STATE OF PLAY: THE RE-EVALUATION OF SWEETENERS

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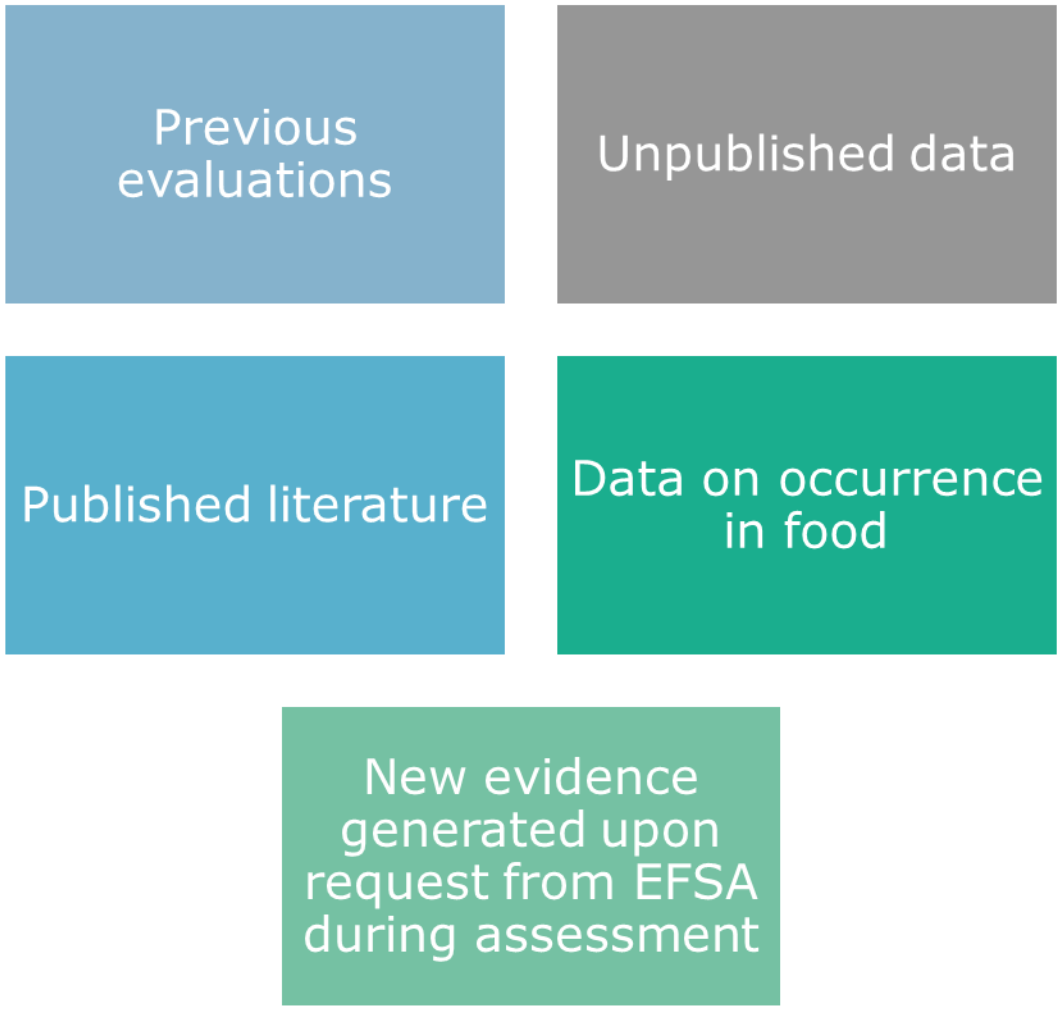
EUROPEAN FOOD SAFETY AUTHORITY

OUTLINE OF PRESENTATION

- What has happened since last stakeholders' event
- Update on sweeteners re-evaluation
- Main issues encountered
- What is coming next

