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, regulatory 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 scientific committee which performs safety assessments and provides 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 *(Fitch et al, 2012; Magnuson et al, 2016; Serra-Majem et al, 2018)*.

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 database 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 an additive, the authorities thoroughly review and assess data on the chemistry, kinetics and metabolism of the substance, the proposed uses and exposure assessment, as well as extensive toxicological studies *(Barlow, 2009)*. 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 *(Barlow, 2009)*.

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). The NOAEL is then divided by a 100-fold safety factor to establish the ADI. The 100-fold safety factor is to cover for possible differences between species and also within species, for example special population groups, such as children and pregnant women *(Renwick, 2006; Barlow 2009)*. 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 *(Renwick, 2006; 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 ADIs of individual sweeteners as established internationally by JECFA are provided in Table 1.

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)

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). *Note: The 'INS' reference for each additive refers to the International Numbering System of the Codex Alimentarius.*

An example comparing aspartame consumption to the sweetener's ADI and NOAEL is presented in Figure 1.

Aspartame consumption compared with the ADI

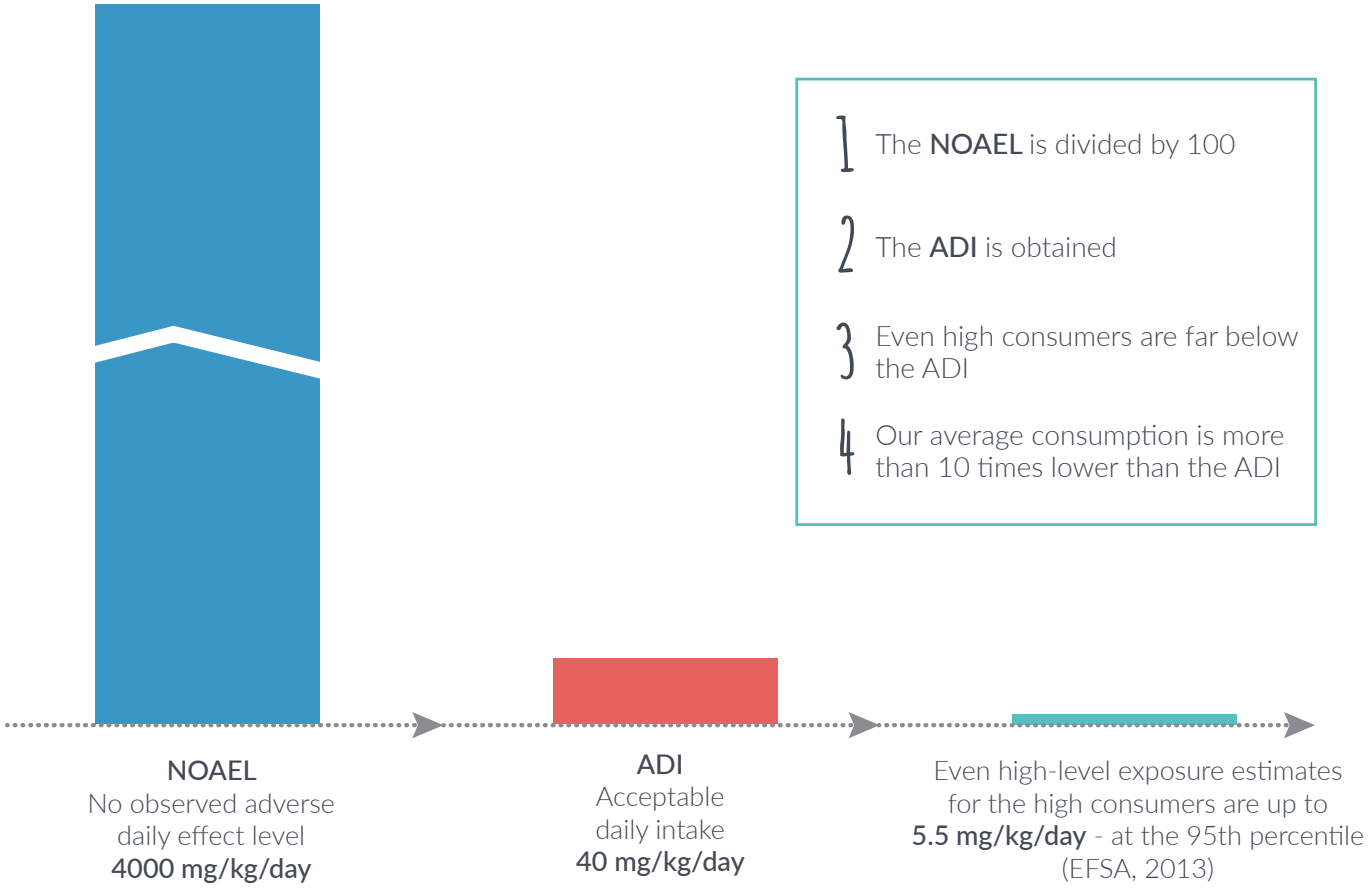

Figure 1: Aspartame consumption (EFSA, 2013) compared to the sweetener's Acceptable Daily Intake (ADI) and No Observed Adverse Effect Level (NOAEL).

Consumption of low/no calorie sweeteners globally

In 2018, a published 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*). The current data also do not suggest a significant shift in exposure over time, with several studies indicating a reduction in intakes *(Renwick, 2006; Renwick, 2008; Martyn et al, 2018)*. Thus, this review provides a significant degree of confidence that there does not appear to be a significant shift in patterns of LNCS intake and that levels of exposure are generally within the ADI limits for the individual sweeteners.

Consumption of sweeteners in Europe

The most refined and analytical exposure assessments of LNCS to date have been conducted in Europe. A total of 19 European peer-reviewed studies on LNCS intake and, further, seven studies from authoritative sources have been published over the last decade, with most studies using a standardized approach *(Martyn et al, 2018)*.

The majority of the studies in Europe were conducted for the general population, with intakes calculated for the mean and high-level consumers (the high-level intake percentile has been most commonly established at the 95th percentile). Generally, **there was no issue with exceeding the ADIs for the individual sweeteners among the evaluated European population groups, even for high consumers.** Furthermore, several studies examined intakes in specific subgroups, including young children and people with diabetes.

