International Sweeteners Association

EFSA follow-up meeting on the web-based Public Consultation on Aspartame:

ISA COMMENTS

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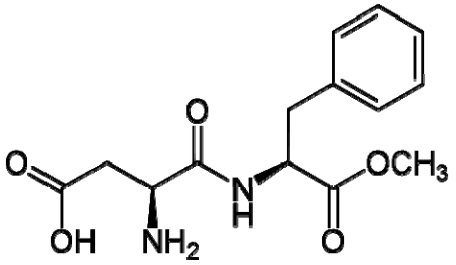
Aspartame



- The safety database on aspartame is one of the most comprehensive and extensive safety databases
- 30 years of widespread use in foods and beverages thus 30 years of safe use
- Aspartame metabolism:

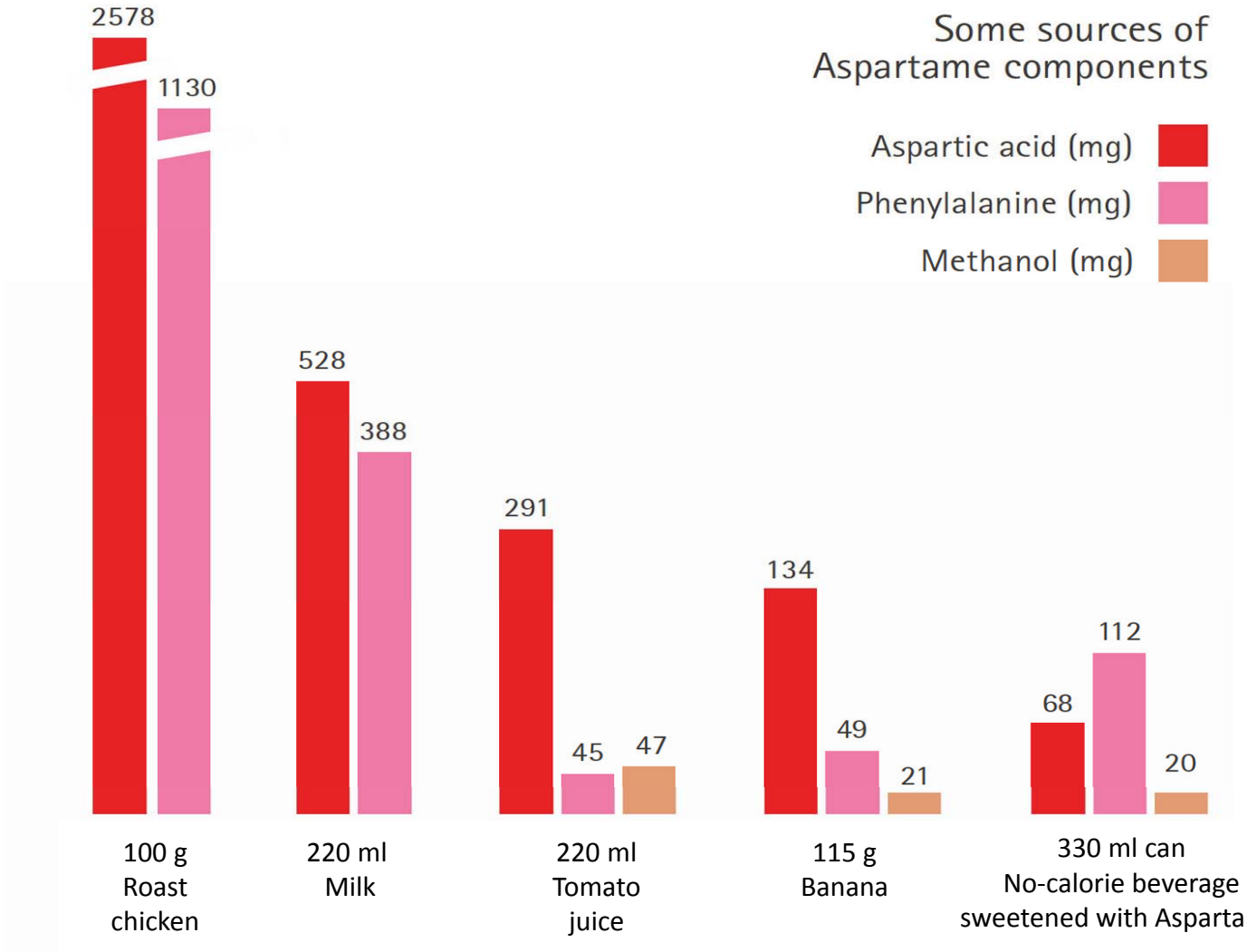
L-aspartyl-L-phenylalanine methyl ester

Hydrolysis in gastro-intestinal tract of animals and humans

Aspartic acid Phenylalanine Methanol

- All components occur naturally in the diet
- All can produce toxicity at very high exposures

Dietary sources of Aspartame components



EFSA Evaluation of Toxicity Studies

- The draft Opinion is the most recent, comprehensive and scientifically sound evaluation of the safety of aspartame.
- The draft Opinion confirms the pivotal role of complete pre-systemic hydrolysis in the safety evaluation.
- The limitations of early studies (compared to current GLP standards) are recognized, but the studies are considered fit for purpose.
- The previous EFSA conclusions on the Ramazzini studies are confirmed.
- The review of methanol shows no human risk from aspartame ingestion.

