

GRAS Notice (GRN) No. 470

<http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm>

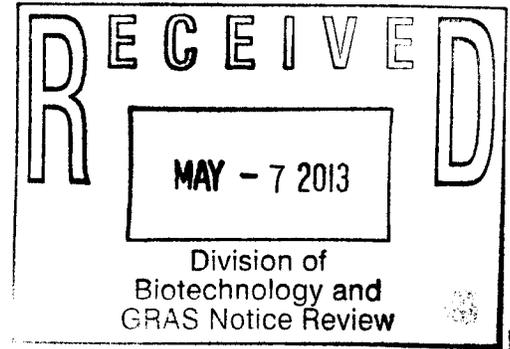
ORIGINAL SUBMISSION



The Dow Chemical Company
Larkin Lab
Midland, MI 48674
U.S.A.

May 3, 2013

Moraima J. Ramos Valle, M.S.
Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740



Re: GRAS Notification for Ethylcellulose

Dear Mrs. Ramos-Valle:

Enclosed please find one hard copy of The Dow Chemical Company's GRAS submission for ethyl cellulose.

Sincerely,

(b) (6)

Jeffrey Pitt, Ph.D.
Senior Product Stewardship Manager
Dow Phama & Food Solutions
The Dow Chemical Company
(989) 859-2633
jpitt@dow.com

Enc



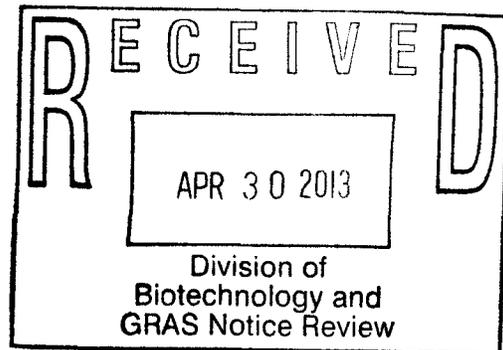
WORLDWIDE PARTNER



The Dow Chemical Company
Larkin Lab
Midland, MI 48674
U.S.A.

April 24, 2013

Moraima J. Ramos Valle, M.S.
Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740



Re: GRAS Notification for Ethylcellulose

Dear Mrs. Ramos-Valle:

Pursuant to proposed 21 CFR 170.36(c), The Dow Chemical Company (Dow) hereby notifies the Food and Drug Administration (FDA) of Dow's determination, on the basis of scientific procedures in accordance with 21 CFR 170.30, that the use of Dow's ethylcellulose product is generally recognized as safe (GRAS) when used in food for multiple technical effects, as described in the enclosed notification document.

It is Dow's opinion that ethylcellulose is properly considered to be exempt from the definition of a food additive and the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act. Dow's conclusion is supported by a review of this GRAS Notification by three well-known toxicologists, experts in the field of food safety, who have concurred with this GRAS determination. The reasons for Dow's GRAS conclusion regarding its ethylcellulose product are discussed in detail in the company's GRAS Notification, which is enclosed: one hard copy and one virus-free electronic copy.

Dow trusts you will find the enclosed Notification acceptable. Should any questions arise during the review process, please do not hesitate to contact me, preferably by telephone or email, so that a response may be made as quickly as possible.

Sincerely,

(b) (6)

(b) (6)

Jeffrey Pitt, Ph.D.
Senior Product Stewardship Manager
Dow Phama & Food Solutions
The Dow Chemical Company
(989) 859-2633
jpitt@dow.com

Enc

CC: Garry Wiltshire



WORLDWIDE PARTNER

Ramos-Valle, Moraima

From: Ramos-Valle, Moraima
Sent: Tuesday, April 30, 2013 4:34 PM
To: Pitt, Jeffrey (J) (JPitt@dow.com)
Cc: Shepherd, Lillian
Subject: RE: GRAS Submission for Ethyl Cellulose

Dear Dr. Pitt,

I just wanted to let you know that we received your package today April 30, 2013. We noted that the cover letter states that enclosed is a hard copy and a CD. We could only locate a cover letter and a CD.

Will the hard copy of the submission come in a separate package?

Thanks,
Moraima

Moraima J. Ramos Valle, M.S.
Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
Phone: (240) 402-1248
Email: Moraima.Ramos-Valle@fda.hhs.gov

From: Pitt, Jeffrey (J) [<mailto:JPitt@dow.com>]
Sent: Tuesday, April 23, 2013 4:15 PM
To: Ramos-Valle, Moraima
Cc: Shepherd, Lillian
Subject: RE: GRAS Submission for Ethyl Cellulose

Dear Moraima,

Thanks! ☺

A couple quick questions for clarification about submitting the USDA-regulated supporting data: If we submit data that supports the conclusion of the Expert Panel, e.g., efficacy data and spoilage masking data that supports use in meat, poultry and fish, will we still need to have an Expert Panel review the revised application? I don't want to hazard a guess either way on this. Second, you previously stated that if it was a long period of time before we submit the USDA-

supporting information, then another Expert Panel review would be required. What is that period of time, e.g., 3 months, 6 months, 9 months etc.?

Thank you very much for your help,
Jeffrey Pitt
Dow Pharma & Food Solutions
(989) 638-2326



I have ideas I haven't thought of yet.

From: Ramos-Valle, Moraima [<mailto:Moraima.Ramos-Valle@fda.hhs.gov>]
Sent: Tuesday, April 23, 2013 3:26 PM
To: Pitt, Jeffrey (J)
Cc: Shepherd, Lillian
Subject: RE: GRAS Submission for Ethyl Cellulose

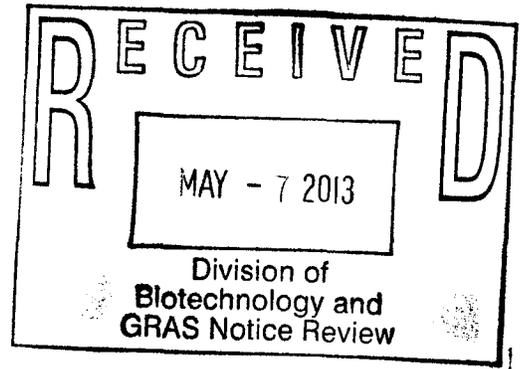
Dear Dr. Pitt,

We looked at your submission and it is fillable. At your earliest convenience, please send us 1 hard copy and a CD. Also in the cover letter please state that the CD is free of viruses.

Thanks and feel free to contact me if you have any questions.

Moraima

Moraima J. Ramos Valle, M.S.
Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
Phone: (240) 402-1248
Email: Moraima.Ramos-Valle@fda.hhs.gov



Notification of the Determination of Ethylcellulose As Being Generally Recognized As Safe

Prepared for
The Dow Chemical Company

Prepared by
EAS Consulting Group, LLC,
1700 Diagonal Road,
Suite 750,
Alexandria, VA 22314;
Phone: 571-447-5501 ;
Fax: 703-548-3270;
E-mail: esteele@easconsultinggroup.com.

Submitted to the United States Food and Drug Administration

February 6, 2013

Notification of the Determination of Ethylcellulose As Being Generally Recognized As Safe

Prepared for
The Dow Chemical Company

Prepared by
EAS Consulting Group, LLC,
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Suite 750,
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Submitted to the United States Food and Drug Administration

February 6, 2013

GRAS NOTIFICATION

I. Claim of GRAS Status

A. Claim of Exemption from the Requirement for Premarket Approval Requirements Pursuant to Proposed 21 CFR § 170.36(c)(1)

Dow Wolff Cellulosics (the notifier) has determined that its ethyl cellulose is Generally Recognized As Safe, consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in food. Therefore, the use of ethyl cellulose is exempt from the requirement of premarket approval.

Signed,

(b) (6)



Date

Feb 6, 2013

Jeffrey Pitt, Ph.D.
Senior Product Steward Manager
Dow Wolff Cellulosics
The Dow Chemical Company
1803 Building
Midland, MI 48674, USA

B. Name and Address of Notifier:

Jeffrey Pitt, Ph.D.
Senior Product Steward Manager
Dow Wolff Cellulosics
The Dow Chemical Company
1691 N. Swede Rd.
Midland, MI 48674, USA

Phone: +1-989-638-2326
Fax: +1 989-638-9836
E-mail: jpitt@dow.com

C. Common or Usual Name of the Notified Substance:

Ethyl cellulose

D. Synonyms

Ethyl cellulose ether; Ethyl ether of cellulose; Modified cellulose; Cellulose Derivatives

E. Conditions of Use:

Ethyl cellulose, prepared from wood pulp or cotton, is intended for use as a food ingredient in Grain Products; Vegetables; Fruits; Milk and Milk Products; Legumes; Nuts and Seeds; Fats and Oils; Sugars and Sweet; and Beverages at a level ranging from 0.0075 to 5.0% of ethyl cellulose. The intended use of ethyl cellulose in the above mentioned food categories is estimated to result in a mean intake of 4.95 g/person/day. The high (90th percentile) intake is estimated as 9.90 g/person/day. For an individual weighing 60 kg, the mean and 90th percentile intakes are estimated as 0.082 and 0.165 g ethyl cellulose/kg body weight (bw)/day, respectively. Ethyl cellulose is not intended to be marketed for use in infant and toddler foods.

F. Basis for GRAS Determination:

A comprehensive search of the scientific and regulatory literature was conducted to assess safety-in-use of ethyl cellulose. The safety of cellulose and cellulose derivatives, including ethyl cellulose as food additives has been extensively evaluated by regulatory bodies including the US Food and Drug Administration (FDA) (21 CFR 182.90- Substances migrating to food from paper and paperboard products), the WHO/FAO Joint Expert Committee on Food Additives (JECFA), the former European Union Scientific Committee on Food (SCF), and the European Food Safety Authority (EFSA). In accordance with 21 CFR §170.30, the intended use of ethyl cellulose has been determined to be generally recognized as safe (GRAS) based on scientific procedures. Several cellulose derivatives, including ethyl cellulose have been permitted for food uses as codified in 21 CFR. These regulatory citations suggest that under the conditions of reported uses described in these citations, the

uses of cellulose derivatives are safe. JECFA has assigned a group acceptable daily intake (ADI) as “not specified” for seven modified celluloses, including ethyl cellulose. This indicates that ethyl cellulose as part of a group ADI established for these celluloses when used as food additives will not have adverse effects on human health at any point in a person’s life, even if they are consumed daily. This “not specified” ADI allows the derivatives to be used in processed foodstuffs at levels equal to *Quantum Satis*. In practice, this means that the use level for the additive corresponds with the level needed to achieve the desired technological effect. The SCF also assigned a group ADI of not specified to five closely related cellulose derivatives in 1994. Subsequently, in 2004, EFSA added ethyl cellulose to the SCF group of cellulose derivatives.

