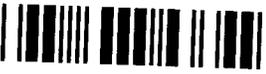


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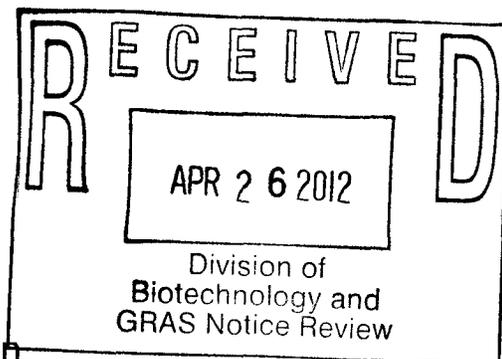
# Chemical Products Corporation

102 Old Mill Road SE  
P.O. Box 2470  
Cartersville, Georgia  
30120-1692

Phone: 770-382-2144  
Fax: 770-386-6053  
e-mail: jcook@cpc-us.com

April 20, 2012

Dr. Dennis M. Keefe, Director  
Office of Food Additive Safety (HFS-200)  
Center for Food Safety and Applied Nutrition  
Office of Foods  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835



**Re:** Notification that **Poloxamer fatty acid esters** have been determined to be generally recognized as safe (GRAS) for their intended use in paper and paperboard products used in food packaging.

Dear Dr. Keefe:

In accordance with proposed 21CFR §170.36 (Notice of a claim for exemption based on a Generally Recognized as Safe (GRAS) determination) published in the *Federal Register* (62FR 18938 - 18964) dated April 17, 1997, Chemical Products Corporation, a Georgia corporation located at 102 Old Mill Road SE, Cartersville, GA 30120-1692, USA, is hereby submitting in triplicate a GRAS Notification for poloxamer esters of common dietary fatty acids derived from animal or vegetable fats and oils (including tall oil).

Poloxamer fatty acid esters, included in the chemical classification polyoxyalkylene glycol fatty acid esters (or simply polyalkylene glycol fatty acid esters), are

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generally recognized as safe for specific use as a pulping aid in the alkaline pulping of lignocellulosic material at levels not to exceed 0.5 percent by weight of the raw lignocellulosic material, and are thus permitted as an indirect food additive under 21CFR 176.170 (a)(2). Poloxamer fatty acid esters are, therefore, determined to be exempt from the premarket approval requirements of the *Federal, Food, Drug and Cosmetic Act*.

Information setting forth the basis for this GRAS determination, which includes detailed information on the notified substance, information on levels of use, and a summary of the basis for the GRAS determination under the intended conditions of use based on common use of polyoxyalkylene glycol fatty acid esters in food prior to January 1, 1958 and scientific procedures, are enclosed for review by the agency.

Should you have any questions regarding this GRAS Notification, please do not hesitate to contact me at any point during the review process so that I may provide a response in a timely manner.

Sincerely,

(b) (6)



Jerry A. Cook  
Technical Director

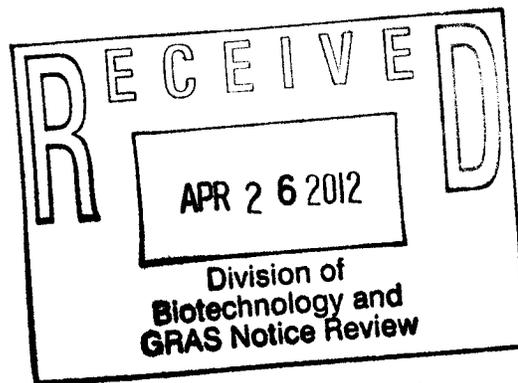
**Generally Recognized as Safe (GRAS)  
Determination Notification for  
Poloxamer Fatty Acid Ester Formulations**

**Submitted to:**

Office of Food Additive Safety (HFS-200)  
Center for Food Safety & Applied Nutrition (CFSAN)  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD  
USA 20740-3835

**Submitted by:**

*Chemical Products Corporation*  
102 Old Mill Road SE  
P.O. Box 2470  
Cartersville, GA 30120-1692



**April 20, 2012**

## GENERALLY RECOGNIZED AS SAFE NOTIFICATION

### I. Claim of GRAS Status

#### A. Claim of Exemption from the Requirement for Premarket Approval Requirements

Pursuant to Proposed 21CFR § 170.36(c)(1) Chemical Products Corporation (CPC) has determined that the use of poloxamer esters of common dietary fatty acids derived from animal or vegetable fats and oils (including tall oil) 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 their intended use as pulping aids in the alkaline pulping of lignocellulosic material at levels not to exceed 0.5 percent by weight of the raw lignocellulosic material. Therefore, the use of poloxamer fatty acid esters is exempt from the requirement of premarket approval.

