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## Safety of low-substituted hydroxypropyl cellulose (L-HPC) to be used as a food additive in food supplements in tablet form

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### Abstract

Low-substituted hydroxypropyl cellulose (L-HPC) is a low-substituted poly(hydroxypropyl) ether of cellulose. L-HPC is proposed for use as a food additive in food supplements in solid form (tablet), with a maximum use level of 20,000 mg/kg and a typical use level of 10,000 mg/kg. Exposure estimates to L-HPC from its proposed use were calculated for both typical and maximum use levels. Due to the close chemical relationship between L-HPC and other celluloses recently re-evaluated by EFSA, the Panel decided to read-across the biological data already evaluated in the context of the re-evaluation programme. The Panel concluded that there was no safety concern from the proposed use and use levels of L-HPC.

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## Summary

Following a request from the European Commission, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) has provided a scientific opinion as regards the authorisation of the use of low-substituted hydroxypropyl cellulose (L-HPC) as a food additive in food supplements in solid form (tablet), with a maximum use level of 20,000 mg/kg and typical use level of 10,000 mg/kg.

L-HPC is a low-substituted poly(hydroxypropyl) ether of cellulose. L-HPC differs from hydroxypropyl cellulose (E 463) with respect to the degree of molar substitution with hydroxypropoxy groups of the glucose ring unit of the cellulose backbone.

Dietary exposure to L-HPC from its proposed use as a new food additive was estimated combining the food consumption data available within the EFSA Comprehensive European Food Consumption Database with the proposed use levels provided by the applicant. The Panel noted that the exposure data from the proposed use and use level of L-HPC was around 2 mg/kg body weight (bw) per day for high-level consumers at the highest use level. This value is very low in comparison with around 500 mg/kg bw per day for high-level consumers of other modified celluloses, which was not considered as a safety concern by the Panel in the re-evaluation of the celluloses.

Due to the close chemical relationship between L-HPC and other celluloses recently re-evaluated by EFSA, the Panel decided to read-across the biological data already evaluated in the context of the re-evaluation programme. In common with the conclusions used in the re-evaluation of the celluloses, the Panel considered that toxicological data on hydroxypropyl cellulose (E 463) would be directly applicable to the evaluation of L-HPC. Using this approach, the Panel concluded that there was no safety concern from the proposed use and use levels of L-HPC.

The Panel concluded that there would be no safety concern at the proposed uses and use levels for L-HPC.

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## 1. Introduction

The present scientific opinion deals with the safety of low-substituted hydroxypropyl cellulose (L-HPC) when used as a food additive in food supplements in tablet form.

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

#### 1.1.1. Background

The use of food additives is regulated under the European Parliament and Council Regulation (EC) No 1333/2008 on food additives.<sup>1</sup> 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 conditions of use specified therein.

An application has been introduced for the authorisation of the use of low-substituted hydroxypropyl cellulose (L-HPC) as a food additive in food supplements in solid form (food category 17.1 of part E of Annex II to Regulation (EC) No 1333/2008) at the following use levels:

Food category	Normal use level (mg/Kg)	Maximum use level (mg/Kg)
<b>17.1 Food supplements supplied in a solid form</b> - Tablets	10,000	20,000

L-HPC is not soluble in water. It absorbs water and expands its volume. This increase in volume causes tablets to quickly disintegrate, ensuring better, faster tablet disintegration.

#### 1.1.2. Terms of Reference

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to perform a risk assessment and to provide a scientific opinion on the safety in use of low-substituted hydroxypropyl cellulose (L-HPC) as a food additive in food supplements in tablet form, in accordance with Regulation (EC) No 1331/2008 establishing a common authorisation on procedure for food additives, food enzymes and food flavourings.<sup>2</sup>

### 1.2. Information on existing evaluations and authorisations

According to the applicant, L-HPC is widely used as an excipient in solid dosage pharmaceutical formulations, and in the United States, L-HPC is taken up in the Code of Federal Regulations.

According to the applicant, both microcrystalline cellulose (E 460i) and hydroxypropyl cellulose (E 463) have been previously evaluated by the WHO/FAO Joint Expert Committee on Food Additives and by the former EU Scientific Committee on Food, resulting in the allocation of an acceptable daily intake (ADI) of 'not specified' for both products.

