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Opinion of the Scientific Committee on Food:

Update on the Safety of Aspartame

(expressed on 4 December 2002)

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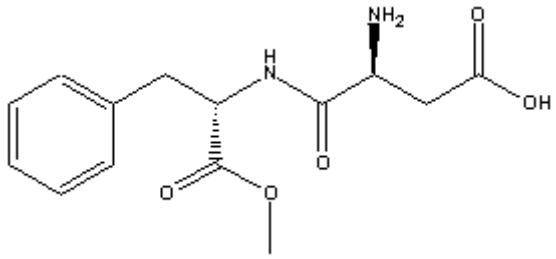
Terms of Reference

The Committee is asked to review all new scientific information on aspartame not having been examined by the SCF previously, taking into account, notably, the literature search carried out in the UK.

Background

The intense sweetener, aspartame, is used in a wide range of food products in many countries around the world and is authorised for use in the EU (E951). It has the following structure:



The Scientific Committee for Food (SCF) initially evaluated aspartame (L-aspartyl-L-phenylalanine methyl ester) during 1984 (SCF, 1985) and subsequently during 1988 (SCF, 1989). At its 107th meeting in June 1997, the SCF also examined the issue of an alleged connection between aspartame and increase in incidence of brain tumours in the USA (SCF, 1997).

Aspartame has also been considered by other bodies including the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1980) the US Food and Drug Administration (FDA, 1984), and the UK Committee on Toxicity (COT, 1992). The toxicity data on aspartame were used by the JECFA, SCF and COT to establish an Acceptable Daily Intake (ADI) of 40 mg/kg body weight/day and an ADI of 50 mg/kg bw/d was established by the FDA. An ADI of 7.5 mg/kg bw/d was also established for a minor cyclic dipeptide derivative of aspartame, a diketopiperazine (DKP), which is formed in some aqueous solutions (JECFA, 1980; SCF, 1985).

The safety issues that have been raised in the past about aspartame have included: (1) the possibility of toxicity from methanol, one of the breakdown products of aspartame; (2) elevations in plasma concentrations of phenylalanine (Phe) and aspartic acid, which could result in increased transport of these amino acids into the

brain, altering the brain's neurochemical composition; (3) the possibility of neuroendocrine changes, particularly increased concentrations in the brain, synaptic ganglia and adrenal medulla of catecholamines derived from Phe and its hydroxylation product, tyrosine; and (4) a postulated link with epilepsy and brain tumours. All these areas have been addressed in the pre-1988 literature and in more recent reviews (Meldrum, 1993; Lajtha *et al.,* 1994; Tschanz *et al.,* 1996).

The safety of aspartame and its metabolic breakdown products (phenylalanine, aspartic acid and methanol) has been assessed in humans generally and in several subgroups, including healthy infants, children, adolescents, adults, obese individuals, diabetics, lactating women, and individuals heterozygous for the genetic disease, phenylketonuria (PKU), who have a compromised ability to metabolise the essential amino acid, Phe.

Since its approval, aspartame has undergone further investigation through clinical and laboratory research, intake studies and postmarketing surveillance of anecdotal reports of adverse health effects.

The present review updates the previous SCF opinions in the light of new reports on the consumption of aspartame in relation to the onset of brain tumours and seizures, headaches, allergies, and changes in behaviour and cognitive function. Information on the safety of aspartame was available from a variety of sources including scientific papers, conference proceedings, abstracts and magazine articles. This review focuses on papers published in the open scientific literature from 1988 to 2001 and draws on the recent extensive review by the Agence Française de Sécurité Sanitaire des Aliments (AFSSA, 2002), which covered mutagenic, carcinogenic and neurological effects.

Exposure assessment

European Commission report on Food Additive Intake

In the European Commission report on Dietary Food Additive Intake in the European Union (EC, 2001), estimates of intake were calculated using a tiered approach. Tier 1 is based on theoretical food consumption data and maximum usage levels for additives as permitted by relevant Community legislation. The second and third tiers refer to assessment at the level of individual Member States, combining national data on food consumption with the maximum permitted usage levels for the additive (Tier 2) and with its actual usage patterns (Tier 3). Aspartame has been examined at Tier 1 for adults and at Tier 2 for children.