Signed

(b) (6)



Jerry A. Cook, Technical Director  
Chemical Products Corporation

Date: April 20, 2012

000005

**B. Name and Address of Notifier:**

Chemical Products Corporation  
102 Old Mill Road SE  
P.O. Box 2470  
Cartersville, GA 30120-1692

**All communications on this matter should be sent to**

Jerry A. Cook, Technical Director  
Chemical Products Corporation  
P.O. Box 2470  
Cartersville, Ga 30120-1692  
Phone: 770-382-2144 Ext. 272  
email: jcook@cpc-us.com

**C. Common or Usual Name of the Notified Substance:**

Poloxamer esters of fatty acids (PEFAs).

Synonyms are:

- ethylene oxide/propylene oxide copolymer fatty acid ester;
- polyoxyethylene/polyoxypropylene copolymer fatty acid diester;
- polyoxyethylene–polyoxypropylene block copolymer fatty acid ester;
- polyethylene oxide–polypropylene oxide block copolymer fatty acid ester;
- polyethylene/polypropylene glycol fatty acid ester.

Several chemically-equivalent names are in common use referring to the polymers of alkylene oxides. All of these polymers are, by definition, glycols because each end of the polymer chain is terminated by a hydroxyl group. Polymers of ethylene oxide are referred to by the synonymous names of polyethylene oxide (or polyethylene oxide glycol), polyoxyethylene (or polyoxyethylene glycol), and polyethylene glycol. Historically, polyoxyethylene (or polyoxyethylene glycol) has tended to refer to polymers of any molecular weight, while polyethylene glycol has referred to polymers with molecular weights below 20,000 g/mole and polyethylene oxide has referred to polymers with molecular weights above 20,000 g/mole. Analogous chemically synonymous names are used for polymers of propylene oxide.

**D. Applicable Conditions of Use:**

The subject PEFAs are intended for use as pulping aids in the alkaline pulping of lignocellulosic material at levels not to exceed 0.5 percent by weight of the raw lignocellulosic material. Minute quantities of the subject PEFAs may thus become an indirect food additive as components of the uncoated food-contact surface of paper and paperboard intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding dry, aqueous, or fatty foods.

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#### **D. Basis for GRAS Determination:**

In accordance with 21CFR 170.30, the intended use of PEFAs (polyoxyalkylene fatty acid esters) has been determined to be Generally Recognized As Safe (GRAS) based a history of use of these compounds as food ingredients and on scientific procedures. A comprehensive search of the scientific literature was conducted for this review. There is sufficient qualitative and quantitative scientific evidence to determine safety-in-use of PEFAs. The safety determination of PEFA is based on the totality of the available evidence as described herein.

#### **E. Availability of Information**

The data and information that are the basis for this GRAS determination are available for the Food and Drug Administration's review and copying or will be sent to FDA upon request.

\* \* \*

The foregoing and attached information considered, it is respectfully submitted that the use of Poloxamer fatty acid esters as pulping aids in the alkaline pulping of lignocellulosic material at levels not to exceed 0.5 percent by weight of the raw lignocellulosic material is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because such use is generally recognized as safe.

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

When ingested, poloxmer fatty acid esters undergo hydrolysis and revert to their constituent poloxamers and fatty acids. Michael and Coots (1971)<sup>(2)</sup> reported on the metabolism of polyglycerol and polyglycerol fatty acid esters. When ingested, the polyglycerol fatty acid esters were found to be hydrolyzed to their constituent polyglycerols and fatty acids. Howes, Wilson, and James (1998)<sup>(3)</sup> also found that a polyglycerol fatty acid ester was digested to give free polyglycerol and fatty acid. The ester linkages in poloxamer fatty acid esters would be as readily hydrolysed as the ester linkages in the polyglycerol fatty acid esters, thus the recognized safety of the constituents of a poloxamer fatty acid ester, a poloxamer and fatty acid, demonstrates the safety of the poloxamer fatty acid esters in this specific indirect food contact application.

