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April 8, 2011

Via Federal Express

Food and Drug Administration
Division of Animal Feeds (HFV-224)
Office of Surveillance and Compliance
Center for Veterinary Medicine
7519 Standish Place
Rockville, Maryland 20855

**Re: CVM GRAS Notification for Polyethylene Glycol (400) Dioleate;
Our File No. EM13458-01**

Dear Sir or Madam:

On behalf of our client, Emerald Carolina Chemicals, LLC (the Notifier), we hereby respectfully request to participate in the pilot program for Generally Recognized as Safe (GRAS) determinations¹ for the safe use of polyethylene glycol (400) dioleate (CAS Reg. No. 9005-07-6) as a component of the Notifier's FoamBlast[®] FMT defoamer, which is used as a processing aid in the production of distillers grains used in animal feed for food-producing animals. As discussed in detail in the enclosed dossier of information, the defoamer product is added to the condensed distillers solubles (*i.e.*, thin stillage concentrate) to assist in separating out corn oil during processing of grain from ethanol distillation. Accordingly, the polyethylene glycol (400) dioleate defoamer component may be present at minute levels as an impurity in distillers grains fed to the food-producing animals.

A submission is provided, in triplicate, for the polyethylene glycol (400) dioleate component of the defoamer. The submission includes a determination, based on scientific procedures, that polyethylene glycol (400) dioleate is GRAS based on its presence as an impurity in animal feed as a result of its use in the processing of distillers grains.

¹ See Substances Generally Recognized as Safe Added to Food for Animals; Notice of Pilot Program, 75 Fed. Reg. 31800 (June 4, 2010).

KELLER AND HECKMAN LLP

Food and Drug Administration

April 8, 2011

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We trust that this submission satisfies the Agency's needs, and will be deemed accepted and complete. Should any questions arise, please contact us, preferably by telephone or e-mail, so that we can promptly respond.



Sincerely,

Devon Wm. Hill

Enclosure

**Generally Recognized As Safe (GRAS)
Notification
for
Polyethylene Glycol (400) Dioleate
(CAS Reg. No. 9005-07-6)**

Prepared for:

US Food and Drug Administration
Center for Veterinary Medicine
Division of Animal Feeds (HFV-224)
7519 Standish Place
Rockville, MD 20855

Notifier:

Emerald Carolina Chemical, LLC
8309 Wilkinson Boulevard
Charlotte, NC 28214-9052

April 8, 2011

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I. Introduction

On behalf of Emerald Carolina Chemical, LLC (Emerald or the Notifier), Keller and Heckman LLP submits the enclosed dossier of information in support of this notification that polyethylene glycol (400) dioleate (CAS Reg. No. 9005-07-6), a component of the Notifier's FoamBlast® FMT defoamer, is Generally Recognized as Safe (GRAS) when present as an impurity in feed for the food-producing target animals, as a result of the defoamer's use as a processing aid in the production of dried and wet distillers grains (DG) with added solubles. More specifically, the 'whole' stillage produced during ethanol distillation is filtered by a mechanical centrifuge to remove water-soluble solids) to produce a 'thin stillage.' The 'thin stillage' is then condensed from 5-10% solids to up to 40% solids into 'condensed distillers solubles' (CDS), which contains corn syrup.

After the defoamer is added, the CDS is processed in a mechanical centrifuge to separate out the corn oil. CDS is a liquid byproduct that contains corn oil, as well as fermentation byproducts, spent yeast cells, and other nutrients which remain after corn grain has been fermented to produce ethanol. The Notifier's defoamer product is added to the CDS at levels up to 100 parts per million (ppm) to assist in separating the corn oil from the CDS. Polyethylene glycol (400) dioleate makes up 64% of the Notifier's defoamer; thus the substance is added at levels up to 64 ppm to the CDS. Once the corn oil has been separated from the CDS, the resulting "de-oiled" CDS is then added to dried and wet DG to produce either wet distillers grains with solubles (WDGS) or dried distillers grains with solubles (DDGS). The WDGS and DDGS may then be used as a component of animal feed and fed to food-producing animals in accordance with normal feeding practice. In addition, the separated corn oil may be used in the production of biodiesel fuel, or added back into certain grades of DG fed to food-producing animals as a source of fat.

The defoamer and its components, including the polyethylene glycol (400) dioleate, serve no technical purpose in the animal feed itself. Accordingly, the GRAS substance that is the subject of this notification is only present as a potential impurity in animal feed containing DG processed with the defoamer.

The determination of GRAS status is on the basis of scientific procedures, in accordance with 21 CFR § 170.30(b) and conforms to the guidance issued by the Food and Drug Administration (FDA) under *proposed* 21 CFR § 170.36, 62 Fed. Reg. 18938 (Apr. 17, 1997) and FDA's Notice of Pilot Program: Substances Generally Recognized as Safe Added to Food for Animals, 75 Fed. Reg. 31806 (June 4, 2010).

We submit information in the following areas:

- identity of the notified substance;
- intended conditions of use and technical effect;
- manufacturing specifications and stability certification;
- description of the ethanol production process and DDGS and WDGS manufacture method of the notified substance;
- toxicology summary;
- dietary exposure assessment for the food-producing target animal species;
- dietary exposure assessment for humans;
- estimation of daily intake for the notified substance; and
- GRAS determination for the notified substance, as a proposed conclusion determined by scientific procedures for use as a component of a processing aid (defoamer) in the production of DDGS and WDGS used in animal feed for food-producing target animals.