Aspartame intakes for adults were estimated at Tier 1 to be 21.3 mg/kg bw/day in the European Union. The Tier 1 approach is likely to be an overestimate of actual intake even by high level consumers of aspartame-sweetened foods. More refined intake

estimates (Tier 2) were performed for children. Information from individual member states showed that the refined estimated intake for children was 1-40% of the ADI. Therefore aspartame was excluded from further consideration as both adults and children were shown to be unlikely to exceed the ADI of 40 mg/kg bw.

Other published intake estimates for European countries

In addition to the Commission report, a number of reports have been published from 1990 onwards with estimates of aspartame intake in European countries (Bär and Biermann, 1992; Butchko and Stargel, 2001; Garnier-Sagne *et al*., 2001; Hinson and Nicol, 1992; Leclercq *et al.,* 1999; MAFF, 1990 and 1995; Renwick, 1990; Salminen and Penttilä, 1999). The table below shows the highest reported intake estimates for different age groups of the general population and people with diabetes. The data are based on actual food consumption combined with the actual sweetener levels present in the foods (equivalent to Tier 3 in the Commission report) or the maximum permitted aspartame levels (Tier 2). The estimates of intake by mean and high level consumers are fairly consistent between European countries even though slightly different approaches were used. High level consumers, both adults and children, are unlikely to exceed the ADI of 40 mg/kg bw for aspartame. Special groups such as diabetics that are likely to be high consumers of foods containing aspartame are also well below the ADI. Therefore, from the available data it appears that no group is likely to exceed the ADI for aspartame on a regular basis.

Table: Highest reported intake estimates for aspartame

Consumer group	**Country**	**Mean consumer intake in mg/kg bw/d**	**High level consumer intake in mg/kg bw/d (percentile quoted)**	**Reference**
Children 1-5 years old	UK	-	2.8 (90)	Hinson & Nicol, 1992
Children 1-6 years old	Finland	-	< 4 (-)	Salminen & Penttilä, 1999
All ages	Netherlands	2.4	7.5 (95)	Butchko & Stargel, 2001
All ages	Norway	3.4	-	Butchko & Stargel, 2001
Diabetics* 2-20 years old	France	2.4	7.8 (97.5)	Garnier-Sagne *et al.*, 2001
Diabetics 2-65 years old	UK	-	10.1 (97.5)	MAFF, 1995

* using maximum permitted level of sweeteners in different food categories (Tier 2 approach). All the other figures are derived using actual sweetener levels present in foods.

Absorption, distribution, metabolism and excretion

The metabolism of aspartame and its metabolic breakdown products in animals, healthy individuals and in PKU subjects has been comprehensively reviewed by Lajtha *et al.* (1994). Aspartame is metabolised by gut esterases and peptidases to three common dietary components - two amino acids (aspartic acid and Phe) and methanol.

Animal studies have demonstrated that the metabolic breakdown products of aspartame are absorbed and metabolised similarly whether they are given alone or derived from aspartame. The extensive presystemic metabolism of aspartame results in little or no parent compound reaching the general circulation.

Initial studies focused on the effects of ingesting single bolus doses of aspartame on plasma aspartate and Phe levels and blood methanol concentrations in normal adults. These studies were done with doses of aspartame approximating current levels of dietary exposure (4 and 10 mg/kg bw), doses representative of premarketing projections of the high level intake and the ADI (34 and 40 mg/kg bw respectively), and 'abuse' doses of 100, 150 and 200 mg/kg bw (Stegink and Filer 1996).

The plasma Phe concentrations in healthy adults administered various doses of aspartame have been compared to values obtained: (1) in the fasting and postprandial state; (2) in individuals who are heterozygous for PKU; and (3) in subjects with various forms of hyperphenylalaninaemia other than PKU (Stegink *et al* 1990; Stegink and Filer, 1996). The data indicated that the plasma Phe concentrations after single bolus doses (ranging between 4 and 50 mg/kg bw) and repeated doses (30 and 69 mg/kg bw given as 3 and 8 divided doses respectively) of aspartame were generally within the normal postprandial range for this amino acid and well below those measured in subjects homozygous for PKU after ingestion of aspartame.

The aspartate component is rapidly metabolised and thus the plasma aspartate concentrations are not significantly elevated following aspartame doses of 34 to 50 mg/kg bw, whereas plasma Phe concentrations may increase depending on dose (Stegink, 1984). Methanol is also rapidly metabolised and blood levels are usually not detectable unless large bolus doses of aspartame (>50 mg/kg bw) are administered.

