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Invited Review

Aspartame, low-calorie sweeteners and disease: Regulatory safety and epidemiological issues

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ABSTRACT

Aspartame is a synthetic sweetener that has been used safely in food for more than 30 years. Its safety has been evaluated by various regulatory agencies in accordance with procedures internationally recognized, and decisions have been revised and updated regularly. The present review summarizes the most relevant conclusions of epidemiological studies concerning the use of low-calorie sweeteners (mainly aspartame), published between January 1990 and November 2012. In the Nurses' Health study and the Health Professionals Followup study some excess risk of Hodgkin lymphoma and multiple myeloma was found in men but not in women; no association was found with leukemia. In the NIH-AARP Diet and Health Study, there was no association between aspartame and haematopoietic neoplasms. US case-control studies of brain and haematopoietic neoplasms also showed no association. The NIH-AARP Diet and Health Study and case-control studies from California showed no association with pancreatic cancer, and a case-control study from Denmark found no relation with breast cancer risk. Italian case-control studies conducted in 1991–2008 reported no consistent association for cancers of the upper aerodigestive tract, digestive tract, breast, endometrium, ovary, prostate, and kidney. Low calorie sweeteners were not consistently related to vascular events and preterm deliveries.

1. Introduction

The safety assessment procedure in the case of both natural and synthetic food additives and various contaminants is well established (EFSA, 2011a,b,c). The first phase involves the identification of the hazard, namely the inherent ability of the molecule to cause damage, using *in silico* models and various *in vitro* and *in vivo* experimental conditions. Recently, the European Food Safety Authority (EFSA) recommended a tiered approach for the testing of food additives that balances data requirements, animal welfare and risk, based on proposed uses and exposure assessment (EFSA, 2012). For aspartame, an extensive database of studies conducted to establish safety-in-use is available.

Regardless of the approach used for evaluation, a health-based guidance value, such as the Acceptable Daily Intake (ADI) for a food additive, is derived from the lowest No-Observed-Adverse-Effect Level (NOAEL), or the BenchMark Dose Lower confidence limit (BMDL) obtained in studies conducted according to internationally recognized test protocols. An ADI is set by dividing the NOAEL or BMDL by an uncertainty factor (usually an uncertainty factor of 100 in the case of animal studies).

The potential health impact posed by the presence of chemical hazards in food is estimated by calculating the likelihood that the consumer will be exposed to a substance and quantifying the extent of such exposure in relation to the health-based guidance value. Exposure assessments combine data on concentrations of a chemical substance present in food with data on the quantity of those foods consumed.

The exposure assessment is intended to cover the population, taking into account the variation in food consumption across countries and between various groups of the population, in particular those considered sensitive such as children and the elderly. This process is often highly conservative if, in the calculation of the exposure, the maximum permitted level in food is used together with the maximum amount of food consumed (worst case approach).

In the present paper, we review key aspects of the toxicity of aspartame and the related epidemiologic evidence.

2. Regulatory history

Aspartame is a dipeptide artificial sweetener composed of the amino acids phenylalanine and aspartic acid plus a small quantity

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of methanol (Butchko et al., 2002a,b). It is 200 times sweeter than sucrose. Since its approval, aspartame has been used in more than 6000 different type of products including soft drinks, dessert mixes, frozen desserts and yogurt, chewable multi-vitamins, breakfast cereals, tabletop sweeteners and pharmaceuticals (Rencüzogullari et al., 2004), and consumed by millions of people around the world (Butchko and Stargel, 2001; Fry, 1999).

Following internationally recognized approaches, key regulatory authorities around the world, including the US Food and Drug Administration (FDA, 1984), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (JECFA, 1980), defined health-based guidance values that regulate the use of aspartame in more than 100 countries. In Europe, scientific bodies responsible for advising on the safety of sweeteners were the Scientific Committee for Food (SCF from 1974 until April 2003), the EFSA Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (from 2003 to 2008), and currently the EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS, from 2008 to present).