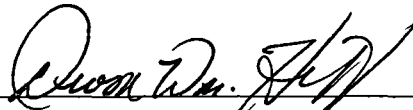
It is the Notifier's expectation that FDA will concur that the information presented in this notification fully supports the determination that polyethylene glycol (400) dioleate is GRAS when presented as an impurity in animal feed as a result of its use as a component of a processing aid (*i.e.*, the Notifier's defoamer product) in the production of WDGS and DDGS. This notification does not attempt to assess use in conjunction with DG as a component of food administered to companion or non-food producing animals.

II. Administrative Information

A. Claim Regarding GRAS Status

Polyethylene glycol (400) dioleate is GRAS, based on scientific procedures, when present as an impurity, at levels up to 64 ppm, in animal feed for the food-producing target animal species as a result of its use as an emulsifier in the production of wet and dried distillers grain with added solubles (WDGS and DDGS, respectively). The WDGS and DDGS may be used as components of animal feed for the food-producing target animals in accordance with normal feeding practice. Polyethylene glycol (400) dioleate serves no technical purpose in the animal feed itself. Accordingly, the GRAS substance that is the subject of this notification is only present as a potential impurity in the WDGS and DDGS due to its use in the processing of the CDS.

The use of polyethylene glycol (400) dioleate in this manner as a component of the Notifier's FoamBlast® FMT defoamer has been determined to be exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 301 *et. seq.*).



Devon Wm. Hill, Esq., Counsel for the Notifier

4-8-11

Date

B. Name and Address of the Notifier

Notifier	Acknowledgement of Receipt of Notification and Inquiries to be directed to:
Mr. Barry Ferguson Sales/Export Manager Emerald Carolina Chemical, LLC 8309 Wilkinson Boulevard Charlotte, NC 28214-9052 barry.ferguson@emeraldmaterials.com Office: 704-391-6419 Cell: 336-250-8533	Keller and Heckman LLP 1001 G Street N.W. Suite 500 West Washington, DC 20001 Mr. Devon Wm. Hill hill@khlaw.com Office: 202-434-4279 Fax: 202-434-4646

A letter authorizing Keller and Heckman to serve as agent for the Notifier is provided as **Appendix 1**.

C. Basis for GRAS Determination

This GRAS determination is based upon the publicly available scientific literature pertaining to the safety of the substance, and a dietary exposure assessment, as demonstrated herein. Furthermore, a current monograph for polyethylene glycol (400) dioleate is established by the Food Chemicals Codex (Fifth Edition), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

D. Availability of Information

Much of the data and information that are the basis for the GRAS determination are enclosed with the notification. The Notifier also will retain copies of all of the data and information that form the basis for the GRAS determination, which are available for FDA's review at reasonable times, and copies will be sent to FDA upon request. Requests for copies and arrangements for review of materials cited herein may be directed to:

Keller and Heckman LLP
1001 G Street, N.W.
Suite 500 West
Washington, DC 20001
ATTN: Devon Wm. Hill, Esq.
hill@khlaw.com
202-434-4279 (tel.)
202-434-4646 (fax)

III. Detailed Information about the Identity of the Notified Substance

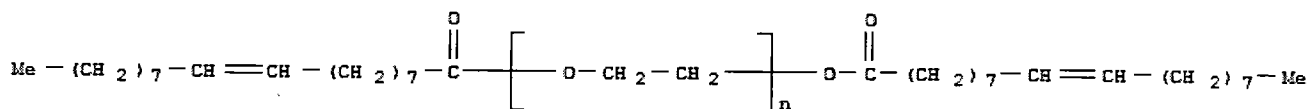
A. Names and Other Identities of the Notified Substance

Chemical Name: Polyethylene Glycol (400) Dioleate

CAS Reg. No.: 9005-07-6

IUPAC Nomenclature: ethane-1,2-diol; (Z)-octadec-9-enoic acid

Structural Formula for Polyethylene Glycol (400) Dioleate:



$\text{C}_{17}\text{H}_{33}\text{COO}(\text{CH}_2\text{CH}_2\text{O})_n\text{COC}_{17}\text{H}_{33}$, where n is equal to 10.

B. Common or Usual Name of the Notified Substance

- Polyethylene glycol (400) dioleate
- Synonym: Polyoxyethylene dioleate

C. Intended Conditions of Use and Technical Effect of the Notified Substance

Polyethylene glycol (400) dioleate will be used as a component (emulsifier constituent) of a processing aid (the Notifier's defoamer product) used in the production of WDGS and DDGS, respectively. As noted above, the defoamer is added to the CDS at levels up to 100 ppm; the polyethylene glycol (400) dioleate comprises 64% of the defoamer and thus is used at level of 64 ppm in the CDS. With respect to the intended technical effect, the defoamer is used as a chemical processing aid to assist in separating the corn oil from the CDS to produce "de-oiled" CDS¹, which is then added to the DDG and WDG to produce WDGS and DDGS, respectively. The WDGS and DDGS may then be used as components of animal feed for the food-producing target animals in accordance with normal feeding practice. The defoamer and its components, including the polyethylene glycol (400) dioleate, serve no technical purpose in the animal feed itself. Accordingly, the GRAS substance that is the subject of this notification is only present as a potential impurity in the WDGS and DDGS due to its use in the processing of the CDS.

¹ The CDS is put through a mechanical centrifuge to separate out the corn oil.

D. Manufacturing Specifications for the Notified Substance

(b) (4)



The Certificates of Analysis for each of the 5 lots are provided in **Appendix 2** and a Food-Grade Assurance Letter from the Notifier's supplier is provided in **Appendix 3**.

