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Artificial sweeteners

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Abstract: Low-calorie sweeteners are authorised food additives in the European Union (EU). The safety of these sweeteners has been evaluated in accordance with internationally agreed principles for the safety evaluation of food additives. So food industry uses various artificial sweeteners which are low in calorie content instead of high calorie sugar. U.S. Food and Drug Administration has approved aspartame, acesulfamek, neotame, cyclamate and alitame for use as per acceptable daily intake (ADI) value. The ADI is the amount of the food additive, expressed on a milligram per kilogram of body weight (bw) basis, that can be ingested daily over a lifetime without any appreciable health risk. The main reasons to use substitutes for sucrose are: to help weight loss (the majority of the sweeteners are virtually calorie free); to diminish the risk of dental disorders, namely cavities; to provide palatable food for some patients such as diabetics; to produce less expensive food items (artificial sweeteners are often cheaper than sucrose and are employed in minute quantities due to their potency in providing a sweet taste); and to avoid post-prandial hyperglycaemia in dietary regimens aimed at controlling insulin response (though this effect is debatable).
Key words: Artificial sweeteners, Low calorie sweetener, Acceptable daily intake (ADI), Metabolism.

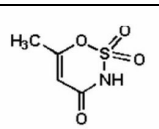
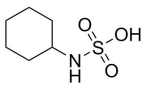
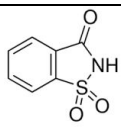
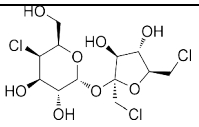
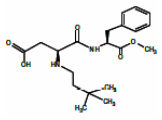
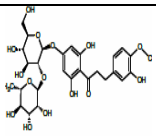
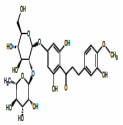
1. Introduction

Sweeteners may be used separately or in combination with other sweeteners, as socalled blends. Nowadays, the common trend in food industry is to use sweetener blends, because some of the sweeteners impart side tastes and aftertastes that can limit their applications in foods and beverages[1]. It was found that mixing such a problematic sweetener with another frequently yields a blend not only lacking unwanted side or aftertastes but also sweeter than the algebraic sum of the components. A very well-known example of such a mixture is saccharin-cyclamate (1:10) blend. The bitter aftertaste of saccharin is masked by cyclamate and the unpleasant aftertaste of cyclamate, sensed by some people, is masked by saccharin. Simultaneously (due to synergistic effect), the sweetening power of the mixture increases. Properly formulated sweetener blends can precisely reproduce the texture and the sweetness profile of traditional sugar-containing products, create new products characterized by an original sweetness profile and improve taste stability[2]. Artificial high-intensity sweeteners, intensely promoted by the food industry are among the most controversial food additives due to suspicions of adverse health effects[3]. These allegations include causing dermatological problems, headaches, mood variations, behavior changes, respiratory difficulties, seizures, allergies and cancer.

Artificial sweeteners are used worldwide as sugar substitutes in remarkable amounts in food, beverages, and also in drugs and sanitary products, such as mouthwashes. They provide no or negligible energy and thus are ingredients of dietary products[4]. The structures of the artificial sweeteners treated in this review are depicted

in Table 1 together with additional data on physicochemical properties, intensity figures for their sweetness (sugar equivalents), and their acceptable daily intake values that a person can safely consume on average every day without risk to health. Owing to their use as food additives, artificial sweeteners are extensively tested for potential adverse health effects on humans[4,5,6]. Although the measured concentrations of some artificial sweeteners range up to microgram per liter levels in surface water, groundwater, and drinking water, there is a huge safety margin regarding potential adverse health effects. Acceptable daily intake values of artificial sweeteners are in the range from 5 to 50 mg/kg of body weight per day and are thus three to four orders of magnitude above the maximum possible daily human intake by drinking water[4,7]. However, their ecotoxicological profiles have only been scarcely investigated. Therefore, the purpose of the current review is to summarize the new studies published between 2009 and 2016, and to provide an updated review to guide future research and public health recommendations.

Table 1. Structures and properties of the seven artificial sweeteners[8].