Poloxamers are polyoxyalkylene glycols (also referred to simply as polyalkylene glycols). Specifically, they are copolymers of ethylene oxide and propylene oxide terminated at each end of the linear polymer chain with a hydroxyl moiety capable of reacting with a carbonylic acid group to form an ester end group.

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Poloxamers are distinguished from other polyoxyalkylene glycols, and other alkylene oxide copolymers, by being composed of two blocks of polyethylene oxide surrounding a single block of polypropylene oxide, thus conforming to the general formula<sup>(1)</sup>:



The polyoxyethylene segments are hydrophilic while the polyoxypropylene central segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene oxide and ethylene oxide added during manufacture.

#### II.A Chemical Name and CAS Registry Number of Poloxamer:

$\alpha$ -Hydro- $\omega$ -hydroxypoly(oxyethylene)poly(oxypropylene)poly-(oxyethylene) block copolymer [9003-11-6]

#### II.B Method of Manufacture

Commercially-available poloxamers of various molecular weights are admixed with a stoichiometric excess of commercially-available oleic acid, sufficient dioctyl sodium sulfosuccinate to promote dispersion and intimate contact of the reactants [the subject of GRAS Notification #000006 for use as a food additive, thus GRAS for use as an indirect food additive under 21CFR176.170(a)(2)], and, optionally, a catalyst are admixed; heated to about 200°C with agitation under a nitrogen blanket; cooled; admixed with water; neutralized with potassium hydroxide; and supplied as an aqueous solution for use in the alkaline pulping of wood chips.

#### III. Summary of the Basis for the Notifier's Determination that Poloxamer fatty acid esters are GRAS

The described use of PEFAs, manufactured from commercially-available poloxamers which have molecular weights above 2000, is generally recognized as safe (GRAS) based on the use of polyoxyalkylene fatty acid esters in foods and scientific procedures, in accordance with 21CFR 170.30, as discussed more fully in the basis for the GRAS determination below. A comprehensive search of the publicly

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#### IV. Basis for a Conclusion that Poloxamer fatty acid esters are GRAS for their Intended Use.

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#### A. Use of polyoxyalkylene fatty acid esters in foods prior to 1958

In December 1958, the National Academy of Sciences – National Research Council published "The Safety of Polyoxyethylene (8) stearate for Use in Foods". A copy of this publication is attached as Appendix 1; it reports multi-year animal studies conducted on this polyoxyalkylene fatty acid ester which the report states was manufactured for use in foods as an emulsifying agent. This report concludes, "There is no consistent indication of toxic activity by the material in experimental animals at a dietary level below 5 per cent(*sp*). It is concluded that the use of polyoxyethylene (8) stearate at levels not greater than 0.05 per cent(*sp*) in the human diet would be safe." PEFAs contain at least 44 monomeric oxyalkylene units compared to the 8 monomeric units in the polyoxyethylene (8) stearate evaluated in this report; thus the polyoxyalkylene "backbone" of the PEFAs will be significantly more inert than the "backbone" of the polyoxyethylene (8) stearate.

#### B. Use of poloxamers as excipients and fillers in drugs

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Poloxamers are used as emulsifying agents in intravenous fat emulsions, and as solubilizing and stabilizing agents to maintain the clarity of elixirs and syrups<sup>(1)</sup>. Poloxamers may also be used as wetting agents; in ointments, suppository bases, and gels; and as tablet binders and coatings. Poloxamer

188 has also been used as an emulsifying agent for fluorocarbons used as artificial blood substitutes, and in the preparation of solid-dispersion systems. More recently, poloxamers have found use in drug-delivery systems.<sup>(1)</sup>

Therapeutically, Poloxamer 188 is administered orally as a wetting agent and stool lubricant in the treatment of constipation. Poloxamers may also be used therapeutically in the treatment of kidney stones.<sup>(1)</sup>

Poloxamer 188 is listed at 21CFR310.545(a)(12)(iii) as a stool softener.

