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SCIENTIFIC OPINION

Statement on two reports published after the closing date of the public consultation of the draft Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive[1]

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the Panel on Food Additives and Nutrient Sources added to Food (ANS) of the European Food Safety Authority (EFSA) was asked to deliver a scientific opinion on the re-evaluation of aspartame (E 951) as a food additive. After the end of the public consultation on the draft opinion on the re-evaluation of aspartame (E951) (15th February 2013, the cut-off date for the inclusion of new literature in the assessment), two papers were brought to the attention of EFSA as relevant for the evaluation of aspartame. One was the evaluation by Gift et al. (2013) of several studies carried out by the European Ramazzini Foundation (ERF) and the second was the Toxicological Review of Methanol (Noncancer) by the US-EPA. The Panel noted that the Gift et al. (2013) review of the ERF studies is consistent with EFSA's conclusions on the lack of carcinogenic activity of aspartame. The Panel also analysed US-EPA's Toxicological Review of Methanol (Noncancer) in the context of the safety assessment of aspartame. The Panel noted that the combination of the endpoint used, a benchmark dose response (BMR) of 5% and the uncertainty factors applied, resulted in a Reference Dose (RfD) for exogenous methanol of 2 mg/kg bw/day that was overly conservative. This RfD was by definition in addition to dietary intakes of methanol which were included in the background exposure estimates used by the US EPA. Taking all these factors into consideration, the Panel concluded that the toxicological review of methanol by US-EPA and the review by Gift et al. (2013) do not alter the conclusions on the risk assessment of aspartame performed by EFSA. EFSA confirmed the Acceptable Daily Intake (ADI) for aspartame of 40 mg/kg bw/day.

KEY WORDS

aspartame, E 951, methanol, carcinogenicity, lymphoma, EPA, exposure

[1] On request from European Commission, Question No EFSA-Q-2013-00900, adopted on 5 December 2013.

[2] Panel members: Fernando Aguilar, Riccardo Crebelli, Birgit Dusemund, Pierre Galtier, David Gott, Ursula Gundert-Remy, Jürgen König, Claude Lambré, Jean-Charles Leblanc, Alicja Mortensen, Pasquale Mosesso, Agneta Oskarsson, Dominique Parent-Massin, Martin Rose, Ivan Stankovic, Paul Tobback, Ine Waalkens-Berendsen, Rudolf Antonius Woutersen and Matthew Wright. Correspondence: ans@efsa.europa.eu

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SUMMARY

Following a request from the European Commission, the Panel on Food Additives and Nutrient Sources added to Food (ANS) of the European Food Safety Authority (EFSA) was asked to deliver a scientific opinion on the re-evaluation of aspartame (E 951) as a food additive.

After the end of the public consultation on the draft opinion on the re-evaluation of aspartame (E951) (15th February 2013, the cut-off date for the inclusion of new literature in the assessment), two papers were brought to the attention of EFSA as relevant for the evaluation of aspartame. One was the evaluation by Gift et al. (2013) of several studies carried out by the European Ramazzini Foundation (ERF) and the second was the Toxicological Review of Methanol (Noncancer) by the US-EPA (EPA, 2013).

The Panel noted that the Gift et al. (2013) review of the ERF studies is consistent with EFSA's conclusions on the lack of carcinogenic activity of aspartame. The Panel also analysed US-EPA's Toxicological Review of Methanol (Noncancer) in the context of the safety assessment of aspartame. The Panel noted that the combination of the endpoint used, a benchmark dose response (BMR) of 5% and the uncertainty factors applied, resulted in a Reference Dose (RfD) for exogenous methanol of 2 mg/kg bw/day that was overly conservative. This RfD was by definition in addition to dietary intakes of methanol which were included in the background exposure estimates used by the US EPA.

Taking all these factors into consideration, the Panel concluded that the toxicological review of methanol by US-EPA and the review by Gift et al. (2013) do not alter the conclusions on the risk assessment of aspartame performed by EFSA. EFSA confirmed the Acceptable Daily Intake (ADI) for aspartame of 40 mg/kg bw/day (EFSA ANS Panel, 2013).