	ACE	CYC	SAC	SUC	Aspartame	Neotame	NHDC
CAS no.	33665-90-6	100-88-9	81-07-2	56038-13-2	22839-47-0	165450-17-9	20702-77-6
Structure							
Molecular formula	$C_4H_5NO_4S$	$C_6H_{13}NO_3S$	$C_7H_5NO_3S$	$C_{12}H_{19}Cl_3O_8$	$C14H_{18}N_2O_5$	$C_20H_{30}N_2O_5$	$C_{28}H_{36}O_{15}$
Molecular weight in (g/mol)	163.15	179.24	183.19	397.63	294.31	378.47	612.58
Sugar equivalence	200[9]	30[10]	300[11]	600[12]	160-220 [11]	7,000-13,000[12]	up to 1,800 [14]
Water solubility in (g/L)	270 (20 °C)[9]	1.000[10], 133[10]	4[12]	283 (20 °C) [15]	~10 (25 °C)[16]	12.6[17]	0.4-0.5[14]
pK_a[a]	2.0[18]	1.9[19]	2.2[19]	11.8c[20]	3.19 and 7.87[21]	3.01 and 8.02[22]	9.7c[20]
log K_{OW}[b]	-1.33[12]	-1.61[12]	0.91[12]	-1.00[12] -0.51±0.05[20]	0.07[12]	2.39 (nonionic species)[20]	0.75 (nonionic species)[20]
Human Excretion	100 % Unchanged[9], Mainly unchanged[4]	mainly unchanged[4], inter-individual variations in conversion to cyclohexylamine[23]	mainly unchanged[4]	>92 % Unchanged[24]	Complete metabolic breakdown into aspartic acid, phenylalanine, and methanol[25]	<2 % [13] (deesterification major metabolic pathway)	complete metabolism by hydrolysis and conjugation is anticipated[26]
ADI mg/kg	9 (potassium salt)[27]	7[23]	5 (sodium salt), 3.8	15[29]	40[25]	2[30]	5[26]

body weight			(free acid)[28]				

ACE acesulfame, ADI acceptable daily intake, CAS Chemical Abstracts Service, CYC cyclamate, NHDC neohesperidine dihydrochalcone, SAC saccharin, SUC sucralose

[a]pK_a is the negative logarithm of the dissociation constant
[b]log K_{OW} is the logarithm of the octanol–water partition coefficient
[c]Calculated pH where 50% of the neutral molecules are dissociated into several corresponding bases

2.1. Aspartame

Aspartame is a dipeptide that is used as an artificial sweetener. It is completely hydrolysed in the gastrointestinal tract to methanol, aspartic acid, and phenylalanine[31]. Aspartame appears to be a safe sweetener, and despite numerous studies of its safety during the past three decades, the incidence of serious adverse effects has been difficult to determine in controlled studies. Since one of the metabolic products of aspartame is phenylalanine, excessive use of aspartame should be avoided by patients with phenylketonuria[32]. Toxicity of another possible metabolic product, methanol, is unlikely, even when aspartame is used in extraordinary amounts[33]. Aspartame has reportedly caused angioedema and urticaria[34].

It is sold under the brand names Equal®, NutraSweet®, and Natra Taste®. Because it is made from amino acids, it provides 4 kcal/g. Aspartame is 200 times sweeter than sucrose and therefore very small amounts are required for sweetening foods, thus making its caloric contribution insignificant. According to the FDA, the acceptable daily intake of aspartame for humans is 50 mg/kg body weight, for both adults and children[35]. Aspartame is used as a sweetener in many products including chewing gum, diet soda, dry drink mixtures, yogurt and pudding, and instant tea and coffee. The flavor profile of aspartame is found to be highly acceptable. In a study on the effects of artificial sweeteners on food intake and satiety, aspartame was found by participants to have a more pleasant taste compared with stevia or sucrose[36]. Furthermore, aspartame does not elicit the same response as sugar does in the brain or the pancreas. A magnetic resonance imaging study showed a decline in activity of the hypothalamus part of the brain after ingestion of sucrose, whereas aspartame does not show similar response. It is suggested that for a hypothalamic reaction to occur there should be the combined stimuli of sweet taste and energy content, as found in sweetened caloric beverages. In the pancreas, aspartame does not stimulate an insulin response as sugar does[37].