EFSA has recently re-evaluated the safety of hydroxypropyl cellulose (E 463), hydroxypropyl ether of cellulose and other celluloses (E 460i, E 460ii, E 461, E 462, E 464, E 465, E 466, E 468, E 469) as food additives within the re-evaluation programme as laid down in the Regulation (EU) No 257/2010 (EFSA ANS Panel, 2018) and concluded that there was no need for a numerical ADI and that there would be no safety concern at the reported uses and use levels for the unmodified and modified celluloses.

## 2. Data and methodologies

### 2.1. Data

The applicant has submitted a dossier in support of its application for the authorisation of L-HPC as a new food additive for the proposed use in food supplements in solid form ('Documentation provided to EFSA' No.1).

<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, pp. 16–33.

<sup>2</sup> Regulation (EC) No 1331/2008 of the European Parliament and of the Council of 16 December 2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings. OJ L 354, 31.12.2008, pp. 1–6.

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database<sup>3</sup>) was used to estimate dietary exposure.

## 2.2. Methodologies

The assessment was conducted in line with the principles described in the EFSA Guidance on transparency in the scientific aspects of risk assessment (EFSA, 2009) and following the relevant existing guidance documents from the EFSA Scientific Committee.

The current 'Guidance for submission for food additive evaluations' (EFSA ANS Panel, 2012) has been followed by the ANS Panel for the evaluation of the application for authorisation of the new food additive L-HPC.

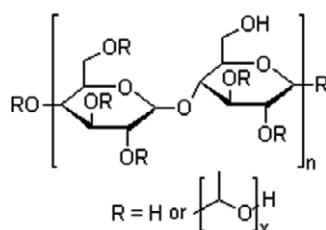
Dietary exposure to L-HPC from its proposed use as a new food additive was estimated combining the food consumption data available within the EFSA Comprehensive European Food Consumption Database with the proposed use levels provided by the applicant.

## 3. Assessment

### 3.1. Technical data

#### 3.1.1. Identity of the substance

According to the information provided by the applicant, L-HPC is a low-substituted poly (hydroxypropyl) ether of cellulose. The general structure of L-HPC is shown in Figure 1.



**Figure 1:** General structural formula of L-HPC. In this structure, 'n' represents the number of anhydrocellobiose repeating units; 'x' represents the number of hydroxypropyl groups

The applicant has provided the following information with respect to the identity of the food additive.

IUPAC name:	Cellulose, 2-hydroxypropyl ether (low substituted)
CAS No.:	9004-64-2
Molecular weight	from 30,000 to 150,000 g/mol

According to the applicant, L-HPC contains on a dried basis, between minimum 5.0% and maximum 16.0% of hydroxypropoxy groups.

L-HPC differs from hydroxypropyl cellulose (E 463) with respect to the degree of molar substitution<sup>4</sup> with hydroxypropoxy groups of the glucose ring unit (0.2 for L-HPC vs 3.5 for E 463) of the cellulose backbone.

According to the applicant, this chemical difference leads to different physical properties: E 463 is soluble in water whereas L-HPC is not soluble in water.

#### 3.1.2. Particle size and particle size distribution

The Panel noted that the applicant provided data on particle size distributions of six non-consecutive lots of L-HPC using size-exclusion chromatography (SEC) as the analytical method. The average (D50) particle size varied between 47.3  $\mu\text{m}$  and 50.3  $\mu\text{m}$ . The D90 value (90% below given value) varied between 126.2  $\mu\text{m}$  and 138  $\mu\text{m}$ . On the basis of the data provided by the applicant, the Panel has no indication that particles in the nano range are present in the commercial material.

<sup>3</sup> <http://www.efsa.europa.eu/en/food-consumption/comprehensive-database>

<sup>4</sup> Average number of substituents per anhydroglucose ring

### 3.1.3. Specifications

The specifications for L-HPC as proposed by the applicant are listed in Table 1.