Genotoxicity and carcinogenicity

The available mutagenicity and long-term carcinogenicity studies on aspartame were recently reviewed by AFSSA (2002). AFSSA noted that:

> "Aspartame is not genotoxic in a reverse mutation test on *S. typhimuriu*m, in two chromosome aberration tests *in vivo* on somatic cells and in Rodent

dominant lethal test on germ cells (JECFA, 1980). Recently, two studies have confirmed the absence of clastogenic potential (Durnev *et a*l., 1995; Mukhopadhyay *et a*l., 2000) of the compound."

The AFSSA report also noted:

> "Trocho *et al.,* (1998) demonstrated that aspartame, radio-labelled on the methanol, induced in the liver stable DNA and protein adducts. According to these authors, the accumulation of these adducts after repeated administration of aspartame could pose problems of toxicity and carcinogenicity in the long term. Besides the fact that aspartame at high doses has never induced liver cancer in rats, Trocho's studies did not identify the radioactivity found in the proteins and DNA. Consequently, the formation of adducts of formaldehyde on the proteins and nucleic acids from aspartame, *in viv*o, remains to be proved (Tephly, 1999)."

As regards the long-term studies, the AFSSA report noted that:

> "In a carcinogenicity study on CD-1 mice (FDA, FR 1981), aspartame administered in feed at doses of 1, 2 and 4 g/kg bw/day for 110 weeks, showed no carcinogenic potential."

> "Three carcinogenicity studies were conducted in Sprague Dawley and Wistar rats. In the first study (1973), post-weaning Sprague Dawley rats were fed doses of aspartame corresponding to 1, 2, 4, 6/8 g/kg bw/day for 104 weeks (6/8 i.e. dose of 6 was increased during the study to 8 g/kg bw/day). In the second study (1974), male and female Sprague Dawley rats, from a two-generation study, were exposed during gestation, lactation and after weaning for 104 weeks, to doses of 0, 2 and 4 g/kg bw/day in their food. The results of these two studies have been widely discussed by the scientific community and the regulatory authorities (FDA). In the first study, the incidence of brain tumours in the treated animals was higher than in the control animals but without any dose-response relationship. In contrast, in the second study the incidence of tumours in the treated rats was lower than in the control group. For these reasons, a third study was conducted under conditions of Good Laboratory Practice in order to ensure the reliability of the experimental data. In this third study (Ishii, 1981), groups of male and female Wistar rats were given doses of aspartame of 0, 1, 2, 4 g/kg bw/day for 104 weeks. Under these conditions, aspartame did not cause any increase in the incidence of brain tumours."

AFSSA concluded as follows on carcinogenicity:

> "Taking into account all the studies that have been conducted, the frequency of spontaneous tumours in laboratory rats, the types of tumours observed and the absence of a dose-response relationship, it was concluded that aspartame had no carcinogenic potential on the brain in experimental animals (FDA FR, 1981-1984; Koestner, 1984; Cornell *et al*., 1984; Flamm, 1997)."

Epidemiological data

Concerning the epidemiological data on brain tumours, the AFSSA (2002) report noted that:

> "In 1996, Olney *et al*. published an article on a possible link between the increase in the frequency of brain tumours in humans and the consumption of aspartame in the United States. Based on the data from the National Cancer Institute (10% of the population) from 1975-1992, the authors concluded that there was a significant increase in the frequency of brain tumours in the mid-1980s, that is to say the period following aspartame came onto the market. The conclusions of this epidemiological study have been criticised by a number of scientists who questioned the methodology, the use of the data and their interpretation (Levy *et al*., 1996; Linet *et al*., 1999; Ross, 1998; Seife, 1999; Smith *et al*., 1998). One of the major criticism is that the authors only took into account the frequency of brain tumours during a selected period (1975-1992). When all the epidemiological data are used (1973-1992) a different conclusion is reached, as the frequency of brain cancers began to increase in 1973 and stabilised from the mid-1980s (Levy *et al*., 1996). Furthermore, Olney *et al.* did not provide any quantitative or qualitative relationship between the exposure of the population to aspartame and the observed frequency of brain tumours. Finally, an increase in the incidence of the tumours can have many causes including, among others, improvements in diagnostic methods (Modan *et al*., 1992)."
>
> "More recently, Gurney *et al*., (1997) published the results of a case-control study on the relationship between the consumption of aspartame and the frequency of brain tumours. The study covered 56 patients affected by tumours in childhood and 94 controls. According to these authors, no relationship could be established between the consumption of aspartame and the frequency of brain tumours."
>
> "In France, data on the incidence of and mortality from brain cancers were supplied by the FRANCIM network (F. Ménégoz *et al*., 2001). These cancers include meninges tumours and tumours of the brain itself. Between 1980 and 1997, the incidence (number of new cases appearing each year) of cerebral tumours was relatively stable in men and showed a slight increase in women. The trend towards an increase in mortality from cancer of the brain and other parts of the nervous system is a longstanding one, as it first appeared in 1950 and continues to the present day, for both sexes. However, during the last decade, mortality in men stabilised and the increase in mortality from brain cancer in women was less pronounced than during the preceding period."
>
> "In France, the epidemiological data from the cancer registers do not enable a definitive indication to be given on a possible aspartame-brain tumour relationship, but they do show that, at the present time, the sale of this food additive in France is not being accompanied by an increase in the frequency of brain tumours or increased mortality from this disease in the general population."