In addition to these regulatory assessments, there are several scientific studies on cellulose derivatives, including ethyl cellulose. There is sufficient qualitative and quantitative scientific evidence, including human and animal data, to determine safety-in-use for ethyl cellulose. The safety determination of ethyl cellulose is based on the totality of available evidence, including animal, human, and *in vitro* studies conducted with ethyl cellulose as well as other cellulose derivatives. The totality of the available evidence suggests that the estimated daily intake of ethyl cellulose (9.90 g/person/day) from the proposed uses, if ingested daily over a lifetime, is safe.

G. Availability of Information:

The data and information that serves as the basis for this GRAS determination will be available for the Food and Drug Administration’s review and copying at the following address or will be provided to FDA at their request:

Edward A. Steele, EAS Consulting Group, LLC, 1700 Diagonal Road, Suite 750, Alexandria, VA 22314; Phone: 571-447-5501 ; Fax: 703-548-3270; E-mail: esteele@easconsultinggroup.com.

The primary toxicologist, Dr. Madhusudan G. Soni, responsible for the preparation of this GRAS monograph and who is also a member of the expert panel can also be contacted for the data and information that serves as the basis for this GRAS determination at the following address: Madhusudan G. Soni, Ph.D., Soni & Associates Inc., 749 46th Square, Vero Beach FL, 32968; Phone: (772) 299-0746; E-mail: sonim@bellsouth.net.

II. Detailed Information About the Identity of the Notified Substance:

A. Physical Characteristics

Ethyl cellulose is a free flowing white to light tan color powder. It is insoluble in water.

B. Chemical Name

Ethyl cellulose is the ethyl ether of cellulose.

C. Chemical Abstract Registry Number:

CAS: 9004-57-3; INS No. 462.

D. Chemical Formula:

Ethyl cellulose products have the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units.

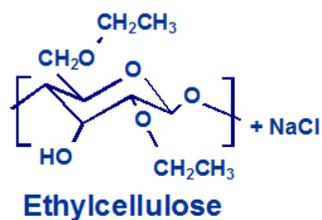
The percentage of ethoxyl groups (-OC₂H₅) in the molecule varies between 44% and 51% on a dry weight basis (equivalent to not more than 2.6 ethoxyl groups on average per anhydroglucose unit). The ethoxyl content assay of Dow product ranges from 48.0 - 49.5% wt.

E. Molecular Weight

Cellulose is a high molecular weight linear homopolymer of about 3000 β-D-glucopyranosyl repeating units joined by (1→4) glycosidic linkages. Its molecular mass is above 500,000 Dalton. The average molecular weight for various grades of currently produced ethyl cellulose by Dow Wolff Cellulosics ranges from 44,900 to 223,200 Daltons.

F. Structure:

Ethyl cellulose polymers are derived from and have the polymeric backbone of cellulose, which is a naturally occurring polymer. The molecule has a structure of repeating anhydroglucose units joined by β-1-4 linkages and each unit (ring) has three -OH (hydroxyl) groups at the 2, 3, and 6 positions. The chemical structure of ethyl cellulose is shown in the diagram below and in Figure 1.



Chemical structure of ethylcellulose

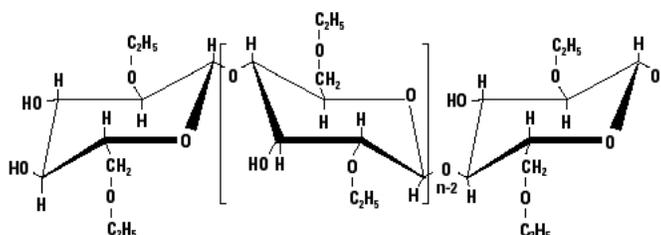


Figure 1. Chemical Structure of Ethyl Cellulose

G. Typical Specifications

Typical food grade specifications of ethyl cellulose are presented in Table 1. It is a free flowing white to light tan powder insoluble in water. Ethyl cellulose produced by Dow Wolff Cellulosics complies with the requirements of the US Food Chemicals Codex (FCC, 2011) as well as JECFA (1982). As described in the FCC, ethyl cellulose is heat-labile; exposure to high temperatures (240°C) causes color degradation and loss of properties. It is practically insoluble in water, in glycerin, and in propylene glycol, but is soluble in varying proportions in certain organic solvents, depending on the ethoxyl content. Ethyl cellulose containing less than 46% to 48% of ethoxyl groups is freely soluble in tetrahydrofuran, in methyl acetate, in chloroform, and in aromatic hydrocarbon-alcohol mixtures. Ethyl cellulose containing 46% to 48% or more of ethoxyl groups is freely soluble in alcohol, methanol, toluene, chloroform, and ethyl acetate. A 1:20 aqueous suspension of ethyl cellulose is neutral to litmus. The functional uses of ethyl cellulose as reported in the FCC (2011) include use as a protective coating, binder and filler.

Table 1. Physical, Chemical and Microbiological Specifications of Ethyl Cellulose

Parameter	Specifications	Assay method*
Physical parameters		
Appearance	Powder	Visual
Color	White to tan	Visual
Odor	Odorless to mild	Organoleptic
Chemical parameters		
Viscosity**	18.0 – 22.0 mPa.s	NF
Labeled as 10 centipoises or more	NLT 90% and NMT 11 0% of the viscosity stated on the label	FCC
Labeled as 10 centipoises or less	NLT 80% and NMT 120% of the viscosity stated on the label	FCC
Ethoxyl content assay	48.0 – 49.5% wt	USP
Loss on drying, moisture	2% wt (max)	USP
Chloride as NaCl	0.05% wt (max)	EP
Residue on ignition	0.40% (max)	USP
Aldehydes	100 ppm (max)	EP
Acidity or Alkalinity	Pass	EP
Residual solvent	Pass	USP
pH (1% colloidal solution)	Pass	E462
Identification FCC, NF	Pass	FCC, NF
Heavy metals		
Lead	2.0 ppm (max)	JP
Arsenic	2.0 ppm (max)	E462
Cadmium	1.0 ppm (max)	E462
Mercury	1.0 ppm (max)	E462
Microbiological parameters		
Aerobic Plate Count	100 CFU/g (max)	USP
Total count combined Yeast and Mold	100 CFU/g (max)	USP
<i>Staphylococcus aureus</i>	Negative	USP
<i>Pseudomonas aeruginosa</i>	Negative	USP
<i>Salmonella</i> Species	Negative	USP
<i>Escherichia coli</i>	Negative	USP

*Current version of all cited methods; **Viscosity varies with molecular weight; EP - European Pharmacopoeia; E462 - European Parliament and Council Directive; FCC - Food Chemicals Codex; JP- Japanese Pharmaceutical Excipients Supplements; NF - National Formulary

H. Manufacturing process

Ethyl cellulose is manufactured according to current Good Manufacturing Practices (cGMP) using appropriate food grade ingredients. During the manufacture of ethyl cellulose, cellulose fibers are combined with a caustic solution and these are reacted with ethyl chloride, yielding the ethyl ether of cellulose (Figure 2). The fibrous reaction product is purified and ground to a fine, uniform powder. All equipment and materials used in the production process have a history of use in food processing. All chemicals used in the processing steps are in compliance with FDA regulations. The steaming and drying steps involved in the manufacturing process remove volatile residues including ethyl chloride. A series of steps involved in the manufacturing of ethyl cellulose are summarized below.

Alkali Cellulose: Wood pulp and, for some products, cotton pulp, is received and dipped in caustic soda solution forming alkali cellulose and then cut into chips.

Reaction: The alkali cellulose chips are transferred to the reactor. Additional caustic

and several processing aids are used to activate the pulp. All of the processing aids have a history of use in food processing; any residuals remaining from the process are within acceptable limits. Ethyl chloride is used as the alkyl group donor; ethyl chloride and pulp are the only reactants and the other ingredients are processing aids or used to activate the pulp. The amount of each raw material is dictated by product-specific recipes. These transfers are monitored with instruments to assure proper operation. The reaction between ethyl chloride and the activated pulp then takes place in accordance with the master production record requirements. **Filtration:** The reactor solution is transferred to a dump tank where it is cooled prior to filtering. The solution is then sent through a filter to remove salt, which is a by-product from the reaction. The filtered solution is then sent to the granulation step. **Granulation:** Water and steam are injected into the solution to precipitate the ethyl cellulose out of the solution. The granule is forwarded on to the wash unit operation as an aqueous slurry. **Washing and Neutralization:** The wash system neutralizes the ethyl cellulose granules with anhydrous hydrochloric acid and sprays heated deionized water to remove residual salt and residual caustic. **Dewatering and Drying:** At the end of the washing and neutralizing unit operation, the granule is centrifuged for further dewatering. The dewatered ethyl cellulose granule is sprayed with an antioxidant (propyl gallate) during the transfer to the dryer. Propyl gallate is GRAS per 21 CFR §184.1662 (d), and is used in food at levels that do not exceed good manufacturing practice in accordance with §184.1(b)(1). ¹The granule enters a rotary steam tube dryer where hot steam tubes inside the dryer vaporize the water as the granule moves through the dryer. The feed rate and dryer temperature are set and monitored by computer control to ensure a dry product. **Densification:** The dried granule is conveyed to a mill where it is densified and ground to the desired particle size. **Bulk Storage:** The densified product enters a tote for bulk storage. **Batch Isolation and Homogenization:** A series of totes are transferred to a blender where the product is homogenized, assigned batch numbers and packaged.

¹ Good manufacturing practice results in a maximum total content of antioxidants of 0.02 percent of the fat or oil content, including the essential (volatile) oil content, of the food.