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

In a series of analytical studies conducted in different European populations in Belgium *(Huvaere et al, 2012)*, Ireland *(Buffini et al, 2018)* and Italy *(Le Donne et al, 2017)*, which were led by the Belgian Scientific Institute for Public Health in collaboration with local organisations in each country, data showed that LNCS intake is well below the ADI for each sweetener and does not pose a risk even for high consumers of low calorie sweetened products. These studies 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 Belgian, Irish and Italian 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.

Recent studies have also focused on children because of their higher intakes of foods and drinks on a body weight basis, and on both children and adults with diabetes, because of their higher potential intakes of LNCS *(Devitt et al, 2004; Husøy et al, 2008; Leth et al, 2008; EFSA, 2013; Vin et al, 2013; EFSA, 2015a; EFSA, 2015b; Mancini et al, 2015; Van Loco et al, 2015; Martyn et al, 2016)*. Overall, these studies also confirm that average intake of LNCS is generally below the relevant ADI values for the individual sweeteners.

EU Legislation on Sweeteners

In the EU, sweeteners are regulated under the EU framework regulation on food additives, Regulation 1333/2008 *(Regulation (EC), 2008)*. Annex II of this legislation, established by Commission Regulation 1129/2011, provides a Community 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 *(Commission Regulation (EU) No 1129/2011)*. Sweeteners must also meet EU purity criteria specifications *(Commission Regulation (EU) No 231/2012)*.

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.

At the request of the European Commission, EFSA is currently carrying out an ambitious re-evaluation of the safety of all food additives, which were approved on the EU market before 20th January 2009. Aspartame is the first sweetener to have undergone this re-evaluation process, which reconfirmed its safety.

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. Previously, the EU relied on the Scientific Committee on Food (SCF). Since April 2003, this has been the responsibility of EFSA.

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 (OECD Test Guidelines and Principles 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, questions raised by EFSA must 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.

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

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.

EFSA opinion on aspartame

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)*.

Highlighting 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".** 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 *(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".

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.

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..

Are low/no calorie sweeteners safe for children and pregnant women?
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. No risk difference, as compared to sweetened beverages, has consistently been reported. 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. 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).

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