These advisory bodies and agencies, working independently, have set ADIs for aspartame of 50 mg/kg/day in the U.S. (FDA, 1984), 0–40 mg/kg bw (JECFA, 1980), and 0–40 mg/kg bw in European Union based on the NOAEL of 4 g/kg bw/day in long-term rat studies (SCF, 1985). Further reviews of aspartame data were carried out in 1988, 1997, 2002 by the SCF (SCF, 1989, 1997, 2002) and more recently by EFSA (2005, 2006, 2009, 2011). An ADI of 7.5 mg/kg bw/day 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).

In the USA the estimated intake of aspartame as sweetener is about 1/10 of the ADI (Butchko et al., 2002a,b), and even exposure by heavy aspartame consumers does not exceed 30% of the ADI (Magnuson et al., 2007). To reach an intake equivalent to the ADI, an adult weighting 60 kg would need to drink on a daily basis and throughout his lifespan, 12 cans (about 4 l) of soft drinks containing aspartame at the maximum level permitted. In this unlikely case, of reaching the ADI, the adult would be exposed to a dose that is one-hundredth of the dose without any effect in the animal long-term experiments.

Mean per capita consumption in a U.S. dietary intake survey including 9701 individuals (Magnuson et al., 2007) was 330.17 mg/day (4.85 mg/kg bw/day), and the 90th percentile mean per capita consumption was 704.8 mg/day (10.43 mg/kg bw/day). Additional analysis of the consumption of aspartame when consumed as a food additive showed that the 30–39 years age group consumed the greatest amount of aspartame, while men consume more aspartame than women.

Hence in addition to the prompt review and opinions on studies that reported evidence of toxic effects, such as different types of tumours and pre-term delivery (EFSA, 2006, 2009, 2011a,b,c), in January 2013 EFSA launched a public consultation on its draft scientific opinion on the safety of the artificial sweetener aspartame (EFSA, 2013).

3. Toxicity

The acute toxicity of aspartame, tested in rats, mice, rabbits and dogs, was very low. Sub-chronic toxicity was also low. Aspartame was found to be non-genotoxic in *in vitro* and *in vivo* studies (Rencüzoğullari et al., 2004; Jeffrey and Williams, 2000; Sasaki et al., 2002; NTP, 2005).

Since, after ingestion aspartame, is very efficiently hydrolysed, one of the main concerns derives from the products of hydrolysis, comprising about 50% phenylalanine (50%), aspartic acid (40%) and methanol (10%) (Ranney et al., 1975), and from the presence of degradation products such as 5-benzyl-3,6-dioxo-2-piperazine acetic acid (DPK) and β-aspartame.

These components are then absorbed into the blood and further metabolized. They do not accumulate in the body and are handled by the organism in the same ways as those derived from other foods. The metabolites of aspartame are indeed found in many common foods for example non-fat milk, tomato juice, etc. (Butchko et al., 2002a,b); the diet typically contains about 60 times more aspartic acid than that which could be released from food containing aspartame, on a daily basis. Similarly, the daily diet contains 35 times more phenylalanine than that derived from aspartame-containing foods.

SCF and EFSA considered methanol formation in their safety assessments of aspartame (SCF 1985, 2002; EFSA, 2013) They also considered new studies on rodents (Soffritti et al., 2002), and the suggestion by some authors (Soffritti et al., 2010; Halldorsson et al., 2010) that methanol was responsible for the potential carcinogenicity and toxicity of aspartame. The SCF and later EFSA concluded that the data available do not indicate a genotoxic and carcinogenic concern for methanol derived from aspartame intake. For average consumers of aspartame, the contribution of aspartame to the overall exposure to methanol reached 10% at the maximum in the general population. Methanol is a natural breakdown product of many commonly consumed foods, and is harmless at doses comparable to those likely to be experienced following the consumption of aspartame at doses below the ADI. The methanol produced during the digestion of aspartame is identical to that which is provided in much larger amounts from many fruits, vegetables and their juices. For example, a glass of tomato juice provides about 6 times as much methanol as an equivalent amount of diet beverage sweetened with aspartame. Methanol rapidly enters the portal circulation and is oxidized in the liver to formaldehyde, which is further oxidized to formic acid to give CO_2. Formaldehyde has a half-life of about 1.5 min, therefore there is no accumulation in the tissue.