E. Stability Certification for the Notified Substance

The polyethylene glycol (400) dioleate used by the Notifier has been certified by the manufacturer as being stable for at least one year if properly stored. See **Appendix 4** for the Certification letter provided by the Notifier's supplier.

F. Manufacturing Method of the Notified Substance

(b) (4)



G. Detailed Description of Ethanol Distillation Process

Ethanol is distilled during the production of non-food grade and food grade ethanol. After distillation is performed to remove the ethanol from the fermentation mash, the remaining distillation residue, known as stillage (or whole stillage), is pumped from the bottom of the distilling column into centrifuges that separate the wet DG without solubles (WDG) from the stillage. The 'thin' stillage that remains after the WDG is removed from the whole stillage is a liquid that contains approximately 5-10% solids. The thin stillage is then routed to fermentation tanks as make-up water, or sent to an evaporation system, which concentrates the thin stillage into CDS (which contains up to 40% solids). CDS, or concentrated thin stillage (which is also known as corn syrup), is high in protein and fat, and contains corn oil as well as fermentation byproducts, spent yeast cells, and other nutrients.

The Notifier's FoamBlast® FMT defoamer is then added at levels up to 100 ppm to the CDS to assist in separating out the corn oil from the corn syrup. Polyethylene glycol (400) dioleate comprises 64% of the defoamer and thus is used at level of 64 ppm in the CDS. After the defoamer is added, the CDS enters a mechanical centrifuge that separates out the corn oil. The polyethylene glycol (400) dioleate is a component in a defoamer used as a chemical additive in the separation of corn oil from the CDS. Once the corn oil has been separated from the CDS and recovered, the resulting solubles-rich "de-oiled" CDS is then mixed back in with the wet DG (without solubles) and/or dried DG (without solubles), creating DDGS and WDGS, respectively. The separated corn oil may be used in the production of biodiesel fuel, sold into the industrial or specialty chemicals market, or added back into certain grades of DG and fed to food-producing animals as a source of fat.

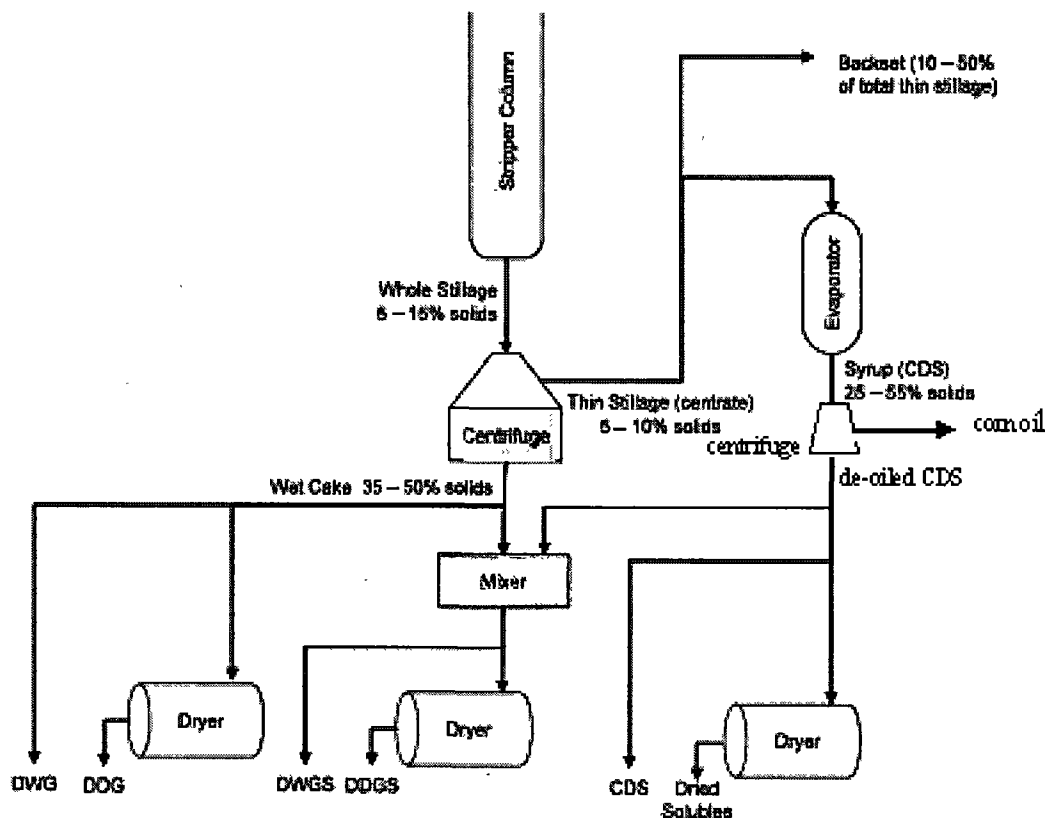
The DDGS and WDGS, which include the reintroduced solubles from the CDS syrup, may be used as a component of feed for food-producing animals in accordance with normal feeding practice.

This GRAS notification is for DG collectively, including at least four non-fermentable residue byproducts of ethanol fermentation including wet distillers grains without solubles

(WDG), dried distillers grains without solubles (DDG), CDS, WDGS and DDGS. (We include WDG and DDG in this notification although they do not *per se* include any de-oiled CDS because they may include re-added corn oil; our calculations will provide for dietary exposure from any polyethylene glycol (400) dioleate that may be present in the corn oil.) For this purpose, data are provided on DDGS to represent the “worst-case” for potential residues.² The reintroduction of the solubles into the grains (by adding the “de-oiled” CDS to the DDG or WDG) will bring any residual polyethylene glycol (400) dioleate that may be in the solubles into the DDGS or WDGS, while subsequent drying of the grains will concentrate any residual polyethylene glycol (400) dioleate in the DDGS or WDGS. Therefore, we consider as the “worst-case” that the residual polyethylene glycol (400) dioleate will be highest in DDGS. *See Figure 1* below.

