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GRAS Notice (GRN) No. 466

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

ORIGINAL SUBMISSION

000001

Date November 19, 2012

**GRAS Exemption Notification Polyglycerol polyricinoleic acid (PGPR) for Use in
Condiments and Spreads, Flavors, and Snacks (Cheese Powders)**

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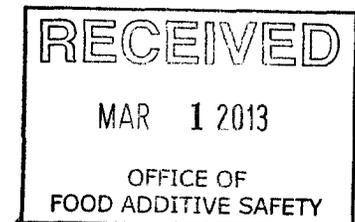
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Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Dear Sir/Madam:

Re: GRAS Notification Exemption Claim from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR § 170.36(c)(1) [62 FR 18938 (17 April 1997)]

Under the GRAS Notification Program and in accordance with FDA proposed rule of April 17, 1997 published in the Federal Register (62 FR 18939-18964), **McCormick & Company, Inc.** claims that the use of polyglycerol polyricinoleic acid (PGPR) has been determined to be Generally Recognized As Safe (GRAS), for use as an emulsifier as defined in CFR Part 21 consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*.

GRAS Exemption Claim

PGPR is exempt from premarket approval according to the requirements of the Federal Food, Drug, and Cosmetic Act as specified in 21 CFR 170.36 (Notice of a claim for exemption based on a GRAS determination). The determination is based on scientific procedures under the conditions of intended use of PGPR in condiments and spreads at use levels up to 0.28%, flavors at use levels up to 0.1%, and snacks (cheese powders) at use levels up to 0.15%. This claim is in addition to the claims previously notified of use of PGPR as an emulsifier in chocolate in GRAS Notification 000009, margarines, low fat margarines, spreads, creamers, and dairy analogues in GRAS Notification 000179, chocolate and vegetable fat coatings in GRAS Notification 000266, and the formulation of color additives intended for addition to processed foods in GRAS Notification 000270. The data and information within these prior GRAS Notifications are incorporated into this GRAS Notification by reference.

I am submitting in triplicate, as the agent to the notifier, McCormick & Company, Inc., a GRAS Notification for additional food categories and use levels for PGPR as an emulsifier in food.

Signed
(b) (6)

[Redacted Signature]

November 19, 2012

Date

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1. Name and Address of Notifier

Sue Tometzak
McCormick & Company, Inc.
18 Loveton Circle
Sparks Glencoe, MD 21152

2. Common Name of the Notified Substance

The substance is commonly known as Polyglycerol polyricinoleic acid or by its acronym PGPR.

3. Applicable conditions of use:

- (a) Foods in which the substance is to be used:
Polyglycerol polyricinoleic acid is intended to be used in the production of condiments and spreads, flavors, snacks (cheese powders) and seasonings (meat)
- (b) Purposes for which the substance is used:
Polyglycerol polyricinoleic acid as an emulsifier.
- (c) Description of the population expected to consume the substance:
Polyglycerol polyricinoleic acid is expected to be used by the general public.

4. Basis for GRAS determination.

- a. Pursuant to 21 CFR 170.30, PGPR determined to be GRAS on the basis of scientific procedures and long history of use in food. This determination is based on the views of experts who are qualified by scientific training and experience to

