

ADOPTED: 5 April 2017

doi: 10.2903/j.efsa.2017.4788

## Re-evaluation of sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) when used as food additives

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS),  
Alicja Mortensen, Fernando Aguilar, Riccardo Crebelli, Alessandro Di Domenico,  
Birgit Dusemund, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy,  
Jean-Charles Leblanc, Oliver Lindtner, Peter Moldeus, Pasquale Mosesso,  
Dominique Parent-Massin, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen,  
Rudolf Antonius Woutersen, Matthew Wright, Maged Younes, Polly Boon,  
Dimitrios Chrysafidis, Rainer Gürtler, Paul Tobback, Andrea Altieri, Ana Maria Rincon and  
Claude Lambré

### Abstract

The Panel on Food Additives and Nutrient Sources added to Food (ANS) provides a scientific opinion re-evaluating the safety of sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) when used as food additives. The Scientific Committee on Food (SCF) allocated an acceptable daily intake (ADI) of 25 mg/kg body weight (bw) per day for E 491, E 492 and E 495 singly or in combination; and a separate group ADI for E 493 and E 494 singly or in combination of 5 mg/kg bw per day calculated as sorbitan monolaurate in 1974. The Panel noted that after oral administration sorbitan monostearate can be either hydrolysed to its fatty acid moiety and the corresponding anhydrides of sorbitol and excreted via urine or exhaled as CO<sub>2</sub> or excreted intact in the faeces. The Panel considered that sorbitan esters did not raise concern for genotoxicity. Based on the no observed adverse effect level (NOAEL) of 2,600 mg sorbitan monostearate/kg bw per day, taking into account the ratio between the molecular weight of sorbitan monostearate (430.62 g/mol) and sorbitan (164.16 g/mol), and applying an uncertainty factor of 100, the Panel derived a group ADI of 10 mg/kg bw per day expressed as sorbitan for sorbitan esters (E 491–495) singly or in combination. This group ADI of 10 mg sorbitan/kg bw per day is equivalent to 26 mg sorbitan monostearate/kg bw per day. The Panel concluded that the exposure at the mean and the 95th percentile level, using *non-brand-loyal scenario*, did not exceed the ADI in any of the population groups. The Panel on the request for an amendment of specifications regarding the removal of 'congealing range' concluded that it could be eventually replaced by another identification parameter such as melting point.

© 2017 European Food Safety Authority. *EFSA Journal* published by John Wiley and Sons Ltd on behalf of European Food Safety Authority.

**Keywords:** food additive, sorbitan monostearate, sorbitan tristearate, sorbitan monolaurate, sorbitan monooleate and sorbitan monopalmitate, sorbitan esters

**Requestor:** European Commission

**Question numbers:** EFSA-Q-2011-00571; EFSA-Q-2011-00572; EFSA-Q-2011-00573; EFSA-Q-2011-00574; EFSA-Q-2011-00575; EFSA-Q-2014-00875

**Correspondence:** [fip@efsa.europa.eu](mailto:fip@efsa.europa.eu)

**Panel members:** Fernando Aguilar, Riccardo Crebelli, Alessandro Di Domenico, Birgit Dusemund, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy, Claude Lambré, Jean-Charles Leblanc, Oliver Lindtner, Peter Moldeus, Alicja Mortensen, Pasquale Mosesso, Dominique Parent-Massin, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen, Rudolf Antonius Woutersen, Matthew Wright and Maged Younes.

**Acknowledgements:** The ANS Panel wishes to acknowledge all European competent institutions, Member State bodies and other organisations that provided data for this scientific opinion.

**Suggested citation:** EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), Mortensen A, Aguilar F, Crebelli R, Di Domenico A, Dusemund B, Frutos MJ, Galtier P, Gott D, Gundert-Remy U, Leblanc J-C, Lindtner O, Moldeus P, Mosesso P, Parent-Massin D, Oskarsson A, Stankovic I, Waalkens-Berendsen I, Woutersen RA, Wright M, Younes M, Boon P, Chrysafidis D, Gürtler R, Tobback P, Altieri A, Rincon AM and Lambré C, 2017. Scientific Opinion on the re-evaluation of sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) when used as food additives. EFSA Journal 2017;15(5):4788, 56 pp. <https://doi.org/10.2903/j.efsa.2017.4788>

**ISSN:** 1831-4732

© 2017 European Food Safety Authority. *EFSA Journal* published by John Wiley and Sons Ltd on behalf of European Food Safety Authority.

This is an open access article under the terms of the [Creative Commons Attribution-NoDerivs](https://creativecommons.org/licenses/by-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited and no modifications or adaptations are made.



The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.



## Summary

Following a request from the European Commission, the Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to re-evaluate the safety of sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) when used as a food additive.

The Panel was not provided with a newly submitted dossier and based its evaluation on previous evaluations and reviews, additional literature that has become available since then and the data available following a public call for data. The Panel noted that not all original studies on which previous evaluations were based were available for re-evaluation by the Panel.

Sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) are authorised as food additives in the European Union (EU) in accordance with Annex II and Annex III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012.

Toxicological data for sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) were evaluated by the Scientific Committee on Food (SCF) in 1978. The Committee established an acceptable daily intake (ADI) of 25 mg/kg body weight (bw) per day for sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495) singly or in combination. The SCF also established a separate group ADI for sorbitan monolaurate (E 493) and sorbitan monooleate (E 494) singly or in combination of 5 mg/kg bw per day calculated as sorbitan monolaurate. The latest evaluation of sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) by Joint FAO/WHO Expert Committee on Food Additives (JECFA) was done in 1982 where an ADI of 0–25 mg/kg bw per day were confirmed.

There were indications from toxicokinetic studies in rats with radiolabelled sorbitan monostearate that this sorbitan ester could be either hydrolysed to its fatty acid moiety and the corresponding anhydrides of sorbitol or excreted intact in the faeces. After absorption, sorbitan and isosorbide moieties, sorbitol or metabolites thereof are excreted via urine or exhaled as carbon dioxide. The fatty acid moiety enters the endogenous metabolism of fatty acids. The Panel considered that in case intact sorbitan monostearate be absorbed it would be hydrolysed presystemically. No absorption, distribution, metabolism and excretion (ADME) data were available for E 492, E 493, E 494 and E 495. However, the Panel considered that these sorbitan esters will follow the same metabolic and excretion pathways as sorbitan monostearate (E 491).

The Panel considered the acute toxicity of sorbitan esters (E 491, E 492, E 493, E 494 and E 495) very low.

The Panel considered that in the subchronic toxicity studies on sorbitan monolaurate the effects on the weight of the kidneys, which in female rats were associated with histopathological tubular changes, could be attributed to the excretion of large quantities of the sorbitan moiety in the urine. Subchronic toxicity studies were not available or too limited for sorbitan oleate, sorbitan monostearate, sorbitan tristearate or sorbitan monopalmitate.

The Panel noted that no experimental *in vitro* and *in vivo* genotoxicity data were available for sorbitan tristearate, sorbitan monooleate, sorbitan monopalmitate and limited studies with different shortcomings were available for sodium monostearate. However, the available data for sorbitan monolaurate and the *in silico* evaluation were sufficient to consider that sorbitan esters – E 491, E 492, E 493, E 494 and E 495 – did not raise concern with respect to genotoxicity.

The Panel considered the validity of the long-term studies performed in rats insufficient to be used for hazard characterisation. In an adequate long-term study in mice, the no observed adverse effect level (NOAEL) was 2% in the diet (equal to 2,600 mg sorbitan monostearate/kg bw per day). Furthermore, there was no indication of carcinogenicity in long-term studies both in mice and rats.

The Panel considered that the available reproductive and developmental toxicity studies with sorbitan monostearate have limitations but no adverse effects were reported.

The Panel considered that the available database on sorbitan monostearate (E 491) was sufficient to allocate an ADI based on the NOAEL of 2,600 mg sorbitan monostearate/kg bw per day in male mice identified in a long-term toxicity study.

The Panel noted that the available biological and toxicological data for sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) were

limited but considered that a read across with data on sorbitan monostearate can be performed. Overall, the Panel considered that there was no need for a separate ADI for sorbitan monolaurate (E 493) and sorbitan monooleate (E 494).

Based on the NOAEL of 2,600 mg sorbitan monostearate/kg bw per day identified in a long-term toxicity study in mice, taking into account the ratio between the molecular weight of sorbitan monostearate (430.62 g/mol) and sorbitan (164.16 g/mol), and applying an uncertainty factor of 100, the Panel derived a group ADI of 10 mg/kg bw per day, expressed as sorbitan, for sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) singly or in combination. This group ADI of 10 mg sorbitan/kg bw per day is, for example, equivalent to 26 mg sorbitan monostearate/kg bw per day.

In the absence of any information on the identity(ies) of the sorbitan ester(s) on which the maximum permitted levels (MPLs) and the reported use levels were expressed, the Panel calculated the exposure to sorbitan esters (E 491–495) by assuming that they were expressed as sorbitan monostearate.

The refined exposure estimates were based on 10 out of 19 food categories in which sorbitan esters (E 491–495) are authorised. Based on the assumption that the food additives are not used in the food categories for which no usage data were provided by food industry, the refined scenario would in general result in an overestimation of exposure according to Annex II of Regulation (EC) No 1333/2008. The Panel noted that no use levels were reported for eight food categories, while information from the Mintel's Global New Products Database (GNPD) showed that, for five out of these eight food categories sorbitan esters (E 491–495) were labelled, representing at most 0.6% of the total food items within the food categories. Overall, the Panel considered that exposure to sorbitan esters (E 491–495) from the food categories for which no usage data were reported was likely to have negligible impact on the refined exposure assessment. The Panel also noted that other potential sources of dietary exposure (in particular according to Annex III Part 1, 2 and 5) to sorbitan esters (E 491–495) were not considered in the exposure assessment scenarios because no data were available. Analytical data on the actual presence of sorbitan esters (E 491–495) in food are needed to reduce the sources of uncertainty.

The Panel selected the *non-brand-loyal refined scenario* as the most relevant exposure scenario for these food additives and performed the risk characterisation by comparing the *non-brand-loyal scenario* exposure estimates of sorbitan esters (E 491–495) with the group ADI of 10 mg sorbitan/kg bw per day, equivalent to 26 mg sorbitan monostearate/kg bw per day. The Panel concluded that the mean and the 95th percentile level did not exceed the ADI in any of the population groups and that there is no safety concern for the use of sorbitan esters (E 491, E 492, E 493, E 494 and E 495) as food additives at the reported uses and use levels.

An additional request to remove the congealing range from the EU specifications for sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495) was submitted to EFSA.

The applicant provided information on the composition of commercial stearic acid used for manufacturing of sorbitan monostearate (E 491) and sorbitan tristearate (E 492). As there is a lack of definition and/or specifications of 'commercial stearic acid', this appeared to contain stearic acid varying from 48.6–50.0% and palmitic acid 48.7–50.0% of the fatty acid moiety. The applicant has also demonstrated that the same samples of the food additives sorbitan monostearate (E 491) and sorbitan tristearate (E 492), when analysed by two of the few internationally available laboratories performing congealing point analysis (one internal and one external), ended up to significantly different values due to a lack of a clear and common methodology.

The Panel noted that congealing point correlates with the content of the fatty acid included in the name of the food additive, especially the content of stearic acid in sorbitan monostearate (E 491) and sorbitan tristearate (E 492). Despite the statement from the industry that nothing has changed in production process for decades, the composition of the raw materials may have changed (i.e. the content of minor constituents, i.e. the content of stearic acid in edible palmitic acid, a raw material for manufacturing of sorbitan monopalmitate (E 495)).

Overall, the Panel concluded that, this removal of the congealing range from the EU specifications would result in less characterisation of the various sorbitan esters of saturated fatty acids, but this identification parameter could be replaced by another one such as melting point.

The Panel recommended that:

- the European Commission should consider revising the maximum levels for sorbitan esters (E 491–495) set in Annex II to Regulation (EC) No 1333/2008 and expressing them as sorbitan equivalents.
- the European Commission should consider lowering the current limits for toxic elements (arsenic, cadmium, lead and mercury) in the EU specifications for sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) in order to ensure that they will not be a significant source of exposure to those toxic elements in food.
- data on the uses and use levels as well as analytical data on the actual presence of sorbitan esters (E 491–495), including information on their use according to Annex III to Regulation 1333/2008, should be provided in order to perform a more realistic refined exposure assessment.

## Table of contents

Abstract.....	1
Summary.....	3
1. Introduction.....	8
1.1. Background and Terms of Reference as provided by the European Commission .....	8
1.1.1. Background as provided by the European Commission .....	8
1.1.1.1. Re-evaluation of sorbitan esters (E 491–495) as food additives.....	8
1.1.1.2. Request for EFSA to consider the information submitted by an applicant regarding the amendment of the specifications of sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495), when providing a scientific opinion on the re-evaluation of those three food additives.....	8
1.1.2. Terms of Reference as provided by the European Commission .....	9
1.1.2.1. Re-evaluation of sorbitan esters (E 491–495) as food additives.....	9
1.1.2.2. Request for EFSA to consider the information submitted by an applicant regarding the amendment of the specifications of sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495), when providing a scientific opinion on the re-evaluation of those three food additives.....	9
1.2. Information on existing evaluations and authorisations.....	9
2. Data and methodologies .....	10
2.1. Data.....	10
2.2. Methodologies.....	10
3. Assessment.....	10
3.1. Technical data.....	10
3.1.1. Identity of the substances.....	10
3.1.2. Specifications.....	12
3.1.2.1. Request for the amendment of the EU specifications of sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495).....	16
3.1.3. Manufacturing process.....	18
3.1.4. Methods of analysis in food.....	18
3.1.4.1. Gas chromatography (GC).....	18
3.1.4.2. High-performance liquid chromatography (HPLC).....	19
3.1.4.3. Capillary Supercritical Fluid Chromatography (CSFC) .....	19
3.1.5. Stability of the substances and reaction and fate in food.....	19
3.2. Authorised uses and use levels.....	19
3.3. Exposure data.....	21
3.3.1. Reported use levels of sorbitan esters.....	21
3.3.1.1. Summarised data on reported use levels in foods provided by industry .....	21
3.3.2. Summarised data extracted from the Mintel's Global New Products Database .....	21
3.3.3. Food consumption data used for exposure assessment .....	22
3.3.3.1. EFSA Comprehensive European Food Consumption Database .....	22
3.3.3.2. Food categories considered for the exposure assessment of sorbitan esters (E 491–495).....	23
3.4. Exposure estimate to sorbitan esters (E 491–495) from their use as food additives.....	23
3.4.1. Regulatory maximum level exposure assessment scenario .....	24
3.4.2. Refined exposure assessment scenario.....	24
3.4.3. Dietary exposure to sorbitan esters (E 491–495) .....	25
3.4.4. Uncertainty analysis.....	25
3.5. Biological and toxicological data .....	26
3.5.1. Absorption, distribution, metabolism and excretion .....	26
3.5.1.1. <i>In vitro</i> .....	27
3.5.1.2. <i>In vivo</i> .....	27
3.5.2. Acute toxicity .....	28
3.5.3. Short-term and subchronic toxicity .....	29
3.5.3.1. Sorbitan monostearate (E 491).....	29
3.5.3.2. Sorbitan monolaurate (E 493) .....	29
3.5.3.3. Sorbitan monooleate (E 494) .....	31
3.5.4. Genotoxicity.....	31
3.5.4.1. <i>In vitro</i> studies.....	31
3.5.4.2. <i>In silico</i> studies .....	33
3.5.5. Chronic toxicity and carcinogenicity .....	33
3.5.5.1. Sorbitan monostearate (E 491).....	33



3.5.5.2. Sorbitan tristearate (E 492).....	35
3.5.5.3. Sorbitan monolaurate (E 493) .....	35
3.5.5.4. Sorbitan monooleate (E 494) .....	35
3.5.5.5. Sorbitan monopalmitate (E 495).....	35
3.5.6. Reproductive and developmental toxicity.....	36
3.5.7. Hypersensitivity, allergenicity and food intolerance.....	36
3.5.8. Studies with other emulsifiers.....	37
3.6. Discussion .....	37
4. Conclusions.....	39
5. Recommendations.....	40
Documentation provided to EFSA .....	40
References.....	41
Abbreviations.....	44
Appendix A – Summary of the reported use levels (mg/kg or mg/L as appropriate) of sorbitan esters (E 491–495) provided by industry .....	46
Appendix B – Number and percentage of food products labelled with sorbitan esters (E 491–495) out of the total number of food products present in Mintel GNPD per food subcategory between 2011 and 2016 .....	48
Appendix C – Concentration levels of sorbitan esters (E 491–495) used in the regulatory maximum level exposure assessment scenario and the refined exposure scenario (mg/kg or mL/kg as appropriate).....	49
Appendix D – Main food categories contributing to exposure to sorbitan esters (E 491–495) according to the regulatory maximum level exposure assessment scenario.....	51
Appendix E – Summary of total estimated exposure of sorbitan esters (E 491–495) from their use as food additives for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day).....	54

## 1. Introduction

The present opinion deals with the re-evaluation of the safety of sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) when used as food additives.

### 1.1. Background and Terms of Reference as provided by the European Commission

#### 1.1.1. Background as provided by the European Commission

##### 1.1.1.1. Re-evaluation of sorbitan esters (E 491–495) as food additives

Regulation (EC) No 1333/2008<sup>1</sup> 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 (EU). 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 Regulation (EU) No 257/2010<sup>2</sup>. 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.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU<sup>3</sup> of 2001. The report 'Food additives in Europe 2000'<sup>4</sup> submitted by the Nordic Council of Ministers to the Commission, provides additional information for the prioritisation of additives for re-evaluation. As colours were among the first additives to be evaluated, these food additives should be re-evaluated with a highest priority.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010, the 2003 Terms of References are replaced by those below.

##### 1.1.1.2. Request for EFSA to consider the information submitted by an applicant regarding the amendment of the specifications of sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495), when providing a scientific opinion on the re-evaluation of those three food additives

The use of food additives is regulated under the European Parliament and Council Regulation (EC) No 1333/2008 on food additives. Only food additives that are included in the Union list, in particular in Annex II to that regulation, may be placed on the market and used in foods under the conditions of use specified therein. Moreover, food additives should comply with the specifications as referred in Article 14 of that Regulation and laid down in Commission Regulation (EU) No 231/2012<sup>5</sup>.

Sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495) are currently authorised food additives in the EU, under Annex II of Regulation (EC) No 1333/2008, and specifications have been adopted for them.

The SCF assessed the information on those food additives and expressed its opinion on a report on Emulsifiers, Stabilizers, Thickeners and Gelling Agents dated from December 1978 (SCF, 1978).

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> COM(2001) 542 final.

<sup>4</sup> Food Additives in Europe 2,000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord 2002:560.

<sup>5</sup> Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p. 1–282.



In addition, also the Joint FAO/WHO Expert Committee on Food Additives (JECFA) assessed and established specifications for those food additives in 2006 (JECFA, 2006).

Commission Regulation (EU) No 257/2010 of 25 March 2010 sets up a programme for the re-evaluation of approved food additives. This programme lays down which additives need to be re-evaluated and the procedure, the priorities and the timelines for the re-evaluation.

Taking into account the application that has been introduced regarding an amendment of the specifications of the additives E 491, E 492 and E 495 and the calendar of the re-evaluation programme, in which sorbitan esters are due to be re-evaluated by 31.12.2016, the European Commission asks EFSA to consider the information submitted by that applicant when providing a scientific opinion on the re-evaluation of those food additives.

### 1.1.2. Terms of Reference as provided by the European Commission

#### 1.1.2.1. Re-evaluation of sorbitan esters (E 491–495) as food additives

The Commission asks EFSA to re-evaluate the safety of food additives already permitted in the 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 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.

#### 1.1.2.2. Request for EFSA to consider the information submitted by an applicant regarding the amendment of the specifications of sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495), when providing a scientific opinion on the re-evaluation of those three food additives

The European Commission asks EFSA to consider the information submitted by an applicant regarding the amendment of the specifications of sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495), when providing a scientific opinion on the re-evaluation of those three food additives.

### 1.2. Information on existing evaluations and authorisations

Sorbitan esters (E 491–495) are food additives authorised according to Annex II and Annex III of Regulation (EC) No 1333/2008. Specific purity criteria on sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) have been defined in Commission Regulation (EU) No 231/2012.

In 1978, the SCF endorsed a group acceptable daily intake (ADI) established by JECFA of 25 mg/kg body weight (bw) per day (JECFA, 1974) for sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495) singly or in combination. The SCF also established a separate group ADI for sorbitan monolaurate (E 493) and sorbitan monooleate (E 494) singly or in combination of 5 mg/kg bw per day. The Committee reviewed the studies of Krantz and the new short-term studies sorbitan monolaurate (E 493) and sorbitan monooleate (E 494). On this evidence, the Committee established a 'global ADI' of 5 mg/kg bw for sorbitan monolaurate (E 493) and sorbitan monooleate (E 494) singly or in combination, calculated as sorbitan monolaurate.

JECFA assessed sorbitan monoesters of palmitic acid and stearic acid and triesters of stearic acid in 1974 and 1982a,b. A group ADI of 0–25 mg/kg bw per day as the sum of the sorbitan esters of palmitic and stearic acid was allocated in 1974 based on a no observed adverse effect level (NOAEL) from long-term feeding studies in rats. This ADI was confirmed by JECFA in 1982 and extended to the esters of lauric and oleic acid.

An additional review, performed by Nordic Council of Ministers concluded that the data on these substances are old and incomplete, and that there is a potential for exceeding the ADI established by JECFA (TemaNord, 2002).

Sorbitan monolaurate is included in the European Union Register<sup>6</sup> of feed additives (Regulation (EC) No 1831/2003<sup>7</sup>). Sorbitan monostearate, sorbitan tristearate, sorbitan monolaurate, sorbitan

<sup>6</sup> Available online: [http://ec.europa.eu/food/food/animalnutrition/feedadditives/comm\\_register\\_feed\\_additives\\_1831-03.pdf](http://ec.europa.eu/food/food/animalnutrition/feedadditives/comm_register_feed_additives_1831-03.pdf)

<sup>7</sup> Regulation (EC) No 1831/2003 of the European Parliament and the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003.

monooleate and sorbitan monopalmitate are permitted as 'emulsifying' in cosmetic products (European Commission database-CosIng<sup>8</sup>).