Reproduction and Developmental toxicity

The derivation of an ADI for aspartame by JECFA (1980) and the SCF (1985) included assessment of single- and multi-generation studies in animals that were specifically designed to examine the possible effects of aspartame and its metabolic conversion products on reproduction, and development, including neuro-development.

The data used by JECFA (1980) were discussed in more recent reviews (Kotsonis and Hjelle, 1996; London and Rorick, 1996; Shaywitz, 1997; AFSSA, 2002), but no additional studies were identified which would impact on the no-observed-adverse-effect level (NOAEL).

Neurological effects

Much of the recent interest in the safety of aspartame has explored whether its consumption is linked with neurological effects. Therefore this end point has been given special consideration in this review.

Shortly after the widespread marketing of aspartame, there were a number of anecdotal reports of health effects, which some consumers related to their consumption of aspartame-containing products (Hull, 1999). Most of the earlier complaints and reports of aspartame-related adverse reactions were analysed by experts at the Centres for Disease Control (CDC) in Atlanta on behalf of the FDA, who concluded that there was no symptom complex that could be assigned to the ingestion of aspartame (Janssen and Van der Heijden, 1988; Tollefson, 1988).

A number of complaints were of a neurological or behavioural type (Tollefson, 1988) and these received special consideration, in part because experiments in animals have shown that high doses (1000mg/kg bw and above in rats) can alter the concentrations of neurotransmitters and their precursors within the central nervous system (Lajtha *et al*., 1994).

As regards the potential effect of aspartame on neurotransmitter levels, the underlying hypothesis was that aspartame, as a source of Phe without the other large neutral amino acids (LNAA) (i.e. tryptophan, valine, leucine, methionine, histidine) which compete for transport across the blood-brain barrier, would increase the serum ratio of Phe to the other LNAA, thereby selectively increasing Phe concentrations in brain. It was further suggested that such increased entry of Phe into the brain may result in disturbances in monoaminergic neurotransmission (Wurtman, 1985).

A number of animal studies were conducted to determine whether increases in plasma Phe concentrations secondary to large doses of aspartame may result in changes in

brain concentrations of norepinephrine, dopamine, or serotonin and their metabolites (reviewed by Schomer *et al*., 1996; Lajtha *et al*., 1994). Although effects on neurotransmitter levels were noted in some acute and repeat-dose studies at high doses in rodents, it was apparent that these effects were not consistent or reproducible. For instance, acute doses of up to 2000 mg/kg bw/d and repeated doses of up to 863 mg/kg bw/d (for 28 days) failed to induce significant changes in brain serotonin or dopamine levels and had no effect on seizure severity in rats genetically prone to epilepsy (Dailey *et al*., 1991).

Some changes in neurotransmitter levels in rodents were also identified in some of the older studies on aspartame (Lajtha *et al*., 1994). In mice given aspartame orally at 13,130 and 650 mg/kg bw, increases of 12, 49 and 47% respectively in norepinephrine were found after 3 hours in the hypothalamus; significant increases in norepinephrine in the medulla oblongata (in the low- and high-dose group animals) and corpus striatum (in the low-dose group animals) were also observed (Coulombe and Sharma, 1986). However, these increases were not dose-related and were accompanied by non-significant changes in serotonin levels. Lack of any significant effects on biogenic amine levels, following higher bolus doses (1000 mg/kg bw) of aspartame, have also been reported in both Sprague-Dawley and Fischer 344 rats (Freeman *et al*., 1990).