The Handbook of Pharmaceutical Excipients, Sixth Edition<sup>(1)</sup> states that the grades of Poloxamers listed in the PhEur 6.0 and USP32-NF27 are:

Poloxamer	Physical form	<i>a</i>	<i>b</i>	Average molecular weight
124	Liquid	12	20	2,090–2,360
188	Solid	80	27	7,680–9,510
237	Solid	64	37	6,840–8,830
338	Solid	141	44	12,700–17,400
407	Solid	101	56	9,840–14,600

where *a* is the number of ethylene oxide monomers in each of the two polyoxyethylene blocks and *b* is the number of propylene oxide monomers in the central polypropylene block.

Poloxamers are listed 25 times as inactive ingredients for oral drug products in FDA's Inactive Ingredients in Approved Drug Products database. Poloxamers are listed 2 times in this FDA database for approved drug products for intravenous injection and 2 times for approved drug products for subcutaneous injection.

Polyoxyethylene fatty acid esters are listed 2 times as an inactive ingredient for an approved drug product (IM - IV - SC; INJECTION; maximum potency not specified; and IM - SC; INJECTION; maximum potency 14%) in FDA's database.

POLYOXYETHYLENE - POLYOXYPROPYLENE 1800 is listed as an inactive ingredient in approved ophthalmic and topical drug products.

Poloxamers are included in the Canadian List of Acceptable Non-medicinal Ingredients.

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**C. Approved uses for polyoxyethylene-polyoxypropylene glycols, polyoxyalkylene glycol esters, and chemically similar compounds in 21CFR**

Approved uses for polyoxyalkylenes and polyoxyalkylene fatty acid esters in 21CFR include:

- 21CFR 178.1010(b)(6) Sanitizing solutions approved for use on food-processing equipment and utensils followed by adequate draining before contact with food include an aqueous solution containing "polyoxyethylene-polyoxypropylene block polymers".

- 21CFR 175.105(c)(5) Approved components of adhesives for use on articles intended to hold food include "Polyoxypropylene-polyoxyethylene condensate (minimum molecular weight 1,900)", "Polyoxyethylene (molecular weight 200-600) esters of fatty acids derived from animal or vegetable fats and oils (including tall oil)", "Polypropylene glycol (minimum molecular weight 150)", and "Polyoxyethylene (40 moles) stearate".

- 21CFR 176.180(b)(2) Approved components of the uncoated or coated food-contact surface of paper and paperboard intended for use in holding dry food include "Polyoxypropylene-polyoxyethylene glycol (minimum molecular weight 1,900)", "Polyethylene glycol (200) dilaurate", and "Polyoxyethylene (minimum 12 moles) ester of tall oil (30%-40% rosin acids)".

- 21CFR 176.200(d)(3) Approved defoaming agents used in coatings of articles intended for use holding food include "Polyoxypropylene-polyoxyethylene glycol (min. mol. wt. 1,900)", "Dipropylene glycol", "Polyethylene glycol (200) dilaurate", "Polyethylene glycol (400) dioleate", "Polyethylene glycol (600) dioleate", "Polyethylene glycol (400) esters of coconut oil fatty acids", "Polyoxyethylene (min. 15 mols) ester of rosin", and "Polyoxyethylene (40) stearate". These defoaming agents are approved, without limitation, for use in the base sheet and coating of cellophane used for packaging food [see 21CFR177.1200(c) below].

- 21CFR 177.1200(c) Approved optional substances permitted to be used in the base sheet and coating of cellophane used for packaging food include "Polyoxypropylene-polyoxyethylene block polymers (molecular weight 1,900-9,000) [Limitation: For use as an adjuvant employed during the processing of cellulose pulp used in the manufacture of cellophane base sheet.]", "Defoaming agents identified in § 176.200 of this chapter", "Polyethylene glycol (600) monolaurate", "Polyethylene glycol (600) monooleate", "Polyethylene glycol (600) monostearate", and "Triethylene glycol".

- 21CFR177.2260(2) Approved substances employed in the finishing of fibers employed in resin-bonded filters to be used in producing, manufacturing, processing, and preparing food include "Fatty acid (C10-C18) mono- and

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diesters of polyoxyethylene glycol (molecular weight 400-3,000)".