² Although CDS can be sold separately as a feed supplement when it is used to control dust and condition dry feed ratios, because de-oiled CDS has a much lower fat content and thus cannot provide a sizeable boost in energy level to animal feed, we expect that all de-oiled CDS will be added back to the distillers grains to produce wet and dry distillers grains with solubles. Therefore, the use of DDGS will provide the maximum dietary exposure to the defoamer components.

Figure 1: Ethanol production process.³



H. Calculated Residual Levels in Distillers Grains

As discussed above, to assist in separating the corn oil from the CDS grains, the defoamer is added to the CDS at levels up to 100 ppm; the polyethylene glycol (400) dioleate comprises 60% of the defoamer and thus is used at level of 64 ppm in the CDS. To determine the “worst-case” residual level of the polyethylene glycol (400) dioleate present in the DDGS and WDGS, we conservatively assume that all of the Notifier’s defoamer product added to the CDS will remain in the de-oiled CDS (and thus, all of the polyethylene glycol (400) dioleate

³ Ethanol Coproducts for Ruminant Livestock Diets. Kenneth Kalscheur and Alvaro Garcia, Dairy Science Department, SDSU, Kurt Rosentrater, USDA - Agriculture Research Service and Cody Wright, Department of Animal and Range Science, SDSU. August 2008. See <http://www.thebeefsite.com/articles/1632/ethanol-coproducts-for-ruminant-livestock-diets>.

present in the defoamer remains in the corn oil-free CDS). This is a conservative assumption because polyethylene glycol (400) dioleate is both hydrophobic and hydrophilic in nature, and thus has no particular affinity for either the corn oil or the de-oiled CDS.⁴ Because CDS has a maximum fat content of 10%⁵, the maximum worst-case residual level of polyethylene glycol (400) dioleate in the de-oiled CDS is 71.1 ppm ($64 \text{ ppm} \div 0.90 = 71.1 \text{ ppm}$).

IV. Detailed Summary of the Basis for Notifier's GRAS Determination

a. Safety Evaluations and Toxicology Summary

i. General Uses and Toxicological Profile of Polyethylene Glycol Fatty Acid Esters

Polyethylene glycol 400 dioleate is a polyethylene glycol fatty acid ester that hydrolyzes to oleic acid and polyethylene glycol on ingestion. The fatty acid ester structure is that of a mono- or diester of polyethylene glycol with certain monobasic carboxylic acids (common dietary fatty acids), with carbon chains that are even-numbered and range from eight to 22 carbons. The physical and chemical characteristics of PEG fatty acids are dependent upon their chemical structure, with their surfactant properties being based on the hydrophilic polyethylene glycol and the hydrophobic fatty acid ester portions of the molecule. Differences in the degree

⁴ This conservative assumption also ensures that all potential sources of dietary exposure to the polyethylene glycol (400) dioleate are covered because, as noted above, the corn oil recovered from the CDS may, in some cases, be used as a component of animal feed (fat source) for food-producing animals.

⁵ CDS typically has a dry matter content of 25-30%, and a fat content (on a dry matter basis) of 20% (Using Distillers Grains in the U.S. and International Livestock and Poultry Industries, B.A Babcock, D.J. Haynes, and J.D. Lawrence eds, The Midwest Agribusiness Trade Research and Information Center, 2008, *see* http://www.card.iastate.edu/books/distillers_grains). In some cases, CDS can have dry matter content as high as 45% (*see* <http://beef.osu.edu/bee/beefAgst29.html>); in that situation, the fat content can be as high as $20\% \times 45\% = 9\%$ in the CDS. We therefore conservatively assume that the entire 10% fat content in the CDS is attributable to the corn oil.

of ethoxylation, the length of the polyethylene glycol moiety, and the carbon chain length of the fatty acid moiety provide for a range of surfactant properties.

Polyethylene glycols (PEGs) are widely in use both in foods and drugs and were evaluated by JECFA in 1987.⁶ The average molecular weights of these polyethylene compounds varied from 200 (PEG 200) to 10,000 (PEG 10,000). The papers cited by JECFA in its evaluation were mostly published in the 1940s and 1950s. Several PEG fatty acids are used as components of cosmetics and pharmaceuticals and have been cleared by the U.S. Food and Drug Administration (FDA) for use as direct or indirect food additives. These products are used in cosmetics, such as bath oils, cleansing preparations, moisturizers, other skin care preparations, shampoos, and suntan/sun block preparations, such as surfactants, emulsifiers, and solvents/cosolvents in concentrations typically in the range from 0.1% to 10% but with some products containing up to 25%.⁷

The principal source of referenced hazard information on PEG fatty acid esters is contained in the Surfactants Task Force (STF) assessment report on various PEG fatty acid esters and related substances published by the Cosmetic Ingredient Review (CIR) Expert Panel.⁸ Additionally, the STF assessment references the fact that PEG fatty acid esters are readily hydrolyzed to their respective fatty acid and polyethylene glycol moieties in the gastrointestinal tract; noting that fatty acids have previously been reassessed by the Agency and provide hazard information on polyethylene glycol.⁹

⁶ WHO. 1987. Evaluation of certain food additives and contaminants. 31st Report of the Joint FAO/WHO Expert Committee on Food Additives.
http://whqlibdoc.who.int/trs/WHO_TRS_759.pdf

⁷ Cosmetic Ingredient Review. 2000. Final Report on the Safety Assessment of PEG-2, -4, -6, -8, -12, -20, -32, -75 and -150 Dilaurate; PEG -2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150 and -200 Laurate; and PEG-2 Laurate SE, *Int. J. Toxicol.*, 19, suppl 2, 29-41.