## 2. Data and methodologies

### 2.1. Data

The Panel on Food Additives and Nutrient Sources added to Food (ANS) was not provided with a newly submitted dossier. EFSA launched public calls for data<sup>9,10,11</sup> to collect information from interested parties.

The Panel based its assessment on information submitted to EFSA following the public calls for data, information from previous evaluations and additional available literature up to February 2017. Attempts were made at retrieving relevant original study reports on which previous evaluations or reviews were based, however not always these were available to the Panel.

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database<sup>12</sup>) was used to estimate the dietary exposure.

The Mintel's Global New Products Database (GNPD) is an online resource listing food products and compulsory ingredient information that should be included in labelling. This database was used to verify the use of sorbitan esters (E 491–495) in food products.

### 2.2. Methodologies

This opinion was formulated following the principles described in the EFSA Guidance on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing guidance documents from the EFSA Scientific Committee.

The ANS Panel assessed the safety of sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494), and sorbitan monopalmitate (E 495) as food additives in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the Scientific Committee on Food (SCF, 2001) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

When the test substance was administered in the feed or in the drinking water, but doses were not explicitly reported by the authors as mg/kg bw per day based on actual feed or water consumption, the daily intake was calculated by the Panel using the relevant default values as indicated in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012) for studies in rodents or, in the case of other animal species, by JECFA (2000). In these cases, the daily intake is expressed as 'equivalent'.

Dietary exposure to sorbitan esters (E 491–495) from their use as food additives was estimated combining food consumption data available within the EFSA Comprehensive European Food Consumption Database with the maximum permitted levels according to Annex II to Regulation (EC) No 1333/2008 and/or reported use levels submitted to EFSA following a call for data. Different scenarios were used to calculate the exposure (see Section 3.3.1). Uncertainties on the exposure assessment were identified and discussed.

## 3. Assessment

### 3.1. Technical data

#### 3.1.1. Identity of the substances

Sorbitan as such is an intermediate in the conversion (via dehydration) of sorbitol to isosorbide. Pathways for sorbitol dehydration have been described by Yamaguchi et al. (2011). The dehydration

<sup>8</sup> Available online: <http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.simple>

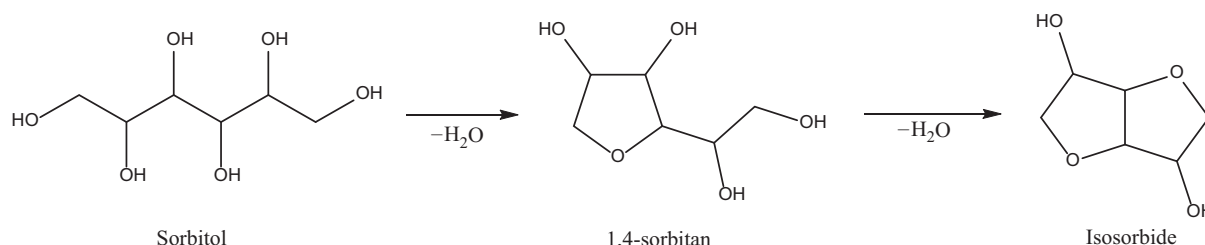
<sup>9</sup> Call for scientific data on food additives permitted in the EU and belonging to the functional classes of emulsifiers, stabilisers and gelling agents. Published: 22 November 2009. Available from: <http://www.efsa.europa.eu/en/dataclosed/call/ans091123>

<sup>10</sup> Call for food additives usages level and/or concentration data in food and beverages intended to human consumption. Published: 27 March 2013. Available online: <http://www.efsa.europa.eu/en/dataclosed/call/130327>

<sup>11</sup> Call for scientific data on selected food additives permitted in the EU- Extended deadline: 1 September 2014 (batch A), 1 November 2014 (batch B) Available online: <http://www.efsa.europa.eu/en/dataclosed/call/140324.htm>

<sup>12</sup> Available online: <http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm>

reaction usually produces sorbitan as a mixture of five- and six-membered cyclic ethers (sorbitol, 1,4-anhydrosorbitol, 1,5-anhydrosorbitol, 2,5-monoanhydrosorbitol, 3,6-monoanhydrosorbitol and 1,4,3,6-dianhydrosorbitol (isosorbide)) with the five-membered 1,4-anhydrosorbitol (1,4-sorbitan) being the dominate product (see also Section 3.1.3) The rate of formation of sorbitan is typically greater than that of isosorbide, which allows it to be produced selectively, provided that the reaction conditions are carefully controlled. The reaction sequence is shown in Figure 1.



**Figure 1:** Dehydration reaction steps of sorbitol (adapted from Li et al., 2013; Published by The Royal Society of Chemistry, CC BY 3.0)

Fatty acid esters of sorbitan fatty acid are non-ionic, partial esters of the common fatty acids (lauric, palmitic, stearic and oleic) and hexitol anhydrides derived from sorbitol. Commercial products may be mixtures of fatty acid esters of 1,4- and 1,5-anhydrosorbitol and 1,4,3,6-dianhydrosorbitol. The Panel noted that the position of the fatty acid moiety in the sorbitan fatty acid molecule is undefined.

According to Commission Regulation (EU) No 231/2012, only the sorbitan esters – sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) – are allowed to be used as food additives. The identity of the food additives is given in Table 1.

**Table 1:** Identity of the sorbitan esters (E 491 – 495)

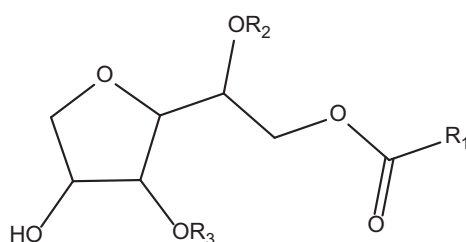
	<b>Sorbitan monostearate (E 491)</b>	<b>Sorbitan tristearate (E 492)</b>	<b>Sorbitan monolaurate (E 493)</b>	<b>Sorbitan monooleate (E 494)</b>	<b>Sorbitan monopalmitate (E 495)</b>
<b>Synonyms<sup>(a)</sup></b>	Sorbitan, monooctadecanoate; Span 60	Sorbitan, trioctadecanoate; Span 65	Sorbitan, monododecanoate; Span 20	Sorbitan, mono-(9Z)-9-octadecenoate; Span 80	Sorbitan, mono-hexadecanoate; Span 40
<b>CAS Registry Number</b>	1338-41-6	26658-19-5	1338-39-2	1338-43-8	26266-57-9
<b>EINECS</b>	215-664-9	247-891-4	215-663-3	215-665-4	247-568-8
<b>Molecular formula</b>	C <sub>24</sub> H <sub>46</sub> O <sub>6</sub>	C <sub>60</sub> H <sub>114</sub> O <sub>8</sub>	C <sub>18</sub> H <sub>34</sub> O <sub>6</sub>	C <sub>24</sub> H <sub>44</sub> O <sub>6</sub>	C <sub>22</sub> H <sub>42</sub> O <sub>6</sub>
<b>Molecular weight (g/mol)</b>	430.62	963.56	346.46	428.60	402.57

CAS: Chemical Abstracts Service; EINECS: European Inventory of Existing Chemical Substances.

(a): Most common synonyms (SciFinder®, online).

The Panel noted that the sorbitan moiety of sorbitan esters (E 491–495) contains four chiral centres (i.e. asymmetrically substituted carbon atoms). Accordingly, it could theoretically exist 16 (2<sup>4</sup>) different optical isomers. Furthermore, according to Thyssen and Andersen (1998), a sorbitan ester may include more than 200 possible congeners. The Panel also noted that the stereochemical composition of the sorbitan esters (E 491–495) is not specified in Commission Regulation (EU) No 231/2012.

Their structural formulae are presented in Figure 2:



Sorbitan monostearate (E 491)	$R_1 = C_{17}H_{35}$	$R_2 = H$	$R_3 = H$
Sorbitan tristearate (E 492)	$R_1 = C_{17}H_{35}$	$R_2 = C_{17}H_{35}$	$R_3 = C_{17}H_{35}$
Sorbitan monolaurate (E 493)	$R_1 = C_{11}H_{23}$	$R_2 = H$	$R_3 = H$
Sorbitan monooleate (E 494)	$R_1 = C_{17}H_{33}$	$R_2 = H$	$R_3 = H$
Sorbitan monopalmitate (E 495)	$R_1 = C_{15}H_{31}$	$R_2 = H$	$R_3 = H$

<sup>(a)</sup> The Panel noted that in Figure 1 only 1 (sorbitan form) out of three forms (sorbitol, sorbitan and isosorbide esters) is presented.

**Figure 2:** General structural formulae for sorbitan esters (E 491–495)<sup>(a)</sup>

### 3.1.2. Specifications

Specifications of the sorbitan fatty acid esters sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) have been defined in Commission Regulation No 231/2012 and by JECFA (2006), as described in Tables 2–6.

**Table 2:** Specifications of sorbitan monostearate (E 491) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation No 231/2012	JECFA (2006)
<b>Definition</b>	A mixture of the partial esters of sorbitol and its anhydrides with edible, commercial stearic acid	
<b>Assay</b>	Content not less than 95% of a mixture of sorbitol, sorbitan, and isosorbide esters	Saponification of 100 g of the sample yields approximately 31.5 g of polyols and 73 g of fatty acid. The polyol content shall be not less than 95% of a mixture of sorbitol, 1,4-sorbitan and isosorbide
<b>Description</b>	Light cream- to tan-coloured beads or flakes or a hard, waxy solid with a slight characteristic odour	
<b>Identification</b>		
Solubility	Soluble at temperatures above its melting point in toluene, dioxane, carbon tetrachloride, ether, methanol, ethanol and aniline; insoluble in petroleum ether and acetone; insoluble in cold water but dispersible in warm water; soluble with haze at temperatures above 50°C in mineral oil and ethyl acetate	Soluble at temperatures above its melting point in toluene, dioxane, carbon tetrachloride, ether, methanol, ethanol and aniline; insoluble in petroleum ether and acetone; insoluble in cold water but dispersible in warm water; soluble with haze at temperatures above 50°C in mineral oil and ethyl acetate
Congealing range	50–52°C	50–52°C
Infrared absorption spectrum	Characteristic of a partial fatty acid ester of a polyol	The infrared spectrum of the sample is characteristic of a partial fatty acid ester of a polyol
<b>Purity</b>		
Water content	Not more than 2% (Karl Fischer method)	Not more than 1.5% (Karl Fischer Method)
Sulfated ash	Not more than 0.5%	–
Acid value	Not more than 10	Not less than 5 and not more than 10

	Commission Regulation No 231/2012	JECFA (2006)
Saponification value	Not less than 147 and not more than 157	Not less than 147 and not more than 157
Hydroxyl value	Not less than 235 and not more than 260	Not less than 235 and not more than 260
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

**Table 3:** Specifications of sorbitan tristearate (E 492) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation No 231/2012	JECFA (2006)
<b>Definition</b>	A mixture of the partial esters of sorbitol and its anhydrides with edible, commercial stearic acid	
<b>Assay</b>	Content not less than 95% of a mixture of sorbitol, sorbitan, and isosorbide esters	Saponification of 100 g of the product shall yield not less than 14 g and not more than 21 g of polyols and not less than 85 g and not more than 92 g of fatty acids; and the polyol content shall be not less than 95% of a mixture of sorbitol, 1,4-sorbitan and isosorbide
<b>Description</b>	Light cream- to tan-coloured beads or flakes or hard, waxy solid with a slight odour	
<b>Identification</b>		
<b>Solubility</b>	Slightly soluble in toluene, ether, carbon tetrachloride and ethyl acetate; dispersible in petroleum ether, mineral oil, vegetable oils, acetone and dioxane; insoluble in water, methanol and ethanol	Slightly soluble in toluene, ether, carbon tetrachloride and ethyl acetate; dispersible in petroleum ether, mineral oil, vegetable oils, acetone and dioxane; insoluble in water, methanol and ethanol
<b>Congearing range</b>	47–50°C	47–50°C
<b>Infrared absorption spectrum</b>	Characteristic of a partial fatty acid ester of a polyol	–
<b>Purity</b>		
<b>Water content</b>	Not more than 2% (Karl Fischer method)	Not more than 1.5% (Karl Fischer Method)
<b>Sulfated ash</b>	Not more than 0.5%	Not more than 0.5%
<b>Acid value</b>	Not more than 15	Not more than 15
<b>Saponification value</b>	Not less than 176 and not more than 188	Not less than 176 and not more than 188
<b>Hydroxyl value</b>	Not less than 66 and not more than 80	Not less than 66 and not more than 80
<b>Arsenic</b>	Not more than 3 mg/kg	–
<b>Lead</b>	Not more than 2 mg/kg	Not more than 2 mg/kg
<b>Mercury</b>	Not more than 1 mg/kg	–
<b>Cadmium</b>	Not more than 1 mg/kg	–

**Table 4:** Specifications of sorbitan monolaurate (E 493) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation No 231/2012	JECFA (2006)
<b>Definition</b>	A mixture of the partial esters of sorbitol and its anhydrides with edible, commercial lauric acid	
<b>Assay</b>	Content not less than 95% of a mixture of sorbitol, sorbitan, and isosorbide esters	Saponification of 100 g of the sample yields not less than 36 g and not more than 49 g of polyols, and not less than 56 g and not more than 68 g of fatty acids. The polyol content shall be not less than 95% of a mixture of sorbitol, 1,4-sorbitan and isosorbide
<b>Description</b>	Amber-coloured oily viscous liquid, light cream- to tan-coloured beads or flakes or a hard, waxy solid with a slight odour	
<b>Identification</b>		
Solubility	Dispersible in hot and cold water	Dispersible in hot and cold water
Infrared absorption spectrum	Characteristic of a partial fatty acid ester of a polyol	–
<b>Purity</b>		
Water content	Not more than 2% (Karl Fischer method)	Not more than 2% (Karl Fischer method)
Sulfated ash	Not more than 0.5%	Not more than 0.5%
Acid value	Not more than 7	Not more than 7
Saponification value	Not less than 155 and not more than 170	Not less than 155 and not more than 170
Hydroxyl value	Not less than 330 and not more than 358	Not less than 330 and not more than 358
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

**Table 5:** Specifications of sorbitan monooleate (E 494) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation No 231/2012	JECFA (2006)
<b>Definition</b>	A mixture of the partial esters of sorbitol and its anhydrides with edible, commercial oleic acid. Major constituent is 1,4-sorbitan monooleate. Other constituents include isosorbide monooleate, sorbitan dioleate and sorbitan trioleate	
<b>Assay</b>	Content not less than 95% of a mixture of sorbitol, sorbitan, and isosorbide esters (E 491)	Saponification of 100 g of the sample yields not less than 28 g and not more than 32 g of polyols, and not less than 73 g and not more than 77 g of fatty acids. The polyol content shall be not less than 95% of a mixture of sorbitol, 1,4-sorbitan and isosorbide
<b>Description</b>	Amber-coloured viscous liquid, light cream- to tan-coloured beads or flakes or a hard, waxy solid with a slight characteristic odour	



	Commission Regulation No 231/2012	JECFA (2006)
<b>Identification</b>		
Solubility	Soluble at temperatures above its melting point in ethanol, ether, ethyl acetate, aniline, toluene, dioxane, petroleum ether and carbon tetrachloride. Insoluble in cold water, dispersible in warm water	Soluble at temperatures above its melting point in ethanol, ether, ethyl acetate, aniline, toluene, dioxane, petroleum ether and carbon tetrachloride; insoluble in cold water, dispersible in warm water
Iodine value	The residue of oleic acid, obtained from the saponification of the sorbitan monooleate in assay, has a iodine value between 80 and 100	The residue of oleic acid, obtained from the saponification of the sorbitan monooleate in assay, has a iodine value between 80 and 100
<b>Purity</b>		
Water	Not more than 2% (Karl Fischer method)	Not more than 2% (Karl Fischer method)
Sulfated ash	Not more than 0.5%	Not more than 0.5%
Acid value	Not more than 8	Not more than 8
Saponification value	Not less than 145 and not more than 160	Not less than 145 and not more than 160
Hydroxyl value	Not less than 193 and not more than 210	Not less than 193 and not more than 210
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

**Table 6:** Specifications of sorbitan monopalmitate (E 495) according to Commission Regulation (EU) No 231/2012 and JECFA (2006)

	Commission Regulation No 231/2012	JECFA (2006)
<b>Definition</b>	A mixture of the partial esters of sorbitol and its anhydrides with edible, commercial palmitic acid	
Assay	Content not less than 95% of a mixture of sorbitol, sorbitan, and isosorbide esters	Saponification of 100 g of the sample yields approximately 37 g of polyols and 65 g of fatty acid. The polyol content shall be approximately 95% of a mixture of sorbitol, 1,4-sorbitan and isosorbide
<b>Description</b>	Light cream- to tan-coloured beads or flakes or a hard, waxy solid with a slight characteristic odour	
<b>Identification</b>		
Solubility	Soluble at temperatures above its melting point in ethanol, methanol, ether, ethyl acetate, aniline, toluene, dioxane, petroleum ether and carbon tetrachloride. Insoluble in cold water but dispersible in warm water	Soluble at temperatures above its melting point in ethanol, methanol, ether, ethyl acetate, aniline, toluene, dioxane, petroleum ether and carbon tetrachloride; insoluble in cold water but dispersible in warm water
Congearing range	45–47°C	45–47°C
Infrared absorption spectrum	Characteristic of a partial fatty acid ester of polyol	The infrared spectrum of the sample is characteristic of a partial fatty acid ester of a polyol
<b>Purity</b>		
Water	Not more than 2% (Karl Fischer method)	Not more than 1.5% (Karl Fischer Method)
Sulfated ash	Not more than 0.5%	
Acid value	Not more than 7.5	Not less than 4.0 and not more than 7.5
Saponification value	Not less than 140 and not more than 150	Not less than 140 and not more than 150

	Commission Regulation No 231/2012	JECFA (2006)
Hydroxyl value	Not less than 270 and not more than 305	Not less than 270 and not more than 305
Arsenic	Not more than 3 mg/kg	–
Lead	Not more than 2 mg/kg	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg	–
Cadmium	Not more than 1 mg/kg	–

The Panel noted that, according to the EU specifications for sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495), impurities of the toxic elements arsenic, cadmium, lead and mercury are accepted up concentrations of 3, 1, 2 and 1 mg/kg, respectively. Contamination at those levels could have a significant impact on the exposure already are close to the health based guidance values or benchmark doses (lower confidence limits) established by EFSA (EFSA CONTAM Panel, 2009a,b, 2010, 2012a,b,c, 2014).

The Panel noted that according to the EU specifications there is no information on the stereochemistry of sorbitol, sorbitans and isosorbides.

### 3.1.2.1. Request for the amendment of the EU specifications of sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495)

Congealing range is included in the identification of the EU specifications for sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495) because they are waxy solids, while for sorbitan monolaurate (E 493) and sorbitan monooleate (E 494) being liquids, no congealing range is included in the EU specifications.

Food additive	Congeeing range (Commission Regulation (EU) No 231/2012)
E 491	50–52°C
E 492	47–50°C
E 495	45–47°C

The applicant requested to remove the congealing range from the EU specifications for sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495) as justified:

- 'As the precision of the analytical method is poor it is not suitable for distinguishing between various sorbitan esters'.
- 'No Contract Research Laboratory which could analyse congealing range according to JECFA method has been found'.
- 'The gap in congealing range between E 491 and E 495 is not logical due to variations in palmitic and stearic acid in commercially available fatty acid raw materials'.
- 'The congealing range does not add extra information as two other identification methods are available (solubility and IR)'.

The applicant provided additional information on the composition of commercial stearic acid used for manufacturing of sorbitan monostearate (E 491) and sorbitan tristearate (E 492) (Documentation provided to EFSA n. 25). As there is a lack of definition and/or specifications of 'commercial stearic acid', this appeared to contain stearic acid varying from 48.6–50.0% and palmitic acid 48.7–50.0% of the fatty acid moiety.

The applicant has also demonstrated that the same samples of the food additives sorbitan monostearate (E 491) and sorbitan tristearate (E 492), when analysed by two of the few internationally available laboratories performing congealing point analysis (one internal and one external), ended up to significantly different values due to a lack of a clear and common methodology.

The Panel noted that:

- the aim of a specification is to establish physicochemical properties of the food additives.
- according to Regulation (EU) 231/2012 (recital (3)) 'It is necessary to take into account the specifications and analytical techniques as set out in the Codex Alimentarius drafted by the Joint FAO/WHO Expert Committee on Food Additives (hereafter JECFA)'. Therefore, when a JECFA method cannot be used, an alternative method can be used, e.g. the one described in

the pharmacopoeia as suggested by the applicant. Nevertheless, a lack of a common methodology could lead to difficulties to conclude on the conformity of the analytical sample of the food additive with EU specifications.

- if variations in the ratio of stearic acid in palmitic acid are high enough to result in a non-conformity with the criterion on congealing range, those food additives do not comply with EU specifications, and are out of the scope of the re-evaluation. Nevertheless, if the purity of the product tested in the pivotal study could also cover those products, the conclusion could be expanded in order to include also those products.
- according to the EU specifications for sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495), the infrared (IR) absorption spectrum is described as 'characteristic of a partial fatty acid ester of a polyol' for all of them. Therefore, the description of the IR absorption spectrum is very general and cannot be used to distinguish between the different sorbitan esters.

According to the applicant (Documentation provided to EFSA n. 24), the request to remove the congealing range from the EU specifications has not an impact in the safety of the substance due to:

- 'The products are produced according to the legislation';
- 'Nothing has been changed in production process for decades';
- 'Congealing range is not included in Japanese legislation';
- 'The EU specifications for E 493 and E 494 do not include the congealing range'.

The applicant remarked that the SCF (1978) opinion indicated that 'The Committee was informed that the toxicological evaluations on sorbitan monopalmitate and sorbitan tristearate were carried out on material conforming to the FAO specifications, in the case of sorbitan monostearate on material conforming to the specifications in the Food Chemicals Codex 1972'. The Panel noted that the JECFA specifications for sorbitan monopalmitate (E 495) and sorbitan tristearate (E 492) contain the congealing range; whilst the Food Chemical Codex (2010–2011) does not specify the congealing range for sorbitan monostearate (E 491).

