 200ml	Twice in a week	18.00	ml	1.75
							8.85

- Calculation: *In the absence of a Total Diet Study / data from authenticated sources, assumptions are made
- Values are rounded off

Dietary exposure is calculated using Theoretical Maximum Daily Intake (TMDI)[1] Approach based on the following assumptions:

Scenario 1

1. A person consumes all the 19 commodities as mentioned above. However, this assumption is also very much unlikely to happen.
2. Calculation of the exposure was done considering upper limit as given by the regulator.
3. The colored food are ingested and nothing is discarded.
4. The amount of the food additive in the food does not change as a result of storage, cooking or processing techniques.

Based on the assumptions made overall dietary exposure was found to be 8.85mg/day.

Scenario 2

1. Divided the 19 commodities under 8 categories. And Assuming may be one category of food is consumed under each commodity.
2. Calculation of the exposure was done considering upper limit as given by the regulator.
3. The colored food are ingested and nothing is discarded.
4. The amount of the food additive in the food does not change as a result of storage, cooking or processing techniques.

Based on the assumptions made overall dietary exposure was found to be 3.38mg/day.

Scenario 3

1. Divided 8 categories under solids and liquids and Assuming may be one category of food is consumed under each commodity.
2. Calculation of the exposure was done considering upper limit as given by the regulator.
3. The colored food are ingested and nothing is discarded.
4. The amount of the food additive in the food does not change as a result of storage, cooking or processing techniques.

Based on the assumptions made overall dietary exposure was found to be 3.38 mg/day.

Food Consumption Data:

1. Using a combination of Poundage Method and Household survey.

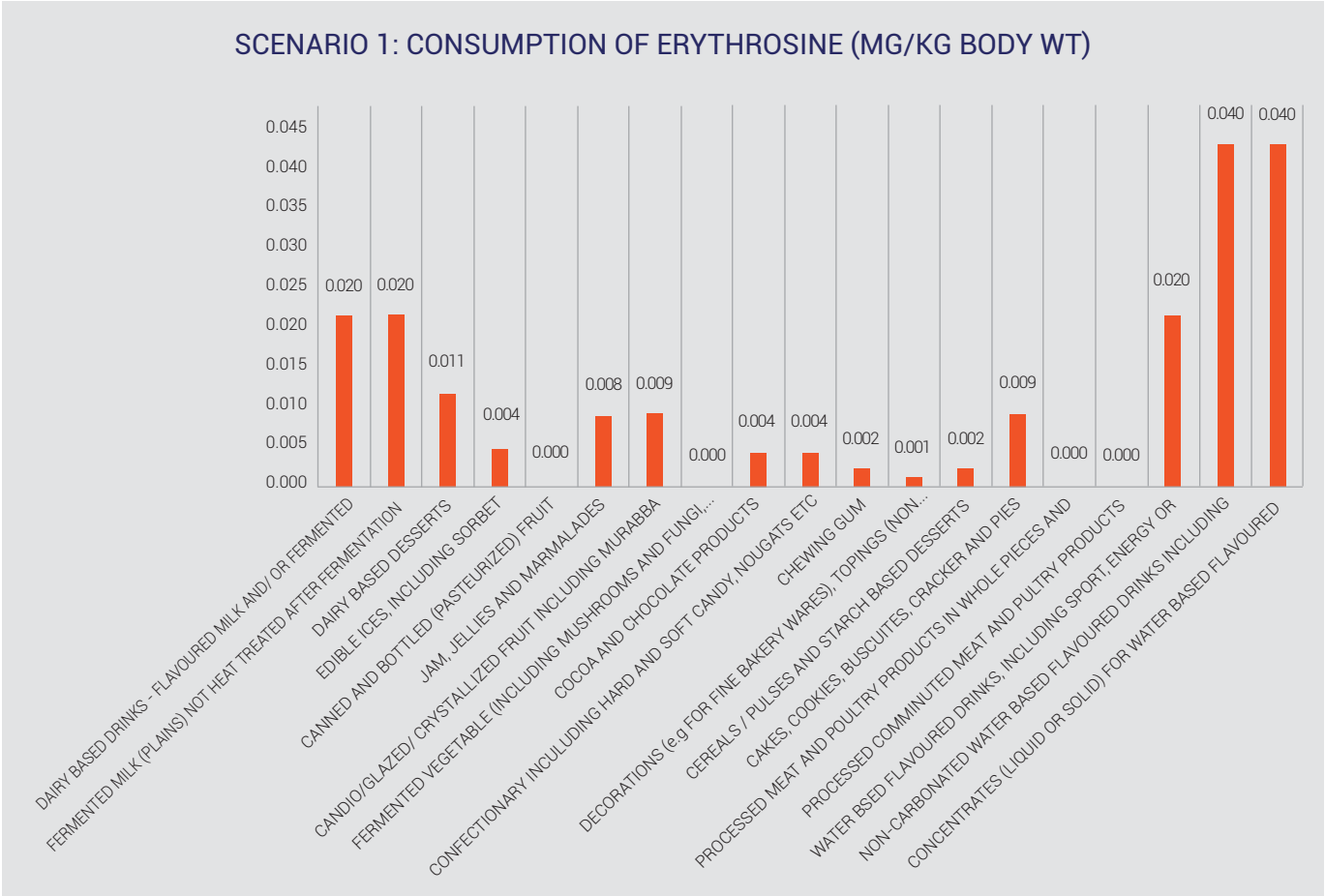
[1] TMDI is calculated by multiplying the average daily consumption of each food (in absence of national per capita food consumption) by the maximum use levels (ML) of the food.

