Draft protocol for the exposure assessment as part of the safety assessment of sweeteners under the food additives re-evaluation programme

EFSA Panel on Food Additives and Flavourings (FAF)

Table of contents

1. Introduction and scope of the protocol

This document outlines the draft protocol for the exposure assessment of sweeteners[1] for their safety re-evaluation in the context of Regulation (EC) No 257/2010[2] by the European Food Safety Authority (EFSA) Panel on Food Additives and Flavourings (FAF Panel). It is supported by the Working Group on the re-evaluation of sweeteners. This draft protocol has been developed with the aim of defining as much as possible beforehand the strategy applied for cleaning and selecting data, appraising the relevant evidence, and analysing and integrating the evidence in order to perform exposure assessments that will be used for the risk characterisation for each sweetener.

This protocol is iterative by nature and will be subject to a pilot phase. Should the need to amend the protocol emerge as the assessment proceeds, such amendments will be clearly documented and justified.

Current best practices, which are subject to continuous review and refinement based on the experience gained during evaluations, are also presented.

2. Background and rationale of the mandate

Regulation (EC) No 1333/2008[3] of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010[2]. This Regulation also foresees that food additives are re-evaluated whenever necessary in light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by group of food additives according to the main functional class to which they belong.

3. Terms of reference as provided by European Commission

The Commission asks the EFSA to re-evaluate the safety of food additives already permitted in the European Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in the Regulation (EU) No 257/2010[2] of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

4. Interpretation of the Terms of Reference

Under the current mandate which covers the re-evaluation of all food additives under Commission Regulation (EU) No 257/2010, this exposure protocol will be applied for the re-evaluation of sweeteners listed in Table 1 only. Scientific evaluation will be conducted for individual sweeteners. Should evidence emerge that two or more substances lead to same adverse effects through the same Mode of Action (MoA), the use of a cumulative assessment group will be considered.

It is out of the scope of this scientific assessment to address possible beneficial health effects of sweeteners.

This protocol is applied to the exposure assessment step of risk assessment. Hazard identification and hazard characterisation will be assessed following a separate protocol. Risk characterisation will be performed based on the outcome of hazard characterisation and exposure assessment.

[1] Sweeteners may be evaluated individually or in group.

[2] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27

[3] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16–33.

In accordance with the provisions of Regulation (EC) No 257/2010, the re-evaluation of all approved sweeteners in the EU prior to 20 January 2009 shall be completed by 31 December 2020. The list of sweeteners approved in the EU as of 20 January 2009 is shown in Table 1.

Table 1: List of food additives, classified as sweeteners, to be re-evaluated under Regulation (EC) No 257/2010

E Number	Food additive(s)		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[(a)]	Aspartame[(a)]		
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		

a) In May 2011, EFSA was asked by the European Commission to bring forward the full re-evaluation of the safety of aspartame (E 951). Re-evaluation already completed by EFSA in 2013 (EFSA ANS Panel, 2013; https://www.efsa.europa.eu/it/efsajournal/pub/3496)

Despite that the re-evaluation of aspartame (E 951) has been completed and will not be re-opened, total aspartame exposure from the use of the salt of aspartame-acesulfame (E 962) and aspartame (E 951) itself should nevertheless be performed.

As a general basis, exposure to impurities and by-products, e.g. heavy metals and process contaminants, will not be estimated by default.

5. Data and Methodologies

5.1. Data

5.1.1. Food additive concentration data availability

In the framework of the re-evaluation programme of food additives that were already permitted in the European Union before 20 January 2009 set up under Regulation (EU) No 257/2010, EFSA has issued several public calls for use levels and/or concentration data (analytical data) on food additives to be re-

evaluated since 2013.[4] In particular, batch 7 was launched in January 2018 to collect data on food sweeteners by October 2018[5].

National authorities/organisations of the Member States and any interested business operators and other interested parties (e.g. individual food manufacturers, food manufacturer associations, research institutions, academia, food business operators and other stakeholders) were invited to submit data on use levels/analytical data of sweeteners in food and beverages intended for human consumption.

An additional call on occurrence data on aspartame (E 951) will be launched to collect new data that will be used to update the assessment of exposure to aspartame (E 951), as well as to assess the total aspartame exposure from the use of the salt of aspartame-acesulfame (E 962) and aspartame (E 951).

