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Artificial sweeteners

A brief review of their safety issues

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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. In the EU, the European Commission's Scientific Committee for Food (SCF) was the scientific guarantor for the safety of food additives until March 2003. Since then this has been taken over by the European Food Safety Authority (EFSA), notably its Scientific Panel on Food Additives and Nutrient Sources Added to Food (ANS Panel). Based on the large number of toxicological studies that are requested for the safety evaluation of food additives, a no observed adverse effect level (NOAEL) is identified for the most sensitive effect in the most sensitive animal species. A safety factor of 100 is normally applied to the NOAEL in order to establish an acceptable daily intake (ADI) for humans. 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 following low-calorie sweeteners have been allocated an ADI by either the SCF or EFSA: acesulfame K, aspartame, cyclamates, neotame, saccharin, steviol glycosides and sucralose.

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Introduction

Sugar substitutes aim to mimic the sweet taste of sugar (sucrose) with minimal caloric contribution. Among such sweeteners, the majority are synthetic in nature and their use must be approved by the appropriate regulatory bodies. There is ongoing controversy over whether the use of artificial sweeteners poses health risks and unsubstantiated claims of potential toxicity often appear in the lay press.

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).

As mentioned, there is widespread perception of safety and toxicological issues regarding the use of sugar substitutes. This article addresses such concerns by reviewing the evidence available for the safety of each of the most popular low-calorie sweeteners: acesulfame K (acesulfame potassium), aspartame, cyclamates, neotame, saccharin, steviol glycosides and sucralose.

Brief review of the evaluation process

How are low-calorie sweeteners evaluated at the European and international levels? First of all, who evaluates sweeteners and other food additives? In the European Union (EU), the European Commission's Scientific Committee for Food (SCF) was the scientific guarantor for the safety of food additives until March 2003. Since then this has been taken over by the European Food Safety Authority (EFSA). Within the EFSA, food additives were evaluated by the Scientific Panel on Food Additives, Flavourings, Processing Aids, and Materials in Contact with Food (AFC Panel) until July 2008, when this task was taken over by the Scientific Panel on Food Additives and Nutrient Sources Added to Food (ANS Panel). International standards for the use of food additives are established by the FAO/WHO Codex Committee on Food Additives (CCFA). The CCFA uses the Joint FAO/WHO Expert Committee on Food Additives (JECFA) as an advisory committee with regard to the safety evaluation of food additives and contaminants.

The safety of the sweeteners has been evaluated in accordance with internationally agreed principles for the safety evaluation of food additives. JECFA issued principles for the safety assessment of food additives in 1987 [1]. These principles have recently been updated [2]. The SCF issued its first guidance for the safety assessment of food additives in 1980 [3] and updated it in 2001 [4]. Within the EFSA, the AFC Panel and its follower, the ANS Panel, formally adopted the SCF's guidance from 2001. However, a new guidance document has now been prepared by the ANS Panel and is expected to be adopted this year (2012). The guidance document advices what data are necessary for the evaluation of the safety of a chemical intended for use as a food additive.

A very important concept is that of the no observed adverse effect level (NOAEL). The NOAEL is defined as "the highest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure" [1] and is determined from the most sensitive study in the most sensitive species tested. The most important concept, however, is the acceptable daily intake (ADI) for humans, which was created by the JECFA in the mid 1950s. The ADI is an estimate of the amount of food additive, expressed on a body weight (bw) basis, which can be ingested daily over a lifetime without appreciable health risk (Fig. 1). The "fathers" of the ADI

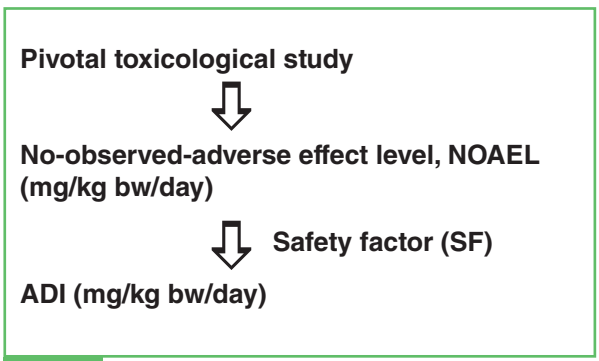

Figure 1 Calculation of the ADI. If the toxicological database is adequate, a safety factor (uncertainty factor) of 100 is used by default, but it may be modified depending on the data are available

suggested the application of a safety (uncertainty) factor to the NOAEL, in order to extrapolate from experimental animals to sensitive humans, keeping in mind that people are exposed to different food components and additives at the same time. When the toxicological database is considered adequate, the NOAEL is by default divided by a

safety factor of 100, but it may be modified when adequate human or other data are available [5].