RISK CHARACTERIATION

Comparison with the ADI of 0.1 mg/kg bw/day was done about all the three scenarios considered during the Exposure Assessment. In all the assumptions, we had calculated the consumption of Erythrosine (mg/kg body wt./day), considering the reference body weight as 50kg.

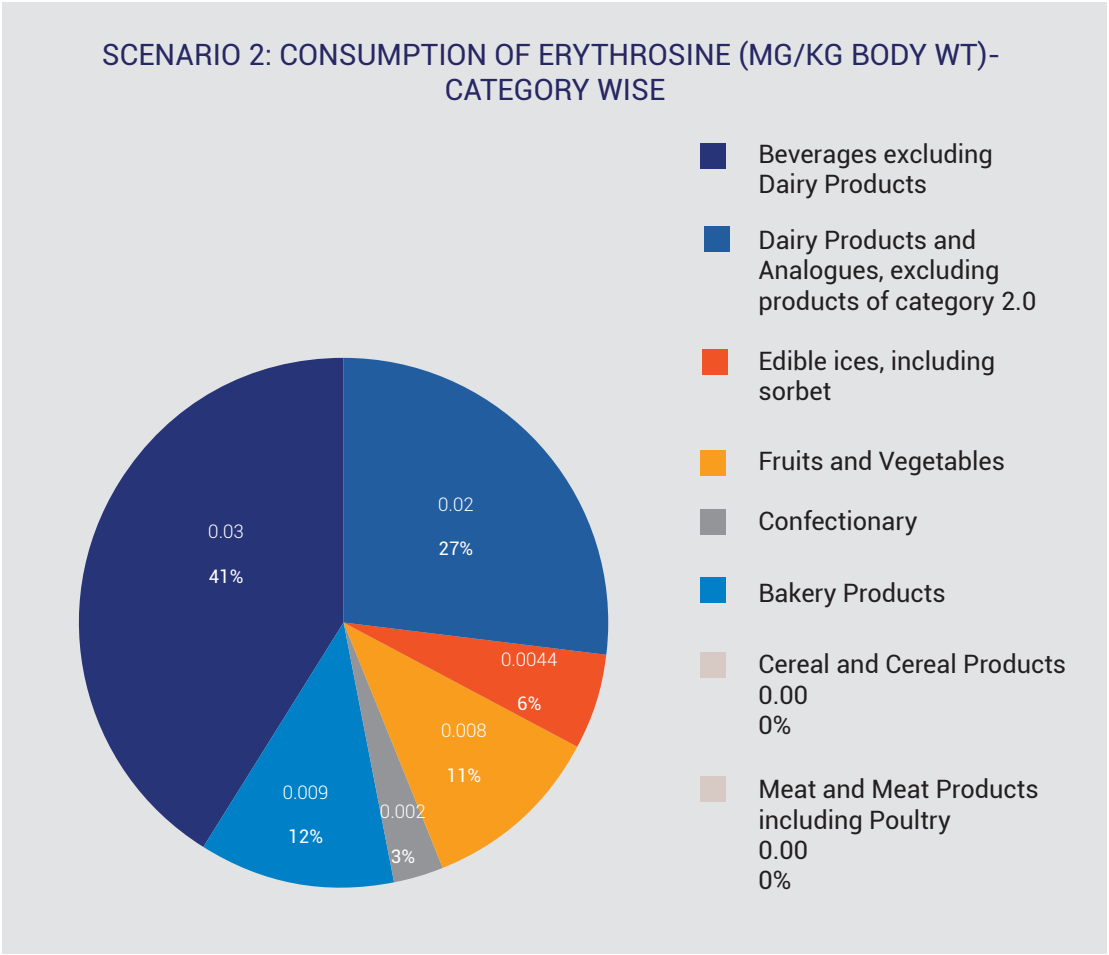
Scenario 1

In Scenario 1, 8.85mg/kg was the dietary exposure and when we divide it by reference body weight of 50 kg, the consumption of erythrosine comes out to be 0.18 mg/kg body weight/day. It is 180% of ADI of Erythrosine i.e. 0.1mg/kg body weight/day, which is also not very high as all the calculations were made on the assumptions and calculated taking into consideration the upper limits. Also, in reality it is unlikely that all the items are consumed every day. Moreover, geographic conditions, climatic conditions, food consumption pattern, population etc. will also vary.