evaluate the safety of PGPR as an emulsifier in food as presented in prior FDA GRAS Notifications with use levels greater than those recommended in the food categories listed in this Notification. PGPR from different specific sources and of slightly different chemical composition are considered GRAS. In 1999, FDA GRAS Notification 000009, in accordance with 21 CFR 170.30, PGPR was determined to be GRAS on the basis of scientific procedures and information provided by Quest International (Quest, 1999). In 2005, FDA GRAS Notification 000179, pursuant to 21 CFR 170.30, of PGPR was determined to be GRAS on the basis of scientific procedures and information provided by Stephan Company on the potential for epichlorohydrin residues in PGPR (Stephan Company, 2005). Also, in 2005, PGPR was the subject of GRAS Notification 000179 to FDA for use as an emulsifier in margarines, low fat margarines, spreads, creamers, and dairy analogs at levels no greater than 1% (Stephan Company, 2005). In 2008, FDA GRAS Notification 000266, pursuant to 21 CFR 170.30, PGPR was determined to be GRAS by scientific procedures for use in vegetable fat coatings based on information provided by Palsgaard A/S (Palsgaard A/S, Denmark, 2008). In 2009, FDA GRAS Notification 000270, pursuant to 21 CFR 170.30, PGPR was determined to be GRAS by scientific procedures for use of the substance in the formulation of color additives intended for addition to processed foods, with limitation based only on Good Manufacturing Practice (Stephan Company). In addition to these GRAS Notifications, PGPR has been the subject of safety evaluations as an emulsifier for food by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1973) and the European Scientific Committee for Food (SCF, 1978). In both instances, PGPR was concluded to be safe as an emulsifier under intended conditions of use in food (SCF, 1978).

- b. Polyglycerol polyricinoleic acid is described in Food Chemical Codex, Sixth Edition that also describes methods of preparation and specifications for the PGPR. The product used by McCormick will meet the specifications as established by Food Chemicals Codex.
5. Availability of Data and Information (references). The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Name
McCormick & Company, Inc.
18 Loveton Circle,
P.O. Box 6000
Sparks Glencoe, MD 21152
410-771-7301

Should the U.S. Food and Drug Administration (FDA) have any questions or additional information requests regarding this notification, McCormick & Company will supply these data and information.

(b) (6)



11/19/2012

Timothy B. Adams, Ph.D.
Scientific and Regulatory Representative:
McCormick and Company, Inc.

Attachments:
Proposed GRAS Listing
Attachments

PROPOSED

GRAS List Entry

GRN No.	Notifier	Substance	Intended Use	GRP #	<i>BASIS</i>	Date of Filing	Closure
	McCormick & Company, Inc.	Polyglycerol polyricinoleic acid	As an emulsifier in the formulation of color additives intended for addition to processed foods, with limitation based only on Good Manufacturing Practice.		Scientific procedures		

1. Identity of the Substance

a. Chemical or common names

9-octadecenoic acid, 12-hydroxy-, (9 Z, 12R)-,
polymer with 1,2,3-propanetriol (9CI)
CAS Registry No. 29894-35-7

b. Common Names

Polyglycerol polyricinoleic acid
Polyglycerol esters of interesterified ricinoleic acid
Polyglycerol polyricinoleate
PGPR

c. Definition

Polyglycerol Polyricinoleic Acid occurs as a clear, light brown, viscous liquid. It is prepared by esterification of polyglycerol with condensed castor oil fatty acids. The castor oil fatty acids are mainly composed of 80% to 90% ricinoleic acid. PGPR is soluble in ether, in hydrocarbons, and in halogenated hydrocarbons. It is insoluble in water and in alcohol.

d. Assay, Identification Test, Purity, Description

Food Chemical Codex, Sixth Edition, page 344, Specifications
Clear light brown viscous liquid

Attachment No. 2

2. Manufacture, Specifications, and Stability

PGPR has been reported in several scientific articles and four previous GRAS Notifications (GRNs 00009, 00178, 00266, and 00270) for use as an emulsifier of foods with a high water to fat ratio. PGPR is defined as an interesterified polymer of polyricinoleic acid and polyglycerol. PGPR is a polymer created by the self-condensation of the 12-hydroxy-9-octadecenoic acid fraction within the fatty acids obtained from castor oil. The condensation reaction is carried out by heating castor oil fatty acids to about 200°C, with or without catalyst, and removing water of reaction. Acceptable catalysts are acids such as phosphoric acid, bases such as sodium hydroxide and lipase enzymes; all of which are currently used to inter-esterify food grade fats and oils. Polyglycerol is obtained either by the controlled polymerization of substituted propyl-2-oxirane or through the direct condensation of glycerin under highly basic conditions. A full description of PGPR is given in the Sixth Edition of the Food Chemical Codex (FCC), published by the Institute of Medicine. Specifications and all analytical chemistry associated with this food additive are included in this reference text. The FCC monograph, PGPR is incorporated by reference with this submission. Stability tests of physical and chemical parameters were performed between 1986 and 1988. The substance was held at a constant temperature of 15°C. No significant change was observed. The stability of PGPR is shown to be excellent.

