2.
Safety and regulation of low/no calorie sweeteners

Low/no calorie sweeteners (LNCS) are amongst the most thoroughly researched ingredients worldwide. Based on a strong body of scientific evidence, food safety bodies around the world confirm their safety.

The regulatory bodies involved in safety assessment

As with all food additives, for an LNCS to be approved for use on the market, it must first undergo a thorough safety assessment by the competent food safety authority. At an international level, the responsibility of evaluating the safety of all additives, including LNCS, rests with the Joint Expert Scientific Committee on Food Additives (JECFA) of the United Nations Food & Agriculture Organization (FAO) and the World Health Organization (WHO). JECFA serves as an independent global risk assessment body responsible for evaluating food additive safety and providing advice to the Codex Alimentarius, a body of the FAO-WHO, and the member countries of these organisations.

Throughout the world, nations rely on regional or international governing bodies and expert scientific committees, such as JECFA, to evaluate the safety of food additives, or have their own regulatory bodies for food safety oversight. For example, many countries in Latin America approve the use of LNCS based on JECFA's safety assessment and the Codex Alimentarius provisions. In the US and in Europe, the safety assessment of all food additives is the responsibility of the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), respectively. These regulatory bodies have consistently confirmed the safety of approved LNCS at current levels of use *(Magnuson et al, 2016; Serra-Majem et al, 2018; Ashwell et al, 2020; Pavanello et al, 2023)*.

Safety evaluation

All LNCS have undergone a thorough and very strict premarket safety evaluation and approval process.

As with all food additives, for an LNCS to be approved, the applicants must present to the food safety body a comprehensive safety dossier relevant to the proposed use of the ingredient and in accordance with the requirements published by the relevant food safety authority *(EFSA 2012; FDA, 2018)*. To determine the safety of LNCS, the authorities thoroughly review and assess data on the chemistry, kinetics and metabolism of the substance, the proposed uses, exposure assessment, extensive toxicological studies, as well as data from observational research and controlled clinical trials in a weight of evidence (WoE) approach *(EFSA, 2020; EFSA 2023)*. The safety assessment process is based on independent expert review of the collective research. **Only when there is strong evidence of no safety concern is a food additive permitted for use in foods.**

In the approval process, the risk assessment experts of the food safety agencies establish an Acceptable Daily Intake (ADI) for each approved LNCS.

Worldwide, low/no calorie sweeteners are among the most thoroughly tested food ingredients. Numerous regulatory bodies around the world have confirmed their safety.

What is the Acceptable Daily Intake (ADI)?

The Acceptable Daily Intake (ADI) is defined as the amount of an approved food additive that can be consumed daily in the diet, over a lifetime, without appreciable health risk. The ADI is expressed on a body weight basis: in milligrams (mg) per kilogram (kg) of body weight (bw) per day *(Fitch et al, 2021)*.

How the Acceptable Daily Intake is Established

Regulatory authorities derive the ADI based on the daily maximum intake that can be given to test animals throughout life without producing any adverse biological effects, known as the No-Observed Adverse Effect Level (NOAEL) *(Barlow, 2011)*. The NOAEL is then divided by a 100-fold safety factor to establish the ADI. The 100-fold safety factor ensures a margin of safety covering possible differences between species (e.g., between test animals and humans) and within species, for example special population groups, such as children and pregnant women *(Fitch et al, 2021)*. The use of the ADI principle for toxicological evaluation and safety assessment of food additives is accepted by all regulatory bodies worldwide.

Usage levels are set, and use is monitored by national and regional authorities so that consumption does not reach ADI levels *(Martyn et al, 2018)*. As the ADI relates to lifetime use, it provides a safety margin large enough for scientists not to be concerned if an individual's short-term intake exceeds the ADI, as long as the average intake over long periods of time does not exceed it *(Renwick, 1999)*. The ADI is the most important practical tool for scientists in ensuring the appropriate and safe use of LNCS *(Renwick, 2006)*. The ADI values of individual LNCS as established internationally by JECFA are provided in Table 1.

Table 1: Acceptable Daily Intake (ADI) for commonly used low/no calorie sweeteners, as established by the Joint Expert Scientific Committee on Food Additives (JECFA) of the United Nations Food & Agriculture Organization (FAO) and the World Health Organization (WHO).

Low/no calorie sweetener	Acceptable Daily Intake (ADI) (mg/ kg BW/ day)
Acesulfame-K (INS 950)	0-15 mg/kg
Aspartame (INS 951)	0-40 mg/kg
Cyclamate (INS 952)	0-11 mg/kg
Saccharin (INS 954)	0-5 mg/kg
Sucralose (INS 955)	0-15 mg/kg
Thaumatin (INS 957)	Not specified (An ADI of "not specified" means that thaumatin can be used according to Good Manufacturing Practice (GMP))
Steviol glycosides (INS 960)	0-4 mg/kg (expressed as Steviol)
Neotame (INS 961)	0-2 mg/kg
Advantame (INS 969)	0-5 mg/kg

Note: The 'INS' reference for each additive refers to the International Numbering System of the Codex Alimentarius.
Source: WHO. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Update of November 2023 (Accessed 14 March 2024).
Available at: https://apps.who.int/food-additives-contaminants-jecfa-database/

Consumption of low/no calorie sweeteners globally

Research from around the world confirms that the intake of approved LNCS is well below the respective ADI levels. In 2018, a review of the global literature regarding the intake of the most commonly used LNCS concluded that, overall, the studies conducted to determine the exposures of LNCS over the last decade raise no concerns with respect to exceedance of the individual sweetener ADIs among the general population globally *(Martyn et al, 2018)*. Also, the reviewed data do not suggest a significant shift in exposure over time, with several studies indicating a reduction in intakes of some sweeteners.