To evaluate if the phenylalanine derived from aspartame could be of concern in terms of potential developmental effects in humans, the EFSA ANS panel (EFSA, 2013) carried out a risk characterization based on comparison of plasma phenylalanine levels following aspartame administration with plasma phenylalanine levels associated with developmental effects in children born to phenylketonuria (PKU) mothers (patients with a severe reduction of the metabolism of phenylalanine). For PKU patients, it is recommended that plasma levels of phenylalanine should not exceed 360 μM, of which 120 μM is normally obtained from the regular diet. The remaining 240 μM plasma concentration has been calculated to be equivalent to a bolus administration of 103 mg aspartame/kg b.w. in normal subjects, and of 59 mg aspartame/kg b.w., for PKU heterozygous patients (subjects with moderate reduction of the metabolism of phenylalanine) (EFSA, 2013). Consequently, EFSA concluded that exposures at or below the ADI were not of safety concern for the endpoints of reproductive and developmental toxicity in normal and PKU heterozygous population.

In addition to methanol and phenylalanine, the draft EFSA re-evaluation of aspartame also presented a risk evaluation for 5-benzyl-3,6-dioxo-2-piperazine acetic acid (DPK) (a degradation product of aspartame), reaching the conclusion that there are no scientific reasons to modify the ADI for aspartame (EFSA, 2013; Stegink et al., 1995, 1990).

Further safety issues were raised when the European Ramazzini Foundation on Oncology and Environmental Sciences (ERF) released two studies claiming that aspartame can increase various malignancies in rats and concluding that aspartame is a potential carcinogen at normal dietary doses (Soffritti et al., 2005; Soffritti et al., 2006). The studies were a large lifetime rat study using 7 dose groups and 100–150 rat/sex/group and a lifetime rat study

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using only two dose groups and 70 rats/sex/group, but including prenatal exposure to aspartame (Soffritti et al., 2007). The findings claimed an increase in malignant tumour-bearing animals, lymphomas/leukemias (in females), transitional cell carcinomas of renal pelvis and ureter, malignant schwannomas of peripheral nerves in the first study, while an increase in malignant tumour-bearing animals, lymphomas/leukemias (in males) and mammary carcinomas was claimed in the second study. There were many critical points in these studies. First of all, the design of the study where male and female Sprague–Dawley rats were administered aspartame (2000, 400, or 0 ppm) were fed from the 12th day of fetal life until natural death (Soffritti et al., 2007), is in contrast with OECD test guideline 451 and other international protocols (OECD 1981, 2009a,b; FDA, 2000, ICH, 1997) that recommend to use young animals and a duration of the study of 24 months for rodents, representing the majority of the normal life span of the animals (Hayes et al., 2011).

Also the reported doses were questioned, since they are "estimates" based on assuming constant food consumption of 20 g/day and constant body weights of 400 g for each rat from *in utero* life to death. Because during the early growth phase rats consume more food per gram of body weight, this assumption may lead to an inaccurate reporting of the dose treatment (Magnuson and Williams, 2008).

In addition, a high incidence of infectious disease (chronic inflammatory changes) interpreted as lymphomas and/or leukemias acted as a confounding factor; hyperplasia was misdiagnosed as malignancies. Studies in the 1960s demonstrated that the progression of chronic pneumonia in rats resulted in lymphoid neoplasms, and elimination of chronic respiratory disease in rat colonies reduced the incidence of pulmonary lymphoid neoplasia to near zero (Roe, 1998). Rats with pulmonary infections developed lesions in multiple sites earlier than rats free from pulmonary disease. The ERF aspartame study raised a lively debate on the role of infections in the appearance of tumours and in particular on *Mycoplasma pulmonis* and lymphoma. While some authors support that the effects observed in the ERF studies on aspartame are unlikely to be due to infections (Caldwell et al., 2008), on the other hand there is robust evidence that lesions of *M. pulmonis* were not the cause of lymphoma but were plausibly misinterpreted as tumours (Schoeb et al., 2009; Schoeb and McConnell, 2011).

Again, in the ERF studies tumours generally were unrelated to aspartame treatment, showed no dose–response relationships or were of no relevance for humans; thus, after the evaluation of such studies EFSA concluded that there was no reason to revise the ADI of 40 mg/kg b.w. (EFSA 2005, 2006); the U.S. FDA agreed with the EFSA assessment (FDA, 2007).