**Table 1:** Specifications for low-substituted hydroxypropyl cellulose (L-HPC) as proposed by the applicant

Specification parameter	Specification value
<b>Synonyms</b>	Cellulose hydroxypropyl ether, low substituted
<b>Definition</b>	Low-substituted hydroxypropyl cellulose is cellulose obtained directly from strains of fibrous plant material and partially etherified with hydroxypropyl groups
Chemical name	Hydroxypropyl ether of cellulose, low-substituted
Chemical formula	The polymers contain substituted anhydroglucose units with the following general formula:  $C_6H_7O_2(OR_1)(OR_2)(OR_3),$ where $R_1, R_2, R_3$ each may be one of the following:  –H –CH <sub>2</sub> CHOHCH <sub>3</sub> –CH <sub>2</sub> CHO(CH <sub>2</sub> CHOHCH <sub>3</sub> )CH <sub>3</sub> –CH <sub>2</sub> CHO[CH <sub>2</sub> CHO(CH <sub>2</sub> CHOHCH <sub>3</sub> )CH <sub>3</sub> ]CH <sub>3</sub>
Molecular weight	From about 30,000 to 150,000
Assay	The average number of hydroxypropoxy groups (–OCH <sub>2</sub> CHOHCH <sub>3</sub> ) corresponds to 0,2 hydroxypropyl groups per anhydroglucose unit on the anhydrous basis
<b>Description</b>	Slightly hygroscopic white or slightly yellowish or greyish odourless and tasteless, granular or fibrous powder
<b>Identification</b>	Passes test
Solubility	Insoluble in water. It dissolves in a dilute solution of sodium hydroxide producing a viscous solution
Assay	Determine the degree of substitution by gas chromatography
pH value	Not less than 5.0 and not more than 8.0 (1% colloidal solution)
Purity	
Loss on drying	Not more than 5% (105°C, 1 h)
Sulphated ash	Not more than 0.8 % determined at 800 ± 25°C
Propylenechlorohydrins	Not more than 0.1 mg/kg (gas chromatography–mass spectrometry (GC–MS))
Arsenic	Not more than 3 mg/kg
Lead	Not more than 2 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg

On the basis of the results on six non-consecutive batch analyses on L-HPC, the Panel considered that L-HPC is compliant with the proposed specifications. However, the Panel noted that in the supporting certificates of analyses, only values are listed for 'heavy metals' (not further specified), of not more than 10 mg/kg (0.001%).

The Panel noted that, based on the analytical results provided by the applicant, lower level of the maximum limits for heavy metals present as impurity should be considered in the proposed specifications.

The Panel noted that a limit of 0.1 mg/kg for propylenechlorohydrins is defined for hydroxypropyl cellulose. In the proposed specifications for L-HPC, the same limit is mentioned.

The Panel further noted that the applicant did not provide methods of analyses; however, references are made to the United States National Formulary and to the Japanese Pharmacopoeia methods in the certificates of analysis provided by the applicant.

### 3.1.4. Manufacturing process

The Panel noted that the applicant provided only limited information on the manufacturing process used for the production of L-HPC. According to this information, pure cellulose (wood pulp) is subjected to partial etherification with propylene oxide. The resulting product is then purified, dried



and milled to yield low-substituted hydroxypropyl cellulose. According to the applicant, L-HPC is manufactured in compliance with Good manufacturing practices (GMP).

The Panel noted that in the patent literature (Obara, 2002), a process for the production of L-HPC was described. In this process, wood pulp is soaked in an aqueous solution of sodium hydroxide (49% w/w) and then pressed to obtain an alkali cellulose preparation. This alkali cellulose is reacted, under an inert atmosphere (N<sub>2</sub> gas), with propylene oxide, under stirring for 1 hour at 40°C and subsequently at 70°C for 1 h. The reaction mixture is diluted in water (65°C), mixed, and neutralised with acetic acid to crystallise the reaction product. The crystalline product is then washed with hot water at 90°C, dehydrated by pressing, dried and pulverised. Data show that the final L-HPC product obtained via this method has a hydroxypropoxy content of 11.0% (by weight) and an apparent average degree of polymerisation of 530.<sup>5</sup>

### 3.1.5. Methods of analysis in food

The Panel noted that no data were provided by the applicant on methods of analysis in foods.

However, the Panel noted that in literature, methods are described for the determination of hydroxypropylcellulose (HPC) (Zhu et al., 2006).

