European Food Safety Authority

The Re-evaluation of Aspartame
- draft scientific opinion -

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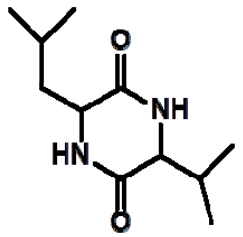
Chair of EFSA's ANS Panel

Follow-up meeting on the web-based public consultation on aspartame
9 April 2013, Bruxelles

Draft Aspartame re-evaluation: Summary (I)

Stability of aspartame

- Degradation of aspartame to DKP in foods and beverages can be extensive (10-20%).
- Safety of DKP was fully evaluated (metabolism, genotoxicity, cancer, developmental toxicity).
- No reason for safety concern for DKP at the current ADI for aspartame.



Draft Aspartame re-evaluation: Summary (II)

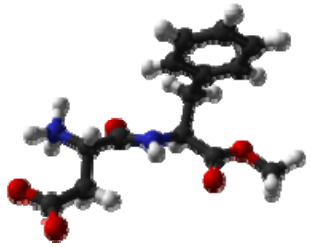
Source of biological and toxicological data

- Original reports of unpublished studies
  - old (1970- 1978), not according to GLP or to OECD guidelines
  - available for earlier evaluations by other scientific bodies
- Decision if consider in the re-evaluation
  - case-by-case basis
  - appropriateness of study design
  - appropriateness of data reporting
- Published literature identified until end of November 2012

Draft Aspartame re-evaluation: Summary (III)

Metabolism of aspartame

- Aspartame is fully degraded in the gut to the natural amino acids phenylalanine and aspartic acid and to methanol. No intact aspartame is absorbed.
- Aspartic acid and Phenylalanine are used for new protein synthesis and some of the formate formed from methanol is used in biosynthetic pathways. Finally Aspartic acid and methanol are metabolised to carbon dioxide which is exhaled.
- Extensive information on aspartame metabolism in humans.



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Toxicity studies on aspartame

Genotoxicity

- The Panel concluded that the available data did not indicate a genotoxic concern for aspartame or its metabolite methanol.

Long-term toxicity and carcinogenicity

- The studies from industry and by the US National Toxicology Program (NTP) on aspartame.
  - The Panel agreed that there was no evidence of aspartame-induced neoplastic or non-neoplastic lesions in any of these studies.
- The studies by Soffritti and co-workers on aspartame and methanol
  - The Panel concluded that due to uncertainties in the tumour diagnosis and health issues with the experimental animals there was insufficient evidence to conclude that aspartame induced tumours in their studies.

Draft Aspartame re-evaluation: Summary (V)

Reproductive and Developmental Toxicity

- The Panel agreed that in the developmental studies on aspartame in rats and rabbits adverse effects were observed.
  - Refusal of feed intake and maternal weight loss associated with abortions, reduced pup weight and malformations (observed only in one study in the rabbit)
- Not clear whether the previous evaluations (FDA, JECFA and SCF) took these effects into account. The Panel decided not to ignore them.

Draft Aspartame re-evaluation: Summary (VI)

Epidemiological studies

- There was no epidemiological evidence for possible associations of aspartame with cancer.

- There may be an association of preterm delivery and consumption of soft drinks, however, irrespective of whether sweetened with sugar or with artificial sweetener.

Mode of Action Analysis (I)

Key Observations

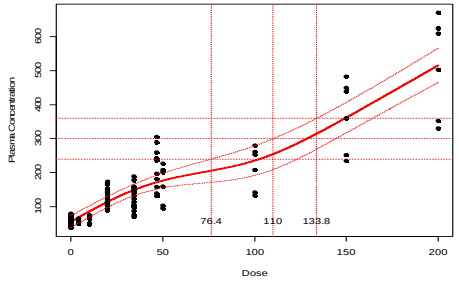
- The metabolite of aspartame, phenylalanine, reproduces the developmental effects of aspartame.

