

## COMMONLY USED ARTIFICIAL SWEETENERS IN EUROPE

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*review paper*

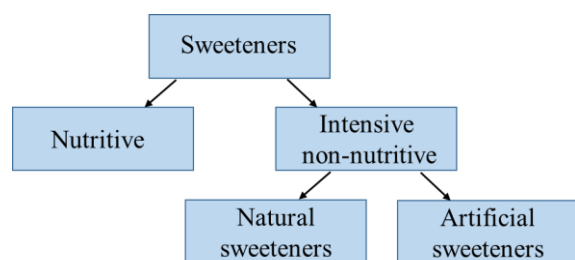
### Summary

It has been known for many years that the excessive consumption of sugar (sucrose) has harmful effects on human health. This fact led to a reduction in sugar consumption and the appearance of artificial sweeteners in the 1800s. The first low-cost and low-calorie sugar alternative was saccharin. Since this sweetener gained great popularity, other artificial sweeteners soon followed, including aspartame, acesulfame-K and cyclamates as the most common ones. As the result of a sharp rise in the obesity pandemic in all populations and ethnic groups, a demand for sweeteners with a minimum caloric value has increased dramatically in the last decade as consumers care more about their health. Due to the different regulation of permitted artificial sweeteners in United States (US) and Europe (EU), there are some controversies and suspicions about the relationship between certain sweeteners and a potential health risk. Despite doubts about the safety of artificial sweeteners, many studies have shown the absence of dangers associated with their use (if used in the acceptable daily intake, ADI). Therefore, artificial sweeteners today are considered as safe for consumption by many competent institutions and organisations. Nowadays, artificial sweeteners are fundamental in the food industry and present in many foodstuffs.

**Keywords:** Acesulfame - K, Aspartame, Cyclamate, Neotame, Saccharine, Sucralose

### Introduction

All sweeteners can be classified into nutritive and intensive non-nutritive sweeteners (known as artificial sweeteners) (Fig. 1). Intensive sweeteners have a high sweetening power (much higher than sucrose) so they are used in small amount in order to replace the sweetness of sucrose. They are called non-nutritive sweeteners due to their caloric contribution which is very low or even zero (AL-Ali and AL-Hilifi, 2021; Carocho et al., 2017; Godshall, 2007). More recently, some sweeteners of natural origin have been discovered and classified as intensive non-nutritive sweeteners. Most commonly, they are present as derivatives of various plants, such as steviol glycoside (approved both in USA and EU) and Luo Han Guo fruit extracts-from monk fruit (approved in the USA) (Mooradian et al., 2017; Pearlman et al., 2017; Purohit and Mishra, 2018). Accordingly, intensive sweeteners can be of natural or synthetic origin (Carocho et al., 2017; Schiano et al., 2021).



**Fig. 1.** Classification of sweeteners

(Carocho et al., 2017; Schiano et al., 2021)

Artificial sweeteners became popular during the First World War, due to the agricultural crisis that led to reduction in sugar production. Some types of artificial sweeteners were known even before that time, but were used in much smaller quantities. Later, in the late 1990s, a series of events occurred that increased demand for low-calorie products with reduced or no sugar content. Most artificial sweeteners are synthetic preparations, have nothing in common with the sugar molecule and were discovered by accident. The beginnings of research and production of artificial sweeteners were focused on copying the characteristics of sugar molecules that would stimulate the taste of sweetness, but these experiments were not successful. Therefore, most artificial sweeteners were obtained as a by-product of chemical experiments in some other research unrelated to artificial sweeteners. Artificial sweeteners as we know today have the ability to bind to the same receptors on taste buds as sucrose, thereby triggering and enabling a sense of sweetness. In addition, intense marketing campaigns within the food industry helped in the promotion and revolution of artificial sweeteners (Mooradian et al., 2017; O'Brien-Nabors, 2016; Purohit and Mishra, 2018).

