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From: ISA <isa@ecco-eu.com>
Sent: Monday, October 24, 2016 8:24 AM
To: P65Public Comments
Subject: 2016 CIC Prioritization
Attachments: ISA Comments_Prop65_ APM_21October2016.pdf; Annex I_EFSA factsheetaspartame.pdf

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Dear Sirs,

Please find enclosed comments from the International Sweeteners Association (ISA) and a related document in response to the 2016 CIC prioritisation.

Thanks you in advance for considering these comments.

Kind regards
Frances Hunt

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By email: P65Public.Comments@oehha.ca.gov

Brussels, 21st October 2016

Dear Sirs,

RE: 2016 CIC Prioritization

The International Sweeteners Association (ISA) is a non-profit organisation with scientific aims representing suppliers and users of low/ no calorie sweeteners. We hereby submit the following comments in response to the public consultation '2016 CIC Prioritization' specifically as regards the low calorie sweetener aspartame.

The ISA would like to draw the Committee's attention to the European Food Safety Authority (EFSA) scientific Opinion on the re-evaluation of Aspartame (E951) as a food additive, published in December 2013, which concluded that aspartame is not a safety concern.¹ The EFSA Opinion on aspartame represents the most comprehensive assessment of the aspartame safety database that has ever been undertaken. As stated in the Opinion, EFSA evaluated all available data to 15th November 2013 including original reports, previous evaluations, additional literature and data made available to EFSA following a public call. Indeed many of the data included in the CIC list of scientific references for aspartame (as published on the OEHHA website) have already been evaluated by EFSA in this comprehensive assessment.

Furthermore we enclose a copy of the EFSA factsheet on aspartame (**Annex I**). This document, which was published by EFSA experts at the time of the Opinion, provides a summary of the safety of aspartame.²

Importantly, at a time when obesity and obesity-related diseases are continuing to rise, low calorie sweeteners such as aspartame are helpful tools in reducing energy intake and body weight.

More information about the ISA and low calorie sweeteners can be found at the following link:
www.sweeteners.org

Thank you for considering these comments.

Best regards,

A handwritten signature in black ink, appearing to read 'F. Hunt'.

Frances Hunt
ISA Secretary General

¹ EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2013. Scientific Opinion on the re-evaluation of aspartame (E 951) as a food additive. EFSA Journal 2013;11(12):3496, 263 pp. doi:10.2903/j.efsa.2013.3496

² This is also available on the EFSA website at the following link:
<http://www.efsa.europa.eu/en/topics/factsheets/factsheetaspartame>

Scientific Opinion on Aspartame

1. What is **aspartame**?
2. What happens to aspartame **after its ingestion**?

3. Is aspartame **safe**?

4. Acceptable **Daily Intake**
5. **Literature** review
6. What happens **next**

Definitions and **attribution**

All food additives authorised in the European Union (EU) undergo a thorough safety assessment. Since January 2002, the European Food Safety Authority (EFSA) has provided independent scientific advice and communication on risks associated with the food chain. As required by EU legislation, EFSA has initiated a programme for the re-evaluation of the safety of all previously authorised food additives. Not only is the re-evaluation of aspartame part of this programme, it is the first time EFSA has carried out a full assessment of the substance.

1. What is **aspartame**?

The food additive aspartame is a low-calorie, artificial sweetener - approximately 200 times sweeter than sugar. It is authorised world-wide, including in the European Union. Aspartame is used in drinks, desserts,

sweets, dairy products, chewing gums, energy-reduced and weight control products, and as a table-top sweetener.

2. What happens to aspartame **after its ingestion**?

Aspartame is made of the two naturally occurring amino acids, phenylalanine and aspartic acid, which are also components of proteins in our body and in food. The phenylalanine in aspartame has been slightly modified by adding a methyl group which gives aspartame its sweet taste.

Proteins in our foods are digested once they reach our intestine. Enzymes break down the ingested proteins into smaller molecules (peptides) and the individual amino acids that make it up. These amino acids are then absorbed by the body. They can then be put back together to produce new proteins in our body or used to generate energy for the body. The exact same process occurs with aspartame.