Since the publication of the review by Martyn et al in 2018, numerous studies have been conducted in different countries worldwide, including in Europe, North and Latin America, Asia and Middle East *(Tennant, 2019; Tennant and Vlachou, 2019; Martínez et al, 2020; ACHIPIA, 2021; Barraj et al, 2021a; Barraj et al, 2021b; Chazelas et al, 2021; Kang et al, 2021; Tran et al, 2021; Wang et al, 2021; Carvalho et al, 2022; Cavagnari et al, 2022; Daher et al, 2022; Duarte et al, 2022; Martyn et al, 2022; Rebolledo et al, 2022; Takehara et al, 2022; Fagundes Grilo et al, 2023; Leninghan et al, 2023; Terami et al, 2023)*. **All studies conducted to date, across all continents, confirm that global levels of exposure are within the ADI limits for the individual sweeteners, and for all population groups.**

Importantly, updated safety evaluations of sweeteners include consideration of all intake research and regulations to ensure that actual consumption of any LNCS remains within the set ADI *(EFSA, 2020)*.

...In Europe

The most refined and analytical exposure assessments of LNCS to date have been conducted in Europe (Martyn et al, 2018). The majority of the studies have been conducted for the general population of adults and children, with intakes calculated for the mean and high-level consumers. In line with previous reviews, recent research indicates no issue with exceeding the ADIs for the individual sweeteners among the evaluated European population groups, even for high consumers of low/no calorie sweetened products *(EFSA, 2013; EFSA, 2015; Martyn et al, 2018; Tennant 2019; Tennant and Vlachou, 2019; Chazelas et al, 2021; Tran et al, 2021; EFSA, 2021; Carvalho et al, 2022; EFSA, 2022)*.

A series of analytical studies in Belgium, Ireland, Italy, and Portugal found that LNCS intake is well below the ADI *(Huvaere et al, 2012; Le Donne et al, 2017; Buffini et al, 2018; Carvalho et al, 2022)*. The studies in Belgium, Ireland and Italy, led by the Belgian Scientific Institute for Public Health, examined exposure to LNCS both at the level of the more conservative approach and when actual concentration levels in foods were taken into account, and found that the studied populations are not at risk of exceeding the corresponding ADI of each sweetener. In fact, even for the very high consumers of low/no calorie sweetened products (the top 1% of the population) the levels of consumption remain well below the ADI. The study using food consumption data from the Portuguese National Food, Nutrition and Physical Activity Survey estimated that exposure levels for the six most consumed LNCS were below the ADI in all assessed scenarios and age groups and concluded that the Portuguese population is not at risk of excessive LNCS exposure *(Carvalho et al, 2022)*.

In the framework of the re-evaluation programme of all food additives that were already permitted in the European Union before 20 January 2009 set up under Commission Regulation (EU) No 257/2010, in 2018 EFSA issued public calls for use levels and/or concentration data (analytical data) of sweeteners to perform the respective exposure assessments *(EFSA, 2020)*. Using some of the use levels submitted to EFSA, Tennant and Vlachou (2019) estimated exposure to common LNCS including acesulfame K, cyclamic acid and its salts, saccharin and its salts, sucralose and thaumatin based on new available data and updated dietary exposure methodologies and concluded that estimates of exposure for the examined sweeteners are generally found to be well within current ADIs for most population groups. In subsequent scientific opinions, EFSA also confirmed that intakes of thaumatin and neohesperidine DC pose no safety concern and are well within the permitted levels *(EFSA 2021; EFSA 2022)*.

...In Latin America

In light of public health recommendations and implemented policies in several Latin American countries aiming to reduce overall sugars intake in the diet in response to rising obesity rates, LNCS have been used as an alternative to sugar to enable sweet tasting foods and beverages with few or no calories. This substitution has led to questions about a possible increase in the consumption of LNCS and a potential risk of exceeding the ADI. To examine this hypothesis, **many analytical exposure assessments have been conducted recently in this region aiming to inform on the intake levels of LNCS in different countries and populations in Latin America confirming that consumption is within the permitted levels and there is no risk of exceeding the respective sweeteners' ADIs** *(Martínez et al, 2020; ACHIPIA, 2021; Barraj et al, 2021a; Barraj et al, 2021b; Cavagnari et al, 2022; Martyn et al, 2022; Takehara et al, 2022; Leninghan et al, 2023).*

In their comprehensive review of global LNCS intakes, Martyn et al (2018) noted that data for Latin America were generally limited. Since 2018, multiple studies have been conducted and confirmed that LNCS intake is below the respective ADI for each individual sweetener in the population of several countries in Latin America, including in Argentina *(Barraj et al, 2021b; Cavagnari et al, 2022)*, Brazil *(Barraj et al, 2021a; Martyn et al, 2022; Takehara et al, 2022; Leninghan et al, 2023)*, Chile *(Martinez et al, 2020; ACHIPIA, 2021; Barraj et al, 2021b)*, Mexico *(Leninghan et al, 2023)* and Peru *(Barraj et al, 2021b)*. **While these studies have used differing methodologies, their conclusions consistently confirm no risk of excessive LNCS exposure, even for the most conservative assessments and for all population groups.**

Current evidence shows that the intakes of approved low/no calorie sweeteners are well below the Acceptable Daily Intake (ADI) values.