World health organization (WHO) studies have shown that metabolic disorders are so common that they are considered as “epidemic in scale” in industrialized countries, with diseases associated with sugar consumption in the rise (Pradhan, 2007; Rani et al., 2016). Furthermore, today’s lifestyle and market offers have caused changes in diet increasing risk

factors for metabolic diseases such as diabetes, obesity, hypertension, metabolic syndrome among others (Costa et al., 2019; Scognamiglio et al., 2019). Due to that, prevalence of diseases associated with sugar consumption have increased and sweeteners became widespread in food products (Kim et al., 2017; Mooradian et al., 2017; Philippe et al., 2014). Since they became available on the market, artificial sweeteners have been considered one of the most significant achievements in the food industry. Despite that, due to different regulations and laws among countries, there are some doubts about the confidentiality of these molecules as foods in human consumption (Basilio et al., 2020). Today, sweeteners have been extensively researched, regarding their sweetening potential, as well as their effect on the health of consumers, economy and society (Mooradian et al., 2017).

Sweeteners have been the subject of controversy for years due to the conflicting opinions. On the one side, there are allegations about the toxicity of some sweeteners to the liver and bladder, about their carcinogenicity, possible influence on fetal malformations, along with other hazards, contrary to the many studies that refuted the relationship between the consumption of artificial sweeteners and the potential diseases (Carocho et al., 2017; Saraiva et al., 2020). Thus, all risk claims were investigated and artificial sweeteners have been defined as safe to use, but there is still some questionable confidence in

them as some artificial sweeteners are allowed in the Europe, while in the United States they are banned (Table 1) (Lobach et al., 2019; Farhat et al., 2019; Nichol et al., 2019; Serra-Majem et al., 2018).

In addition to the impact on health as a criterion for choosing the food used, consumers choose food according to sensory properties, so consumers are increasingly resorting to foods that consist of artificial sweeteners because they want (unchanged) sweet taste with lower or even no caloric value. As a result, consumers and food producers are showing increasing interest in food sweeteners that replace sucrose in food, improve the taste of food and at the same time reduce the caloric value of food and the risk of caries (Godshall, 2007; Sorensen et al., 2003; Whitehouse et al., 2008). The criteria for selecting a sweetener are the influence on the aroma of the product and the relative sweetness of the sweetener. In addition, sweeteners should be easy to produce, store and transport and should not be too expensive (O'Brien-Nabors, 2016).

Artificial sweeteners are defined as food additives that give a sweet taste, and known as low-calorie or non-caloric sweeteners (Lohner et al., 2017). Although having similar taste to the sucrose, artificial sweeteners have much higher sweetening power that can vary from a few dozen to a few hundred times sweeter than sucrose, and yet, having negligible caloric value (Bellisle and Drewnowski, 2007; Frank et al., 2008; Hunter et al., 2019; Mueller et al., 2015).

**Table 1.** Intensive sweeteners approved in the USA and EU (Mooradian et al., 2017; Schiano et al., 2021)

Name	Origin	Number of times sweeter than sucrose	ADI by the US FDA (mg/kg)	ADI by the EU EFSA (mg/kg)
Acesulfame-K	Artificial	200	15	9
Advantame	Artificial	20000	32.8	5
Aspartame	Artificial	200	50	40
Cyclamate	Artificial	30-50	Not approved for consumption	0-11
Neohesperidine DC	Artificial	300-2000	Not approved for consumption	5
Neotame	Artificial	700-1300	0.5	2
Saccharin	Artificial	200-700	15	5
Sucralose	Artificial	600	5	15
Steviol glycosides	Natural	200-400	4	4
Luo Han Guo fruit extracts	Natural	100-250	Not specified	Not approved for consumption

In addition to giving foods a pleasant sweet taste, sweeteners also improve the overall aroma of the product without added sugar and calories, which is important in specific diets (Martyn et al., 2016; Whitehouse et al., 2008). Artificial sweeteners are widely used in the food industry (in candies, beverages, chewing gums, jams, gelatines, bakery and many others foodstuffs). They can be used

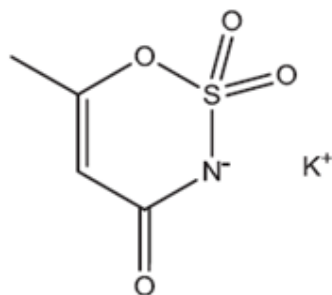
singularly or in combination with other sweeteners (Grembecka, 2015; Huvaere et al., 2012).