In 2010 a carcinogenicity study in mice was published by the ERF claiming that aspartame induced cancer of the liver and lungs (Soffritti et al., 2010). EFSA concluded that the study could not be evaluated based on the information given but noted that the type of tumours observed in Swiss mice were irrelevant for human risk assessment and confirmed the previously established ADI for aspartame (EFSA, 2011a,b).

4. Epidemiological data on cancer

Since the 1970s, when experimental studies on animals reported an excess risk of bladder cancer in rodents treated with extremely high doses of saccharin (Weihrauch and Diehl, 2004), a potential role of low-calorie sweeteners in cancer risk has been widely debated. A few epidemiological studies also found some relationships between saccharin and bladder cancer risk in humans (Howe et al., 1977; Bravo et al., 1987; Sturgeon et al., 1994; Andreatta et al., 2008), but most – and the largest – studies found no association (Hoover and Strasser, 1980; Walker et al., 1982; Elcock and Morgan, 1993). Moreover, the carcinogenic effect of saccharin is species-specific, i.e. it is specific to (male) rats administered high doses of sodium saccharin, following the formation of amorphous precipitates in (male) rat urine (Cohen, 1995; Capen et al., 1995). Q4 Therefore, the role of saccharin in bladder cancer risk is not considered in the present report.

With reference to aspartame and other low-calorie sweeteners, most animal studies have failed to show a carcinogenic activity (Weihrauch and Diehl, 2004; National Toxicology Program, 2003; Magnuson et al., 2007). Only two experimental studies on rats treated with variable doses of aspartame and followed until natural death found an excess incidence of malignant neoplasms, including in particular lymphomas and leukemia in females, but not in males (Soffritti et al., 2006, 2007). As discussed earlier, such an apparent excess can be explained by the longer duration of study, as well as by the higher rates of infections of the study animals (EFSA, 2006). A subsequent long-term carcinogenicity study on mice from the same group with transplacental exposure to aspartame found an increased incidence of hepatocellular carcinomas and alveolar/bronchiolar carcinomas in males only (Soffritti et al., 2010).

Below, we review the epidemiological evidence on use of low-calorie sweeteners and beverages (including mainly aspartame) from studies on humans published between January 1990 (i.e., a few years after the use of aspartame became common in several foodstuffs) and November 15, 2012. Table 1 gives the main characteristics and results of the case-control and cohort studies considered.

4.1. Brain cancer

On the basis of an ecologic analysis of data from the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER), Olney et al. (1996) suggested a direct association between aspartame and the incidence of brain cancer. However, the study was later criticized because of uncertainties on brain cancer trends and intrinsic limitations of ecologic investigations (Ross, 1998; Trichopoulos and Schwartz, 1999). It was concluded that there was no connection between aspartame and increased incidence of brain tumours and in 2002 the SCF declared that there was no need to revise the ADI of 40 mg/kg bw following a thorough review of all available safety data (SCF, 2002).

Moreover, the association between aspartame and brain cancer was not evident in animal studies (Butchko, 1997), and subsequent case-control studies on brain cancer found no consistent evidence of an excess risk in relation to aspartame and aspartame-based soft drinks in humans (Gurney et al., 1997; Bunin et al., 2005; Lim et al., 2006).

In particular, a case-control study from the USA based on 56 children with brain cancer found no excess risk either for intake of aspartame from all sources (odds ratio, OR = 1.1, 95% confidence interval, CI, 0.5–2.6) or for diet drinks (OR = 0.9, 95% CI 0.3–2.4) (Gurney et al., 1997). Moreover, this study did not find any relation with age at first consumption, duration, or frequency of consumption for both aspartame from all sources and from diet drinks.

Another US case-control study, which investigated brain cancer in 315 children in relation to the mother's diet during pregnancy, also found no association for consumption of diet soda either in the peri-conception period (OR = 1.3 for $\geqslant$2 soda/day versus <1/month) or in mid-pregnancy (OR = 1.3, 95% CI 0.8–2.4) (Bunin et al., 2005).

