



Review of Non-nutritive Sweeteners

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The Australian Beverages Council Ltd

By

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1. Background

Low- or reduced-kilojoule sweeteners (referred to throughout this statement as non-nutritive sweeteners) are widely consumed in Australia. A recent report by Food Standards Australia New Zealand (FSANZ) found that approximately 66% of Australians consume non-nutritive sweeteners with around 51% consuming them in the form of diet beverages [1]. Consumers often select foods and beverages with these sweeteners to achieve a sweet taste without the extra kilojoules sugar provides, to reduce their chances of tooth decay, or to assist with the management of conditions such as diabetes [2]. There are a variety of non-nutritive sweeteners approved for use in beverages in Australia all of which have been thoroughly evaluated. These include aspartame, acesulphame K, saccharin, sucralose, cyclamate, neotame and thaumatin [1]. In order to gain regulatory approval the safety of non-nutritive sweeteners must be proven through extensive animal and human studies. Table one outlines the average daily intakes of these non-nutritive sweeteners in Australia. A combination of non-nutritive sweeteners is often used to sweeten diet beverages. This position statement reviews the health effects and safety of the sweeteners aspartame, acesulphame K, saccharin, sucralose, cyclamate, neotame and thaumatin.

Table 1: Average daily intakes of non-nutritive sweeteners in Australia and sweetness relative to sucrose [1]

Sweetener	Acceptable Daily Intake (mg/kg of body weight per day)	Current intake in Australia (mg/kg of body weight)	Relative sweetness to sucrose [3]
Aspartame	40	2.56 (max ^m 7.46)	180
Acesulphame K	15	0.53 (max ^m 1.39)	200
Saccharin	5	0.5 (max ^m 2.54)	300-500
Sucralose	15	0.45 (max ^m 2.44)	600
Cyclamate	11	3.08 (max ^m 9.89)	30
Neotame	2	N/A*	8000
Thaumatin	Not specified#	N/A*	1600

establishment of an ADI is not deemed necessary because of a good safety profile

* no products were identified that contained either neotame or thaumatin at the time of the survey

Table adapted from Food Standards Australia and New Zealand, Consumption of Intense Sweeteners in Australia and New Zealand. 2004 [1].

2. Aspartame

- The majority of the scientific literature has demonstrated that aspartame is safe for human consumption at levels up to the ADI (except for individuals with phenylketonuria (PKU)).

2.1 Background

Aspartame was discovered in 1965 and is one of the most widely used non-nutritive sweeteners in food products as its taste is very similar to that of sucrose (table sugar) [2]. It is most stable at low temperatures and in dry and weakly acidic conditions so is ideal for dry-product applications. Although it is affected by heat, aspartame can withstand high temperature short-time processing such as that typically used for dairy products and juices [3]. The United States Food and Drug Administration (USFDA) approved aspartame for use in carbonated beverages in 1983 [4] and then for use as a general purpose sweetener in 1996. The National Health and Medical Research Council approved aspartame for use in Australia in 1986.

Once consumed, aspartame is rapidly metabolised to aspartic acid, phenylalanine and methanol, all products which are found naturally in foods [3]. For example, methanol is found in many plant products and fruit juices, and phenylalanine and aspartic acid occur naturally in foods as protein components [2]. Aspartame provides 16 kilojoules per gram – the same as protein and sugar – however it is around 180 times sweeter than sugar so only small amounts are needed to sweeten a food or beverage [2].

2.2 Current intake in Australia

- Current intakes of aspartame in Australia are well within ADI levels.

According to a 2004 report by FSANZ, the mean daily exposure to aspartame in Australia is well below the acceptable daily intake (ADI) (table 1) [1]. The ADI of aspartame is 40mg/kg body weight per day, a level determined by the WHO/FAO Joint Expert Committee on Food Additives (JECFA) [5]. This amount was derived from the estimated level that caused no toxic effect in rats. To reach the ADI for aspartame, a person weighing 70kg would need to consume 2.8g per day. This amount is equivalent to approximately 20 cans of diet sparkling beverage or over 100 standard 1g packets of sweetener.

2.3 Contraindications

- People with PKU should keep their intake of foods and drinks containing aspartame to a minimum.

Individuals with the rare metabolic disease PKU lack the enzyme necessary for digesting phenylalanine one of the breakdown products of aspartame. These people must follow a low phenylalanine diet so need to minimise their intake of products containing aspartame as well as reduce their intake of foods with naturally high phenylalanine levels[6]. As a result all aspartame-containing products must bear a label indicating the product contains phenylalanine.