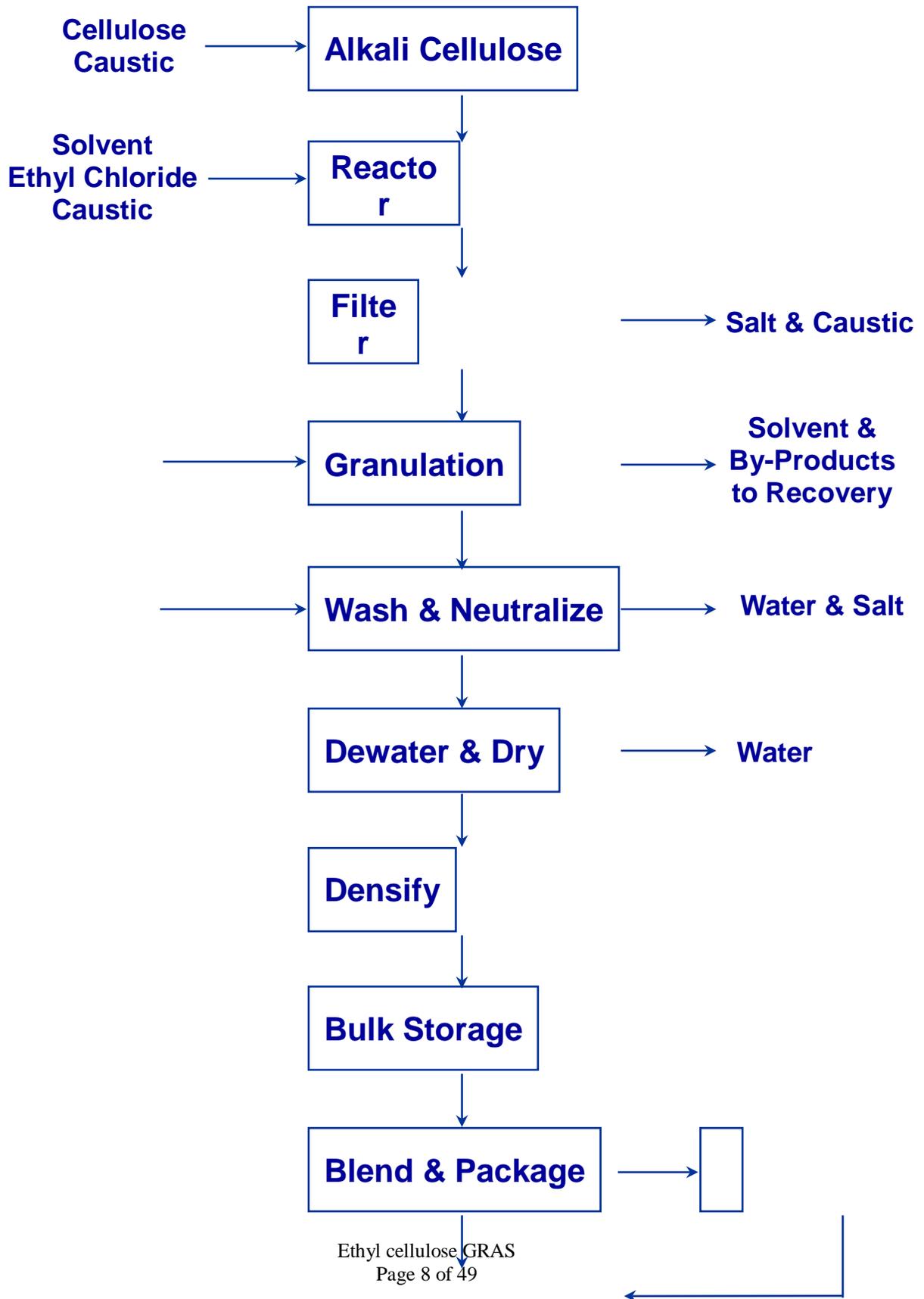


Figure 2. Manufacturing Process of Ethyl Cellulose

III. Summary of the Basis for the Notifier's Determination that Ethyl Cellulose is GRAS

An independent panel of recognized experts, qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was requested by Dow Wolff Cellulosics to determine the Generally Recognized As Safe (GRAS) status of ethyl cellulose intended for use as a food ingredient. A comprehensive search of the scientific literature was also conducted to identify relevant safety studies for this assessment.

Based on a critical evaluation of the pertinent data and information summarized herein, the Expert Panel members have individually and collectively determined by scientific procedures that the addition of ethyl cellulose at levels ranging from 0.0075 to 5.0% of ethyl cellulose to Grain Products; Vegetables; Fruits; Milk and Milk Products; Legumes; Nuts and Seeds; Fats and Oils; Sugars and Sweet; and Beverages, meeting the specifications cited above and manufactured according to current Good Manufacturing Practice, is Generally Recognized As Safe (GRAS) under the conditions of intended use in selected foods, as specified herein.

In coming to its decision that ethyl cellulose is GRAS, the Expert Panel reviewed published toxicology studies and other relevant corroborative information relating to the safety of the product and concluded that neither ethyl cellulose nor any of its degradation products pose any toxicological hazards or safety concerns at the intended use levels. It is also the opinion of the Expert Panel members that other qualified and competent scientists, reviewing the same publicly available toxicological and safety information, would reach the same conclusion.

In addition, the Expert Panel reviewed the production and safety data on ethyl cellulose in both the EFSA and JECFA assessments, as well as in GRN 213 on hydroxypropyl methylcellulose, another cellulose derivative. The information in these documents is incorporated in their entirety by reference into this document. Cellulose and several cellulose derivatives, including ethyl cellulose, are the subject of a report prepared by the Select Committee On GRAS Substances (SCOGS) for FDA in 1975. Based on that report FDA issued a proposed rule in the Federal Register (44 FR 10751; February 23, 1979²) in which it proposed to affirm the GRAS status of cellulose and several cellulose derivatives for use in food, including the then known use of ethyl cellulose in paper and paperboard. The SCOGS also acknowledged that there was evidence that ethyl cellulose was used directly in food in hard candy and

² The withdrawal of the proposed rule can be accessed at: <https://www.federalregister.gov/articles/2003/04/22/03-9865/withdrawal-of-certain-proposed-rules-and-other-proposed-actions-notice-of-intent>

chewing gum³. FDA subsequently withdrew this proposal in a Federal Register notice on April 23, 2003. FDA implied in the notice announcing the withdrawal of the proposed rule that it did not have any safety concerns with the proposed uses of cellulose and the derivatives at that time.

³ The SCOGS report can be accessed at:
<http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=78>.

IV. Basis for a Conclusion that Ethyl Cellulose is GRAS for its Intended Use.

EXPERT PANEL STATEMENT

**DETERMINATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS)
STATUS OF ETHYL CELLULOSE AS A FOOD INGREDIENT**

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DETERMINATION OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF ETHYL CELLULOSE AS A FOOD INGREDIENT

1. INTRODUCTION

The undersigned, an independent panel of recognized experts (hereinafter referred to as the Expert Panel)⁴, qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was convened at the request of Dow Wolff Cellulosics, USA, to determine the Generally Recognized As Safe (GRAS) status of ethyl cellulose as a food ingredient in Grain Products; Vegetables; Fruits; Milk and Milk Products; Legumes; Nuts and Seeds; Fats and Oils; Sugars and Sweet; and Beverages at a level ranging from 0.0075 to a maximum of 5.0% of ethyl cellulose when not otherwise precluded by a standard of identity. A comprehensive search of the scientific literature for safety and toxicity information specifically on ethyl cellulose and its analogues was conducted through August 2012 and made available to the Expert Panel. Dow Wolff Cellulosics assures that all unpublished information in its possession and relevant to the subject of this determination have been provided for this assessment and have been summarized in this GRAS monograph. The Expert Panel independently and critically evaluated materials submitted by Dow Wolff Cellulosics, USA, and other information deemed appropriate or necessary. Following an independent, critical evaluation, the Expert Panel conferred on December 18, 2012 and unanimously agreed to the decision described herein.

1.1. Background

Cellulose derivatives are used for various purposes such as adhesives, thickening agents in food, moisture-proof coatings, etc. Addition of alkyl residues, such as ethyl or methyl groups, to cellulose increases the hydrophobicity of the polymer chain (Majewicz and Poldas, 2004). By increasing the hydrophobicity, a polymer may be produced that is a surfactant thus conferring on the polymer chain a host of physicochemical characteristics that are important in the context of food products and processing. For over 60 years, ethyl cellulose polymers have provided excellent functionality in several applications such as pharmaceuticals, personal care, food, feed, printing ink, etc. Ethyl cellulose is commonly used in food supplements and flavorings in capsules. It functions as a binding and filling agent or serves as a protective coating. Given the potential uses of ethyl cellulose in the food industry, Dow Wolff Cellulosics intends to market ethyl cellulose for use in selected conventional food products. Dow Wolff Cellulosics notes that although there are few new food uses of ethyl cellulose, overall the intended uses will serve as a substitute for other cellulose derivatives. As such, the overall exposure to cellulose and its derivatives is not expected to increase significantly.

1.2. Description, Specifications and Manufacturing Process

Ethyl cellulose, the ethyl ether of cellulose, is a free flowing white to tan color powder insoluble in water. Food grade specifications of ethyl cellulose manufactured by

⁴Modeled after that described in section 201(s) of the Federal Food, Drug, and Cosmetic Act, As Amended. See also attachments (curriculum vitae) documenting the expertise of the Panel members.

Dow Wolff Cellulosics are summarized in Table 1 (Section II- H). Ethyl cellulose is prepared from wood pulp or cotton by treatment with alkali followed by ethylation with ethyl chloride. The resulting product is then further steamed and dried. Extensive analysis for potential external contaminants of ethyl cellulose such as heavy metals (cadmium, arsenic, mercury, lead), and microbial contaminants, such as aerobic plate count, yeast and mold, *S. aureus*, *P. aeruginosa*, *Salmonella* Species and *E. coli* that are generally associated with food products, suggest either the absence of these contaminants or their presence at very low levels that are considered as safe. Similarly, the presence of processing aids and by-products from the manufacturing are minimized in the final product to levels that are safe for human consumption. The product complies with the purity requirements of the FCC (2011). Ethyl cellulose is manufactured according to current Good Manufacturing Practices (cGMP).

1.3. Technical Effects

Ethyl cellulose offers a number of functions in various food categories. Some of the properties of ethyl cellulose such as viscosity modification, thickening, film-forming, stabilization, filler and thermal gelation can enhance processed foods. Ethyl cellulose exerts these functional changes in food products without undergoing or initiating chemical changes that would alter the nutritional value of the food products. Ethyl cellulose is currently used as a direct human food additive.

1.4. Current Food Uses and Regulatory Status

Several chemically modified forms of cellulose are used in food processing for their special properties. For example, carboxymethylcellulose (water absorbing characteristics) is used, as a whipping agent, in ice-cream, confectionery, jellies, etc.; methylcellulose (viscosity) is used as a thickener and emulsifier, and in foods formulated to be low in gluten; other cellulose derivatives such as hydroxypropylcellulose, hydroxypropyl-methylcellulose, and ethyl-methylcellulose are used as emulsifiers. The following cellulose derivatives are listed either as GRAS or permitted for direct addition to food as food additives: sodium carboxymethyl cellulose; methyl cellulose; cellulose acetate; ethyl cellulose and hydroxypropylmethyl cellulose. Ethyl cellulose is approved as a multipurpose additive for its use as a binder and filler, as a component of protective coating for vitamin and mineral tablets, and as a fixative in flavoring compounds. The current regulatory approvals of cellulose and its derivatives, including ethyl cellulose, are summarized in Table 2.

In addition to the above cited FDA regulatory status of cellulose and its derivatives, other international regulatory agencies such as EFSA (2004) and JECFA (1983) has also evaluated the safety of ethyl cellulose in food products and determined that it is safe and permitted for use as a food additive.