Reported Effect	APM	PHE
Decreased maternal feed intake	✓	✓
Decreased maternal weight	✓	✓
Decreased pup weight	✓	✓
Abortions and resorptions	✓	✓
Malformations	✓	✓

- The effects of aspartame are assumed to be mediated by phenylalanine.
  - Mode of Action analysis for role of phenylalanine in developmental toxicity in animal studies on aspartame is plausible.
  - Phenylalanine at high blood levels is associated with developmental toxicity in PKU patients.

Mode of Action Analysis (II)

- Considerable knowledge about the toxicity of phenylalanine in humans.
  - Clinical guidelines to maintain 'safe' blood phenylalanine levels (<360 µM).
- For the risk characterisation of aspartame for humans information on effects and dose response in PKU patients and human pharmacokinetic data were more appropriate than the results of animal studies of reproductive and developmental toxicity.
- 'Dose-concentration' modeling to predict blood phenylalanine levels from aspartame consumption.
  - Conservative level of 240 µM blood phenylalanine set as a safe level of aspartame exposure.
  - The Panel considered that following even repeated bolus consumption of the current ADI dose in a day would keep blood phenylalanine <240 µM.



Mode of Action Analysis (III)

Uncertainties, inconsistencies and data gaps

➢Animal data

- The gastrointestinal symptoms in the rabbit may be species specific, thus not relevant for humans.
- No measures of plasma PHE levels from the rat and rabbit. reproductive studies constitute a data gap, as contemporary measures would increase confidence in the assumption that PHE was responsible for the effects seen in these studies.

➢Human data

- It was possible to model reliably the peak plasma PHE levels
- Estimates of other pharmacokinetic parameters were limited.

Mode of Action Analysis (IV)

Considerations of need of additional UFs

- Additional allowance for toxicodynamic variability not required.
  - Analysed data were from human reproductive and developmental data of PKU patients who are more susceptible than the general population and PKU heterozygous individuals.
- Additional allowance for toxicokinetic variability not required.
  - The 'dose-concentration' modelling was based on data from PKU heterozygous individuals.

Health-based guidance value for aspartame in the draft re-evaluation

- Combination of long-term studies in rats and MOA analysis for developmental studies was used.
- Chronic endpoints (cancer) could not be incorporated in the postulated MOA.
- The Panel considered that the ADI previously derived by JECFA and SCF of 40 mg/kg bw/day remained appropriate for the evaluation of long-term effects of aspartame.

Refined exposure for aspartame and its metabolites

1. Conservative estimates of exposure to aspartame for the general population were up to 36 mg/kg bw/day (toddlers) at the 95th percentile (for comparison: up to 28 mg/kg bw/day in adults).
2. Estimates of DKP exposure from aspartame consumption are below the ADI of 7.5 mg DKP/kg bw/day even for high level exposure.
3. Conservative estimates of exposure to methanol are less than 10% of the total mean anticipated exposure to methanol from all sources (intake from food and endogenous production)
4. Conservative estimates of exposure to phenylalanine and aspartic acid are less than 10% of the total mean anticipated exposure from dietary protein.

Draft opinion on Aspartame - Conclusions

- Scientific evidence shows that there is no need to revise the current ADI of 40 mg/kg bw.
- Aspartame does not cause cancer or pose any risk to the developing fetus at the current ADI. Aspartame is safe for human consumption. The ADI does not apply to population suffering from medical condition of PKU.
- Exposure estimates to aspartame for the general population were up to 36 mg/kg bw per day which is below the current ADI.
- Estimates of DKP exposure from aspartame consumption up to the current ADI are below the ADI of 7.5 mg DKP/kg bw per day.
- Uncertainties and limitations of the risk assessment are transparently outlined in the opinion.

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Thank you for your comments and attention

Acknowledgement

to members of ANS Panel, WG and FIP Unit