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SCIENTIFIC OPINION

Safety of feed additives consisting of hydroxypropyl methyl cellulose (E 464) and methyl cellulose (E 461) for all animal species (International Cellulosics Association)

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Abstract

Following a request from the European Commission, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety of hydroxypropyl methyl cellulose and methyl cellulose as technological feed additives for all animal species. In its previous opinions on the safety and efficacy of the products, the FEEDAP Panel could not conclude on proper identification and characterisation as required for a feed additive. The occurrence of potential toxic impurities could also not be assessed. Based on the new data provided, the feed additives hydroxypropyl methyl cellulose and methyl cellulose were properly identified and characterised and were shown to meet the specifications set for the food additives. Therefore, the conclusions of the safety assessments reached in the previous opinions for hydroxypropyl methyl cellulose and methyl cellulose meeting the food additive specifications, apply to the hydroxypropyl methyl cellulose and methyl cellulose under assessment as feed additives. The additives are considered safe for all animal species, the consumer and the environment. In the absence of data, the FEEDAP Panel is not in the position to conclude on the safety for the user.

KEYWORDS

characterisation, hydroxypropyl, methyl cellulose, methyl cellulose, safety, technological additive

CONTENTS

1 | INTRODUCTION

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

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition and, in particular, Article 9 defines the terms of the authorisation by the Commission.

The applicant, International Cellulosics Association (ICA), is seeking a Community authorisation of hydroxypropyl methyl cellulose E 464 and methyl cellulose E 461 as feed additives to be used as emulsifiers, stabilisers, thickeners, gelling agents and binders for all animal species (Table 1).

TABLE 1 Description of the substances.

Category of additive	Technological additives
Functional group of additive	Emulsifiers, stabilisers, thickeners, gelling agent and binders
Description	Methyl Cellulose E 461 and Hydroxypropyl Methyl Cellulose E 464
Target animal category	All animal species
Applicant	International Cellulosics Association (ICA)
Type of request	New opinion

On 2 July 2020, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) of the European Food Safety Authority (EFSA), in its opinion on the safety and efficacy of the product, could not conclude on the safety for the user of methyl cellulose E 461 and hydroxypropyl methyl cellulose E 464 in all animal species.

The Commission gave the possibility to the applicant to submit supplementary information and data in order to complete the assessment and to allow a revision of the EFSA's opinion. The new data have been received on 05 May 2021 and the applicant has been requested to transmit them to EFSA as well.

In view of the above, the Commission asks the Authority to deliver a new opinion on methyl cellulose E 461 and hydroxypropyl methyl cellulose E 464 as a feed additive for all animal species based on the additional data submitted by the applicant, in accordance with Article 29(1)(a) of Regulation (EC) No 178/2002.[2]

1.2 | Additional information

Methyl cellulose (E 461) and hydroxypropyl methyl cellulose (E 464) are currently authorised as feed additives for all animal species, without a minimum and a maximum content.

EFSA issued one opinion on the safety and efficacy of hydroxypropyl methyl cellulose E 464 when used in feed for all animal species (EFSA FEEDAP Panel, 2020a), and one on the safety and efficacy of methyl cellulose E 461 when used in feed for all animal species (EFSA FEEDAP Panel, 2020b).

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) adopted in 2017 an opinion on the re-evaluation of celluloses E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469 as food additives (EFSA ANS Panel, 2018) and the EFSA Panel on Food Additives and Flavourings (FAF) adopted in 2022 an opinion on the re-evaluation of sodium carboxy methyl cellulose (E 466) as a food additive in foods for infants below 16 weeks of age and follow-up of its re-evaluation as food additive for uses in foods for all population groups (EFSA FAF Panel, 2022).

2 | DATA AND METHODOLOGIES

2.1 | Data

The present assessment is based on data submitted by the applicant in the form of supplementary information[3] to previous applications on the same products.[4]

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers, other scientific reports, to deliver the present output.

[1]Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2]Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1.
[3]Dossier reference: EFSA-Q-2022-00439.
[4]Dossier reference: Hydroxypropyl methyl cellulose FAD-2016-0066; Methyl cellulose FAD-2016-0063.