Table 2. Regulatory Status of Cellulose and Cellulose Derivatives

Ingredient Name	Regulatory Status	Food Uses	Specifications
Cellulose	GRAS (unpublished)	In food generally consistent with GMP	FCC; USP
Ethyl cellulose	21 CFR §172.868; 73.1	Binder, filler in vitamins; tablet coating; fixative in	FCC; USP

		flavorings	
	21 CFR §182.90 (GRAS)	Substances migrating to food from paper and paperboard products.	
	21 CFR §73.1	Diluents in color additive mixtures for food use exempt from certification. For marking foods and for coloring egg shell	
Methyl cellulose	21 CFR §182.1480	Multipurpose food use	FCC; USP
Methyl ethyl cellulose	21 CFR §172.872	In food generally consistent with GMP	21 CFR 172.872(b)
Hydroxypropyl cellulose	21 CFR §172.870; GRN 190	In food generally consistent with GMP	
Hydroxypropyl methyl cellulose	21 CFR §172.874; GRN 213	In food generally consistent with GMP	FCC
Carboxymethyl cellulose	21 CFR §175.105; §175.300; §182.70; unpublished GRAS for direct food uses	Multipurpose food use	
Sodium carboxymethyl cellulose	21 CFR §182.1745	Multipurpose food use	FCC; USP

1.5. Intake from Existing Uses

As indicated above, ethyl cellulose is approved for some specific food uses (Table 2) and as a pharmaceutical excipient. Thus, these approved uses suggest that there exists some background intake of ethyl cellulose. The use of ethyl cellulose as a binder or filler in tablets is typically at use levels of 300 mg for a tablet weighing 1000 mg. A maximum daily intake of 900 mg of ethyl cellulose would result from consuming 3 vitamin tablets. For an individual weighing 60 kg, this would result in a human intake of 15 mg/kg bw/day. Another approved use as a film coating for a vitamin preparation contributes to around 10% of the weight. The ethyl cellulose content in the film is approximately 30%. For a 1000 mg tablet, this results in 30 mg ethyl cellulose/tablet. A typical intake for this application is 5 tablets/day. This use would result in a daily exposure of 150 mg ethyl cellulose or 2.5 mg/kg bw/day. Another exposure may also occur from migration to food from paper and paperboard products. The migration control layer in a pizza box is about 50 g. The use level of ethyl cellulose in the layer is 0.3%. Assuming an intake of one pizza/day the intake of ethyl cellulose would be 150 mg or 2.5 mg/kg bw/day assuming all the ethyl cellulose migrates to food. Thus the total background intake of ethyl cellulose from its approved uses is estimated as 1200 mg/person/day (20 mg/kg bw/day).

1.6. Intended Food Uses

Dow Wolff Cellulosics intends to use ethyl cellulose as a food ingredient in selected food categories such as Grain Products; Vegetables; Fruits; Milk and Milk products; Legumes; Nuts and Seeds; Fats and Oils; Sugars and Sweet; and Beverages at use levels ranging from 0.0075 to 5.0% of ethyl cellulose. The proposed food categories/products and the intended use levels of ethyl cellulose are summarized in Table 3. Foods that are intended for infants and toddlers, such as infant formulas or foods formulated for babies or toddlers are excluded from the list of intended food uses of the

subject ethyl cellulose. The intake analysis was performed using the expected daily consumption for these products.

1.6.1. Estimated Daily Intake from the Intended and Existing Uses

Intake estimates of ethyl cellulose from the proposed food-uses and use levels were determined using consumption estimates data included in the United States Department of Agriculture's (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII 1994-1996) (Smiciklas-Wright et al., 2002) for quantities of foods consumed daily. Using USDA estimated intakes of the food categories [Grain Products; Vegetables; Fruits; Milk and Milk Products; Legumes; Nuts and Seeds; Fats and Oils; Sugars and Sweet; and Beverages] for which ethyl cellulose is proposed to be added, the possible daily intake of ethyl cellulose from each of the categories is summarized in Table 3. The figures in Table 3 represent average per capita intakes, but the total estimated intake may be regarded as a per user intake since nearly everyone in the population is a user of at least one of these foods. The results of projected maximum consumption and thus exposure suggest that the use of ethyl cellulose in the proposed food categories will result in a mean estimated daily intake of 4.95 g of ethyl cellulose/person (Table 3). In order to estimate the 90th percentile consumption of ethyl cellulose, the corresponding mean total intake value from all food categories was multiplied by two on the grounds that the high or 90th percentile consumption rarely exceeds the mean by more than a factor of two (FDA, 2006). These assumptions and the analysis above indicate that the mean and 90th percentile estimated daily intakes of the ethyl cellulose from the intended food uses will be 4.95 and 9.90 g/person/day (82 and 165 mg/kg bw/day), respectively.

The estimated intake of ethyl cellulose from the intended uses will add to the existing or background intake from the approved uses of ethyl cellulose. As indicated above, the maximum daily intake of ethyl cellulose from its approved uses is approximately 1200 mg/person/day (20 mg/kg bw/day). Thus the total maximum intake of ethyl cellulose from the proposed and existing uses is estimated as 11.10 g/person/day or 185 mg/kg bw/day.

It is recognized that the expected food use categories and concentrations of ethyl cellulose used in these food categories are highly conservative estimates; the estimated value of the total mean intake of ethyl cellulose is higher than what would actually occur.

Table 3. Intended Use Levels and Possible Daily Intake of Ethyl Cellulose (EC) Based on USDA Data¹

USDA Table	Product	Mean Quantity Consumed per Individual (grams)*	Proposed use level (%)	Mean intake (g/day)
Grain products	Yeast, breads, and roll	50	0.35%	0.175
	Cereals and pasta: Ready-to-eat-cereals	16	1.00%	0.16
	Quick breads, pancakes, french toast, e.g., EC used in oils/fats	19	1.88%	0.3572
	Cakes, cookies, pastries, pies, e.g., EC used in oils/fats/chocololate/glazes	38	1.88%	0.7144

	Crackers, popcorn, pretzels, corn chips, e.g., EC used in oils/fats	12	1.88%	0.2256
Vegetables	Dark-green vegetables, e.g., EC as protecting coating	12	0.05%	0.006
	Deep-yellow vegetables, e.g., EC as protecting coating	8	0.05%	0.004
	Tomatoes, e.g., EC as protecting coating	28	0.05%	0.014
	Other vegetables, e.g., EC as protecting coating	45	0.05%	0.0225
Fruits	Other fruits, mixtures and juices (total), e.g., EC as protecting coating	96	0.05%	0.048
Milk and milk products	Milk desserts, e.g., EC in ice cream, puddings, foamed desserts	27	1.00%	0.27
	Cheese	16	1.00%	0.16
Legumes; nuts and seeds; fats and oils; sugars and sweets	Legumes, i.e., veggie burgers, meat substitutes	25	2.00%	0.5
	Nuts and seeds, i.e., peanut butter	4	0.05%	0.002
	Fats and oils: Table fats	4	5.00%	0.2
	Fats and oils: Salad dressings	8	5.00%	0.4
	Sugars and sweets: Candies, e.g., EC used in oils/fats/chocolate/glazes	7	0.50%	0.035
Beverages	Alcoholic: total, e.g., EC as Flavor fixative, stabilizer	103	0.0075%	0.007725
	Fruit drinks and aides: total, e.g., EC as Flavor fixative, stabilizer	95	0.0075%	0.007125
	Carbonated soft drinks: total, e.g., EC as Flavor fixative, stabilizer	332	0.0075%	0.0249
Total				4.95

¹The daily intake calculations are based on USDA's 1994-96 Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey

2. SAFETY OF ETHYL CELLULOSE

Several studies of cellulose and its derivatives in different species following oral and non-oral routes have been published. The toxicological data on modified celluloses include acute toxicity, subchronic and chronic toxicity and genotoxicity as well as reproductive and developmental toxicity and can be found in a number of reviews. The safety assessment of ethyl cellulose is based on the totality of available evidence including metabolic, mutagenicity, and toxicological data in general, and on the resulting exposure to ethyl cellulose from its proposed uses. As indicated earlier, ethyl cellulose has been approved as a multipurpose additive for its use as a binder and filler, as a

component of protective coating for tablets, and as a fixative in flavoring compounds. Ethyl cellulose has been assessed for safety-in-use by national and international regulatory and other agencies. In these comprehensive safety evaluations as part of regulations, cellulose and its derivatives, including ethyl cellulose has been extensively reviewed and demonstrated to be safe for use as a food ingredient or dietary supplement at the levels described in those assessments.

2.1. Safety Assessments by Regulatory Agencies

2.1.1. EFSA Assessment of Ethyl Cellulose

The EU Scientific Committee on Food (SCF) has evaluated a number of modified celluloses and in 1994 an Acceptable Daily Intake of “not specified” was allocated by the SCF to five closely related cellulose derivatives, i.e., methyl cellulose (E461), hydroxypropyl cellulose (E463), hydroxypropyl methyl cellulose (E464), ethyl methyl cellulose (E465) and carboxymethyl cellulose (E466). In 2004, the EFSA Scientific Panel on Food Additives, Flavorings, Processing Aids and Materials in Contact with Food critically evaluated the safety of ethyl cellulose for its uses in the formulation of food supplements, as a thickener/binder in hydrophobic matrices, as an emulsion stabilizer in water/oil systems, and as a barrier layer to control the diffusion of ingredients in, e.g., pizza preparations (EFSA, 2004). For the evaluation of ethyl cellulose, the EFSA Panel considered the safety data of the whole group of closely related cellulose derivatives as the basis for determining its safety. Given the strong hydrophobic character of ethyl cellulose together with its high molecular mass (> 500 kD), the EFSA Panel considered that following oral ingestion, ethyl cellulose will pass essentially unchanged through the gastrointestinal tract and is unlikely to cause adverse effects. Following its review, the EFSA Panel decided to include ethyl cellulose in the group ADI “not specified” for modified celluloses established by the SCF.

In 2006, per European Parliament directive 2006/52/EC⁵, and based on EFSA opinion, Directive 95/2/EC was amended to include ethyl cellulose. Per this amendment, ethyl cellulose was included in the group ADI ‘not specified’ for modified celluloses. Ethyl cellulose was allocated an E number of E462. The main application of ethyl cellulose approved was for use in food supplements and encapsulated flavorings. The use of ethyl cellulose was permitted in a way similar to that for other celluloses.

