



**Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission related to
a new long-term carcinogenicity study on aspartame**

Question number EFSA-Q-2005-122

Adopted on 3 May 2006

SUMMARY

The European Food Safety Authority (EFSA) has been asked by the European Commission to assess the carcinogenicity study performed by the European Ramazzini Foundation of Oncology and Environmental Sciences (ERF) on the artificial sweetener aspartame, which was reported in publications in 2005 and 2006. The ERF considered that the results of their study indicate that aspartame is a 'multipotential carcinogenic agent', based on increases in malignant tumour-bearing animals, lymphomas/leukaemias (primarily in female rats), transitional cell carcinomas of the renal pelvis and ureter, also in female rats, and malignant schwannomas of peripheral nerves. EFSA asked its Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) to review the study as a matter of high priority.

Aspartame has been used as a sweetener in foods and as a table-top sweetener for more than 20 years in many countries throughout the world. In Europe, it was first authorised for use by several Member States during the 1980s and was approved for use throughout the European Union in 1994, following thorough safety evaluations by the European Commission (EC) Scientific Committee on Food (SCF).

Aspartame has undergone extensive testing in animals and studies in humans, including four animal carcinogenicity studies conducted during the 1970s and early 1980s. These studies, together with studies on genotoxicity, were evaluated by regulatory bodies worldwide and it

was concluded that they did not show evidence of genotoxic or carcinogenic potential for aspartame. Since its approval, however, the safety of aspartame has been repeatedly questioned, with discussions focusing not only on the safety of aspartame itself, but also on the safety of its breakdown products, aspartic acid, phenylalanine and methanol. All these substances occur naturally in the body. In response to such questions, the SCF undertook a further review of all the data on aspartame in 2002 and concluded that there was no need to revise the outcome of their earlier risk assessment or the previously established Acceptable Daily Intake (ADI) for aspartame, of 40 mg/kg body weight (bw).

The AFC Panel has assessed the new carcinogenicity study, using not only the ERF publications but also a more extensive report provided to EFSA by the ERF at the end of 2005 and further data from the same study provided by ERF in April 2006. The Panel noted that this lifetime study, using more dose groups and more animals per group than conventional carcinogenicity studies, represented a substantial effort and had the potential to be more sensitive to low incidence effects. After its evaluation the Panel considers that the study has flaws which bring into question the validity of the findings, as interpreted by the ERF. In particular, the high background incidence of chronic inflammatory changes in the lungs and other vital organs and tissues and the uncertainty about the correctness of the diagnoses of some tumour types were major confounding factors in the interpretation of the findings of the study.

The Panel's conclusions on the findings of the ERF study include the following:

- The increased incidence of lymphomas/leukaemias reported in treated rats was unrelated to aspartame, given the high background incidence of chronic inflammatory changes in the lungs and the lack of a positive dose-response relationship. It is well-known that such tumours can arise as a result of abundant lymphoid hyperplasia in the lungs of rats suffering from chronic respiratory disease. The most plausible explanation of the findings in this study with respect to lymphomas/leukaemias is that they have developed in a colony suffering from chronic respiratory disease. The slight increase in incidence of these tumours in rats fed aspartame is considered to be an incidental finding of the ERF study and can therefore be dismissed.
- The preneoplastic and neoplastic lesions of the renal pelvis, ureter and bladder occurring primarily in female rats along with renal calcification were most probably treatment-related, at least at the higher doses. It is widely accepted that the effect is a high dose effect of irritant chemicals or chemicals producing renal pelvic calcification as a result of imbalances in calcium metabolism, specific to the rat. The Panel considers that these effects are of no relevance for humans.
- The data on total malignant tumours do not provide evidence of a carcinogenic potential of aspartame. In the opinion of the Panel, the aggregation of all malignant tumour incidences or all malignant tumour-bearing animals for statistical purposes is not justified, given that, as explained above, the lymphomas/leukaemias and the renal tumours should have been excluded from the analysis.
- Concerning the malignant schwannomas, the Panel notes that the numbers of tumours were low, the dose-response relationship, while showing a positive statistical trend in males, was very flat over a wide dose range and there is also uncertainty about the diagnosis of these tumours. The Panel concludes that this finding can only be fully

evaluated following a histopathological peer-review of all relevant slides related to the nervous system in the ERF study and if necessary also from the historical controls.

The Panel takes note of the previous evaluations of aspartame by the SCF and other expert bodies, the negative results of recent carcinogenicity studies carried out by the US National Toxicology Program on aspartame in transgenic mice. The Panel was also informed about a recent epidemiological study carried out by the US National Cancer Institute in which no increase in brain or blood related cancers was reported to be associated with aspartame consumption. The Panel also takes note of the comprehensive studies on the substance indicating that aspartame does not have genotoxic activity.

Kinetic data in humans indicate that dose levels around the acceptable daily intake (ADI) (40 mg/kg bw/d), even when taken as a bolus dose, do not lead to systemic exposure to aspartame. Furthermore, exposure to any of its breakdown products, including methanol or formaldehyde, is negligible.

The Panel considers that no significant new data have emerged since 2002 on aspects other than carcinogenicity and there is therefore no reason to review the previous SCF opinion on aspartame.

The Panel notes that dietary exposure to intense sweeteners in the population has been assessed in a number of European countries. In all of these studies, dietary exposure to aspartame was well below the ADI of 40 mg/kg bw (up to 10 mg /kg bw), even in high consumers.

In summary, the Panel concludes, on the basis of all the evidence currently available from the ERF study, other recent studies and previous evaluations that there is no reason to revise the previously established ADI for aspartame of 40 mg/kg bw.

KEYWORDS

Aspartame, L-aspartyl-L-phenylalanine methyl ester, artificial sweetener, lifetime study, CAS No. 22839-47-0, E 951, intense sweetener