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010[4]. This Regulation also foresees that food additives are re-evaluated whenever necessary in light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by group of food additives according to the main functional class to which they belong.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU[5] of 2001. The report 'Food additives in Europe 2000[6]' submitted by the Nordic Council of Ministers to the Commission, provides additional information for the prioritisation of additives for re-evaluation. As colours were among the first additives to be evaluated, these food additives should be re-evaluated with a highest priority.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010 the 2003 Terms of References are replaced by those below.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Commission asks the European Food Safety Authority to re-evaluate the safety of food additives already permitted in the Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in the Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

Interpretation of the Terms of reference

Two papers published after the cut-off date of 15 February 2013 for the inclusion of new literature in the re-evaluation of aspartame in 2013, which were alleged to alter the conclusions of the re-evaluation of aspartame were brought to the attention of EFSA. The Panel has considered these in parallel to the opinion on the re-evaluation of aspartame.

[4] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a program for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19-27.

[5] Report from the Commission on dietary food additive intake in the European Union. Commission of the European Communities, COM (2001) 542 final.

[6] Food Additives in Europe 2000. Status of safety assessments of food additives presently permitted in the EU. Nordic Council of Ministers, TemaNord 2002:560.

EVALUATION

1. Introduction

In May 2011, the European Commission asked EFSA to bring forward the full re-evaluation of the safety of aspartame (E 951). Previously planned for completion by 2020, the review of this sweetener is part of the systematic re-evaluation of all food additives authorised in the EU prior to 20th January 2009, as anticipated under Regulation EU 257/2010[7].

EFSA launched a public call for scientific data as well as a thorough literature review. EFSA received access to a large number of both published and unpublished scientific studies and datasets following the call for data, which closed on 30th September 2011. The Authority published the full list of these scientific studies and also made publicly available previously unpublished scientific data including the 112 original documents on aspartame which were submitted to support the request for authorisation of aspartame in Europe in the early 1980s.

The ANS Panel started its risk assessment of aspartame in early 2012. In the course of its scientific evaluation, the Panel found that there were too little data available on 5-benzyl-3,6-dioxo-2-piperazine acetic acid (DKP) and other potential degradation products that can be formed from aspartame in food and beverages when stored under certain conditions. EFSA therefore launched an additional call for data on DKP and other degradation products of aspartame.

All available information was considered for the re-evaluation of the safety of aspartame (E 951) when used as a sweetener added to foods, including its use as a tabletop sweetener. The draft 'scientific opinion on the re-evaluation of aspartame (E 951) as a food additive' was prepared and endorsed for public consultation by the ANS Panel on 20th December 2012.

The public consultation on the draft scientific opinion lasted 6 weeks, from 8th January until the 15th February 2013. EFSA received written comments from interested parties including industry, non-governmental organisations, national agencies and individuals.

The closing date of the public consultation, 15th February 2013, was also the deadline to take into account new literature. After this date, scientific literature was however screened up to 15th November 2013.

This statement describes the analysis by the ANS Panel of two publications published in September 2013 that were brought to the attention of EFSA, namely the Gift et al., 2013 paper and the US EPA Toxicological Review of Methanol (Noncancer) (EPA, 2013). These publications deal with issues that were relevant in the risk assessment process: the methanol carcinogenicity study conducted by the European Ramazzini Foundation (ERF) and the methanol toxicological review by US-EPA. Therefore, the Panel considered it important to analyse these reports and publish their conclusions in a separate document at the same time as the opinion.

2. Scientific Consideration for Evaluating Cancer Bioassays Conducted by the Ramazzini Institute by Gift et al. (2013)

The ERF has conducted a large number of cancer bioassays over the past decades on a number of compounds that are of potential concern to humans because of environmental or dietary exposure. Among these are three bioassays on the sweetener aspartame. According to the ERF, all three studies show that aspartame is a multisite carcinogen that is able to induce tumours in rats and mice. In addition, the ERF has published a study which concluded that the aspartame metabolite methanol also induced tumours in rats.

[7] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a program for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19-27.

In response to perceived problems with the ERF methanol study among other ERF studies, the US EPA appointed a pathology working group (PWG) of the US National Toxicology Program with the task to review five ERF cancer bioassay studies, including the methanol study. The NTP PWG review of the methanol study concluded that the diagnosis of leukaemias could not be confirmed; moreover, these appeared to originate from misinterpreted sites of respiratory infections.