5.1.1.1. Information on use levels submitted

The amount of information received for each sweetener varies considerably, ranging from few data (e.g. lactitol, salt of aspartame-acesulfame) to data covering nearly all authorised uses (e.g. acesulfame K, sucralose) laid down in Annex II to Regulation (EC) No 1333/2008 on food additives.

The majority of the information provided so far has been made available by food industry associations that collect data from their members.

Typically, very limited information is provided about the representativeness of the use levels submitted with respect to their market share. In some cases, data providers specify whether a level refers to a niche product. A niche product is identified by industry e.g. as only used by a specific population group. Niche products might be treated differently in the exposure assessment (see section 5.2.3).

5.1.1.2. Information on analytical data submitted

The analytical data collection was undertaken according to the requirements of the EFSA Guidance on Standard Sample Description for Food and Feed (EFSA, 2010) using the data model 'Standard sample description' (SSD1 or SSD2) (EFSA, 2010; EFSA, 2013). Analytical data on sweeteners were mainly submitted by European national authorities/organisations.

The number of data provided per sweetener varied from no analytical data (e.g. thaumatin, salt of aspartame-acesulfame) up to several thousands (e.g. acesulfame K, saccharin). Analytical results were thoroughly evaluated; this included cleaning and validation steps. Following the EFSA Standard Operating Procedure (SOP)[6], the initial data set was carefully evaluated applying several steps to guarantee an appropriate quality of the data used in exposure assessment. Special attention was devoted to the identification of duplicates and to the accuracy of different parameters such as 'Sampling strategy', 'Sampling method', 'Sampling year', 'Sampling country', 'Analytical methods', 'Reporting unit', 'limit of detection (LOD)/limit of quantification (LOQ)', and to the correctness of the food classification codification of the different samples under the FoodEx2 classification system and the food categorisation of Annex II, Part D (Reg (EC) No 1333/2008).

A number of analytical results submitted to EFSA may report occurrence of sweeteners in food and beverages for which their use is not authorised according to Annex II to Regulation (EC) No 1333/2008. In this case, the presence of the sweetener in those foods (positive results i.e. greater than LOD or LOQ) could be, for instance, due to carry-over, or to natural occurrence (for the polyols only).

Furthermore, products in which sweeteners have not been added, despite being authorised, might have been analysed within the monitoring programmes. A number of monitoring programmes conducted by the data providers used multi-analyte methods in which two or more (and often several) sweeteners are analysed together. As a consequence, a large number of left-censored data (i.e. either below the LOD or LOQ) submitted, pertain to food categories in which the sweetener is not permitted. Similarly, some left-censored data submitted will be for food categories in which the sweetener is permitted but was not added to the particular product tested. It is therefore expected that a significant part of the

[4] http://www.efsa.europa.eu/en/calls/data

[5] https://www.efsa.europa.eu/en/consultations/call/180122

[6] Standard operating procedure 008 for the data collection and validation: https://www.efsa.europa.eu/en/corporate/pub/sops

analytical results submitted to EFSA is left censored. As described in section 5.2, the methodology used for the exposure assessment of sweeteners is based on the identification of the food categories which are assumed to contain sweeteners. In this context, the left-censored data will be excluded in order not to bias the results. The assessment of exposure to sweeteners is therefore based on the assumption that food and beverages containing the sweetener are identified (from the data set) and its level is derived from the quantified analytical results only.

Only authorised uses with quantified analytical results at or below the Maximum Permitted Level (MPL) are considered because results above MPL are part of risk management measures, e.g. non-compliance purpose. For this reason, such results are not taken into account, except in specific cases as appropriate (e.g. in case of natural occurrence for polyols). This is in line with the dietary exposure assessments of food additives[7]. However, any non-compliant cases will be reported in each opinion. In case a significant (based on expert judgement) number/frequency of analytical data exceed the MPLs and/or presence in foods in which the sweetener is not authorised, the Panel might include these data in an additional exposure assessment scenario.

5.1.2. Food consumption database

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database) provides a compilation of existing national information on food consumption at individual level. Details on how the Comprehensive Database is used are published in the Guidance of EFSA (EFSA, 2011). The food consumption data gathered by EFSA in the Comprehensive Database are the most complete and detailed data currently available in the European Union (EU). The latest version of the Comprehensive Database is used. The most recent version updated in 2018, contains results from a total of 60 different dietary surveys carried out in 25 different Member States covering 119,458 individuals.