RE-EVALUATION OF SWEETENERS….SINCE LAST STAKEHOLDERS' EVENT (DEC 2019)



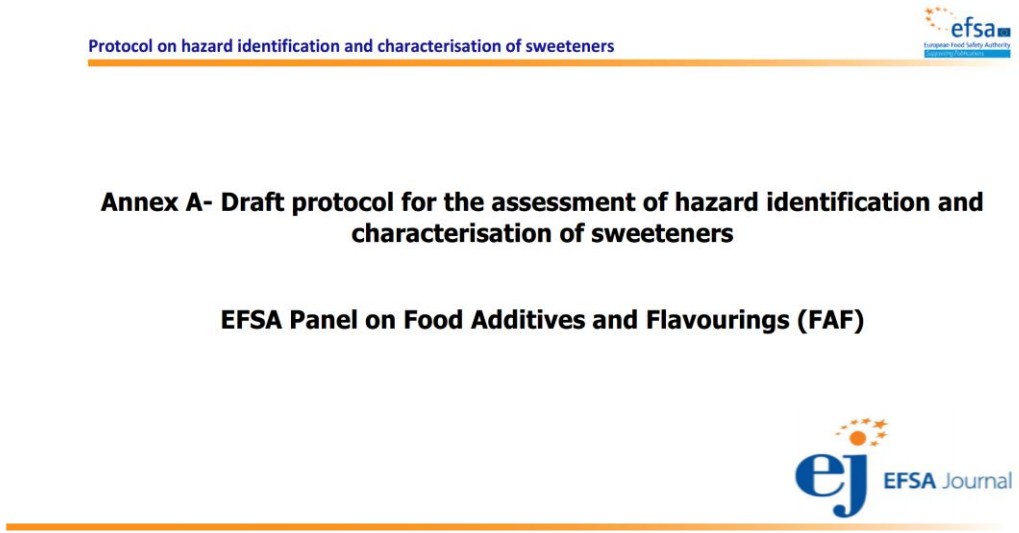
- Criteria for selecting, appraising and integrating in the opinion described in two protocols
  - Hazard identification and characterisation
  - Dietary exposure assessment
- Several calls for data published by EFSA to support re-evaluation

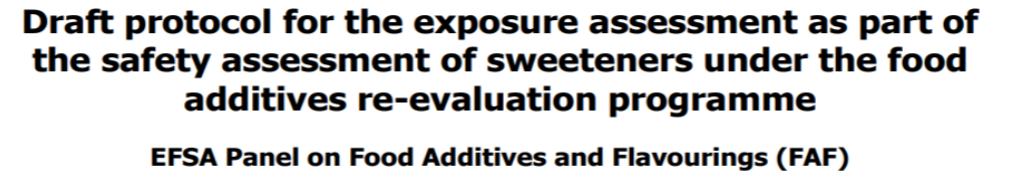
SWEETENERS CALLS FOR DATA

- **Technical/Biological and toxicological data**: closed in June 2018
- **2nd call for Technical data:** information on particle size and particle size distribution closed in February 2020
- **Occurrence data:** (Batch 7) closed in October 2018
  - New call on occurrence data on aspartame (E 951): closed in October 2020
- **Call for technical data** (sucralose and saccharin): closed in February 2022
- **Call for genotoxicity data:** for some of the sweeteners closed in March 2022 or December 2023 (for maltitols and sorbitols)

TWO PROTOCOLS DEVELOPED AND IMPLEMENTED

- Protocol on hazard identification and characterisation of the sweeteners (2020)
- **Revised Protocol** on Hazard Identification and Characterisation of Sweeteners | Zenodo **(2023)**
- Protocol for the exposure assessment of the sweeteners (2020)
- Revised protocol on exposure (**ongoing, 2024**)





EFSA GUIDANCE ON PROTOCOL DEVELOPMENT (SEPTEMBER, 2023)

- Implement fit for purpose protocol development and publication, including problem formulation