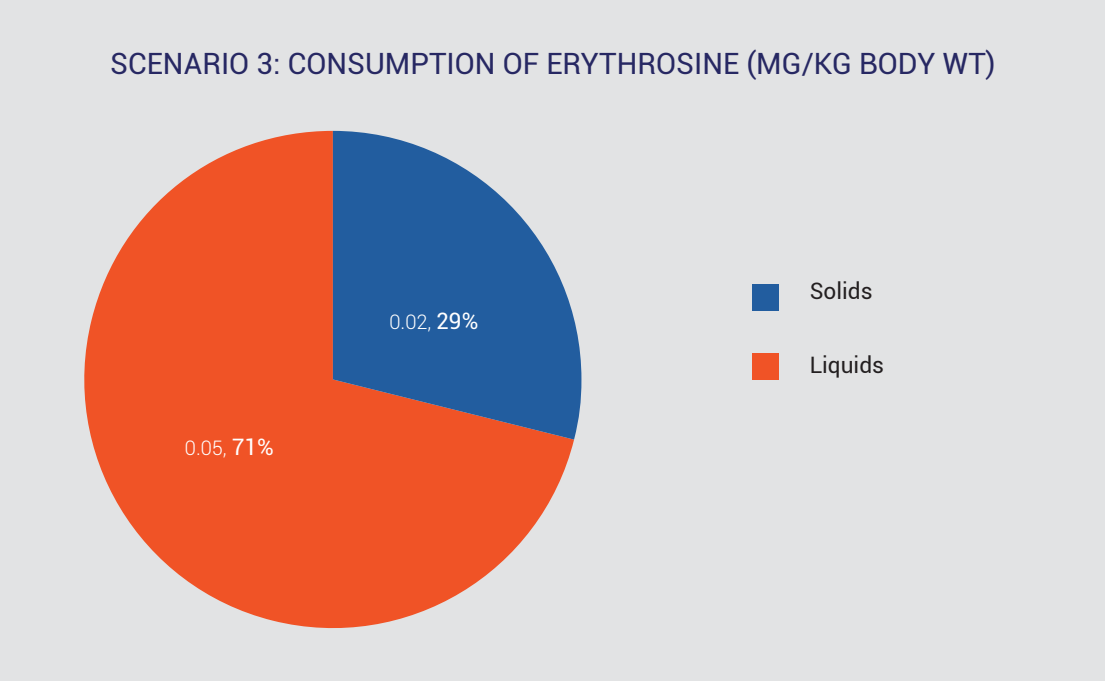
Scenario 2

In Scenario 2, 3.38 mg/day was the dietary exposure and based on the calculation the consumption of Erythrosine comes out to be 0.07 mg/kg body weight/day, which is 70% of the ADI value of Erythrosine 0.1mg/kg body weight/ day. In this scenario also, calculations were done considering the upper limits it is unlikely that these items will be consumed every day. Hence, the exposure would be far less than the calculated value.



Scenario 3

In Scenario 2, 3.38 mg/day was the dietary exposure and based on the calculation the consumption of Erythrosine comes out to be 0.07 mg/kg body weight/day, which is 70% of the ADI value of Erythrosine 0.1mg/kg body weight/ day. Also, consumption of Erythrosine accounts for 71% from the liquid category and only 29% from the solid. Moreover, overall also based on calculation, the consumption of Erythrosine would be far less that the calculated value.



CONCLUSION:

The toxicity of the erythrosine is well defined. Supplementary studies published since JECFA last considered the toxicity of erythrosine were evaluated (in 2018 -no change in the ADI). The new studies provided no indication of and safety issues related to Erythrosine. *(16)*
Comparison of the ADI of 0.1 mg/kg bw/day with the three scenario's detailed above clearly indicates that the exposure of erythrosine is unlikely to pose a significant health risk.

Case Study 2: Caffeine

TOR: In case of Caffeine there is an intake from natural sources as well as when it is added to foods. It is of concern that it will lead to adverse effect due to excessive intake. Determine if caffeine intake is beyond the safe levels at the current exposure levels for general population, however excluding the specific population groups (For e.g. pregnant women, children or population consuming caffeine as health supplements). *(17,19,20,21,22,23)*

RISK ASSESSMENT

Hazard Identification

Introduction