Many aspartame-containing products also carry a label indicating that these products should not be used in baking or cooking. This is a recommendation not a health warning, because aspartame loses most of its sweetness when it is heated [2].

There have been numerous claims of adverse health effects following consumption of aspartame, however these are generally based on anecdotal evidence or unsubstantiated scientific studies and observations. Most anecdotal reports claim an association between aspartame and neurological symptoms such as headaches and seizures [7, 8] while much of the scientific literature critical of aspartame usage focuses on its effect on cancer and body weight regulation/appetite. These areas are reviewed below.

2.4 Health effects: anecdotal reports

- There is a lack of scientific evidence to support many of the theories linking aspartame to adverse health effects.

Some anecdotal reports relating to aspartame use and adverse health effects claim that it causes a range of behavioural and neurological problems such as headaches and seizures [2]. Many of these claims are thought to be based on the mistaken belief that consuming aspartame can cause blood levels of aspartic acid and/or phenylalanine to rise to levels that can trigger neurological symptoms [2]. However, research into aspartame and brain function has shown no consistent effects of large amounts of aspartame on brain neurotransmitter systems [9, 10]. In 1984, the USFDA requested assistance from the Centers for Disease Control and Prevention (CDC) to evaluate aspartame, following an increase in consumer complaints it had received about aspartame-containing products in late 1983 [11]. The CDC concluded that there was no evidence for the existence of serious, widespread or adverse health consequences associated with the use of aspartame. Similarly in Australia, when considering the use of aspartame, FSANZ reviewed the USFDA data and agreed there was a lack of evidence aspartame had negative health effects. As a result aspartame was approved for use in certain products under the Australia New Zealand Food Standards Code [12].

2.5 Health effects: the scientific literature

- There is a lack of evidence to support claims that aspartame plays a role in cancer.

Aspartame's role in cancer has been debated since an early study proposed a link between increasing brain cancer rates in the US and aspartame's introduction to the food supply in 1981 [13]. This study received widespread media attention despite its many methodological flaws. The authors linked the then recent increase in brain tumours to the introduction of aspartame into food and beverages [13]. This observation received a lot of criticism from the scientific community as there was no evidence that individuals who developed brain tumours actually consumed aspartame. In addition, if aspartame were to be the causative factor in the increase in brain tumours, there would have been a latent effect [14], that is, brain tumours would not have increased for many years after the introduction of aspartame into foods and beverages. More recent scientific reviews have also failed to show an association between aspartame use and brain cancer [14-16]. A European review of case-control studies found no association between aspartame and brain tumours [16], and a case-control study in the US concluded that children with brain tumours were no more likely to have consumed aspartame than children in the control group [17]. A 2004 review of studies on aspartame and health risks also concluded that "despite unscientific articles in the mass media and scientific press, there is no evidence that the sweetener aspartame bears a carcinogenic risk" [14]. In 2006, results from a rat study by the European Ramazzini Foundation (ERF) were released that linked

aspartame consumption with an increased risk of certain cancers [18]. However, an extensive review of this study by the FDA showed that the data did not demonstrate cancer incidence was directly related to aspartame consumption [19]. The European Food Safety Authority (EFSA) also reviewed the ERF study on aspartame and reached the same conclusion [20]. A second study released in 2007 by the same research group supported their original findings [21], and once again received extensive media attention. After reviewing the new study the FDA maintained the same conclusion, that the data did not support the conclusion that aspartame was a carcinogen and the use of aspartame is safe [19]. The EFSA is currently reviewing the evidence presented in this new study.

2.6 Health effects: appetite and hunger

- More research is required before an association between aspartame and appetite/hunger can be either supported or refuted.

There have been suggestions that aspartame and other non-nutritive sweeteners may increase carbohydrate cravings following consumption, leading to possible weight gain. These assumptions stem from an early study that showed hunger ratings increased after consumption of aspartame, prompting the authors to argue that kilojoule savings achieved with aspartame could be offset by increased energy intake at subsequent meals [22]. Some additional research has also found a stimulating effect of aspartame on appetite [23, 24], however a number of confounding factors have been identified such as time, sweetener concentration and gender, meaning that even if the studies showed a positive association, the results cannot be directly attributed to the intake of aspartame. Most of the literature on aspartame and appetite consists of short-term studies of only a few hours to a few days in duration and there are currently no long-term studies that adequately assess the effects of aspartame on appetite. In addition, the majority of the more recent scientific literature does not support the claims that aspartame has a stimulating effect on appetite [25-27]. Other research has suggested that aspartame neither increases nor decreases appetite, energy intake or body weight compared with consumption of sucrose [28]. A number of reviews have also failed to show a direct link between aspartame intake and appetite [29, 30].