A series of analytical studies by Barraj and colleagues recently assessed the intake of six LNCS (acesulfame potassium, aspartame, cyclamate, saccharin, steviol glycosides, and sucralose) in Brazil *(Barraj et al, 2021a)* and Argentina, Chile and Peru *(Barraj et al, 2021b)* and compared it to the ADIs established by JECFA. Results showed that the estimated intakes by the total population of the analysed countries, including by children, were well below the JECFA ADIs. This applies to all identified scenarios, including the most conservative ones. These results are in line with the outcomes of other recent studies in these countries including an analysis performed by the Chilean Food Safety and Quality Agency (ACHIPIA) aiming at assessing the dietary exposure of Chilean population (including children) to four authorised LNCS (acesulfame potassium, aspartame, sucralose, and steviol glycosides). ACHIPIA concluded that the estimated consumption of these four sweeteners is below the ADI for each sweetener in all exposure scenarios represented and all age groups *(ACHIPIA, 2021)*.

Consumption of low/no calorie sweeteners by children and pregnant women

When it comes to children, a frequent consideration is whether the intake levels of LNCS remain within the ADI because of their higher intakes of foods and drinks on a body weight basis. The ADI represents the daily amount that can be safely consumed over a lifetime without appreciable health risk. When establishing the ADI the agencies take into account all population groups, including children. It is worth mentioning that toxicity studies cover infants as well as young children. Nevertheless, considering the specific nutritional requirements to allow for rapid growth and development, LNCS are not approved for use in foods for infants (defined as children under the age of 12 months) and young children (defined as children between 1-3 years).

Globally, many recent studies have focused on evaluating LNCS exposure in children confirming that intake of LNCS is generally well below the relevant ADI values for the individual sweeteners *(Martyn et al, 2016; Martyn et al, 2018; Garavaglia et al, 2018; Martínez et al, 2020; ACHIPIA, 2021; Barraj et al, 2021a; Barraj et al, 2021b; Kang et al, 2021; Tran et al, 2021; Wang et al, 2021; Carvalho et al, 2022; Martyn et al, 2022; Rebolledo et al, 2022; Takehara et al, 2022; Fagundes Grilo et al, 2023; Terami et al, 2023)*. Similarly, studies that have evaluated LNCS consumption levels among pregnant women confirm that intakes are below the respective ADIs *(Fuentealba Arévalo et al, 2019; Duarte et al, 2022)*.

The Acceptable Daily Intake (ADI) is a guarantee of safety, representing the average amount of a low/no calorie sweetener that can be safely consumed on a daily basis throughout a person's lifetime.

Are low/no calorie sweeteners safe for pregnant women and children?

Dr Carlo La Vecchia: Consumption of LNCS, within the ADI set by the regulatory authorities, is safe during pregnancy, because all low/no calorie sweeteners have been subject to appropriate testing. The variety of foods and drinks sweetened with LNCS can help satisfy a pregnant woman's taste for sweetness while adding few or no calories. Pregnant and breastfeeding women, however, do need to consume adequate calories to nourish the foetus or infant and should consult with a physician about their nutritional needs. It is important to remember that weight control remains a priority, particularly in pregnancy.

LNCS are also safe for children. It is also important, however, to keep in mind that children, particularly young children, need ample calories for rapid growth and development. Considering the nutritional requirements of infants and young children (below 3 years of age), sweeteners are not permitted in foods for this age group.

EU Legislation on Sweeteners

Under EU legislation, all food additives including sweeteners, must be authorised before they can be used in foods. In the EU, sweeteners are regulated under the EU framework regulation on food additives *(Regulation (EC) 1333/2008)*. Annex II of this legislation, provides an EU list of sweeteners approved for use in foods, beverages and table-top sweeteners and their conditions of use. Where appropriate, maximum use levels are specified.

Within the EU, the eleven LNCS currently authorised for use are acesulfame-K (E950), aspartame (E951), aspartame-acesulfame salt (E962), cyclamate (E952), neohesperidine DC (E959), saccharin (E954), sucralose (E955), thaumatin (E957), neotame (E961), steviol glycosides (E960) and advantame (E969). The 'E' reference for each sweetener refers to Europe and shows that the ingredient is authorised and regarded as safe in Europe. In effect, the E-classification system is a robust food safety system introduced in 1962 and intended to protect consumers from possible food-related risks. Food additives must be included either by name or by an E number in the ingredients list.