Acesulfame-K, aspartame, cyclamate, neotame, saccharin and sucralose are intensive sweeteners approved in the EU and recognized as the most widely used artificial sweeteners (Carocho et al., 2017; Mortensen, 2006; Whitehouse et al., 2008). This review will provide insight of those artificial sweeteners considering their characteristics,

invention, application, chemical composition and impact on consumer health.

### *Acesulfame-K*

Acesulfame-K is the potassium salt of acesulfame (Fig. 2). As a sweetener, acesulfame-K was found in 1967 when chemist Karl Claus accidentally noticed the sweet taste of substance from his finger during laboratory work (Claus and Jensen, 1970). This sweetener is a white crystalline powder that is very soluble in water (Chattopadhyay et al., 2014). Acesulfame-K is over 200 times sweeter than sucrose with clear taste without residual aromas. Due to that, and the fact that it has no caloric value, this sweetener is one of the most commonly used artificial sweeteners. It is used in pastries, candies, frozen desserts, beverages, cough drops and mints (Carocho et al., 2017; Whitehouse et al., 2008).



**Fig. 2.** Chemical structure of acesulfame – K (Carocho et al., 2017)

Acesulfame-K is thermally stable, which makes it suitable for use in baking and cooking (O'Brien-Nabors, 2002). If used alone in sweetening food and drink, it may have a bitter aftertaste wherefore it is often mixed with other sweeteners (usually aspartame or sucralose) (Horne et al., 2002). In the mixture, each sweetener masks the taste of the other and shows synergistic effects making the mixture sweeter than its components. Acesulfame-K cannot be metabolized in the human body and 95% of it excreted unchanged in the urine after its consumption. Therefore, it does not affect the energy and caloric value and potassium intake (despite the potassium content) (Chattopadhyay et al., 2014). In 1988, the use of acesulfame-K was approved in a variety of dry foods and alcoholic beverages.

Although many studies have shown its safety for human health, there have been studies that have indicated some kind of toxicity caused by this sweetener, but these studies have been later refuted

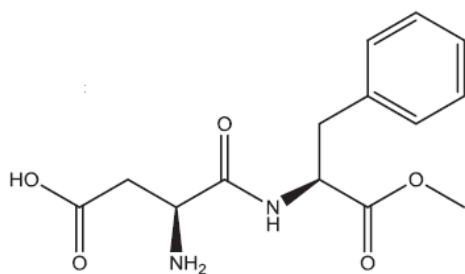
(Carocho et al., 2014; Shankar et al., 2013). One degradation product of acesulfame-K called acetoacetamide has potential toxicity if ingested in very large quantities, but human exposure to this compound has been shown to be negligible so FDA has concluded that acesulfame-K is harmless and no further investigation is required (Chattopadhyay et al., 2014; George et al., 2010). Monitoring the effect of acesulfame-K sweetener intake and potential risks was performed mostly by cytogenetic studies in mice. Mukherjee and Chakrabarti (1997) examined certain doses of acesulfame-K on the cytogenetic changes in mice. When applying this sweetener in the dose of ADI there were no genetic changes compared to control mice, while much higher doses of acesulfame-K showed clastogenic and genotoxic properties. In the conclusion, depending on the dose, acesulfame-K may interact with DNA and create genetic damage. According to the recommendation for further research of this problem, later studies confirmed the same conclusion – the negative effect of acesulfame-K is observed only in doses significantly above ADI (Whitehouse et al., 2008). Sylvetsky et al. (2011) reported presence of acesulfame-K in the breast milk of breastfeeding mothers after its consumption, but there are no studies showing the effect on breastfed infants (Sylvetsky et al., 2011). Furthermore, Uebanso et al. (2017) investigated effects of maximum ADI acesulfame-K on the gut microbiome in mice, compared to sucralose intake. Both sweeteners did not show an increased food intake, body weight or organ fat. Furthermore, consumption of acesulfame-K did not change relative amount of faecal microbiomes (Uebanso et al., 2017). Recent studies showed acesulfame-K as a safe substance that is not cytotoxic, carcinogenic or teratogenic (Fowler, 2016; O'Sullivan et al., 2017; Tian et al., 2020).

