Technical Stakeholder Event: Re-evaluation of authorised food additives- focus on sweeteners

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Assessment of sweeteners: Protocol on hazard identification and characterisation

Ursula Gundert-Remy- FAF Panel member

(For the members of the WG Sweeteners)

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The assessment of sweeteners : a systematic review with a protocol

- **In a systematic review, the methods to be used in all steps of the review process are made explicit a priori in a protocol**

The protocol

Identifies the aim of the review (PECO)

- ❖Problem
- ❖Exposure
- ❖Comparator
- ❖Outcome/endpoint

Describes how to

- search for research studies
- appraise the studies
- extract the data from the included studies
- synthesise the data from the included studies
- deal with uncertainties

The safety sub-questions in the sweeteners protocol

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?

Inclusion/exclusion criteria

Inclusion criteria for genotoxicity studies (as example for inclusion criteria)

Study type	**In**	***In vitro* studies in bacteria (*Salmonella* Typhimurium, *Escherichia coli*) and mammalian cells** **In vivo studies in insects (Drosophila), rodents (mice, rats, hamsters)** **Studies in humans**
	Out	**Studies in fungi, plants** **Studies in other prokaryotic and eukaryotic systems**
End-point	**In**	**Gene mutation, recombination and gene conversion, sister chromatid exchanges, structural and numerical (aneuploidy) chromosome aberrations** **DNA binding, DNA damage (comet assay), DNA repair (UDS) and DNA Damage Response (DDR)**
	Out	**Cytotoxicity, necrosis/apoptosis, DNA synthesis inhibition**

Language	**In**	**English**
	Out	**Other languages**
Time	**In**	**From the latest evaluation of SCF or EFSA**
	Out	**Before the date of the latest evaluation of SCF or EFSA**
Publication type	**In**	**Primary research studies *(i.e.* studies generating new data); systematic reviews (only for identification of primary studies).**
	Out	**Narrative reviews** **Books and book chapters** **Expert opinions, editorials, and letters to the editor** **PhD Theses** **Extended abstracts, conference proceedings**

Examples of adverse effects (apical and non-apical endpoints) for human studies

Target	Apical endpoints	Non-apical endpoints (examples)
Chronic metabolic diseases		
Adipose tissue	Obesity incidence	Body weight, BMI Body composition (body fat, lean body mass) Waist circumference, skinfold thickness, waist-to-height ratio Ectopic fat deposition (muscle, VAT)
Glucose homeostasis	T2DM incidence	Insulin sensitivity Hb A_{1c} Blood glucose
Cardiovascular system	CVD incidence/ mortality	Blood pressure Blood lipids (cholesterol, triglyceride)

Endpoints (examples)

Evaluation of the risk of bias for animal studies

Number	Question	Applies to study type	Domain of bias	Rating (++, +, -, --)
1 X	Was administered dose or exposure level adequately randomized?	EA	Selection	
2	Was allocation to study groups adequately concealed?	EA	Selection	
3 X	Were experimental conditions identical across study groups?	EA	Performance	
4 X	Were the research personnel blinded to the study group?	EA	Performance	
5	Were outcome data complete without attrition or exclusion from analysis?	EA	Attrition/exclusion	
6 X	Can we be confident in the exposure characterization?	EA	Detection	
7 X	Can we be confident in the outcome assessment?	EA	Detection	
8	Were all measured outcomes reported?	EA	Selective reporting	
10	Were statistical methods appropriate?	All	Other sources of bias	

X Key question

Assessment of the risk of bias

Tier 1:

- **All the key questions are scored + /++**

  AND

- **No more than one non-key question is scored –**

  AND

- **No non-key question is scored --**

Tier 2:

- **All the other combinations not falling under tier 1 or 3**

Tier 3:

- **Any question is scored --**

  OR

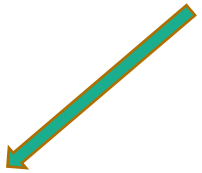
- **More than one key question is scored -**

Weight of evidence assessment

Grouping together studies (animal or human) with the same endpoint measured in the study.

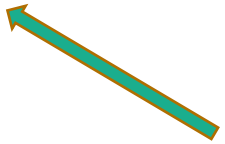
Initial weight of evidence

- **Outcome and exposure assessed on an individual level**
- **Controlled versus uncontrolled experimental conditions**
- **Appropriateness of the comparison group and study population**



Downgrading

- Risk of bias-evaluation
- Relevance of endpoints (for animal studies only)
- Unexplained inconsistency
- Imprecision



Upgrading

- Apical endpoint
- Dose-response
- Consistency, across study design type, dissimilar populations, animal models, species or gender
- Large magnitude of effect (e.g. incidence, degrees of severity)

Result of the WOE after up-/downgrading

- High confidence (++++) in the association between exposure to the substance and the outcome. The true effect is highly likely to be reflected in the apparent relationship.
- Moderate confidence (+++) in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship.
- Low confidence (++) in the association between exposure to the substance and the outcome. The true effect may be different from the apparent relationship.
- Very low confidence (+) in the association between exposure to the substance and the outcome.

Summarising and synthesising the evidence

After the step in which the weight of evidence is assessed the next step in the assessment process is to summarise and to synthesise the evidence to finally conclude on the probability of existence of a hazard.

Synthesising the evidence - Methods

- Best professional judgement → no formal method
- Causal criteria according to Bradford Hill → criteria
- Rating criteria → based on Bradford Hill criteria with additional guidance provided for integrating the evidence
- Quantification → statistical methods; e.g metaanalyses for studies with the same endpoint, multicriteria decision analysis for integrating differnt types of studies, machine learning techniques

Guidance on the use of the weight of evidence approach in scientific assessments, EFSA 2017

Results from the synthesis of evidence

i. High Level of Evidence of a Health effect
ii. Moderate Level of Evidence of a Health effect
iii. Low Level of Evidence of a Health effect
iv. Inadequate Evidence

What the protocol does not cover

- Analysis of the dose-response data (surely Benchmark, if possible)

- When to go from a reference point (RF, otherwise POD) to a HBGV or to apply the MOS approach

Dealing with and communicating uncertainty

- **qualitative** identification of all possible sources of uncertainty relevant for the risk assessment
- **qualitative** characterization in terms of direction (↑, −, ↓) and magnitude (low, medium and high)
- sources of uncertainty judged to be "high" with an influence on overall outcome of the risk assessment detailed assessment of impact will be performed (incl. **quantitative** analyses)

Results will be presented in table format and the potential implications for each source will be discussed proportionally to the estimated relevance.

Final remarks

- Where are we in the risk assessment when we work according to the protocol?

We will have in hands the result of a highly transparent process with increased credibility.

- Will all people be satisfied with the results?

This is hard to answer.

At least, because of the transparency, also of the subjectivity („expert judgement“) the steps where discrepant opinions originate might be better identified.

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