2.7 Health effects: body weight regulation

- Aspartame may be a useful inclusion in a weight loss diet to maintain the palatability of the diet without affecting total kilojoule intake.

In long-term intervention studies that involve energy restriction, the inclusion of non-nutritive sweeteners such as aspartame has been shown to increase compliance to a low energy diet and help maintain weight loss [31]. One study compared weight loss after three years following either consumption of, or abstinence from aspartame, and found those consuming aspartame lost significantly more weight and regained significantly less weight than those who were abstaining [31]. One review on the effectiveness of aspartame in helping with weight control concluded that using foods and drinks sweetened with aspartame instead of those sweetened with sucrose is an effective way to maintain and lose weight without reducing the palatability of the diet [32]. A 2007 review on aspartame and body weight found that although there is a lack of conclusive evidence on aspartame's role in appetite, when aspartame is added to diet beverages, the energy density of the beverage is reduced, indicating that diet beverages sweetened with aspartame may be the best use of non-nutritive sweeteners in the context of a weight control strategy [33].

Based on the available scientific evidence, aspartame does not appear to increase food intake, hunger, appetite or weight gain. The American Dietetic Association's position on the intake of non-nutritive sweeteners such as aspartame in relation to weight management is that "Individuals who wish to lose weight may choose to use non-nutritive sweeteners but should do so within the context of a sensible weight management program including a balanced diet and exercise" [34].

2.8 Conclusion

Despite anecdotal reports and popular allegations relating its use to adverse health effects, aspartame has been found in the majority of the scientific literature to have no detrimental effects on human health and may assist long-term compliance to a low energy diet. Aspartame is hence safe for individuals to consume within ADI levels with the exception of those who have the rare metabolic disease phenylketonuria.

3. Acesulphame potassium (K)

- Acesulphame K is commonly used along with aspartame as a beverage sweetener. To date there have been no studies relating its consumption to adverse health effects and it is hence safe for human consumption.

3.1 Background

Acesulphame K was discovered in 1967. It is approximately 200 times sweeter than sugar and is heat stable [35], allowing it to be used in cooking and baking as well as a sweetener for foods and beverages. Acesulphame K is not metabolised by the body, hence it provides no kilojoules. It also has no influence on potassium intake even though it does contain potassium as its name suggests [34]. Acesulphame K is generally used in combination with other sweeteners as it can have a bitter aftertaste when used on its own [36]. When small amounts of acesulphame K are mixed with other non-nutritive sweeteners, the resulting taste is similar to that of sucrose [37]. Acesulphame K underwent rigorous safety testing prior to its approval for use in foods and beverages in the US and Australia. The USFDA approved its use in non-alcoholic beverages in 1998 [38] and as a general purpose sweetener in 2003 [39]. In Australia, acesulphame K was approved for use in 1987 where it is commonly used in combination with aspartame to flavour diet sparkling beverages.

3.2 Health effects: the scientific literature

- The scientific literature indicates acesulphame K is safe to consume within ADI levels.

Acesulphame K has had no human health problems associated with its use, and has been consumed for over 20 years in many countries around the world. One breakdown product of acesulphame K, acetoacetamide, is known to be toxic if consumed in very large doses. However, the amount of this substance that could be present in an acesulphame K-sweetened product is extremely small and negligible. In approving its use, the USFDA therefore concluded no further testing of acesulphame K was necessary [2].

3.3 Current intake in Australia

Intake of acesulphame K in Australia is estimated to be well below the ADI of 15mg/kg body weight per day (table 1) [1], as determined by the JECFA [40]. This amount was derived from the estimated level that caused no toxic effect in rats.

3.4 Conclusion

Over fifty scientific studies on the effect of acesulphame K in the body support its safety as a non-nutritive sweetener. Acesulphame K is hence safe for individuals to consume within ADI levels.

4. Saccharin

- Despite early literature linking saccharin consumption to adverse health effects (particularly in rats) recent scientific studies have not supported this and it is considered safe for human consumption.

4.1 Background

Saccharin is the oldest non-nutritive sugar substitute, being initially synthesised in 1879, and is the most widely researched of all sweeteners [14]. It is approximately 300 to 500 times sweeter than sugar and is heat stable, allowing it to be used in cooking and baking as well as a sweetener for foods and beverages. In the early 1900s, saccharin was popular as a sugar substitute in the diets of people with diabetes and other medical conditions [2]. It was also used extensively as a replacement for strictly rationed sugar in Europe during both World Wars [2]. Saccharin is absorbed but not metabolised by the body and is excreted in the urine, hence provides no kilojoules [41]. It is generally used in combination with other sweeteners as it can have a bitter aftertaste when used on its own. It is approved for use in over 100 countries. In Australia it is primarily used in food as a table-top sweetener, in water-based beverages, and in some cordials/fruit drinks [1]

4.2 Current intake in Australia

Intake of saccharin in Australia is estimated to be well below the ADI level (table 1) [1]. The ADI for saccharin is 5mg/kg body weight per day, which was determined by JECFA [40]. This amount was derived from the estimated level that caused no toxic effect in rats. Much of the scientific literature critical of saccharin usage focuses on its effect on bladder cancer, and this literature is discussed below.