The age classes considered are the following:

- Infants: from 16 weeks to <12 months old
- Toddlers: ≥12 months to <36 months old
- Other children: ≥36 months to <10 years old
- Adolescents: ≥10 years to <18 years old
- Adults: ≥18 years to <65 years old
- Elderly: ≥65 years.

Mannitol (E 421) is the only sweetener permitted in foods for infants and young children (food category 13.1 which covers foods for infants during the first months of life), however its authorised use is limited as carrier for vitamin B12 (according to Annex III, Part 5, section B, to Regulation No 1333/2008). The FAF Working Group on the re-evaluation of sweeteners, jointly with the FAF Working Group on the re-evaluation of food additives permitted for use in foods for infants below 16 weeks of age, will evaluate this special application of mannitol (E 421) according to the guidance on the risk assessment of substances present in food intended for infant below 16 weeks of age (EFSA Scientific Committee, 2017).

Four additional surveys provided information on specific population groups: 'Pregnant women' and 'Lactating women'. Exposure for these specific population groups will be assessed if the Panel considered it relevant.

The Comprehensive Database is regularly updated. When for one country and age class, two different dietary surveys will be available, only the most recent one will be used.

Consumption data were collected using single or repeated 24-h or 48-h dietary recalls or dietary records covering from 3 to 7 days per subject. Due to differences in the methods used for data collection, direct country-to-country comparisons may not be appropriate. Detailed information on the different dietary surveys available in the Comprehensive Database can be found on the dedicated page of the EFSA website[8].

[7] See EFSA statement: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.5042

[8] http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

5.1.3. Food labelling data

EFSA has access to the food label database developed by Mintel, the Global New Products Database (GNPD).[9] This database is an online database, which observes product introductions in consumer-packaged goods marketed worldwide. The GNPD contains data of EU food markets since 1996 and currently 25 of its 28 member countries and Norway are represented in the GNPD.[10] New foods are regularly added to the database.

For the purpose of exposure assessments in the scientific opinions of the FAF Panel, the GNPD is used to check food product labels for sweeteners as GNPD shows the compulsory ingredient information presented on product labels. Only the food additives authorised under Annex II to Regulation (EC) No 1333/2008 are mandatory to be labelled on the ingredient information. When information on a sweetener is available in the GNPD, the number (and percentage) of foods labelled with the sweetener per food category for the last 5 years will be reported in each opinion stratified according to food categories.

The GNPD is a source of information used to compare the food categories for which use and/or analytical data were reported to EFSA with the list of foods labelled to contain the sweetener, together with the list of authorised uses by the EU legislation. The main aim of using the GNPD is to support the identification of the food categories containing the sweeteners and to evaluate a possible under/overestimation of the calculated exposure.

5.2. Methodologies

5.2.1. Food classification systems

Data on use levels are reported by the data provider according to the food categories (FCs) of Annex II, Part D to Regulation (EC) No 1333/2008, including the original name of each product. In addition, analytical data on sweeteners are reported according to the FoodEx2 food classification system, as prescribed in the SSD. When the classification according to the FCs of Annex II, Part D to Regulation (EC) No 1333/2008 was not provided, EFSA will reclassify the foods accordingly.

Since 2018, all consumption records in the Comprehensive Database are as well codified according to the FoodEx2 classification system. The most detailed common link between food consumption information and chemical concentration data is therefore FoodEx2. Thus, the lowest FoodEx2 level will be used to assess dietary exposure in combination with the food categories listed in Annex II, Part D (Reg (EC) No 1333/2008). Nomenclature from the FoodEx2 classification system has been linked to the FCs of Annex II, Part D, to Regulation (EC) No 1333/2008. To link all consumption events to the FCs of Annex II, Part D to Regulation (EC) No 1333/2008, in addition to FoodEx2, the original food descriptor was occasionally used, especially for the dietary surveys data provided to EFSA before 2018. The link between the FoodEx2 classification system and the food sub-categories used in GNPD is reported in Appendix A.