EFSA Scientific Committee Guidance Document: (link)

- provide a harmonised and flexible framework for developing or updating protocols for EFSA 'generic mandates': **relevant to all EFSA scientific panels and units**

- **replace the** *"Draft framework for protocol development for EFSA's scientific assessments (EFSA 2020)"*: (link)

SWEETENERS TO BE RE-EVALUATED

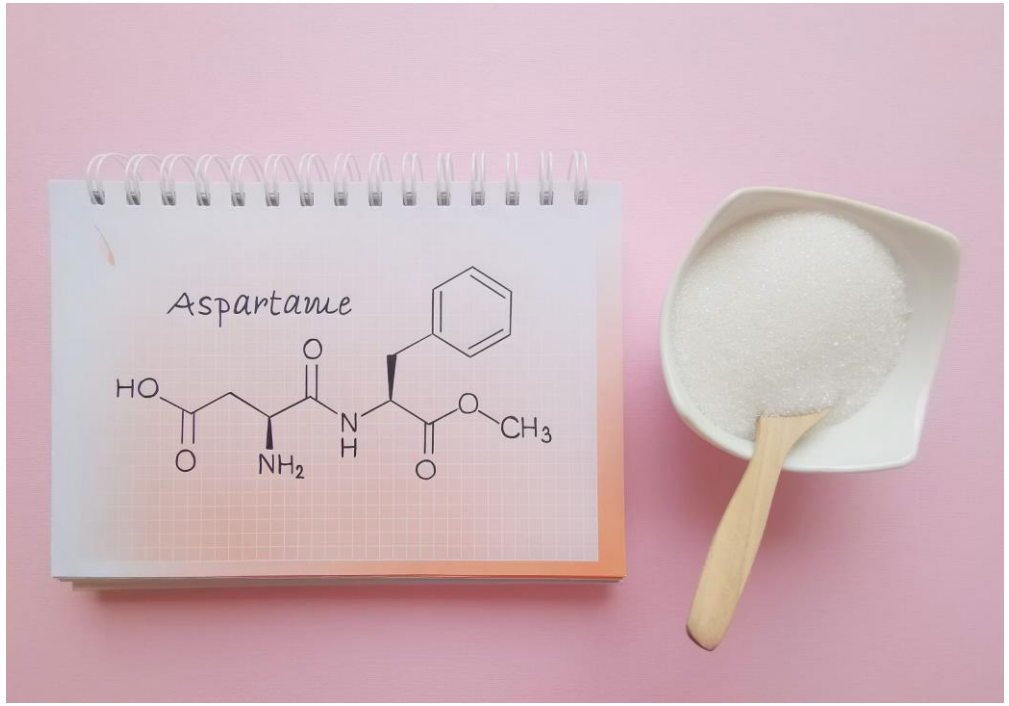
E Number	Food additive(s)	Sub number	Substance
E 420	Sorbitols	E 420 (i) E 420(ii)	Sorbitol Sorbitol syrup
E 421	Mannitols	E 421(i) E 421(ii)	Mannitol by hydrogenation Mannitol manufactured by fermentation
E 950	Acesulfame K		
E 951	Aspartame		
E 952	Cyclamates	E 952(i) E 952(ii) E 952(iii)	Cyclamic acid Sodium cyclamate Calcium cyclamate
E 953	Isomalt		
E 954	Saccharin and its Na, K and Ca salts	E 954(i) E 954(ii) E 954(iii) E 954(iv)	Saccharin Sodium saccharin Calcium saccharin Potassium saccharin
E 955	Sucralose		
E 957	Thaumatin		
E 959	Neohesperidine dihydrochalcone		
E 961	Neotame		
E 962	Salt of aspartame-acesulfame		
E 965	Maltitols	E 965(i) E 965(ii)	Maltitol Maltitol syrup
E 966	Lactitol		
E 967	Xylitol		
E 968	Erythritol		