4.3 Health effects: the early scientific literature

- While early rat studies indicated a link between saccharin and bladder cancer, this theory has not been supported in human studies.

Significant concerns have been raised about the safety of saccharin consumption, the primary concern being based on early animal studies that found an increased incidence of bladder cancer when rats were fed high amounts of saccharin in their diet from birth [42]. However, following later analysis, it was suggested that impurities, not saccharin, may have caused the cancers in this particular research. Early research looking at saccharin and cancer risk in humans consists of mainly small epidemiological studies. In the UK, a longitudinal study failed to show an increase in bladder cancer incidence during World War II, when population saccharin consumption was at its highest [43]. Another study looked at death certificates from the UK between 1966 and 1972 and compared the bladder cancer mortality between people with diabetes, who used non-nutritive sweeteners more frequently, and people without diabetes. This study did not find any significant differences between the groups [44]. A Danish study could not detect an increase of bladder cancer mortality in people aged up to 30 years old, who were born between 1941 and 1945, when saccharin use was higher than in the years before and after [45]. However, in 1977, a study that looked specifically at the role of impurities found evidence that saccharin itself may have been causing bladder cancer in rats [46]. As a result, the FDA proposed to ban saccharin for all uses except as a table-top sweetener. This FDA proposal prompted a public outcry, fuelled in part by media reports that the test rats

were fed the equivalent of 800 diet sparkling beverages sweetened with saccharin per day. Congress responded by passing the Saccharin Study and Labeling Act, which placed a two year moratorium on any ban of the sweetener while additional safety studies were conducted and required all saccharin sweetened foods and beverages to carry a warning label. The moratorium on the ban was extended numerous times on the basis of the need for further scientific study and continued consumer demand for the sweetener. The mandatory warning label was removed in 2000 [3].

4.4 Health effects: the recent scientific literature

A number of more recent case-control studies found no significant link between consumption of saccharin and bladder cancer [47-50], and the largest case-control study analysing this issue, including 3010 cases of bladder cancer, found no relation with all non-nutritive sweeteners [48]. It was also later shown that the metabolism of saccharin was species specific, and that saccharin intake does not lead to the formation of bladder cancer in humans [51]. As a result, in 1991 the FDA withdrew its proposal to ban the use of saccharin.

No carcinogenic effect has been observed in mice, hamsters, or monkeys, and the majority of epidemiological studies provide no consistent evidence that saccharin increases the risk of bladder cancer in humans when consumed in amounts below the ADI [52].

4.5 Conclusion

Saccharin is the oldest and mostly widely researched non-nutritive sweeteners. Despite negative health effects of saccharin observed in a small number of rat studies, there is an extensive body of scientific evidence supporting saccharin's safety for human consumption... Saccharin is hence safe for individuals to consume within ADI levels.

5. Sucralose

- Sucralose has been found to be safe for human consumption and well tolerated by the majority of the scientific literature.

5.1 Background

Sucralose was discovered in 1976 and was approved for use in Australia in 1993. It is approximately 600 times sweeter than sucrose and is heat stable during cooking and baking. Sucralose is commonly sold under the trademark Splenda. It is made from sucrose by a chemical process that substitutes three chlorine atoms for three hydroxyl groups on the sucrose molecule [2]. Although sucralose is made from sugar, the human body does not recognise it as a sugar and does not metabolise it [2], hence it provides no kilojoules. Sucralose is not hydrolysed in the intestine and less than 25% of any ingested amount is absorbed. The small proportion that is absorbed is not metabolised and is excreted unchanged in the urine [53]. Sucralose is mainly used in Australia in confectionery, table-top sweeteners and sparkling beverages [1].

5.2 Current intake in Australia

Intake of sucralose in Australia is estimated to be well below the ADI level (table 1) [1]. The ADI for sucralose is 15mg/kg body weight per day, which was determined by JECFA [40].

5.3 Health effects: the scientific literature

- The scientific literature indicates sucralose is safe to consume within ADI levels.