Glutamic and aspartic acids act as excitatory neurotransmitters at glutamate receptor sites to which aspartic acid also shows affinity. A more recent study evaluated brain glutamatergic receptor kinetics following perinatal exposure to large doses of aspartame (500 mg/kg bw/day) (Reilly and Lajtha, 1995). In this study aspartame in drinking water was administered to Sprague-Dawley rats throughout gestation and lactation. The kinetics of the N-methyl-D-aspartate receptor and total glutamatergic binding in cerebral cortex and hippocampus of the offspring (20-22 days old) were found to be unaffected by perinatal exposure to aspartame. However, statistically significant but reversible reductions in glutamic acid levels in both brain regions and of aspartate in the hippocampus were noted. The same group of workers reported an absence of effects on dopaminergic, adrenergic and serotonergic receptor binding kinetics in adult rat brain with chronic exposure to aspartame (Reilly *et al*., 1989).

Behaviour, Cognition and Mood

Some years ago, it was hypothesised that aspartame, primarily due to its content of Phe, could have an effect on human behaviour, cognition, and possibly on measures of physiological function (Wurtman, 1985). However, no consistent and reproducible effects were observed in a number of older animal studies investigating the effects of aspartame on neurotransmitter levels.

Only a limited number of studies on behavioural aspects in animals have been published in the last ten years. A proportion of these focused on seizure activity but a causal link with aspartame could not be established; no adverse effects on other aspects of behaviour and cognition were reported in experimental animals when aspartame was given at oral dose levels of up to 2000 mg/kg bw/day (Yirmiya *et al*., 1989; Tilson *et al*., 1991; Mullenix *et al*., 1991; Vitulli *et al*., 1996; LaBuda and Hale, 2000; Goerss *et al*., 2000).

A number of anecdotal reports in humans were received by the manufacturers of aspartame in early to mid 1980's relating to a variety of symptoms following the marketing of aspartame in the USA. About two-thirds of these symptoms fell into the neurobehavioural category (Butchko and Stargel, 2001). These consisted mostly of headaches (see below), mood alterations, insomnia, and dizziness. More than 500 reports were received by CDC, and almost half underwent follow-up and evaluation. A post-marketing surveillance system was developed by the NutraSweet company (Butchko and Kotsonis, 1994; Butchko *et al*., 1996), which was followed by scientific research on these neurological symptoms (see below).

A number of scientific studies were carried out in healthy and potentially sensitive individuals, including children, to test whether the consumption of aspartame was associated with behavioural and cognitive changes. The potentially sensitive individuals studied were, heterozygotes for PKU, individuals suffering from depression, Attention Deficit Disorder (ADD), Parkinson's Disease, epilepsy or other suspected seizures. They included double-blind studies in children (Saravis *et al*., 1990; Shaywitz *et al*., 1994) in which no effects were observed on behaviour, mood or learning when aspartame was given as a drink at single and multiple doses of 34 mg/kg bw/day for up to two weeks. The longer term study of Shaywitz *et al.* (1994) examined the effect of aspartame in children with ADD and included an assessment of liver function as well as measurement of plasma levels of amino acids, serotonin and monoamine metabolites. Treatment-related effects were also absent in a study of pre-school children who were given aspartame at 32 mg/kg bw/day and described as sugar sensitive by their parents (Wolraich *et al*., 1994).

A number of double-blind behavioural studies of variable quality in healthy adults, involving single and repeated administrations of aspartame have also been conducted. No treatment-related effects were noted in tests on a range of cognitive parameters in studies employing single administrations of aspartame at doses of up to 60 mg/kg bw/day (Lieberman *et al*., 1988; Lapierre *et al*., 1990; Pivonka and Grunewald, 1990; Stokes *et al*., 1991, 1994). However, it can be argued that single dosing studies employing high amounts of aspartame do not reflect typical consumption patterns.

A number of longer term studies with a double-blind design involving multiple dosing in healthy individuals also failed to highlight any treatment-related adverse effects on

behaviour (Spiers *et al*., 1998; Leon *et al*., 1989). As noted with shorter-term studies, no treatment-related effects on behaviour were noted even when aspartame was tested at 74 mg/kg bw/day for periods extending up to 24 weeks. Although Phe concentrations increased significantly as a result of treatment with aspartame, there were no significant effects noted on behaviour, mood or electroencephalogram (EEG) patterns, nor on a comprehensive battery of clinical laboratory tests. Headache was the most frequently reported adverse effect in placebo- and aspartame-treated groups but there were no significant differences noted between groups.