Toxicological evaluation of the most popular sugar substitutes

The first sweetener to be reviewed in this article is acesulfame K, whose chemical formula is shown in Fig. 2. What is important about acesulfame K is that it is rapidly absorbed from food and is excreted unchanged mainly in the urine. The SCF evaluated acesulfame K for the first time in 1984, based on a one-year study in dogs and a two-year study in rats showing no toxicity. EFSA used the dog study for its assessment because the doses used in this study were the lowest. The safety factor used was 100, so the ADI became 9 mg/kg bw [6]. The question was raised several times whether the rat model would provide more useful information regarding the ADI. The question was dismissed by the SCF in 2000 and the ADI kept at 9 mg/kg bw [7]. The JECFA, instead, used the rat study, which included pregnant rats and pups, and established an ADI of 0–15 mg/kg bw [8].

Acesulfame - K

- Freely soluble in water.
- Stable under normal usage and storage conditions.
- Rapidly absorbed and excreted mainly in the urine.
- Not metabolised in the body.

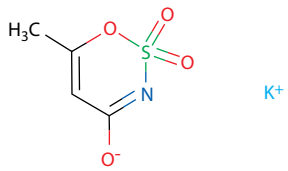

Figure 2 Chemical structure and main characteristics of acesulfame K

The next group of sweeteners to be mentioned is that of cyclamates (Fig. 3). These compounds are rapidly, but only partly, absorbed and excreted in the urine, mainly unmetabolised. However, the gut microflora can convert part of the unabsorbed cyclamates to cyclohexylamine (CHA). CHA has been tested in rats and showed testicular toxicity. Therefore, based on the NOAEL for testicular toxicity of CHA of 100 mg/kg bw/day in the rat, a temporary ADI of 11 mg/kg bw was established using a safety factor of 100 and a conversion factor (cyclamate to CHA) of 11 [6]. The conversion factor has remained controversial and based on new data available in 2000 the ADI was lowered to a full ADI of 7 mg/kg bw [9].

Cyclamates
(cyclamic acid, calcium and sodium cyclamate)

- Soluble in water.
- Stable under normal usage and storage conditions.
- Rapidly absorbed from the gut and excreted mainly in the urine.
- Not metabolized in the body, but the gut microflora metabolised non-absorbed cyclamate to cyclohexylamine (CHA).

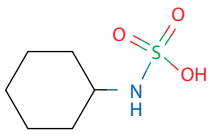

Figure 3 Chemical structure and main characteristics of cyclamates

The next sweeteners to be discussed are saccharin and its sodium, potassium and calcium salts (Fig. 4). Saccharin is one of the oldest known sweeteners and is not metabolised by the body. There has been controversy over the safety of saccharin

Saccharin

- Slightly soluble in water.
- Stable under normal usage and storage conditions.
- Not metabolised in the body.
- Controversy over safety in the past (tumours in the bladder of male rats).

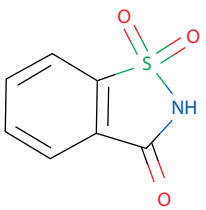

Figure 4 Chemical structure and main characteristics of saccharin (marketed as sodium, potassium and calcium salts)

in the past. Old feeding studies indicated that sodium saccharin at high doses produced tumours in the bladder of male rats. This effect was evaluated by the SCF in 1977, when a NOAEL of 500 mg/kg bw/day was determined for this effect. In this case the EFSA established a temporary ADI of 2.5 mg/kg bw using a safety factor of 200 instead of the default factor of 100 [10]. Since then, several animal and human studies have provided information on the mechanisms behind this carcinogenic response in the male rat and demonstrated no carcinogenic effect of saccharin in other animal species. It is now clear that saccharin is not genotoxic, and in 1995 the SCF decided to remove the temporary status and allocate a full ADI to sodium saccharin, which is nowadays 5 mg/kg bw (3.8 mg/kg bw when the ADI is expressed as the free acid) [11].

Sucralose is composed of two sugar molecules, which are chlorinated (Fig. 5). A small percentage (8–22%) of sucralose is absorbed in the body and the rest is excreted in the faeces. However, a proportion of the ingested sucralose can be hydrolysed to yield two molecules (one containing one chlorine atom and the other containing two chlorine atoms). In 1989 sucralose was evaluated by the SCF, who turned it down because the available studies were insufficient to demonstrate safety [12]. In the year 2000, a number of new studies on the parent molecule and its hydrolysis products had become available and the NOAEL was determined at 1500 mg/kg bw/day, translating into an ADI of 15 mg/kg bw using a safety factor of 100 [13].