Studies investigating the safety of acute and chronic consumption of sucralose at ADI levels have not reported any adverse effects on human [54, 55] or animal health [56, 57]. Studies have shown that sucralose is well tolerated by humans in single doses up to 10mg/kg and repeated doses increasing to 5mg/kg per day for 13 weeks [54]. A number of studies were conducted that looked at the effect of sucralose on reproduction, growth and development. One such study looked at the effect of sucralose on fertility in rats. Adult female and male rats were fed high levels of sucralose (1500mg/kg body weight per day) prior to mating, throughout gestation and lactation. The first generation pups were then weaned to the same diets their mother consumed and this was repeated for a number of generations. No adverse effects of sucralose on any parameters tested were observed. Lifetime carcinogenicity studies in both rats and dogs have not demonstrated any adverse effects following consumption of sucralose.

Individual tolerance to sucralose consumption has been assessed in the literature. One study observed tolerance to sucralose in a 13 week ascending dose study in healthy men and women [58]. A similar study looked at the same outcomes in individuals with type 2 diabetes [59]. Both studies demonstrated that sucralose was well tolerated at doses two to four times the estimated average population daily intake and showed no adverse health effects.

5.4 Health effects: anecdotal reports

- The scientific literature does not support any of the anecdotal reports that link sucralose consumption to adverse health effects.

Chlorine (in the form of chloride) is in many foods and beverages in the food supply, as well as in most natural water supplies. Due to the presence of chlorine atoms within the sucralose molecule, it is sometimes referred to as a chlorinated carbohydrate or monosaccharide [58]. Some of the controversy surrounding the safety of sucralose is based on the theory that because it contains chlorine, it exerts a toxic effect in the body similar to that exerted by some chlorinated hydrocarbons. The molecular structure of sucralose is in fact quite different from chlorinated compounds. Chlorinated hydrocarbons are fat soluble compounds and can accumulate in body fat stores. Sucralose on the other hand is poorly soluble in fats, does not accumulate in body fat stores and does not break down into chlorinated compounds in the body [56].

5.5 Conclusion

Sucralose a derivative of sucrose is well tolerated and has not been shown to have any adverse health effects in either animals or humans. Sucralose is therefore safe for individuals to consume within ADI levels.

6. Cyclamate

- Despite early studies linking cyclamate consumption with adverse health effects, the majority of the scientific literature has found that when consumed within ADI limits, it is safe for human consumption.

6.1 Background

Cyclamate was discovered in 1937, and was widely used as a non-nutritive sweetener in the US throughout the 1950s and 1960s [2]. Cyclamate is heat stable however it is less sweet than other non-nutritive sweeteners, being only 30 times sweeter than sucrose. As a result, larger amounts (in comparison with other non-nutritive sweeteners) need to be used to sweeten a food or beverage [2]. It is often used in a 10:1 blend with saccharin, a mixture that has a sweeter taste than that of either sweetener alone [60]. Once consumed 37% of cyclamate is absorbed by the body and excreted unchanged. A few individuals however can convert cyclamate into cyclohexylamine [3]. Cyclamate is currently approved for use in foods and beverages in over 50 countries including Australia, but not in Canada or the US [34]. Cyclamate has very low acute toxicity, but can have a laxative effect at high doses (6 to 16g/day in humans; or 5 to 15 cans of diet beverage). In 1969 the FDA withdrew permission to add cyclamate to foods based on studies linking saccharin/cyclamate mixtures to cancer incidence in rats. In Canada, cyclamate is not approved for use in foods but can be sold as a table-top sweetener [61]. In Australia, cyclamate is mainly used to sweeten cordials, fruit drinks and diet water-based beverages, and is the most widely consumed of the non-nutritive sweeteners approved for use [1]. Further studies on the metabolism of cyclamate in humans are needed before the FDA will allow widespread use of this sweetener in foods and beverages.

6.2 Current intake in Australia

- Cyclamate is safe to consume within ADI levels.

The ADI for cyclamate is 11mg/kg body weight per day, which was determined by JECFA [40]. This amount was derived from the estimated level that caused no toxic effect in rats (100mg/kg body weight per day). The average intake of cyclamate in Australia is estimated to be well below the ADI (table 1), however some consumers are believed to have an intake that exceeds the 95th percentile exposure level [1]. Groups with a higher overall intake of cyclamate include people with diabetes, teenagers (12-17yrs) and adults (25-39yrs) [1]. Children under 12 years of age were not included as part of the FSANZ survey, hence exposure of Australian children aged 2-11 to cyclamate was determined through food consumption data collected in the 1995 National Nutrition Survey (NNS). Using this approach, mean and 95th percentile exposure to cyclamate among Australian children aged 2-11 years who were consumers of cyclamate-containing foods was estimated to be approximately 50% and 200% of the ADI respectively [62]. As a result of these findings, FSANZ has reviewed cyclamate permission levels in foods and beverages and recommended that the maximum permitted level (MPL) of cyclamate used in water based flavoured drinks be reduced from 600mg/kg to 350mg/kg [63]. It is thought that this amount will ensure that consumption of cyclamate would then be well within the ADI levels for all age groups [62].