2.1.2. JECFA Assessment of Cellulose Derivatives

Since 1974, at several of its meetings, JECFA evaluated the safety of cellulose derivatives. Initially, in 1974, the JECFA evaluated the five modified celluloses and established a group ADI of 0-25 mg/kg bw (JECFA 1974). At later meetings, JECFA decided that this group ADI should also apply to ethyl cellulose and ethylhydroxyethyl cellulose (JECFA 1982; JECFA, 1983). At the 35th meeting, a group ADI “not specified” was allocated to these seven modified cellulose derivatives (JECFA 1990). Thus ethyl cellulose was independently and thoroughly reviewed as a food additive by JECFA. A Group ADI of “not specified” for modified celluloses was established at the 35th meeting included ethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose,

⁵ Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:204:0010:0022:EN:PDF>

hydroxypropylmethyl cellulose, methyl cellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose. Subsequently at the 59th meeting, cross-linked sodium carboxymethyl cellulose was added. The toxicological monograph for the JECFA evaluation concluded that modified celluloses as a group are of very low toxicity. Thus, the JECFA review and evaluation supports a general interpretation of the toxicological properties of modified celluloses as reflecting the non-absorption of the ingredients and, hence, their general lack of bioavailability. This suggests that the toxicological literature of modified celluloses, as discussed below, supports this interpretation of the data.

The JECFA evaluation of ethyl cellulose allocated the ADI as “not specified”. JECFA noted that in some human studies, particularly with methyl cellulose and carboxymethylcellulose, laxative effects were noted. Based on these effects, JECFA reported, “The ability to produce laxation should be taken into account when using these substances as food additives.” The report described that at higher doses, diarrhea has been reported in some subjects, but in others constipation developed. Human studies did not exceed the addition of 30 g/person/day. In general, for dietary fiber an intake of 30 g/day has been recommended as the upper safe level. JECFA further explains the estimate of ADI as “not specified”: This term is applicable to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological, and other), the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food does not, in the opinion of JECFA, represent a hazard to health. For that reason, and for the reasons stated in individual evaluations, the establishment of an acceptable daily intake expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance.

2.1.3. GRAS Notice on Cellulose Derivative

In 2007, the FDA received a GRAS notification on a cellulose derivative, hydroxypropyl methylcellulose (HPMC) (GRN 213) from Dow Chemical Company (FDA, 2007). As the subject of the GRAS notice contains 16-31.5% methyl groups and 2-32% hydroxypropyl groups, and considering the existing approved uses of HPMC with different (lower) ranges for methyl content and hydroxypropyl content, the FDA referred to the subject of the notice as “HPMC - expanded substitution pattern” (HPMC-ESP). In its notification, Dow noted that the subject of the notice is similar, though not identical, to food-grade HPMC specifications of JECFA, FCC or USP-NF. The technical effects of HPMC-ESP in food included film former, stabilizer, and thickener. The notifier lists examples of potential foods to which HPMC-ESP could be added, including: white breads, breakfast cereals, pasta, tortillas, cakes, cookies, biscuits and granola bars, fruit juices, fish sticks, frozen dinners and canned pastas, omelets and egg white substitutes, veggie burgers and meat substitutes, peanut butter, sugar substitutes, candy bars, and fruit roll-up type snacks. The estimated intake of HPMC-ESP was determined as approximately 18 g/person/day, based on the intended uses of HPMC-ESP.

In the HPMC GRAS notice (Dow, 2007) several published toxicology studies were described including acute oral, repeated dose, genetic toxicity, carcinogenicity,

reproductive, developmental, pharmacokinetic, and metabolism for both HPMC and its analogues. The notifier stated that the results of published studies on mice, rats, dogs, and humans and indicates the substitution ranges and viscosities of the HPMC or analogue studied, when available. In these studies no frank toxic effects were observed, except at feeding levels that interfered with the ability of test animals to consume adequate nutrients and calories. The data were consistent among all cellulose types, including unmodified celluloses, all molecular weights and viscosities, and all types of modifications, including cross-linking. The notifier asserted that toxicology of the class of modified cellulose, and HPMC specifically, is determined by the absence of absorption from the gastrointestinal system and, therefore, the absence of systemic bioavailability. Based on the available information, it was concluded that the substitution range for HPMC-ESP, as defined in the notice, is supported by the scientific literature and the toxicology of the class of modified cellulose. The FDA did not question the acceptability and suitability of the available evidence to support the safe in use of HPMC-ESP.

2.2. Biological and Toxicological Information

2.2.1. Preamble

Because of the importance of cellulose or cellulose fiber and the difficulty in unraveling its secrets regarding structure, biosynthesis, chemistry, and other aspects, there has been a significant effort by researchers to elucidate the biological role of cellulose and related molecules. The safety of cellulose and its alkyl derivatives has been extensively investigated by researchers and reviewed by national and international regulatory agencies such as FDA, EFSA, JECFA, etc. In general, no adverse toxicological effects for cellulose ethers have been reported. In these regulatory and safety assessments, particularly from JECFA and EFSA, the safety evaluations of cellulose ethers was undertaken for groups of cellulose derivatives that also included ethyl cellulose. FDA has reviewed a GRAS notice on hydroxypropyl methylcellulose (HPMC) that also included a significant information and data on cellulose analogues. FDA did not question the acceptability and suitability of the available evidence to support the proposed uses of HPMC. In this notice, the estimated daily intake of HPMC was determined as 18 g /person/day.

The discussion presented in the FDA response letter to HPMC GRAS notice (GRN 213) suggests that the agency is comfortable with the GRAS determination of HPMC-ESP for its intended uses. In a series of dose-dependent, long-term toxicity studies (subchronic and chronic/carcinogenicity) with methyl cellulose (closely related to ethyl cellulose) and HPMC of different viscosities, McCollister et al. (1973) did not observe any treatment-related effects. These studies indicate that changes in viscosity grade or the substitution pattern of the alkyl moiety on the cellulose backbone are unlikely to affect the toxicity outcome. In the GRN 213 (Dow, 2007), it is quoted, "There have been no toxicological differences observed when HPMC with different substitution ratios have been tested." As the subject of the present GRAS determination, ethyl cellulose, a derivative of cellulose, is substantially similar to the product of the FDA notifications, the studies described in the FDA notification can also be utilized to support the safety determination in the present GRAS assessment for ethyl cellulose. Although there are some differences (alkyl chain) in the chemical structure of the cellulose

derivatives, the available information, particularly from a metabolic perspective, indicates that these molecules will be handled similarly in the body.

Given all this, and as the safety-related information of cellulose derivatives has been extensively reviewed by JECFA, EFSA and FDA, in the following section the safety of other derivatives of cellulose is briefly mentioned, while an attempt has been made to extensively review the safety data of ethyl cellulose to support its intake from the intended uses. A summary of available safety-related information of several alkyl derivatives of cellulose, along with ethyl cellulose is presented in Appendix I.

2.2.2. Absorption

As humans lack the digestive enzyme necessary to generate the β -1-4-linked glucose monomers, ethyl cellulose and cellulose derivatives are unlikely to be metabolized. No specific studies on absorption of ethyl cellulose have been found in the published literature. However, there is a close structural relationship with the other cellulose derivatives that are not absorbed from the gastrointestinal tract. Taking into account the hydrophobic character of ethyl cellulose and also taking into account the high molecular weight of ethyl cellulose, it is likely that this cellulose derivative will pass essentially unchanged through the gastrointestinal tract following oral ingestion. Absorption of one closely related derivative, methyl cellulose, was studied by Braun et al. (1974). In this study, the disposition of orally administered radio-labeled methyl cellulose was measured in rats (n=6) given a single oral dose of 500 mg/kg bw/day. Another group of rats (n=6) received daily doses of methyl cellulose for five days. During the 48-hour period following administration of the single dose, 102.2% of the total dose of radio-labeled activity was eliminated in the feces. No radioactivity was detected in the respired air. Less than 0.1% of the original dose was found in the urine, selected tissues and remaining carcass. No accumulation of radio-labeled activity was detected in the body or in selected tissues after multiple dosing. Similar disposition of radio-labeled hydroxyethyl cellulose in rats, HPMC in rats and dogs has been reported. The available information on cellulose derivatives suggests that ethyl cellulose is unlikely to be absorbed following oral ingestion.

Similar to other cellulose derivatives, ethyl cellulose is also unlikely to affect the absorption of vitamins. In a 28-day study, Ellingson and Massengale (1952) reported that oral administration of methyl cellulose to groups of 10 rats (some normal and others vitamin-depleted) did not affect the absorption of either 6 μ g of thiamine or 3 units of vitamin A/day, as determined by weight gain or growth response.

2.2.3. Acute Toxicity

The acute LD₅₀ of ethyl cellulose following oral administration to rats or dermal application to rabbits has been reported to exceed 5 g/kg (Opdyke, 1981). These observations suggest that ethyl cellulose is practically non-toxic. Similarly, a number of acute oral toxicity studies on modified celluloses have also demonstrated the relatively low oral toxicity of this family of compounds.

2.2.4. Irritation and Sensitization Studies

Application of ethyl cellulose (full strength) to intact or abraded rabbit skin for 24 hours under occlusion was slightly irritating (Opdyke, 1981). In a human study, dermal

application of ethyl cellulose at 12% in diethylphthalate (DEP) produced no irritation after a 48 hour closed patch test on human subjects (Opdyke, 1981).

The sensitization potential of ethyl cellulose was evaluated on 25 human subjects using the Maximization Test. Ethyl cellulose was tested at a concentration of 12% in DEP. In this study, ethyl cellulose was non-sensitizing at the concentrations tested (Opdyke, 1981).

2.2.5. Repeat-Dose Toxicity

In an early study, Deichmann and Witherup (1945) investigated the potential adverse effects of ethyl cellulose in rats. In this study, young albino male and female rats were divided into three groups of 80. The rats were fed diets, containing either control diet, ethyl cellulose or methyl cellulose for eight months. The level of ethyl cellulose in the diet was 1.2%, which amounted to an average dose of 182 mg/rat/day, equivalent to approximately 600 mg/kg bw/day. No evidence of adverse effects was noted in rats as judged by appearance, behavior, growth, gross and microscopic examination of tissue. The investigators concluded that the feeding of ethyl cellulose is harmless. Additional details of the study were not available.