Labelling of low/no calorie sweeteners

LNCS are clearly labelled on the packaging of all food and beverage products that contain them. In Europe, according to EU labelling regulation *(Regulation (EU) No 1169/2011)*, the presence of an LNCS in foods and beverages must be labelled twice on food products. The name of the LNCS (e.g. saccharin) or the E-number (e.g. E954) must be included in the list of ingredients. In addition, the term 'with sweetener(s)' must be clearly stated on the label together with the name of the food or beverage product.

The Regulatory Bodies involved in Europe

Regulatory approval of LNCS in the EU is granted by the European Commission on the basis of the scientific advice of EFSA. The EFSA panel dealing with the safety of sweeteners is the FAF Panel (Food Additives and Flavourings), an independent panel composed of scientific experts appointed on the basis of proven scientific excellence.

How a Low/no Calorie Sweetener is Approved for use in Foods and Drinks in the EU

The authorisation and conditions of use of an LNCS, like any other food additive, is harmonised at EU level. EFSA is responsible for the provision of scientific advice and scientific technical support for European Union legislation and policies in all fields that have a direct or indirect impact on food and food safety. Applicants (e.g. ingredient manufacturers) can only apply for approval of an LNCS after extensive safety tests have been completed and evidence provided of the product's safety and utility. The design and nature of studies to be conducted are expected to follow specific guidelines of Good Laboratory Practice (GLP). The petition provides technical details about the product and comprehensive data obtained from safety studies.

The safety data are then examined by EFSA. At any time during this process, questions raised by EFSA need to be answered by the applicant. Sometimes this may require additional studies. Completing and analysing the safety studies may take up to 10 years. In the approval process, an ADI is set for each LNCS by EFSA. Following the publication of a scientific opinion by EFSA, the European Commission drafts a proposal for authorisation of use of the LNCS in foods and drinks available in European Union countries.

Following the required procedure and only if the regulators are fully satisfied that the ingredient is safe, the approval will be given. This means that all LNCS available on the EU market are safe for human consumption.

EFSA re-evaluation of sweeteners

At the request of the European Commission under the Regulation (EU) No 257/2010, EFSA has been re-evaluating the safety of all food additives, including sweeteners, which were already approved on the EU market before 20th January 2009. Aspartame is the first sweetener to have undergone this re-evaluation process by EFSA, which reconfirmed its safety. *(EFSA, 2013)* The re-evaluations of thaumatin *(EFSA, 2021)* and neohesperidine DC *(EFSA 2022)* have also been completed, with EFSA affirming the safety of both sweeteners.

Re-evaluation of sweeteners in Europe and around the world: the example of aspartame

Aspartame is one of the most studied food additives in the human food supply. More than five decades of research has proven the safety of this ingredient, as assessed by the responsible regulatory bodies around the world, including EFSA [1], the U.S. FDA [2], FAO/WHO JECFA [3], and regulatory agencies in over 100 countries.

In Europe, aspartame was first evaluated and confirmed to be safe by the Scientific Committee for Food (SFC) in 1984. In December 2013, as part of the re-evaluation process and following one of the most comprehensive scientific risk assessments undertaken on a food additive, EFSA published its opinion on aspartame, re-confirming that aspartame is safe for consumers at levels currently permitted *(EFSA, 2013)*. [4]

Following the publication of the opinion on its website, EFSA pointed out, "Experts of ANS Panel have considered all available information and, following a detailed analysis, have concluded that the current Acceptable Daily Intake (ADI) of 40mg/kg bw/day is protective for the general population". [4] EFSA also highlighted that the breakdown products of aspartame (phenylalanine, methanol and aspartic acid) are also naturally present in other foods. For instance, methanol is found in fruit and vegetables and is even generated in the human body by endogenous metabolism. Importantly, EFSA affirmed that current exposures to aspartame and its degradation product were below their respective ADIs. An example comparing aspartame consumption to the sweetener's ADI and NOAEL is presented in Figure 1.

In the US, the FDA first issued a regulation for aspartame in 1974 for use as a tabletop sweetener and in chewing gum, cold breakfast cereals, and dry bases for certain foods (for example, beverages, instant coffee and tea, gelatins, puddings and fillings, and dairy products and toppings). [2] Since that time, the FDA approved aspartame for other uses, including most recently as a general-purpose sweetener in 1996, and is continuously monitoring the scientific literature for new information on aspartame. [5]

At a global level, JECFA, the leading scientific body of FAO/WHO responsible for evaluating the safety of food additives, first evaluated aspartame in 1981 and found it to be safe *(JECFA, 1981)*. [3] On 14th July 2023, JECFA re-affirmed the safety of aspartame and re-confirmed the ADI of 40 mg/kg body weight *(JECFA 2023a, 2023b)*. [6,7] Following review of an extensive evidence base, JECFA concluded that there was no convincing evidence from experimental animal or human data that aspartame has adverse effects after ingestion. [7] JECFA also evaluated carcinogenic potential of aspartame, concluding that there was "no concern for carcinogenicity in animals from oral exposure to aspartame," and that the "evidence of an association between aspartame consumption and cancer in humans is not convincing". [6] As part of its comprehensive risk assessment, JECFA examined the conclusions of the International Agency for Research on Cancer (IARC) who classified aspartame as "possibly carcinogenic to humans (Group 2B)" *(Riboli et al, 2023)* [8], and found no concern for human health. Contrary to the full risk assessment by JECFA, IARC conducted a hazard assessment, which means it identified an exposure that has the potential to harm people, but it did not assess the risk of this occurring. IARC is not a food safety body and its 2B classification does not consider intake levels or actual risk, making an IARC review far less comprehensive than the thorough reviews conducted by food safety bodies like JECFA. *(Goodman et al, 2023)*. [9]