⁸ U.S. Environmental Protection Agency. 2005. Action Memorandum-Inert Reassessment-PEG Fatty Acid Esters.

⁹ *Id.*

Based upon the referenced hazard information included in the STF assessment and other available data, PEG fatty acid esters are low toxicity chemicals. In animal studies, effects were only seen at limit dose levels which are far greater than exposures resulting from their use as other industrial products. Various referenced acute oral toxicity studies on PEG fatty acid esters in the STF assessment indicate that PEG fatty acid esters are of low acute oral and dermal toxicity and are not eye or skin irritants or dermal sensitizers. The referenced acute oral toxicity studies reported LD₅₀ values of greater than 10,000 mg/kg, making them very low toxicity chemicals.

The STF assessment referenced a number of subchronic oral toxicity studies in rats and hamsters with PEG fatty acid esters in which effects were seen only at doses exceeding limit dose levels (greater than 5% of the diet). While some local effects at the site of application were noted in a subchronic rabbit dermal toxicity study, such effects have not been reported in association with the use of PEG fatty acid esters in dermally applied cosmetics.

The STF assessment referenced a number of chronic oral toxicity studies in which no effects were seen at dose levels up to 4% PEG fatty acid esters in the diet. Hepatic cysts and cecal enlargement were observed in a two-year oral rat study and only at the two highest dose levels of 10% and 25% in the diet. No additional chronic toxicity data were presented in the STF assessment.

No studies on neurotoxicity, mutagenicity or carcinogenicity were identified in the STF assessment. Based on the structure activity relationship analysis of PEG fatty acid esters did not identify any concerns for either neurotoxicity, mutagenicity or carcinogenicity.

Taking into consideration all available information on PEG fatty acid esters as a whole, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to PEG fatty acid esters used as inert ingredients, when considering dietary exposure and all other non-occupational sources of exposure.

ii. Polyethylene (PEG) 400 Dioleate

There is no publicly available toxicology data on polyethylene glycol (400) dioleate, per se. However, because the carbon chain length (C₁₈) of the oleate moiety and the stearate moiety

are identical (with the exception of the presence of an unsaturated bond in the oleate moiety), their toxicological properties are expected to be substantially identical. Thus, results of toxicological testing on polyethylene glycol (400) distearate can be applied to the toxicology profile for polyethylene glycol (400) dioleate. In *Federal Register* Notice 62 Fed. Reg. at 18943 (April 17, 1997), FDA clearly indicated that substantial equivalence is a valid basis for making a GRAS determination. Therefore, based on the substantial similarities between PEG stearate and PEG 400 dioleate, the toxicological properties of both these compounds will also be similar and that the intended use of each is GRAS. The toxicological profile of polyethylene glycol stearates as a surrogate for polyethylene glycol 400 dioleate is described in greater detail below.

1. Polyethylene Glycol Stearate

Ethoxylated stearates are mixtures of mono- and distearate esters of mixed macrogols (polyoxyethylene polymers) and corresponding free glycols. The general formula for the compounds is $C_{17}H_{35}COO.(O.CH_2CH_2)_n.COOC_{17}H_{35}$. The average length or the molecular weight of the ethoxy polymer chain is often indicated in the name of the specific substance, *e.g.*, the molecular weight of the $(OCH_2CH_2)_n$ polymer group in polyethylene glycol (400) dioleate is 400 Daltons, and as the molecular weight of the OCH_2CH_2 unit is 40 Daltons, there are approximately 10 ethylene oxide units in the ethoxy polymer chain.

In 1973, the JECFA established an ADI of 25 mg/kg for the compounds polyethylene glycol-8-stearate and polyethylene glycol-40-stearate.¹⁰

2. Absorption, Distribution, Metabolism, and Excretion

No data on metabolism and pharmacokinetics of polyethylene glycol (15) hydroxystearate and polyethylene glycol stearates is available.¹¹ However, based on the STF

¹⁰ EMEA. 2003. Committee for Veterinary Medicinal Products. Polyethylene Glycol Stearates and Polyethylene Glycol 15 Hydroxystearate. <http://www.emea.europa.eu/pdfs/vet/mrls/039298en.pdf>

¹¹ *Id.*

assessment, PEG fatty acid esters are hydrolyzed to their respective fatty acids and polyethylene glycol moieties in the gastrointestinal (GI) tract. The resultant fatty acids are common components of a wide variety of foods, are readily absorbed, and are primary components of lipid metabolism. The STF assessment also includes references stating that polyethylene glycols are poorly absorbed from the GI tract, with absorption decreasing as the molecular weight increases, and the absorbed polyethylene glycols generally being excreted, unmetabolized, in the urine and feces.¹²

No residue depletion studies are being carried out with polyethylene glycol (15) stearate and polyethylene glycol stearates. However, taking into account the poor GI absorption of polyethylene glycol stearates and polyethylene glycol (15) hydroxy stearates, as well as their low oral toxicity, it may be concluded that they are unlikely to result in residues in food products of animal origin at concentrations of toxicological relevance to the consumer.