2.2 | Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of active substance (trade name of the product) is in line with the principles laid down in Regulation (EC) No 429/2008[5] and the relevant guidance documents: Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEEDAP Panel, 2017), Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles (EFSA Scientific Committee, 2021), Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health (EFSA Scientific Committee, 2021).

3 | ASSESSMENT

Hydroxypropyl methyl cellulose and methyl cellulose are intended to be used as technological additives in feed (functional group: emulsifiers, stabilisers, thickeners, gelling agents and binders), with no minimum or maximum content.

In its previous opinions (EFSA FEEDAP Panel, 2020a, 2020b), the Panel was not in the position to properly identify and characterise the two additives. No analytical data to support the identification of the active substances and the batch-to-batch consistency of the additives, as well as information on dusting potential of the additives and their particle size distribution, was made available. In addition, owing to the lack of analytical data, the occurrence of potential toxic impurities in the additives could not be assessed. In the absence of proper identification, the FEEDAP Panel limited its conclusion on safety to hydroxypropyl methyl cellulose and methyl cellulose meeting the food additive specifications. The Panel concluded that hydroxypropyl methyl cellulose and methyl cellulose are safe for all animal species, consumers and the environment, but could not conclude on the safety for users due to the absence of data.

In order to address the limitations in the data submitted in the original application, the applicant provided new data on the characterisation of the additives and on their impurities.

3.1 | Characterisation

3.1.1 | Characterisation of hydroxypropyl methyl cellulose

Hydroxypropyl methyl cellulose is identified with the single Chemical Abstracts Service (CAS) number 9004-65-3, and the European Inventory of Existing Chemical Substances (EINECS) number 232-674-9.

The feed additive hydroxypropyl methyl cellulose is claimed to be manufactured to meet the specifications set for its use as a food additive,[6] i.e. methoxyl groups ≥ 19 and ≤ 30%, hydroxypropoxyl groups ≥ 3 and ≤ 12%, loss on drying < 10%, sulfated ash < 1.5% (for products with viscosity of 50 mPa.s or above) or < 3% (for products with viscosity below 50 mPa.s). In the original application, no evidence of the identity of the active substance in the additive was provided, as well as no analysis of methoxyl groups, hydroxypropoxyl groups and sulfated ash, impurities and the dusting potential of the additive.

In the present application, the identity of the active substance was confirmed by the analysis of five recent batches of the additive by infrared (IR) spectroscopy.[7] Ten batches of the additive[8] showed the following results: methoxyl groups 22.6%–23.8%, hydroxypropoxyl groups 8.6%–9.2%, loss on drying range 1.6%–3.2% and sulfated ash 0.3%–1.2%, which demonstrated compliance with the proposed specifications for use as food additive.

Five batches of the additive[9] were analysed for cadmium, lead, mercury and arsenic concentrations, showing in all batches concentrations below the limit of quantification (LOQ).[10]

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), dioxin-like polychlorinated biphenyls (DL-PCBs) and non-DL-PCBs were analysed in six batches of the additive. The calculated upper bound (UB) concentration was in the range between 0.066 and 10.4 ng WHO_{2005}-TEQ/kg for the sum of PCDD/Fs, and between 0.105 and 12.4 ng WHO_{2005}-TEQ/kg for the sum of PCCD/Fs and DL-PCBs. The UB for the sum of non-DL-PCBs ranged between 0.38 and 5.22 µg/kg.[11] In addition, in two batches of the raw pulp material from which hydroxypropyl methyl cellulose is derived, the calculated UB concentration was < 0.071 ng WHO_{2005}-TEQ/kg for the sum of PCDD/Fs and < 0.113 ng WHO_{2005}-TEQ/kg for the sum of PCDD/Fs and PCBs. The UB for the sum of non-DL-PCBs was < 0.41 µg/kg.[12]

[5]Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

[6]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 Text with EEA relevance. OJ L 83, 22.3.2012, p. 1–295.

[7]Technical dossier/Annex 7.

[8]Supplementary Information April 2023/Annex II and Annex IV.

[9]Supplementary Information April 2023/Annex II and Annex IV.

[10]Limit of quantification: cadmium 0.02 mg/kg, lead 0.02 mg/kg, mercury 0.02 mg/kg and arsenic 0.02 mg/kg.