A review of the literature regarding safety aspect of caffeine to be done based on the daily intake of caffeine from all sources both natural and added.

Caffeine's chemical name is 1, 3, 7 – trimethylxanthine and is a naturally occurring alkaloid substance found in leaves, seeds and fruits of more than 63 plant species worldwide. Some of the common sources of caffeine are the kola nut (Cola acuminate), cacao bean (Theobroma cacao), yerba mate (Ilex paraguariensis) and guarana berries (Paullinia cupana), however, roasted coffee beans (Coffea Arabica and Coffea robusta) and tea leaves (Camellia sinensis) are the world's primary sources of dietary caffeine.

Caffeine is also found in so called energy drinks, alongside other ingredients such as taurine and D – glucurono -y- lactone. It is also found in soft drinks, as well as products containing cocoa or chocolate and a variety of medications and dietary supplements (Barone Roberts 1996; Andrews and others 2007).

Recommendations on maximum levels of caffeine consumption for general population has been derived by different national and international bodies taking into account a variety of health outcomes and same is tabulated below:

Sl. No.	Studies	Population Affected	Consumption Level	Remarks
1	Landolt et al., 1995	General Adult	• 400 mg per day	• Based on the review, no health concerns in relation to acute toxicity, calcium balance (under adequate calcium intakes), cardiovascular health, cancer risk or male fertility.
			• Single dose - 1.4 mg/kg bw and above, taken at bedtime	• When taken at bedtime, impair sleep in some individuals
2	Nickell and Uhde, 1994	General Adult	• Single doses - 3 mg/kg bw and above	• Increase anxiety in some cases
3	Bernstein et al., 1994	General Adult	• Not to exceed 2.5 mg/kg bw per day (Single dose)	• Food Standards Australia and New Zealand expert group (FSANZ), 2000 • Health Canada, 2006 • Nordic Working Group on Food Toxicology and Risk Evaluation (NNT), 2008 • Belgium Superior Health Council (SHC), 2012