Aspartame consumption compared with the ADI

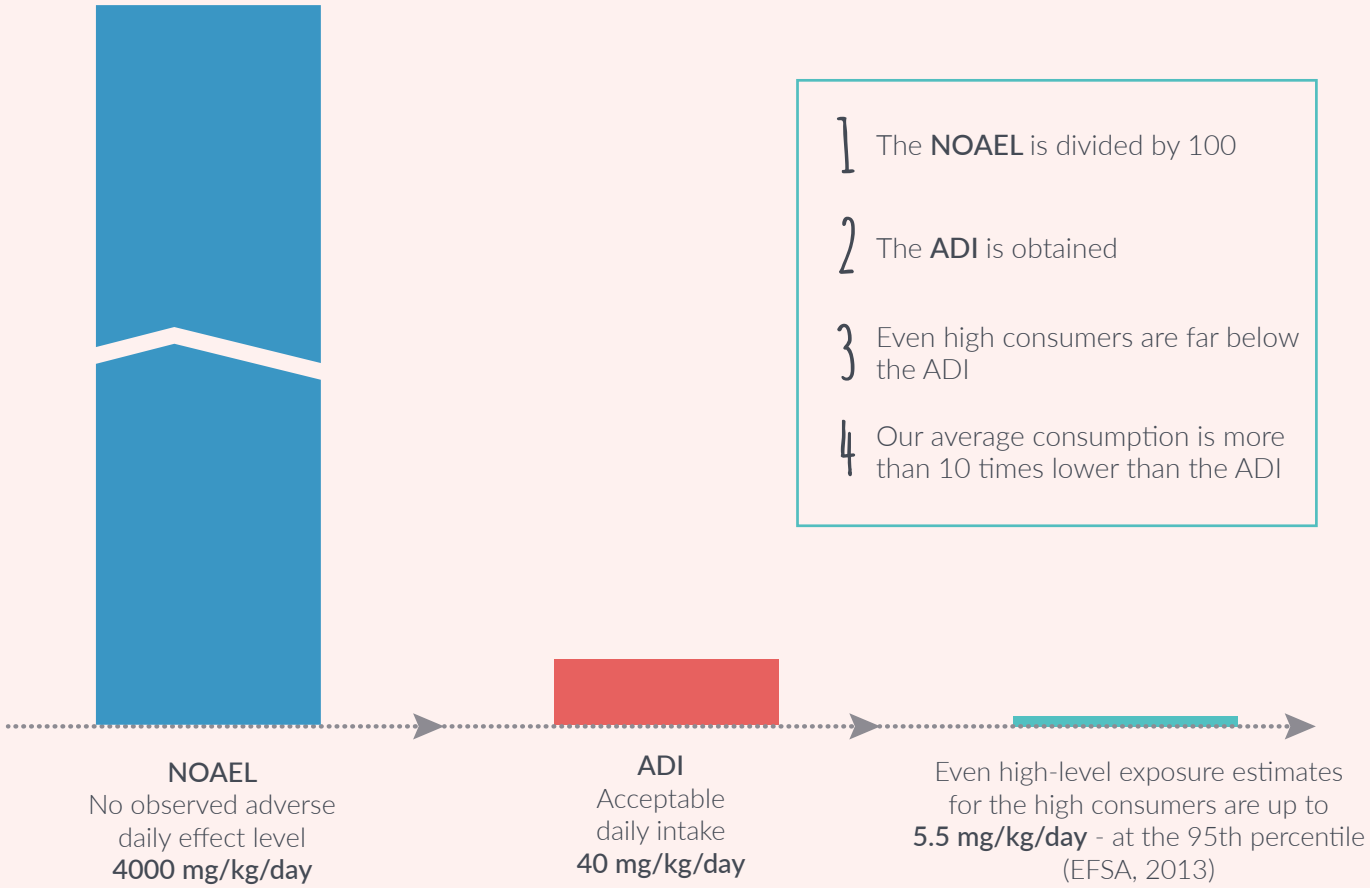

Figure 1: Aspartame consumption compared to the sweetener's Acceptable Daily Intake (ADI) and No Observed Adverse Effect Level (NOAEL) *(EFSA, 2013)*.

What is the case with the use of aspartame in phenylketonuria (PKU)?

Phenylketonuria (PKU) is a rare inherited condition affecting about 1 in 10,000 people. Throughout most of Europe, PKU is screened for shortly after birth. Those who have it, lack the enzyme that converts phenylalanine into the amino acid tyrosine. Phenylalanine is an essential amino acid required for protein biosynthesis. It is also a component of aspartame. For those with PKU, consuming protein-containing food leads to a build-up of phenylalanine in the body. People with PKU must avoid the intake of phenylalanine in the diet.