The USP method for the quantification of, specifically, HPC consists in hydrolysing the alkoxy groups with hydroiodic acid and to quantify the resulting halogenated derivatives by redox titration. In the USP document, identification of, specifically, L-HPC is performed using a solution of anthrone in sulphuric acid (USP, 2003).

Other spectrophotometric methods using anthrone reagent to react with the cellulosic polymer have been described in literature (Viles and Silverman, 1949; Black, 1951; Koehler, 1952; Yemm and Willis, 1954).

SEC was used for the separation and quantification of polymers, i.e. for the analysis of HPC, hydroxyethyl cellulose (HEC) or hydroxypropylmethyl cellulose (HPMC) in pharmaceutical formulations (Delker et al., 1995; Whelan et al., 2002; Marcelo et al., 2007).

### 3.1.6. Stability of the substance and reaction and fate in food

The applicant has provided information on the stability of L-HPC stored at ambient condition from 2009 to 2013 ('Documentation provided to EFSA' No. 1). No significant variation in the appearance, loss on drying, hydroxypropoxy content and pH occurred during the storage.

The Panel concluded that under standard conditions, L-HPC is stable.

## 3.2. Proposed uses and use levels

The applicant has submitted an application to use L-HPC as a food additive in food supplements in solid form at the typical level of 10,000 mg/kg food. The applicant suggested a maximum level (ML) of use of 20,000 mg/kg food.

The food category for which an authorisation is sought with the current application is 17.1 Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children.

## 3.3. Exposure data

### 3.3.1. Food consumption data used for the exposure assessment

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

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with data on national 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>6</sup> added in the Comprehensive database were also taken into account in this assessment.<sup>7</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

<sup>5</sup> number of hydroxypropoxy units in the cellulose chain

<sup>6</sup> Available online: <http://www.efsa.europa.eu/en/press/news/150428.htm>

<sup>7</sup> Available online: <http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm>



category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' under-reporting 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 population groups, 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, as listed in Table 2.

**Table 2:** Population groups considered for the exposure estimates of low-substituted hydroxypropyl cellulose (L-HPC)

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

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

Consumption records were codified according to the FoodEx classification system (EFSA, 2011b). Nomenclature from the FoodEx classification system has been linked to the Food Classification 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.

### 3.3.2. Exposure to low-substituted hydroxypropyl cellulose from its proposed use as a food additive

#### 3.3.2.1. Estimate of exposure based on the Food Additives Intake Model (FAIM) template

The applicant has provided an estimate of the exposure to L-HPC based on the output obtained using the FAIM model (version 1) ('Documentation provided to EFSA' No.1).

The Panel decided not to use the estimate exposure generated from the FAIM tool version 1 and provided by the applicant since a new EFSA version of the FAIM tool (version 2)<sup>8</sup> has become available since the receipt of the current application.

The Panel, therefore, decided to perform a new estimate exposure using the FAIM tool (version 2). The results of the estimate exposure are reported in Table 3.

The exposure estimate to L-HPC from its proposed use was calculated for both typical and maximum levels for average population and high consumers only at p95.

**Table 3:** Estimate exposure to low-hydroxypropyl cellulose (L-HPC) from its proposed use as a food additive: at the proposed use levels and at the proposed MLs

Estimate exposure (mg/kg bw per day)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
<b>Proposed typical use level: 10,000 mg/kg</b>				
Mean	0–0.26	0–0.095	0–0.25	0–0.54
High level	0–0.94	0–0.44	0–0.85	0–0.85

<sup>8</sup> <http://www.efsa.europa.eu/en/applications/foodingredients/tools>

Estimate exposure (mg/kg bw per day)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
<b>Proposed maximum use level: 20,000 mg/kg</b>				
Mean	0–0.52	0–0.19	0–0.5	0–1.08
High level	0–1.89	0–0.88	0–1.7	0–1.7

The Panel further decided to consider the estimate of exposure as valid and not to perform a more refined assessment.