3. Acute Studies

a. Oral Studies

A number of acute oral toxicity studies have been conducted on polyethylene glycol stearates. The oral LD₅₀ values in these studies were reported to be more than 10,000 mg/kg.^{13,14,15,16} The specific polyethylene glycol stearates utilized in these studies were those

¹² U.S. Environmental Protection Agency. 2005. Action Memorandum-Inert Reassessment-PEG Fatty Acid Esters.

¹³ Cosmetic Ingredient Review. 2000. Final Report on the Safety Assessment of PEG-2, -4, -6, -8, -12, -20, -32, -75 and -150 Dilaurate; PEG -2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150 and -200 Laurate; and PEG-2 Laurate SE, *Int. J. Toxicol.*, 19, suppl 2, 29-41.

¹⁴ Cosmetic Ingredient Review. 2000. Final Report on the Safety Assessment of PEG-25 Propylene Glycol Stearate, PEG-75 Propylene Glycol Stearate, PEG-120 Propylene Glycol Stearate, PEG-10 Propylene Glycol, PEG-8 Propylene Glycol Cocoate, and PEG- 55 Propylene Glycol Oleate, *Int. J. Toxicol.*, 19, suppl 4, 13-26.

¹⁵ Elder RL, ed., Final Report on the Safety Assessment of Propylene Glycol Stearate and Propylene Glycol Stearate Self-Emulsifying, *J. Am. Coll. Toxicol.*, 2, (1983) 101-124.

with 2, 8, 12, 20, 40, 50, 100 and 150 moles of ethylene oxide. Harris, *et al.* reported a study on rats in which certain PEG fatty acids at very high dietary dosage rates produced toxic effects. In that study, rats were fed a diet containing 25% polyethylene glycol stearates, along with other polyethylene glycol fatty acids, for 59 days. The group of rats fed polyethylene glycol stearate showed a mild decrease in weight gain compared to the control group. The extreme dietary dosage of polyethylene glycol fatty acids in this study contributed to the development of toxic effects in other groups, excluding polyethylene glycol stearate.¹⁷

In Elder, *et al.*, a diet of 5% or 15% polyethylene glycol monostearates was fed for 2-10 weeks. The treatment resulted in the development of lesions in the GI tract, liver, kidneys and testis. Yet no signs of toxicity were noted in rats fed a diet of up to 4% polyethylene glycol stearate.¹⁸

Anderson reported a 90-day study on free polyethylene glycol in rats that produced no toxic symptoms of polyethylene glycol at doses at or below 4% in the diet or in drinking water.¹⁹

The European Committee of Veterinary Medicinal Products reports the oral LD₅₀ of polyethylene glycol 12-hydroxystearate (12 moles of ethylene oxide, which signifies average number of moles of monomer in the polyethylene moiety) in mice as more than 20,000 mg/kg.²⁰ The oral LD₅₀ of PEG 12-hydroxystearate (8 mol EtO) in rats was reported to be 250 mg/kg b.wt.

¹⁶ Anderson FA, ed., Final Report on the Safety Assessment of PEG -2, -3, -4, -6, -8, -9, -12, -20, -32, -75, -120, -150, and -175 Distearate, *Int. J. Toxicol.*, 18 (1999) 51-59.

¹⁷ Harris RS, Sherman H, Jetter WW. 1951. Nutritional and pathological effects of sorbitan monolaurate, polyoxyethylene sorbitan monolaurate, polyoxyethylene monolaurate, and polyoxyethylene monostearate when fed to rats. *Arch Biochem.* 34(2):249-58.

¹⁸ Elder RL, ed., Final Report on the Safety Assessment of Propylene Glycol Stearate and Propylene Glycol Stearate Self-Emulsifying, *J. Am. Coll. Toxicol.*, 2, (1983) 101-124.

¹⁹ Anderson FA, ed., Final Report on the Safety Assessment of PEG -2, -3, -4, -6, -8, -9, -12, -20, -32, -75, -120, -150, and -175 Distearate, *Int. J. Toxicol.*, 18 (1999) 51-59.

²⁰ Committee for Veterinary Medicinal Products, Polyethylene Glycol Stearates and Polyethylene Glycol 15 Hydroxystearate Summary Report, EMEA/MRL/392/98-Ginal-Rev, 1 (2003). [Cosmetic Ingredient Review] URL: www.emea.eu.int/pdfs/vet/mrls/039298en.pdf.

No details on the conditions of the study were provided and consequently, its reliability is uncertain. Therefore, when compared to the acute oral toxicity results of each of the other studies reviewed, the results obtained on this hydroxylated fatty acid compound does not appear to be representative of the general class of PEG stearate fatty acids.

b. Mutagenicity

Mutagenicity studies with PEG distearates (PEG-8) were negative in the Chinese hamster ovary cell mutation test and the SCE test. At concentrations up to 150 g/L, PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay. Stearic acid was not mutagenic in the Ames test. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to rodents. A low incidence of carcinomas, sarcomas, and lymphomas was evident in mice receiving multiple subcutaneous injections of steric acid.²¹

c. Intraperitoneal (IP) and Intravenous (IV)

PEG monostearate (8 mol RtO) was the subject of one study using the IP exposure route. In this study, the IP LD₅₀ was found to be more than 9ml/kg in rats given 2 ml injections. In addition, the National Institute of Occupation Safety and Health (NIOSH) reported a study on mice which resulted in a IP LD₅₀ of more than 200 mg/kg. No details were available on the latter study. These studies indicated that PEG fatty acids present a low hazard level for lethality by the IP route.²²

Four reports of acute toxicity via the IV route in mice were also reported.²³ These reports indicated an IV LD₅₀ for PEG distearate (8 and 20 mol EtO) to be 365 mg/kg and 220 mg/kg respectively.^{24, 25}

²¹ Claudia Fruijtier-Pölloth. 2005. Safety assessment on polyethylene glycols (PEGs) and their derivatives as used in cosmetic products. *Toxicology*, 214, (1-2), 1-38.