### *Aspartame*

Aspartame was found in 1965 while studying new ways to treat stomach ulcers using a tetrapeptide normally produced in the stomach. During the synthesis of this tetrapeptide, the intermediate aspartyl-phenylalanine methyl ester is formed. This compound accidentally ended up on pharmacist's taste buds who noticed the sweet taste of the compound (Mazur, 1984). The first approval of aspartame by the FDA was in 1981 when approved as a table-top sweetener, whereupon in 1996 it was approved for general-purpose in all foods and beverages (Whitehouse et al., 2008). Since then, aspartame has been recognized worldwide as it is used by large number of consumers in more than

6000 products (Butchko and Stargel, 2001). Aspartame has a pure sweet taste and its sweetness is 200 times greater than sucrose. It can be found in a wide range of foodstuffs: in sweets, drinks, chewing gums, frozen desserts and yoghurt, gelatines, dessert mixes, puddings and fillings, table-top sweeteners and certain medicines (vitamins and cough drops) (Chattopadhyay et al., 2014; Whitehouse et al., 2008).

Aspartame contains two amino acids, phenylalanine and aspartate (Fig. 3). It can form methanol by hydrolysis in strongly acidic or alkaline conditions. Furthermore, it is easily soluble in water at room temperature with increasing solubility even with lower or higher pH as well as with elevated temperature. Maximum stability of aspartame in aqueous solution is at pH 4.3 (Mazur, 1984). Aspartame is unstable on higher temperatures so it does not tolerate heating and therefore cannot be used in cooking or baking. Also, it is unstable during storage because it decomposes in liquids (Chattopadhyay et al., 2014).



**Fig. 3.** Chemical structure of aspartame (Carocho et al., 2017)

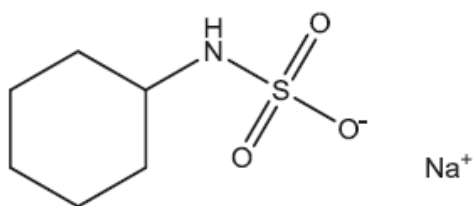
The metabolism of aspartame can result in formation of formaldehyde, formic acid and diketopiperazine, which makes its safety questionable (George et al., 2010; Kroger et al., 2006). Due to that, aspartame is by far the most controversial artificial sweetener. Although some research demonstrates potential carcinogenic properties of this sweetener, such studies were performed on rats so their association with the human health is not considered relevant. One study (Ferland et al., 2007) examined the influence of aspartame consumption on glucose and insulin levels in male subjects with type 2 diabetes during acute exercise. Results showed that aspartame intake through breakfast simulates the rise in glucose and insulin similar to sucrose intake. According to these results, it is not recommended for diabetics to continue intake of this sweetener as it affects the glucose levels similar to sucrose. Gallus et al. (2007) have been

researching the association of artificial sweeteners with cancer risks. Reviewing some case studies, they pointed out the existence of a connection between brain cancer and the use of aspartame. However, the hypothesis of this study has not been confirmed in animal or human studies (Ferland et al., 2007; Gallus et al., 2007; Whitehouse et al., 2008). Furthermore, some published studies showed the correlation between aspartame consumption and migraines. In an experiment with subjects aged 40, 32 and 26 years, migraine occurred as a consequence of using chewing gum with aspartame as a sweetener. This conclusion was reached and confirmed as migraine was alleviated in all subjects when they stopped taking aspartame through chewing gum (Blumenthal, 1997). Headache and/or migraine have been shown to be one of the most common side effects related to the use of aspartame, but it is important to note that this side effect rarely occurs after a single dose of this sweetener (Jacob and Stechschulte, 2008; Lindseth et al., 2014; Lipton et al., 1989; Sun-Edelstein and Mauskop, 2009). The aspartame molecule consists of methanol, aspartic acid and phenylalanine. Since phenylalanine is a controversial substance in people with phenylketonuria, consumption of aspartame is prohibited for such consumers. However, it should be considered that this amino acid is not metabolized equally in rodents and humans, so only the results obtained in studies with primates can be taken into account. Several studies with human subjects showed that despite an increase in phenylalanine due to consumption of a certain dose of aspartame (2-100 mg/kg), there was no visible effect on cognitive-behavioural abilities (Carocho et al., 2017; Lohner et al., 2017; Whitehouse et al., 2008). Many government and advisory organizations proclaimed aspartame safe for human consumption in more than 90 countries (Magnuson et al., 2007). The European Food Safety Authority (EFSA), as the reference institution for food safety, conducted rigorous analyses of various studies on animal and human models on the health effects of aspartame, after which it reached a final conclusion on the use of aspartame and its daily intake. EFSA concluded that aspartame was safe to use if administered up to the prescribed value of ADI, which is 40 mg/kg body weight per day. Experts claim that this intake does not increase the risk of cancer, damage to the nervous system and brain function, nor does it affect the behaviour of adults and children, as indicated by some previous studies (Fitch and Keim, 2012; Kirkland and Gatehouse, 2015; Martyn et al., 2018).