In FoodEx2, facets are used to add further description, in relation to different properties and aspects of foods, to the information provided by the food list term. The following facets can be used to identify products that could contain sweeteners: "Without added sugar", "Sugar free", "Low / Reduced sugar" and "Light". In addition, the presence of artificial sweetener(s) among the ingredients of a given food can as well be reported by means of an ad-hoc facet. These FoodEx2 facets are not always related to the reduction of sugar/addition of sweetener(s), and a case by case decision was needed. For example, "Light" for certain foods, is related to the reduction of fats rather than sugar.

5.2.2. Food categories used for the assessment of exposure

According to the available literature for EU countries, Non-alcoholic beverages and Table-top sweeteners are expected to be the main contributors to the exposure for most of the sweeteners (Garnier-Sange et al., 2001; Ilbäck et al., 2003; Arcella et al, 2004; Le Donne et al., 2017). Food Supplements, Desserts

[9] http://www.gnpd.com/sinatra/home/

[10] Missing Cyprus, Luxembourg and Malta.

and Confectionery (e.g. chewing gum, candies, etc.) could as well represent a significant source of exposure (Arcella et al, 2004; Vin et al., 2013; Le Donne et al., 2017). Alcoholic beverages have been mentioned by Le Donne et al. (2017) as additional potential sources.

The percentage of products within the food sub-categories used in GNPD labelled to contain at least one sweetener is reported in Appendix B. The GNPD food sub-categories presenting the highest % of products labelled to contain at least one sweetener are Artificial Sweeteners (99%), Gum (89%), Meal Replacements & Other Drinks (58%), Sports Drinks (57%) and Medicated Confectionery (49%). When looking at the food categories from the legislation (Annex II, Part D to Regulation (EC) No 1333/2008) expected to be the main contributors to the exposure according to the literature, at least one sweetener is reported on the label for 31% of Carbonated Soft Drinks, 32% of Energy Drinks and 21% of Vitamins & Dietary Supplements. This percentage is lower in Cakes, Pastries & Sweet Goods (17%), Desserts (GNPD food sub-categories: Frozen Desserts (10%), Shelf-Stable Desserts (10%), Soft Cheese Desserts (9%), Chilled Desserts (9%) and Dessert Toppings (5%)) and confectionary other than gums (GNPD food sub-categories: Other Sugar Confectionery (14%) and Other Chocolate Confectionery (2%)). The percentage of products with sweeteners on the label of Cold cereals and Savoury Biscuits/Crackers is below 1% and is, as well, negligible in Alcoholic beverages: Beer (2%), Cider (1.4%), Liqueur (0.2%), Wine (0.02%).

The FAF Panel proposes to use the FoodEx2 facets to identify eating occasions of foods containing sweeteners in the Comprehensive Database for the assessment of exposure. In practice, when an eating occasion refers to a food for which a FoodEx2 facet was reported specifying the presence of sweetener(s) as an ingredient, the food is assumed to contain the sweetener under evaluation and the eating occasion is included in the assessment of exposure. Of course, this is done only if the sweetener under consideration is authorised in the specific food category and adequate analytical results and/or use levels are available.

The FoodEx2 facets are based on information obtained from the survey participants where the survey protocol required data at a higher level of detail. The reliability when using these facets to identify the possible presence of sweeteners in food categories varies according to the different dietary surveys and food categories. Food consumption statistics (consumers only) per country and age class are reported in Appendix C for each combination of GNPD food sub-category and FoodEx2 category. The percentage of eating occasions and in quantity for which at least one of the above-mentioned facets was reported, is shown in Appendix D. These appendices have been used to evaluate the information reported through the facets (e.g. percentage of foods reported with facets and respective consumption amounts of foods with and without facets of interest) and, consequently, the availability of the consumption data related to products containing sweeteners.

An analysis of the facets was carried out on the food categories expected to be the main contributors to the exposure to sweeteners according to the aforementioned literature.

Facets were rarely reported for FoodEx2 categories linked to the GNPD food sub-category Artificial Sweeteners (e.g. Table-top sweeteners formulations, Table-top sweeteners in liquid form, Table-top sweeteners in powder form and Table-top sweeteners in tablets). For example, in the case of adults, only Belgium, France and Italy reported one of the above-mentioned facets in more than 50% of eating occasions.