Much of the scientific literature critical of cyclamate usage focuses on the effect of one of its breakdown products, cyclohexylamine, and its effect on cancer. This literature is discussed below.

6.3 Health effects: animal studies

- Despite some early research linking cyclamate consumption to adverse health effects in animals, these results have not been replicated in humans.

Numerous animal and human studies have been conducted with both cyclamate and cyclohexylamine, and a number of reviews of the toxicological data have been published. In 1970, a two year chronic toxicity study in rats linked consumption of cyclamate to an increased risk of bladder cancer [64]. This study is what prompted the withdrawal of cyclamate from the food supply in the US. JECFA evaluated this study in 1970 and concluded that the findings were only tentative pending a complete evaluation [65]. Further experiments with rats and dogs showed that cyclohexylamine caused testicular atrophy and impaired spermatogenesis [66, 67]. One long-term toxicity study with cyclamate has been conducted in non-human primates [68]. Monkeys were fed either 100 or 500mg/kg (the equivalent of 30 cans of diet sparkling beverage) of cyclamate daily for over 20 years. The authors found a higher incidence of malignant tumours in animals consuming 500mg/kg daily. However, the results were not significant and no bladder cancers were observed; a different result to the original rat study that led to the ban of cyclamate from the food supply.

6.4 Health effects: human studies

- The majority of the scientific literature has been unable to prove an association between cyclamate consumption and adverse health effects.

The controversy surrounding the use of cyclamates in foods and beverages is based on studies that show, in some individuals, cyclamate is not entirely metabolised in the body and can be converted to cyclohexylamine, a potential carcinogen and promoter of [69] cardiovascular disease [70]. Although the majority of individuals excrete most or all of cyclamate from the body unchanged, a small number of individuals can convert as much as 85% into cyclohexylamine, meaning cyclamate may have adverse health effects in these people. To date there have been few descriptive or case-control studies looking at cyclamate in humans as it was approved after saccharin, and most products contain both of these non-nutritive sweeteners [14]. One case-control study has been conducted in Spanish men attending an infertility clinic [71]. Semen evaluation, urine analysis for cyclamate and cyclohexylamine excretion and dietary questionnaires were compared between the two groups. Mean estimated cyclamate intake was 0.72mg/kg body weight per day for the case group and 0.55mg/kg body weight per day for the control group. No statistically significant differences in levels of cyclohexylamine were found in urine samples between the groups, hence it was concluded that consumption of low levels of cyclamate had no effect on male fertility [71].

6.5 Conclusion

Systematic reviews of the scientific literature by the FDA and the National Academy of Sciences have reversed the original conclusion that consumption of cyclamate is associated with an increased cancer risk [72]. FSANZ has determined that as most individuals (89%) do not metabolise cyclamate to cyclohexylamine and therefore exceeding the ADI somewhat would not represent a health risk for these individuals [62]. For individuals with metabolising ability, if occasionally the ADI were slightly exceeded, no adverse effects would be anticipated [62].

7. Neotame

- There are no known adverse health effects associated with consumption of neotame

7.1 Background

Neotame is the newest non-nutritive sweetener, having only been discovered in 1990. It was approved in Australia in 2001 and by the FDA as a general purpose sweetener in 2002. The owners of Neotame confirm that it is now used in many products in Australia, most of which are beverages. Neotame is 8000 (7000-13000) times sweeter than sucrose therefore only very small amounts are required for use. It provides no kilojoules and is heat stable during cooking and baking. Neotame is a derivative of a dipeptide composed of aspartic acid and phenylalanine. Although it contains three of the same chemical components as aspartame it has very different chemical properties. Unlike aspartame the bond between aspartic acid and phenylalanine is not broken during metabolism. Approximately 20% to 30% of ingested neotame is absorbed and rapidly metabolised to demethylated neotame (and methanol) and completely excreted from the body [3] [2]. There have been concerns regarding neotame's potential to adversely affect health which have stemmed mainly from the misconception that Neotame acts similarly to aspartame. These claims are unsubstantiated given the differences between the two sweeteners and the extensive scientific support justifying the use of neotame. This is discussed in more detail below.