In a subchronic study, aqueous dispersion of ethyl cellulose (Aquacoat[®]ECD) containing cetyl alcohol and sodium lauryl sulphate as stabilizers was administered to Sprague-Dawley rats (5/sex/group) by oral gavage at doses of 903, 2709 or 4515 mg/kg bw/day (dry weight basis) for 90 days (Kotkoskie and Freeman, 1998). The control group received water. Body weights and feed consumption were recorded weekly. Survivors underwent complete necropsies on days 91-94. Prior to the study termination, blood was collected for hematology and clinical chemistry assessments. Selected organs were weighed and subjected to histological examination. The only treatment-related clinical sign noted was pale feces in animals receiving 2709 and 4515 mg/kg bw/day of Aquacoat[®]ECD. As compared to the control group, administration of Aquacoat[®]ECD did not show statistically significant differences in body weights, body weight gains, feed consumption, and organ weights. Similarly, no treatment-related effects in hematology parameters were noted. The results of clinical chemistry parameters revealed significantly decreased total protein and globulin levels and increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in male rats receiving 2709 and 4515 mg Aquacoat[®]ECD/kg bw/day. The histopathological examinations did not reveal any lesions that could be attributed to Aquacoat[®]ECD treatment. The no-observed-adverse-effect level (NOAEL) of Aquacoat[®]ECD dispersion for female rats was found to be in excess of 4515 mg/kg bw/day; the NOAEL for male rats was determined as 903 mg/kg bw/day. The investigators suggested that the observed effects on liver enzymes are likely attributable to the cetyl alcohol component. Cetyl alcohol has been shown to raise the serum AST levels in dogs. It should be noted that cetyl alcohol is not a permitted food additive and that the substance is not present in the ethyl cellulose that is the subject of the present assessment for ethyl cellulose.

In another subchronic study performed per OECD guidelines, DeMerlis et al. (2005) investigated the potential toxicity of spray-dried aqueous ethyl cellulose

dispersion (Surelease[®] ⁶) following dietary exposure to Sprague Dawley CD rats (20/sex/group) at dose levels of 0, 2000, 3500, and 5000 mg/kg bw/day for a period of at least 3 months. In the article it is stated that Surelease[®] is manufactured as a 25% solids aqueous ethyl cellulose dispersion and was spray dried to a powder for use in this study. Based on this, the likely dose of ethyl cellulose in the above treated animals will be 0, 500, 875, and 1250 mg/kg bw/day. During the course of the study, and at termination, a series of parameters including neuropathological evaluations were studied. No mortality was noted during the study. Clinical observations, ophthalmology, body weight, feed consumption, hematology, coagulation, clinical chemistry, urinalysis, functional observational assessments, motor activity, organ weights and ratios, and macroscopic and microscopic observations did not reveal any significant, consistent, dose-dependent test article-related adverse effects. There were occasional statistically significant and apparently dose-related effects noted (for example, sodium, chloride and hematology), but in the absence of functional changes and histopathological findings, these effects were not considered as toxicologically or biologically significant by the investigators. Based on the results of this study, the investigators determined the NOAEL as 5000 mg Surelease[®]/kg bw/day, or 1250 mg ethyl cellulose/kg bw/day, the highest dose tested.

2.3. Carcinogenicity

Hueper (1959) studied the carcinogenicity of a series of water soluble and insoluble macromolecules, including ethyl cellulose. In this study, rats (n=25) were subcutaneously injected with ethyl cellulose at a dose level of 500 mg/kg bw/day and evaluated 2 years later. The details of the protocol were not clear in the article. At the end of 2 years, no increase in localized or distant site tumors was noted following examination. Additionally, other cellulose derivatives such as HPMC, methyl cellulose methyl ethyl cellulose and carboxymethyl cellulose were also tested in carcinogenicity studies (reviewed by JEFCA) and no increase in tumors or mortality were observed.

2.4. Developmental Toxicity

Palmieri et al. (2000) investigated the developmental effects of Aquacoat[®]ECD in rats. In this study, groups of 25 presumed-pregnant Charles River Sprague-Dawley CD rats received doses of 0, 903, 2709 & 4515 mg/kg bw/day (dry weight basis) of Aquacoat[®]ECD administered undiluted once daily via oral gavage on days 6-15 of gestation. On day 20 of gestation, all surviving dams underwent caesarian sectioning and fetuses were weighed, euthanized and subjected to external, visceral and skeletal evaluations. No test article-related maternal deaths occurred. On day 14 of gavage, one high-dose female died due to gavage error. The only treatment-related clinical sign noted among dams receiving 2709 mg/kg bw/day and greater was pale feces which was attributed to the presence of the test material in the feces. No statistically significant differences were noted among the measured maternal parameters. Fetal sex ratios and body weights were similar in all groups. The results of external and visceral fetal evaluations revealed no treatment-related alterations. The only statistically significant findings noted during the skeletal evaluation were increased litter incidences of incompletely ossified or wavy ribs noted among fetuses receiving 4515 mg/kg bw/day,

⁶ Surelease is a formulated product that contains purified water, ethyl cellulose, ammonium hydroxide, medium chain triglycerides, and oleic acid.

and a significant increase in the litter incidence of thickened ribs at doses of 2709 and 4515 mg/kg bw/day. Given the nature of these findings and the lack of effects on any other parameter measured in this study, the noted effects were not considered as adverse effects of the treatment. The results of this study suggest the maternal and fetal NOAEL in excess of 4515 mg/kg/day.

2.4.1. Genotoxicity Studies

In a series of genotoxicity tests conducted according to OECD guidelines by DeMerlis et al. (2005), spray-dried aqueous ethyl cellulose dispersion (Surelease[®]) showed no evidence of mutagenic activity in the bacterial reverse mutation test with and without metabolic activation and in the *in vitro* cell mutation assay. Surelease[®] did not show any evidence of causing chromosome damage or bone marrow cell toxicity when administered by gavage in the mouse micronucleus *in vivo* test.

2.4.1.1. Ames Assay

The mutagenic potential of ethyl cellulose was assessed using the Bacterial Reverse Mutation Assay, i.e., the Ames test (DeMerlis et al., 2005). For this experiment, conducted according to standard OECD guidelines, *Salmonella typhimurium*, strains TA1535, TA1537, TA98 and TA100, and a tryptophan-dependent mutant of *Escherichia coli*, strain WP2uvrA/pKM101 (CM891) were used and the test was conducted in the presence or absence of a S9 metabolic activation system. Spray-dried aqueous ethyl cellulose dispersion (Surelease[®]) was tested at levels up to 5 mg/plate. No signs of toxicity were observed towards the tester strains in either mutation test. No evidence of mutagenic activity was seen at any concentration of Surelease[®] in either mutation test.

2.4.1.2. Mouse Lymphoma Test

In another *in vitro* test, Surelease[®] was tested for mutagenic potential in the mammalian cell mutation assay. This test system is based on detection and quantitation of forward mutation in the subline 3.7.2.c of mouse lymphoma L5178Y cells, from the heterozygous condition at the thymidine kinase locus (TK+/-) to the thymidine kinase deficient genotype (TK-/-) (DeMerlis et al., 2005). Two independent mutagenicity tests were carried out in both the absence and presence of S9 mix with a 3 hour exposure, and one in the absence of S9 mix with a 24 hour exposure. The maximum concentration of Surelease[®] to which the cells were exposed was limited by solubility. The solvent chosen was ethanol, and the highest final concentration that was judged to be usable was 250 µg/ml. In these experiments, methyl methanesulphonate was used as a positive control in the absence of the S9 fraction and 3-methylcholanthrene was used as a positive control in the presence of the S9 fraction.

As compared to Day 0 relative survival in the presence or absence of S9 mix, Surelease[®] was relatively non-toxic in this mammalian cell culture system in all tests. At least two precipitating concentrations were assessed in the main mutagenicity tests, with the effects of a maximum concentration of 250 µg/ml tested on each occasion. No significant increases in mutant frequency were noted in the first main test in the presence of S9 mix or in the second main test in either the absence or presence of S9 mix. In the absence of S9 mix in first main mutagenicity test, exposure to 250 µg/ml of Surelease[®] for 3 hour was associated with a statistically significant increase in mutant frequency, where Day 0 relative survival was 78% of the controls. However, the mutant frequency of

0.000268 lay within the upper 95% confidence limits for the negative historical control. Other concentrations tested, such as 12.5, 25, 50, 100 and 200 µg/ml, where Day 0 relative survival values ranged 106-80% of solvent controls, did not cause any significant increases in mutant frequency. In all tests, the positive control substances increased mutant frequency significantly. The investigators concluded that Surelease[®] did not demonstrate mutagenic potential in this *in vitro* cell mutation assay under the experimental conditions (DeMerlis et al., 2005).

2.4.1.3. *In vivo* Micronucleus Assay

The mammalian peripheral blood micronucleus test was conducted in accordance with the OECD guideline for such a study (DeMerlis et al., 2005). Spray-dried aqueous ethyl cellulose dispersion (Surelease)[®] was administered orally to male mice (n=7/group) at dose levels of 0, 500, 1000, and 2000 mg/kg bw. The negative control group received the vehicle, corn oil and the positive control group (n=5) received mitomycin C at 12 mg/kg bw. Bone marrow smears were obtained at 24 hours after dosing. In addition, bone marrow smears were obtained from the negative control and high dose treatment groups 48 hours after dosing. Compared to control, treatment of mice with spray dried Surelease[®] aqueous ethyl cellulose dispersion did not reveal statistically significant increases in the frequency of micronucleated immature erythrocytes and no substantial decreases in the proportion of immature erythrocytes at 24 or 48 hour. The positive control compound, mitomycin C, produced significant increases in the frequency of micronucleated immature erythrocytes. The investigators concluded that Surelease[®] did not show any evidence of causing chromosome damage or bone marrow cell toxicity when administered orally by gavage.

3. SUMMARY

Dow Wolff Cellulosics intends to market ethyl cellulose as an ingredient for uses in foods. It is a free flowing white-to-light tan color powder. Ethyl cellulose is produced according to current Good Manufacturing Practices (cGMP) using appropriate food grade ingredients and processing aids in compliance with FDA regulations. The product meets or exceeds the specification or purity requirements of the FCC, USP and JECFA. Several cellulose derivatives, including ethyl cellulose, have been permitted for food uses as codified under 21 CFR. Ethyl cellulose is approved as a multipurpose additive for use as a binder and filler, as a component of a protective coating for vitamin and mineral tablets, and as a fixative in flavoring compounds. The EFSA and JECFA have evaluated and permitted the use of ethyl cellulose as a food additive. For modified celluloses, including ethyl cellulose, both EFSA and JECFA assigned a group ADI “not specified.” Additionally, the FDA did not question the conclusions of the GRAS Notification for the use of a cellulose derivative, hydroxypropyl methylcellulose (GRN 213) with expanded substitution pattern at levels resulting in an intake of 18 g/person/day.

Dow Wolff Cellulosics intends to use ethyl cellulose in Grain Products; Vegetables; Fruits; Milk and Milk Products; Legumes; Nuts and Seeds; Fats and Oils; Sugars and Sweet; and Beverages at use levels ranging from 0.0075 to 5.0% of ethyl cellulose. The intended uses of ethyl cellulose will result in mean and 90th percentile estimated daily intakes of 4.95 and 9.90 g/person/day (82 and 165 mg/kg bw/day), respectively. The maximum daily background intake of ethyl cellulose from its existing

uses is estimated as 1.2 g/person/day (20 mg/kg bw/day). The total maximum intake from the proposed and existing uses is estimated as 11.10 g/person/day (185 mg/kg bw/day).