A rather new sweetener called neotame was evaluated by EFSA in 2007 [14], but surprisingly this has not given rise to much public debate, although it shows chemical similarity to aspartame. The structure is shown in Fig. 6. Similar to aspartame, it is esterified with methanol. A large number of toxicological studies were evaluated by the EFSA. More than 30% of neotame is absorbed in all species considered and, as is the case of aspartame, neotame releases methanol upon hydrolysis in the body. In 2007, the 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 [14].

Another issue that concerns neotame, but not aspartame, is that neotame contains a secondary

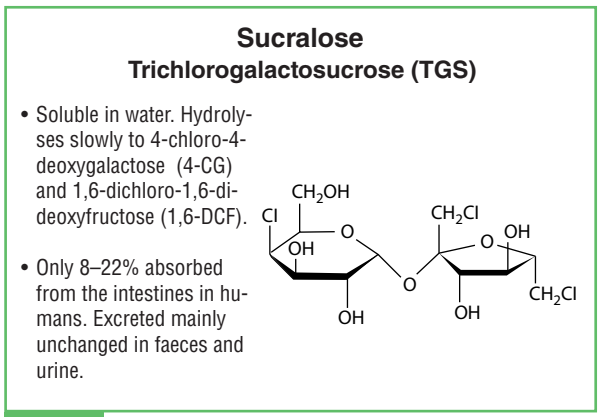

Figure 5 Chemical structure and main characteristics of sucralose

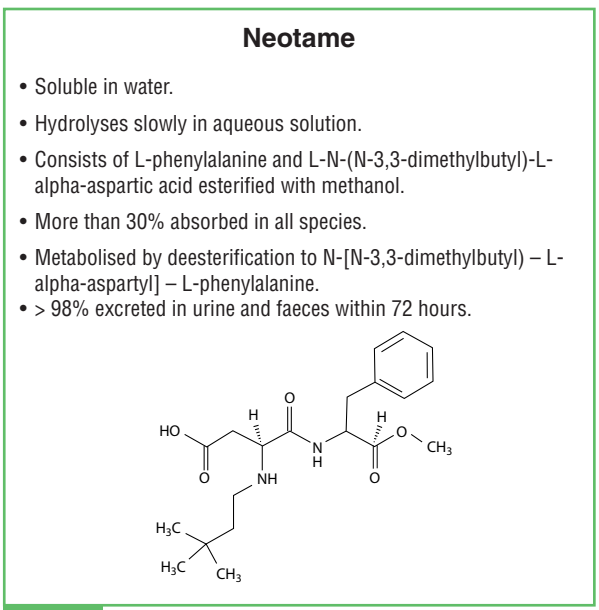

Figure 6 Chemical structure and main characteristics of neotame

amino group, which suggests the possibility that the compound and a metabolite react with nitrite from food or saliva to form nitrosamines (N-nitroso compounds). From the available evidence, many nitrosamines are strong genotoxic carcinogens. However, the relevant nitrosamines were synthesised and tested for genotoxicity by the producer. No genotoxicity was reported, allowing the EFSA to derive an ADI for neotame of 2 mg/kg bw [14]. Steviol glycosides (Fig. 7) were evaluated by the EFSA in 2010 and allocated an ADI of 4 mg/kg bw [15]. Even though they are heralded as natural products which are extracted from the leaves of the *Stevia rebaudiana* Bertoni plant, the food additive that has been approved is a tightly specified and purified product of glycosides. The authorised product shall contain no less than 95% of stevioside and/or rebaudioside A (the latter contains an additional glucose moiety). The steviol glycosides are digested by the gut flora to yield free steviol, which is the compound that is absorbed into the organism and thus of toxicological interest. Steviol glycosides have been evaluated several times in the past by the SCF, who rejected the allegations due to insufficient documentation. This gave rise to rumours about industrial attempts to block introduction of such "natural" products into the market. However, the truth is that the documentation provided earlier was insufficient for a safety evaluation. Nowadays an extensive toxicological database has been provided on steviol glycosides, and both the JECFA and EFSA have recently established an ADI of 4 mg/kg bw, expressed as steviol, based on a NOAEL of 967 mg stevioside/kg bw/day obtained in a long-term rat toxicity study [15].

