COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

EFSA public consultation on DRAFT Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive.

1. The European Food Safety Authority (EFSA) is undertaking a public consultation on a Draft Opinion of the Panel on Food Additives and Nutrient Sources added to Food (ANS) on the re-evaluation of aspartame (E 951) as a food additive. The draft opinion is appended at Annex 1. In response to the EFSA public consultation, the COT are asked to comment on the opinion.

Introduction.

2. EFSA at the request of the European Commission is systematically re-evaluating the safety of food additives already permitted in the European Union before 2009 based on the priorities, procedures and deadlines that are enshrined in relevant European Regulations.

3. Aspartame (E 951) is an artificial non-saccharide sweetener authorised as a food additive in the EU. Aspartame was previously evaluated by a number of bodies including by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the EU Scientific Committee for Food (SCF), COT and EFSA. JECFA and SCF established an ADI of 40 mg/kg bw/day.

Procedure for developing the draft opinion.

4. The ANS was not provided with a newly submitted dossier and based its evaluation on previous evaluations, additional literature that has become available since those evaluations and the information submitted following public calls for data. The data submitted included the reports of 112 original studies submitted to support the request for authorisation of aspartame in Europe in the early 1980s (http://www.efsa.europa.eu/en/dataclosed/call/110601.htm). The selection criteria to be applied to both the existing published and unpublished scientific literature were agreed at the 28th ANS Plenary meeting on 25-27 October 2011 and were published with the minutes of that meeting. Although many of the studies were old and were not performed according to current standards provided the design of such studies and the reporting of the data were considered appropriate, they were considered in the re-evaluation of the sweetener. The re-evaluation of aspartame also considered the safety of its metabolites (methanol, phenylalanine and aspartic acid) together with its degradation products and impurities (5-benzyl-3,6-dioxo-2-piperazine acetic acid (DKP) and β-aspartame).

5. The process for developing the opinion was that a preparatory document compiling the information in the 112 original studies submitted following public calls for data was prepared for EFSA by an external contractor. A Working Group was formed comprising members of the ANS Panel and external experts to review the literature The Working Group produced a first draft which was discussed by the ANS Panel in July 2012.

6. The ANS agreed an approach to finalising the opinion in September 2012 which required additional work on the mode of action analysis, reviewing data on phentylketonuria (PKU) and pregnancy and aspartame dose-plasma phenylalanine concentration response modelling. This additional work and further drafting was undertaken by EFSA in consultation with a small drafting group comprising ANS Panel members from the Working Group. The ANS Panel reached conclusions in December 2012 and finalised the text of the draft opinion for public consultation.

Involvement of COT members and Secretariat in the EFSA opinion.

7. Professor Harrison was a member of the Working Group until Summer 2012 and involved in the review of the toxicological data in the draft discussed by the Panel in July. Professor Coggon was a member of the Working Group (although his name has been inadvertently omitted from the list of Working Group members on the draft opinion) and involved in the review of the epidemiological data included in the opinion including studies published in Autumn 2012.

8. Dr Gott is Vice Chair of the ANS Panel and a member of both the Working Group and drafting group. As part of the drafting group, Dr Gott was involved in the development of the mode of action analysis, the PKU review, the dose-response modelling and the discussions.

Summary of conclusions in the draft opinion.

9. The main conclusions and rationales in the draft opinion are described briefly below.

10. Studies in experimental animals and humans have shown that after oral ingestion, aspartame is fully hydrolysed within the gastro-intestinal tract. The products resulting from these reactions are methanol and the amino acids aspartic acid and phenylalanine, which are absorbed and enter normal endogenous metabolic pathways. Hydrolysis of aspartame releases a corresponding 10% by weight of methanol. The amount of intact aspartame that enters the bloodstream has been reported as undetectable in multiple studies in various species, including rats, dogs, monkeys and humans. The potential intermediate metabolite, phenylalanine methyl ester, is rapidly broken down to phenylalanine and methanol in the gastro-intestinal tract in monkeys and pigs.

11. Aspartame has been tested for genotoxicity in a number of *in vitro* and *in vivo* studies. Despite a number of limitations, the ANS concluded that the available data do not indicate a genotoxic concern for aspartame.

12. The ANS concluded that chronic toxicity and reproductive and developmental toxicity were the critical endpoints in the animal database. The ANS considered that the evaluation of long-term effects of aspartame should continue to be based upon the animal data. The ANS evaluated three chronic toxicity and carcinogenicity studies in rats and one in mice, the US National Toxicology Program studies in genetically modified mice and the studies from the Ramazzini Institute. The ANS considered that the validity of the findings reported in the Ramazzini Institute studies was questionable because of methodological flaws, a high background incidence of chronic inflammatory changes in the lungs and other organs and tissues, uncertainty about the correctness of the diagnoses of some tumour types, the laboratory's historical control ranges and the US pathology peer reviews of studies from the Ramazzini Institute. Overall, the ANS derived a no observable adverse effect level (NOAEL) of 4000 mg/kg bw/day from the three chronic toxicity and carcinogenicity studies in rats and one in mice.