The recent paper by Gift et al. (2013) reports a number of scientific considerations that the authors describe as important for the evaluation of the cancer bioassays conducted by the ERF based on the PWG review and on some general considerations on cancer bioassay designs. This paper is pertinent to the re-evaluation of the safety of aspartame carried out by EFSA. The latter is also cited by Gift et al. (2013).

The paper by Gift et al. (2013) raised the following three main issues.

1. The first issue was the discrepancy in the diagnosis of leukaemias between the ERF and the NTP PWG. While the NTP PWG did not review any of the aspartame studies, the main type of tumours identified by the ERF were the same type of pulmonary leukaemias seen in the methanol study. Gift et al. (2013) state that the diagnosis of leukaemia from the inflammatory sites in the lung is problematic and conclude that '*RI*[8] *bioassay results for cancer endpoints other than respiratory tract lymphoma/leukemia, and inner ear and cranium neoplasms, are generally consistent with those of NTP and other laboratories. Concerns regarding a possible link between respiratory infections and the development of lymphomas have been considered (Caldwell et al. 2008). However, a causal association between infections and lymphomas is less likely than the possibility that RI study results have been misinterpreted due to confounding end-of-life respiratory infections.*' Therefore, the inability of the NTP PWG to confirm the diagnosis of the leukaemias proposed by ERF adds support to the previous interpretation of these findings by EFSA (EFSA, 2006, 2009a; EFSA ANS Panel, 2013) and by the UK Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment (COC, 2006).
2. The second issue was the general concordance in the diagnosis of solid tumours between ERF and the NTP PWG. Pertinent to the aspartame evaluation are several solid tumours described in the ERF studies (e.g. mammary carcinomas, schwannomas, hepatomas). The significance of these tumours in the safety assessment of aspartame had already been addressed by EFSA in 2006, 2009, 2011 and 2013, and in each case, with the conclusion reached that they did not provide evidence for a carcinogenic effect of aspartame.
3. The third issue raised was on the experimental approaches and protocols used by ERF and their advantages and disadvantages over current OECD test guidelines. These had no impact on the current or previous evaluations by EFSA. Even with extended dosing protocols, in utero exposure and increased number of animals per test group there was no evidence that aspartame induced cancer (EFSA, 2006, 2009a, 2011; EFSA ANS Panel 2011a, 2013).

3. Toxicological Review of Methanol (Noncancer) in Support of Summary Information on the Integrated Risk Information System (IRIS) by EPA (2013)

In its assessment of the safety of methanol in the context of the re-evaluation of aspartame, the Panel used the inhalation study in mice by Rogers et al. (1993) to derive a NOAEL for developmental effects, because mice were more sensitive than rats to the developmental toxic effects of methanol. The Panel considered 1000 ppm as the NOAEC in mice in the study of Rogers et al. (1993). A NOAEL for oral exposure was calculated from the studies as described by Alexander et al. (2008) and a corresponding oral dose level of 560 mg/kg bw/day was calculated by the Panel. The overall NOAEL of 560 mg/kg bw/day is considered as conservative by the Panel (EFSA, 2013).

[8] RI, Ramazzini Institute

The United States Environmental Protection Agency (EPA) recently published (available at http://www.epa.gov/iris/supdocs/0305index.html) a Toxicological Review of Methanol (Noncancer) that supports the summary information in their Integrated Risk Information System (summary at http://www.epa.gov/iris/subst/0305.htm). This provides the scientific evidence and rationale for the hazard identification and dose response assessment of the non-cancer effects of chronic exposure to exogenous methanol in addition to background (i.e. dietary and endogenous) levels.