The source material from which ethyl cellulose is derived is a commonly used innocuous material. Additionally, as indicated earlier, alkyl derivatives of cellulose, including ethyl cellulose, are permitted for use in foods for human consumption. All this information suggests that there is a common knowledge of safe consumption of cellulose derivatives from different food sources or products. From a chemical perspective, cellulose is a linear polymer made of glucose subunits linked by β -1,4 bonds. Humans specifically do not produce enzymes capable of cleaving the beta glycosidic linkage in cellulose. Thus the backbone of cellulose derivatives, including ethyl cellulose is unlikely to be metabolized in the human gastrointestinal tract. The primary structure of alkyl derivatives of cellulose is similar except for the alkyl group. In spite of these minor structural differences, the metabolic fate of cellulose derivatives is similar and resembles that of non-digestible/fermentable carbohydrates.

The safety of cellulose derivatives has been extensively investigated in several published studies. As described earlier and summarized in Appendix I, the toxicity data on cellulose derivatives include acute toxicity, subchronic and chronic toxicity and genotoxicity as well as reproductive and developmental toxicity. The safety data of ethyl cellulose include acute toxicity, irritation and sensitization studies, repeat-dose toxicity, developmental toxicity, and genotoxicity studies. These studies did not reveal any significant adverse effects of ethyl cellulose. The safety of the class of modified cellulose, particularly alkyl derivatives, is supported by the absence of absorption from the gastrointestinal system and, therefore, the absence of systemic bioavailability. The data are consistent among all cellulose types, including unmodified celluloses, all molecular weights and viscosities, and all types of modifications, including crosslinking: no frank toxic effects were observed, except at feeding levels that interfered with the ability of test animals to consume adequate nutrients and calories.

The results of a subchronic rat study with aqueous dispersion of ethyl cellulose (Aquacoat[®]ECD) containing cetyl alcohol and sodium lauryl sulfate showed a NOAEL of 4515 and 903 mg/kg bw/day for female and male rats, (1355 and 271 mg ethyl cellulose/kg bw/day) respectively. In this study the observed effects on liver enzymes in male rats were attributed to the presence of cetyl alcohol in the dispersion and not to ethyl cellulose. In a developmental toxicity study with aqueous dispersion of ethyl cellulose in rats, the maternal and fetal NOAEL was found to exceed 4515 mg/kg bw/day or 1355 mg ethyl cellulose/kg bw/day. In another subchronic toxicity study, the NOAEL of a spray-dried aqueous ethyl cellulose dispersion (Surelease[®]) was reported as 5000 mg/kg bw/day (1250 mg ethyl cellulose/kg bw/day), the highest dose tested. These studies suggest that ethyl cellulose is safe at doses up to 1355 mg/kg bw/day in rats. The results of *in vitro* and *in vivo* mutagenicity studies did not reveal any genotoxicity of ethyl cellulose. In addition to these studies of ethyl cellulose, a series of studies with other similar alkyl derivatives of cellulose support the safety of ethyl cellulose. Furthermore, the safety of ethyl cellulose as a food additive has been reviewed in the EU (E462) (EFSA, 2004) and by JECFA (1983). The subject of the present GRAS assessment is the same substance as E462 and that evaluated by JECFA. The safety of ethyl cellulose at the proposed use levels is based on the totality of available evidence, including studies conducted with

ethyl cellulose as well as other cellulose derivatives and assessments by the national regulatory agencies as well as international authorities.

In summary, on the basis of scientific procedures⁷ and history of exposure from approved uses of ethyl cellulose and its closely related derivative, the consumption of ethyl cellulose as an added food ingredient is considered safe at the maximum estimated daily intake of 11.10 g/person/day (185 mg/kg bw/day) from the proposed and existing uses. The intended uses are compatible with current regulations, *i.e.*, ethyl cellulose will be used in Grain Products; Vegetables; Fruits; Milk and Milk Products; Legumes; Nuts and Seeds; Fats and Oils; Sugars and Sweet; and Beverages at use levels ranging from 0.0075 to 5.0% of ethyl cellulose, when not otherwise precluded by a Standard of Identity, and it is produced according to current good manufacturing practices (cGMP).

⁷ 21 CFR §170.3 Definitions. (h) Scientific procedures include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance.

4. CONCLUSION

Based on a critical evaluation of the publicly available data summarized above, the Expert Panel members whose signatures appear below, have individually and collectively concluded that ethyl cellulose, meeting the specifications cited above, and when used as a food ingredient in selected food products (Grain Products; Vegetables; Fruits; Milk and Milk Products; Meat, Poultry and Fish; Eggs; Legumes; Nuts and Seeds; Fats and Oils; Sugars and Sweet; and Beverages) at use levels ranging from 0.0075 to 5.0% of ethyl cellulose when not otherwise precluded by a Standard of Identity as described in this monograph and resulting in the 90th percentile all-user estimated intake of 11.10 g/person/day (185 mg/kg bw/day) is safe and Generally Recognized As Safe (GRAS).

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that ethyl cellulose, when used as described, is safe and GRAS based on scientific procedures.

Signatures

(b) (6)

[Redacted Signature]

Robert L. Martin, Ph.D.

Dec. 20, 2012

Date

(b) (6)

[Redacted Signature]

Madhusudan G. Soni, Ph.D., FACN, FATS

Dec. 21, 2012

Date

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Stanley M. Tarka, Jr., Ph.D.

19 December 2012

Date

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5. Appendix I

Summary Toxicity Data for Ethyl Cellulose and Several Analogues

<u>Toxicity</u>	Ethyl Cellulose (EC)	Methyl Ethyl Cellulose (MEC)	Cellulose (CEL), Cellulose Acetate (CAc)	Methyl Cellulose (MC)	<u>Additional Water Soluble Alkylcelluloses</u> Hydroxypropyl Cellulose (HPC), Ethyl Hydroxyethyl Cellulose (EHEC), Hydroxypropyl-methyl Cellulose (HPMC), Carboxymethyl Cellulose (CMC)
Acute Oral Toxicity	^{1,2} LD ₅₀ in rats >5000 mg/kg.		<u>CEL</u> : ¹¹ LD ₅₀ in rats >3160 mg/kg.	¹⁹ Rats ingesting up to 12,500 mg/kg/day for 30 days without mortality.	<u>HPC</u> : ⁴⁸ LD ₅₀ in rats = 10,200-15,000 mg/kg. <u>EHC</u> : ⁴⁹ LD ₅₀ in rats = 5000-10000 mg/kg. <u>HPMC</u> : ⁵⁰ LD ₅₀ in rats > 1000 mg/kg. ¹⁹ LD ₅₀ in rats > 4000 mg/kg. <u>CMC</u> : ⁸ LD ₅₀ in rats = 15,000-27,000 mg/kg.
Acute Dermal Toxicity	^{1,2} LD ₅₀ in rabbits >5000 mg/kg.				<u>HPC</u> : ⁵¹ LD ₅₀ in rabbits >5000 mg/kg.

Table 1 (Continued)

	EC	MEC	CEL, CAc	MC	HPC, EHEC, HPMC, CMC
Acute Toxicity- Other Routes			<u>CEL</u> : ¹¹ LD ₅₀ IP in rats >3160 mg/kg.	²⁰ In dogs, single IV injection of 40 mL of 0.7-2.8% solutions in saline - anemia, leucopenia and increased sedimentation rate.	<u>HPC</u> : ⁵² LD ₅₀ IP in rats >2500 mg/kg. <u>HPMC</u> : ¹⁹ LD ₅₀ IP in rats = 5000 mg/kg/day ¹⁹ LD ₅₀ IP in mice = 5000 mg/kg/day. <u>CMC</u> : ²⁰ In dogs, single IV injection of 40 mL of 0.25% solution in saline caused transient leucopenia.
Dermal Irritation	^{1,2} Non-irritating to normal and abraded Rabbit skin in 24 hr occluded test. ³ Non-irritating in 48-hr human volunteer patch test as 12% solution in diethylphthalate.			²¹ Non-irritating in rabbits in 24 hr occluded patch test.	<u>HPC</u> : ⁵³ RIPT in human subjects (10 repeated patches of 10% aqueous solution plus re-challenge) resulted in no irritation. <u>EHEC</u> : ⁴⁹ In abraded skin of albino rabbits, very mild irritant reactions (0.75-1.0). <u>HPMC</u> : ⁵⁴ Repeated rabbit dermal irritation study (10 applications of 24 h each), intact and abraded skin, dry or moistened (dose not given). Minor erythema secondary to skin adhesion of moistened and no systemic effects. <u>CMC</u> : ⁵⁵ Repeated rabbit dermal irritation study (5 applic./wk for 4 wk)

					to intact skin. No irritation noted. ⁵⁶ Large human volunteer and patient subject studies report no irritation of skin or mucus membranes.
Dermal Sensitization	³ Negative in human “Maximization Test” as a 12% solution in diethylphthalate.				<p><u>HPC</u>: ⁵³Repeated human patch testing (50 subjects, 10 repeated patches of 10% aqueous solution plus rechallenge) resulted in no sensitization.</p> <p><u>EHEC</u>: ⁴⁹Negative in the Guinea pig Maximization test.</p> <p><u>HPMC</u>: ²¹Negative in both the Guinea pig Maximization and Maguire Tests.</p>

Table 1 (Continued)

	EC	MEC	CEL, CAc	MC	HPC, EHEC, HPMC, CMC
Repeated-Dose Toxicity	<p>⁴Dietary study in rats at 1.2% for 8 months NOEL > 182 mg/kg/day.</p> <p>⁵Oral gavage study in rats at 903, 2709, 4515 mg/kg/day for 90 days NOAEL = 903 (M; minor Clinical Chemistry changes), 4515 (F).</p>	<p>^{8,9}Dietary study in rats at 0.1% and 1% (WHO, 1990 review) or 1% and 10% (McElligott and Hurst, 1968 publication) for 2 years, slight body weight reduction in males at high dose (1% or 10%). NOAEL >1% or >10%.</p> <p>^{8,9}Dietary study in mice at 0.1% and 1% (WHO, 1990 review) or 1% and 10% (McElligott and Hurst, 1968 publication) for 2 years, slight body weight reduction in males at high dose (1% or 10%). NOAEL >1% or >10%.</p>	<p><u>CEL</u>: ¹²Dietary study in rats comparing normal cellulose fiber to dry or gelled microcrystalline cellulose at 30% for up to 72 weeks. Reported effects in several organ systems lacked consistency between groups and/or between sexes.</p> <p><u>CAc</u>: ¹³Dietary study in rats at up to 5000 mg/kg/day for 94-96 days. No treatment-related effects.</p>	<p>²²Dietary study in rats at up to 10% for 95 days. No significant findings.</p> <p>²²Drinking water study in rats at up to 1% in water for 8 months. No significant findings.</p> <p>^{23,24}Dietary studies in rats at up to 5% for 6 and 8 months. No significant findings.</p> <p>²⁴Dietary study in rats at up to 50% in diet for 90 days. No significant findings.</p>	<p><u>HPC</u>: ⁴⁸Dietary study in rats at up to 5000 mg/kg/day for 90 days. Increased food consumption at high dose only and no significant untoward effects noted.</p> <p>⁵⁷Dietary study in rats at up to 6000 mg/kg/day for up to 6 months. No effects at 6000 mg/kg/day following 30 days. Following 6 months; no effects at 6000 mg/kg/day (F), decreased Hb at 3000 and 6000 mg/kg/day (M).</p> <p><u>EHEC</u>: ⁵⁸Dietary study in rats at up to 2500 mg/kg/day for 90 days. Decrease in liver relative weights without a histopathologic correlate at highest dose tested.</p> <p><u>HPMC</u>: ⁵⁹Oral gavage study in rats for 3 months at 505, 1020, 2100 mg/kg/day.</p>