The Panel noted that:

- based on the information provided, congealing point correlates with the content of the fatty acid included in the name of the food additive, especially the content of stearic acid in sorbitan monostearate (E 491) and sorbitan tristearate (E 492).
- If the reference to congealing point would be deleted, the product would become less identifiable and the only remaining criterion, solubility, may not be sufficient to distinguish those products.
- Despite the statement by the applicant that nothing has changed in production process for decades, the Panel noted that the composition of the raw materials may have changed (i.e. the content of minor constituents, i.e. the content of stearic acid in edible palmitic acid, a raw material for manufacturing of sorbitan monopalmitate (E 495)).
- 'Commercial stearic acid' mentioned as a starting material in the definition of the EU specifications of the food additives sorbitan monostearate (E 491) and sorbitan tristearate (E 492) appeared to consist only of 50% stearic acid. Under consideration that the rest of the starting material 'commercial stearic acid' consists mainly of palmitic acid, the use of the food additive sorbitan monostearate (E 491) and sorbitan tristearate (E 492), containing an equimolecular mixture of stearic and palmitic acid, would not raise a safety concern regarding their fatty acid moiety. Nevertheless, the fact that the food additive sorbitan monostearate (E 491) could consist of sorbitan monostearate and monopalmitate in equal amounts, and that sorbitan tristearate (E 492) consists of sorbitan tristearate and tripalmitate in equal amounts, would mislead consumers regarding the nature and identity of the food additive according to Regulation (EU) No 1169/2011<sup>13</sup>.

<sup>13</sup> Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/e/EC and Commission Regulation (EC) No 608/2004. OJ L 304, 22.11.2011, p. 18–46.

- (article 7 paragraph 1 (a)). Furthermore, as no data on the fatty acid composition of the food additive sorbitan monopalmitate (E 495) have been provided to the Panel, it cannot be excluded that sorbitan monostearate (E 491) and sorbitan monopalmitate (E 495) are identical.
- Finally, if there is still a need to differentiate between sorbitan monostearate (E 491) and sorbitan monopalmitate (E 495) or to restrict the content of fatty acids others than stearic acid for sorbitan tristearate (E 492), congealing range could be replaced by another identification parameter such as melting range.

### 3.1.3. Manufacturing process

The sorbitan esters of fatty acids are obtained by direct esterification of commercial, food-grade stearic, lauric, oleic or palmitic acid with food-grade sorbitol (SCF, 1978; CIR, 1985; TemaNord, 2002; Cottrell and van Peij, 2015).

According to the EU specifications for sorbitan esters (E 491–495), commercial stearic, palmitic, lauric or oleic acid can be used as a starting material for the production of the food additives. According to information from EFEMA (Technical dossier [Documentation provided to EFSA n. 24]), commercial stearic acid which is used for the productions of the food additives may contain up to 48.7–50.0% palmitic acid. No information has been provided on the purity of commercial palmitic, lauric and oleic acid.

According to Cottrell and van Peij (2015), sorbitan esters of fatty acids are derived from a reaction of sorbitol and a commercial grade fatty acid. Sorbitol is produced from D-glucose which is obtained from maize or tapioca. The purity of the fatty acids depends on the raw material source as well as on the manufacturing process, fatty acids derived from vegetable sources being the most used. Sorbitan esters are produced by direct esterification of sorbitol with fatty acids. Usually, an acidic catalyst such as phosphoric acid, and a caustic soda-type catalyst are used together. The final sorbitan ester is not a pure compound but 'a heterodispersed soup of components, all related but dissimilar'.

Stockburger (1981) described a process in which sorbitan fatty acid esters were prepared from anhydro sorbitols as starting material. Dehydration of sorbitol was carried out at about 120°C, under reduced pressure (e.g. 5 mm absolute), in the presence of *p*-toluenesulfonic acid as the acid catalyst. According to the authors, dehydro sorbitols so obtained were a mixture of sorbitans containing 1,4-sorbitan, 2,5-sorbitan and 3,6-sorbitan, with small amounts of isosorbide and unreacted sorbitol; 1,4-sorbitan is the largest constituent of the dehydro sorbitol. Dehydro sorbitans were then reacted under an inert atmosphere (nitrogen), in an anhydrous medium in the presence of the appropriate fatty acids. Sodium hydroxide was used as catalyst and activated carbon was added as decolourising agent. According to the author, the reaction temperature should not exceed 215°C. Required reaction times are about 2.5–5 h. After completion, the reaction was terminated by cooling down the reaction product mixture and adding a small amount of phosphoric acid sufficient to neutralise the alkali present. The products obtained by the process were mixtures of sorbitan esters of fatty acids; it is indicated by the author that also some sorbitol and sorbide esters were present.

### 3.1.4. Methods of analysis in food

Several publications are available for the analysis of sorbitan esters in food. An overview of the methods is given by Wood et al. (2004).

#### 3.1.4.1. Gas chromatography (GC)

Sahasrabudhe and Chadha (1969) described a procedure for the separation and identification of sorbitan esters, which had been synthesised in the laboratory. The final step of identification has been carried out by GC as trimethylsilyl ethers, after a thin-layer chromatography (TLC) separation. No information was given on limits of detection (LODs). No real food samples were tested.

Lundquist and Meloan (1971) analysed samples of whipped cream spiked with sorbitan monostearate. The esters were extracted, saponified and the polyol formed was measured via GC on a polar column without derivatisation. Only one out of the three expected peaks of polyols (sorbitol, isosorbide and sorbitan) appeared in the chromatogram. No information was given on the performance of the method.

Tsuda et al. (1984) analysed confectionery samples spiked with sorbitan monostearate by using saponification, followed by a derivatisation of sorbitan, isosorbide and sorbitol, and GC analysis. The LOD was 0.01% equal to 100 mg/kg.

An alternative approach for sorbitan esters involved extraction with tetrahydrofuran and purification by silica gel chromatography. After clean-up with solvents, sorbitan esters were eluted with methanol,

converted to their trimethylsilyl ether derivatives and determined by GC. The performance of the method in ice cream was reported as obtaining a recovery of > 90%, with a LOD of 50 ppm (Yomota et al., 1986; Burch et al., 2007).

### 3.1.4.2. High-performance liquid chromatography (HPLC)

Garti et al. (1983) have performed an analysis of the pure food additives sorbitan monostearate, sorbitan tristearate and sorbitan monooleate via HPLC, where the proportions of the various constituents of the food additives could be demonstrated. No real food samples were tested.

A reversed-phase HPLC method employing a CIS column has been developed by Wang and Fingas (1994a) for the separation of sorbitan esters used as surfactants for sea-water treatment after an oil spoilage and the quantitative distribution of the sorbitan mono-, di-, tri-, and tetraester fractions. Six samples of sorbitan esters were studied by using relative response factors obtained from analysis of pure glycerides of fatty acids. The effects of mobile phase composition on the accuracy and reliability of the distribution of the sorbitan esters were investigated. No real food samples were tested.

Thyssen and Andersen (1998) described a method for the determination of sorbitan tristearate in vegetable oils, according to which the sample was diluted in heptane and then treated with a silica cartridge and hydrolysed on the column. Sorbitol together with isosorbide and sorbitan were eluted, but only sorbitol and sorbitan could be quantified by HPLC equipped with a refractive index detector. The reported recovery of sorbitan tristearate of a food additive with a known composition of the sorbitol esters was 97–109%, with a standard deviation of 5.7–11.2, and LOD of 0.4% equal to 4,000 mg/kg (Burch et al., 2007). The Panel noted that the LOD of the method lied high above the maximum level for sorbitan esters (E 491–495) in edible oils and fats (Regulation (EC) No 1333/2008).

### 3.1.4.3. Capillary Supercritical Fluid Chromatography (CSFC)

An approach to identify sorbitan esters used as surfactants for sea-water treatment after an oil spoilage has been developed by Wang and Fingas (1994b) by using CSFC. Hydrophilic–lipophilic balance, which describes the hydrophilic and hydrophobic characteristics of surfactants, could be correlated with the distribution of the sorbitan esters. A combination of solid-phase extraction and CSFC was used to separate, concentrate and analyse sorbitan esters of fatty acids. No real food samples were tested.

The Panel noted that out of all analytical methods available, GC analysis appears to deliver the most accurate and reliable results, fit for purposes of food controls.

### 3.1.5. Stability of the substances and reaction and fate in food

Undiluted sorbitan fatty acid esters, as well as neutral, mildly alkaline or mildly acidic solutions, were stable at room temperature within a pH range of 2–12. In contrast, hydrolysis occurred in the presence of water at excessively high or low pH conditions (CIR, 1985).

Autoxidation of fatty acids leads to the formation of hydroperoxides, which decompose to oxygen-containing products such as aldehydes, ketones and hydroxy compounds. The effect of atmospheric oxygen on fatty acids depends primarily on the temperature, the number of double bonds and the molecular structure. Saturated fatty acids showed little tendency to undergo autoxidation, whereas unsaturated fatty acids and especially polyunsaturated acids, were very susceptible to autoxidation (Anneken et al., 2012).

According to industry (Croda, online), 'sorbitan esters are stable in mild acids, alkalis and electrolytes and do not react with ionic ingredients or active'.

## 3.2. Authorised uses and use levels

Maximum levels of sorbitan esters (E 491–495) have been defined in Annex II and III to Regulation (EC) No 1333/2008 on food additives, as amended. In this opinion, these levels are named maximum permitted levels (MPLs).

Table 7 summarises foods that are permitted to contain sorbitan esters (E 491–495) and the corresponding MPLs as set by Annex II to Regulation (EC) No 1333/2008.



**Table 7:** MPLs of sorbitan esters (E 491–495) in foods according to Annex II to Regulation (EC) No 1333/2008

Food category number	Food category name	E-number/Group	Restrictions/exception	MPL (mg/L or mg/kg as appropriate)
01.4	Flavoured fermented milk products including heat-treated products	E 491–495		5,000
01.8	Dairy analogues, including beverage whiteners	E 491–495	Only milk and cream analogues	5,000 <sup>(a)</sup>
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	E 491–495		10,000 <sup>(a)</sup>
03	Edible ices	E 491–495		500 <sup>(a)</sup>
04.2.5.2	Jam, jellies and marmalades and sweetened chestnut purée as defined by Directive 2001/113/EC	E 493	Only jelly marmalade	25
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC	E 492		10,000
05.2	Other confectionery including breath freshening microsweets	E 491–495	Only sugar confectionery	5,000 <sup>(a)</sup>
05.2	Other confectionery including breath freshening microsweets	E 492	Only cocoa-based confectionery	10,000
05.3	Chewing gum	E 491–495		5,000 <sup>(a)</sup>
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	E 491–495		5,000 <sup>(a)</sup>
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	E 492	Only cocoa-based confectionery	10,000
07.2	Fine bakery wares	E 492		10,000
12.6	Sauces	E 491–495	Only emulsified sauce	5,000 <sup>(a)</sup>
12.8	Yeast and yeast products	E 491–495	Only dry yeast and yeast for baking	<i>Quantum satis</i>
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	E 491–495		5,000 <sup>(a)</sup>
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)	E 491–495		5,000 <sup>(a)</sup>
14.1.5.2	Other non-alcoholic beverages	E 491–495	Only liquid tea concentrates and liquid fruit and herbal infusion concentrates	500 <sup>(a)</sup>
16	Desserts excluding products covered in categories 1, 3 and 4	E 491–495		5,000 <sup>(a)</sup>
17.1 <sup>(b)</sup>	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	E 491–495		<i>Quantum satis</i> <sup>(a)</sup>
17.2 <sup>(b)</sup>	Food supplements supplied in a liquid form	E 491–495		<i>Quantum satis</i>
17.3 <sup>(b)</sup>	Food supplements supplied in a syrup-type or chewable form	E 491–495		<i>Quantum satis</i>

MPL: maximum permitted level.

(a): The additives may be added individually or in combination.

(b): FCS 17 refers to food supplements as defined in Directive 2002/46/EC of the European Parliament and of the Council excluding food supplements for infants and young children.



According to Annex III, Part 1 of Regulation (EC) No 1333/2008, sorbitan esters (E 491–495) are also authorised as a carrier in food additives (colours and antifoaming agents, glazing agents for fruit) at *quantum satis* (QS), and as food additives other than carriers in food additives (preparations of colours, anti-foaming agents and glazing agents for fruit) at QS according to Part 2 of the same Annex. According to Part 5, Section A, sorbitan esters (E 491–495) are furthermore authorised as food additives in nutrients (in beta carotene, lutein, lycopene and vitamin E preparations at QS and in vitamin A and D preparations at 2 mg/kg in final food).

### 3.3. Exposure data

#### 3.3.1. Reported use levels of sorbitan esters

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment, especially for those food additives for which no MPL is set and which are authorised according to QS.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued public calls<sup>14,15</sup> for occurrence data (usage level) on sorbitan esters (E 491–495). In response to this call, information on the use levels of sorbitan esters (E 491–495) in foods was made available to EFSA by industry. No analytical data were submitted to EFSA by Member States.

##### 3.3.1.1. Summarised data on reported use levels in foods provided by industry

Industry provided EFSA with data on use levels (n = 42) of sorbitan esters (E 491–495) in foods for 16 out of the 19 food categories in which sorbitan esters (E 491–495) are authorised.

Updated information on the actual use levels of sorbitan esters in foods was made available to EFSA by the Federation of European Specialty Food Ingredients Industries (ELC), FoodDrinkEurope (FDE), the International Chewing Gum Association (ICGA), Food Supplements Europe (FSE), and Mars.

The Panel noted that some data were submitted by ELC, an association of food ingredient producers that recommend usage levels to users of food additives, which might, ultimately, use different levels. The Panel furthermore noted that the data supplied by ELC were always equal to the MPLs (with the exception of FCS 02.2.2). Thus, it cannot be excluded that the supplied levels are recommended use levels instead of actual use levels. The Panel decided therefore to use the data from ELC only in the *regulatory maximum level exposure assessment scenario* for the food categories in which the use of sorbitan esters (E 491–495) is permitted at QS.

The Panel noted that 14 usage levels on fat and oil emulsions (n = 1), decorations (n = 3), yeast products (n = 7), desserts (n = 2) and food supplements (n = 1) referred to niche products. Since other usage levels were not available for these food categories, the Panel decided to use them for exposure assessment (Section 3.4).

No use levels related to the use of sorbitan esters (E 491–495) according to Annex III (Section 3.2) were provided to EFSA. This possible source of exposure could therefore not be addressed in this opinion.

Appendix A provides the use levels of sorbitan esters (E 491–495) in foods as reported by industry (food industry and sorbitan esters producers).

#### 3.3.2. Summarised data extracted from the Mintel's Global New Products Database

The Mintel GNPD is an online database which monitors product introductions in consumer packaged goods markets worldwide. It contains information of over 2 million food and beverage products of which more than 900,000 are or have been available on the EU food market. Mintel started covering EU's food markets in 1996, currently having 20 out of its 28 member countries and Norway presented in the Mintel GNPD.<sup>16</sup>

<sup>14</sup> <http://www.efsa.europa.eu/sites/default/files/consultation/ans091123.pdf>

<sup>15</sup> <http://www.efsa.europa.eu/en/dataclosed/call/ans091123>

<sup>16</sup> Missing Bulgaria, Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta and Slovenia.

For the purpose of this Scientific Opinion, the Mintel GNPD<sup>17</sup> was used for checking the labelling of food products containing sorbitan esters (E 491–495) within the European's food products as the Mintel GNPD shows the compulsory ingredient information presented on food product labels.

According to the Mintel GNPD, sorbitan esters (E 491–495) are labelled on more than 700 food products published in the GNPD database between 2011 and 2016.

Appendix B presents the percentage of the food products labelled with sorbitan esters (E 491–495) between 2011 and 2016, out of the total number of food products per food subcategory according to the Mintel GNPD food classification.

The Mintel GNPD was also used to identify food subcategories containing food products labelled with sorbitan esters (E 491–495), which were not considered in the current exposure assessment. Of the 36 food subcategories containing foods labelled with sorbitan esters (E 491–495), 13 were not accounted for in the refined exposure assessment. Of these, sorbitan esters (E 491–495) are not authorised in eight food subcategories (i.e. pizzas, bread and bread products, wet soup, sandwiches/wraps, meal kits, fish products, pasta, and meat pastes & pates). The five food subcategories in which sorbitan esters (E 491–495) are authorised include dessert toppings, dairy-based frozen products, flavoured milk, other frozen desserts and popcorn. The percentage of foods in these subcategories that were labelled to contain sorbitan esters (E 491–495) was maximally 0.6% (Appendix B).

### 3.3.3. Food consumption data used for exposure assessment

#### 3.3.3.1. EFSA Comprehensive European Food Consumption Database

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a)). New consumption surveys recently<sup>18</sup> added in the Comprehensive database were also taken into account in this assessment.<sup>12</sup>

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons should be interpreted with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database represents the best available source of food consumption data across Europe at present.

Food consumption data from the following population groups: infants, toddlers, children, adolescents, adults and the elderly were used for the exposure assessment. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 8).

**Table 8:** Population groups considered for the exposure estimates of sorbitan esters (E 491–495)

Population	Age range	Countries with food consumption surveys covering more than one day
Infants	From more than 12 weeks up to and including 11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Spain, UK
Children <sup>(a)</sup>	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Spain, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK

<sup>17</sup> <http://www.gnpd.com/sinatra/home/> accessed on 16/10/2016.

<sup>18</sup> Available online: <http://www.efsa.europa.eu/en/press/news/150428.htm>

Population	Age range	Countries with food consumption surveys covering more than one day
The elderly <sup>(a)</sup>	From 65 years of age and older	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Romania, Sweden, UK

(a): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a).

Consumption records in the EFSA Comprehensive Database were codified according to the FoodEx classification system (EFSA, 2011b). Nomenclature from the FoodEx classification system has been linked to the food categorisation system (FCS) as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform exposure estimates. In practice, FoodEx food codes were matched to the FCS food categories.

### 3.3.3.2. Food categories considered for the exposure assessment of sorbitan esters (E 491–495)

The food categories in which the use of sorbitan esters (E 491–495) according to Annex II of Regulation (EC) No 1333/2008 is authorised were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system), at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b).

One food category is not referenced in the EFSA Comprehensive Database and could therefore not be taken into account in the exposure estimate. This may have resulted in an underestimation of the exposure. This was the case for one food category (Appendix C). The food category which was not taken into account is described below:

- 05.4 Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4.

For the following food categories, the restrictions/exceptions which apply to the use of sorbitan esters (E 491–495) could not be taken into account, and therefore, the whole food category was considered in the exposure assessment. This applies to three food categories (Appendix C). This may have resulted in an overestimation of the exposure:

- 05.2 Other confectionery including breath refreshing microsweets, only sugar confectionery
- 12.8 Yeast and yeast products, only dry yeast and yeast for baking
- 14.1.5.2 Other non-alcoholic beverages, only liquid tea concentrates and liquid fruit and herbal infusion concentrates.

In the EFSA Comprehensive database, no information is provided on the type of food supplements consumed by infants and young children. In the exposure assessment, even if this food category refers in the EU regulation to foods supplements excluding infants and young children, it was assumed that the food supplements consumed in these population groups were the same as those consumed in the other population groups for which concentration data were supplied, resulting in an overestimation of the exposure to sorbitan esters (E 491–495) in these two population groups.

For the remaining food categories, the refinements considering the restrictions/exceptions as set in Annex II to Regulation No 1333/2008 were applied.

In the refined exposure scenario, in addition to food category 05.4, eight other food categories were not taken into account because no reliable usage data were provided to EFSA. Of the 19 food categories in which sorbitan esters are authorised (Table 7), 18 were included in the maximum level exposure assessment to sorbitan esters (E 491–495) and 10 in the refined exposure assessment (Appendix C).

## 3.4. Exposure estimate to sorbitan esters (E 491–495) from their use as food additives

The Panel estimated chronic exposure to sorbitan esters (E 491–495) for the following population groups: infants, toddlers, children, adolescents, adults and the elderly. Dietary exposure to sorbitan esters (E 491–495) according to Annex II of Regulation (EC) No 1333/2008 was calculated by multiplying sorbitan esters (E 491–495) concentrations for each food category (Appendix C) with their respective consumption amount per kilogram body weight for each individual in the Comprehensive Database. The exposure per food category was subsequently added to derive an individual total

exposure per day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Dietary surveys with only one day per subject were excluded as they are considered as not adequate to assess repeated exposure.

The exposure was estimated for all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 8). Based on these distributions, the mean and 95th percentile of exposure were calculated per survey and per population group. High percentile exposure was only calculated for those population groups where the sample size was sufficiently large to allow calculation of the 95th percentile of exposure (EFSA, 2011a). Therefore, in the present assessment, high levels of exposure for infants from Italy and for toddlers from Belgium, Italy and Spain were not estimated.

Exposure assessment to sorbitan esters (E 491–495) was carried out by the ANS Panel based on: (1) MPLs as set down in the EU legislation (defined as the *regulatory maximum level exposure assessment scenario*); and (2) reported use levels (defined as the *refined exposure assessment scenario*). These two scenarios are discussed in detail below.

A possible additional exposure from the use of sorbitan esters (E 491–495) as food additives in accordance with Annex III to Regulation (EC) No 1333/2008 (Parts 1, 2 and 5) was not considered in the following scenarios.

In the absence of any information on the identity(ies) of the sorbitan ester(s) in which the MPLs and the reported use levels were expressed, the Panel calculated the exposure to sorbitan esters (E 491–495) by assuming that they were expressed as sorbitan monostearate.

### 3.4.1. Regulatory maximum level exposure assessment scenario

The regulatory maximum level exposure assessment scenario to sorbitan esters (E 491–495) was based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008 and listed in Table 7.

For the food category 12.8, in which sorbitan esters (E 491–495) are authorised at QS (Table 7), the maximum use level as provided by food industry (FDE, 2013) was used. For the food categories 17.1, 17.2 and 17.3, in which sorbitan esters (E 491–495) are also authorised at QS, the maximum use level of food category 17.1 and 17.3 provided by ELC (2010) was used (Appendix C). For food category 05.2, the highest MPL was considered.

The Panel considered the exposure estimates derived following this scenario as the most conservative since it is assumed that the consumer will be continuously, over a longer period, exposed to sorbitan esters (E 491–495) present in food at MPL.

### 3.4.2. Refined exposure assessment scenario

The refined exposure assessment scenario is based on use levels reported by industry or analytical data provided by Member States, when available. This exposure scenario can consider only food categories for which these data were available to the Panel.

For sorbitan esters (E 491–495), only reported use levels were used to calculate the refined exposure, since no analytical data were submitted.