7.2 Safety: the scientific literature

- The scientific literature shows that consumption of neotame is safe within ADI levels.

The ADI for neotame is 2mg/kg body weight per day, which was determined by JECFA [40]. There are no known adverse effects related to neotame consumption within this ADI level. Prior to approval for use in foods and beverages, neotame underwent extensive scientific investigation. Neotame consumed at 100 times the ADI in animals has not been shown to produce adverse neurological, behavioural or reproductive effects [34]. In human studies, there have been no adverse effects observed following neotame ingestion compared to control subjects [73]. On the basis of a review of over 100 studies looking at short-term, subchronic and chronic toxicity of neotame in humans, as well as developmental, reproductive and carcinogenicity studies, and an additional 32 exploratory and screening studies, the FDA approved neotame as a general purpose sweetener [73].

The exposure to methanol from neotame is toxicologically insignificant because people are exposed to much larger amounts of methanol from natural dietary sources. Traces of methanol are found in fruits, vegetables and fruit juices [74]. It has been estimated that the methanol content of a neotame-sweetened beverage would be about 1.37mg/L [73]; for comparison, the methanol content of fruit juice is approximately 140mg/L [74]. A very small amount of phenylalanine from neotame may also be released into the plasma. However, exposure to phenylalanine from neotame is very low; even if the 90th percentile of the estimated daily intake were consumed, phenylalanine intake would only be 2.6mg [2]. This amount is not clinically significant for individuals with PKU as it represents less than 0.5% of the daily

phenylalanine intake (phenylalanine-restricted diets usually contain between 400-600mg/day). As a result, products containing neotame do not need to carry a statement that they contain phenylalanine.

7.3 Conclusion

Neotame is the newest non-nutritive sweetener and has been extensively studied in both animal and human studies. Despite misconceptions that it is similar to aspartame most of the scientific literature has shown neotame has no adverse health effects when consumed within ADI levels.

8. Thaumatin

- There are no known health effects associated with consumption of thaumatin

8.1 Background

Thaumatococcus daniellii [75]. Thaumatin is one of six known naturally occurring intensely sweet-tasting plant proteins, and is isolated from the West African plant *Thaumatococcus daniellii* [75]. Thaumatin is currently approved for use in Australia however it has not yet been used extensively in the food industry as a non-nutritive sweetener. It is marketed under the trademark Talin. Thaumatin is approximately 1600 times sweeter than sucrose hence only very small amounts are required for use. Similar to any plant protein, thaumatin is digested into its constituent amino acids in the gastrointestinal tract prior to absorption [41]. A JECFA review of the biologic, toxicologic, teratogenic, allergenic, short-term testing and some studies of this sweetener in humans suggest that thaumatin is not toxic [76]. As a result, JECFA set an ADI of “not specified” (i.e. no need for a tolerance level) [34]. Very few clinical trials have been performed, but animal studies suggest that it is safe for human consumption [75].

8.2 Conclusion

The small number of clinical trials that have been conducted using thaumatin have not linked its consumption with adverse health effects. Consumption of thaumatin is therefore safe.

9. Special groups

9.1 Non-nutritive sweeteners during pregnancy

For ethical reasons, scientific studies on the consumption of intense sweeteners during pregnancy and lactation have only been conducted in animals. The breakdown products of aspartame are phenylalanine, aspartic acid and methanol, and these substances do not cause toxic effects in the body. Phenylalanine does cross the human placenta, although maternal phenylalanine levels after consumption of aspartame have been consistently below toxic levels [77]. Toxicity from aspartic acid is non-existent as it does not cross the human placenta [78]. Methanol toxicity is also not a concern during pregnancy as methanol levels in maternal serum are only slightly elevated following consumption [78]. Rodent studies have shown that saccharin can cross the placenta and can, due to slow foetal metabolism, remain in the foetal tissues longer than in those of adults [77] and as a result, the American Pregnancy Association questions the use of saccharin during pregnancy [79]. In Australia saccharin is approved as safe for everyone [80]. Rat studies have demonstrated that acesulphame K, sucralose and neotame are safe for consumption during pregnancy [58, 73]. Consistent with this are The American Dietetic Association and the American Pregnancy Association positions are that consumption of aspartame, sucralose, neotame and acesulphame K during pregnancy is safe [34, 79].