- 21CFR177.2800(d) Approved substances employed in the production of or added to textiles and textile fibers to be used as articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food include "Fats, oils, fatty acids, and fatty alcohols described in the preceding item reacted with one or more of the following substances: Diethylene glycol, Polyethylene glycol (molecular weight 400-3,000), Propylene glycol", and "CASTOR OIL FATTY ACIDS, POLYOXYETHYLENE ESTERS".

- 21CFR176.210(d) Approved defoaming agents to be used in the manufacture of paper and paperboard, up to and including in the sheet forming process, intended to hold food include "(2) Fatty triglycerides, and marine oils, and the fatty acids and alcohols derived therefrom (paragraph (d)(1) of this section) reacted with one or more of the following, with or without dehydration, to form chemicals of the category indicated in parentheses: Polyoxyethylene, molecular weights 200, 300, 400, 600, 700, 1,000, 1,540, 1,580, 1,760, 4,600 (esters); and Polyoxypropylene, molecular weight 200-2,000 (esters)" and "(3) Miscellaneous: Polyoxypropylene-polyoxethylene condensate, minimum molecular weight 950; and Polyoxypropylene, molecular weight 200-2,000", and "Castor oil fatty acids, polyoxyethylene esters".

#### D. Entries from FDA's EAFUS food additives database

The following entries are found in FDA's EAFUS food additives database

ASP	449	ETHYLENE OXIDE/PROPYLENE OXIDE COPOLYMER	009003-11-6	172.808 173.340 178.3570
NUL	2066	ETHYLENE OXIDE/PROPYLENE OXIDE COPOLYMER (AVG M W 14,000)	977057-87-6	172.808
NUL	2067	ETHYLENE OXIDE/PROPYLENE OXIDE COPOLYMER (AVG M W 9,760 - 13,200)	977057-91-2	172.808
NUL	2065	ETHYLENE OXIDE/PROPYLENE OXIDE COPOLYMER (AVG M W 3,500-4,125)	977057-83-2	172.810 172.808
NUL	2068	ETHYLENE OXIDE/PROPYLENE OXIDE COPOLYMER (MIN AVG M W 1,900)	977057-63-8	172.808
NIL	1291	POLYOXYETHYLENE DIOLEATE	009005-07-6	
NUL	2564	POLYOXYETHYLENE (600) DIOLEATE	977028-99-1	173.340
ASP	1292	POLYOXYETHYLENE (600) MONO- RICINOLEATE	977137-78-2	173.340
ASP	1293	POLYOXYETHYLENE 40 MONOSTEARATE	009004-99-3	173.340 175.105

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NIL 1294 POLYPROPYLENE GLYCOL (M W 025322-69-4  
1,200-3,000)

173.340  
173.310  
175.300  
176.170  
178.3740  
175.105

#### E. Summary of the Basis for the Notifier's Determination that Poloxamer fatty acid ester formulations are GRAS

The safety of poloxamer fatty acid esters under the intended conditions of use is supported by the available scientific safety studies. A comprehensive search of the publicly available scientific databases (PubMed, Toxline, etc.) for safety and toxicity information of poloxamers and poloxamer fatty acid esters was conducted through March 2012 and was utilized for this assessment. Based on a critical evaluation of the pertinent data and information summarized herein, and employing scientific procedures, it is determined that under the conditions of their intended use as pulping aids in the alkaline pulping of lignocellulosic materials at levels not to exceed 0.5 percent by weight of the raw lignocellulosic material, poloxamer fatty acid esters are 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.

#### References

1. Handbook of Pharmaceutical Excipients, Sixth Edition (2009)  
Edited by Raymond C Rowe, Paul J Sheskey, Marian E Quinn  
Published by the Pharmaceutical Press, 1 Lambeth High Street, London SE1 7JN, UK  
100 South Atkinson Road, Suite 200, Grayslake, IL 60030-7820, USA  
and the American Pharmacists Association, 2215 Constitution Avenue, NW, Washington, DC  
20037-2985, USA  
ISBN 978 1 58212 135 2 (USA); pages 506-509.
2. Michael WR and Coots RH; Metabolism of polyglycerol and polyglycerol esters; Toxicol Appl. Pharmacol; 20(3):334-345 (Nov 1971).
3. Howes D, Wilson R, James CT; The fate of ingested glyceran esters of condensed castor oil fatty acids [polyglycerol polyricinoleate (PGPR)] in the rat; Food Chem Toxicol; 36(9-10):719-38 (Sep-Oct 1998).