### 3.4. Biological and toxicological data

The Panel has recently evaluated microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) and the modified celluloses (methyl cellulose (E 461), hydroxypropyl cellulose (E 463), hydroxypropyl methyl cellulose (E 464), ethyl methyl cellulose (E 465), sodium carboxymethyl cellulose (E 466), cross-linked sodium carboxymethyl cellulose (E 468) and enzymatically hydrolysed carboxymethyl cellulose (E 469)) (EFSA ANS Panel, 2018). L-HPC is closely related to hydroxypropyl cellulose (E 463) differing only in the lower extent of hydroxypropyl substitution. In common with the conclusions used in the re-evaluation of the celluloses, the Panel considered that toxicological data on hydroxypropyl cellulose (E 463) would be directly applicable to the evaluation of L-HPC and that data from other modified celluloses could be read across to address any deficiencies in this database.

### 3.5. Discussion

According to the applicant, L-HPC is proposed for use as a food additive in food supplements in tablet form at the typical use level of 10,000 mg/kg and a ML of 20,000 mg/kg.

The food category for which an authorisation is sought with the current application is 17.1 Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children.

According to the information provided by the applicant, L-HPC is a low-substituted poly (hydroxypropyl) ether of cellulose.

L-HPC differs from hydroxypropyl cellulose (E 463) with respect to the degree of molar substitution with hydroxypropoxy groups of the glucose ring unit (0.2 for L-HPC vs 3.5 for E 463) of the cellulose backbone.

According to the applicant, this chemical difference leads to different physical properties: E 463 is more soluble in water than L-HPC.

Due to the close chemical relationship between L-HPC and other celluloses recently re-evaluated by EFSA, the Panel decided to read-across the biological data already evaluated in the context of the re-evaluation programme.

Exposure estimates to L-HPC from its proposed use were calculated for both typical and maximum use levels.

Taking into account:

- their structural, physicochemical and biological similarities permits read-across of toxicological data from all the substituted celluloses to L-HPC
- animal and human data demonstrate that microcrystalline cellulose (E 460(i)) and powdered cellulose (E 460(ii)) are not absorbed intact in the gastrointestinal tract but could be fermented by intestinal microbiota. Chemically modified celluloses are not absorbed intact nor fermented, but are excreted intact via the faeces
- using the read-across approach, adequate data on short- and long-term toxicity and carcinogenicity and reproductive toxicity are available for fermentable and non-fermentable celluloses,
- despite the limitations of some of the studies, the available data do not indicate a genotoxic concern for microcrystalline cellulose, methyl cellulose and carboxy methyl cellulose, and by read-across, of the other modified and unmodified celluloses
- no adverse effects were reported after repeated doses up to 35 g/person of microcrystalline cellulose or powdered cellulose; oral ingestion of some modified celluloses up to 6,000 mg/person per day for 8 months in patients suffering from diarrhoea or constipation was well tolerated;

- the exposure data from the proposed use and use level of L-HPC which was around 2 mg/kg body weight (bw) per day for high-level consumers at the highest use level. This value compares to around 500 mg/kg bw per day for high-level consumers of other modified celluloses which was not considered as a safety concern by the Panel in the re-evaluation of the celluloses (EFSA ANS Panel, 2018).

The Panel concluded that there would be no safety concern at the proposed uses and use levels for L-HPC.

#### 4. Conclusions

The Panel concluded that there would be no safety concern at the proposed uses and use levels of L-HPC as a food additive.

#### 5. Recommendation

The Panel recommended lower specification limits for lead, mercury, cadmium and arsenic, given that levels proposed in the specifications could have a significant impact on the exposure to these toxic elements.

#### Documentation provided to EFSA

- 1) Dossier 'Technical dossier Low-substituted hydroxypropyl cellulose (L-HPC)'. October 2016. Submitted by SE Tylose.

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## Abbreviations

ADI	acceptable daily intake
ANS Panel	EFSA Panel on Food additives and Nutrient Sources added to Food
bw	body weight
CAS	Chemical Abstracts Service
FAIM	Food Additives Intake Model
FAO	Food and Agriculture Organization
FCS	Food Classification System
GC–MS	gas chromatography–mass spectrometry
GMP	good manufacturing practices
HEC	hydroxyethyl cellulose
HPC	hydroxypropyl cellulose
HPMC	hydroxypropylmethyl cellulose
IUPAC	International Union of Pure and Applied Chemistry
L-HPC	low-substituted hydroxypropyl cellulose
ML	maximum level
MS	mass spectroscopy
SEC	size-exclusion chromatography
USP	United States Pharmacopeia
WHO	World Health Organization