This means that high protein foods such as meat, cheese, poultry, eggs, milk/ dairy products and nuts are not permitted. The amount of phenylalanine contributed to foods from aspartame, as compared to that provided by common protein sources, like meat, eggs and cheese, is very small.

For the benefit of persons with PKU, foods, drinks and healthcare products that contain the LNCS aspartame must legally carry a label statement indicating that the product contains phenylalanine: “Contains a source of phenylalanine”.

Sources:
1. EFSA. Sweeteners. Last review date: 20 December 2023 (Accessed 14 March 2024). Available at: https://www.efsa.europa.eu/en/topics/topic/sweeteners
2. FDA, US. Aspartame and other sweeteners in foods. Content current as of 14 July 2023 (Accessed 14 March 2024). Available at: https://www.fda.gov/food/food-additives-petitions/aspartame-and-other-sweeteners-food
3. WHO. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Aspartame. 2023 (Accessed 14 March 2024). Available at: https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/62
4. EFSA. Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive. EFSA Journal. 2013;11:3496. Available at: https://www.efsa.europa.eu/en/efsajournal/pub/3496
5. FDA, US. Timeline of selected FDA activities and significant events addressing aspartame. Content current as of 30 May 2023 (Accessed 14 March 2024). Available at: https://www.fda.gov/food/food-additives-petitions/timeline-selected-fda-activities-and-significant-events-addressing-aspartame
6. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Ninety-sixth meeting (Safety evaluation of certain food additives). 14 July 2023a (Accessed 14 March 2024). Available at: https://www.who.int/publications/m/item/ninety-sixth-meeting-joint-fao-who-expert-committee-on-food-additives-(jecfa)
7. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Evaluation of certain food additives: ninety-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization and Food and Agriculture Organization of the United Nations; 2023b (WHO Technical Report Series, No. 1050). Licence: CC BY-NC-SA 3.0 IGO. Available at: https://iris.who.int/bitstream/handle/10665/376279/9789240083059-eng.pdf?sequence=1
8. Riboli E, Beland FA, Lachenmeier DW, et al. Carcinogenicity of aspartame, methyleugenol, and isoeugenol. Lancet Oncol. 2023 Aug;24(8):848-850
9. Goodman JE, Boon DN, Jack MM. Perspectives on recent reviews of aspartame cancer epidemiology. Glob Epidemiol. 2023 Aug 3;6:100117

Low/no calorie sweeteners do not increase the risk of developing cancer

Dr Carlo La Vecchia: There is no consistent scientific evidence that links the consumption of LNCS to cancer. Several toxicological and epidemiological studies were published during the last five decades on this topic.

A recent review *(Pavanello et al, 2023)* provided a comprehensive quantitative revision of the toxicological and epidemiological evidence on the possible relation between LNCS and cancer. The toxicological section included the evaluation of genotoxicity and carcinogenicity data for several LNCS, including acesulfame K, advantame, aspartame, cyclamates, saccharin, steviol glycosides and sucralose, while the epidemiological section included the results of a systematic search of 22 cohort and 46 case-control studies.

The large majority of the studies showed no association of LNCS with cancer risk. Some risks for bladder, pancreas and hematopoietic cancers found in a few studies were not confirmed in other studies. An issue on liver cancer was recently raised, but subsequently not supported by data from the Women's Health Initiative *(Zhao et al, 2023)*, which found no association between LNCS, cirrhosis and liver cancer.

Based on both the experimental data on genotoxicity or carcinogenicity of the specific LNCS evaluated, and the epidemiological studies, there is therefore now no evidence of cancer risk associated to LNCS consumption.

