The re-evaluation of sweeteners by the European Food Safety Authority (EFSA)

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Outline of presentation

- Food additives re-evaluation
- Re-evaluation of sweeteners
- Protocol on hazard identification and characterisation
- Working Group Sweeteners
Re-evaluation vs New Application

Re-evaluation

Food additives already permitted before

Food additives authorised after

New applications

20 Jan 2009
Re-evaluation vs New Application

Single mandate

European Commission

EFSA

Manufacturers

Researchers

Food business operators

Other scientific bodies

Calls for data:
Technical, exposure, biological/toxicological

Dossier

• Scientific information

Applicant

EFSA

9 months (+ stop-the-clock) from receipt of a valid application

All available data

• Published literature
• Previous evaluations
• Unpublished reports

20 Jan 2009
Scientific Assessment

Technical part

• Identity of the substance
• Specifications
• Analytical results
• Manufacturing process
• Methods of analysis in food
• Stability and fate in food

Questions

• What is the food additive?
• Are we talking about the same substance that it was assessed at the time of the initial authorisation?
• What are residuals/by products resulting from manufacturing process/storage/interaction with food?

HAZARD IDENTIFICATION
Scientific Assessment

**Biological and toxicological data**

- ADME (absorption, metabolism, distribution, excretion)
- Genotoxicity (in vitro, in vivo)
- General toxicity (short-term, sub-chronic, chronic, carcinogenicity)
- Reproductive toxicity
- Immunotoxicity
- Other studies

**Questions**

- What happens to the additive once it is ingested with the diet? Is it absorbed? To what is it metabolised?
- Are adverse effects identified from the available studies?
- If yes: can a dose response be identified?
- If no: true lack of effect or lack of data?
- Are the data available still reliable compared to today’s standards?

**HAZARD CHARACTERISATION**
Re-evaluation of sweeteners: list of substances

- Sweeteners to be re-evaluated under Regulation (EC) No 257/2010

<table>
<thead>
<tr>
<th>E Number</th>
<th>Food additive(s)</th>
<th>Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>E 420</td>
<td>Sorbitols</td>
<td>E 420 (i) Sorbitol</td>
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<tr>
<td></td>
<td></td>
<td>E 420(ii) Sorbitol syrup</td>
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<tr>
<td>E 421</td>
<td>Mannitols</td>
<td>E 421(i) Mannitol by hydrogenation</td>
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<tr>
<td></td>
<td></td>
<td>E 421(ii) Mannitol manufactured by fermentation</td>
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<tr>
<td>E 950</td>
<td>Acesulfame K</td>
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<tr>
<td>E 951</td>
<td>Aspartame (a)</td>
<td></td>
</tr>
<tr>
<td>E 952</td>
<td>Cyclamates</td>
<td>E 952(i) Cyclamic acid</td>
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<tr>
<td></td>
<td></td>
<td>E 952(ii) Sodium cyclamate</td>
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<tr>
<td></td>
<td></td>
<td>E 952(iii) Calcium cyclamate</td>
</tr>
<tr>
<td>E 953</td>
<td>Isomalt</td>
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</tr>
<tr>
<td>E 954</td>
<td>Saccharin and its Na, K and Ca salts</td>
<td>E 954(i) Saccharin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E 954(ii) Sodium saccharin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E 954(iii) Calcium saccharin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E 954(iv) Potassium saccharin</td>
</tr>
<tr>
<td>E 955</td>
<td>Sucralose</td>
<td></td>
</tr>
<tr>
<td>E 957</td>
<td>Thaumatin</td>
<td></td>
</tr>
<tr>
<td>E 959</td>
<td>Neohesperidine dihydrochalcon</td>
<td></td>
</tr>
<tr>
<td>E 961</td>
<td>Neotame</td>
<td></td>
</tr>
<tr>
<td>E 962</td>
<td>Salt of aspartame-acesulfame</td>
<td>E 965(i) Maltitol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E 965(ii) Maltitol syrup</td>
</tr>
<tr>
<td>E 965</td>
<td>Maltitols</td>
<td></td>
</tr>
<tr>
<td>E 966</td>
<td>Lactitol</td>
<td></td>
</tr>
<tr>
<td>E 967</td>
<td>Xylitol</td>
<td></td>
</tr>
<tr>
<td>E 968</td>
<td>Erythritol</td>
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(a) Aspartame: re-evaluation already completed by EFSA in 2013

Deadline: by end December 2020
Technical/Biological and toxicological data: closed in June 2018
- Procurement contract (ended June 2019): inventory and synthesis

Occurrence data: Call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 7) closed in October 2018

2nd call for Technical data: information on particle size and particle size distribution launched on 13 May 2019 - deadline 13 September 2019
Re-evaluation sweeteners: new literature search

- New procurement contract: started on 28 October 2019

→ to perform extensive literature searches in order to identify and retrieve all related information on both technical and biological/toxicological data on the 15 sweeteners, published after the last evaluation of the SCF or EFSA.
Background information:

As outlined in Regulation (EC) No 257/2010 on the re-evaluation of food additives, in the course of the re-evaluation procedure “EFSA shall:

a) examine the original opinion and the working documents of the Scientific Committee on Food (‘SCF’) or EFSA;

b) examine, where available, the original dossier;

c) examine the data submitted by the interested business operator(s) and/or any other interested party;

d) examine any data made available by the Commission and Member States;

e) identify any relevant literature published since the last evaluation of each food additive”.

Two protocols have been developed:

- One framing the scope of the assessment from the general mandate from EC (for all steps of RA, except exposure)

- One focussing on exposure assessment
Aim:
To define as much as possible beforehand the strategy applied for collecting and selecting data, appraising the relevant evidence, and analysing and integrating the evidence in order to draw conclusions that will form the basis for the scientific opinions.