In the case of Chewing gum and Gum drops (linked to the GNPD food sub-category Gum and Medicated confectionary, respectively), the percentage of eating occasions for adults presenting the facets ranges from 50 to 100%, with Austria, Czech Republic, Finland, Romania, Spain and Sweden never reporting any facet. Facets were never reported for FoodEx2 categories linked to the GNPD categories Other Sugar Confectionery and Other Chocolate Confectionery.

In the case of Energy drinks (linked to the GNPD food sub-category Energy drinks) the percentage of eating occasions for adults presenting the facets ranges from 0.1 to 17%, with 10 countries out of 17 never reporting any facet.

In the case of FoodEx2 categories linked to the GNPD food sub-category Vitamins & Dietary Supplements, only in Italy and Germany were facets used to identify products containing sweeteners (10% and 0.4% of Vitamin only supplements, respectively).

In the case of FoodEx2 categories related to desserts, facets used to identify products containing sweeteners were reported for Compote of fruit / vegetables (6 countries, from 9 to 38% of eating occasions), Starchy pudding (4 countries, from 3 to 14%), Custard (3 countries, from 1 to 15%), Fruit or fruit-vegetable purée (2 countries, from 26% to 100%), Other desserts spoonable (2 countries, from 31 to 50%), Dairy desserts spoonable (1 country, 40%) and Rice pudding (1 country, 5%).

FoodEx2 categories Diet soft drink with caffeine, Diet soft drinks with fruit juice and Diet soft drinks with flavours (linked to the GNPD food sub-category Carbonated Soft Drinks) always implicitly present at least one of the facets used to identify products containing sweeteners. For Cola beverages, caffeinic, the most largely consumed FoodEx2 category linked to Carbonated Soft Drinks, the percentage of eating occasions in adults presenting the facets ranges from 2 to 60%, with 10 countries out of 17 never reporting any facet. But in most of these 10 countries the category Diet soft drink with caffeine was used instead, suggesting still a relatively good identification products containing sweeteners for soft drinks.

From an analysis of the percentage of eating occasions presenting at least one of the facets used to identify products containing sweeteners, the FAF Panel noted a likely underestimation of eating occasions of products containing sweeteners in relation to Table-top sweeteners, Chewing gum, Gum drops, Energy drinks and Vitamin and mineral supplements. Since these categories are expected to be major contributors to the exposure according to the literature and present a relatively high percentage of products labelled to contain at least one sweetener, the FAF Panel proposes to always include these food categories in the exposure assessment independent of the presence of facets. In order not to underestimate the exposure, these categories should always be assumed to contain the sweetener under evaluation, if authorised and if adequate analytical results and/or use levels are available. The facets used to identify products containing sweeteners are considered more reliable for the FoodEx2 categories linked to the GNPD food sub-category Carbonated Soft Drinks. In order not to overestimate the exposure, the FAF Panel proposes therefore to use the facets to identify the eating occasions assumed to contain the sweetener under evaluation.

The FAF Panel also proposes to apply the same approach to all other food categories which are not expected to be a significant source of exposure, based on the aforementioned literature and on the low percentage of products labelled to contain sweeteners in the GNPD. In these cases, the uncertainty related to the reliability of the facets is not expected to lead to a considerable underestimation of the exposure.

5.2.3. Exposure assessment of sweeteners under re-evaluation

The Panel estimates chronic exposure to sweeteners. Exposure assessments of sweeteners under the re-evaluation programme are carried out by the FAF Panel based on two different sets of concentration data: (a) MPLs of use set down in the EU legislation (defined as *regulatory maximum level exposure assessment scenario*) and (b) use levels and/or analytical data provided through the calls for data (defined as *refined exposure assessment scenario*).

These scenarios will be used for single substances and for co-occurring substances. Co-occurrence exists in the case of the salt of aspartame-acesulfame (E 962), which liberates aspartame and acesulfame on disassociation and this should be taken into account together with the single use of these two sweeteners as such. Should evidence emerge that two or more substances lead to same adverse effects through the same Mode of Action (MoA), the use of a cumulative assessment group will be considered.

In case other cumulative effects need to be considered within re-evaluation or by a separate mandate this might need adaptation of these scenarios.

The *regulatory maximum level exposure assessment scenario* is based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008. For the food additives authorised according to *quantum satis* (QS) in all or part of food categories, a *maximum level exposure assessment* scenario is estimated based on maximum reported use levels/highest reliable percentile different from the maximum (depending on the number of observations) of analytical data provided to EFSA, as described in the EFSA Conceptual framework (EFSA ANS Panel, 2014).