Appendix C summarises the concentration levels of sorbitan esters (E 491–495) used in the refined exposure assessment scenario. Based on the available data set, the Panel calculated two refined exposure estimates based on different model populations:

- The brand-loyal consumer scenario: It was assumed that a consumer is exposed long-term to sorbitan esters (E 491–495) present at the maximum reported use level for one food category. This exposure estimate is calculated as follows:
  - Combining food consumption with the maximum of the reported use levels for the main contributing food category at the individual level.
  - Using the mean of the typical reported use levels for the remaining food categories.
- The non-brand-loyal consumer scenario: It was assumed that a consumer is exposed long-term to sorbitan esters (E 491–495) present at the mean reported use levels in food. This exposure estimate is calculated using the mean of the typical reported use levels for all food categories.



### 3.4.3. Dietary exposure to sorbitan esters (E 491–495)

Table 9 summarises the dietary exposure to sorbitan esters (E 491–495) from their use as food additives in six population groups according to the different exposure scenarios. Detailed results per population group and survey are presented in Appendix E.

**Table 9:** Summary of dietary exposure to sorbitan esters (E 491–495) from their use as food additives in the *regulatory maximum level exposure assessment scenario* and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg sorbitan monostearate/kg bw per day)

	Infants (12 weeks– 11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
<b>Regulatory maximum level exposure assessment scenario</b>						
Mean	0.2–18.2	26.1–88.9	21.4–78.4	10.9–34.3	3.7–22.1	4.3–21.2
95th percentile	0.4–75.4	80.1–211.2	54–183.4	27.4–75.4	11.3–50.1	9.7–45.0
<b>Refined estimated exposure assessment scenario</b>						
<b>Brand-loyal scenario</b>						
Mean	0.03–12.0	2.6–33.3	4.7–34.4	2.6–18.1	1.7–12.5	1.6–11.8
95th percentile	< 0.01–51.4	10.1–81.7	11.5–86.3	5.8–46.2	6.0–35.9	5.1–31.5
<b>Non-brand-loyal scenario</b>						
Mean	0.02–2.1	1.2–10.6	3.6–9.1	1.9–4.7	0.6–2.8	0.5–2.8
95th percentile	< 0.01–9.5	3.7–24.1	7.5–19.9	4.1–10.3	1.8–7.0	1.6–6.4

In the *regulatory maximum level exposure assessment scenario*, mean exposure to sorbitan esters (E 491–495) from their use as food additives according to Annex II of Regulation (EC) No 1333/2008 ranged from 0.2 mg sorbitan monostearate/kg bw per day in infants to 88.9 mg sorbitan monostearate/kg bw per day in toddlers. The 95th percentile of exposure ranged from 0.4 mg sorbitan monostearate/kg bw per day in infants to 211.2 mg sorbitan monostearate/kg bw per day in toddlers.

In the *refined estimated brand-loyal exposure scenario*, mean exposure to sorbitan esters (E 491–495) ranged from 0.03 mg/kg bw per day in infants to 34.4 mg sorbitan monostearate/kg bw per day in children. The 95th percentile to sorbitan esters (E 491–495) ranged from < 0.01 mg/kg bw per day in infants to 86.3 mg sorbitan monostearate/kg bw per day in children. In the *non-brand-loyal scenario*, mean exposure to sorbitan esters (E 491–495) ranged from 0.02 mg sorbitan monostearate/kg bw per day in infants to 10.6 mg sorbitan monostearate/kg bw per day in toddlers. The 95th percentile of exposure to sorbitan esters (E 491–495) ranged from < 0.01 mg sorbitan monostearate/kg bw per day in infants to 24.1 mg sorbitan monostearate/kg bw per day in toddlers.

Main food categories contributing to exposure to sorbitan esters (E 491–495) are presented in Appendix D.

### 3.4.4. Uncertainty analysis

Uncertainties in the exposure assessment of sorbitan esters (E 491–495) have been discussed above. In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the sources of uncertainties are summarised and evaluated in Table 10.

**Table 10:** Qualitative evaluation of influence of uncertainties on the dietary exposure estimates of sorbitan esters (E 491–495) from their use as food additives according to Annex II to Regulation (EC) No 1333/2008

Sources of uncertainties	Direction <sup>(a)</sup>
Consumption data: different methodologies/representativeness/underreporting/misreporting/no portion size standard	+/-
Use of data from food consumption survey of a few days to estimate long-term (chronic) exposure for high percentiles (95th percentile)	+
Correspondence of reported use levels to the food items in the EFSA Comprehensive Food Consumption Database: uncertainties to which types of food the levels refer to	+/-
Food categories selected for the exposure assessment: exclusion of food categories due to missing FoodEx linkage (n = 1/19 food categories)	-
Food categories selected for the exposure assessment: inclusion of food categories without considering the restriction/exception (n = 3/19 food categories)	+
Concentration data: <ul style="list-style-type: none"> <li>levels considered applicable to all relevant items within the entire food category,</li> </ul>	+
Regulatory maximum level exposure assessment scenario: <ul style="list-style-type: none"> <li>food categories which may contain sorbitan esters (E 491–495) due to carry-over (Annex III) not considered</li> <li>use of MPLs and maximum use levels in food categories authorised at QS according to Annex II to Regulation (EC) No 1333/2008</li> </ul>	- +
Refined exposure assessment scenarios: <ul style="list-style-type: none"> <li>food categories which may contain sorbitan esters (E 491–495) due to carry-over (Annex III) not considered</li> <li>exposure calculations based on the maximum or typical mean levels (reported use from industries)</li> <li>Food categories included in the exposure assessment: no data available for certain food categories which were therefore not considered in the refined exposure assessment (n = 8 out of 19 food categories)</li> </ul>	- +/- -
Uncertainty in possible national differences in use levels of food categories	+/-

(a): +, uncertainty with potential to cause over-estimation of exposure; -, uncertainty with potential to cause underestimation of exposure.

Overall, the Panel considered that the uncertainties identified would, in general, result in an overestimation of the dietary exposure to sorbitan esters (E 491–495) from their use as food additives according to Annex II of Regulation (EC) No 1333/2008 in European countries for the regulatory maximum level exposure assessment scenario.

Based on the assumption that the food additive is not used in the food categories for which no usage data were provided by food industry, the refined scenario would in general result in an overestimation of exposure according to Annex II of Regulation (EC) No 1333/2008. The Panel noted that no use levels were reported for eight food categories, while information from the Mintel GNPD database showed that, for five out of these eight food categories sorbitan esters (E 491–495) were labelled, representing at most 0.6% of the total food items within the food categories. Overall, the Panel considered that exposure to sorbitan esters (E 491–495) from the food categories for which no usage data were reported was likely to have negligible impact on the refined exposure assessment.

The Panel noted that other potential sources of dietary exposure (in particular according to Annex III Parts 1, 2 and 5 of Regulation (EC) No 1333/2008) to sorbitan esters (E 491–495) were not considered in both exposure scenario assessments, because no data were available.

### 3.5. Biological and toxicological data

#### 3.5.1. Absorption, distribution, metabolism and excretion

Data on toxicokinetics were available for sorbitan monostearate but not for sorbitan tristearate, sorbitan monolaurate, sorbitan monooleate or sorbitan monopalmitate.



### 3.5.1.1. *In vitro*

The aim of the study performed by Krantz (1951 [Documentation provided to EFSA n. 9]) was to determine whether sorbitan monostearate is hydrolysed by pancreatic lipase *in vitro*. After 24 h of incubation at 37°C, in the presence of pancreatic lipase 5.4% of fatty acids present in the ester were liberated. However, this study was poorly reported.

### 3.5.1.2. *In vivo*

In a feeding study (Oser and Oser, 1957a) in Wistar rats, the coefficients of digestibility of the fatty acid moieties were calculated by the authors as the percentage of unexcreted fatty acid to the dietary intake. The intake figures were corrected for the amounts of fatty acids contributed by the basal diet alone. At a dose level of 20% in the diet, the fatty acid moiety of sorbitan monostearate has a coefficient of digestibility of 53%.

Toxicokinetics of sorbitan monostearate were studied by Wick and Joseph (1953a) in non-fasted male rats (no data about strain; body weight 190–210 g) after gavage by a single dose of <sup>14</sup>C-labelled sorbitan monostearate, as either a water emulsion (8 mL/rat) or a solution in 4 mL corn oil; the dose range was 0.5–2 g/kg bw, and in one experiment 6.5 g/kg bw. Six rats were given sorbitan monostearate with the polyol moiety radiolabelled, whereas the other five rats were given the compound with the label in the stearate moiety. For each experimental design, one rat was used except four rats in experiments with radiolabelled polyol moiety in corn oil at a dose 0.5 g/kg bw. The animals were placed in individual metabolism chambers, and the expired CO<sub>2</sub> was collected at 6 h intervals for 48 h. Urine and faeces were also collected as single sample at termination. After 48 h, the animals were sacrificed and liver, kidneys, intestinal tract and a sample of the hind leg muscle were taken from the carcasses for measurement of radioactivity. The results are presented in Table 11.

**Table 11:** Summary of toxicokinetics in rats after oral exposure to <sup>14</sup>C-labelled sorbitan monostearate in different vehicles (Wick and Joseph, 1953a). Values are presented in percent of applied radioactivity

Radioactivity recovered within 48 h	Vehicle oil <sup>(a)</sup>		Vehicle water <sup>(b)</sup>	
	Polyol labelled	Stearate labelled	Polyol labelled	Stearate labelled
In exhaled CO <sub>2</sub>	18–24%	21–33%	14–15%	7–18%
In urine	44–66%	1%	16–25%	1%
In faeces	14–20% (6–8% soluble in chloroform)	35–39% (33–37% soluble in chloroform)	58–66% (31–54% soluble in chloroform)	73–81% (69–76% soluble in chloroform)
In all organs and carcass combined	5–7%	32–41% <sup>(c)</sup>	3%	10–15%
Total recovery	91–108%	98–105%	88–99%	97–101%

(a): Solution in corn oil.

(b): Emulsion in water.

(c): Main amount was chloroform soluble and found in carcass.

The vehicle influences the absorption of <sup>14</sup>C-labelled sorbitan monostearate: using water as vehicle resulted in a lower absorption than using oil. In experiments with stearate-labelling, there was less absorption of radioactivity using the vehicle water compared with a solution in the vehicle oil. Similar results were obtained with the polyol-labelled ester in the two different vehicles. Radioactivity excreted via faeces (soluble in chloroform) was considered to be either the non-absorbed ester or the non-absorbed products of hydrolysis or both. For the absorbed amount of sorbitan monostearate, complete hydrolysis was apparent either in the intestinal tract or after its absorption, or both, to stearic acid and the anhydrides of sorbitol. Generally, the extent of absorption of the polyol-labelled compound or the products of hydrolysis was roughly estimated to be 50% in water emulsion and 90% in oil; but the stearate-labelled compound reached estimated absorption rates of ~30% in water and 70% in oil. These data suggested some differences in absorption between the sorbitan and the fatty acid moiety after hydrolysis in the gastrointestinal tract. The radioactivity in urine (44–66% of the applied <sup>14</sup>C-polyol) was considered to represent the presumably unchanged anhydrides or sorbitol which were liberated by hydrolysis of the ester. However, analytical data on the structure of excreted substances were not available. Sorbitol or anhydrides of sorbitol were excreted by the kidneys to a large extent

before they could be oxidised. In contrast to the  $^{14}\text{C}$ -polyol compound, the  $^{14}\text{C}$ -labelled stearate was integrated in body tissues.

In a further study on accumulation after repeated oral exposure (Wick and Joseph, 1953b), nine rats (no further details provided) were fed *ad libitum* for 28 days a synthetic diet containing 0.1% sorbitan monostearate labelled with  $^{14}\text{C}$  in the polyol moiety. The authors used the same labelled material fed in the previous single-dose study (Wick and Joseph, 1953a). After 28 days of exposure, the fat stores of rats were then analysed for residual radioactivity. The radioactivity of crude fat, fatty acids, glycerol and residue was determined. A small portion of 0.35–0.49% (range of nine rats) of the radioactivity was in crude fat, 0.15–0.32% was found in fatty acids, 0.01–0.07% in glycerol and 0.04–0.09% in the residue (presumed to be sorbitan). The authors concluded that the polyol moiety of sorbitan stearate did not accumulate in body fat stores.

Similar results were obtained in a gavage study in rats using sorbitan trioleate (Treon et al., 1967). The Panel noted that sorbitan trioleate is not authorised as a food additive according to Regulation (EC) No 1333/2008. However, the data reported supported the possibility of read-across with sorbitan monooleate. This also supported possible read-across between sorbitan monooleate and monostearate. The dependency of the absorption rate on the vehicle used was not observed. The radiolabelled compound was prepared either with  $^{14}\text{C}$ -sorbitan or  $^{14}\text{C}$ -oleate. A dose level of 500 mg/kg bw was administered in a 40% aqueous emulsion or in 40% safflower oil solution (1–4 rats/experimental design; body weight 100 g; no further details given). The expired  $\text{CO}_2$  was collected at the following intervals: 0–2, 2–4, 4–6, 6–12, 12–18 and 18–24 h. After administration of sorbitan  $^{14}\text{C}$ -trioleate, the appearance of  $^{14}\text{C}$ - $\text{CO}_2$  in the expired air reached a peak at about 6 h (36–39% of the applied oleate-labelling) and amounted to a mean of 30–35% of the administered labelling during the  $\text{CO}_2$  sampling period 0–24 h after application. The vehicle has no or a minor effect on the amount oxidised to  $\text{CO}_2$  or the absorption rate. The faeces and gastrointestinal tract contained 37–42% of the  $^{14}\text{C}$ -label at termination. About 3% of applied  $^{14}\text{C}$  appeared in the urine, the liver contained 3% and the carcass about 22%, independently of the vehicle used. After administration of the polyol-labelled ester, there was a difference in absorption rate depending on the vehicle used: 20–28% (range) were not absorbed and detected in faeces/gastrointestinal (GI) tract after gavage of the aqueous emulsion but 35–40% after gavage of the solution in oil. The excretion pathways of the polyol-labelled compound were altered compared to the  $^{14}\text{C}$ -oleate but no difference was detected concerning the used vehicle. The proportions recovered of that applied were as follows: Only 2–5% of the applied label was recovered as  $^{14}\text{C}$ - $\text{CO}_2$  in exhaled air but 53–74% in the urine, 1% in the liver and 5% in the carcass. The total recovery in all experiments averaged between 98% and 108%. In conclusion, in experiments with  $^{14}\text{C}$ -sorbitan trioleate, the effect of the vehicle which has been shown in the study with sorbitan monostearate was not reproduced. In contrast, a slight increase in the absorption rate was found using an aqueous emulsion as vehicle instead of oil. This effect was only detected with a label of the polyol moiety but not of the oleate moiety. The absorption rate varied between 60% and 80% of applied radioactivity. Distribution and excretion patterns of the  $^{14}\text{C}$ -label-sorbitan or  $^{14}\text{C}$ -label-oleate were similar to the study with sorbitan monostearate.

Overall, the Panel noted that there were indications from toxicokinetic studies in rats with radiolabelled sorbitan monostearate that this sorbitan ester can be either hydrolysed to its fatty acid moiety and the corresponding anhydrides of sorbitol, or excreted intact in the faeces. After absorption, as indicated by radioactivity, sorbitan and isosorbide moieties, sorbitol or metabolites thereof were excreted via urine or exhaled as  $\text{CO}_2$ . The fatty acid moiety entered the endogenous metabolism of fatty acids. The Panel considered that in case intact sorbitan monostearate be absorbed it would be hydrolysed presystemically.

### 3.5.2. Acute toxicity

From different studies in rats, the oral median lethal dose ( $\text{LD}_{50}$ ) values were more than 40,000 mg/kg bw for sorbitan monostearate, sorbitan monolaurate, and more than 15,900 mg/kg bw for sorbitan monooleate and sorbitan tristearate and sorbitan monopalmitate (the highest doses tested) (Quigley AD, 1966a,b,c, 1967 [Documentation provided to EFSA n. 18, 19, 20 and 21]).

The available data indicated that all five sorbitan esters have low acute toxicity.

### 3.5.3. Short-term and subchronic toxicity

#### 3.5.3.1. Sorbitan monostearate (E 491)

In 1982, JECFA reported the following subacute toxicity studies which were not available to the Panel.

'Groups of 10 young rats were fed for 6 weeks diets containing 1% or 4% of sorbitan monostearate. There was no effect on weight gain, nor were there any significant changes histopathologically in the liver, kidneys, intestine and bladder' (Krantz, 1946; as referred to by JECFA 1982a).

'Sodium monostearate was added to diets designed to induce hepatic necrosis in rats. Levels up to 10% tended to prolong the survival time and had no significant effect upon the hepatic changes over periods up to 120 days' (Gyorgy et al., 1958; as referred to by JECFA 1982a).

'Two rhesus monkeys, fed daily with 0.7–0.8 g/kg bw of sorbitan monostearate for 5 weeks, appeared unharmed throughout. No damage to the liver or kidneys was seen post mortem' (no further details; Krantz, 1946; as referred to by JECFA 1982a).

#### *Dogs*

Four dogs (two males and two females) were fed 0% or 5% sorbitan monostearate in the diet for 19–20 months. The dose level corresponded to 490–780 mg/kg bw per day. There was no clear difference between tested and control dogs in food intake, body weight, longevity, findings at necropsy or detailed histopathology (Fitzhugh et al., 1959).

#### 3.5.3.2. Sorbitan monolaurate (E 493)

#### *Rats*

'White male rats of unspecified strain, initial weight 60 g, were distributed into groups of 4 or 5 and fed diets containing 0, 1 and 4% sorbitan monolaurate for 6 weeks. A significant reduction in growth rate occurred in the high-dose group. No significant histopathological changes were reported in liver, intestine or bladder, but coagulated fluid was present in the renal tubules' (Krantz, 1946; as referred to by JECFA, 1982a).

Groups of six female Holtzman rats (21–24 days old) were exposed for 21 days via the diet at dose levels of 0%, 155% or 20% of sorbitan monolaurate in the diet (equivalent to 0, 17, 550 and 23,400 mg/kg bw per day). All animals of both treatment groups showed diarrhoea, alopecia, unthrifty appearance, reduced body weight gain and increased mortality. There was no gross or microscopical pathology examination (Ershoff, 1960).

Groups of 14 weanling male Sprague–Dawley rats were fed sorbitan monolaurate for 59 days at dietary levels of 0% or 25% (equivalent to 0 and 29,500 mg/kg bw per day) (Harris et al., 1951a). Treatment-related effects included reduced body weight gain, reduced food consumption, diarrhoea, nasal haemorrhage and gangrenous tails. Only 1 out of 14 rats survived the treatment, presenting a stunted appearance resembling starvation. In a second trial, 14 male and 16 female rats were fed sorbitan monolaurate in doses increasing to 25% by day 10 of the study. This high dose level was continued for 60 additional days. The toxic effects were similar to those reported in the previous trial. Results from pair-fed controls indicated that the reduction in growth was not caused solely by reduced food consumption. Haematology at termination of the study showed a treatment-related decrease in haemoglobin value. At autopsy, increased relative organ-to-body weight was observed for the brain, kidney, heart, spleen, lung and liver. However, these effects might be related to reduced body weight in the treated group. Histopathology showed mild degenerative lesions in the kidney, necrosis of the liver, and incomplete maturation of testes. No other effects were reported.

In a subchronic toxicity study (Cater et al., 1978), groups of 15 male and 15 female Wistar rats were fed for 90 days sorbitan monolaurate (95% of a mixture of the partial esters of sorbitol and its mono- and dianhydrides with lauric acid) at dose levels of 0%, 2%, 5% or 10%, equal to 0, 2,100, 4,200 and 8,000 mg/kg bw per day in male and 0, 2,300, 4,500 and 8,400 mg/kg bw per day in female; and in a further group with lauric acid at dose levels of 3,700 and 4,000 mg/kg bw per day in male and female respectively. Additional groups of five rats (sex/group) received sorbitan monolaurate in the diet at dose levels of 0, 4,200 and 8,000 mg/kg bw per day in male and 0, 4,500 and 8,400 mg/kg bw per day in female, and were examined after 2 or 6 weeks for haematology and pathology. The Panel noted that the design of this study is comparable to current guidelines. No clinical signs and no mortality were detected in this study. In a comparison with lauric acid, the body

weight in the treated groups was significantly lower at the dose group of 4,200 and 8,000 mg/kg bw per day in male and 4,500, and 8,400 mg/kg bw per day in female. Relative and absolute liver weights were significantly increased in males and females after 2, 6 and 13 weeks at the highest dose. After 13 weeks, the relative kidney weights increased dose dependently and significantly in males and females at all doses. Signs of early respiratory disease were common in all groups including controls. No treatment related histopathological findings could be demonstrated in the kidney or other tissues, except in the liver. Fat staining of the liver showed increased periportal vacuolisation in females of the mid- and high-dose groups and in males of the high-dose group. The validity was restricted by limited documentation (e.g. incidences in histopathology), partly incomplete histopathology (e.g. mammary gland or accessory genital organs not examined), clinical chemistry (e.g. glucose not tested) and haematology (e.g. blood clotting potential not tested). Furthermore, infection of the respiratory tract was found in all groups. The authors considered that the decrease of the body weight gain at the low-dose group were not toxicologically relevant compared to the 5% lauric acid group. At the mid- and high-dose groups, the effect on body weight was treatment related. Haematological effects occurred in males and females at the mid- and high-dose groups; however, the relevance of these effects was questionable. Liver lipidosis was detected in females at the mid- and high-dose groups, in males only at the highest dose tested. According to the authors, this effect might be related to the fatty acid moiety and was more pronounced at the highest dose tested. The Panel considered that the NOAEL of this study was 2,100 mg/kg bw per day and 2,300 mg/kg bw per day for males and females, respectively.