Sl. No.	Studies	Population Affected	Consumption Level	Remarks
4	EFSA's panel on Dietetic Products, Nutrition and Allergies	Adult	• Single dose of caffeine up to 200mg – about 3mg/kg bw	• From all sources do not raise safety concerns for the general healthy adult population. The same amount of caffeine does not raise safety concerns when consumed less than two hours prior to intense physical exercise under normal environmental conditions. However, no studies are available in pregnant women or middle aged/ elderly subjects undertaking intense physical exercise.
			• Single doses of caffeine 100mg (about 1.4mg/kg bw)	• It may affect sleep duration and patterns in some adults, particularly when consumed close to bedtime.
			• Intake up to 400mg per day (about 5.7mg/kg bw per day)	• If consumed throughout a day do not raise safety concerns for healthy adults in the general population, except pregnant women.
5	Nawrot 2003	Adult	• ≤400 mg/day in adults	• Acute Toxicity: Studies conducted, found no acute toxicity associated due. to caffeine intake , 400mg caffeine/day or 2.5 mg/kg/day • Bone and Calcium- No significant impact on fracture and fall rates, bone mineral density and osteoporosis or altered calcium hoeostatis, particularly under conditions of adequate calcium intake. • Cardiovascular – Acceptable intake not found associated with adverse cardiovascular effects in healthy adults. • Behavior- 400mg caffeine/day was found to be an acceptable intake which is not associated with significant concern for adverse behavioural effects.

Hazard Characterization

We do not have an ADI for caffeine. Based on above studies and review, up to 400mg/day in general population is considered safe for human consumption and is considered appropriate for dietary risk assessment purposes, subject to exposure assessment.

Exposure Assessment

The purpose of the dietary exposure assessment was to estimate dietary intake of caffeine for the Indian population both from natural and added. Dietary Exposure was estimated for the addition of caffeine in the specified food according to the recommended maximum levels as well as naturally present quantity.

Caffeine content is assumed based on EFSA's (2015) scientific opinion which provided information on the concentrations of caffeine that are found in common caffeine-containing food and beverages*:

- Tea (220 ml) - 50 mg
- Coffee (filter, one cup, 200 ml) - 90 mg
- Coffee (espresso, 60 ml) - 80 mg
- A bar of plain chocolate (50 g) - 25 mg
- A bar of milk chocolate (50 g) - 10 mg

*Caffeine content can vary depending on the manufacturing process, raw ingredients, product composition and other factors.

Below are the commodities mentioned under Food Safety and Standards (Food Product Standards and Food Additives) Regulations along with the prescribed limits for the caffeine content as well as common caffeine containing food and beverages where the caffeine content is assumed based on EFSA's scientific opinion.

Overall Quantity of caffeine (mg/day) calculation shown in the below table:

Sl. No.	Commodity Name	Standard	Remarks	How many times we consume (in a day/week)	Average Consumption per day (g/ml/mg)	Quantity of Caffeine (mg/day)
	ADDED CAFFEINE					
1	Caffeinated Beverage *(Energy Drink)	300mg/lt	250ml	3 times in a week	106.8	32
2	Carbonated Water	145mg/lt	300ml	2 times in a week	85.5	12.5
3	Non-Carbonated Water Based Beverages	145mg/lt	300ml	2 times in a week	85.5	12.5
4	Plain Chocolate	25mg/50g	Bar Size: 50g	Alternate day	25.0	13
5	Milk Chocolate	10mg/50g	Bar Size: 50g	Alternate day	25.0	5
	NATURALLY PRESENT					
1	Tea (A cup of black tea)	50mg/220ml	A serve size: 150ml	Daily (three times)	450	102
2	Coffee (A cup of filter coffee)	90mg/200ml	A serve size: 150ml	Daily (three times)	450	184
			Total Quantity of Caffeine (mg/day)			361

*In the absence of a Total Diet Study / data from authenticated sources, assumptions are made

*Few values are rounded off

Dietary exposure is calculated based on the following assumptions:

Scenario 1

1. A person consumes all the 7 commodities as mentioned above.
2. Calculation of the exposure was done for the products where caffeine is naturally present as well as for the products where caffeine is added considering the upper limit as provided by the regulators.