Attachment No. 3

3. Anticipated Uses

PGPR allows for the reduction in fat content of a variety food products without reducing pleasing taste properties. Generally, consumers tend to avoid unpleasing foods regardless of the health benefit the food may provide. PGPR has been found to be an effective water-in-oil emulsifier, which when incorporated with Lecithin in low fat spreads allows for a greater reduction in overall fat content and enhances the pleasing creaminess and low splatter when used to fry foods. This is of commercial importance in low fat spreads where the fat content approaches 40% of the composition; PGPR is an essential emulsifier in the effort to reduce dietary fat.

Attachment No. 4

Anticipated Uses

4) Polyglycerol polyricinoleic acid previously has been determined to be GRAS in chocolates at levels up to 0.3% (GRN #0009) and in margarines, low fat margarines, spreads, creamers, and low fat dairy analogs at levels up to 1.0% (GRN 00179), in vegetable fat coatings (GRN 00266), and as an emulsifier of color additives commonly used in foods at levels up to 0.1 % of PGPR in the color additive with a maximum of 5% by weight of the formulation being used (GRN 00270). Recommended use levels in the food categories listed in Table 1 of this GRAS Notification do not exceed 0.3%

Table I- Use levels and single portion intakes of PGPR in foods

Food Category	Use Level (%w/w)	Max Weight/Serving (g)	Servings/day	Intake /day (g)	Daily Intake PGPR/day, g
Condiments and Spreads	0.28	28	3	84	0.235
Flavors	0.10	-	-	-	<0.002
Cheese Powders (Snacks)	0.15	0.84	10	8.4	0.0126

Attachment No. 5

5) Safety Evaluation

A) Estimated Daily Intake

1) Menu census method

Based on the use levels, portions sizes, and number of daily servings provided in Table 1, it is estimated that the total estimated daily intake (EDI) of PGPR from all listed food categories is <0.25 g/day (250 mg/day). Based on an adult body weight of 60 kg, the estimated intake is approximately 4.17 mg/kg bw/day. The category of condiments and spreads accounts for approximately 93% of the intake of PGPR from these three food sources.

The use of PGPR in margarines, low fat margarines, spreads, creamers, and dairy analogs was the subject of a prior GRAS Notification (GRN 000179). The average EDI for these uses was reported to be 2.7 mg/kg/day. This GRAS Notification also includes the category of spreads and the EDI for use of PGPR is 0.235 g/person/day or 3.92 mg/kg/day (see Condiments and Spreads, Table I). The total EDI for the remaining two categories in this Notification is 0.0146 g/person/d or 0.24 mg/kg/day. Based on the higher intake for the spreads category, the cumulative conservative EDI for the three food categories is estimated to be 4.17 mg/kg/d.

In the first GRAS Notification for the use of PGPR in chocolate, the average EDI was estimated to be 2.4 mg/kg/d (GRN 000009). A second GRAS Notification for use in vegetable coatings using the same concentration limits as noted for chocolate in GRN 000009 (GRN 000266). With respect to the intakes expected with the use of PGPR in formulation aid in color additives (GRN 000270), the functional effect of an emulsifier would be achieved at the addition of 0.03%. The NASINRC Food Color Publication, 1971, reports that the amount of certified colors used in food is self-limiting and reports the major categories of foods with average ppm in each type of food. If one assumed that the food colors would be added to all processed foods (approximately 1 kg of food/person/day), this would calculate to be an average EDI of 0.25 mg/kg/body weight. If one considers the additional two uses of PGPR, the cumulative EDI from all food categories would be 6.82 mg/kg/d (4.17 + 2.4 + 0.25 mg/kg/d). It is obvious that the use of PGPR as an emulsifier in food color additives, in flavors, and in snacks does not significantly increase the EDI for the use of PGPR in food. Although these cumulative exposures must be considered exaggerated estimates of intake, the total EDI estimate is below the established EDI (7.5 mg/kg/body weight).