Aspartame is fully broken down in our gut to aspartic acid and phenylalanine, which are absorbed and enter our body. In addition, the methyl group from the modified phenylalanine is released in the gut to form methanol. Methanol is also absorbed by the body and most of it used to produce energy.

All the scientific studies to date in animals and human volunteers have shown that the breakdown of aspartame in the gut is very rapid and complete. No aspartame has ever been found in the blood or any organ after ingestion. This finding has important implications on how scientists assess the safety of aspartame. Any effect reported to occur in the body following ingestion of aspartame will be caused by one of more of the three constituents, aspartic acid, phenylalanine or methanol.



3. Is aspartame safe?

The safety of aspartame has been tested in hundreds of different studies. Leading scientists from across Europe examined all these studies, which have looked at the short-term and long-term effects of aspartame in experimental animals, including whether aspartame has the potential to cause cancer or neurotoxicity and the effects of aspartame on the reproductive function, on fetal development and on its potential to cause damage to our genes.

One of the challenges faced by EFSA was that many of the studies were old, dating back to the 1970s. This is not unusual with long established food additives. While standards in the design and conduct of studies have markedly developed since then through the introduction of standardised protocols, the consensus opinion of EFSA's experts was that the quality and number of animal studies available was sufficiently high to allow conclusions.

DNA damage and cancer

EFSA's experts could rule out a potential risk of aspartame causing damage to genes and inducing cancer. Included in the risk assessment were the animal studies conducted more recently (including the studies performed by the European Ramazzini Foundation), which did not produce any scientific evidence supporting a carcinogenic effect of aspartame.

Furthermore, there is no evidence to suggest that aspartame induces cancer according to existing large human population studies.

Brain damage and behavioural effects

EFSA's scientific experts also concluded that aspartame does not cause any damage to the brain or cause behavioural effects, such as hyperactivity.

Reproductive and developmental effects

The studies performed in rabbits to identify any possible effects of aspartame on the development of the unborn organism (fetus) showed that the pups were born with smaller weights and in smaller numbers. This was due to an increased number of abortions in the mothers receiving very high doses of aspartame. In the same studies, high doses of the amino acid phenylalanine caused similar effects on pup weight and abortions. This similarity suggests that the effects of high doses of aspartame on rabbit development were mediated by phenylalanine.

Therefore, experts decided that it was more appropriate to use the available body of experimental and medical human data on phenylalanine for the risk assessment of aspartame. EFSA used a "mode of action analysis" (see Box Mode of Action overleaf) to assess the effects of aspartame on reproductive toxicity.

Adverse effects of excessive phenylalanine levels on pregnancy are not unique to animals but also occur in humans who have impaired metabolism of phenylalanine. This disease is called phenylketonuria (PKU) and causes an increased level of phenylalanine in blood which is toxic to the brain. If left untreated, it can affect the development of the fetus and of the brain and cause mental retardation, mood disorders and behavioural problems.

In PKU patients, a restriction of foods rich in protein (meat, fish, eggs, bread, dairy products, nuts and seeds), as well as avoidance of drinks containing aspartame help control blood phenylalanine levels. The developing fetus of women suffering from PKU is particularly sensitive to their mother's phenylalanine levels.

The experts compared blood phenylalanine levels in humans after consuming aspartame, with blood phenylalanine levels associated with developmental effects in children born from PKU mothers.

Current clinical guidelines recommend that to avoid risks to the developing child, levels of phenylalanine in the mother's blood are maintained below 6 mg/dl.

Mild effects have been associated with levels in the mother's blood of 10-13 mg/dl, whilst significant detrimental effects have been associated with levels of 18-20 mg/dl of phenylalanine in the blood (See Box Phenylalanine, overleaf).

In calculating a safe level of aspartame exposure (based on blood phenylalanine concentrations), the scientific experts assumed a scenario that intake of aspartame occurs in combination with a meal (containing naturally occurring sources of phenylalanine), and estimated a worst-case scenario contribution to phenylalanine levels from that meal. They also included many additional conservative assumptions.