[11]Supplementary Information April 2023/Annex III. Upper bound concentrations are calculated on the assumption that all values of the different congeners below the limit of quantification are equal to the limit of quantification. TEQ = toxic equivalency factors for dioxins, furans and dioxin-like PCBs established by the WHO in 2005 (Van den Berg et al., 2006).

[12]Technical dossier/Annex 5 and 6.

Three batches of the additive were analysed for mycotoxins concentration (aflatoxins [B1, B2, G1, G2], ochratoxin A, deoxynivalenol, zearalenone and T-2 and HT-2 toxins), showing values below the respective LOQs.[13] In addition, two batches of raw pulp material from which hydroxypropyl methyl cellulose is derived were analysed for aflatoxins (B1, B2, G1, G2) concentration,[14] showing values below the LOQ of 0.1 μg/kg. Three batches of the additive[15] were analysed for pesticides (organochlorine pesticides and pyrethroids, organophosphorus pesticides), which were not detected in any sample.

Ten batches of the additive[16] were analysed for microbiological contamination by the determination of *Escherichia coli* and *Salmonella* spp. with no detection in 1 g and in 25 g (nine batches) or 10 g (one batch), respectively. *Pseudomonas aeruginosa*, *Staphylococcus aureus* and coliforms were also absent in 10 g of each batch of the additive. Total aerobic microbial counts and total yeast and moulds counts were < 10 colony forming unit (CFU)/g.

The detected amounts of the above-described undesirable substances and the microbial impurities do not raise safety concerns.

The dusting potential of six batches of hydroxypropyl methyl cellulose[17] was determined using the Stauber-Heubach method and showed values on average of 2748 mg/m^3 (range 2100–3483 mg/m^3) (mg airborne dust per m^3 of air).

Three batches of the additive[18] were analysed for particle size distribution by laser diffraction. The results showed that 69%–71% of the particles had a size below 105 μm, 26%–29% of the particles was below 50 μm and 1.5%–1.6% of the particles was below 9 μm. In addition, the applicant analysed the same batches with scanning electron microscopy (SEM). However, in line with the opinion of the FAF Panel on the re-evaluation of sodium carboxy methyl cellulose (E 466) (EFSA FAF Panel, 2022), the FEEDAP Panel notes that 'currently no standardised methods are available for the polysaccharide thickening and gelling agents used as food additives, such as sodium carboxy methyl cellulose (E 466) to measure the particle size distribution by number'.

The FAF Panel further considered that: 'Based on the data on particle size distribution […] and the criteria set in the relevant EFSA Scientific Committee Guidance (EFSA Scientific Committee, 2021a), the Panel concluded that the presence of small particles, including nanoparticles, cannot be confirmed or excluded in the pristine food additive'; in addition, 'The Panel noted, however, that polysaccharide thickening, and gelling agents used as feed additives, to exert their technical function in general swell in liquid environments. This also applies to carboxymethyl cellulose. The FAF Panel considers that carboxymethyl cellulose will not be present in the gastrointestinal tract in the pristine form taking into account the capacity to absorb and swell in water, and the volume of fluid in the stomach and gastrointestinal tract'. The FEEDAP Panel considers that the above would apply also to hydroxypropyl methyl cellulose used as a feed additive.

3.1.2 | Characterisation of methyl cellulose

Methyl cellulose is identified with the single CAS number 9004-67-5, and the EINECS number 232-674-9. It is manufactured from wood pulp or cotton by treatment with alkali to form alkali cellulose, which is then methylated with methyl chloride.

Methyl cellulose is in the form of white or yellowish-white or greyish-white granules or powder and is almost insoluble in hot water, acetone, ethanol and toluene. It dissolves in cold water giving colloidal solution.

The feed additive methyl cellulose is claimed to be manufactured to meet the specifications set for its use as a food additive,[19] i.e. methoxyl groups ≥ 25 and ≤ 33%, loss on drying < 10%, sulfated ash < 1.5% and pH > 5 and < 8. In the original application, no evidence of the identity of the active substance in the additive was provided, as well as no analyses of methoxyl groups, impurities and dusting potential of the additive.