Based on the assumptions made overall dietary exposure was found to be 361 mg/day.

Scenario 2

1. A person only consumes products in which caffeine is naturally present either tea or coffee and one beverage and one chocolate.
2. Calculation of the exposure was done considering the average, assuming the person is either consuming tea or coffee or both also but overall thrice in a day.

Based on the assumptions (Coffee+ Carbonated/Non Carbonated + Plain chocolate) - overall dietary exposure was found to be 209.5 mg/day.

Based on the assumptions (Tea+ carbonated/Non Carbonated+ Milk chocolate) - overall dietary exposure was found to be 119.5 mg/day.

Scenario 3

1. Divided the categories under solids and liquids and took the average.
2. Calculation of the exposure was done for the products where caffeine is naturally present as well as for the products where caffeine is added considering the upper limit as provided by the regulators.

Based on the assumptions made overall dietary exposure was found to be 171 mg/day.

Food Consumption Data:

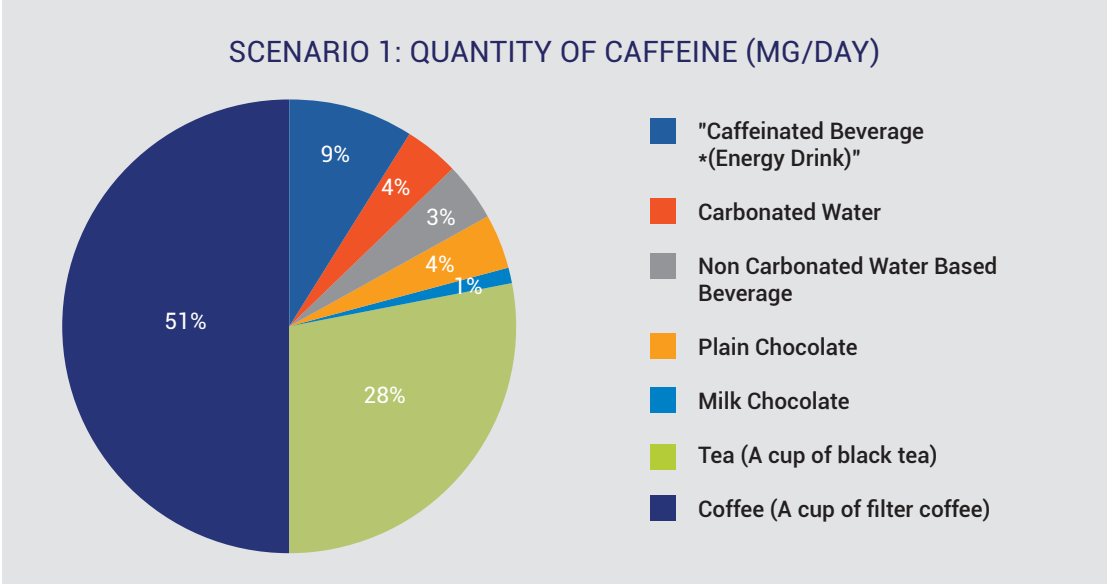
1. Using a combination of Poundage Method and Household survey.

RISK CHARACTERIATION

Comparison with 400mg/day for caffeine in general population was done considering the three scenarios that were considered during the Exposure Assessment.

Scenario 1

In Scenario 1, quantity of caffeine calculated per day was 361 mg/day. It is less than the supposed safe limit of 400mg/day. Also, in reality it is unlikely that all the items are consumed every day, so the quantity of caffeine will be even less than the arrived value. Moreover, geographic conditions, climatic conditions, food consumption pattern, population etc. will also vary.