- 16 sweeteners to be re-evaluated

- 4 of them already re-evaluated (aspartame in 2013)

ASPARTAME (E 951)

- **Aspartame (E 951)** already re-evaluated by EFSA in **2013,** concluding that the sweetener and its breakdown products are **safe** at current levels of exposure;
- **IARC (July, 2023):** classified aspartame as **possibly carcinogenic to humans (Group 2B);**
- **JECFA (July, 2023)**: **no need to revise the ADI** of 40 mg/kg bw/day;
- EFSA is **currently re-evaluating** the safety of the salt of **aspartame-acesulfame (E 962):**
  - In this re-evaluation EFSA will also **consider new evidence on aspartame** that have become available after the publication of the scientific opinion on aspartame in 2013.
  - **no new opinion** on aspartame (E 951) is foreseen at the moment.



SWEETENERS ALREADY RE-EVALUATED

2021

Re-evaluation of thaumatin (E 957) as food additive

Published: 30 November 2021 | **Adopted:** 30 September 2021

Share:

Re-evaluation of neohesperidine dihydrochalcone (E 959) as a food additive

Published: 17 November 2022 | **Adopted:** 29 September 2022

Share:

2022

2023

Re-evaluation of erythritol (E 968) as a food additive

Published: 20 December 2023 | **Adopted:** 25 October 2023

Share:

SWEETENERS COMMUNICATION

Eurotox 2021

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

Federica Lodi, Stefania Barmaz, Ana Campos Fernandes, Consuelo Civitella, Galvin Eyong Ndip, Alessandra Giarola, Ana Maria Rincon, Camilla Smeraldi, Alexandra Tard, Giorgia Vianello, Claudia Roncancio Peña (FIP Unit, Food Additives Team)

INTRODUCTION

This presentation aims at providing an overview on the main steps of the protocol on the assessment of the hazard identification and characterisation of the sweeteners.
According to Regulation (EC) No 1333/2008, all food additives permitted before 20 January 2009 should be subject to a new risk assessment by the European Food Safety authority (EFSA) and a programme for the re-evaluation of approved food additives has been set up by Commission Regulation (EU) No 257/2010.

Sweeteners to be re-evaluated according to this programme include 15 substances: sorbitols (E 420); mannitols (E 421); acesulfame K (E 950); cyclamates (E 952); isomalt (E 953); saccharins (E 954); sucralose (E 955); thaumatin (E 957); neohesperidine DC (E 959); neotame (E 961); salt of aspartame-acesulfame (E 962); maltitols (E 965); lactitol (E 966); xylitol (E 967) and erythritol (E 968).

METHODOLOGY

Data: In order to gather all information available, EFSA launched calls for data to invite the interested business operators to submit all data available (covering both technical and biological/toxicological data as well as occurrence data). These data are complemented with any relevant literature published since the latest opinions of the Scientific Committee on Food (SCF) or EFSA.

Methodology: To ensure impartiality and methodological rigour along the process, two protocols have been developed in line with the principles of the EFSA PROMETHEUS project (PROmoting METHods for Evidence Use in Scientific assessments: one on the assessment of the hazard identification and characterisation of sweeteners, and the other one focusing on the exposure assessment. Both protocols underwent a public consultation period and the comments received were considered in the finalisation of the two protocols.

Figure 1 highlights the main features of the protocol on hazard identification and characterisation, summarising the different steps to be applied during the risk assessment.