#### *Cyclamate*

Although cyclamate was found back in 1937, it was used as a sweetener (in the US) from 1950 to 1969 when US FDA revoked the status of GRAS (Generally Recognized As Safe) for this sweetener, and in 1970 completely banned it. This ban was based on a study linking the metabolism of cyclamate to a toxic compound named cyclohexylamine. Later studies showed that this metabolism is related only to a small population, but this fact was not enough for the FDA to lift the ban. In 1982, one study showed that a mixture of saccharin and cyclamate had caused cancer in laboratory rats, but after reviewing scientific evidence FDA's Cancer Assessment Committee infer that cyclamate has no carcinogenic properties. This finding was confirmed in 1985 by the National Academy of Sciences. Consequently, this sweetener is the best exemplar of legislative differences between the EU and the US since the use of this sweetener in food is permitted in EU, but banned in US (Chattopadhyay et al. 2014; Fitch and Keim, 2012; Renwick et al., 2004).

Cyclamate is a salt of cyclohexyl sulphuric acid (Fig. 4) that can be used in food in two forms, as sodium cyclamate and calcium cyclamate. Both forms of cyclamate show good stability at low and high temperatures. Sodium cyclamate is used as an artificial sweetener and the analogue calcium salt is used mostly in low sodium diets. It is soluble in water, which can be enhanced by preparing sodium or calcium salts (Bopp et al., 1986; Chattopadhyay et al., 2014; Fitch and Keim, 2012).



**Fig. 4.** Chemical structure of Na-cyclamate (Carocho et al., 2017)

The largest producers of this sweetener are China, Indonesia, Taiwan and Spain. Production of this sweetener is the cheapest along with saccharin (O'Brien-Nabors, 2001). In the EU, the recommended daily intake is 11 mg/kg of body weight. Cyclamates are used in baked and processed foods, in many desserts, soft drinks, gelatines, canned fruit, and as a table-top sweetener (Carocho et al., 2014). Cyclamates have no energy value. Although sweetening capacity of cyclamates is 35-50 times greater than sucrose, its disadvantage is mild sour

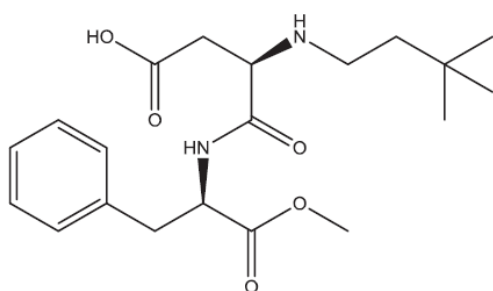
taste. Therefore, it is usually combined with other artificial sweeteners, mostly with saccharin, pointing good sweet synergy. In addition, in such mixtures cyclamate has the property of long-lasting sweetness since mixing with saccharin rejects its sour taste. Thus, a mixture containing 1% saccharin and 99% cyclamate proved to be very suitable for use in human nutrition (Martins et al., 2010; Mitchell, 2006; Renwick et al., 2004; Roberts, 2016).