13. A number of reproductive and developmental toxicity studies were available in the rat, mouse and rabbit. A range of NOAELs from 1000 to 5700 mg/kg bw/day were reported. There were a number of limitations with the studies in rats and rabbits, however the ANS considered they could not be disregarded. Based on a Mode of Action analysis and the weight-of-evidence, the ANS considered that the reproductive and developmental toxicity in animals was due to phenylalanine released from aspartame and concluded that the basis for evaluation of the reproductive and developmental endpoint should be the available data in humans. The ANS decided to base the risk characterisation on comparison of plasma phenylalanine levels following aspartame administration with plasma phenylalanine levels associated with developmental effects in children born from mothers homozygous for phenylalanine hydroxylase mutations (PKU patients).

14. Current clinical guidelines recommend that plasma levels of phenylalanine should be maintained below 360 µM. In calculating a safe level of aspartame exposure (based on plasma phenylalanine concentrations), the ANS assumed the worst-case scenario that intake of aspartame occurs in combination with the meal which leads to circulating plasma phenylalanine concentrations of 120 µM (the maximum plasma concentration based on conservative assumptions of dietary exposure to phenylalanine). The concentration of plasma phenylalanine derived from aspartame was therefore set to 240 µM (i.e. 360 µM minus 120 µM) by the ANS. The aspartame dose-plasma phenylalanine concentration response was modelled based on the bolus administration studies carried out in normal and PKU heterozygotic individuals.

15. In reaching their conclusions the ANS considered the following:

- the conservative assumptions used in the modelling, which would all overestimate peak plasma concentrations
- the available information on adverse effects on development in humans with PKU

- comparison with a concentration of 240 μM to allow for simultaneous ingestion of phenylalanine from other components of the diet in order to not exceed the current clinical guideline of 360 μM
- results of the modelling
- data from repeated oral administration of aspartame in humans
- bolus intakes based on consumption of one litre of soft drink containing aspartame at the maximum permitted level (MPL) of 600 mg/L by a child of 20-30 kg are unlikely to exceed 30 to 20 mg/kg bw, respectively

16. Based on these considerations and evaluations, the ANS concluded that under realistic conditions, phenylalanine plasma levels would not exceed 240 μM in normal or PKU heterozygous individuals. This was considerably below the concentrations at which adverse effects in the fetus are reported and is also below the current clinical guideline (360 μM) for prevention of effects in the fetuses of pregnant PKU patients...

17. The ANS considered that it was currently not possible to include chronic endpoints in the postulated MoA. The ADI previously derived by JECFA and SCF of 40 mg/kg bw/day appeared to be based on the long-term animal studies using the default uncertainty factor of 100. The ANS considered that this remained appropriate for the evaluation of long-term effects of aspartame.

18. The current evaluation was based on analysis of human reproductive and developmental effects of phenylalanine in PKU patients, who are more susceptible than the general and PKU heterozygous population. Therefore, no additional allowance for toxicodynamic variability was required. The modelling of the aspartame dose-phenylalanine concentration response was based on data from PKU heterozygous individuals who at any dose would have a higher plasma phenylalanine concentration than the normal population; therefore, no additional allowance for toxicokinetic variability was required. The ANS concluded that exposures at or below the current ADI were not of safety concern for reproductive and developmental toxicity in humans excluding PKU homozygous individuals.

19. The ANS concluded from the present assessment of aspartame that there were no safety concerns at the current ADI of 40 mg/kg bw/day. Therefore, there was no reason to revise the ADI for aspartame.

20. The ANS emphasised that its evaluation of phenylalanine plasma levels from a dose of aspartame at the ensuing ADI is not applicable to PKU patients. These individuals require total control of dietary phenylalanine intake to manage the risk from elevated phenylalanine plasma levels. Risk managers have recognised this by requiring appropriate labelling to indicate that aspartame is a source of phenylalanine.

21. Conservative estimates of exposure to aspartame made by the ANS for the general population were up to 36 mg/kg bw/day at the 95th percentile. These were below the ADI. The current ADI for DKP is 7.5 mg/kg bw/day. Estimates of DKP

exposure at the ADI for aspartame are below this ADI based on the current specification for DKP in aspartame (1.5%). The ANS noted that high-level exposure estimates for the general population are up to 5.5 mg/kg bw/day at the 95th percentile, which is below the ADI. Finally, conservative estimates of exposure to methanol showed that aspartame-derived methanol contributed to less than 10% of the total mean anticipated exposure to methanol from all sources.

Questions asked of the Committee

22. Members are invited to discuss the draft EFSA opinion and agree comments that should be submitted as part of the consultation.

i. Members are invited to comment on the overall structure and content of the draft EFSA opinion at Annex A. In particular Members are asked whether there are significant papers which have been overlooked and to provide citations for them.

ii. Members are asked whether they consider the mode of action and dose response modelling approaches in the draft opinion appropriate.

iii. Members are asked whether the evidence and arguments described are sufficient to support the conclusions reached in the draft opinion.

iv. Members may wish to make more detailed comments.

COT Secretariat
January 2013

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The draft opinion is available at
http://www.efsa.europa.eu/en/consultations/call/130108.pdf

COT Secretariat
January 2013