2) Annual Volume Intake Method

The McCormick & Company estimates that the annual volume of use of PGPR will be 68,000 kg. Based on the conservative assumption that only 10% of the US population (31×10^6) would consume all of the PGPR on an annual basis, the estimated daily *per capita*

intake (“eaters only”) would be approximately 6mg/day or 0.1 mg/kg/day. Because the foods that would contain PGPR would be consumed daily by the vast majority of the population, it is likely that the daily *per capita* intake would approach 0.01 mg/kg/day

B) Acceptable Daily Intake (ADI)

An ADI 0-7.5 mg/kg/d was established in 1973 by JECFA (JECFA, 1973). The basis for the ADI was a study in rats with a level causing no toxicological effects on 15000 ppm (1.5%, highest dose) equivalent to 750 mg/kg in a long-term study in rats. The safety factor of 100 was used to derive the 7.5 mg/kg/day ADI value. In other long-term studies liver and kidney enlargement was noticed at much higher doses, 5 and 10% equivalent to 2400 and 4800 mg/kg/day, respectively. The cumulative EDI of 6.83 mg/kg bw/day derived from the menu census survey assuming that an individual would consume multiple portions of each food containing PGPR every day over a lifetime is below the ADI of 7.5 mg/kg/day. In the more likely scenario (annual volume method) that 10% of the population consumes the PGPR daily over a lifetime, the intake of PGPR from the three listed food categories is estimated to be at least 750 times less than the JECFA ADI. In conclusion these additional uses of PGPR would not lead to a significant increase in exposure to PGPR.

Additional Safety Data

Extensive safety data has been reported in the previous GRAS Notifications (GRNs 000009, 000179, 000266, and 000270) and the data supporting these GRAS claims has appeared in the peer-reviewed scientific literature (e.g., Wilson and Smith, 1998a, 1998b). Since lipase induces hydrolysis of PGPR following ingestion (GRN 000009), data on the hydrolysis product ricinoleic acid is relevant to the safety evaluation of PGPR. Ricinoleic acid has long history of use as a laxative. Recent data on the absorption and distribution of ricinoleic acid has been reviewed (CIR 2007) and its action on the gastrointestinal epithelia has been studied (Tunaru, 2012). In two earlier experiments, the accumulation of ricinoleic acid in depot fat in rats was studied. In the first experiment, adult male rats were fed ricinoleic acid (5% emulsion, 20 mL) for 7 days. In the second experiment, the animals were fed for 27 days. Lipid extraction from the fat tissue was followed by hydrolysis to yield a fatty acid mixture. Appreciable amounts of the following hydroxy fatty acids with shorter chain lengths than ricinoleic acid: 10-hydroxyhexadecenoic acid (experiment 1: 0.60% of total fatty acids; experiment 2: 0.33% of total fatty acids), 8-hydroxytetradecenoic acid (experiment 1: 0.03% of total fatty acids; experiment 2: 0.08% of total fatty acids), and 6-hydroxydodecenoic acid (experiment 2: 0.03% of total fatty acids) were identified. Ricinoleic acid comprised 0.51% of total fatty acids in experiment 1 and 3.85% of total fatty acids in experiment 2. Based on these data, ricinoleic acid is readily incorporated into the fatty acid pathway of animals (Uchiyama et al., 1963).