Problem formulation	•Is there a dose-response relationship between the dietary exposure to sweeteners and adverse effects in humans/experimental animals?
Extensive Literature Searches	•Open-ended searches; from last SCF/EFSA opinion •Refinement if needed
Screening the studies for relevance	•Two steps: TI/Ab_full text •Setting of inclusion/exclusion criteria
Evaluation of the Risk of Bias/Data extraction	•Adapted from the OHAT rating tool (NTP, 2015;2019); 3 tiers •Modified from the EFSA BPA protocol, 2017
Weighing the body of evidence	•Modified version of the OHAT (NTP, 2015; 2019) and EFSA Guidance on WoE (2017) •Grouping animal/human studies on the same endpoint
Synthesis of the evidence and uncertainties	•EFSA Guidance on WoE, 2017 •EFSA Guidance on Uncertainties, 2018

RESULTS

The protocol on hazard identification and characterisation of sweeteners defines the strategy to be applied during the risk assessment: addressing the questions to be answered (problem formulation), collecting (Extensive literature search) and selecting data (screening the studies for relevance), appraising the relevant evidence (evaluation of the risk of bias and data extraction), and analysing and integrating the evidence (weighing and synthesis of the body of evidence) in order to draw conclusions that will form the basis for the scientific opinions.
Figure 2 illustrates the sub-questions to be addressed in the protocol for assessment of the hazard identification and characterisation of sweeteners. In this respect, question 1 a,b,c,d, 2 and 4 are addressed following a narrative approach, whereas question 3a and 3b are addressed using a systematic review approach.

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

Figure 3 reports the outcome of the evaluation of the Risk of Bias (RoB) as an example of the implementation phase (RoB step) of the protocol on hazard identification and characterization applied in the re-evaluation of thaumatin (E 957). The questions addressed to assess the RoB in the human and animal studies are presented in Table 8 and Table 9 of the protocol. For each question, the response are: Definitely low risk of bias (++), Probably low risk of bias (+), Probably high risk of bias (-), Definitely high risk of bias (--). Studies are classified into Tiers from 1 to 3, corresponding to decreasing levels of internal validity.

In order to analyse and integrate the data, a weight of evidence (WoE) analysis for different health outcomes, grouped by endpoint as appropriate, is performed. The confidence in the evidence for the absence or presence of adverse effects in animal and human studies are assessed in a WoE approach. For each health outcome, the initial confidence rating is downgraded (based on RoB, unexplained inconsistency, relevance of endpoints and/or imprecision) or upgraded (based on magnitude of effect, evidence of dose-response and consistency across studies). The overall confidence in the body of evidence is rated as "high", "moderate", "low" or "very low". The confidence rating is finally translated into levels of evidence for the presence of health effect as "high", "moderate" ,"low" or "inadequate" (adapted from NTP-OHAT 2019).

CONCLUSIONS

The main features of the protocol on hazard identification and characterization, summarising the different steps to be applied during the risk assessment, as well as some developments on the implementation phase have been presented. The protocol development is an iterative process which should always ensure the possibility for adapting and responding to new reality, therefore flexibility should be maintained along the whole process. Nevertheless, any changes or deviations from the protocol established upfront the assessment, should be documented and justified.

Acknowledgments

EFSA wishes to acknowledge the members of the Panel on Food Additives and Flavourings (FAF) and the members of the Working Group on Sweeteners as well as all European competent institutions, Member State bodies and other organisations that provided data on these food additives.

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efsa European Food Safety Authority

One Conference 2022

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

Federica Lodi, Stefania Barmaz, Consuelo Civitella, Alessandra Giarola, Ana Maria Rincon, Antonio Rivas Cornejo, Camilla Smeraldi, Alexandra Tard, Giorgia Vianello, Riccardo Vriz, Claudia Roncancio Peña

Introduction

A programme for the re-evaluation of approved food additives (before January 2009) has been set up by the Commission Regulation (EU) No 257/2012. Among these, food additives used as sweeteners are also included. This presentation provides an overview of the EFSA's work on the re-evaluation of sweeteners, illustrating the main steps of the developed protocol for the assessment of the hazard identification and characterisation of sweeteners and how EFSA has engaged with stakeholders along this process.