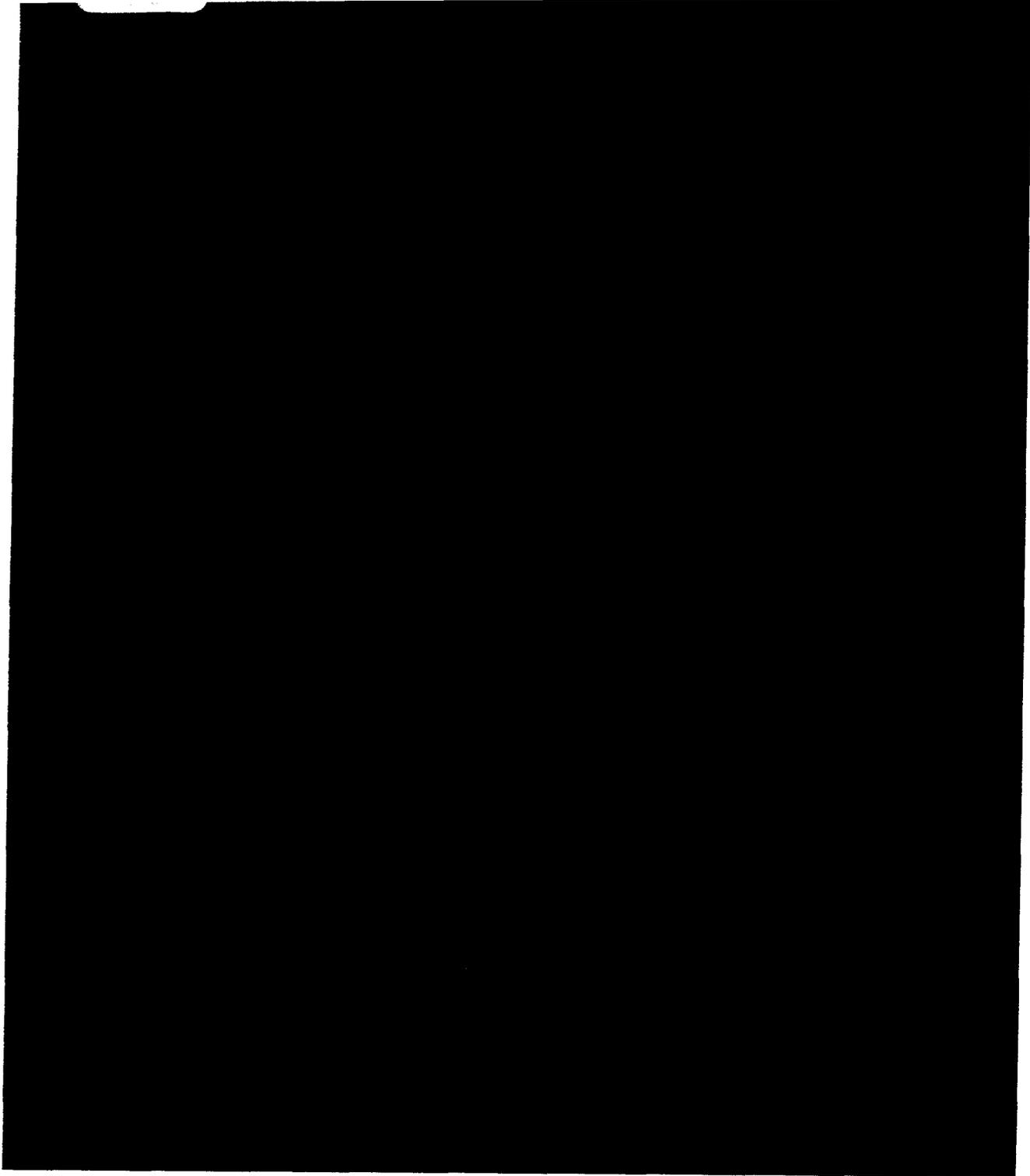
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# Appendix 1