In another critical experiment, the metabolism of hydroxyl fatty acids was evaluated using male albino rats. The rats received 1.5 g ricinoleic acid or an emulsion containing 5% (w/v) ricinoleic acid by stomach tube three times per day for a desired period. Feces were collected every 24 hr until the animals were killed. The animals were killed 20 hr after the last dose, and subcutaneous adipose tissue was removed for analyses. Oral dosing with ricinoleic acid resulted in a fecal excretion rate (for ricinoleic acid) ranging from 1% to 4%. Following oral administration for up to 30 days, the accumulation of hydroxyl acids by 5% of fatty acids in fat tissue was noted. Analyses of adipose tissue indicated an occurrence of shorter chain hydroxyl acids other than ricinoleic acid (Okui et al. 1964).

In a metabolism study three healthy subjects were administered castor oil (10 to 15 mL) orally. Urine was collected between 2 and 8 hr post dosing. The following three epoxydicarboxylic acids were excreted in the urine: 3,6-epoxyoctanedioic acid; 3,6-epoxydecanedioic acid; and 3,6-epoxydodecanedioic acid. These three ricinoleic acid metabolites were also detected in the urine of rats. These data support experiments cited above that indicate shorter chain fatty acids form from ricinoleic acid in the fatty acid pathway (CIR, 2007). These data support the conclusion that PGPR hydrolyses via intestinal lipase and produced ricinoleic acid that subsequently enters the fatty acid pathway.

Related Biochemical Data

The laxative effects of castor oil are mediated by ricinoleic acid. The prostanoid receptor 3 (EP₃) is specifically activated by ricinoleic acid and it mediates the pharmacological effects. In mice lacking EP₃ receptors, the laxative effect and the uterus contraction induced via ricinoleic acid are absent. Although a conditional deletion of the EP₃ receptor gene in intestinal epithelial cells did not affect castor oil-induced diarrhea, mice lacking EP₃ receptors only in smooth-muscle cells were unresponsive to ricinoleic acid. Thus, the castor oil metabolite ricinoleic acid activates intestinal and uterine smooth-muscle cells via EP₃ prostanoid receptors. (Tunaru, 2012).

Several other studies have shown that relatively high concentrations (e.g., >2.5 g) of ricinoleic acid can cause ultrastructural alterations in the villous tips of the intestinal mucosa. Expression of EP₃ receptors has been reported in the intestine as well as in the uterus, the major sites of ricinoleic acid effects (Woodward et al., 2011; Sugimoto and Narumiya, 2007). In the mammalian intestine, EP₃ receptors have been shown to be expressed in epithelial cells, enteric ganglia cells, immune cells, as well as in longitudinal but not circular smooth-muscle layers. These laxative and inflammatory effects occur at dose levels far exceeding those levels of ricinoleic acid derived from hydrolysis of PGPR. By comparison, the intake of ricinoleic acid that result in laxative effects exceeds anticipated dietary intake of PGPR, a source of ricinoleic acid, by at least three orders of magnitude.

A mixture of ricinoleic acid (34%), methyl ricinoleate (48%), and Z,Z-octadecadienoic acid (14%) exhibit significant antioxidant activity with radical producing agents such as

hydrogen peroxide or 2,2'-diphenyl-1-picrylhydrazyl radical. Their antioxidant activity was approximately equivalent to that of butylated hydroxy anisole, Vitamin C, or alpha-tocopherol (G. Oleyede, 2012).

Database Search: Toxnet, PubMed, STN, NTP, HSBC DB, US ASTDR, OECD SIDS, HPVIS, RIFM, Agricola

Combinational Search Terms: castor oil, *Rinicus communis*, ricinoleic acid, methyl ricinoleate, toxicity, metabolism, genotoxicity, rodents, intestinal motility, gastrointestinal, mode of action, prostaglandin E receptor.

References

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- GRAS Notification, Stephan Company, Report 179. The safety of polyglycerol polyricinoleic acid emulsifier for use in margarine, low fat margarines, spreads, creamer, and dairy analogs. Received 07/19/2005; Closure 01/20/2006.
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SUBMISSION END

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