Experts modelled the effects of consuming doses of aspartame exceeding several fold the current Acceptable Daily Intake by using data on phenylalanine concentrations in blood following aspartame ingestion. The results of the analysis showed that an adult weighing 60 kg drinking 12 (330ml) cans of a diet soft drink (containing aspartame at the maximum permitted levels of use), every hour would still have a blood phenylalanine concentration below 6 mg/dl as recommended by current clinical guidelines and that is with no reported health effects.

Effects of aspartame's metabolite, methanol

The experts included methanol in its risk assessment of aspartame. Like aspartic acid and phenylalanine, methanol is also naturally present in other foods including fruits and vegetables. By far the largest amount of methanol in humans (some 90% on average) is produced naturally by the body from the consumption of pectin-containing fruits such as apples and citrus fruits.

Methanol is a safety concern when exposure is extremely high, such as from consumption of some home-distilled alcoholic spirits.

Based on the available scientific evidence, EFSA's experts concluded that dietary exposure to methanol including from aspartame would not cause adverse effects as it constitutes only a very small portion compared to the natural production by the body. They also concluded that methanol from aspartame is processed by the body in the same way as methanol derived from other dietary sources.

4. Acceptable Daily Intake

The first safety assessment of aspartame carried out in Europe was published by the Scientific Committee on Food (SCF) in 1984 and an Acceptable Daily Intake (ADI) for aspartame of 40 mg/kg body weight was established. In carrying out the present full re-evaluation of the safety of aspartame, EFSA's experts concluded that the ADI for aspartame

set by the SCF is safe for the population (except PKU patients) and that exposure of consumers to this sweetener is below the ADI. PKU patients are excluded from this evaluation. Labelling of aspartame in order to inform this population of the presence of phenylalanine in aspartame is mandatory.

5. Literature review

The comprehensive review was made possible following two public calls for data which made available a large body of scientific information, comprising both published and previously unpublished data and studies, and exhaustive literature searches. This included the 112 original

documents on aspartame that were submitted to support the request for authorisation of aspartame in the early 1980s. In the interests of transparency, EFSA published the full list of these studies and made available the previously unpublished data.

6. What happens next?

The re-evaluation of aspartame is part of a systematic re-evaluation of all food additives authorised in the EU prior to 20 January 2009. This

scientific advice will be provided to risk managers for their consideration.



Definitions

The Mode of Action

The Mode of Action (MoA) framework was developed by the World Health Organisation's International Programme on Chemical Safety (IPCS) to provide a structured approach to assess the relevance for humans of experimental observations in animals. The MoA requires an understanding of how and why a chemical is toxic in experimental animals. Moreover, it takes into account anatomical, physiological, and biochemical variations among species. This information can be used to assess how the chemical could be toxic in humans.

Phenylketonuria

Phenylketonuria (PKU) is the most common inherited disorder of amino acid metabolism. Due to a functional deficiency of the enzyme phenylalanine hydroxylase (PAH), phenylalanine cannot be metabolised and accumulates in body fluids.

In **PKU**, both copies of the PAH gene are mutated to produce an inactive PAH enzyme. In patients affected by this disease, plasma phenylalanine levels exceed 20 mg/dl without treatment.

Elevated phenylalanine levels in the blood may result in brain damage and affect cognitive function. Unless levels are controlled through dietary or pharmacologic treatment, individuals with PKU almost always suffer from intellectual disabilities.

The overall birth prevalence of PKU in the European population is approximately 1/10,000 although its prevalence varies between different ethnic groups and geographical regions. PKU is usually diagnosed through newborn screening testing that is done shortly after birth on a blood sample (heel prick test, sometimes known as a Guthrie test). The blood sample is sent to a laboratory where levels of phenylalanine are measured. Individuals diagnosed for PKU require a strict adherence to a low phenylalanine diet and medications.

Acceptable Daily Intake

The Acceptable Daily Intake (ADI) is an estimate of the amount of a food additive, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable health risk. The ADI for aspartame is 40 mg/kg body weight.

Attribution

Lay Summary

This lay summary is an explanation of the scientific opinion on aspartame produced by staff in EFSA's Food Ingredients and Packaging (FIP) unit.