## The Safety of Polyoxyethylene (8) Stearate for Use in Foods

A Report of the Food Protection Committee of the Food and Nutrition Board  
December 1958

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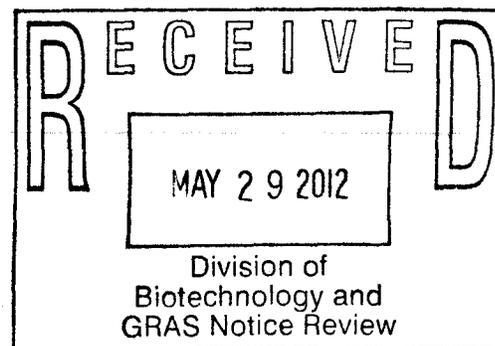
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Pages 00016 - 00039 removed in accordance with copyright laws. The removed reference is:

Title: The safety of polyoxyethylene (8) stearate for use in foods: a report  
Issue 646 of Publication (National Research Council (U.S.)), National  
Research Council (U.S.).  
National Research Council  
Author: National Research Council (U.S.). Food Protection Committee  
Publisher: National Academy of Sciences, National Research Council, 1958

**Ramos-Valle, Moraima**

**From:** Jerry Cook [jcook@cpc-us.com]  
**Sent:** Tuesday, May 29, 2012 11:38 AM  
**To:** Ramos-Valle, Moraima  
**Subject:** Re: GRAS submission  
**Attachments:** Amended page 4 of Poloxamer fatty acid esters notification.pdf



Dear Ms. Ramos-Valle;

An amended page 4 bearing my signature is attached. If this page is not acceptable, please telephone me and I will amend it further.

Thank you for your assistance.

Best Regards,

Jerry

On 5/23/2012 11:10 AM, Ramos-Valle, Moraima wrote:

Dear Mr. Cook,

This message is regarding your GRAS submission for poloxamer fatty acid esters. While reviewing your submission for filing suitability, we found that on section D "Basis for GRAS Determination" (page 4) the notifier states that the GRAS determination of poloxamer is based on "history of use of these compounds as food ingredients and on scientific procedures".

As stated on The GRAS Proposed Rule (62 FR 18938) notifiers shall submit the following information:

1. *A claim, dated and signed by the notifier, or by the notifier's attorney or agent, or (if the notifier is a corporation) by an authorized official, that a particular use of a substance is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the act) because the notifier has determined that such use is GRAS. Such GRAS exemption claim shall include:*
  - i. *The name and address of the notifier;*
  - ii. *The common or usual name of the substance that is the subject of the GRAS exemption claim (i.e., the "notified substance");*
  - iii. *The applicable conditions of use of the notified substance, including the foods in which the substance is to be used, levels of use in such foods, and the purposes for which the substance is used, including, when appropriate, a description of the population expected to consume the substance;*
  - iv. *The basis for the GRAS determination (i.e., through scientific procedures **OR** through experience based on common use in food); and*
  - v. *A statement that the data and information that are the basis for the notifier's GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at reasonable times at a specific address set out in the notice or will be sent to FDA upon request.*

The basis for a GRAS determination has to be made based on one or the other. (Please see "iv" above). Also under section E "Availability of Information" (page 4) we need the specific address where this information can be obtain. (Please see "v" above)

Please send me an amended page that includes: the basis of the poloxamer GRAS determination and the address needed under section E.

Keep in mind that FDA has not reviewed the content of your submission, this initial review is just to

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determine if the submission includes all the elements listed above. You can submit your amendment by email as a PDF file as long as it includes the notifier's signature.

For more information about GRAS please visit our website:

<http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm>

Feel free to contact me if you have any questions.

Sincerely,

Moraima J. Ramos Valle, M.S.  
Consumer Safety Office  
HHS/FDA/CFSAN/OFAS/DBGNR

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5/29/2012

#### **D. Basis for GRAS Determination:**

In accordance with 21CFR 170.30, the intended use of PEFAs (polyoxyalkylene fatty acid esters) has been determined to be Generally Recognized As Safe (GRAS) through scientific procedures. A comprehensive search of the scientific literature was conducted for this review. There is sufficient qualitative and quantitative scientific evidence to determine safety-in-use of PEFAs. The safety determination of PEFAs is based on the totality of the available evidence as described herein.