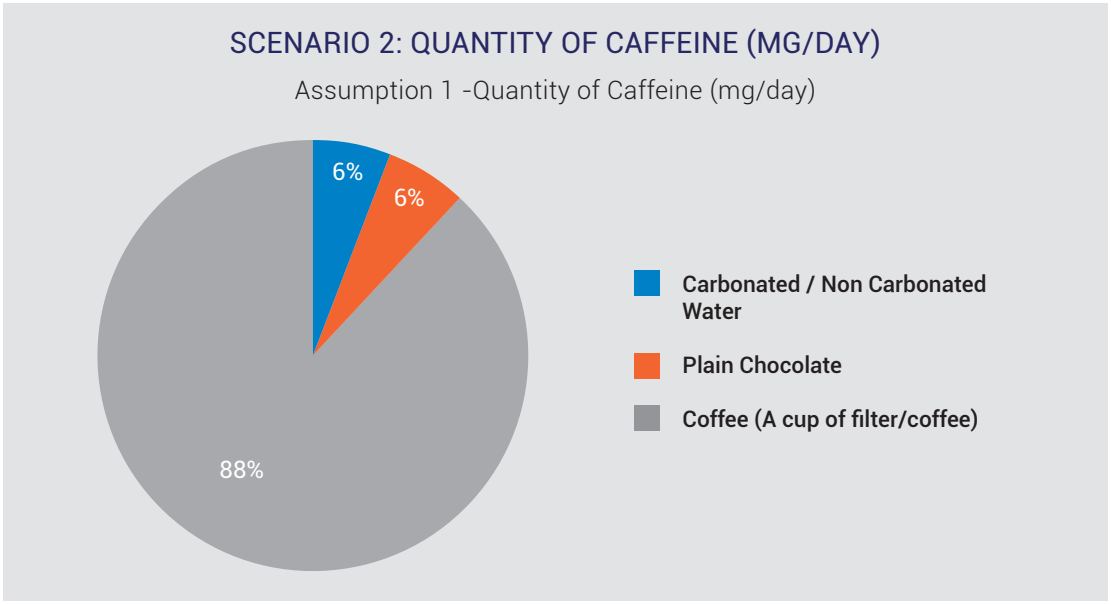


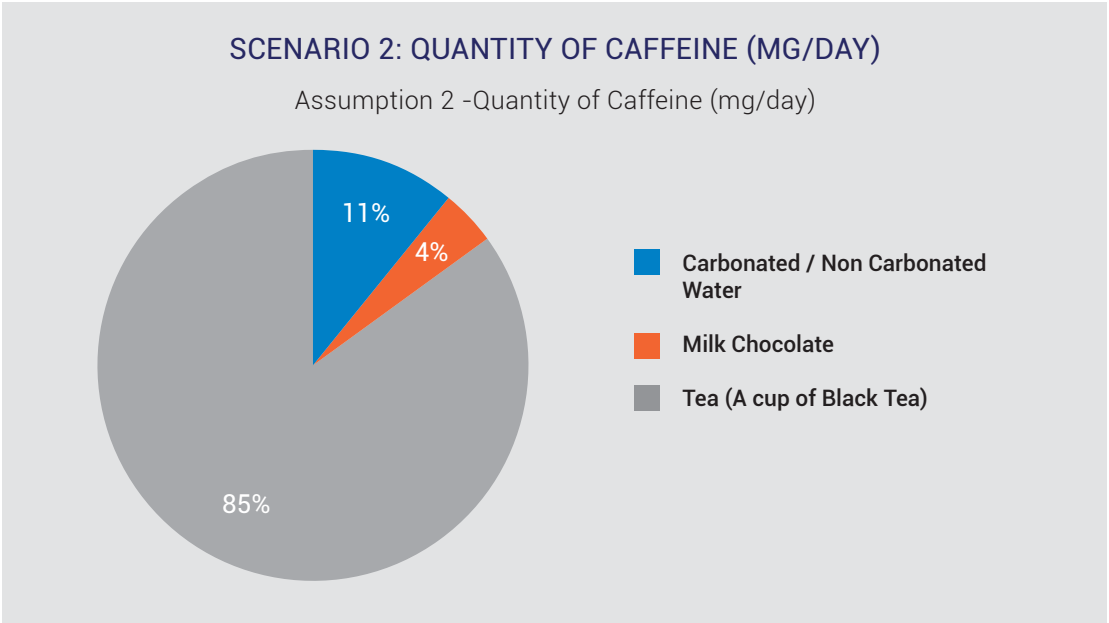
Scenario 2

In Scenario 2, 1st assumption (Coffee + Carbonated /Non Carbonated +Plain Chocolate) - quantity of caffeine calculated per day was 209.5 mg/day. It is less than the supposed safe limit of 400mg/day.

2nd assumption (Tea + Carbonated/ Non Carbonated + Milk Chocolate) - quantity of caffeine calculated per day was 119.5 mg/day. It is less than the supposed safe limit of 400mg/day.

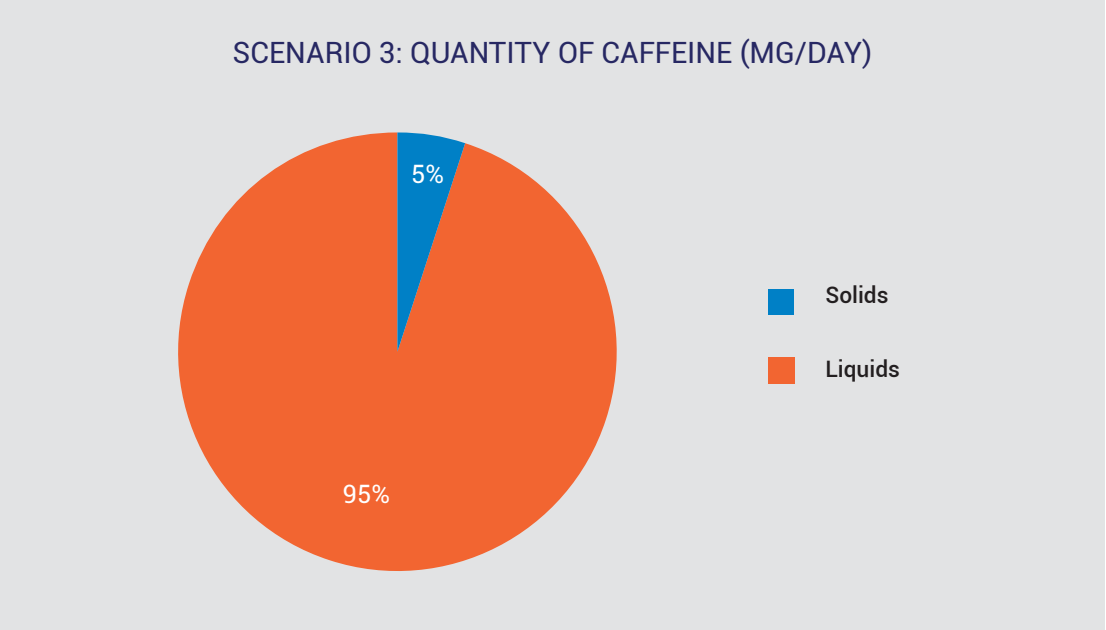
Also, from the below pie charts, it is clear that the consumption of caffeine from beverages and other sources where the caffeine is added does not significantly contribute to the overall daily intake of caffeine. And the major contributors are tea and coffee where the caffeine is naturally present.





Scenario 3

In Scenario 3, overall 171 mg/day was the dietary exposure both from solid and liquid category. Also, consumption of caffeine accounts for 95% from the liquid category and only 5% from the solid.



CONCLUSION:

Caffeine is not an additive but a chemical with addictive property. The safety of the caffeine intake has been published and reviewed by several national regulatory scientific committees for use at the levels of consumption estimated by their respective populations.
Comparison of the quantity of caffeine of 400mg/day with the three scenario's detailed above clearly indicates that the exposure of caffeine is unlikely to pose a significant health risk.

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