Steviol Glycosides

- Not less than 95% stevioside and/or rebaudioside A.
- Stevioside is shown. Rebaudioside contains an extra glucose moiety.
- Good stability in food, except after heating and baking (at high temperatures).
- Does not induce a glycaemic response after ingestion.
- The glycosides are poorly absorbed, but are hydrolysed to steviol by the gut microflora.
- Steviol is readily absorbed, conjugated and excreted in bile and urine.

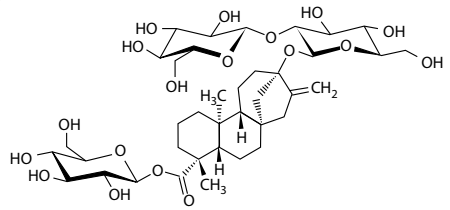

Figure 7 Chemical structure and main characteristics of stevia derivatives

There is also considerable interest in steviol glycosides because of their purported hypotensive activities in humans at high doses. This led to a hold up of the safety evaluation by the JEFCA, who asked for human studies to ensure that an intake at the ADI level had no adverse effect on persons with normal and sub-normal blood pressure. Several studies have been performed, including also studies in diabetics, which led to the conclusion that this sweetener has no blood pressure-lowering effect in healthy people when ingested at the ADI level [15]. Indeed, such use of steviol glycosides should be medically regulated rather than nutritionally and toxicologically addressed for food additive use as a sweetener.

Aspartame and its main features are shown in Fig. 8. Aspartame is metabolised in the gut to

Aspartame

- Consists of two amino acids, L-phenylalanine and L-aspartic acid esterified with methanol.
- Unstable upon prolonged heating (cooking, baking) and in aqueous solutions
- It is metabolised in the gut to three common dietary components: **phenylalanine** (50%), **aspartic acid** (40%) and **methanol** (10%).
- The body utilises the 3 components in the same way as from foods.

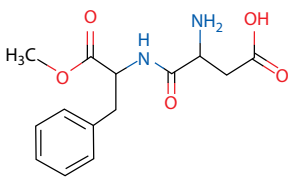

Figure 8 Chemical structure and main characteristics of aspartame

yield three major components, phenylalanine, aspartic acid and methanol, which are normal dietary constituents and utilised by the body. The SCF and EFSA have evaluated aspartame several times. The first evaluation by the SCF in 1985 provided an ADI of 40 mg/kg bw, which was derived from a NOAEL of 4 g/kg bw/day obtained in a long-term toxicity and carcinogenicity study in rats [6]. Subsequent evaluations by the SCF took into consideration claimed behavioural effects of aspartame, but did not result in a revision of the ADI. Allegations of increased incidence of brain tumour after exposure to aspartame were also dismissed by regulatory agencies worldwide. Several reviews from expert panels and regulatory agencies have been published to show that aspartame is not genotoxic and does not cause cancer [16].

One research institute has published two papers during the 2000s in which they claimed that aspartame causes cancer when administered for prolonged periods of time at "nutritional" doses to rats [17,18]. Increases in malignant tumour-bearing animals, lymphomas/leukaemias (in females), transitional cell carcinomas of renal pelvis and ureter, and malignant schwannomas of peripheral nerves were reported in the first study [17] and increases in malignant tumour-bearing animals, lymphomas/leukaemias (in males) and mammary carcinomas were reported in the second study [18]. The EFSA carefully evaluated these two studies and reached the conclusion that they were not conducted according to international standards and that some malignancies were misdiagnosed. In addition, the effects were partly contradictory, generally unrelated to aspartame treatment, showed no dose-response relations or were of no relevance for humans [19–21].

In 2010, the same institution published a study in mice that claimed that aspartame causes cancer of liver and lungs [22]. A quick evaluation by the EFSA dismissed the results as irrelevant to human risk assessment. Based on the available evidence, the EFSA concluded that there was no need to revise the ADI [23]. However, on the request of the European Commission the EFSA has been asked to review the safety of aspartame based on all available evidence.

Finally, a study, published in 2010 by a Danish group reported an association between pre-term delivery and exposure to artificially sweetened soft drinks [24]. The association was strongest for artificially sweetened carbonated soft drinks. It should, however, be noted that this type of study is not able to reveal a casual relationship and additional studies are needed to confirm or disprove these observations [23].

Conclusions

The low-calorie sweeteners discussed have undergone extensive toxicological testing *in vitro* and in experimental animals as well as numerous tolerance, biochemical and epidemiological studies in humans. Provided that exposures are kept below their respective ADIs, there are no safety concerns about the use of low-calorie sweeteners in food.

Conflict of interest

The author has no interests in sweeteners but was a member of the SCF from 2001 to 2003 and of EFSAs Panels dealing with food additives from 2003 until July 2011.

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