Groups of 10 male and 10 female Osborne–Mendel rats were fed for 23 weeks diets containing 0%, 15, 20 or 25% sorbitan monolaurate (equivalent to 0, 12,150, 16,200 and 20,250 mg/kg bw per day for males and 0, 13,650, 18,200 and 22,750 mg/kg bw per day for females, respectively) (Fitzhugh et al., 1960). Treated animals showed clinical signs like diarrhoea and an unkempt appearance at all dose levels; severity of diarrhoea was reduced during exposure period. At the high dose level, only one animal of each sex survived the study. Body weight gain was severely retarded at the low- and mid-dose group. At necropsy, the livers of treated animals showed paleness and enlargement, with a marked enlargement of the common bile duct. Histopathology showed marked liver damage at all dose levels which consisted of fatty changes, fibrosis, chronic hepatitis and rarely focal liver cell necrosis. There was no bile duct proliferation but the common bile duct showed a fibrous thickening of the wall together with marked enlargement. The incidence of focal nephritis was elevated. There was an increase in the incidence of foamy alveolar macrophages in the lungs of treated animals. No other organs exhibited treatment related effects. The Panel noted that in this study the lowest dose tested was very high.

### *Hamsters*

In the feeding study in hamsters (no details about strain/species) weanling males and females (14–22 animals per sex at start of experiment) were fed diets containing sorbitan monolaurate at levels of 5% or 15% for 68 days (Harris et al., 1951b). Paired fed controls received 5% or 15% hydrogenated oil. No further control groups were used. Mortality up to 22% in the high-dose group occurred in treatment but also in the control groups (8% at the high dose level and 18% at the low dose; not discussed by the authors). Compared to the paired fed controls the body weight gain was dose dependently reduced. Treated animals of the high-dose group but not paired fed controls developed transient diarrhoea which disappeared at day 26. Two animals per group were necropsied biweekly starting the third week of exposure, 6–14 survivors per dose per sex were sacrificed at termination. Effects on relative organ weight were not detected (no details given). Treatment-related effects were noted in the gastrointestinal tract, including mucosal and intramural hyperaemia and oedema, with mild inflammation. In the kidney of treated animals, the cortical tubular epithelium exhibited fraying at the free edges of cells, eosinophilic granularity and nuclear pyknosis; no necrosis was found but the tubular lumen was frequently filled with eosinophilic acellular material. The kidney alterations were regarded as reversible by the authors. No details about the dose were given but it can be assumed that histopathological effects were also recorded at the 5% level. The authors stated that incomplete maturation in testes and ovaries was more frequent in treated animals, no further details were reported. The Panel noted that in this study the lowest dose tested was very high.

### *Monkeys*

According to JECFA (1982a) 'two *Macacus rhesus* monkeys of unspecified sex (initial weights 2.25 and 2.85 kg) were fed 2 cc of sorbitan monolaurate per day in their diet for 6 weeks. Because no



control animals were used in the study, the haematology and growth results were difficult to interpret. Histological sections from the liver and spleen were reported to be normal in appearance. However, some kidney damage was evident, including shrinking and slight serous exudation into some of the glomerular spaces, swelling of the lining epithelium of the convoluted tubules, and fragmentation and debris in the lumina of some tubules. Because of the absence of tissue sections from control animals, the apparent kidney damage cannot be unequivocally ascribed to treatment' (Krantz, 1946; as referred to by JECFA, 1982a).

### 3.5.3.3. Sorbitan monooleate (E 494)

According to JECFA (1982a), 'groups of 10 male white rats of unspecified strain, initial weight 100 g, were fed sorbitan monooleate at dietary levels of 0 and 10% for 6 weeks [equivalent to 1,180 mg/kg bw per day]. Reductions in food consumption and in rate of growth, and mild diarrhoea occurred in treated animals. Histological sections from liver and kidney showed no differences between control and treated animals. Haematological and serum clinical chemistry were carried out at weeks 3 and 6 of the study. There were no significant differences between test and control animals. At autopsy (3 weeks and 6 weeks), gross pathological and histological studies of selected organs (liver and kidney) from 3 rats showed no compound-related effects' (Krantz, 1953; as referred to by JECFA, 1982a).

In a subchronic toxicity study (Ingram et al., 1978), groups of 15 male and 15 female Wistar rats were fed a diet containing 0%, 2.5%, 5% or 10% sorbitan monooleate (95% of a mixture of the partial esters of sorbitol and its mono- and dianhydrides with oleic acid), equivalent to 0, 2,015, 4,050 and 8,100 for male and to 0, 2,275, 4,550 and 9,100 mg/kg bw per day for female. Additional control group was fed with 4,050 or 4,550 mg oleic acid/kg bw per day for male and female, respectively, for 16 weeks. Groups of five rats of each sex were given the same treatments (except the 2.5% diet) for 2 or 6 weeks. In addition, two groups of 10 male rats were pair-fed with 0% or 10% for 17 weeks. The Panel noted that the design of this study was comparable to current guidelines according to blood and urine analysis and histopathological examination. No clinical signs were detected. Animals exposed to the mid- and high-dose groups of sorbitan monooleate showed a decreased weight gain related to a reduction in food intake presumably due to unpalatability. Reduced water intake at the mid- and high-dose groups was related to the decrease in food consumption. Haematology studies showed lower values for haemoglobin, haematocrit and erythrocyte counts only in female rats fed 10% sorbitan monooleate and reduced leukocyte counts in high-dose group males. However, increases in relative liver and kidney weights were considered by the authors to be treatment related. Relative weights of both organs were also increased in paired-fed males (10% level). Relative liver weights in the main study were increased in males and females of the high dose group after 6 or 17 weeks of treatment, effects on absolute weight were not consistent (decreased in males but increased in females). Relative kidney weights were dose dependently increased after 6 and 17 weeks of treatment in both sexes, in the main study at all doses. Histopathology revealed renal tubular damage in the females given 5 or 10% sorbitan monooleate for 16 weeks. In females of the high-dose group also periportal fatty changes in the liver were reported. No other compound-related histopathological effects were detected. The validity was restricted by limited reporting (e.g. incidences in histopathology), partly incomplete histopathology (e.g. mammary gland or accessory genital organs not examined), clinical chemistry (e.g. glucose not tested) and haematology (e.g. parameter on blood clotting). The authors concluded that in view of the increased kidney weights at all treatment levels, it was not possible to establish a 'no-untoward-effect level' in this study. The Panel agreed with the conclusion of the authors.

### 3.5.4. Genotoxicity

#### 3.5.4.1. *In vitro* studies

##### *Unspecified sorbitan fatty acid ester*

In the study by Isihdate et al. (1984), an unspecified sorbitan fatty acid ester was assessed for its mutagenicity in the reverse mutation assay using *Salmonella* Typhimurium strains TA1535, TA1537, TA92, TA94, TA98 and TA100, at a maximum concentration of 5.0 mg/plate, in dimethylsulfoxide (DMSO) both in the absence and presence of rat S9 metabolic activation and no mutagenicity was observed. The Panel noted that the study complies with current OECD Guideline 471 with the exception that tester strains TA102 or WP2uvrA bearing AT mutation were not used. However, due to reporting deficiencies concerning the identity of the sorbitan fatty acid ester, the test result had only limited relevance.

In a chromosomal aberration assay using a Chinese hamster fibroblasts cell line, an unspecified sorbitan fatty acid ester was assessed for its clastogenicity in the absence of S9 metabolic activation only (Isihdate et al., 1984). Equivocal results were observed for induction of chromosomal aberrations (maximum incidence of 8%) and for polyploidy (5%) at 48 h sampling time at a concentration of 0.3 mg/mL in the absence of metabolic activation. However, the Panel noted that the identity of the test item is not clear, that gaps were included in the analysis of chromosomal aberrations, that the sampling time was set at 48 h, a time laps excessively long compared to the current recommendation indicated in the OECD Guideline 473 of 1.5 cell cycle (e.g. 18–20 h) and that the results were not reported in detail. Therefore, the relevance of the result was low.

#### *Sorbitan monostearate (E 491)*

Inoue et al. (1980) tested sorbitan monostearate (commercial product, no further details) for induction of gene mutation in the Ames test with *S. Typhimurium* tester strains TA98 and TA100 in the absence and presence of a rat S9 metabolic activation system at concentrations up to 2,000 µg/plate. No mutagenic activity was found. However, the Panel considered the study of limited validity since further strains were not tested and the top concentration used did not reach the recommended maximum level of 5 mg/plate and no cytotoxic effects were observed.

Callander et al. (1995 [Documentation provided to EFSA n. 1]) report that sorbitan monostearate did not induce mutagenicity in *S. Typhimurium* tester strains TA98 and TA100 in the presence and absence of rat S9 metabolic activation system. The Panel noted that the reliability of this study was limited due to deviations from the OECD guideline 471 concerning the number of bacterial strains used.

In a study reported by US-EPA (2010) (no original reference given), the potential of sorbitan monostearate to induce chromosomal aberrations was investigated in Chinese hamster lung cells at concentrations of 130, 250 or 500 µg/mL in the absence and 1,100, 2,200 or 4,300 µg/mL in the presence of a metabolic activation system. The results obtained indicated induction of aneugenic effects and chromosomal aberrations at any of the concentrations assayed in the presence of S9 metabolic activation. Due to reporting deficiencies, the reliability of this study and the relevance of the result cannot be evaluated.

#### *Sorbitan monolaurate (E 493)*

The mutagenic potential of sorbitan monolaurate (purity greater than 80%) was assessed in the *in vitro* mammalian cell gene mutation assay using L5178Y (Tk<sup>+/−</sup>) mouse lymphoma cells in two independent repeats (NOTOX BV, 2010a [Documentation provided to EFSA n. 12]). In the first experiment, sorbitan laurate was assayed up to concentrations of 175 and 250 µg/mL both in the absence and presence of a rat liver S9 metabolism (8% v/v), respectively, following a treatment of 3 h. In the second independent experiment, sorbitan laurate was assayed up to concentrations of 225 µg/mL in the absence of rat liver S9 metabolism following 24 h treatment and up to concentrations of 275 µg/mL following a treatment of 3 h in the presence of rat liver S9 metabolism (12% v/v). In both experiments, the highest levels of cytotoxicity reported ranged from 83% to 88% and precipitation of sorbitan laurate in culture medium was observed starting from concentration of 150 µg/mL. The results obtained indicated that the mutation frequencies were similar to (and not significantly different from) those observed in concurrent vehicle controls at all sorbitan monolaurate experimental points analysed both in the absence and presence of rat liver S9 metabolism indicating sorbitan monolaurate was not mutagenic under the reported experimental conditions. The Panel noted that the study was conducted according to Good Laboratory Practice (GLP) and following the OECD guideline No. 476. The Panel agreed with the conclusion of the author.

Sorbitan monolaurate (purity greater than 80%) was also assayed for its ability to induce chromosome aberrations in cultured peripheral human lymphocytes (Notox BV, 2010b [Documentation provided to EFSA n. 13]). Short treatments (3 h) and sampling of cultures at 24 h were performed up to concentration of 333 µg/mL, both in the absence and presence of rat liver S9 metabolism. For the short treatment, an extended sampling time at 48 h was also performed up to concentration of 300 µg/mL. Long treatments (24 and 48 h) were performed in the absence of rat liver S9 metabolism with sampling at 24 and 48 h, respectively. The concentrations used were up 600 and 500 µg/mL in the 24 and 48 h treatments, respectively. Precipitation of sorbitan monolaurate in culture medium was observed starting from concentration of 300 µg/mL. The results obtained indicated that the frequencies of chromosomal aberrations were similar to (and not significantly different from) those observed in concurrent vehicle controls at all experimental points analysed both in the absence and



presence of rat liver S9 metabolism indicating the absence of a clastogenic potential of sorbitan monolaurate *in vitro*. In addition, no increases in the number of both polyploid and endoreduplicated cells were observed both in the absence and presence of rat liver S9 metabolism indicating that sorbitan monolaurate did not interfere with mitotic processes and cell cycle progression. The Panel noted that the study was conducted according to GLP and following the OECD guideline No. 473. The Panel agreed with the conclusions of the author.

### 3.5.4.2. *In silico* studies

An *in silico* study was performed with the OECD QSAR Toolbox<sup>19</sup> to predict the potential genotoxic effect of sorbitan esters (E 491, E 492, E 493, E 494 and E 495). No relevant structural alerts for genotoxicity were highlighted in the following profilers:

- i) 'DNA binding by OECD' and 'DNA binding by OASIS';
- ii) *in vitro* genotoxicity: 'Alerts for Ames, chromosomal aberrations and micronuclei by Oasis 1.2';
- iii) *in vitro* mutagenicity by ISS';
- iv) 'Carcinogenicity (genotoxic and nongenotoxic) by ISS'.

The two alerts detected by the profiler '*in vivo* mutagenicity (micronucleus) alerts by ISS', namely the 'Hacceptor-path3-Hacceptor' and 'Oxolane' were considered not relevant. The 'Hacceptor-path3-Hacceptor' refers to the possibility of non-covalent binding to DNA or proteins as a result of the presence of two bonded atoms connecting two hydrogen bond acceptors. However, the Panel noted that the positive predictivity of such alerts for *in vivo* genotoxicity was quite low, ranging from 'none' (34%) to just 63% depending on the database, with a high incidence of false positives (Benigni et al., 2010, 2012).

Concerning the 'Oxolane' alert, the Panel noted that the oxolane (tetrahydrofuran) moiety represents the chemical skeleton of biologically important aldopentoses, including cyclic sorbitol, and that the alleged positive of this structure for the *in vivo* micronucleus test is secondary to the presence of the oxolane moiety in the nucleoside-analogue drugs included in the ISSMIC database. Substances bearing the oxolane moiety and that were positive in the *in vivo* micronucleus were in fact nucleoside analogues able to inhibit DNA polymerase function and/or to be incorporated into DNA as fraudulent nucleosides (i.e. azidothymidine, 8-chloroadenosine monophosphate, 2,3 dideoxyadenosine, 5-azacytidine, ribavirin, cytarabine hydrochloride, 2,3-dideoxycytidine). On the other hand, such activity is not associated with simple oxolanes, e.g. ribose, and not mechanistically plausible for polysorbates, which are structurally unrelated to nucleosides (OECD QSAR Toolbox).

Overall, the Panel noted that no experimental *in vitro* and *in vivo* data were available for sorbitan tristearate, sorbitan monooleate, sorbitan monopalmitate and limited studies with different shortcomings were available for sodium monostearate. However, for sorbitan monolaurate the results obtained in the *in vitro* chromosomal aberrations assay in cultured peripheral human lymphocytes and in the *in vitro* mammalian cell gene mutation assay in L5178Y (Tk<sup>+/−</sup>) mouse lymphoma cells, both performed according to GLP and following the OECD Guidelines 473 and 476, were considered by the Panel sufficient to evaluate its genotoxicity at gene, chromosome and genome level and to cover by read-across the limited (sorbitans monostearate) or missing data for sorbitan tristearate, sorbitan monooleate and sorbitan monopalmitate. Furthermore, no relevant structural alert for genotoxicity for both, *in vitro* (Ames test, chromosomal aberrations and micronucleus assays) and *in vivo* (micronucleus test), have been observed for any of the sorbitan esters – E 491, E 492, E 493, E 494 and E 495 – when assessed *in silico* (OECD QSAR Toolbox).

Therefore, the Panel considered that sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) did not raise concern with respect to genotoxicity.

### 3.5.5. Chronic toxicity and carcinogenicity

#### 3.5.5.1. Sorbitan monostearate (E 491)

##### *Mice*

Sorbitan monostearate was tested in a feeding study for chronic oral toxicity in TO mice (Hendy et al., 1978). The test substance consisted of approximately 95% of a mixture of the partial esters of

<sup>19</sup> OECD QSAR Toolbox, version 3.3.5.17 (July 2015).

sorbitol and its mono- and dianhydrides with stearic acid. Groups of 48 male and 48 female mice were fed *ad libitum* diets containing 0%, 0.5%, 2.0% or 4.0% (equal to 0, 650, 2,600 and 5,200 mg/kg bw per day for male and to 0, 835, 3,340 and 6,680 mg/kg bw per day for female) for 80 weeks. Clinical signs were recorded 'frequently' (no further details given) and moribund animals were sacrificed and necropsied except autolytic animals. In 16 males per dose, the body weight was measured at monthly intervals. Blood sampling was performed in 10 mice per dose per sex at week 12 and 52 as well as in survivors at week 80 for haematology (haemoglobin, red and white blood cell counts, haematocrit, differential white cell counts). At week 80, all mice were sacrificed and numerous organs were examined histopathologically. No clinical signs were detected. There was no difference in mortality rate between controls and treated groups. Body weight gains of males were normal except for the high dose group; a transient reduction in body weight was found, significant at week 37. At termination, the body weight in males was significantly reduced at the low- and high-dose groups without any dose dependency. Haematology at week 80 revealed no effects at the lowest doses. At the highest dose, the males had significant higher erythrocyte count ( $6.74 \times 10^6/\text{mm}^3$  vs  $5.93 \times 10^6/\text{mm}^3$  in controls) and females lower leukocyte count ( $7.3 \times 10^3/\text{mm}^3$  vs  $11.0 \times 10^3/\text{mm}^3$  in controls) but increased neutrophils (27% vs 17% in control); historical data were not given. Dose-dependent consistent effects on organ weights were not found except increased absolute and relative kidney in high-dose group females. Histopathology revealed no effects except a significant increase in the incidence of nephrosis in male and female mice at the 4% dose level. No increase in tumour incidences was found. According to the authors, the NOAEL in this study was 2% in the diet (equal to 2,600 mg/kg bw per day in male and 3,340 mg/kg bw per day in female). The Panel agreed with this NOAEL.

### Rats

Thirty rats were fed a diet containing 5% sorbitan monostearate for up to 2 years. Growth rate and survival were similar to those of the controls. There were no histological abnormalities post mortem that could be attributed to the treatment (Krantz, 1947a; as referred to by JECFA, 1982a).

In a screening study on seven different emulsifiers (Oser and Oser, 1956a, 1957a,b), sorbitan monostearate was fed *ad libitum* at concentrations of 0%, 5%, 105 and 20% in the basal diet (equivalent to 0, 2,200, 4,500 and 9,000 mg/kg bw per day in male and to 0, 2,900, 5,800 and 11,600 mg/kg bw per day in female) to groups of 12 male and 20 female Wistar rats for 2 years. Matings of  $F_0$  within the same dose group started 5 weeks after initiation of exposure, the first litter was discarded at weaning, the second matings of  $F_0$  for  $F_1$  generation started after 12 weeks. Totally four generation were examined:  $F_0$ – $F_3$  (see details in the reproduction Section 3.5.6). Statistically significant reduction in body weight gain as compared with the controls was found in males but not in females at the 20% level; no significant effects were detected in the low- and mid-dose groups. Result on food consumption data of  $F_0$ – $F_3$  ( $n = 5$  per sex) were combined for both sexes so that a comparison with body weight gain was hampered. Data on efficiency of caloric utilisation (the weight gain per 100 cal. consumed) did not reveal any significant differences in  $F_0$ – $F_3$  (Oser and Oser, 1956a). The initial generation and presumably also the succeeding generations (limited documentation) showed no effect at any dose level (Oser and Oser, 1957a). Neither the percentage of survival at week 104 nor the mean survival time of  $F_0$  was influenced by the treatment (Oser and Oser, 1957b). No deviation from the normal range was found at any dose in blood analysis. Urinalysis showed no difference with control (Oser and Oser, 1957a). Complete histopathology was performed only in two rats per sex at the high-dose group. Histopathology of the liver and kidney was available in all groups but histopathology was further restricted to 8–10 organs examined per dose level (sexes combined). Lungs of both test and control animals showed pathologic alteration suggesting respiratory disease. Kidney weights were dose dependently increased, slightly at the mid dose (20% increase compared with control) but marked at the high dose (70% increase). Focal liver necrosis was detected in 3/9 rats of the high-dose group and in 1/8 mid-dose group but not in 9 controls. The authors reported an increased organ weight for these affected livers. Chronic glomerular nephritis was not found in controls but in 3/8 rats of the mid-dose group and in 3/10 high-dose group (Oser and Oser, 1957b). Although this long-term feeding study has several limitations (insufficient reporting, low number of animals, limited histopathology and organ weight data, no statistical analysis, infection of the respiratory tract in all groups), the results suggested treatment related effects in the liver at the highest dose tested and in the kidney at the mid- and high-dose tested. According to the authors, the NOAEL in this study was considered to be the 5% level equivalent to 2,200 and 2,900 mg/kg bw per day for male and female, respectively. The Panel considered this study too limited for the identification of a reliable NOAEL for the hazard characterisation.

The chronic oral toxicity of sorbitan monostearate was evaluated in a 2-year feeding study using weanling Osborne–Mendel rats (Fitzhugh et al., 1959). Sorbitan monostearate was fed *ad libitum* at concentrations of 0%, 2%, 5%, 10% and 25% (equivalent to 0, 900, 2,200, 4,500 and 11,250 mg/kg bw per day in male and to 0, 1,160, 2,900, 5,800 and 14,500 mg/kg bw per day in female) to groups of 12 males and 12 females during 104 weeks. Clinical signs were recorded ‘frequently’ as stated by the authors (no further details available), and body weights and food intake were reported weekly. Survival rates were significantly decreased in the 10% and 25% groups, no effects were seen at dose equal and inferior to 5% in the diet. Haematology revealed no effects on erythrocyte and leukocyte counts, haemoglobin or differential blood counts in any treatment group. Organ weights of the liver (absolute weight  $40.3 \pm 2.3$  g vs  $25.8 \pm 1.0$  g in control) and kidneys were significantly increased (no details available) (males and females combined in the document) at the highest dose, and a slight increase in hepatic cell vacuolation was found in histopathology at the high-dose level. These effects were considered by the authors to be indicative of fatty change. No effects were reported in the kidney. This long-term feeding study in rats suggested a NOAEL of 5% in the diet (equivalent to 2,200 and 2,900 mg/kg bw per day for male and female, respectively) with respect to the effects on survival. However, the Panel considered that the reliability of this study was limited due to the low number of treated animals, limited reporting (e.g. no data on incidences), and the absence of clinical chemistry and urinalysis data.

### 3.5.5.2. Sorbitan tristearate (E 492)

According to JECFA (1982a), ‘a life-span (2-year) chronic feeding study was conducted on 30 male rats, using 5% sorbitan tristearate in their diet. From this experiment it was concluded that there was no alteration in the growth pattern or survival of the test rats as compared to the controls, nor were there any abnormalities that could be attributed to the experimental diet’ (Krantz, 1947b; as referred to by JECFA, 1982a).