- Iterative/ Planning phase

✓ Impartiality & methodological rigour along the process
General European population: the following age groups will be considered a priori:

- Infant below 16 weeks of age, only for Mannitol (E 421), which is the only sweetener permitted in foods for infants and young children, as a carrier for vitamin B12
- Infants ≥ 4 to < 12 months
- Toddlers (young children) ≥ 1 to < 3 years
- Other children ≥ 3 to < 10 years
- Adolescents ≥ 10 to < 18 years
- Adults ≥ 18 to < 65 years
- Elderly adults ≥ 65 years

Sub-populations with anticipated high levels of intake (i.e. diabetics) and sub-population with distinct vulnerabilities to the intake of sweeteners (e.g. individuals with inborn errors of phenylalanine metabolism) will be considered during the assessment.
### Sub-questions to be addressed in the hazard identification and characterisation of sweeteners

<table>
<thead>
<tr>
<th>Number</th>
<th>Sub-question</th>
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<tbody>
<tr>
<td>1a</td>
<td>What is the ADME of sweeteners in humans?</td>
</tr>
<tr>
<td>1b</td>
<td>What is the ADME of sweeteners in mammalian animal species?</td>
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<tr>
<td>1c</td>
<td>How do the human and animal ADME data correlate?</td>
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<tr>
<td>1d</td>
<td>Are there any biomonitoring data that contribute to the assessment of ADME?</td>
</tr>
<tr>
<td>2</td>
<td>Do any of the substances included in the assessment show a genotoxic potential?</td>
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<tr>
<td>3a</td>
<td>Is there a dose-response relationship between the dietary exposure to sweeteners and adverse effects in humans (observational and interventional studies)?</td>
</tr>
<tr>
<td>3b</td>
<td>Is there a dose-response relationship between exposure to sweeteners and adverse effects in toxicological studies conducted in experimental animals?</td>
</tr>
<tr>
<td>4</td>
<td>Which could be the potential mode(s) of action for the relationships found, if any, between sweeteners intake and the adverse health outcomes?</td>
</tr>
</tbody>
</table>

1 (a-d), 2 and 4 (ADME, genotoxicity, MoA): narrative approach 3 (a, b) (animal and human studies): systematic review
### Protocol for assessment of hazard identification and characterisation of sweeteners

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Problem formulation</strong></td>
<td>• Is there a dose-response relationship between the dietary exposure to sweeteners and adverse effects in humans/experimental animals?</td>
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<tr>
<td><strong>Extensive Literature Searches</strong></td>
<td>• Open-ended searches; from last SCF/EFSA opinion</td>
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<tr>
<td></td>
<td>• Refinement if needed</td>
</tr>
<tr>
<td><strong>Screening the studies for relevance</strong></td>
<td>• Two steps: Ti/Ab_full text</td>
</tr>
<tr>
<td></td>
<td>• Setting of inclusion/exclusion criteria</td>
</tr>
<tr>
<td><strong>Evaluation of the Risk of Bias/Data extraction</strong></td>
<td>• Adapted from the OHAT rating tool (NTP, 2015); 3 tiers</td>
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<tr>
<td></td>
<td>• Modified from the EFSA BPA protocol, 2017</td>
</tr>
<tr>
<td><strong>Weighing the body of evidence</strong></td>
<td>• Modified version of the OHAT (NTP, 2015) and EFSA Guidance on WoE (2017)</td>
</tr>
<tr>
<td></td>
<td>• Grouping animal/human studies on the same endpoint</td>
</tr>
<tr>
<td><strong>Synthesis of the evidence and uncertainties</strong></td>
<td>• EFSA Guidance on WoE, 2017</td>
</tr>
<tr>
<td></td>
<td>• EFSA Guidance on Uncertainties, 2018</td>
</tr>
</tbody>
</table>
Steps and timeline: protocol for assessment of hazard identification and characterisation of sweeteners

- **2019 March**
  - First presentation at Open FAF Panel

- **2019 April-June**
  - Finalisation of draft protocol

- **Ongoing: 5 July-19 September 2019**
  - Public consultation

- **15 Nov 2019:**
  - Adoption protocol

- **End 2019-2020**
  - Implementation
Steps and timeline: protocol on exposure assessment

- **September 2019**: Protocol endorsed for public consultation by the FAF Panel
- **July 2019**: Protocol endorsed by the Sweetener WG
- **October 2018**: Brainstorming started
- **January 2020**: Protocol adopted by the FAF Panel
- **2020**: Assessment of exposure based on the protocol
Re-evaluation of sweeteners

Impartiality and Methodological rigour along the process

- Plan ahead: protocol development
- Systematic review process

Engagement and transparency along the process

- Open FAF Plenary (26-28 March, 2019)
- Public consultations (2nd part 2019)
- Stakeholder event: food additive re-evaluation with focus on sweeteners, Paris, 3 December 2019:


PRINCIPLES for the scientific assessment process

- Impartiality
- Methodological rigour
- Transparency
- Engagement
Current organisation of Working Group on sweeteners:

- *Sub-group for overall strategy for the assessment*
- *Sub-group for technical part*
- *Sub-group for exposure assessment*

Interaction between the three subgroups
Working Group Sweeteners enlargement

- Will evolve in a fully multidisciplinary WG with all areas of expertise:
  - Chemistry
  - Exposure,
  - Subchronic/chronic toxicity, genotoxicity, reproductive/developmental toxicity, general toxicology, epidemiology, etc....

- Engage with Art.36 organizations (but not only): attract experts to be part of this WG, according to their expertise
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