In both exposure assessment scenarios (regulatory or refined exposure assessment scenarios), food additive concentration values (MPLs, use levels and/or analytical data) are combined, at individual level, with national food consumption data from the EFSA Comprehensive Database considering the six different population groups above mentioned (see Section 5.1.2).

In the refined exposure assessment scenario, the concentration levels considered by the Panel are extracted from the whole dataset received (i.e. reported use levels and analytical data) and are pooled together assuming a European market.

A use level(s) referring to a niche product can be provided for a food category for which already use levels are reported for generic products in that food category. In such a case, that use level reported for a niche product will be excluded from the refined exposure assessment. If no other level, use or analytical data, is available, the reported use level for a niche product will be taken into account. The possible under/overestimation of the contribution of the food category to which the niche product belongs to the overall exposure should be stated in the opinion in the uncertainty section.

Use levels reported by food additive producers will not be considered with the same priority as those provided by food industry. The FAF Panel considered that food additive producers might recommend use levels to the food industry, but the final levels used might, ultimately, be different. Therefore, unless food additive producers confirm that the recommended levels are used by the food industry, they will not be considered in the refined exposure scenario. Data from food additive producers will only be used in the *maximum level exposure assessment* scenario in case of QS authorisation and when no data are available from food industry. In this way, the most comprehensive exposure estimates will be calculated. All reported use levels will be presented in the appendices of the scientific opinion for acknowledgment and information.

Mean and 95th percentile exposure results will be reported for each dietary survey and population group and for consumers only of at least one food category containing the sweetener under evaluation according to Annex II to Regulation No 1333/2008. The main food categories of Annex II, Part D to Regulation (EC) No 1333/2008 contributing to the total mean exposure to the sweeteners will be provided in each opinion for each scenario. In addition, exposure results will also be calculated for consumers only for each food category separately and on ad-hoc basis will be included in an Annex to the respective re-evaluation.

Due to limited number of consumption data for diabetics, it is not possible to perform an exposure assessment for this specific population sub-group. Nevertheless, it is expected that diabetics are exposed to levels in the same range as the subjects in the right-hand-side (high) end of the exposure distribution for consumers only of at least one food category containing the sweetener under evaluation.

The *regulatory maximum level exposure assessment scenario* is the only scenario which would not be influenced by future changes of food additive use in the market.

5.2.3.1. Regulatory maximum level exposure assessment scenario

The *regulatory maximum level exposure assessment scenario* is based on MPLs of use as set in Annex II to Regulation No 1333/2008. Therefore, it only includes food categories authorised according to this Annex or any other legislation clearly defining the food or food category in which the sweetener might be added with an MPL as a numerical level (e.g. Annex III of the same Regulation).

Under the MPL scenario, all FoodEx2 codes will be assumed to possibly contain a sweetener, unless Regulation No 1333/2008, Annex II, indicates that sweeteners can be added only under specific restrictions/exceptions e.g. "only energy reduced or with no added sugar". In this case, the food selection approach described in section 5.2.2 applies.

As mentioned above, for food additives authorised according to QS in all or part of the food categories, a *maximum level exposure assessment scenario* will be performed based on the maximum reported use levels provided by industry or on the highest reliable percentile different from the maximum (depending of the number of observations) of analytical data provided by MSs, whichever is highest or available.

Food categories authorised at QS and for which use or analytical data are not available or adequate (e.g. unreliable analytical methods), are not considered in this scenario.

The exposure estimates derived following this scenario should be considered as the most conservative for the food categories considered as it assumes that the population group will be exposed to a sweetener present in food at the MPL or maximum reported use level or the highest reliable percentile different from the maximum of the analytical level in case of QS authorisation, over a long period of time.

However, when in this scenario, only a few authorised food categories are considered due to limited data, it is uncertain whether the *maximum level exposure assessment scenario* is conservative for overall dietary exposure or only for the food categories considered. This may apply especially to situations where the additive is authorised at QS in many food categories. This uncertainty will be indicated in the appropriate section of each opinion.