EFSA Evaluation of Toxicity Studies

- The MOA (mode of action) relating blood levels of phenylalanine, PKU and human risk from aspartame represents a valuable clarification of the reproductive effects reported in animals given large amounts of either phenylalanine or aspartame.
- The MOA raised the possibility of extending the use of blood levels to support inter-species extrapolation, and of developing a chemical-specific adjustment factor (CSAF) (page 104). This proposal was further discussed in the recent ANSES review of the draft EFSA Opinion

Exposure to phenylalanine

"….. the CEAG (ANSES - collective emergency assessment group*) regrets the absence of kinetic data on plasma phenylalanine in animals treated with aspartame as an exposure marker to strengthen hypotheses which would validate the use of human data." (ANSES, 2013)*

- The risk assessment of the phenylalanine component of aspartame is based on the known adverse effects of phenylalanine in humans (in utero neurotoxicity in PKU subjects) related to blood levels in humans.
- The human data are extensive and do not require validation. The data provide a sound basis for risk assessment.
- An interspecies CSAF based on blood levels would be redundant given the human adverse effect data.

Exposure to methanol

Section 3.4 on methanol toxicity. (ANSES, 2013)

- This section is not an evaluation of the draft EFSA Opinion, but raises a number of issues, such as neurotoxicity, that have been evaluated on numerous previous occasions or that are simply speculative without a scientific basis
- There is no consideration of the context of human exposure to methanol arising from aspartame metabolism or of other dietary and metabolic sources of methanol
- There is no mention of other evaluations of methanol or formaldehyde, such as the WHO or COT

Exposure to methanol

- COT (UK) statement on the effects of chronic dietary exposure to methanol, 2011 (Para.68)

Given that

a) Intake of methanol from the diet, including from currently permitted levels of aspartame, is below that which would occur from occupational exposure at the OEL;

b) There is no increase in blood formate either after experimental inhalational exposure at the OEL, or after oral dosing with aspartame at doses well in excess of its ADI; and

c) No adverse health effects have been reported from long-term occupational exposures to methanol at levels below the OEL;

we conclude that exposure to methanol at the levels found in the diet, both naturally occurring and from currently permitted levels of aspartame, would not be expected to result in adverse effects.

Interactions between Aspartame components

"…. the hypothesis of complementary mechanisms of toxicity or synergic action between different compounds in explaining the observed effects in animals, especially the teratogenic effects, may be ventured. "

"Pending the results of further investigations on the mode of action and potential synergies between metabolites of aspartame, it would seem appropriate to:
i. retain the NOAELs derived from studies of reproductive … toxicity, ***or***
ii. …[use]…an additional uncertainty factor (UF_D) ……. " (ANSES, 2013)

- Speculation about possible interactions between the components of aspartame seems to be a primary justification for the use of an additional uncertainty factor in the final conclusions.

Interactions between Aspartame components

- The ANSES comments about possible interactions between the components of aspartame do not take into account recent knowledge on the scientific basis of toxicological interactions.
- Additive or synergistic chemical interactions can arise from
  i. Toxicokinetic interactions – in which one compound interferes with the absorption, metabolism or elimination of the other or
  ii. Toxicodynamic interactions – in which both compounds have the same target(s) for toxicity and one increases the action of the other (usually via a different but complementary mode of action).

Interactions between Aspartame components

Toxicokinetics

- The metabolites of aspartame do not share common metabolic pathways and each would be handled in the body independently, so there is no scientific basis for proposing any additive or synergistic interaction based on kinetics.

Toxicodynamics

- Even at high doses in animal studies the metabolites of aspartame do not share any common high dose effect, apart non-specific body weight changes associated with decreased food intake, so there is no scientific justification for proposing any additive or synergistic interaction based on dynamics.

Amounts of Aspartame components in the diet

- Finally, the ANSES comments do not take into account:

i. that humans ingest much larger amounts of each of the components of aspartame from normal dietary sources, or
ii. that the rise in plasma levels of phenylalanine and aspartic acid following administration of aspartame at doses up to 50 mg/kg bw do not exceed those observed postprandially.

Conclusions

- The amounts of phenylalanine, aspartic acid and methanol in the daily diet exceeds significantly that contributed by aspartame.
- Methanol is formed from natural precursors in fresh fruits and vegetables.
- Aspartame is unique among the intense sweeteners in that the intake of its component parts can be compared with intakes of the same substances from natural foods. (SCF, 2002)