### 3.5.5.3. Sorbitan monolaurate (E 493)

According to JECFA (1982a), ‘a life-span (2-year) study was conducted with 30 white male rats (strain unspecified, initial weights 54–63 g) that were given 5% sorbitan monolaurate in their daily diet. No effect on growth or mortality of the test rats, as compared with controls, could be attributed to the test compound. Blood chemistry, haematology, histopathological examinations and gross pathological examinations of liver, kidney, spleen, brain, adrenals, urinary bladder, gastrointestinal tract, pancreas, thyroid, heart, lung, testicle, salivary gland, prostate, parathyroid, pituitary, striated muscle and bone marrow were carried out both during the study, following interim sacrifice at 6, 12 and 17 months, and at termination of the study. No treatment-related changes were reported’ (Krantz, 1950a; as referred to by JECFA, 1982a).

### 3.5.5.4. Sorbitan monooleate (E 494)

According to JECFA (1982a) ‘a group of 30 white male rats (strain unspecified, initial weight (54–63 g) were maintained on a diet containing 5% sorbitan monooleate for a period of 2 years [equivalent to 2,250 mg/kg bw per day]. There was a minor retardation of growth, and no effect on mortality. Haematology and serum clinical chemistry tests were carried out at months 6, 12 and 17 of the study. No compound-related effects were reported. At months 6, 12 and 17, 1 control and 1 test animal were sacrificed for histopathological examination of liver, kidney and bone marrow, and at week 104, all surviving animals were sacrificed. At autopsy, gross pathological and histopathological examination of brain, spleen, pancreas, thyroid, parathyroid, prostate, pituitary gland, salivary gland, adrenal, bladder, bone marrow, heart, lymph node, lung, testicle and muscle did not show any compound-related effects’ (Krantz, 1950b; as referred to by JECFA, 1982a).

### 3.5.5.5. Sorbitan monopalmitate (E 495)

According to JECFA (1982a) ‘a life-span (2-year) study in 30 male rats given 5% sorbitan monopalmitate [equivalent to 2,250 mg/kg bw per day] in their daily diet showed no alteration in the growth pattern or survival of the test rats, as compared with controls, and no abnormalities that could be attributed to the experimental diet. Blood studies and histopathological studies of the principal viscera were made during and at the end of the experiment. Examination of the brain, spleen, pancreas, adrenal gland, bladder, bone marrow, heart, lymph nodes, lung, testicle and muscle, revealed nothing of a pathological nature attributable to the experimental diet’ (Krantz, 1947a; as referred to by JECFA, 1982a).

Overall, the Panel considered the validity of the long-term studies performed in rats insufficient to be used for hazard characterisation. In an adequate long-term study in mice, the NOAEL was 2% in the diet (equal to 2,600 mg sorbitan monostearate/kg bw per day). Furthermore, there was no indication of carcinogenicity in long-term studies in mice and rats.

### 3.5.6. Reproductive and developmental toxicity

In a long-term feeding study (Oser and Oser, 1956a,b, 1957a,b) sorbitan monostearate was fed *ad libitum* at concentrations of 0%, 5%, 10%, and 20% in the basal diet (equivalent to 0, 2,220, 4,500 and 9,000 mg/kg bw per day in male and to 0, 2,900, 5,800 and 11,600 mg/kg bw per day in female) to groups of 12 male and 20 female Wistar rats for 2 years. In Oser and Oser (1956b), effects on reproduction and lactation were reported. Other endpoints are documented in Section 3.5.5. Matings were continued in the F<sub>0</sub> generation throughout the entire 2-year period resulting in totally six matings. First litters were discarded at weaning. From the second litters, 10 rats per sex were selected for F<sub>1</sub> generation. These F<sub>1</sub> generation animals were raised to maturity and mated like the F<sub>0</sub> generation. The second litters of the F<sub>2</sub> generation were carried through the same breeding programme. Similarly, F<sub>3</sub> rats were raised to maturity for growth observations but not mated because the entire study was terminated when the F<sub>0</sub> rats reached 2 years on test.

Litter production through entire F<sub>0</sub> generation (20–21 females per group) was not affected; but the viability index was reduced at the 10% level (83% in control vs 64%). In the high-dose F<sub>0</sub> group, the viability index was 51%. A dose-dependent reduction in the body weight of weanling rats was observed for the high-dose group (30.7 g vs 43.3 g). Similar results were obtained in F<sub>1</sub> and F<sub>2</sub> rats (data on two matings summarised). In the 20% group, the viability index in F<sub>1</sub> was reduced to 60% (vs. 86% in control) and the body weight of weanling rats reduced to 31.5 g vs 40.9 g in control. In F<sub>2</sub> additionally, a reduced fertility index was found at the high dose level (30% vs 84%) but not at the mid- and low-dose groups. The Panel noted that no statistical analyses of the data were done. Fertility and gestation parameters for the F<sub>0</sub> generation were not affected but post-natal viability and pup weight at weaning were reduced in the 20% dose group. Similar results were reported in F<sub>1</sub> and F<sub>2</sub> generation. The authors suggested that this was due to maternal neglect and reduced milk production. In the F<sub>2</sub> generations, the fertility index was reduced at the high dose level which was not discussed by the authors. The reliability of the study was limited by discrepancies between methodological documentation and reported results and missing statistical analysis. The Panel considered that the study was not sufficient for evaluation of the reproductive toxicity.

In a prenatal developmental toxicity study (Takada et al., 1986), pregnant Wistar rats were administered by gavage once daily throughout the entire gestation period. Sorbitan monostearate (95% purity) was dissolved in squalane, the concentration in vehicle was a maximum of 20%. Rats received a dose of 500 or 1,000 mg/kg bw per day, the two control groups received the vehicle squalane or distilled water. Initially 20 mated rats per group were used. Clinical signs and body weight of dams were recorded daily. Necropsy was performed at gestation day 20 after Caesarean section. In each group, 12 or 13 dams underwent Caesarean section for observation of term fetuses. The number of corpora lutea, number of implantations, number of live and dead fetuses, fetal weight and external malformations were recorded. The fetal skeletons were examined. Five dams per group were allowed to deliver naturally and dams nursed the pups up to 3 weeks of age for evaluation of post-natal development. The offspring was then sacrificed, necropsied and skeletons of the pups were examined. Fetal examinations for soft tissue alterations were not done. No adverse effects on all parameters were noted. The Panel noted that the design of this study was comparable to OECD TG 414. However, the validity was restricted due to the fact that no soft tissue alterations were investigated in the fetuses and the number of mated females was too low. The Panel considered that under the experimental conditions used in this gavage study no developmental toxicity was detected in rats after gavage of the recommended limit dose of 1,000 mg/kg bw per day, the highest dose tested.

Overall, the Panel considered that the available data were not sufficient to assess the reproductive and developmental toxicity of sorbitan monostearate.

### 3.5.7. Hypersensitivity, allergenicity and food intolerance

No data on hypersensitivity, allergenicity or intolerance for sorbitan esters (E 491–495) used as food additives were available to the Panel.



### 3.5.8. Studies with other emulsifiers

In several recent studies, some other emulsifiers have been reported to alter the gut microbiota, to promote gut inflammation, obesity and to impair glycaemic control (Swidsinski et al., 2009a,b; Renz et al., 2012; Merga et al., 2014; Cani and Everard, 2015; Chassaing et al., 2015; Romano-Keeler and Weitkamp, 2015; Lecomte et al., 2016). The Panel noted that, even though some of these effects are not systematically studied in toxicity studies performed according to toxicity testing guidelines, they would be investigated on a case by case basis if indicated by the results of the general toxicity testing as recommended in the Guidance for submission of food additives (EFSA ANS Panel, 2012). The Panel considered that additional studies will be needed to show the relevance of the effects seen in mice for human health.

## 3.6. Discussion

The Panel noted that the sorbitan moiety of sorbitan esters (E 491–495) contains four chiral centres (i.e. asymmetrically substituted carbon atoms). Accordingly, it could theoretically exist 16 ( $2^4$ ) different optical isomers. Furthermore, according to Thyssen and Andersen (1998), a sorbitan ester may include more than 200 possible congeners. The Panel also noted that the stereochemical composition of the sorbitan esters (E 491–495) is not specified in Regulation (EU) No 231/2012. Geometrical and optical isomers of substances may have different properties resulting in possible variability in their absorption, distribution, metabolism, elimination and toxicity. However, since the stereochemical composition of the sorbitan esters is not indicated in the available toxicological data nor in the reported uses, the possible stereoisomerism could not be considered in this assessment.

The Panel noted that recent studies with other emulsifiers had demonstrated effects on the microbiota, which might also be relevant to emulsifiers in general; however, there were no specific studies on sorbitan esters and effects on the microbiota itself.

The Panel noted that there were indications from toxicokinetic studies in rats with radiolabelled sorbitan monostearate that this sorbitan ester could be either hydrolysed to its fatty acid moiety and the corresponding anhydrides of sorbitol or excreted intact in the faeces. The Panel noted that the hydrolysis of sorbitan esters will result in the release of sorbitol which is authorised as a sweetener (E 420), isosorbide, sorbitan and fatty acids. After absorption, sorbitan and isosorbide moieties, sorbitol or metabolites thereof were excreted via urine or exhaled as CO<sub>2</sub>. Fatty acids (E 570) including lauric acid, palmitic acid, stearic acid and oleic acid have been re-evaluated by the ANS Panel and concluded that the food additive fatty acids (E 570) was of no safety concern at the reported uses and use levels (EFSA ANS Panel, 2017). The fatty acid moiety enters the endogenous metabolism of fatty acids. The Panel considered that in case intact sorbitan monostearate be absorbed it would be hydrolysed presystemically.

No ADME data were available for E 492, E 493, E 494 and E 495. However, the Panel considered that these sorbitan esters will follow the same metabolic and excretion pathways as sorbitan monostearate (E 491).

The Panel considered that sorbitan esters (E 491, E 492, E 493, E 494 and E 495) had a very low acute toxicity.

The Panel considered that in the subchronic toxicity studies on sorbitan monolaurate the effects on the weight of the kidneys, which in female rats were associated with histopathological tubular changes, could be attributed to the excretion of large quantities of the sorbitan moiety in the urine. Subchronic toxicity studies were not available or too limited for sorbitan oleate, sorbitan monostearate, sorbitan tristearate or sorbitan monopalmitate.

The Panel noted that no experimental *in vitro* and *in vivo* genotoxicity data were available for sorbitan tristearate, sorbitan monooleate, sorbitan monopalmitate and limited studies with different shortcomings were available for sodium monostearate. However, the available data for sorbitan monolaurate and the *in silico* evaluation were sufficient to consider that sorbitan esters – E 491, E 492, E 493, E 494 and E 495 – did not raise concern with respect to genotoxicity.

The Panel considered the validity of the long-term studies performed in rats insufficient to be used for hazard characterisation. In an adequate long-term study in mice, the NOAEL was 2% in the diet (equal to 2,600 mg sorbitan monostearate/kg bw per day). Furthermore, there was no indication of carcinogenicity in long-term studies in mice and rats.

The Panel considered that the available reproductive and developmental toxicity studies with sorbitan monostearate had limitations but no adverse effects were reported.



The Panel considered that the available database on sorbitan monostearate (E 491) was sufficient to allocate an ADI based on the NOAEL of 2,600 mg sorbitan monostearate/kg bw per day in male mice identified in a long-term toxicity study (Hendy et al., 1978).

The Panel noted that the available biological and toxicological data for sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) were limited but considered that a read across with data on sorbitan monostearate can be performed based on:

- the assumption that sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) were hydrolysed, similarly to sorbitan monostearate, to sorbitol, isosorbide, sorbitan and their corresponding fatty acids.
- the presumption that the adverse effects (increased kidney weight and nephrosis) observed in the long-term toxicity study in mice, exposed to sorbitan monostearate were due to the sorbitan moiety which is in common to all sorbitan esters.
- structural similarities between sorbitan monostearate (E 491), sorbitan monolaurate (E 493) and sorbitan monopalmitate (E 495). All of them contain saturated fatty acids, the difference being in the number of carbons in the carbon chain; 12, 16 and 18 for sorbitan monolaurate (E 493), sorbitan monopalmitate (E 495) and sorbitan monostearate (E 491), respectively.
- sorbitan monooleate (E 494) contains oleic acid, a *cis*-mono unsaturated fatty acid with 18 carbons and a double bond which is reduced in the first step of its metabolism. Thereafter, it follows the same degradation pathway as the saturated fatty acids.
- the degradation pathway of fatty acids, which was the same whatever the number of carbons in saturated fatty acids, resulting in the final production of CO<sub>2</sub>.

Accordingly, the Panel considered that there was no need for a separate ADI for sorbitan monolaurate (E 493) and sorbitan monooleate (E 494).

Based on the NOAEL of 2,600 mg sorbitan monostearate/kg bw per day identified in a long-term toxicity study in mice, taking into account the ratio between the molecular weight of sorbitan monostearate (430.62 g/mol) and sorbitan (164.16 g/mol), and applying an uncertainty factor of 100, the Panel derived a group ADI of 10 mg/kg bw per day expressed as sorbitan for sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) singly or in combination. This group ADI of 10 mg sorbitan/kg bw per day is, for example, equivalent to 26 mg sorbitan monostearate/kg bw per day.

To assess the dietary exposure to sorbitan esters (E 491–495) from their use as food additives according to Annex II to Regulation 133/2008, the exposure was calculated based on (1) MPLs (defined as the *regulatory maximum level exposure assessment scenario*) and (2) reported use levels (defined as the *refined exposure assessment scenario*) for the brand-loyal and the non-brand-loyal scenario.

In the absence of any information on the identity(ies) of the sorbitan ester(s) on which the MPLs and the reported use levels were expressed, the Panel calculated the exposure to sorbitan esters (E 491–495) by assuming that they were expressed as sorbitan monostearate.

Sorbitan esters (E 491–495) are used as emulsifying agents in a wide range of foods and it is therefore not expected that brand-loyalty will result in higher exposures in certain individuals. The Panel therefore selected the *non-brand-loyal* refined scenario as the most relevant exposure scenario for these food additives. In the *non-brand-loyal scenario*, mean exposure to sorbitan esters (E 491–495) ranged from 0.02 mg sorbitan monostearate/kg bw per day in infants to 10.6 mg sorbitan monostearate/kg bw per day in toddlers. The 95th percentile of exposure to sorbitan esters (E 491–495) ranged from < 0.01 mg sorbitan monostearate/kg bw per day in infants to 24.1 mg sorbitan monostearate/kg bw per day in toddlers. The Panel noted that the main food contributing to exposure in this scenario were fine bakery wares and desserts excluding products covered in categories 1, 3 and 4.

The refined exposure estimates were based on 10 out of 19 food categories in which sorbitan esters (E 491–495) are authorised. Based on the assumption that the food additives are not used in the food categories for which no usage data were provided by food industry, the refined scenario would in general result in an overestimation of exposure according to Annex II of Regulation (EC) No 1333/2008. The Panel noted that no use levels were reported for eight food categories, while information from the Mintel GNPD showed that, for five out of these eight food categories sorbitan esters (E 491–495) were labelled, representing at most 0.6% of the total food items within the food categories. Overall, the Panel considered that exposure to sorbitan esters (E 491–495) from the food categories for which no usage data were reported was likely to have negligible impact on the refined exposure assessment.

The Panel noted that other potential sources of dietary exposure (in particular according to Annex III Part 1, 2 and 5) to sorbitan esters (E 491–495) were not considered in both exposure assessment scenarios because no data were available. Analytical data on the actual presence of sorbitan esters (E 491–495) in food are needed to reduce the sources of uncertainty.

The Panel performed the risk characterisation by comparing the *non-brand-loyal scenario* exposure estimates of sorbitan esters (E 491–495) with the group ADI of 10 mg sorbitan/kg bw per day equivalent to 26 mg sorbitan monostearate/kg bw per day. The Panel noted that the mean and the 95th percentile level did not exceed the ADI expressed as 26 mg sorbitan monostearate/kg bw per day in any of the population groups.

An additional request to remove the congealing range from the EU specifications for sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495) was submitted to EFSA.

The applicant provided information on the composition of commercial stearic acid used for manufacturing of sorbitan monostearate (E 491) and sorbitan tristearate (E 492). As there is a lack of definition and/or specifications of 'commercial stearic acid', this appeared to contain stearic acid varying from 48.6–50.0% and palmitic acid 48.7–50.0% of the fatty acid moiety. The applicant has also demonstrated that the same samples of the food additives sorbitan monostearate (E 491) and sorbitan tristearate (E 492), when analysed by two of the few internationally available laboratories performing congealing point analysis (one internal and one external), ended up to significantly different values due to a lack of a clear and common methodology.

Based on the information provided, Panel noted that:

- congealing point correlates with the content of the fatty acid included in the name of the food additive, especially the content of stearic acid in sorbitan monostearate (E 491) and sorbitan tristearate (E 492).
- if the reference to congealing point would be deleted, the product would become less identifiable and the only remaining criterion, solubility, may not be sufficient to distinguish those products. It has also to be highlighted, that there is no definition in JECFA for 'dispersible' in solubility.
- despite the statement from the industry that nothing has changed in production process for decades, the composition of the raw materials may have changed (i.e. the content of minor constituents, the content of stearic acid in edible palmitic acid that is a raw material for manufacturing of sorbitan mono palmitate (E 495)).
- 'Commercial stearic acid' mentioned as a starting material in the definition of the EU specifications of the food additives sorbitan monostearate (E 491) and sorbitan tristearate (E 492) appears to consist only of 50% stearic acid. Under consideration that the rest of the starting material 'commercial stearic acid' consists mainly of palmitic acid, the use of the food additive sorbitan monostearate (E 491) and sorbitan tristearate (E 492), containing an equimolecular mixture of stearic and palmitic acid, would not raise a safety concern regarding their fatty acid moiety. Nevertheless, the fact that the food additive sorbitan monostearate (E 491) could consists of sorbitan monostearate and monopalmitate in equal amounts and sorbitan tristearate (E 492) consists of sorbitan tristearate and tripalmitate in equal amounts would mislead consumers regarding the nature and the identity of the food additive according to Regulation (EU) No 1169/2011 (article 7 paragraph 1 a). Furthermore, as no data on the fatty acid composition of the food additive sorbitan monopalmitate (E 495) have been provided to the Panel, it cannot be excluded that sorbitan monostearate (E 491) and sorbitan monopalmitate (E 495) are identical.

Finally, if there is a need to differentiate between sorbitan monostearate (E 491) and sorbitan monopalmitate (E 495), or to restrict the content of fatty acids other than stearic acid for sorbitan tristearate (E 492), congealing range could be replaced by another identification parameter such as melting range.

## 4. Conclusions

The Panel concluded that the present data set give reason to revise the ADI of 25 mg/kg bw per day for sorbitan monostearate (E 491), sorbitan tristearate (E 492) and sorbitan monopalmitate (E 495) and the ADI of 5 mg/kg bw per day for sorbitan monolaurate (E 493) and sorbitan monooleate (E 494) allocated by the SCF in 1978.

The Panel concluded that there is no need for a separate ADI (E 493 and E 494) and established a group ADI of 10 mg/kg bw per day, expressed as sorbitan, for sorbitan esters (E 491, E 492, E 493, E 494 and E 495) singly or in combination based on the NOAEL of 2,600 mg sorbitan monostearate/kg bw per day identified in a long-term toxicity study in mice, taking into account the ratio between the molecular weight of sorbitan monostearate (430.62 g/mol) and sorbitan (164.16 g/mol) and applying an uncertainty factor of 100.

The Panel concluded that considering the *non-brand-loyal* scenario, the mean and the 95th percentile level did not exceed the ADI in any of the population groups and that there is no safety concern for the use of sorbitan esters (E 491, E 492, E 493, E 494 and E 495) as food additives at the reported uses and use levels.

The Panel on the request for an amendment of specifications regarding the removal of 'congealing range' concluded that, this removal would result in less characterisation of the various sorbitan esters of saturated fatty acids, but this identification parameter could be replaced by another one such as melting point.

## 5. Recommendations

The Panel recommended that:

- the European Commission should consider revising the maximum levels for sorbitan esters (E 491–495) set in Annex II to Regulation (EC) No 1333/2008 and expressing them as sorbitan equivalents.
- the European Commission should consider lowering the current limits for toxic elements (arsenic, cadmium, lead and mercury) in the EU specification for sorbitan monostearate (E 491), sorbitan tristearate (E 492), sorbitan monolaurate (E 493), sorbitan monooleate (E 494) and sorbitan monopalmitate (E 495) in order to ensure that they will not be a significant source of exposure to those toxic elements in food.
- data on the uses and use levels as well as analytical data on the actual presence of sorbitan esters (E 491–495), including information on their use according to Annex III to Regulation 1333/2008, should be provided in order to perform a more realistic refined exposure assessment.

## Documentation provided to EFSA

- 1) Callander RD, 1995. Zeneca Central Toxicology Laboratory. Genetic Toxicology Screening. Ref. CTL/L/6405. Unpublished study. Submitted by Croda Europe Ltd, September 2015.
- 2) EFEMA (European Food Emulsifiers Manufacturers Association), 2014. Response to the EFSA Call for scientific data on selected food additives permitted in the EU (published March 2014). Ten publications (from 1951 to 1957) related to sorbitan esters (E 491–495). Submitted by EFEMA, October 2014.
- 3) ELC (Federation of EU Specialty Food Ingredients Industries), 2010. Tier 3-Category I additives. Questionnaire for food additive manufacturers. Sorbitan esters (E 491–495). Submitted by EFEMA, January 2011.
- 4) FDE (FoodDrinkEurope), 2009. CIAA Intake Data Collection-Food additives falling in prioritisation category I-2nd updated September 2009. Table 12-E 491–495. Submitted by EFEMA, January 2011.
- 5) FDE (FoodDrinkEurope), 2011. FoodDrinkEurope's compilation on usage data on E 220–228, E 483, E 491–495 and E 175. Submitted by FDE, November 2011.
- 6) FDE (FoodDrinkEurope), 2013. Data on usage levels of E 491–495 in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 2). Submitted to EFSA on 29 November 2013.
- 7) FSE (Food Supplements Europe), 2014. Data on usage levels of E 491–495 in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 2). Submitted to EFSA on 9 March 2015.
- 8) ICGA (International Chewing Gum Association), 2012. Data on usage levels of E 491–495 in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (Batch 2). Submitted to EFSA on 30 September 2014.