²² U.S. Environmental Protection Agency. 2005. Action Memorandum-Inert Reassessment-PEG Fatty Acid Esters.

²³ *Id.*

4. Chronic Studies

a. Oral Studies

Elder reported a study on rats fed a diet of 4% PEG stearate (8 mol EtO) or 2% PEG stearate (100 mol EtO) for two years. The study did not demonstrate any treatment-related symptoms. In the same review, Elder also reported a study on hamsters fed 5% to 15% PEG monostearate for 28-39 weeks in which numerous symptoms were reported, including increased mortality, chronic diarrhea, atrophic testis, and hemosiderosis.²⁶

Anderson, *et al.* (1999) evaluated chronic effects of free PEG in dogs. In this study, dogs were fed PEG (8, 32, or 75 mol EtO) for one year. The results of this study indicated no observed toxic effects in dogs.²⁷

b. Reproductive and Developmental Effects

In a multi-generational study, rats were fed a diet of 10% to 20% PEG stearate (8 or 20 mol EtO). The result of this study exhibited decreased newborn litter survival time due to maternal neglect, impairment of lactation, lower weaning weight, increased mortality of nurslings, and decreased reproductive performance in the F3 generation. Rats fed 5% PEG stearate exhibited none of these effects.²⁸

²⁴ Cosmetic Ingredient Review. 2000. Final Report on the Safety Assessment of PEG-2, -4, -6, -8, -12, -20, -32, -75 and -150 Dilaurate; PEG -2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150 and -200 Laurate; and PEG-2 Laurate SE, *Int. J. Toxicol.*, 19, suppl 2, 29-41.

²⁵ Hopper SS, Hulpieu HR and Cole VV. 1949. Some toxicological properties of surface active agents, *J. Amer. Pharm. Assn.* 38, 428-432.

²⁶ Elder RL, ed., Final Report on the Safety Assessment of Propylene Glycol Stearate and Propylene Glycol Stearate Self-Emulsifying, *J. Am. Coll. Toxicol.*, 2, (1983) 101-124.

²⁷ Anderson FA, ed., Final Report on the Safety Assessment of PEG -2, -3, -4, -6, -8, -9, -12, -20, -32, -75, -120, -150, and -175 Distearate, *Int. J. Toxicol.*, 18 (1999) 51-59.

²⁸ Elder RL, ed., Final Report on the Safety Assessment of Propylene Glycol Stearate and Propylene Glycol Stearate Self-Emulsifying, *J. Am. Coll. Toxicol.*, 2, (1983) 101-124.

Another reproductive study on free PEG (6, 32 and 75 mol EtO) in which no adverse reproductive effects were exhibited in either a chronic (2 year) at doses up to 0.62 g/kg/day for PEG (6 and 32 mol EtO) and 1.69 g/kg/day for PEG (75 mol EtO) or a subchronic study at doses up to 0.23 g/kg/day (75 mol EtO).²⁹

c. Summary of Toxicological Effects

Based on the available data in the public domain, the acute toxicity of this class of compounds is low. The only subchronic and chronic duration studies which show significant systemic effects are those in which the dietary dose was in excess of five percent of the total diet. Similar results were also obtained by US EPA in its review of the glycerol esters of fatty acids.³⁰ The Joint FAO/WHO Expert Committee on Food Additives has recognized five percent in the diet (2500 mg/kg/day) as the NOAEL for PEG stearates (8 and 40 mol EtO) and has set an allowable daily intake (ADI) of 25 mg/kg/day using the standard 100X safety factor.³¹

The above toxicology studies have demonstrated that polyoxyethylene fatty acids in general are hydrolyzed to their respective fatty acids and polyethylene glycol moieties in the gastrointestinal tract. Any unhydrolyzed polyoxyethylene fatty acids will be passed, unabsorbed, through the intestinal tract. The resultant fatty acids from hydrolysis are common components of a wide variety of foods, are readily absorbed, and are primary components of lipid metabolism. Polyethylene glycols are poorly absorbed from the gastrointestinal tract, with absorption decreasing as the molecular weight increases, and the absorbed polyethylene glycols generally

²⁹ Anderson FA, ed., Final Report on the Safety Assessment of PEG -2, -3, -4, -6, -8, -9, -12, -20, -32, -75, -120, -150, and -175 Distearate, *Int. J. Toxicol.*, 18 (1999) 51-59.

³⁰ Cosmetic Ingredient Review. 2000. Final Report on the Safety Assessment of PEG-25 Propylene Glycol Stearate, PEG-75 Propylene Glycol Stearate, PEG-120 Propylene Glycol Stearate, PEG-10 Propylene Glycol, PEG-8 Propylene Glycol Cocoate, and PEG- 55 Propylene Glycol Oleate, *Int. J. Toxicol.*, 19, suppl 4, 13-26.

³¹ JECFA. 1974. Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives, World Health Organization Technical Report Series 1974, No. 539; FAO Nutrition Meetings Report Series 1974, No. 53. See: www.inchem.org/documents/jecfa/jecmono/v05je48.htm

are excreted unmetabolized in the urine and feces. Additionally, polyethylene glycol is not affected by the action of intestinal microorganisms. It is recovered quantitatively unchanged from the feces.