2.2. Cyclamates

Sodium cyclamate is a potent sweetening agent. It has been subjected to numerous safety and carcinogenicity studies. Animal data led to warning against excessive and indiscriminate use a long time ago, causing the World Health Organization in 1967 to adopt a safety limit of 50 mg/kg. However, in 1982 a joint FAO/WHO expert committee on food additives revised this recommendation to allow for a maximum daily intake of up to 11 mg/kg of sodium or calcium cyclamate (as cyclamic acid)[38]. Nevertheless, since in certain climates and populations the amount of cyclamates in soft drinks and other beverages can exceed these limits, more epidemiological data are needed to evaluate, for example, a possible association with cancer of the uropoietic system[39] and with histological and radiological abnormalities of the small intestine and malabsorption[40]. Cyclamate is commercially available in the sodium and calcium salt forms. Both of these are colourless and odourless solids. Cyclamate in its acid form is a strong acid with pK_a of 1.71[41]. Interestingly, the acid form of cyclamate has been demonstrated by X-ray crystallography to exist in the zwitterionic state[42].

Cyclamates exhibit excellent solubility characteristics for use in essentially all imaginable applications. Although the acid form is sufficiently water-soluble (133 g/L), its high acidity results in preference for the very soluble sodium (200 g/L) or calcium (250g/L) salts[43]. To illustrate the more than adequate solubility of sodium cyclamate, consider an application in which cyclamate is used in a binary blend with a sweetener such as saccharin. In such a situation, it is generally desired that cyclamate should provide half of the total sweetness desired that would typically be, allowing for sweetness synergy, sweetness equivalent to approximately 4% sucrose. Hydrolytic degradation of cyclamate salts yields cyclohexylamine and inorganic sulfate. As a consequence of the adverse biological activity of cyclohexylamine, FDA scientists conducted a comprehensive evaluation of cyclohexylamine levels in a range of food products[44].

2.3. Acesulfame

The studies on the basis of which acesulfame gained approval showed no evidence in animals of mutagenicity, teratogenicity, or adverse reproductive effects; a 2-year toxicology study in beagles showed no untoward adverse effects. The incidence of lymphocytic leukemia was slightly increased in high-dosed female mice, but not beyond the spontaneous variation with this strain. No other evidence of potential carcinogenicity was obtained, and it has been concluded that at the estimated level of exposure, acesulfame and its metabolites are not a health hazard[45].

2.4. Neotame

In the year 2000, a number of new studies on the parent molecule and its hydrolysis products had become available and the no observed adverse effect level (NOAEL) was determined at 1500 mg/kg bw/day, translating into an ADI of 15 mg/kg bw using a safety factor of 100[46]. In 2007, the European Food Safety Authoriy (EFSA) allocated an ADI of 2 mg/kg bw to neotame, based on studies in dogs. No effects were seen in rats, but in dogs two different studies recorded an increase in serum alkaline phosphatase, indicative of liver toxicity at 600 mg/kg bw/day. The toxicological relevance of this effect has been debated, but EFSA decided to take these data into consideration and used them to set the NOAEL at 200 mg/kg bw/day[47].

2.5. Saccharin

Saccharin has been considered to be a possible human carcinogen on the basis of animal experiments. This suspicion has now been discredited. There is no evidence that people with diabetes, who consume larger quantities of saccharin than non-diabetics, are at greater risk of developing bladder cancer[48] or other malignancies. However, in the USA, saccharin-containing medicines are required to carry the following warning: "Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals"[49].

Saccharin is commercially available in acid form as well as in sodium and calcium salt forms. All of these are white odourless solids. Saccharin in acid form is a strong acid with pK_a of 2.32[50]. To be used in foods and beverages, a non-caloric sweetener must be sufficiently soluble and many non-caloric sweeteners do not meet this requirement. Commonly, sweetness intensity levels at least equivalent to 10% sucrose are required and in some systems (e.g. frozen desserts), sweetener levels matching the sweetness of 15–20% sucrose are needed. In addition, for many food systems, rapid dissolution is critical to comply with manufacturing requirements. For example, in carbonated soft drinks, concentrates of the sweetener-flavour system complex are prepared and it is important that all components rapidly dissolve. Thus, high solubilities and rapid dissolution rates are very desirable properties for non-nutritive sweeteners. In addition, a commercially viable non-caloric sweetener must be sufficiently stable to hydrolysis as well as to thermal and photochemical breakdown to be used in beverages, baked goods and confectionery.