With reference to studies on adults, a cohort from the USA (the NIH-AARP Diet and Health Study), based on more than 500,000 subjects and including 315 cases of glioma, found no association with aspartame-containing beverages, the adjusted relative risk

Table 1
Findings from observational studies considering the relation between low-calorie sweeteners and cancer risk.

First author, year	Country; study acronym	Type of study	Cancer	N. cases	Type of sweetener	Category of exposure	OR (95% CI)
Ewertz and Gill, 1990	Denmark	Case-control	Breast	1.486	Artificial sweeteners	Yes versus no	0.94 (0.73–1.20)
Gurney et al., 1997	USA	Case-control	Brain	56	Aspartame	Any intake versus no	1.1 (0.5–2.6)
					Diet drinks		0.9 (0.3–2.4)
Bunin et al., 2005	USA	Case-control	Medulloblastoma and primitive neuroectodermal tumors	315	Diet soda	⩾2 soda/day versus <1/month	1.3 (0.8–2.4)[a]
							1.3 (0.7–2.5)[b]
Lim et al., 2006	USA; NIH-AARP Diet and Health Study	Cohort	Glioma	315	Aspartame-containing beverages	⩾400 mg/day versus none	0.73 (0.46–1.15)
			Hematopoietic	1.888		⩾600 mg/day versus none	0.98 (0.76–1.27)
			Lymphoid	1.279		⩾600 mg/day versus none	0.95 (0.70–1.29)
Gallus et al., 2007	Italy	Case-control	Oral cavity/ pharynx	598	Low-calorie sweeteners	>2 sachets/day versus none	0.77 (0.36–1.64)
			Esophagus	304			1.24 (0.54–2.81)
			Colon	1.225			0.89 (0.65–1.21)
			Rectum	728			0.80 (0.54–1.19)
			Larynx	460			2.34 (1.20–4.55)
			Breast	2.569			0.70 (0.54–0.91)
			Ovary	1.031			0.56 (0.38–0.81)
			Prostate	1.294			1.19 (0.80–1.79)
			Kidney	767			0.96 (0.64–1.42)
Bao et al., 2008	USA; NIH-AARP Diet and Health Study	Cohort	Pancreas	1.258	Diet soft drinks	Highest quintile versus never drinkers	1.11 (0.86–1.44)
Bosetti et al., 2009	Italy	Case-control	Stomach	230	Low-calorie sweeteners	Users versus nonusers	0.80 (0.45–1.43)
			Pancreas	326			0.62 (0.37–1.04)
			Endometrium	454			0.96 (0.67–1.40)
Chan et al., 2009	USA	Case-control	Pancreas	532	Low-calorie cola	⩾1/day versus <1/ month	1.7 (1.2–2.4)
					Low-calorie caffeine-free cola	⩾1/day versus <1/ month	1.1 (0.7–2.0)
					Other low-calorie carbonated beverages	⩾1/day versus <1/ month	1.4 (0.8–2.5)
Schernhammer et al., 2012	USA; NHS and HPFS	Cohort	NHL	1.324	Diet soda	⩾1 serving/day versus none	1.13 (0.94–1.34)
							1.31 (1.01–1.72)[c]
							1.00 (0.78–1.26)[d]
					Aspartame	Highest quintile versus lowest	1.16 (0.93–1.43)
							1.64 (1.17–2.29)[c]
							0.91 (0.69–1.20)[d]
			MM	285	Diet soda	⩾1 serving/day versus none	1.29 (0.89–1.89)
							2.02 (1.20–3.40)[c]
							0.79 (0.45–1.36)[d]
					Aspartame	Highest quintile versus lowest	1.03 (0.62–1.72)
							3.36 (1.38–8.19)[c]
							1.03 (0.62–1.72)[d]
			Leukemia	339	Diet soda	⩾1 serving/day versus none	1.42 (1.00–2.02)
							1.47 (0.92–2.35)[c]
							1.36 (0.80–2.31)[d]
					Aspartame	Highest quintile versus lowest	1.23 (0.80–1.91)
							1.56 (0.79–3.06)[c]
							1.04 (0.58–1.85)[d]

HPFS: health professionals follow-up study; MM: multiple myeloma; NHL: nonHodgkin lymphoma; NHS: nurses' health study.
[a] Peri-conception.
[b] Mid-pregnancy.
[c] Men.
[d] Women.