For their Toxicological Review, US-EPA considered the diet to be a contributor to the background levels of methanol primarily from ingestion of fruit and vegetables. Using the daily endogenous production of methanol and dietary exposure estimates from the COT statement in 2011 (COT, 2011) and a sample background distribution derived from relevant study groups the US-EPA estimated that a diet that included fruits and vegetables that naturally contain methanol or have components (e.g., plant pectin) that convert to methanol would not increase methanol blood levels above 2.5 mg/L. Using blood levels of methanol at or below 2.5 mg/L as the background, the US-EPA derived inhalation reference concentration (RfC) and oral reference dose (RfD) for a life-time exposure considered to be without an appreciable risk of deleterious effects to the human population. The US-EPA also developed methanol PBPK models that took into account the dose routes applied, existing toxicokinetic information and the most likely mode of action (MoA) to allow the extrapolation of rat methanol inhalation-route internal dose metrics to human equivalent inhalation exposure concentrations (HECs) or oral exposure doses (HEDs). Using the developmental data from the Rogers et al. (1993) methanol inhalation study and performing a benchmark dose (BMD) analysis using a benchmark response (BMR) of 5% and using physiologically based pharmacokinetic (PBPK) modelling, the US EPA derived a chronic RfD for exogenous methanol of 2 mg/kg bw/day for developmental (skeletal) effects based on increase in cervical ribs/litter in gestationally exposed fetal mice. They also derived from the rat methanol inhalation study by NEDO (1987) a chronic RfD for exogenous methanol exposure of 7.1 mg/kg bw/day for reduced brain weight of gestationally and lactationally exposed neonatal rats at 6 weeks of age.

The Panel analysed US-EPA's Toxicological Review of Methanol (Noncancer) in the context of the safety assessment of aspartame.

The Panel noted that the US-EPA Toxicological Review derived its internal RfD from both the Rogers et al. (1993) and the NEDO (1987) studies by performing a BMD analysis using a BMR of 5% instead of the 10% recommended in the case of quantal data (EFSA, 2009b; EFSA ANS Panel, 2011b). When applying a BMR of 10%, the chronic RfD calculated by US-EPA increased from 2 mg/kg bw/day to 4 mg/kg bw/day. The Panel further noted that the $BMDL_{05}$ computed by the US-EPA was '*divided by 100 to account for uncertainties associated with human variability (UF_H), the animal-to-human extrapolation (UF_A) and the database (UF_D), and to reduce it to a level that was within the range of blood levels for which the human PBPK model was calibrated*' (EPA, 2013). The UF of 3 was used for experimental animal database insufficiencies for which US-EPA argued that the monkey data were not conclusive, and there was insufficient evidence to determine if the primate fetus is more or less sensitive than rodents to methanol-induced teratogenesis (EPA, 2013). The Panel considered that this approach double counted the uncertainty linked to the primate-human extrapolation, once for the animal-to-human extrapolation and a second time for experimental animal database insufficiencies.

The US-EPA derived a background and dietary exposure to methanol of 23 mg/kg bw/day using the upper bound of the combined endogenous and dietary exposures estimated in the UK (COT, 2011). The Panel noted that the combined exposure estimates in the aspartame opinion concerning methanol arising from endogenous production and the normal diet, including aspartame, were lower than the 23 mg/kg bw/day used by US-EPA. One exception was toddlers and children. Their background and dietary exposure to methanol including that from aspartame was higher than the upper bound of 23 mg/kg bw/day (COT, 2011). The Panel noted that the RfD of 2 mg/kg bw/day derived from a developmental endpoint (transient appearance of extracervical ribs after exposure during gestation) would not be applicable to this population group. Instead, the Panel considered that the RfD of 7 mg/kg bw/day based on brain development would be more appropriate for this age group.

The Panel noted that the US EPA acknowledged that '*the inhalation reference concentration (RfC) and oral reference dose (RfD) that are derived in this assessment represent estimates (with uncertainty spanning perhaps an order of magnitude) of daily exposures to the human population (including sensitive subgroups) that are likely to be without an appreciable risk of deleterious effects during a lifetime*.' (EPA, 2013).

CONCLUSIONS

The Panel concluded that the toxicological review of methanol by US-EPA and the review by Gift et al. (2013) do not alter the conclusions on the risk assessment of aspartame performed by EFSA. EFSA confirmed the ADI for aspartame of 40 mg/kg bw/day (EFSA ANS Panel, 2013).

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ABBREVIATIONS

ADI	Acceptable Daily Intake
ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food
BMD	benchmark dose
BMR	benchmark response
bw	body weight
COC	UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
DKP	5-benzyl-3,6-dioxo-2-piperazine acetic acid
EFSA	European Food Safety Authority
EC	European Commission
ERF	European Ramazzini Foundation
EU	European Union
MoA	Mode of Action
NOAEL	No Observed Adverse Effect Level
SCF	Scientific Committee on Food
UK COT	UK Committee on toxicity of chemicals in food, consumer products and the environment
US EPA	US Environmental Protection Agency