According to some studies, the compounds that are formed by the breakdown of cyclamate in the intestines under the influence of bacterial flora are cyclohexamines that are carcinogenic, and in some cases they have caused bladder and kidney cancer in the examined rats. Subsequently, further studies did not confirm the association between cyclamate and tumor formation in humans leading to the conclusion that the mechanism of tumor formation due to cyclamate is specific exclusively to animals (Fitch and Keim, 2012). Furthermore, there was a suspicion that cyclamates cause infertility, so a study was conducted that monitored the effect of cyclamates on testicular atrophy in humans, which did not prove any association between infertility and elevated concentrations of cyclamates and cyclohexamine in humans (Serra-Majem et al., 2018). The association of cyclamate with hypertension and tachycardia was tested in study with volunteers. This study showed that the concentration of cyclamate and cyclohexamine did not affect the occurrence of these problems. Consequently, global opinion on cyclamates is that they are not dangerous to human health if consumed in the recommended amounts. This view is not taken only by the competent US institutions, where cyclamates are still banned, but their use has been approved in 55 countries, which speaks volumes about the safety of use of this sweetener (Carocho et al., 2017; Fitch and Keim, 2012).

#### Neotame

Neotame is the latest artificial sweetener discovered in the 1980s. It is a derivative of aspartame, obtained by reductive alkylation of aspartame. Thus, it has a very similar chemical structure to aspartame (Fig. 5), aspartame and neotame are isomers, respectively. The FDA approved this sweetener in 2002 and it is currently the strongest sweetener available on the market with a sweetening power of 7000 to 13000 times greater than sucrose. In addition, the advantage of neotame is that it has no calories despite its high sweetness. Neotame is approved as a general-purpose sweetener, except in meat and poultry. It is used in pastries, soft drinks, frozen desserts, processed fruits,

chewing gum, glazes, jellies, jams, gelatines, puddings, additives and syrups (Mayhew et al., 2003; Whitehouse et al., 2008). Neotame has a pure taste, without sour or metallic taste or after taste. Despite that, neotame is mostly mixed with some other sweeteners (except with acesulfame-K and saccharin). Since neotame does not contain phenylalanine in its composition, it is safe for patients with phenylketonuria and for diabetics (Carocho et al., 2017). The range of uses of neotame is wide; it is added to drinks, lemon tea, sauces, chewing gum, yogurts. Furthermore, it is used as a table-top sweetener and to enhance natural flavours (mostly sour fruit flavours) (Zhu et al., 2016).



**Fig. 5.** Chemical structure of neotame (Carocho et al., 2017)

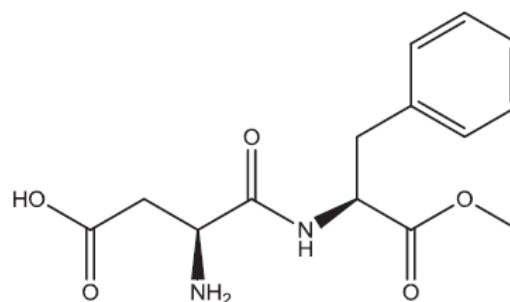
This sweetener is white, odourless crystalline powder that is not hygroscopic so it is stable in dry storage conditions. Regarding metabolism, half of the ingested neotame is excreted in the urine as an esterified neotame, while the other half is not absorbed. Neotame meets basic criteria for the commercial viability of a non-nutritive sweetener (taste, stability, solubility, safety and cost) (O'Brien-Nabors, 2016; Whitehouse et al., 2008).

In terms of safety, neotame, like the rest of the sweetener, has undergone a series of studies that have shown that even doses higher than its ADI are not associated with toxicity or any danger to the consumer. No adverse effects of neotame use have been reported in studies performed in mice and other experimental animals (O'Brien-Nabors, 2001; Nofre and Tinti, 2000; Zhu et al., 2016). Some studies related to neotame reveal changes in body weight in rats. It has been observed that these effects are not caused by neotame toxicity, but because of the tastelessness of the food containing this sweetener consumed by rats. Therefore, rats reduced their daily food intake, resulting in long-term weight loss and less weight gain (Carocho et al., 2017; Whitehouse et al., 2008). Many studies showed no adverse effects of

neotame in mice and other experimental animals after physical and pathology examinations (Mitchell, 2006; O'Brien-Nabors, 2001; Nofre and Tinti, 2000; Zhu et al., 2016).