				<p>²⁵⁻²⁸10-112 day IP/IV studies in rats (1-2.5% solutions) = increased spleen weight, MC deposits in renal glomeruli, arterial hypertension.</p> <p>²⁹Dietary study in dogs at up to 100g daily. No significant findings.</p>	<p>Decreased body weight in high dose animals.</p> <p>^{33,60-64}Up to 121-day dietary studies in rats: up to 30% in diet. Mortality and decreased bodyweight attributed to nutrition loss noted at 25% and 30% doses but only decreased body weight at 20% or lower doses. No histopathological changes noted.</p> <p>¹⁹Up to 25% in diets of rabbits for 30 days, no findings noted.</p> <p>^{33,64,65}Up to 9.6% in diet of dogs for up to 94 days. Only decreased body weight at 9.6% but, no significant findings noted at 6% or lower.</p> <p><u>CMC</u>: ⁸Dietary studies in rats (up to 20%), “rodents” (up to 15%), Guinea pigs (up to 1000 mg/kg/day), rabbits (up to 9%) and dogs</p>
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					<p>(up to 1000 mg/kg/day) for 2 weeks to 8 months with little or no effect.</p> <p>⁹Rat and mouse dietary studies at 0.1% and 1% (WHO, 1990 review) or 1% and 10% (McElligott and Hurst, 1968 publication) for 2 years. Body weights of male rats and both sexes of mice decreased at 1%.</p> <p>⁶⁶Oral gavage study in rats at 50 mg/kg/day for 2 years. No effects noted.</p> <p>⁶⁶Oral gavage study in mice at 50 mg/kg/day for 2 years. No effects noted.</p> <p>⁵⁶Dietary study in rats at up to 1000 mg/kg/day for 2 years and involving 3 generations also dosed. No effects noted.</p>
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Table 1 (Continued)

	EC	MEC	CEL, CAc	MC	HPC, EHEC, HPMC, CMC
Genetic Toxicity				Negative in ^{30,31} AMES, ³² reverse mutagenesis, ³² mitotic recombination, ³¹ chromosomal aberration, ³³ C.A. induction, ³² dominant lethal assays.	<u>HPMC</u> : ⁶⁷ Cytogenetics (chrom. aberration) Assay of bone marrow cells from rats administered up to 5% HPMC for 90 days. Negative. <u>CMC</u> : ⁸ Several Ames' Bacterial Mutagenicity Assays, Yeast Recombinogenicity Assay, CHL Chrom. Aberration Assay. All negative.
Carcinogenicity	⁶ SC injection of rats with 500 mg/kg/day and evaluated 2 years later. No increase in localized or distant site tumors.	^{8,9} Dietary study in rats at up to 1% (WHO, 1990 review) or 10% (McElligott and Hurst, 1968 publication) for 2 years. No increased incidence of tumors. ^{8,9} Dietary study in mice at up to 1% (WHO, 1990 review) or 10% (McElligott and Hurst, 1968 publication) for 2 years. No increased incidence of tumors.		³³ Dietary study in SD rats at up to 5% in diet for 2 years. No increased incidence of tumors. ³⁴ Dietary study in rats and mice at up to 1% for 2 years. No increased incidence of tumors.	<u>HPMC</u> : ² Rat dietary study at up to 20% for 2 years. No increased incidence of tumors. <u>CMC</u> : ⁹ Rat and mouse dietary studies at 0.1% and 1% (WHO, 1990 review) or 1% and 10% (McElligott and Hurst, 1968 publication) for 2 years. No increased incidence of tumors. ⁶⁶ Oral gavage study in rats at 50 mg/kg/day for 2 years. No increased incidence of tumors.

					<p>⁶⁶Oral gavage study in mice at 50 mg/kg/day for 2 years. No increased incidence of tumors.</p> <p>⁵⁶Dietary study in rats at up to 1000 mg/kg/day for 2 years. No increased incidence of tumors.</p>
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Table 1 (Continued)

	EC	MEC	CEL, CAc	MC	HPC, EHEC, HPMC, CMC
Reproductive Toxicity	Lack of toxicity to gonads in repeated dosing studies.	Lack of toxicity to gonads in repeated dosing studies.	Lack of toxicity to gonads in repeated dosing studies. <u>CEL</u> : ¹⁴ Dietary study in rats comparing normal cellulose fiber to dry or gelled microcrystalline cellulose at 30% for three generations. Poor reproductive performance attributed to poor nutritional state.	Lack of toxicity to gonads in numerous subchronic repeated dose studies in males and females of rats and dogs. ³⁵ Reduced pregnancy rate in surviving high-dose females (1600 mg/kg/day), increase in resorption rates.	<u>All Test Materials</u> : Lack of gonadal toxicity in numerous subchronic repeated dose studies in males and females of several species. <u>HPC</u> : ⁶⁸ Combined teratology/one-generation reproduction study in rats at 5000 mg/kg/day. No effect on reproduction noted. <u>CMC</u> : ⁵⁶ Dietary multigeneration (three) study in rats at up to 1000 mg/kg/day. No effects upon reproduction noted. ⁶⁹ Oral gavage one-generation reproduction study in rats at 200 mg/kg/day. No effects upon reproduction noted.

Table 1 (Continued)

	EC	MEC	CEL, CAc	MC	HPC, EHEC, HPMC, CMC
Developmental Toxicity	⁷ Oral gavage study in rats at up to 4515 mg/kg/day on GD 6-15. No teratogenic effect noted. NOAEL maternal and fetal >4515 mg/kg/day.		<u>CEL</u> : ¹⁴ Dietary study in rats comparing normal cellulose fiber to dry or gelled microcrystalline cellulose at 30% for three generations. No “deformities” observed.	³⁶ Developmental toxicity study in mice. No teratogenic effect noted. ^{35,37} Developmental toxicity study in rats. Increased centers of ossification in ribs of fetuses as evidence of delayed development only. ³⁵ Developmental toxicity study in rabbits. No teratogenic effect noted.	<u>HPC</u> : ⁶⁸ Rat combined teratology/one-generation reproduction study at 5000 mg/kg/day. No teratologic effect. ⁷⁰ Rabbit teratology study at 5000 mg/kg/day. No teratologic effect. <u>CMC</u> : ⁷¹ Rat teratology study at up to 1600 mg/kg/day gd 6-15. No teratologic effect. ⁷¹ Mouse teratology study at up to 1600 mg/kg/day gd 6-15. No teratologic effect.

Table 1 (Continued)

	EC	MEC	CEL, CAc	MC	HPC, EHEC, HPMC, CMC
Pharmacokinetics & Metabolism		¹⁰ Oral ingestion of single 0.6 gram dose by rats. 90% recovered in feces by 96 hours.	<p><u>CEL</u>: ¹⁵Human volunteers ingesting total of 150 grams of ¹⁴C-microcrystalline cellulose. All excreted in feces, none in urine or as CO₂.</p> <p>¹⁶Human volunteers ingesting 30 grams of microcrystalline cellulose/day for 5.5 weeks. Unchanged test material in feces.</p>	<p>³⁸Balance study in rats at a bolus dose of 500 mg/kg. 102.2% excreted via feces in rats within 48 hours.</p> <p>³⁹Some evidence of transference to rat pups via milk, causing transient anemia in pups.</p>	<p><u>HPC</u>: ^{48,72}Oral balance study in rats. 8.32% - 102.7% excreted in the feces in the first 48-96 hours.</p> <p><u>HPMC</u>: ⁷⁰Oral balance study in rats. >99% excreted in feces after a single bolus dose in rats. After 5 repeated doses, 97-102% was excreted via feces suggesting no tendency of accumulation in tissues.</p> <p>⁴⁷Oral study in humans ingesting up to three doses of 8.9g. 97% recovered in feces.</p> <p><u>CMC</u>: ⁸Oral balance studies in rats, rabbits and dogs demonstrated quantitative recovery in feces.</p> <p>⁷⁴Oral study in human volunteers ingesting 20 or 30 grams/day for 4 days. Approx. 90% recovered in feces.</p>

Table 1 (Continued)

	EC	MEC	CEL, CAc	MC	HPC, EHEC, HPMC, CMC
Human Data			<p><u>CEL</u>: ¹⁷Diet supplemented with 30 grams daily for six weeks. No effects noted.</p> <p>¹⁸Diet supplemented with 30 grams daily for two weeks. No effects noted.</p> <p>¹⁶Ingestion of 30 grams of microcrystalline cellulose ingested/day for 5.5 weeks resulted in no gastro-intestinal effects.</p>	<p>⁴⁰In man, single oral doses of 5g and 10g were well tolerated.</p> <p>^{29,41-46}Repeated ingestion of up to 6g/day for up to 23 days resulted in transient changes in fecal consistency & movement frequency.</p> <p>⁴⁷Acute ingestion of up to 8.9 grams resulted in “minor” laxative or constipating effects.</p>	<p><u>EHEC</u>: ⁷⁵Volunteers ingesting 1.0-1.5g 3x daily for >2 months to humans with GI problems. No toxicity noted.</p> <p><u>HPMC</u>: ^{47,9}Volunteers ingesting up to three doses of 8.9g each. Only mild laxative or constipating effect noted.</p> <p><u>CMC</u>: ⁷⁴Volunteers ingesting 20-30 grams/day for 7 days. No untoward effects.</p> <p>⁷⁶Patients ingesting 10 grams/day for up to 6 months. Abdominal discomfort in some subjects.</p> <p>⁸Patients ingesting 2-6 grams/day for “more than a year” as a laxative. No adverse effects noted.</p> <p>^{77,78}Volunteers ingesting 15 grams/day for 23 days. Fecal bile acid excretion increased, but no untoward effects noted.</p>

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