Several subpopulations of individuals who may potentially be sensitive to aspartame have also been studied. From a double-blind study with a cross-over design in 13 depressed patients, Walton *et al*. (1993) concluded that aspartame (30 mg/kg bw/day for 7 days) increased the frequency and severity of adverse experiences in these individuals. These authors concluded that the use of aspartame in individuals with mood disorder should be discouraged. However, it is difficult to interpret this study since the authors numerically combined unrelated adverse effects to show a statistically significant result in depressed patients and only a limited number of subjects were available for evaluation due to premature termination of the study.

The effect of aspartame on behaviour, cognition and EEG patterns has also been investigated in PKU heterozygotes. Older studies in PKU homozygotes and those heterozygous for the condition have been reviewed elsewhere (de Sonneville and Benninger, 1996, and references therein). Overall, the authors concluded that aspartame did not affect cognitive function and EEG profiles in either the general population or those heterozygous for PKU. In a more recent double-blind study, which included assessment of plasma amino acid levels and EEG patterns (Trefz *et al*., 1994), the subjects ingested aspartame (15 or 45 mg/kg bw/day) and placebo for 12 weeks. The battery of behavioural tests included tests for short-term memory, reaction time and various attention tasks. Although headaches were among the mild adverse symptoms reported, there was no statistically significant difference between treatments. There was a significant rise in Phe in the high-dose group in contrast to the low-dose group and this was also the case for the ratio of Phe to LNAA. However, aspartame had no significant effect on cognitive function or EEG profiles.

Headaches

Headache was one of the more common symptoms that was reported to the FDA and evaluated by the CDC (Janssen and Van der Heijden, 1988; Tollefson, 1988). Several studies were carried out to test the potential association between aspartame intake and the onset of headaches. Although the results of a questionnaire-based study (Lipton *et al*., 1989) and two double-blind out-patient investigations (Koehler and Glaros, 1988; Van Den Eeden *et al*., 1994) employing daily doses of up to 30 mg/kg bw/day indicated a potential association between aspartame intakes and

headache, it was not possible to deduce causality as the effect of diet had not been adequately controlled for and the interpretation of the data was complicated by a high drop out rate and a limited experimental design.

Another study employing a controlled environment, which was also a randomised double-blind placebo-controlled cross-over trial, concluded that aspartame was no more likely than placebo to trigger headaches (Schiffman *et al*., 1987). This study consisted of 40 subjects who complained of aspartame-related headaches. Subjects received aspartame challenges on days three or five at a total dose of 30 mg/kg bw (for a 70 kg person); subjects received placebo on the other days. While 35% of subjects developed headaches while on aspartame, 45% developed headaches while on placebo. In addition, no treatment related effects were detected in blood pressure, or plasma concentrations of cortisol, insulin, glucagon, histamine, epinephrine or norepinephrine. The subjects who had headaches had lower plasma concentrations of norepinephrine and epinephrine just before the development of headache. This study has been criticised for using tightly controlled experimental conditions which did not mimic normal life (Edmeads, 1988), but Schiffman *et al*. (1987) argued that the nature of the study and the primary focus of the questions raised by CDC dictated that they use carefully controlled conditions at a hospital setting.

Epilepsy

The AFSSA (2002) report noted that

> "Among the possible adverse effects of aspartame, researchers have paid particular attention to seizures. Several studies have suggested a relationship between the consumption of large amounts of aspartame and the triggering of epileptic seizures. In an old study (1972), on new-born monkeys (2-3 animals per group) treated with doses of aspartame of 1, 3 and 4g/kg bw/day for 52 weeks, epileptic seizures were recorded at the highest doses, after 218 days of treatment. Thereafter, sporadic convulsions were observed during handling of the animals. These symptoms were identical with those observed in young monkeys treated with phenylalanine."
>
> "In contrast, in a similar study also conducted on young monkeys, no effect was observed at doses of aspartame of 2 and 2.7 g/kg bw/day. The different results observed in the two studies could be explained by differences in the exposure conditions, the food and the state of health of the animals (JECFA, 1980)."
>
> "Walton *et al*. (1993) reported, in a study conducted on 13 patients suffering from depression, that the administration of 30 mg/kg bw/day of aspartame for 7 days caused severe side effects in these patients which led the authors to conclude that the use of this sweetener in depressive patients should be avoided. The same author (Walton, 1986) reported a case of 7 epileptic

seizures and serious behavioural problems in a woman being treated with anti-depressants who ingested large quantities of tea containing aspartame."