### Saccharin

Saccharin was discovered back in 1878, which makes it the first artificial sweetener. It is found at Johns Hopkins University in Baltimore and like most artificial sweeteners, saccharin was discovered accidentally while working in the laboratory on some other issue (Chattopadhyay et al., 2014). Nowadays, this sweetener is produced by a process called *Maumee* and its production reaches industrial proportions. This process is named after the company that evolved this technique (Maumee Chemical Company) (Carocho et al., 2014). As the molecular saccharin is an aromatic organic compound that can be used in the two forms, as a sodium or calcium salt (Fig. 6) (Chattopadhyay et al., 2014). Saccharin is stable at low pH and at high temperatures, making it an ideal sweetener for use in the food production. In addition, it has the advantage of low cost (Charocho et al., 2017; Gupta, 2018; O'Sullivan et al., 2017). It has a sweet taste, but also slightly sour and bitter, so it is used usually in combination with cyclamate and aspartame. It may have 300 times more sweetening power than sucrose, but it has the lowest ADI of all artificial sweeteners (5 mg/kg of body weight) (Charocho et al., 2017; Gupta et al., 2018).



**Fig. 6.** Molecular structure of saccharin (Carocho et al., 2017)

Saccharin does not metabolize in the body but excretes in the urine after the consumption. Despite that, it is possible for saccharin to pass over the placenta of a pregnant woman and through breast milk, therefore it is not recommended for pregnant or breastfeeding women. Wide use of saccharin is in fruit juices, processed fruits, gelatines, jams, wraps, sauces, desserts, chewing gum, and table-top

sweeteners (Carocho et al., 2017; Chattopadhyay et al., 2014; O'Brien-Nabors, 2001). Saccharin can also be found in cosmetic products (lip-gloss and mouthwash), in vitamins and medications (Whitehouse et al., 2008).

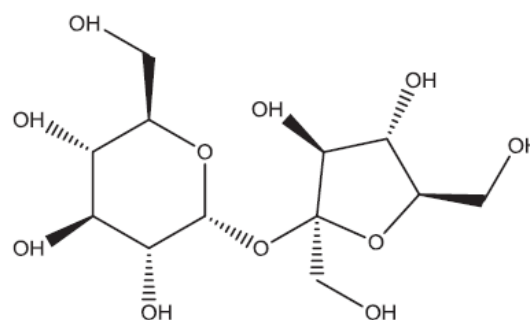
The safety of saccharin consumption has always been questioned, as Canada banned its use in 1977 after some studies on animal showed toxic effect of extremely high doses of saccharin in rats (Chowaniec and Hicks, 1979). Subsequent research has shown that normal amounts of saccharin do not cause cancer in mice, monkeys, and humans (Zurlo and Squire, 1998). All studies that suggested the suspicion of saccharin consumption were based on the formation of tumors in rats, but due to the different anatomy between rodents and humans, the danger to humans is excluded (Carocho et al., 2017; Schiano et al., 2021). One research pointed that saccharin can have effect on the liver increasing the concentrations of liver enzymes. This study was conducted on elderly women with symptoms of chronic fatigue who were taking three medications of which two contained saccharin. Results showed increased liver enzymes during consumption of those medications and its reduction after taking them off (Whitehouse et al., 2008). Today, due to the numerous studies, saccharin is known to be safe for consumption, encouraging increasing use worldwide (Shankar et al., 2013). Also, consumption of saccharin showed very rare presence of side effects (Gupta, 2018). Furthermore, the FDA states that saccharin is not directly linked to cancer in humans and many studies confirmed that saccharin is safe for human consumption (Amin and Al Muzafar, 2015; Andrejić et al., 2013; Azeez et al., 2019; Basilio et al., 2020; Whitehouse et al., 2008). Moreover, available data showed common practice at healthcare professionals of usage saccharin in patients with obesity or diabetes in order to reduce weight, as well as in practice of reducing dental cavities (Al Humaid, 2018; Lohner et al., 2020). Today, saccharin is used and approved worldwide (in more than 100 countries) (Schiano et al., 2021).