In the present application, the identity of the active substance was confirmed by the analysis by near-IR spectroscopy of five recent batches of the additive.[20] Ten batches of the additive[21] showed the following results on average: methoxyl groups 29.7%–30.3%, loss on drying 0.8%–2.5%, sulfated ash 0.1%–1.1% and pH 6.3–7.4.

Three batches of the additive were analysed for cadmium, lead, mercury and arsenic concentrations, showing in all batches concentrations below the LOQ.[22]

[13]Supplementary Information April 2023/Annex III. Limit of quantification: aflatoxins (B1, B2, G1, G2) 0.5 μg/kg, ochratoxin A 1 μg/kg, deoxynivalenol 20 μg/kg, zearalenone 10 μg/kg and T-2 and HT-2 toxins 20 μg/kg.

[14]Technical dossier/Annex 4.

[15]Supplementary Information April 2023/Annex III.

[16]Supplementary Information April 2023/Annex II and Annex IV.

[17]Supplementary Information April 2023/Annex V.

[18]Supplementary Information April 2023/Annex Ia.

[19]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 Text with EEA relevance. OJ L 83, 22.3.2012, p. 1–295.

[20]Technical dossier/Annex 5.

[21]Supplementary Information April 2023/Annex VI and Annex VIII.

[22]Supplementary Information April 2023/Annex VI and Annex VIII. Limit of quantification: cadmium 0.02 mg/kg, lead 0.02 mg/kg, mercury 0.02 mg/kg and arsenic 0.02 mg/kg.

Polychlorinated dibenzo-*p*-dioxins, PCDFs, DL-PCBs and non-DL-PCBs were analysed in six batches of the additive. The calculated UB concentration ranged between 0.067 and 8.49 ng WHO_{2005}-TEQ/kg for the sum of PCDD/Fs, and between 0.105 and 10.1 ng WHO_{2005}-TEQ/kg for the sum of PCCD/Fs and DL-PCBs. The UB for the sum of non-DL-PCBs ranged between 0.38 and 4.25 μg/kg.[23] In addition, in two batches of the raw pulp material from which hydroxypropyl methyl cellulose is derived, the calculated UB concentration was < 0.071 ng WHO_{2005}-TEQ/kg for the sum of PCDD/Fs and < 0.113 ng WHO_{2005}-TEQ/kg for the sum of PCDD/Fs and DL-PCBs. The upper bound for the sum of non-dioxin-like PCBs was < 0.41 μg/kg.[24]

Three batches of the additive were analysed for mycotoxins concentration (aflatoxins (B1, B2, G1, G2), ochratoxin A, deoxynivalenol, zearalenone and T-2 and HT-2 toxins), showing values below the respective LOQs.[25] In addition, aflatoxins (B1, B2, G1, G2) concentrations were analysed in two batches of the raw pulp material,[26] showing values below the LOQ of 0.1 μg/kg.

Three batches of the additive[27] were analysed for pesticides (organochlorine pesticides and pyrethroids, organophosphorus pesticides), which were not detected in any sample.

Five batches of the additive[28] were analysed for microbiological contamination by the determination of *Escherichia coli* and *Salmonella* spp. with no detection in 1 g and in 25 g (four batches) or 10 g (one batch), respectively. *Pseudomonas aeruginosa*, *Staphylococcus aureus* and coliforms were also absent in 10 g (four batches) or 1 g (one batch) of each batch of the additive. Total aerobic microbial counts and total yeast and moulds counts were < 10 CFU/g.

The detected amounts of the above-described undesirable substances and the microbial impurities do not raise safety concerns.

The dusting potential of four batches of methyl cellulose[29] was determined using the Stauber-Heubach method and showed values on average of 3259 mg/m^3 (range 1550–4886 mg/m^3) (mg airborne dust per m^3 of air).

Three batches of the additive[30] were analysed for particle size distribution by laser diffraction. The results showed that 57%–59% of the particles had a size below 105 μm, 24%–26% of the particles was below 50 μm and no particles had the diameter < 9 μm. In addition, the applicant analysed the same batches by SEM. However, in line with the opinion of the FAF Panel on the re-evaluation of sodium carboxy methyl cellulose (E 466) (EFSA FAF Panel, 2022), the FEEDAP Panel notes that 'currently no standardised methods are available for the polysaccharide thickening and gelling agents used as food additives, such as sodium carboxy methyl cellulose (E 466) to measure the particle size distribution by number'.