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(RR) being 0.73 (95% CI 0.46–1.15) for ⩾400 mg/day of aspartame versus no consumption (Lim et al., 2006).

Thus, on the basis of available epidemiologic data there is no evidence linking aspartame and other low-calorie sweeteners to the risk of brain cancer, either in children or adults.

4.2. Hematopoietic neoplasms

The possible association between aspartame and hematopoietic malignancies has been considered in the NIH-AARP Diet and Health Study cohort (Lim et al., 2006), including 1.888 hematopoietic cancers. The overall multivariate RRs of hematopoietic cancers were 1.01 (95% CI 0.84–1.21) for 200–400 mg/day of aspartame, 1.05 (95% CI 0.85–1.29) for 400–600 mg/day, and 0.98 (95% CI 0.76–1.27) for ⩾600 mg/day; corresponding RRs of all lymphoid neoplasms (N = 1.279) were 0.98 (95% CI 0.78–1.22), 1.06 (95% CI 0.82–1.35), and 0.95 (95% CI 0.70–1.29), respectively. The RRs for the highest consumption levels of aspartame were 0.7 (95% CI for Hodgkin's lymphoma, HL), 1.03 (95% CI for multiple myeloma, MM), and between 0.77 and 1.25 for various types of non-Hodgkin's lymphoma (NHL) and leukemia, none of these being significant. Thus, despite the high intake levels considered, no association was observed between aspartame and hematopoietic cancers.

On the basis of data from the Nurses' Health Study (NHS) and of the Health Professionals Follow-up Study (HPFS), including 1.324 NHL, 285 MM, and 339 leukemia, Schernhammer et al. (2012) found no consistent association between consumption of diet soda – including mainly aspartame containing beverages – and NHL or MM risk. Some excess risks of NHL and MM were reported in men only, with RR for ⩾1 serving/day of diet soda versus no consumption of 1.31 (95% CI 1.01–1.72) and 2.02 (95% CI 1.20–3.40), respectively for NHL and MM. Similarly, the RR for the highest quartile of aspartame consumption (⩾143 mg/day for men and ⩾129 mg/day for women) versus no consumption were 1.64 (95% CI 1.17–2.29) for NHL and 3.36 (95% CI 1.38–8.19) for MM in men, in the absence, however, of a significant excess in women and in the two sexes combined. A significant excess risk of NHL in men was reported also for high consumption of regular, sugar-sweetened sodas (RR = 1.66, 95% CI 1.10–2.51). For leukemia, there was no significant association with diet sodas in sex-stratified analyses, and the RR for ⩾1 diet sodas per day was 1.42 (95% CI 1.00–2.02), of borderline significance, in both sexes combined. Moreover, no significant associations with leukemia were observed in relation to aspartame, both in sex-stratified analyses and in the two sexes combined. Thus, the observation of some excess risk of NHL and MM among users of aspartame-containing beverages in men only – in the absence of excess risks for NHL and MM in women and in both sexes combined – and the increased risk of NHL observed in men also in relation to consumption of regular soda, weighs against the existence of a real association between diet soda and NHL.

All taken into-account, the available epidemiological evidence on low-calorie sweeteners – and specifically aspartame – and hematopoietic neoplasms does not support the existence of a consistent association.

4.3. Other cancers

With reference to other cancer sites, a case-control study from Denmark on 1.336 women reported no association between use of artificial sweeteners and breast cancer risk (OR = 0.94, 95% CI 0.73–1.20 for use versus non-use) (Ewertz and Gill, 1990).

In the NIH-AARP Diet and Health Study cohort (Bao et al., 2008), including 1.258 cases of pancreatic cancer, no trend in risk was reported for diet soft drinks, with a multivariate RR of 1.11 (95% CI 0.86–1.44) for the highest quintile of consumption versus never drinkers.