"Wurtman (1985) indicated that the administration of aspartame, due to an increase in phenylalanine absorption in the brain, could affect the synthesis of catecholamines or serotonin and cause seizures. He based his findings on three examples of heavy consumers of "diet" drinks and on experimental studies on animals demonstrating that the consumption of aspartame reduced the threshold of sensitivity to chemically induced seizures (Maher *et al*., 1987; Guiso *et al*.,1988; Pinto *et al*., 1988). Finally Camfield *et al.* (1992) demonstrated that aspartame could increase the duration of certain types of epileptic seizure in children."

"The ATIC on the Internet reported a large amount of evidence from people who have identified aspartame as the cause of their health problems and in particular of seizures. These statements should be taken into account but with the reservation that they have not been examined according to any academic standard. They may, however, in certain cases, reflect the hypersensitivity of certain individuals to aspartame or its metabolites. Effects on seizures have been reported with phenylalanine, aspartic acid and methanol but these were under specific conditions (high doses, individual sensitivity, types of seizures, etc.) which are not representative of the general population and of current use of this sweetener in food (Anderson *et a*l., 1996). This causal relationship between aspartame and epileptic seizures has been refuted by a large number of scientists who base their opinions on numerous experimental studies conducted on laboratory animals or on clinical or tolerance studies in humans (Anderson *et al.,* 1996; Gaull, 1985; Rowan *et al.,* 1995; Shaywitz *et al*., 1994; Tollefson *et al*., 1992; 1993; Dailey *et al*., 1991; Zhi *et al*., 1989; Sze, 1989; Tilson *et al*., 1989)."

"The Epilepsy Institute in the USA has also concluded that aspartame is not the cause of epileptic seizures (Congressional Record, June 20, 1986). In the United States various consumer complaints about aspartame have been collected by the Special Nutritionals Adverse Event Monitoring System (SN/AEMS). The sources of these reports were the FDA, federal and local health agencies, consumers and health professionals. Of 2621 side effects reported, concerning 3451 products, some ten cases concerned preparations concerning aspartame (mixtures also containing vitamins, amino acids and various nutritional supplements). The effects reported included seizures, death, nervous and cardiac symptoms, oedema and fever. Still in the United States, the Center for Disease Control assessed 517 complaints about aspartame (1983). The symptoms reported were headaches, mood changes, insomnia, abdominal pain, nausea, convulsions, etc… These symptoms are observed frequently in the general population. Although it might be possible that certain individuals are particularly sensitive to aspartame, these data, which relate to a large number of people, have not enabled any relationship to be demonstrated between the consumption of aspartame and the occurrence of convulsive seizures."

Other effects

Idiosyncratic reactions described as allergic-like (hives, rashes) were reported by some consumers to CDC in response to aspartame (Tollefson, 1988). However, the results of a multi-centre, randomised, double-blind, placebo-controlled, cross-over study in individuals who were convinced they were allergic to aspartame indicated that aspartame and its conversion products are no more likely than placebo to cause urticaria and angio-oedema (Geha *et al*., 1993). This finding was supported by the outcome of another study, which also demonstrated that alleged allergic reactions to aspartame were not reproducible under blinded conditions (Garriga *et al*., 1991). However as with the Geha *et al*. (1993) study, the authors reported major difficulties in enrolling subjects with a history of allergy/hypersensitivity reactions to aspartame.

A number of other studies focused on the effects of aspartame on hunger and food intake (Rolls and Shide, 1996) and in the control of body weight (Kanders *et al*., 1996). Sensory and post-ingestion experience with aspartame was reported by these reviewers not to be associated with increased energy intake or increases in body weight.

Comments

Since the SCF's extensive reviews of aspartame were carried out in 1984 and 1988 (SCF, 1985, 1989), the objective of the present review was to identify any more recent data suggesting there might be additional endpoints requiring evaluation or effects at lower doses than those previously considered. To this end, consideration has been given to aspects of metabolism and toxicity as well as to clinical studies conducted to address the reported adverse effects of aspartame in healthy and potentially sensitive individuals. Consideration has also been given to recent estimates of intake.