References

1. ACHIPIA (Chilean Food Safety and Quality Agency), Miranda C, Martinez N, Sotomayor G. Chronic dietary exposure assessment on sweeteners in food consumed by the Chilean population. 2021 (Accessed 19 March 2024). Available at: https://www.achipia.gob.cl/wp-content/uploads/2021/06/2021_ACHIPIA_Informe-EED-Cronica-Edulcorantes-MINSAL-ACHIPIA_Nueva-Version_final-con-abstract-English.pdf
2. Ashwell M, Gibson S, Bellisle F, et al. Expert consensus on low-calorie sweeteners: facts, research gaps and suggested actions. Nutr Res Rev. 2020;33(1):145-154
3. Barlow SM. Toxicology of Food Additives. In General, Applied and Systems Toxicology (eds B. Ballantyne, T.C. Marrs, T. Syversen, D.A. Casciano and S.C. Sahu). 2011. https://doi.org/10.1002/9780470744307.gat138.
4. Barraj L, Scrafford C, Bi X, Tran N. Intake of low and no-calorie sweeteners (LNCS) by the Brazilian population. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2021a;38(2):181-194
5. Barraj L, Bi X, Tran N. Screening level intake estimates of low and no-calorie sweeteners in Argentina, Chile, and Peru. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2021b;38(12):1995-2011
6. Buffini M, Goscinny S, Van Loco J, et al. Dietary intakes of six intense sweeteners by Irish adults. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2018;35(3):425-438
7. Carvalho C, Correia D, Severo M, et al. Dietary exposure to artificial sweeteners and associated factors in the Portuguese population. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2022;39(7):1206-1221
8. Cavagnari BM, Gómez G, Kovalskys I, Quesada D, Brenes JC; ELANS: Estudio Latinoamericano de Nutrición y Salud. Consumo de edulcorantes no calóricos en la población adulta de Argentina [Non-caloric sweeteners consumption in the adult population of Argentina]. Medicina (B Aires). 2022;82(6):881-890
9. Chazelas E, Druesne-Pecollo N, Esseddik Y, et al. Exposure to food additive mixtures in 106,000 French adults from the NutriNet-Santé cohort. Sci Rep. 2021;11(1):19680
10. Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.
11. Commission Regulation (EU) No 1129/2011 of 11 November 2011 amending Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council by establishing a Union list of food additives. Available at: http://data.europa.eu/eli/reg/2011/1129/oj
12. Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council Text with EEA relevance. Available at: http://data.europa.eu/eli/reg/2012/231/oj
13. Daher M, Fahd C, Nour AA, Sacre Y. Trends and amounts of consumption of low-calorie sweeteners: A cross-sectional study. Clin Nutr ESPEN. 2022;48:427-433
14. Duarte LM, Ferreira SMR, Almeida CCB, et al. Dietary exposure to low-calorie sweeteners in a sample of Brazilian pregnant women. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2022;39(10):1650-1662
15. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); Guidance for submission for food additive evaluations. EFSA Journal. 2012;10(7):2760. [65 pp.]. https://doi.org/10.2903/j.efsa.2012.2760
16. EFSA. Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive. EFSA Journal. 2013;11:3496. https://doi.org/10.2903/j.efsa.2013.3496
17. EFSA. Scientific opinion on the safety of the extension of use of steviol glycosides (E 960) as a food additive. EFSA Journal. 2015;13:4146. https://doi.org/10.2903/j.efsa.2015.4146
18. EFSA. Outcome of the public consultation on a draft protocol for assessing exposure to sweeteners as part of their safety assessment under the food additives re-evaluation programme. EFSA supporting publication 2020: 17(8): EN-1913. 52 pp. https://doi.org/10.2903/sp.efsa.2020.EN-1913
19. EFSA FAF Panel (EFSA Panel on Food Additives and Flavouring). Scientific Opinion on the re-evaluation of thaumatin (E 957) as food additive. EFSA Journal. 2021;19(11):6884, 72pp. https://doi.org/10.2903/j.efsa.2021.6884
20. EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings). Scientific Opinion on the re-evaluation of neohesperidine dihydrochalcone (E 959) as a food additive. EFSA Journal. 2022; 20(11):7595, 81pp. https://doi.org/10.2903/j.efsa.2022.7595
21. EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings). Revised Protocol on Hazard Identification and Characterisation of Sweeteners. Zenodo. 2023. (Accessed 14 March 2024). https://doi.org/10.5281/zenodo.7788969
22. EFSA. Sweeteners. Last review date: 20 December 2023 (Accessed 14 March 2024). Available at: https://www.efsa.europa.eu/en/topics/topic/sweeteners
23. Fagundes Grilo M, Marinho Duarte L, Crispim SP, de Azevedo Barros Filho A, Duran AC. Consumption of low-calorie sweeteners: findings from the Campinas Nutrition and Health Survey. Br J Nutr. 2023;130(1):103-113
24. Fitch SE, Payne LE, van de Ligt JLG, et al. Use of acceptable daily intake (ADI) as a health-based benchmark in nutrition research studies that consider the safety of low-calorie sweeteners (LCS): a systematic map. BMC Public Health. 2021;21(1):956
25. Fuentealba Arévalo F, Espinoza Espinoza J, Salazar Ibacahe C, Durán Agüero S. Consumption of non-caloric sweeteners among pregnant Chileans: a cross-sectional study. Nutr Hosp. 2019;36(4):890-897
26. Garavaglia MB, Rodríguez García V, Zapata ME, et al. Non-nutritive sweeteners: children and adolescent consumption and food sources. Arch Argent Pediatr. 2018;116(3):186-191
27. Goodman JE, Boon DN, Jack MM. Perspectives on recent reviews of aspartame cancer epidemiology. Glob Epidemiol. 2023;6:100117
28. Huvaere K, Vandevijvere S, Hasni M, Vinkx C, Van Loco J. Dietary intake of artificial sweeteners by the Belgian population. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2012;29(1):54-65.

29. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Ninety-sixth meeting (Safety evaluation of certain food additives). 14 July 2023a (Accessed 14 March 2024). Available at: https://www.who.int/publications/m/item/ninety-sixth-meeting-joint-fao-who-expert-committee-on-food-additives-(jecfa)
30. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Evaluation of certain food additives: ninety-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva: World Health Organization and Food and Agriculture Organization of the United Nations; 2023b (WHO Technical Report Series, No. 1050). Licence: CC BY-NC-SA 3.0 IGO. Available at: https://iris.who.int/bitstream/handle/10665/376279/9789240083059-eng.pdf?sequence=1
31. Kang HH, Yun CI, Choi S, Oh KS, Kim YJ. Occurrence and risk characterization of non-nutritive sweeteners in selected food products from Korea. Food Sci Biotechnol. 2021;31(1):37-48
32. Le Donne CL, Mistura L, Goscinny S, et al. Assessment of dietary intake of 10 intense sweeteners by the Italian population. Food and Chemical Toxicology. 2017;102:186-197.
33. Lenighan YM, Meetro J, Martyn DM, et al. Low- and no-calorie sweetener intakes from beverages - an up-to-date assessment in four regions: Brazil, Canada, Mexico and the United States. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2023;40(1):26-42
34. Magnuson BA, Carakostas MC, Moore NH, Poulos SP, Renwick AG. Biological fate of low-calorie sweeteners. Nutr Rev. 2016;74(11):670-689.
35. Martínez X, Zapata Y, Pinto V, et al. Intake of Non-Nutritive Sweeteners in Chilean Children after Enforcement of a New Food Labeling Law that Regulates Added Sugar Content in Processed Foods. Nutrients. 2020;12(6):1594
36. Martyn DM, Nugent AP, McNulty BA, et al. Dietary intake of four artificial sweeteners by Irish pre-school children. Food Addit. Contam. Part A Chem. Anal. Control. Exp. Risk Assess. 2016;33:592–602.
37. Martyn D, Darch M, Roberts A, et al. Low-/No-Calorie Sweeteners: A Review of Global Intakes. Nutrients. 2018;10(3):357.
38. Martyn D, Darch M, Floyd S, Ngo K, Fallah S. Low- and no-calorie sweetener intakes in the Brazilian population estimated using added sugar substitution modelling. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2022;39(2):215-228
39. Pavanello S, Moretto A, La Vecchia C, Alicandro G. Non-sugar sweeteners and cancer: Toxicological and epidemiological evidence. Regul Toxicol Pharmacol. 2023;139:105369.
40. Rebolledo N, Reyes M, Popkin BM, et al. Changes in nonnutritive sweetener intake in a cohort of preschoolers after the implementation of Chile's Law of Food Labelling and Advertising. Pediatr Obes. 2022;17(7):e12895
41. Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. Available online: http://data.europa.eu/eli/reg/2008/1333/oj
42. Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers.
43. Renwick AG. Incidence and severity in relation to magnitude of intake above the ADI or TDI: use of critical effect data. Regul Toxicol Pharmacol. 1999;30(2 Pt 2):S79-86.
44. Renwick AG. The intake of intense sweeteners - an update review. Food Addit Contam. 2006;23:327-38
45. Riboli E, Beland FA, Lachenmeier DW, et al. Carcinogenicity of aspartame, methyleugenol, and isoeugenol. Lancet Oncol. 2023 Aug;24(8):848-850
46. Serra-Majem L, Raposo A, Aranceta-Bartrina J, et al. Ibero–American Consensus on Low- and No-Calorie Sweeteners: Safety, nutritional aspects and benefits in food and beverages. Nutrients. 2018;10:818.
47. Takehara CT, Nicoluci ÍG, Andrade TFS, Arisseto-Bragotto AP. A comprehensive database of declared high-intensity sweeteners in Brazilian commercial products and updated exposure assessment. Food Res Int. 2022;161:111899
48. Tennant DR. Estimation of exposures to non-nutritive sweeteners from consumption of tabletop sweetener products: a review. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2019;36(3):359-365
49. Tennant DR, Vlachou A. Potential consumer exposures to low/no calorie sweeteners: a refined assessment based upon market intelligence on use frequency, and consideration of niche applications. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2019;36(8):1173-1183
50. Terami S, Kubota H, Koganesawa N, et al. Estimation of daily intake of food additives by Japanese young children using the market basket method in 2018. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2023;40(3):328-345
51. Tran NL, Barraj LM, Hearty AP, Jack MM. Tiered intake assessment for low- and no-calorie sweeteners in beverages. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2021;38(2):208-222
52. U.S. Food and Drug Administration (FDA). Determining the regulatory status of a food ingredient. Content current as of 20/9/2018 (Accessed 19 March 2024). Available at: https://www.fda.gov/food/food-ingredients-packaging/determining-regulatory-status-food-ingredient
53. U.S. Food and Drug Administration (FDA). Aspartame and other sweeteners in foods. Content current as of 14 July 2023 (Accessed 14 March 2024). Available at: https://www.fda.gov/food/food-additives-petitions/aspartame-and-other-sweeteners-food
54. U.S. Food and Drug Administration (FDA). Timeline of selected FDA activities and significant events addressing aspartame. Content current as of 30 May 2023 (Accessed 14 March 2024). Available at: https://www.fda.gov/food/food-additives-petitions/timeline-selected-fda-activities-and-significant-events-addressing-aspartame
55. Wang Y, Li C, Li D, et al. Estimated assessment of dietary exposure to artificial sweeteners from processed food in Nanjing, China. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2021;38(7):1105-1117
56. WHO. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Aspartame. 2023 (Accessed 14 March 2024). Available at: https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/62
57. WHO. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Update of November 2023 (Accessed 14 March 2024). Available at: https://apps.who.int/food-additives-contaminants-jecfa-database/
58. Zhao L, Zhang X, Coday M, et al. Sugar-Sweetened and Artificially Sweetened Beverages and Risk of Liver Cancer and Chronic Liver Disease Mortality. JAMA. 2023;330(6):537-546.