- 9) Krantz JC, 1951. Effect *in vitro* of Pancreatic Lipase on the Following: Corn oil Tween 60 (polyoxyethylene sorbitan monostearate) Tween 65 (polyoxyethylene sorbitan tristearate) Tween 80 (polyoxyethylene sorbitan monooleate) Myrj 45 (polyoxyethylene (8) stearate) Myrj 52 (polyoxyethylene (40) stearate) Span 60 (sorbitan monostearate). Ref. WER-149-329 Lipase. Unpublished document. Submitted by Croda Europe Ltd, September 2015.
- 10) Mars, 2010. Data on usage levels of sorbitan esters (E 491–495) in foods in response to the EFSA call for scientific data on food additives permitted in the EU and belonging to the functional classes of emulsifiers, stabilisers and gelling agents (2009). Submitted to EFSA in May 2010.
- 11) Masson, 1987. EVIC-CEBA. Ref. F396/4403. Sorbitan palmitate oral toxicity skin irritation. Unpublished report. Submitted by Stearinerie Dubois, September 2015.
- 12) NOTOX BV, 2010a. Evaluation of the ability of Sorbitan Laurate to induce chromosome aberrations in cultured peripheral human lymphocytes (with repeat experiment). NOTOX project 493368. NOTOX substance 202174/A. Unpublished study. Submitted by Croda Europe Ltd, September 2015.
- 13) NOTOX BV, 2010b. Evaluation of the mutagenic activity of Sorbitan Laurate in an *in vitro* mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat). NOTOX project 493369. NOTOX substance 202174/A. Unpublished report. Submitted by Croda Europe Ltd, September 2015.
- 14) Potokar, 1983a. Eumulgin SML 20 (Lot 201) und Dehymuls SML (Lot 202) – toxikologische Grundprüfung. Dehymuls SML, acute oral. Ref. 1338-39-2. Unpublished report. Submitted by BASF Personal Care and Nutrition, September 2015.
- 15) Potokar, 1983b. Disponil STS 100 spezial – akute Toxizität (Limit test). Ref. 26658-19-5 acute oral sorbitan trioctadecanoate. Unpublished report. Submitted by BASF Personal Care and Nutrition in September 2015.
- 16) Potokar, 1984. Experimentelle Untersuchungen über die allgemeine und lokale Verträglichkeit. 1338-41-6 Ref. Sorbitan monostearate acute oral Unpublished report. Submitted by BASF Personal Care and Nutrition, September 2015.
- 17) Pre-evaluation document prepared by Fraunhofer, September 2011.
- 18) Quigley AD, 1966a. Span 20. Ref. Sorbitan esters acute oral 1. Unpublished report. Submitted by Croda Europe Ltd, September 2015.
- 19) Quigley AD, 1966b. Acute oral Toxicity of Span® Products in Rats. Ref 1338-41-6 Span 60 acute oral. Ref Treon60A. Unpublished report. Submitted by Croda Europe Ltd, September 2015.
- 20) Quigley AD, 1966c. Acute oral Toxicity of Span® Products in Rats. Ref. Span 65 sorbitan esters acute oral 1. Unpublished report. Submitted by Croda Europe Ltd, September 2015.
- 21) Quigley AD, 1967. Arlacel® products – acute oral toxicity in Rats. Ref. Sorbitan esters acute oral 2. G1742. Unpublished report. Submitted by Croda Europe Ltd, September 2015.
- 22) Saatman, 1977. Span 40 Acute Toxicity. Ref. 26266-57-9 DAW77015-16 AOT rat. Unpublished report. Submitted by Croda Europe Ltd, September 2015.
- 23) Solowski, 2006. Salmonella typhimurium reverse mutation assay with HW 2130 (HC-2006-74) Final report. Harlan project NO.: 67-0-0163-06. Ref. 91844-53-0 1049200 Ames. Unpublished report. Submitted by Evonik Nutrition and Care GmbH, September 2015.
- 24) Technical dossier. EFEMA dossier- Modification in specifications of E491, 492 and 495. 28 February 2014.
- 25) Technical dossier- EFEMA dossier: Additional data. 22 September 2016.

## References

- Anneken DJ, Both S, Christoph R, Fieg G, Steinberner U and Westfechtel A, 2012. Fatty acids. Ullmann's Encyclopedia of Industrial Chemistry, 14, 73–116.
- Benigni R, Bossa C and Worth A, 2010. Structural analysis and predictive value of the rodent *in vivo* micronucleus assay results. *Mutagenesis*, 25, 335–341.
- Benigni R, Bossa C, Tcheremenskaia O, Battistelli CL and Crettaz P, 2012. The new ISSMIC database on *in vivo* micronucleus and its role in assessing genotoxicity testing strategies. *Mutagenesis*, 27, 87–92.
- Burch R, Topping J and Haines J, 2007. Final report for food standards agency: Review of literature relating to the extraction of additives from complex food matrices. Project number A01058.



- Cani PD and Everard A, 2015. Keeping gut lining at bay: impact of emulsifiers. *Trends in Endocrinology and Metabolism*, 26, 273–274.
- Cater BR, Butterworth KR, Gaunt IF, Hooson J, Grasso P and Gangolli SD, 1978. Short-term toxicity study of sorbitan monolaurate (Span 20) in rats. *Food and Cosmetics Toxicology*, 16, 519–526.
- Chassaing B, Koren O, Goodrich JK, Poole AC, Srinivasan S, Ley RE and Gewirtz AT, 2015. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature*, 519, 92–96.
- CIR (Cosmetic Ingredient Review), 1985. Final Report on the safety assessment of sorbitan stearate, sorbitan laurate, sorbitan sesquioleate, sorbitan oleate, sorbitan tristearate, sorbitan palmitate, and sorbitan trioleate. *Journal of the American College of Toxicology*, 4, 65–121.
- Cottrell T and van Peij J, 2015. Emulsifiers in food technology. In: Nord V (ed.). *Sorbitan Esters and Polysorbates*, 2nd Edition. John Wiley & sons, Ltd., West Sussex, UK. pp. 271–293.
- Croda, online. Available online: [file:///C:/Users/rincoan.EFSA/Downloads/span-tween%20\(4\).pdf](file:///C:/Users/rincoan.EFSA/Downloads/span-tween%20(4).pdf) [Accessed: 28 March 2017]
- 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. <https://doi.org/10.2903/j.efsa.2007.438>
- EFSA (European Food Safety Authority), 2011a. Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment. *EFSA Journal* 2011;9(3):2097, 34 pp. <https://doi.org/10.2903/j.efsa.2011.2097>
- EFSA (European Food Safety Authority), 2011b. Evaluation of the FoodEx, the food classification system applied to the development of the EFSA Comprehensive European Food Consumption Database. *EFSA Journal* 2011;9(3):1970, 27 pp. <https://doi.org/10.2903/j.efsa.2011.1970>
- EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources Added to Food), 2012. Guidance for submission for food additive evaluations. *EFSA Journal* 2012;10(7):2760. <https://doi.org/10.2903/j.efsa.2012.2760>
- EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), Mortensen A, Aguilar F, Crebelli R, Di DA, Dusemund B, Frutos MJ, Galtier P, Gott D, Gundert-Remy U, Leblanc J-C, Lindtner O, Moldeus P, Mosesso P, Parent-Massin D, Oskarsson A, Stankovic I, Waalkens-Berendsen I, Woutersen RA, Wright M, Younes M, Boon P, Chrysafidis D, Gürtler R, Tobback P, Rincon AM, Gergelova P, Rincon AM and Lambré C, 2017. Scientific opinion on the re-evaluation of fatty acids (E 570) as a food additive. *EFSA Journal* 2017;15(4):4785, 48 pp. <https://doi.org/10.2903/j.efsa.2017.4785>
- EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2009a. Scientific opinion on cadmium in food. *EFSA Journal* 2009;7(10):980, 139 pp. <https://doi.org/10.2903/j.efsa.2009.98>
- EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2009b. Scientific Opinion on arsenic in food. *EFSA Journal* 2009;7(10):1351, 199 pp. <https://doi.org/10.2903/j.efsa.2009.1351>
- EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2010. Scientific Opinion on lead in food. *EFSA Journal* 2010;8(4):1570, 151 pp. <https://doi.org/10.2903/j.efsa.2010.1570>
- EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2012a. Scientific Opinion on the risk for public health related to the presence of mercury and methylmercury in food. *EFSA Journal* 2012;10(12):2985, 241 pp. <https://doi.org/10.2903/j.efsa.2012.2985>
- EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2012b. Scientific Opinion on lead dietary exposure in the European population. *EFSA Journal* 2012;10(7):2831, 59 pp. <https://doi.org/10.2903/j.efsa.2012.2831>
- EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2012c. Scientific Opinion on cadmium dietary exposure in the European population. *EFSA Journal* 2012;10(1):2551, 59 pp. <https://doi.org/10.2903/j.efsa.2012.2831>
- EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2014. Scientific Opinion on dietary exposure to inorganic arsenic in the European population. *EFSA Journal* 2014;12(3):3597, 68 pp. <https://doi.org/10.2903/j.efsa.2014.3597>
- EFSA Scientific Committee, 2009. Guidance of the Scientific Committee on Transparency in the Scientific Aspects of Risk Assessments carried out by EFSA. Part 2: General Principles. *EFSA Journal* 2009;7(7):1051, 22 pp. <https://doi.org/10.2903/j.efsa.2009.1051>
- EFSA Scientific Committee, 2012. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. *EFSA Journal* 2012;10(3):2579, 32 pp. <https://doi.org/10.2903/j.efsa.2012.2579>
- Ershoff BH, 1960. Beneficial effects of alfalfa meal and other bulk-containing or bulk-forming materials on the toxicity of non-ionic surface active agents in the rat. *Journal of Nutrition*, 70, 484–490.
- Fitzhugh OG, Bourke AR, Nelson AA and Frawley JP, 1959. Chronic oral toxicities of four stearic acid emulsifiers. *Toxicology and Applied Pharmacology*, 1, 315–331.
- Fitzhugh OG, Schouboe PJ and Nelson AA, 1960. Oral toxicities of lauric acid and certain lauric acid derivatives. *Toxicology and Applied Pharmacology*, 2, 59–67.
- Food Chemical Codex, 2010–2011. *FCC7. The United States Pharmacopeial Convention*, 7th Edition. pp 972–977.



- Garti N, Wellner E, Aserin A and Sarig S, 1983. Analysis of sorbitan fatty acid esters by HPLC. *Journal of the American Oil Chemists' Society*, 60, 1151–1154.
- Gyorgy P, Forbes M and Goldblatt H, 1958. Effect of non-ionic emulsifiers on experimental dietary injury of the liver in rats. *Journal of Agricultural and Food Chemistry*, 6, 139–142.
- Harris RS, Sherman H and Jetter WW, 1951a. Nutritional and pathological effects of sorbitan monolaurate, polyoxyethylene sorbitan monolaurate and polyoxyethylene monolaurate when fed to hamsters. *Archives of Biochemistry and Biophysics*, 34, 259–265.
- Harris RS, Sherman H and Jetter WW, 1951b. Nutritional and pathological effects of sorbitan monolaurate, polyoxyethylene sorbitan monolaurate, polyoxyethylene monolaurate, and polyoxyethylene monostearate when fed to rats. *Archives of Biochemistry and Biophysics*, 34, 249–258.
- Hendy RJ, Butterworth KR, Gaunt IF, Kiss LS and Grasso P, 1978. Long-term toxicity study of sorbitan monostearate (Span 60) in mice. *Food and Cosmetic Toxicology*, 16, 527–534.
- Ingram AJ, Butterworth KR, Gaunt IF, Grasso P and Gangolli SD, 1978. Short-term toxicity study of sorbitan monooleate (SPAN 80) in rats. *Food and Cosmetic Toxicology*, 16, 535–542.
- Inoue K, Sunakawa T and Takayama S, 1980. Studies of *in vitro* cell transformation and mutagenicity by surfactants and other compounds. *Food and Cosmetic Toxicology*, 18, 289–296.
- Isihdate M, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M and Matsuoka A, 1984. Primary mutagenicity screening of food additives currently used in Japan. *Food and Chemical Toxicology*, 22, 623–636.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1974. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. WHO Food Additive Series, No. 5, Geneva.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1982a. 547. Sorbitan monoesters of palmitic, stearic, oleic and lauric acids and trimesters stearic acid. WHO Food Additive Series, 17,
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1982b. Evaluation of certain food additives and contaminants. Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. In: WHO Technical Report Series, No. 683, Geneva.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2000. Guidelines for the preparation of toxicological working papers for the Joint FAO/WHO Expert Committee on Food Additives. Geneva, Switzerland.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2006. Monograph 1. Combined compendium of food additive specifications. Available online: <http://www.fao.org/ag/agn/jecfa-additives/search.html>
- Krantz JC Jr, 1946. Unpublished report No. WER-149-102 to the Atlas Chemical Co, as referred to by JECFA (1982a).
- Krantz JC Jr, 1947a. Unpublished reports Nos. WER-149-171/201/ 232/232A/232B to the Atlas Chemical Co, as referred to by JECFA (1982a).
- Krantz JC Jr, 1947b. Unpublished reports Nos. WER-149-172/202/ 230/230A/230B to the Atlas Chemical Co, as referred to by JECFA (1982a).
- Krantz JC Jr, 1950a. Feeding of SPAN 20 (sorbitan monolaurate) to the white rat (lifespan). Unpublished interim and final reports Nos. WER-149-173/200/231/231A/231B from the University of Maryland School of Medicine to the Atlas Chemical Co. Submitted to the US Food and Drug Administration, 1982, as referred to by JECFA (1982a).
- Krantz JC Jr, 1950b. Feeding of SPAN 80 (sorbitan monooleate) to the white rat (lifespan) (final report). Unpublished interim and final reports Nos. WER-149-180/205/240/240A/240B from the University of Maryland School of Medicine to the Atlas Chemical Co. Submitted to the US Food and Drug Administration, 1982, as referred to by JECFA (1982a).
- Krantz JC Jr, 1953. Feeding studies with SPAN 60, SPAN 80 and hydrogenated tallow. Unpublished report No. WER-149-355 from the University of Maryland School of Medicine to the Atlas Chemical Co. Submitted to the US Food and Drug Administration, 1982, as referred to by JECFA (1982a).
- Lecomte M, Couedelo L, Meugnier E, Plaisancie P, Letisse M, Bérengère B, Gabert L, Penhoat A, Durand A, Pineau G, Joffre F, Gélouën A, Vaysse C, Laugerette F and Michalski MC, 2016. Dietary emulsifiers from milk and soybean differently impact adiposity and inflammation in association with modulation of colonic goblet in high-fat fed mice. *Molecular Nutrition and Food Research*, 60, 606–620.
- Li J, Spina A, Mouljin JA and Kakke M, 2013. Sorbitol dehydration into isosorbide in a molten salt hydrate medium. *Catalysis Science & Technology*, 3, 1540–1546.
- Lundquist G and Meloan CE, 1971. Determination of polysorbates in food products by reaction gas chromatography. *Analytical Chemistry*, 43, 1122–1123.
- Merga Y, Campbell BJ and Rhodes JM, 2014. Mucosal barrier, bacteria and inflammatory bowel disease: possibilities for therapy. *Digestive Diseases*, 32, 475–483.
- Oser BL and Oser M, 1956a. Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. 1. General plan and procedures: growth and food utilization. *Journal of Nutrition*, 60, 367–390.
- Oser BL and Oser M, 1956b. Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. 2. Reproduction and Lactation. *Journal of Nutrition*, 60, 489–505.
- Oser BL and Oser M, 1957a. Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. 3. Clinical and metabolic observations. *Journal of Nutrition*, 61, 149–166.

- Oser BL and Oser M, 1957b. Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. 4. Mortality and post-mortem pathology: general conclusions. *Journal of Nutrition*, 61, 235–252.
- Renz H, Brandtzaeg P and Hornef M, 2012. The impact of perinatal immune development on mucosal homeostasis and chronic inflammation. *Nature Reviews-Immunology*, 12, 9–23.
- Romano-Keeler J and Weitkamp JH, 2015. Maternal influences on fetal microbial colonization and immune development. *Pediatric Research*, 77, 189–195.
- Sahasrabudhe MR and Chadha RK, 1969. Chromatographic analysis of sorbitan fatty acid esters. *Journal of the American Oil Chemists' Society*, 46, 8–12.
- SCF (Scientific Committee for Food), 1978. Report from the Scientific Committee for Food, seventh series. Report of the Scientific Committee for Food on emulsifiers, stabilizers, thickeners, and gelling agents, opinion expressed 30 November 1978.
- SCF (Scientific Committee for Food), 2001. Guidance on submissions for food additive evaluations by the Scientific Committee on Food. SCF/CS/ADD/GEN/26 Final. 12 July 2001.
- Stockburger GJ, 1981. United States Patent, 4,297,290. Process for preparing sorbitan esters. October, 27, 1981.
- Swidsinski A, Loening-Baucke V and Herber A, 2009a. Mucosal flora in Crohn's disease and ulcerative colitis – an overview. *Journal of Physiology and Pharmacology*, 60, (Suppl. 6), 61–71.
- Swidsinski A, Ung V, Sydora BC, Loening-Baucke V, Doerffel Y, Verstraelen H and Fedorak RN, 2009b. Bacterial overgrowth and inflammation of small intestine after carboxymethylcellulose ingestion in genetically susceptible mice. *Inflammatory Bowel Diseases*, 15, 359–364.
- Takada K, Momma J, Horiuchi S, Suzuki Y and Tobe M, 1986. Effect of oral administration of sorbitan monostearate on prenatal and postnatal development of the rat. *Eisei Shikenjo Hokoku*, 104, 58–64.
- TemaNord, 2002. E 491-2 and E 495 Sorbitan monostearate, sorbitan tristearate and sorbitan monopalmitate and E 493-4 Sorbitan monolaurate and sorbitan monooleate. *Food Additives in Europe 2000 – Status of safety assessments of food additives presently permitted in the EU*, pp. 498–504.
- Thyssen K and Andersen KS, 1998. Determination of sorbitan tristearate in vegetable oils and fats. *Journal of the American Oil Chemists' Society*, 75, 1855–1860.
- Treon JF, Gongwer LE, Nelson MF and Kirschman LC, 1967. Physiologic and metabolic patterns of non ionic surfactants. In: *Chemistry, Physics, and Application of Surface Active Substances*, Proceedings of the fourth International Congress, 3, pp. 381–395.
- Tsuda T, Nakanishi H, Kobayashi S and Morita T, 1984. Improved gas chromatographic determination of sorbitan fatty acid esters in confectionery products. *Journal of the Association of Official Analytical Chemists*, 67, 1149–1151.
- US-EPA (US Environmental Protection Agency), 2010. Screening-level hazard characterisation; Sorbitan Esters Category. Sponsored Chemical. June, 2010. Available online: [http://www.epa.gov/chemrtk/hpvis/hazchar/Category\\_Sorbitan%20Esters\\_June%202010.pdf](http://www.epa.gov/chemrtk/hpvis/hazchar/Category_Sorbitan%20Esters_June%202010.pdf).
- Wang Z and Fingas M, 1994a. Analysis of sorbitan ester surfactants. Part I: High performance liquid chromatography. *Journal of High Resolution Chromatography*, 17, 15–19.
- Wang Z and Fingas M, 1994b. Analysis of sorbitan ester surfactants. Part II: Capillary supercritical fluid chromatography. *Journal of High Resolution Chromatography*, 17, 85–90.
- Wick AN and Joseph L, 1953a. The metabolism of sorbitan monostearate. *Food Research*, 18, 79–84.
- Wick AN and Joseph L, 1953b. Sorbitan monostearate metabolism. Lack of deposition upon chronic feeding. *Journal of Agricultural and Food Chemistry*, 1, 398–399.
- Wood R, Foster L, Damant A and Key P, 2004. *Analytical Methods for Food Additives*. CRC Press LLC, Boca Raton, pp. 216–218.
- Yamaguchi A, Hiyoshi N, Sato O and Shirai M, 2011. Sorbitol dehydration in high temperature liquid water. *Green Chemistry*, 13, 873–881.
- Yomota C, Toyoda M and Ito Y, 1986. A determination of emulsifiers in various foods. *Journal of the Food Hygienic Society of Japan (Shokuhin Eiseigaku Zasshi)*, 27, 37–43.

## Abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
ANS	EFSA Scientific Panel on Food Additives and Nutrient Sources added to Food
bw	body weight
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
CONTAM	EFSA Panel on Contaminants in Food Chain
CSFC	Capillary Supercritical Fluid Chromatography
DMSO	dimethylsulfoxide
EFEMA	European Food Emulsifiers Manufacturers Association
EINECS	European Inventory of Existing Chemical Substances
ELC	Federation of European Speciality Food Ingredient Industries

FAO	Food and Agriculture Organization of the United Nations
FCS	food categorisation system
FDE	FoodDrinkEurope
FSE	Food Supplements Europe
GC	gas chromatography
GI	gastrointestinal
GLP	Good laboratory practice
GNPD	Global New Products Database
HPLC	high-performance liquid chromatography
ICGA	International Chewing Gum Association
IR	infrared
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD <sub>50</sub>	median lethal dose
LOD	limit of detection
MPL	maximum permitted level
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
QS	<i>quantum satis</i>
SCF	Scientific Committee on Food
TemaNord	is a publishing series for results of the often research-based work that working groups or projects under Nordic Council of Ministers have put in motion
TLC	thin-layer chromatography
US-EPA	US Environmental Protection Agency
WHO	World Health Organization

## Appendix A – Summary of the reported use levels (mg/kg or mg/L as appropriate) of sorbitan esters (E 491–495) provided by industry

Food Category Number	Food category name	MPL	Restrictions/ exceptions	N	Typical mean (range)	Max	Information provided by
01.8	Dairy analogues, including beverage whiteners	5,000	Only milk and cream analogues	2	5,000	5,000	ELC (2010)
01.8	Dairy analogues, including beverage whiteners	5,000	Only milk and cream analogues	1	3,000	5,000	FDE (2011)
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	10,000		1	5,000	10,000	ELC (2010)
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	10,000	(a)	1	2,500	2,500	FDE (2013)
03	Edible ices	500		1	500	500	ELC (2010)
04.2.5.2	Jam, jellies and marmalades and sweetened chestnut puree as defined by Directive 2001/113/EC	25	Only jelly and marmalade	1	12.5	25	ELC (2010)
04.2.5.2	Jam, jellies and marmalades and sweetened chestnut puree as defined by Directive 2001/113/EC	25	Only jelly and marmalade	1	1.65	3.3	FDE (2011)
05.1	Cocoa and chocolate products as covered by Directive 2000/36/EC	10,000		1	10,000	10,000	ELC (2010)
05.1	Cocoa and chocolate products as covered by Directive 2000/36/EC	10,000		1	2,000	4,000	FDE (2011)
05.1	Cocoa and chocolate products as covered by Directive 2000/36/EC	10,000		1	2,960	5,100	MARS (2010)
05.2	Other confectionery including breath refreshing microsweets	5,000	Only sugar confectionery	1	2,500	5,000	ELC (2010)
05.2	Other confectionery including breath refreshing microsweets	5,000	Only sugar confectionery	1	4,000	5,000	FDE (2011)
05.3	Chewing gum	5,000		5	500	5,000	ICGA (2012)
05.3	Chewing gum	5,000		1	2,500	5,000	ELC (2010)
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	5,000	(a)	1	2,500	5,000	ELC (2010)
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	5,000		3	2,093	3,700	FDE (2013)

Food Category Number	Food category name	MPL	Restrictions/exceptions	N	Typical mean (range)	Max	Information provided by
07.2	Fine bakery wares	10,000		1	10,000	10,000	ELC (2010)
07.2	Fine bakery wares	10,000		1	1,575	9,000	FDE (2011)
12.6	Sauces	5,000	Only emulsified sauces	1	5,000	5,000	ELC (2010)
12.8	Yeast and yeast products	QS	Only dry yeast and yeast for baking <sup>(a)</sup>	1	9,000	9,000	ELC (2010)
12.8	Yeast and yeast products	QS	Only dry yeast and yeast for baking	7	8,193	13,000	FDE (2013)
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)	5,000		1	2,500	5,000	ELC (2010)
14.1.5.2	Other non-alcoholic beverages	500	Only liquid tea concentrates and herbal liquid fruit and herbal infusion concentrates	1	250	500	ELC (2010)
16	Desserts excluding products covered in categories 1, 3 and 4	5,000		1	2,500	5,000	ELC (2010)
16	Desserts excluding products covered in categories 1, 3 and 4	5,000	<sup>(a)</sup>	2	1,475	2,500	FDE (2013)
17.1	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	QS		1	5,000	5,000	ELC (2010)
17.1	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms	QS	<sup>(a)</sup>	1	0.5	0.9	FSE (2014)
17.3	Food supplements supplied in a syrup-type or chewable form	QS		1	5,000	5,000	ELC (2010)

FCS: Food Categorisation System; FDE: FoodDrinkEurope; ELC: Federation of European Speciality Food Ingredient Industries; ICGA: the International Chewing Gum Association; FSE: Food Supplement Europe; MPL: maximum permitted level; QS: *quantum satis*.  
<sup>(a)</sup>: Nice product(s).



## Appendix B – Number and percentage of food products labelled with sorbitan esters (E 491–495) out of the total number of food products present in Mintel GNPD per food subcategory between 2011 and 2016

Food sub-category <sup>(a)</sup>	Total number of products	Products labelled with sorbitan esters (E 491–495)	
		Number	%
Cakes, pastries & sweet goods	10,083	322	3.2
Baking ingredients & mixes	6,553	128	2.0
Non-individually wrapped chocolate pieces	4,083	55	1.3
Chocolate countlines	1,883	23	1.2
Other chocolate confectionery	230	2	0.9
Sweet biscuits/cookies	13,548	103	0.8
Individually wrapped chocolate pieces	2,038	14	0.7
Rice snacks	306	2	0.7
Pizzas	3,174	18	0.6
Dessert toppings	475	3	0.6
Seasonal chocolate	4,344	23	0.5
Snack/cereal/energy bars	3,695	17	0.5
Other sugar confectionery	876	4	0.5
Dairy-based frozen products	5,738	21	0.4
Flavoured milk	1,123	4	0.4
Other frozen desserts	1,214	4	0.3
Popcorn	833	2	0.2
Liquorice	608	1	0.2
Marshmallows	412	1	0.2
Bread & bread products	7,938	4	0.1
Chocolate tablets	6,179	7	0.1
Chilled desserts	4,749	5	0.1
Wet soup	2,978	2	0.1
Sandwiches/wraps	1,867	2	0.1
Meal kits	1,542	1	0.1
Toffees, caramels & nougat	1,533	1	0.1
Snack mixes	1,189	1	0.1
Margarine & other blends	842	1	0.1
RTD (iced) coffee	688	1	0.1
Fish products	9,495	1	0
Pasta	7,372	1	0
Cold cereals	4,680	1	0
Savoury biscuits/crackers	3,687	1	0
Hors d'oeuvres/canapes	3,081	1	0
Shelf-stable desserts	2,428	1	0
Meat pastes & pates	2,371	1	0
<b>Total sample</b>	<b>123,835</b>	<b>779</b>	<b>0.6<sup>(b)</sup></b>

(a): According to Mintel food categorisation.

(b): In total, around 0.6% of the foods available on the Mintel GNPD are labelled with sorbitan esters (E 491–495) between 2011 and 2016.

## Appendix C – Concentration levels of sorbitan esters (E 491–495) used in the regulatory maximum level exposure assessment scenario and the refined exposure scenario (mg/kg or mL/kg as appropriate)

FCS Category number	FCS Food category	Restrictions/exception	MPL	Concentration levels used in the refined exposure assessment scenario (only reported use levels)		Comments
				Mean	Maximum	
01.4	Flavoured fermented milk products including heat-treated products		5,000	–	–	Not taken into account in refined exposure scenario (no use data available)
01.8	Dairy analogues, including beverage whiteners (only milk and cream analogues)	Only milk and cream analogues	5,000	3,000	5,000	
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions		10,000	2,500	2,500	
03	Edible ices		500	–	–	Not taken into account in refined exposure scenario (no use data available)
04.2.5.2	Jam, jellies and marmalades and sweetened chestnut purée as defined by Directive 2001/113/EC	Only jelly and marmalade	25	1.65	3.3	
05.1	Cocoa and Chocolate products as covered by Directive 2000/36/EC		10,000	2,480	5,100	
05.2	Other confectionery including breath freshening microsweeteners	Only sugar confectionery	5,000	4,000	5,000	
05.2	Other confectionery including breath freshening microsweeteners	Only cocoa-based confectionery	10,000	–	–	Not taken into account in refined exposure scenario (no use data available)
05.3	Chewing gum		5,000	500	5,000	
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4		5,000	–	–	Not taken into account in both exposure scenarios (no consumption data available)
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	Only cocoa-based confectionery	10,000	–	–	Not taken into account in both exposure scenarios (no consumption data available)

FCS Category number	FCS Food category	Restrictions/exception	MPL	Concentration levels used in the refined exposure assessment scenario (only reported use levels)		Comments
				Mean	Maximum	
07.2	Fine bakery wares		10,000	1,575	9,000	
12.6	Sauces	Only emulsified sauces	5,000	–	–	Not taken into account in refined exposure scenario (no use data available)
12.8	Yeast and yeast products	Only dry yeast and yeast for baking	13,000	8,193	13,000	
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)		5,000	–	–	Not taken into account in refined exposure scenario (no use data available)
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)		5,000	–	–	Not taken into account in refined exposure scenario (no use data available)
14.1.5.2	Other non-alcoholic beverages	Only liquid tea concentrates and liquid fruit and herbal infusion concentrates	500	–	–	Not taken into account in refined exposure scenario (no use data available)
16	Desserts excluding products covered in categories 1, 3 and 4		5,000	1,475	2,500	
17.1	Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms		5,000	0.5	0.9	
17.2	Food supplements supplied in a liquid form		QS <sup>(a)</sup>	–	–	Not taken into account in refined exposure scenario (no use data available)
17.3	Food supplements supplied in a syrup-type or chewable form		5,000	–	–	Not taken into account in refined exposure scenario (no use data available)

FCS: Food Categorisation System; MPL: maximum permitted level; QS: *quantum satis*.

(a): A level of 5,000 mg/kg was used in the maximum scenario.

## Appendix D – Main food categories contributing to exposure to sorbitan esters (E 491–495) according to the regulatory maximum level exposure assessment scenario

**D.1:** Main food categories contributing to exposure to sorbitan esters (E 491–495) using maximum permitted levels (> 5% to the total mean exposure) and number of surveys in which each food category is contributing

Food category number	Food category name	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of % contribution to the total exposure (number of surveys) <sup>(a)</sup>					
01.4	Flavoured fermented milk products including heat-treated products	6.2–58.7 (6)	5.6–82.6 (10)	7.5–56.1 (16)	6.4–43.3 (15)	6.7–23.6 (15)	8.6–18 (11)
01.8	Dairy analogues, including beverage whiteners	6.3 (1)	–	–	–	–	–
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	12.5–23.8 (2)	6.5–13.4 (4)	6.2–19.4 (7)	5.9–21.5 (7)	6.2–23.4 (7)	5.4–26.9 (10)
05.1	Cocoa and chocolate products as covered by Directive 2000/36/EC	29.8 (1)	6.3–12.2 (4)	5.2–23.4 (13)	5–27.3 (17)	5.2–17.5 (10)	11.1 (1)
05.2	Other confectionery including breath refreshing microsweets	–	–	5.2–10 (4)	5.4–10.5 (4)	7.9 (1)	–
07.2	Fine bakery wares	13.8–75.7 (4)	5.9–83.3 (10)	15.9–85.4 (17)	13.8–77.5 (16)	20.4–73.2 (17)	25.1–74.2 (14)
14.1.5.2	Other non-alcoholic beverages	17.5–28.8 (3)	6.7–11 (2)	5.4–13.1 (5)	5.6–18.5 (8)	6.5–35.9 (14)	7.5–45 (14)
16	Desserts excluding products covered in categories 1, 3 and 4	8.1–22.8 (3)	5.8–16.1 (7)	5.3–13.3 (10)	5.2–9.9 (5)	5.4–13.1 (5)	6.6–12 (5)
17	Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children	10.9 (1)	–	–	–	–	–

(a): The total number of surveys may be greater than the total number of countries as listed in Table 3, as some countries submitted more than one survey for a specific population.

**D.2:** Main food categories contributing to exposure to sorbitan esters (E 491–495) using the brand-loyal refined exposure scenario (> 5% to the total mean exposure) and number of surveys in which each food category is contributing

Food category number	Food category name	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of % contribution to the total exposure (number of surveys) <sup>(a)</sup>					
01.8	Dairy analogues, including beverage whiteners	42.5 (1)	19.1 (1)	11.3 (1)	7.5 (1)	–	–
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	14.1–39.9 (2)	11.8–15.2 (2)	12.7–24.7 (2)	13.3–19.9 (2)	5.6–15.2 (5)	5.3–17.5 (7)
05.1	Cocoa and chocolate products as covered by Directive 2000/36/EC	100 (1)	5–12.2 (3)	5.2–20.8 (8)	5.2–24.5 (6)	9.5–14.5 (3)	9 (1)
05.2	Other confectionery including breath refreshing microsweets	–	14.3 (1)	5.4–30.9 (6)	5.3–36.1 (5)	5.3–18 (2)	5.8–8.5 (2)
07.2	Fine bakery wares	13.8–99.8 (5)	51.6–98 (10)	36.4–97.3 (17)	29–96.3 (16)	46.9–96.4 (17)	62.6–97.7 (14)
12.8	Yeast and yeast products	–	7 (1)	9.2 (1)	6.2–12.1 (2)	–	–
16	Desserts excluding products covered in categories 1, 3 and 4	6.6–23.9 (3)	6.5–17.6 (7)	5.1–13.1 (7)	5.2–6.8 (2)	7.1–8.4 (3)	6.1–10.8 (4)

(a): The total number of surveys may be greater than the total number of countries as listed in Table 3, as some countries submitted more than one survey for a specific population.



**D.3:** Main food categories contributing to exposure to sorbitan esters (E 491–495) using the non-brand-loyal refined exposure scenario (> 5% to the total mean exposure) and number of surveys in which each food category is contributing

Food category number	Food category name	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of % contribution to the total exposure (number of surveys) <sup>(a)</sup>					
01.8	Dairy analogues, including beverage whiteners	36.5 (1)	26 (1)	9.1 (1)	6.8 (1)	–	–
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	6.2–57 (3)	13–33.3 (4)	8.4–29.8 (7)	5.7–24 (9)	6–40.8 (12)	7.3–43.1 (11)
05.1	Cocoa and chocolate products as covered by Directive 2000/36/EC	5.3–100 (3)	7–26 (6)	5.1–24.8 (17)	7.4–27.2 (17)	5.1–21.2 (17)	5.5–16 (10)
05.2	Other confectionery including breath refreshing microsweets	–	5.7–25.5 (5)	5.3–33.9 (14)	6.9–35.6 (13)	5–28.9 (8)	6.7–17.2 (3)
07.2	Fine bakery wares	22.7–98.8 (4)	17.6–89.2 (10)	10.6–86.1 (17)	8.3–81.5 (16)	14.6–81.9 (17)	23–88.4 (14)
12.8	Yeast and yeast products	–	5.2–11.9 (2)	5.5–10.4 (2)	6.6–13.5 (3)	5.4–11.7 (4)	5.6–7.3 (2)
16	Desserts excluding products covered in categories 1, 3 and 4	22.3–48.4 (3)	5.7–37.1 (8)	5.4–32.1 (12)	5.1–18.7 (11)	5–25 (12)	5–26.6 (10)

(a): The total number of surveys may be greater than the total number of countries as listed in Table 3, as some countries submitted more than one survey for a specific population.

## Appendix E – Summary of total estimated exposure of sorbitan esters (E 491–495) from their use as food additives for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg/kg bw per day)

	Number of subjects	MPL scenario		Brand-Loyal scenario		Non-Brand-Loyal scenario	
		Mean	P95	Mean	P95	Mean	P95
Infants							
Bulgaria (NUTRICHILD)	659	17.6	66.0	12.0	51.4	2.1	9.0
Germany (VELS)	159	18.2	74.3	7.9	35.9	1.9	6.9
Denmark (IAT 2006_07)	826	16.7	75.4	3.4	13.0	1.5	5.5
Finland (DIPP_2001_2009)	500	0.2	0.4	0.03	<0.01	0.02	<0.01
United Kingdom (DNSIYC_2011)	1,369	13.6	57.0	5.8	26.5	1.9	9.5
Italy (INRAN_SCAI_2005_06)	12	4.2	–	0.6	–	0.3	–
Toddlers							
Belgium (Regional_Flanders)	36	76.5	–	29.4	–	9.4	–
Bulgaria (NUTRICHILD)	428	43.5	103.4	33.3	81.7	6.1	14.6
Germany (VELS)	348	53.4	108.6	25.3	58.7	7.2	16.0
Denmark (IAT 2006_07)	917	31.8	83.9	7.8	19.5	3.6	7.8
Spain (enKid)	17	54.1	–	17.2	–	6.1	–
Finland (DIPP_2001_2009)	500	26.1	101.0	2.6	10.1	1.2	3.7
United Kingdom (NDNS-RollingProgrammeYears1-3)	185	40.6	90.9	24.8	61.8	6.4	15.3
United Kingdom (DNSIYC_2011)	1,314	30.8	80.1	18.0	51.2	4.8	14.6
Italy (INRAN_SCAI_2005_06)	36	37.6	–	20.2	–	4.3	–
Netherlands (VCP_kids)	322	88.9	211.2	29.7	71.3	10.6	24.1
Children							
Austria (ASNS_Children)	128	34.3	91.7	23.7	57.9	5.0	14.0
Belgium (Regional_Flanders)	625	73.7	164.0	29.0	65.7	9.1	19.8
Bulgaria (NUTRICHILD)	433	43.3	100.8	34.4	86.3	6.5	15.4
Czech Republic (SISP04)	389	48.0	102.6	25.0	59.9	7.2	16.5
Germany (EsKiMo)	835	26.5	61.2	12.4	34.6	4.1	9.5
Germany (VELS)	293	52.0	97.8	26.5	59.0	7.6	15.3
Denmark (DANSIDA 2005-08)	298	21.4	54.0	7.0	17.3	3.6	7.5
Spain (enKid)	156	43.5	105.1	19.4	57.5	5.5	14.4
Spain (NUT_INK05)	399	44.8	97.5	17.2	42.4	4.4	10.7
Finland (DIPP_2001_2009)	750	32.0	73.4	4.7	11.5	3.6	8.1
France (INCA2)	482	54.2	102.9	33.3	68.1	9.0	18.1
United Kingdom (NDNS-RollingProgrammeYears1-3)	651	36.6	78.2	25.1	61.1	5.8	13.7
Greece (Regional_Crete)	838	41.4	88.7	30.9	73.7	6.0	13.8
Italy (INRAN_SCAI_2005_06)	193	31.9	72.6	22.6	52.8	4.7	11.7
Latvia (EFSA_TEST)	187	33.0	87.6	21.2	57.7	5.0	14.6
Netherlands (VCP_kids)	957	78.4	183.4	26.7	66.9	8.9	19.9
Netherlands (VCPBasis_AVL2007_2010)	447	58.7	126.5	25.1	62.4	7.7	16.8
Sweden (NFA)	1,473	51.1	109.6	24.7	58.0	5.8	12.6

	Number of subjects	MPL scenario		Brand-Loyal scenario		Non-Brand-Loyal scenario	
		Mean	P95	Mean	P95	Mean	P95
Adolescents							
Austria (ASNS_Children)	237	17.5	45.4	12.5	35.6	2.5	6.5
Belgium (Diet_National_2004)	576	18.3	43.4	11.2	30.4	2.7	7.4
Cyprus (Childhealth)	303	13.1	32.1	9.5	26.5	2.3	5.8
Czech Republic (SISP04)	298	29.8	71.1	18.1	46.2	4.2	10.2
Germany (National_Nutrition_Survey_II)	1,011	17.4	49.1	9.1	33.2	2.2	7.2
Germany (EsKiMo)	393	19.0	44.0	9.0	26.3	2.9	6.5
Denmark (DANSDA 2005-08)	377	10.9	27.4	3.8	10.5	2.1	4.8
Spain (AESAN_FIAB)	86	15.5	39.8	9.6	25.3	2.4	6.2
Spain (enKid)	209	21.9	50.7	12.5	36.0	3.2	8.3
Spain (NUT_INK05)	651	22.1	47.9	11.0	29.2	2.7	6.8
Finland (NWSSP07_08)	306	13.5	29.8	2.6	5.8	1.9	4.1
France (INCA2)	973	26.7	61.1	17.2	42.3	4.4	10.1
United Kingdom (NDNS-RollingProgrammeYears1-3)	666	21.1	50.6	14.5	37.8	3.1	7.4
Italy (INRAN_SCAI_2005_06)	247	18.2	47.4	13.3	34.7	2.7	7.3
Latvia (EFSA_TEST)	453	23.1	61.3	14.7	41.0	3.4	10.1
Netherlands (VCPBasis_AVL2007_2010)	1,142	34.3	75.4	16.0	39.3	4.7	10.3
Sweden (NFA)	1,018	30.3	64.9	16.7	41.8	3.9	8.9
Adults							
Austria (ASNS_Adults)	308	19.0	49.0	12.5	35.9	2.6	7.0
Belgium (Diet_National_2004)	1,292	15.5	37.9	7.9	25.0	2.3	6.1
Czech Republic (SISP04)	1,666	13.4	37.3	8.8	28.2	1.9	5.6
Germany (National_Nutrition_Survey_II)	10,419	17.3	44.4	8.4	27.3	2.0	5.8
Denmark (DANSDA 2005-08)	1,739	7.5	16.7	2.6	6.6	1.2	2.7
Spain (AESAN)	410	11.9	32.2	6.5	21.9	1.8	5.4
Spain (AESAN_FIAB)	981	10.8	29.1	6.6	20.3	1.7	5.0
Finland (FINDIET2012)	1,295	17.2	41.7	7.6	22.5	2.1	5.8
France (INCA2)	2,276	15.7	35.0	9.5	24.0	2.3	5.7
United Kingdom (NDNS-RollingProgrammeYears1-3)	1,266	16.6	37.4	8.2	22.9	1.7	4.7
Hungary (National_Repr_Surv)	1,074	7.3	20.1	2.2	9.1	0.9	2.8
Ireland (NANS_2012)	1,274	15.7	36.0	6.2	17.4	1.4	3.8
Italy (INRAN_SCAI_2005_06)	2,313	9.2	26.2	6.3	19.2	1.3	3.7
Latvia (EFSA_TEST)	1,271	12.5	36.3	7.9	27.5	1.8	5.7
Netherlands (VCPBasis_AVL2007_2010)	2,057	22.1	50.1	9.0	23.7	2.8	6.9
Romania (Dieta_Pilot_Adults)	1,254	3.7	11.3	1.7	6.0	0.6	1.8
Sweden (Riksmaten 2010)	1,430	15.8	38.5	8.9	27.0	2.2	6.0
The elderly							
Austria (ASNS_Adults)	92	17.4	40.3	11.8	31.5	2.3	5.7
Belgium (Diet_National_2004)	1,215	15.1	35.3	7.3	20.5	2.5	6.4
Germany (National_Nutrition_Survey_II)	2,496	17.9	44.8	8.9	27.3	2.0	5.8
Denmark (DANSDA 2005-08)	286	7.3	17.8	2.5	6.8	1.0	2.2
Finland (FINDIET2012)	413	15.5	39.1	8.3	22.6	2.1	5.7
France (INCA2)	348	12.0	30.5	7.0	19.2	1.8	4.7
United Kingdom (NDNS-RollingProgrammeYears1-3)	305	19.6	41.2	8.3	24.0	1.9	5.2

	Number of subjects	MPL scenario		Brand-Loyal scenario		Non-Brand-Loyal scenario	
		Mean	P95	Mean	P95	Mean	P95
Hungary (National_Repr_Surv)	286	7.3	19.2	2.8	11.7	0.9	2.7
Ireland (NANS_2012)	226	19.8	42.4	6.9	19.7	1.6	4.3
Italy (INRAN_SCAI_2005_06)	518	7.1	20.1	4.9	13.6	0.9	2.7
Netherlands (VCPBasis_AVL2007_2010)	173	20.6	42.9	8.9	20.7	2.6	6.2
Netherlands (VCP-Elderly)	739	21.2	39.8	8.1	17.4	2.8	6.1
Romania (Dieta_Pilot_Adults)	128	4.3	9.7	1.6	5.1	0.5	1.6
Sweden (Riksmaten 2010)	367	16.7	37.7	10.7	25.7	2.3	5.3

MPL: maximum permitted level; bw: body weight; P95, 95th percentile.