In a population-based case-control study from Northern California on 532 pancreatic cancer cases (Chan et al., 2009), a significant increased risk was reported for low-calorie cola (OR = 1.7, 95% CI 1.2–2.4, for ⩾1/day versus non-drinkers), particularly in men, but no significant associations were reported for low-calorie caffeine-free cola (OR = 1.1, 95% CI 0.7–2.0) or other low-calorie carbonated beverages (OR = 1.4, 95% CI 0.8–2.5).

A study based on an integrated network of case-control studies conducted in Italy between 1991 and 2008 found no association between consumption of low-calorie sweeteners and the risk of various common cancers, including those of the oral cavity and pharynx, esophagus, colorectum, breast, ovary, prostate, and kidney (Gallus et al., 2007). The ORs for >2 sachets-day of low-calorie sweeteners versus no consumption were 0.77 (95% CI 0.36–1.64) for cancers of the oral cavity and pharynx, 1.24 (95% CI 0.54–2.81) for oesophagus, 0.89 (95% CI 0.65–1.21) for colon, 0.80 (95% CI 0.54–1.19) for rectum, 0.70 (95% CI 0.54–0.91) for breast (significantly below unity), 0.56 (95% CI 0.38–0.81) for ovarian (significantly below unity), 1.19 (95% CI 0.801.79) for prostate, and 0.96 (95% CI 0.64–1.42) for kidney cancer. Only for laryngeal cancer a significant increase in risk was observed, with ORs of 2.34 (95% CI 1.20–4.55) for >2 sachets-day. In the same dataset, a similar association with laryngeal cancer was, however, found also for sugar consumption (OR = 1.46, significant for ⩾5 versus <1 teaspoon/day).

A companion study found no relation with low-calorie sweeteners and cancers of the stomach, pancreas and endometrium, adding further evidence on the absence of an adverse effect of low-calorie sweeteners on the risk of common neoplasms (Bosetti et al., 2009). After allowance for various confounding factors, the ORs for ever- versus non-users of artificial or low-calorie sweeteners were 0.80 (95% CI 0.45–1.43) for gastric, 0.62 (95% CI 0.37–1.04) for pancreatic, and 0.96 (95% CI 0.67–1.40) for endometrial cancer. Thus, these data indicate a lack of association between aspartame and other low-calorie sweeteners and the risk of several common neoplasms.

5. Epidemiologic data on vascular events

Information on artificial (and sugar) sweetened beverage consumption and the risk of coronary heart disease (CHD) was provided from the NHS, including 423 cases of CHD among daily users of low-calorie beverages and 301 among daily users of sugar-sweetened beverages (Fung et al., 2009). The study reported RRs of 1.07 (95%, CI 0.96–1.20) for low-calorie beverages and 1.59 (95% CI 0.92–2.74) for sugar-sweetened beverages.

Data from the Northern Manhattan Study showed an association, of borderline significance, between both diet and sugar-sweetened soft drinks and combined vascular events (myocardial infarction, stroke or vascular death combined), with hazard ratios (HR) for daily consumption of 1.59 (95% CI 0.92–2.74) for diet soft beverages and of 1.57 (95% CI 1.05–2.35) for sugar-sweetened beverages (Gardener et al., 2012). These estimates were based on 15 combined events only for diet soft beverages daily users, and 41 combined events for sugar-sweetened beverages daily users. The continuous HRs were 1.03 (95% 1.00–1.07) for diet soft beverages and 1.02 (95% CI 0.99–1.04) for sugar-sweetened beverages. Since diet soft beverages tend to be more frequently used by subjects who are prone to weight gain to control body weight (Dhingra et al., 2007), reverse causation may partly or largely account for the modest and non-significant association between diet soft beverages and vascular disease observed in this study (Gardener et al., 2012).

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The pooled RR from the two studies (Fung et al., 2009; Gardener et al., 2012) – obtained combining the study estimates by meta-analytic methods (Greenland, 1987) – was 1.19 (95% CI 0.84–1.67) for regular (⩾1 times per day) consumption of low-calorie beverages as compared to non-users, and 1.29 (95% CI 1.13–1.48) for regular consumption of sugar-sweetened beverages.

Available epidemiologic data thus indicate that, while use of sugar-sweetened beverages appears to be related to increased risk of cardiovascular disease, consumption of low-calorie beverages is not significantly related.