Figure 1: Principles for the scientific assessment process

Methodology

EFSA launched calls for data to invite the interested parties to submit technical, biological/toxicological and occurrence data available. Two protocols have been developed to ensure impartiality and methodological rigour along the process: one on the hazard identification and characterisation of sweeteners and one on the exposure assessment. The other pillars of the risk assessment, engagement, openness and transparency, have been also implemented through public consultations, plenary meetings open to observers and a stakeholder event (Figure 1).

Results

The protocol on hazard identification and characterisation of sweeteners defines upfront the strategy to be applied during the safety assessment: addressing the questions to be answered (problem formulation), collecting (extensive literature search) and selecting data (screening the studies for relevance), appraising the relevant evidence (evaluation of the risk of bias and data extraction), and analysing and integrating the evidence (weighing and synthesis of the body of evidence). The main features of this protocol, summarising the different steps to be applied during the risk assessment, are presented (Figure 3). In order to analyse and integrate the data, a weight of evidence (WoE) analysis for different health outcomes, grouped by endpoint as appropriate, is performed.

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E 420	Sorbitols	E 420 (i) E 420(ii)	Sorbitol Sorbitol syrup
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E 968	Erythritol		

Figure 2: The list of sweeteners to be re-evaluated

Problem formulation	•Is there a dose-response relationship between the dietary exposure to sweeteners and adverse effects in humans/experimental animals?
Extensive Literature Searches	•Open-ended searches; from last SCF/EFSA opinion •Refinement if needed
Screening the studies for relevance	•Two steps: TI/Ab_full text •Setting of inclusion/exclusion criteria
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Synthesis of the evidence and uncertainties	•EFSA Guidance on WoE, 2017 •EFSA Guidance on Uncertainties, 2018

Figure 3: Main steps of the protocol on hazard identification and characterization of sweeteners

Conclusions

The confidence in the body of evidence (integration of animal and human data) is translated into a level of evidence for the absence or presence of a health effect. The protocol development is an interactive activity which should always ensure the possibility for adapting and responding to new reality, therefore flexibility should be maintained along the whole process. Nevertheless, any changes or deviations from the protocol, established upfront the assessment, should be documented and justified.

Aknowledgments

EFSA wishes to acknowledge the members of the Panel on Food Additives and Flavourings (FAF) and the members of the Working Group on Sweeteners, as well as all European competent institutions, Member State bodies and other organisations that provided data on these food additives.

Further information

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EU-FORA Induction Trainings (2021; 2022; 2023)
Keeping Sweet Healthy Webinar (2022)
International Food Chemical Safety Liaison Group (2023)
Interaction with EMA and IARC (2022-2023)

PROTOCOL FOR ASSESSMENT OF HAZARD IDENTIFICATION AND CHARACTERISATION OF SWEETENERS

Problem formulation	• Is there a dose-response relationship between the dietary exposure to sweeteners and adverse effects in humans/experimental animals?
Extensive Literature Searches	• Open-ended searches; from last SCF/EFSA opinion • Refinement if needed
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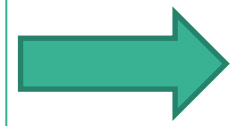
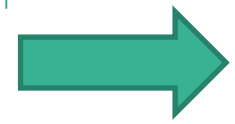
PROTOCOL FOR ASSESSMENT OF HAZARD IDENTIFICATION AND CHARACTERISATION OF SWEETENERS

- Sub-questions that are being addressed:

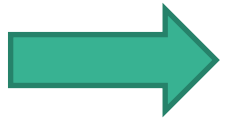
Number	Sub-question
1a	What is the ADME of sweeteners in humans?
1b	What is the ADME of sweeteners in mammalian animal species?
1c	How do the human and animal ADME data correlate?
1d	Are there any biomonitoring data that contribute to the assessment of ADME?
2	Do any of the substances included in the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



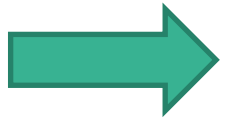
narrative approach



Stand-alone endpoint



systematic review



narrative approach

GENOTOXICITY ASSESSMENT: SUB-QUESTION 2

Genotoxicity is a stand-alone endpoint, cannot be overruled by negative carcinogenicity data