Aspartame is unique among the intense sweeteners in that the intake of its component parts can be compared with intakes of the same substances from natural foods. It is clear that the consumption of aspartame represents only a minor source of aspartic acid, Phe or methanol in the diet (Renwick, 1990). The available estimates of intake of aspartame by mean and high level consumers are fairly consistent among European countries, even though different approaches were used for the assessment. They show that intakes in high level consumers, including adults, children, and diabetics of all ages, range up to 10 mg/kg bw/day and thus are unlikely to exceed the current ADI for aspartame of 40 mg/kg bw established by the SCF (1985, 1989).

Studies both in healthy subjects and in PKU heterozygotes confirm the SCF's earlier conclusion (SCF, 1989) that despite the plasma variations in Phe levels following single and repeated administrations of aspartame, Phe levels generally remain within normal postprandial limits.

In 1996, a report suggesting a connection between aspartame and an increase in the incidence of brain tumours in the USA was published (Olney *et al*., 1996). The SCF considered this report and concluded that the data did not support the proposed biphasic increase in the incidence of brain tumours (SCF, 1997). The issue had also been considered earlier by the FDA and by the UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC). The FDA stated that analysis of the National Cancer Institute database on cancer incidence in the USA did not support an association between the use of aspartame and increased incidence of brain tumours (FDA, 1996). The COC agreed that the findings provided no evidence of the proposed biphasic increase in the incidence or either all brain tumours or selected tumour types in the USA during the 1980's and concluded that the data published by Olney *et al*. did not raise any concerns with regard to the use of aspartame in the UK (COC, 1996). The recent review by AFSSA (2002) covered all the original experimental studies and concluded that aspartame and DKP are not genotoxic and that none of the carcinogenicity tests on rodents indicate a relationship between treatment with aspartame and the appearance of brain tumours. The Committee agrees with this conclusion concerning the experimental studies. AFSSA also reviewed more recent publications on the human epidemiological data and concluded that "The epidemiological study by Olney *et al.,* which suggested a link between the placing on the market of aspartame and a possible increase in the frequency of brain cancers in humans, did not provide any scientific evidence to justify or demonstrate a basis for this suggestion; to date it has not been confirmed." (AFSSA, 2002). The Committee agrees with this view and reaffirms its conclusion of 1997 (SCF, 1997).

The Committee has also reviewed the study by Trocho *et al*. (1998), who reported the occurrence of stable DNA and protein adducts in the liver of rats following aspartame administration. The Committee noted that the study used aspartame radiolabelled on the methanol portion, and that during metabolism of aspartame in the gut, radiolabelled methanol will be split off and enter the body's one-carbon pool, with the potential to appear anywhere there is methylation. The Committee therefore agrees with the analysis of Tephly (1999) that formation of DNA adducts has not been demonstrated.

AFSSA (2002) has also evaluated the scientific literature on epilepsy and EEG anomalies and concluded that there is a lack of evidence, based on the current state of knowledge, which would enable a causal link to be established between the consumption of aspartame and the occurrence of epileptic seizures or anomalies on an electro-encephalogram. The Committee agrees with this conclusion of AFSSA.

The present review also addressed the data on other neurological endpoints including cognition, mood and behaviour. Although the data varied in quality, evidence for a causal relationship between aspartame consumption and these endpoints could not be

established. The Committee noted that despite targeted animal studies, no consistent effects of aspartame on neurotransmitters or their precursors have been observed. Studies have also been specifically designed to follow up individuals reporting that they were sensitive to aspartame during post-marketing surveillance, together with studies on individuals, including children, who, because of underlying medical conditions, might be considered sensitive to aspartame. Aspartame administration did not induce changes in behaviour, cognition, mood or learning. The data on headaches received special consideration as this was a commonly reported symptom during post-marketing surveillance. The data on headaches vary in quality, but the one well, controlled double-blind, cross-over trial showed that aspartame was no more likely than placebo to be associated with headaches.

Studies on allergic-like reactions in individuals who themselves reported such reactions to aspartame have not confirmed their occurrence when later studied under controlled conditions.

Conclusion

The Committee concluded that on the basis of its review of all the data in animals and humans available to date, there is no evidence to suggest that there is a need to revise the outcome of the earlier risk assessment or the ADI previously established for aspartame.

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