### Sucralose

Sucralose is artificial sweetener that was also discovered accidentally. It was in 1976 when the British sugar company Tate & Lyle investigated many ways to use sucrose as a chemical intermediate. As one of the results of this experiment, halogenated sugars were synthesized and tested. During those tests, the graduate student misunderstood the requirement to "test" chlorinated sugar as a requirement for "tasting". This misunderstanding brought the discovery that many chlorinated sugars

are not only sweet, but much sweeter than sucrose (Whitehouse et al., 2008).

Sucralose is obtained by industrial substitution of three hydroxyl groups in sucrose (Fig. 7). This transformation makes this molecule 600 times sweeter than sucrose. Profile of quality and intensity of sweetness of sucralose is very similar to the profile of sucrose. This sweetener has a pleasant sweet taste and modest synergy with other sweeteners (Olivier-Van Stichelen et al., 2019). Sucralose has good water solubility as well as stability over a wide range of temperatures and pH. When stored at high temperature, sucralose releases HCl and creates some sort of colour change (Arora et al., 2009; Chattopadhyay et al., 2014; Roberts, 2016).



**Fig. 7.** Chemical structure of sucralose (Carocho et al., 2017)

Although it is made from sucrose, human body does not recognize sucralose as sucrose (sugar). Therefore, sucralose does not metabolize in human body and does not provide energy or calorie. The majority of ingested sucralose does not absorb and is secreted directly in the faeces, while 11 - 27 % is absorbed. Absorbed part is mainly removed by the kidneys from the bloodstream and excreted in the urine. Sucralose is present in many foodstuff; in ice cream, yogurts, canned fruit, caramels, biscuits, soft drinks, dairy products, bakery products, gelatine, jams, chewing gums and many others (Mitchell, 2006; O'Brien-Nabors, 2001).

Sucralose is an organochloride. Although some organochlorides are known to be significantly toxic (Patel et al., 2006), sucralose has been recognized as non-toxic (Olivier-Van Stichelen et al., 2019). Anyway, several studies pointed the potential mutagenicity of high concentrations of sucralose (Berry et al., 2016; de Oliveira et al., 2015; Eisenreich et al., 2020; Grotz, 2008; Sasaki et al., 2002). Furthermore, many preclinical and clinical trials have shown that sucralose has an effect on

levels of glucose and insulin (Pepino et al., 2013). Some studies pointed that sucralose has an effect on the microbial composition of the digestive system by reducing beneficial bacteria (Abou-Donia et al., 2008; Turnbaugh and Gordon, 2009). Recent review by Berry et al. (2016) showed that there is no possible association of sucralose consumption with cancer, even at higher doses. Furthermore, some earlier studies also showed that there is no risk of using this sweetener, and many human studies indicate the general safety of sucralose (Grotz and Munro, 2009). Systematic literature review provided by Fitch and Keim (2012) showed that sucralose does not have an effect on appetite in adults or weight gain in children and adolescents. In addition, this study pointed that, based on limited studies in humans, there is no association between untoward effects and sucralose consumption in the general population (Fitch and Keim, 2012). More than 110 human and animal studies were reviewed by FDA for determining the safety of sucralose. Consequently, FDA characterizes sucralose as safe for human consumption. Only in the case of excessive consumption, sucralose has possible links with migraines, intestinal problems, and colon inhibition (Carocho et al., 2017; Chattopadhyay et al., 2014; Patel et al., 2006).

## Conclusion

Artificial sweeteners have long been in vogue and are now an integral part of many processed foods. They are useful substances because they not only provide the sweetness, but increase and enhance the taste of food without added sugar and calories, which is important in specific diets. They are used to control obesity and diabetes, as they provide sweetness in foods without added caloric values. Moreover, an additional advantage of artificial sweeteners over sucrose is that they do not cause caries, as they do not constitute a substrate for the development of bacteria. Although they can reduce calorie intake, their excessive consumption (greater than ADI) can cause certain side effects, so their use should be dosed with caution. Since most artificial sweeteners are not metabolized in the human body, they are considered as safe for consumption. However, there are still some doubts about these compounds due to conflicting data on the consumption of some artificial sweeteners. Nevertheless, both sides certainly agree on one thing - use of artificial sweeteners within recommended daily values is safe for the health of the consumer, therefore should pay the most attention to the amount of sweetener used.

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