6. Epidemiological data on preterm delivery

The issue of a possible association between low-calorie sweeteners and the risk of preterm birth was raised in 2010 in a study from the Danish National Birth Cohort (1996–2002), including 59,334 women and a total of 2739 cases of preterm births (<37 weeks) (Halldorsson et al., 2010). The study showed a significant trend of increasing risk for increasing consumption of artificially sweetened carbonated soft drinks, with a RR of 1.78 (95% CI 1.19–2.66) for drinkers of ⩾4 servings/day. The RRs were 1.06 for <1 serving/week, 1.12 for 1–6 servings/week, 1.27 for 1 serving/day; however, the significant RRs for the two highest exposure categories were based on 51 and 27 cases only, i.e., less than 2% and 1% of the cases. Moreover, there was an appreciable difference between carbonated and non-carbonated drinks, with an RR appreciably lower (1.29) among heavy drinkers of artificially sweetened non-carbonated soft drinks (105 cases), and not substantially different from that of heavy drinkers of sugar-sweetened non-carbonated soft drinks (RR = 1.16, 102 cases). No material excess risk was observed up to 2 drinks per day (RR = 1.09) when carbonated and non-carbonated low-calorie drinks were combined (La Vecchia, 2013). A possible effect of low-calorie soft drinks on low birth weight in that study was therefore limited and inconsistent, confounded by the two types of drinks (carbonated and non-carbonated) (La Vecchia, 2010), as well as by residual confounding due to likely differences in baseline characteristics of pregnant women drinking low-calorie versus sweetened, and carbonated versus non-carbonated drinks.

In the Norwegian Mother and Child Study cohort (Englund-Ögge et al., 2012) including 60,761 women and 3281 (5.4%) preterm deliveries (<37 weeks), the RR was 1.01 for <1 serving/week of artificially sweetened beverages versus non-use, 1.09 for 1–6 servings/week, 1.20 for 1 serving/day, 1.01 for 2–3 servings/day, and 1.12 for ⩾4 servings/day. The test for trend was of borderline significance ($p = 0.053$), and there was no linear dose-risk relation, the RR being 1.01 for both women reporting sporadic use (<1 serving/week) and for those with regular use (2–3 drinks per day). A moderate association between frequency of use of sugar sweetened beverages and the risk of preterm deliveries was also observed.

When the main findings of the two studies were pooled (La Vecchia, 2013), the RR was 1.25 (95% CI 1.09–1.43) for ⩾4 servings/day of low-calorie beverages. However, for lower levels of consumption risk estimates were close to unity and, most important, similar risk estimates were found for sugar-sweetened beverages (RR = 1.23, 95% CI 1.06–1.42 for ⩾4 servings/day).

7. Conclusions

Food additive approval is based on a robust hazard and risk characterization, leading to the establishment of an ADI and often a maximum permitted level (MPL) in foods. They must be subjected to a wide range of tests, devised to assess potential risks to the consumer, before they are allowed in food. Tests assess how the additive reacts in the body and also look for any toxic effects at and above the levels the additive is to be used in food. This includes testing to see if there is any chance of genetic damage or cancers being caused by the long-term use of the additive. A formal process for safety evaluation exists at national and international levels for analysing the test data on food additives, setting the ADIs and publishing the results.

In Europe, food additives permitted before 20 January 2009 must go through a new risk assessment by EFSA; furthermore, at any time, the authority can revise its decision on the basis of new data reporting toxicological effects. In the case of aspartame, this process was undertaken almost every year, with the production of a relevant number of opinions and statements, all confirming no safety concerns below the established ADI.

With reference to epidemiologic data, evidence on low-calorie sweeteners – and specifically aspartame – does not support the existence of a consistent association with hematopoietic neoplasms, brain cancer, digestive sites, breast, prostate and several other neoplasms, similarly, low-calorie sweeteners are not related to vascular events and preterm deliveries.

Conflict of interest

The authors declare there are no conflicts of interest.

8. Uncited references

Capen et al. (1999); EC (Commission of the European Communities) (2001); European Commission (2000); Halldorsson (2010); SCF (Scientific Committee on Food) (1984). Q5

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