#### **E. Availability of Information**

The data and information that are the basis for this GRAS determination are available for the Food and Drug Administration's review and copying at the office of Chemical Products Corporation, 102 Old Mill Road SE, Cartersville, GA 30120; or will be sent to FDA upon request.

\* \* \*

The foregoing and attached information considered, it is respectfully submitted that the use of Poloxamer fatty acid esters as pulping aids in the alkaline pulping of lignocellulosic material at levels not to exceed 0.5 percent by weight of the raw lignocellulosic material is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because such use is generally recognized as safe.

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

When ingested, poloxmer fatty acid esters undergo hydrolysis and revert to their constituent poloxamers and fatty acids. Michael and Coots (1971)<sup>(2)</sup> reported on the metabolism of polyglycerol and polyglycerol fatty acid esters. When ingested, the polyglycerol fatty acid esters were found to be hydrolyzed to their constituent polyglycerols and fatty acids. Howes, Wilson, and James (1998)<sup>(3)</sup> also found that a polyglycerol fatty acid ester was digested to give free polyglycerol and fatty acid. The ester linkages in poloxamer fatty acid esters would be as readily hydrolysed as the ester linkages in the polyglycerol fatty acid esters, thus the recognized safety of the constituents of a poloxamer fatty acid ester - a poloxamer and fatty acid - demonstrates the safety of the poloxamer fatty acid esters in this specific indirect food contact application.

Poloxamers are polyoxyalkylene glycols (also referred to simply as polyalkylene glycols). Specifically, they are copolymers of ethylene oxide and propylene oxide terminated at each end of the linear polymer chain with a hydroxyl moiety capable of reacting with a carbonylic acid group to form an ester end group.

(b) (6)



**Ramos-Valle, Moraima**

---

**From:** Ramos-Valle, Moraima  
**Sent:** Wednesday, May 23, 2012 11:10 AM  
**To:** 'jcook@cpc-us.com'  
**Cc:** Ramos-Valle, Moraima; Farias, Bianca \*  
**Subject:** GRAS submission

Dear Mr. Cook,

This message is regarding your GRAS submission for poloxamer fatty acid esters. While reviewing your submission for filing suitability, we found that on section D "Basis for GRAS Determination" (page 4) the notifier states that the GRAS determination of poloxamer is based on "history of use of these compounds as food ingredients and on scientific procedures".

As stated on The GRAS Proposed Rule (62 FR 18938) notifiers shall submit the following information:

1. *A claim, dated and signed by the notifier, or by the notifier's attorney or agent, or (if the notifier is a corporation) by an authorized official, that a particular use of a substance is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the act) because the notifier has determined that such use is GRAS. Such GRAS exemption claim shall include:*
  - i. *The name and address of the notifier;*
  - ii. *The common or usual name of the substance that is the subject of the GRAS exemption claim (i.e., the "notified substance");*
  - iii. *The applicable conditions of use of the notified substance, including the foods in which the substance is to be used, levels of use in such foods, and the purposes for which the substance is used, including, when appropriate, a description of the population expected to consume the substance;*
  - iv. *The basis for the GRAS determination (i.e., through scientific procedures **OR** through experience based on common use in food); and*
  - v. *A statement that the data and information that are the basis for the notifier's GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at reasonable times at a specific address set out in the notice or will be sent to FDA upon request.*

The basis for a GRAS determination has to be made based on one or the other. (Please see "iv" above). Also under section E "Availability of Information" (page 4) we need the specific address where this information can be obtain. (Please see "v" above)

Please send me an amended page that includes: the basis of the poloxamer GRAS determination and the address needed under section E.

Keep in mind that FDA has not reviewed the content of your submission, this initial review is just to determine if the submission includes all the elements listed above. You can submit your amendment by email as a PDF file as long as it includes the notifier's signature.

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For more information about GRAS please visit our website:

<http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm>

Feel free to contact me if you have any questions.

Sincerely,

Moraima J. Ramos Valle, M.S.  
Consumer Safety Office  
HHS/FDA/CFSAN/OFAS/DBGNR

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**SUBMISSION END**

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