5.2.3.2. Refined exposure assessment scenario

The *refined exposure assessment scenario* is based on information on actual use levels and/or analytical data, rather than MPLs, and can only be carried out if sufficient and adequate data have been reported. These refined scenarios should be performed taking into account the authorised food categories according to Annex II to Regulation No 1333/2008.

If both use and analytical data are available for the same food group, the highest reliable value (based on expert judgement) for the food category under consideration will be used.

Considering the specific food consumption patterns of foods containing sweeteners, exposure assessment will be based on the brand-loyalty principle. In practice, estimates will be based on the assumption that an individual is a long-term brand-loyal consumer of one food category containing the sweetener at the highest level reported/highest reliable percentile different from the maximum level analysed and non-brand loyal to the other food categories in the diet, which contain the sweetener at the mean/median of typical reported use level or analytical data. This exposure estimate will be calculated as follows:

- Combining food consumption with the maximum reported use levels (or highest reliable percentile different from the maximum level analysed) available for the food category having, at the individual consumer level, the highest contribution to the total individual mean exposure,
- Using the mean of the typical reported use levels or the mean/median of analytical results for the remaining food categories.

As mentioned previously, food categories for which no- or inadequate information regarding the use/occurrence of a sweetener is available to EFSA (obtained from industry or from MSs) cannot be included. Consequently, the exposure assessment carried out by the FAF Panel will be limited to those food categories for which information is available. Exclusion of food categories for which data is not available might result in underestimation of the true exposure. The percentage of the food taken into account in the refined exposure estimates out of all food categories authorised should be provided.

Overall, the *refined exposure assessment scenario* is suitable to calculate the most realistic exposure estimates to sweeteners given the available data. Moreover, assigning the mean concentration of the food additive to processed food consumed by a given population, is consistent with general chronic exposure approaches.

5.2.3.3. Other exposure assessment scenarios

Additional exposure scenarios might be considered if concentration levels are made available to EFSA on food categories which are not authorised according to Annex II to Regulation No 1333/2008. In order to consider the presence of sweeteners due to carry-over (Annex III to Regulation No 1333/2008) or due to natural occurrence (relevant only for polyols), additional exposure scenarios may be performed considering the availability of data.

5.2.3.4. Comparison with human urinary biomonitoring studies

Exposure estimates made using published human urinary biomonitoring studies will be used as a cross-check of the estimates made using the scenarios described above.

Some of the sweeteners are either not metabolised or are metabolised only poorly. So they are excreted completely or almost completely unchanged in the urine. Examples are acesulfame-K, saccharin and cyclamates. This gives the possibility to estimate exposure to sweeteners using human urinary biomonitoring, whereby the concentration in urine can be used to estimate the exposure of that person in the relevant period of time prior to urine collection.

It may also be the case that even if metabolism is extensive, the metabolites of a sweetener may be unique and could be ascribed to the parent substance. In such a case, if the molar fraction of the urinary excreted metabolite can be related to the parent substance without too much uncertainty (e.g. inter- or intra-person variability), then measurements of the metabolite(s) could be used to derive estimates of exposure to the parent sweetener.

This would require therefore that the biomonitoring data available are suitable and kinetic models are available to allow the conversion of biomonitoring data into doses

Human biomonitoring data comprises a picture of the tested individual(s) at the moment/period of measurement and their use is based on extrapolation of the derived results to the general population. Human biomonitoring also captures exposure to a substance from all sources, not only dietary. For these reasons the cross-checking shall be performed to look for a general alignment of the different estimates of exposure rather than requiring any exact agreement. This shall be described in a narrative approach.

5.2.4. Uncertainty analysis

In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the sources of uncertainties considered are summarised in each opinion in a table. They are related to the food consumption data and to the concentration data (use or analytical data) used, and to the scenarios presented in the opinions.

An uncertainty paragraph will summarise the uncertainties listed in the table and will indicate whether the exposure estimates can be considered as under- or overestimations of the true exposure.

In order to evaluate the possible maximum underestimation related to the use of the FoodEx2 facets, an additional refined exposure scenario considering all foods (irrespective of the facets) authorised to contain a sweetener, will always be assessed and reported in the uncertainties section.

The GNPD will be used as a qualitative tool to evaluate the uncertainty related to the available use/analytical data. As mentioned in Section 5.1.3, for each specific sweetener, a table will be produced listing the numbers and percentages of products in which the sweetener is listed among the ingredients per food (sub-) category according to the GNPD food classification and over all foods categories analysed in the opinion. This should give information on the use of sweeteners in products as available in the market.