To be commercially viable, a non-caloric sweetener must be stable to degradation from hydrolytic, pyrolytic or photochemical processes that may be encountered in food or beverage applications. Stability is critical for three reasons. First, the rate of degradation must not be such that product shelf life is affected. Second, degradation must not cause any 'off' taste or odour. And third, since non-caloric sweeteners are food additives, any degradation products formed must also be safe. In the United States, for any food or beverage application, if exposure to the degradation product may reach or exceed 12.5 μg/kg, then safety assessment studies equivalent to those required for the sweetener itself must be conducted before regulatory approval is granted[51]. Saccharin is very stable to all the conditions to which it may be exposed in food and beverage applications. Accelerated stability studies on saccharin as a function of pH and temperature (100°C, 125°C and 150°C) were first reported in 1952 by DeGarmo and coworkers (Monsanto Chemical Company)[52]. Later, accelerated studies at a single temperature (120°C) were carried out at the Sherwin Williams Company[53]. Interestingly, the degradation pathway was found to be pH dependent. At acidic pH, the exclusive hydrolysis product is 2-sulfobenzoic acid, while under alkaline conditions, the sole degradation product is 2-sulfonamidobenzoic acid. Both of these compounds are sometimes found as trace contaminants in commercial samples of saccharin. As a consequence of saccharin's high stability, neither loss of sweetness during food or beverage product lifetime nor degradation product safety is a significant concern.

2.6. Sucralose

This nonnutritive sweetener is made from sucrose by a process that substitutes 3 chloride atoms for 3 hydroxyl groups on the sucrose molecule[54]. Sucralose is 450–650 times sweeter than sucrose, has a pleasant sweet taste and its quality and time intensity profile is very close to that of sucrose[55]. It has a moderate synergy with other nutritive and non-nutritive sweeteners[56]. It is very much soluble in water and is stable over a wide range of pH and temperature. It does liberate HCl when stored at high temperature and produce some kind of discoloration[56]. The synthesis of sucralose involves a series of selective protection and deprotection steps so that the 4-hydroxyl group can be converted to a chloro atom with inversion of configuration. Treatment of the free hydroxyl groups with sulfuryl chloride produce trichlorodisaccharide which is then deprotected to give the sucralose[57]. The use of enzymes or microbial cultures to augment synthetic organic chemistry and carry our selected functionalization of complex molecule has been widely documented in the growing field of biocatalysis[58]. Metabolism and health aspect although sucralose is made from sugar, the human body does not recognize it as a sugar and does not metabolize it therefore it provides no calories. The bulk of sucralose ingested does not leave the gastrointestinal tract and is directly excreted in the feces while 11–27% of it is absorbed[59]. The amount that is absorbed from the gastro intestinal tract is largely removed from the blood stream by the kidneys and eliminated in the urine. As it is an organo chloride and some of which are known to have significant toxicity[60] but sucralose is not known to be toxic. In addition sucralose does not breakdown or dechlorinate. In determining the safety of sucralose, the FDA reviewed data from more than 110 studies in human and animals. Many of the studies were designed to identify possible toxic effects including carcinogenic reproductive and neurological effects but no such effects were found. Food and Drug Administration (FDA) approval is based on the findings that sucralose is safe for human consumption. U.S. Food and Drug Administration (USFDA) approved sucralose as a generalpurpose sweetener. The acceptable daily intake (ADI) for sucralose in US is 5mg/kg body weight/day. The estimated daily intake for percentile consumers as calculated by USFDA is 1.6mg/kg body weight/day[61].

5. Conclusion

Food additive approval is based on a robust hazard and risk characterization, leading to the establishment of an ADI and often a maximum permitted level (MPL) in foods. They must be subjected to a wide range of tests, devised to assess potential risks to the consumer, before they are allowed in food. Tests assess how the additive reacts in the body and also look for any toxic effects at and above the levels the additive is to be used in food. This includes testing to see if there is any chance of genetic damage or cancers being caused by the long-term use of the additive. A formal process for safety evaluation exists at national and international levels for analysing the test data on food additives, setting the ADIs and publishing the results. In Europe, food additives permitted before 20 January 2009 must go through a new risk assessment by EFSA; furthermore, at any time, the authority can revise its decision on the basis of new data reporting toxicological effects. With reference to epidemiologic data, evidence on low-calorie sweeteners – and specifically aspartame – does not support the existence of a consistent association with hematopoietic neoplasms, brain cancer, digestive sites, breast, prostate and several other neoplasms; similarly, low-calorie sweeteners are not related to vascular events and preterm deliveries.

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