The FAF Panel further considered that: 'Based on the data on particle size distribution […] and the criteria set in the relevant EFSA Scientific Committee Guidance (EFSA Scientific Committee, 2021a), the Panel concluded that the presence of small particles, including nanoparticles, cannot be confirmed or excluded in the pristine food additive'; in addition, 'The Panel noted, however, that polysaccharide thickening, and gelling agents used as feed additives, to exert their technical function in general swell in liquid environments. This also applies to carboxymethyl cellulose. The FAF Panel considers that carboxymethyl cellulose will not be present in the gastrointestinal tract in the pristine form taking into account the capacity to absorb and swell in water, and the volume of fluid in the stomach and gastrointestinal tract'. The FEEDAP Panel considers that the above would apply also to methyl cellulose used as a feed additive.

3.2 | Safety

In its previous opinions (EFSA FEEDAP Panel, 2020a, 2020b), the FEEDAP Panel concluded that a proper identification and characterisation of hydroxypropyl methyl cellulose and methyl cellulose as feed additives was not possible. Therefore, the FEEDAP Panel could only assess the safety of hydroxypropyl methyl cellulose and methyl cellulose meeting the specifications set for their use as food additives. In particular, the Panel concluded that both hydroxypropyl methyl cellulose and methyl cellulose meeting the specifications set for its use as food additives (i) are considered safe for all animal species, (ii) are of no concern for consumer safety, (iii) are safe for the environment, (iv) in the absence of data, the FEEDAP Panel was not in the position to conclude on the safety for the user.

The FEEDAP Panel considers that both hydroxypropyl methyl cellulose and methyl cellulose have been fully characterised in the current application and comply with the specifications set for their use as food additives. Therefore, the conclusions on the safety of hydroxypropyl methyl cellulose and methyl cellulose reached in the previous opinions apply to hydroxypropyl methyl cellulose and methyl cellulose as feed additives.

[23]Supplementary Information April 2023/Annex VII. Upper bound concentrations are calculated on the assumption that all values of the different congeners below the limit of quantification are equal to the limit of quantification. TEQ = toxic equivalency factors for dioxins, furans and dioxin-like PCBs established by WHO in 2005 (Van den Berg et al., 2006).

[24]Technical dossier/Annex 5.

[25]Supplementary Information April 2023/Annex VII. Limit of quantification: aflatoxins (B1, B2, G1, G2) 0.5 μg/kg, ochratoxin A 1 μg/kg, deoxynivalenol 20 μg/kg, zearalenone 10 μg/kg and T-2 and HT-2 toxins 20 μg/kg.

[26]Technical dossier/Annex 4.

[27]Supplementary Information April 2023/Annex VII.

[28]Supplementary Information April 2023/Annex VI and Annex VIII.

[29]Supplementary Information April 2023/Annex IX.

[30]Supplementary Information April 2023/Annex Ib.

4 | CONCLUSIONS

Based on the data provided, the feed additives hydroxypropyl methyl cellulose and methyl cellulose were properly identified and characterised and were shown to meet the specifications set for the food additives. Therefore, the conclusions of the safety assessment reached in the previous opinions for hydroxypropyl methyl cellulose and methyl cellulose meeting the food additive specifications apply to hydroxypropyl methyl cellulose and methyl cellulose as feed additives. The additives are considered safe for all animal species, the consumer and the environment. In the absence of data, the FEEDAP Panel is not in the position to conclude on the safety for the user.

ABBREVIATIONS

ANS *EFSA Scientific Panel on Additives and Nutrient Sources added to Food*
CAS Chemical Abstracts Service
CFU colony forming unit
DL dioxin-like
EINECS European Inventory of Existing Chemical Substances
FAF EFSA Panel on Food Additives and Flavourings
FEEDAP EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
LOQ limit of quantification
PCBs polychlorinated biphenyls
PCDDs polychlorinated dibenzo-*p*-dioxins
PCDFs polychlorinated dibenzofurans
SEM Scanning electron microscopy
TEQ toxic equivalent
WHO World Health Organization

CONFLICT OF INTEREST

If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

REQUESTOR

European Commission

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