- There is consistency between the amount of use/analytical data for foods and beverages with usage information from the GNPD: low uncertainty.
- There is no consistency between the amount of use/analytical data for foods and beverages with usage information from the GNPD: high uncertainty.

The approach described in Section 5.2.2. introduces different levels to the inclusion/exclusion of the consumption events based on percentage of products labelled to contain at least one sweetener within the corresponding sub-categories from GNPD. Possible uncertainties are identified as follows:

i) FoodEx2 categories for which all eating occasions are always assumed to contain the sweetener: from low to high uncertainty depending on the food category. The uncertainty section should report an acknowledgement on the possible overestimation of the exposure estimates.

ii) FoodEx2 facets are used to identify eating occasions of foods containing sweeteners: from low to high uncertainty depending on the food category. The uncertainty section should report an acknowledgement on the possible underestimation of the exposure estimates when the food product contained the sweetener, but was not reported as a facet.

References

Arcella, D et al., 2004. Dietary estimated intake of intense sweeteners by Italian teenagers. Present levels and projections derived from the INRAN-RM-2001 food survey. Food and Chemical Toxicology, 42(4), 677-685.

EFSA European Food Safety Authority), 2007. Scientific opinion of the Scientific Committee related to uncertainties in dietary exposure assessment. EFSA Journal 2007;5(1):438, 54 pp. doi:10.2903/j.efsa.2007.438

EFSA (European Food Safety Authority), 2010. Standard sample description for food and feed. EFSA Journal 2010; 8(1):1457, 54 pp. doi:10.2903/j.efsa.2010.1457.

EFSA (European Food Safety Authority), 2011. Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment. EFSA Journal 2011;9(3):2097, 34 pp. doi:10.2903/j.efsa.2011.2097

EFSA (European Food Safety Authority), 2013. Standard Sample Description ver. 2.0. EFSA Journal 2013;11(10):3424, 114 pp., doi:10.2903/j.efsa.2013.3424

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources), 2014. Statement on a conceptual framework for the risk assessment of certain food additives re-evaluated under Commission Regulation (EU) No 257/2010. EFSA Journal 2014;12(6):3697, 11 pp. doi:10.2903/j.efsa.2014.3697

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2017. Statement on approach followed for the refined exposure assessment as part of the safety assessment of food additives under re-evaluation. EFSA Journal 2017;15(10):5042, 9 pp. https://doi.org/10.2903/j.efsa.2017.5042

EFSA Scientific Committee, 2017. Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age. EFSA Journal 2017;15(5):4849, 58 pp. https://doi.org/10.2903/j.efsa.2017.4849

Garnier-Sagne I and al., 2001. Calculation of the intake of three intense sweeteners in young insulin-dependent diabetics. Food and Chemical Toxicology, 39, 745-749.

Ilback NG et al, 2003. Estimated intake of the artificial sweeteners acesulfame-K, aspartame, cyclamate and saccharin in a group of Swedish diabetics. Food Additives and Contaminants; 20(2), 99-114.

Le Donne, C et al., 2017. Assessment of dietary intake of 10 intense sweeteners by the Italian population. Food and Chemical Toxicology, 102, 186-197.

Vin K et al, 2013. Estimation of the dietary intake of 13 priority additives in France, Italy, the UK and Ireland as part of the FACET project. Food Additives and Contaminants; 30(12), 99-114.

523 # Abbreviations

EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
FAF Panel	EFSA Panel on Food Additives and Flavourings
FCs	Food Categories
GNPD	Global New Products Database
LOD	Limit of detection
LOQ	Limit of Quantification
MoA	Mode of Action
MPL	Maximum Permitted Level
MSs	Member States
QS	Quantum satis
SOP	Standard Operating Procedure
SSD	Standard Sample Description

524

525

Appendix A – Link between the FoodEx2 classification system and the food sub-categories used in Mintel GNPD

Appendix B – Percentage of products within the food sub-categories used in Mintel GNPD labelled to contain at least one sweetener

Appendix C – Food consumption statistics (consumers only) per country and age class (in g/day)

Appendix D – Percentage of eating occasions and in quantity for which at least one relevant facet was reported

526