9.2 Non-nutritive sweeteners in diabetes

In Australia, non-nutritive sweetener consumption amongst people with diabetes is more common than in the general population, with aspartame and cyclamate being the most widely consumed non-nutritive sweeteners [1]. The safety of aspartame use in people with diabetes has been widely researched and it has been consistently shown that consumption of aspartame, even at three times the ADI, has no effect on glycaemic control [81] or insulin levels [81, 82]. Daily consumption of saccharin, cyclamate or sucralose, below ADI levels, has also been shown to have no negative effects on blood glucose concentrations or blood lipids in people with diabetes [59, 83, 84]. Neotame ingestion also does not have a significant effect on fasting plasma glucose or insulin levels in individuals with type 2 diabetes [85]. Due to their low use level and low kilojoule content, aspartame, saccharin, cyclamate, sucralose and acesulphame K can be useful for people with diabetes who are trying to lose weight. Consumption of these non-nutritive sweeteners is supported by the American Diabetes Association [86] as well as Diabetes Australia [87].

9.3 Non-nutritive sweeteners in children

Children can safely consume non-nutritive sweeteners within ADI levels. Due to their smaller size and relatively higher sparkling and flavoured beverage intake compared to adults, it is likely that children will also have higher relative intakes of non-nutritive sweeteners per kilogram of body weight per day [34]. A 2004 survey by FSANZ found that consumption is well below the ADI for all non-nutritive sweeteners in children with the exception of cyclamate in the age group 2-11 years [1]. Data from other countries also indicates that overall consumption of non-nutritive sweeteners by children is well below the ADI [88]. A review on aspartame intake in children found that average consumption was well below the ADI in various countries around the world, including Australia [88]. There is a wide range of non-nutritive sweeteners in use in Australia meaning intake of any one sweetener is likely to be less

than in countries with limited sweeteners available in the food supply. Many of the approved sweeteners in Australia are blended in beverages, reducing the risk of any individual non-nutritive sweetener exceeding ADI levels in children [34].

9.4 Non-nutritive sweeteners and dental health

It is well established that a person's diet can impact on their dental health. There is a large evidence base showing that frequent consumption of sugars such as sucrose can lead to an increased risk of tooth decay. To date no research interventions have addressed the effect of aspartame, saccharin, neotame, thaumatin, cyclamate or acesulphame K on dental health in humans. The existing research is on aspartame's effect on tooth decay in rats. Rat studies have found that compared to sucrose, intake of non-nutritive sweeteners such as aspartame results in a lower incidence of tooth decay and may even be protective [89]. Studies conducted *in vitro* have supported this finding [90]. Research in the area of dental health suggests that replacing sugar in foods with non-nutritive sweeteners may lead to a reduction in the incidence of tooth decay [91]. However, it is important to note that consumption of diet sparkling beverages can increase the risk of demineralisation of tooth tissue and subsequent dental erosion due to their acid content [92, 93]. The overall composition of a beverage and the way it is consumed should therefore be considered when assessing the impact of a product on dental health.

10. Summary

Despite popular allegations linking the use of non-nutritive sweeteners to adverse health effects such as cancer, neurological symptoms and effects on appetite, the scientific literature does not support these theories. The majority of the scientific literature on the non-nutritive sweeteners approved for use in Australia has found no adverse effects of these sweeteners on human health. Consumption of these non-nutritive sweeteners can exert a beneficial effect for certain people, in particular those with diabetes and those interested in managing their weight, due to their low kilojoule content and sweet taste.

Overall, when consumed within ADI levels as currently done in Australia, the non-nutritive sweeteners aspartame, acesulphame K, saccharin, neotame, sucralose, cyclamate and thaumatin have been shown to have no association with adverse health effects and can be an enjoyable addition to the diets of those who are concerned with their dental health, limiting their kilojoule intake or controlling their blood glucose levels.

10.1 Evidence-based key messages

- Aspartame, acesulphame K, saccharin, cyclamate, sucralose, neotame and thaumatin can safely be consumed as general purpose, non-nutritive sweeteners by the general population.
- Those with phenylketonuria (PKU) need a low phenylalanine diet so should minimise their intake of products sweetened with aspartame.
- Foods and beverages sweetened with non-nutritive sweeteners can be consumed in moderation as part of a healthy, balanced diet and lifestyle that also includes regular physical activity.
- Non-nutritive sweeteners are safe to use during pregnancy.
- Non-nutritive sweeteners can be used to replace added sugars in the diet in an effort to reduce the risk of tooth decay however the impact on dental health will be determined by the overall composition of the food or beverage within which the non-nutritive sweetener is added.
- Beverages containing non-nutritive sweeteners can be included in moderation as part of a balanced diet and healthy lifestyle that also includes physical activity.

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12. For further information

Sharon Natoli
Accredited Practising Dietitian
Food & Nutrition Australia Pty Ltd.

Telephone: 1300 926212
Facsimile: 02) 9262 1279
Email: snatoli@foodnut.com.au