- Basic battery of *in vitro* tests (EFSA SC, 2011; EFSA SC, 2017):
  - bacterial reverse mutation assay (OECD TG 471)
  - an in vitro micronucleus assay (OECD TG 487)

- In case of positive results in vitro, *in vivo* follow-up would be needed

DATA GAP GENOTOXICITY IDENTIFIED

No need for additional data

- E 420 Sorbitols
  - E 420(i) Sorbitol
  - E 420(ii) Sorbitol syrup
- E 421 Mannitols
  - E 421(i) Mannitol by hydrogenation
  - E 421(ii) Mannitol manufactured by fermentation
- E 965 Maltitols
  - E 965(i) Maltitol
  - E 965(ii) Maltitol syrup
- E 968 Erythritol
- E 954 Saccharin and its Na, K, Ca salts
  - E 954(i)Saccharin
  - E 954(ii) Sodium saccharin
  - E 954(iii) Calcium saccharin
  - E 954(iv) Potassium saccharin

Sorbitol and maltitol: new calls for data launched/closed in 2023

Call for data

- E 950 Acesulfame K
- E 952 Cyclamates
  - E 952(i) Cyclamic acid
  - E 952(ii) Sodium cyclamate
  - E 952(iii) Calcium cyclamate
- E 953 Isomalt
- E 955 Sucralose
- E 959 Neohesperidine dihydrochalcone
- E 961 Neotame
- E 962 Salt of aspartame-acesulfame
- E 966 Lactitol
- E 967 Xylitol

Call for data published by EFSA on 30 June 2021

6 months timeframe according to EFSA Indicative timelines document for submitting data

Deadline: 30.12.2021: Extension of 3 months (31 March 2022)

GENOTOXICITY ASSESSMENT OF SWEETENERS

- Protocol on hazard identification and hazard characterization of sweeteners (inclusion/exclusion criteria and data extraction) (EFSA, 2020)
- Reliability/Relevance (Klimisch et al., 1997; ECHA, 2011; EFSA, 2011; EFSA Scientific Committee, 2017a; EFSA Scientific Committee, 2021)
- Complementary approach for assessing genotoxicity studies (agreed by cross-cutting EFSA Working Group genotoxicity) (EFSA, April 2023; Revised protocol on sweeteners, Appendix B)
- Harmonised approach for reporting reliability and relevance of genotoxicity (EFSA, September 2023, link)
- Weight of Evidence (narrative)

SWEETENERS STILL ON HOLD (GENOTOXICITY DATA)

Neotame (E 961):
data received in November 2023

- Further data requested (further clarifications needed): **timeline tbc**

Cyclamates (E 952):
data received in October 2023

- **Sodium cyclamates: no further data needed**
- **Cyclohexylamine (CHA):** new Comet assay for stomach and colon (by February 2024; **timeline tbc**)

Sucralose (E 955):
data received in September 2023

- Ongoing genotoxicity studies (**by end April 2024**)
- Further data requested on stability and ADME of sucralose (formation of 1,6 DCF)

OPINIONS ESTIMATED IN 2024 (TENTATIVE)

Saccharin (E 954):
Q2/Q3 2024

Acesulfame K (E 950):
by end 2024/1Q 2025

Maltitols (E 965):
by end 2024/1Q 2025

OPINIONS ESTIMATED IN 2025 (TENTATIVE)

Salt of aspartame acesulfame (E 962)

Cyclamates (E 952): timeline tbc, on hold ?

Neotame (E 965): timeline tbc, on hold ?

Sucralose (E 955) or some polyols ?

Timelines for the other 5 polyols (i.e. xylitol, lactitol, isomalt, mannitols, sorbitols): depending on the finalisation of the other opinions (reprioritisation if some sweeteners are on hold)

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