V. Correlation of Data to Target Animal Species

Although the animal species tested were predominantly mice, rats, and dogs, and the target species are livestock animals consisting of both poultry and ruminants, we believe the toxicology data presented above is equally applicable to the target animal species. When consumed, the polyethylene glycol (400) dioleate will be hydrolyzed (in the digestive tract of both the animals tested and the target animals) to oleic acid and polyethylene glycol (with a molecular weight of 400). The oleic acid will be readily absorbed and metabolized by both types of animals as a fatty acid. The polyethylene glycol will not be absorbed, but will pass through both types of animals' digestive tracts; any trace amounts of polyethylene glycol absorbed through the intestinal tract will be eliminated from the body (in unmetabolized form) in the urine. Any unhydrolyzed polyethylene glycol (400) dioleate will not be absorbed into the bodies of either type of animal, and will readily pass through their digestive tracts. As polyethylene glycol is not affected by the action of microorganisms that may be present in ruminal fluids of certain target animals, we expect that there will be no breakdown of the polyethylene components when consumed by ruminants. Thus, the ADI of 25 mg/kg/day presented above is equally applicable to all target animals.³²

³² Report of the Scientific Committee for Animal Nutrition on the Use of Polyethylene Glycol 6000 and of a Polyoxypropylene-polyoxyethylene polymer in Feeding Stuffs, January 15, 1980, see http://ec.europa.eu/food/fs/sc/oldcomm6/other/21_en.pdf.

VI. Dietary Exposure Assessment for Target Animals

As discussed above, the Notifier intends to use the defoamer at a maximum use level of 100 ppm in the CDS; the polyethylene glycol (400) dioleate comprises 64% of the defoamer and thus is used at level of 64 ppm in the CDS.³³ Once the defoamer has been added to the CDS, and the corn-oil separated out, the de-oiled CDS is then added to either dried DG to create DDGS or wet DG to create WDGS, which can then be used as components of animal feed for the food-producing target animals. As indicated above, the worst-case residual level of the polyethylene glycol (400) dioleate in the de-oiled CDS is approximately 71.1 ppm, conservatively assuming the entire 10% fat content in CDS is attributable to the removed corn oil. Once de-oiled, CDS syrup is then incorporated into the DG at a maximum level of 25% by weight on a solids basis³⁴; the resulting solubles-enriched DG product (either as WDGS or DDGS) is typically added to animal feed at a maximum level of 30% on a solids basis³⁵. Although the corn-oil free CDS can be sold separately as a feed supplement when it is used to control dust and condition dry feed

³³ (100 ppm)(0.60) = 60 ppm.

³⁴ Whole stillage with an 85-90% water content (10%-15% solids) is separated into a wet DG stream with a water content of 65-70% (*i.e.*, 30-35% solids) and a thin stillage stream with a water content of 90-95% (*i.e.*, 5 -10% solids). The thin stillage stream is condensed in an evaporator into CDS with a water content of 60% (*i.e.*, 40% solids). While the water and solids contents noted above vary depending on the production plant and processing techniques, and although a portion of the thin stillage is recycled back to the fermentation vessel, we can use the approximate water and solid contents to conservatively determine the maximum amount of CDS solids that are added to wet or dry DG to make WDGS or DDGS, respectively. In this regard, we note that a whole stillage stream with 1 kg of DG contains approximately 7.3 kg of water. The whole stillage stream is then separated into wet DG with a maximum solids content of 35% (which we assume contains the bulk of the 1kg of DG), and into a thin stillage stream with a solids content of about 5% (consisting of 5.5 kg of water and 0.33 kg of solids). The thin stillage is then condensed to 40% solids, but still contains 0.33 kg of solids which is then added back to the 1 kg of solids in the wet DG prior to drying. Therefore, the “addition rate” of the CDS to DG is 0.33/1.33 kg or 25% on a solids basis. In an actual process, the ratio of solids in the condensed thin stillage stream is expected to be much less than 25%, so this provides a worst-case addition of CDS containing polyethylene glycol (400) dioleate to the DDGS.

³⁵ “Using Distillers Grains in the U.S. and International Livestock and Poultry Industries,” B.A. Babcock, D.J. Haynes, and J.D. Lawrence eds, The Midwest Agribusiness Trade Research and Information Center, 2008, *see* http://www.card.iastate.edu/books/distillers_grains.

ratios, because of its much lower fat content, the de-oiled CDS cannot provide a sizeable boost in energy level when added directly into animal feed. Accordingly, we expect that all de-oiled CDS will be added back to the DG to produce WDGS and DDGS. Therefore, the use of DDGS will provide the maximum dietary exposure to the defoamer components.

De-oiled CDS typically has a solids content of 40%; with a polyethylene (400) dioleate concentration of 71.1 ppm. Polyethylene glycol (400) dioleate therefore has a concentration of 178 ppm based on CDS solids.³⁶

Because the de-oiled CDS is added to the DG at 25% on a solids basis, the maximum potential concentration of polyethylene glycol (400) dioleate in animal feed is: $178 \text{ ppm} \times 0.25 = 45 \text{ ppm}$ on a solids basis.

Distiller's grains are typically fed as a portion of daily feed to target animals such as cattle, dairy cows, sheep, swine, turkeys, and broiler chickens. The recommended daily feed diets for cattle, dairy cows, sheep, turkeys and swine include up to 30% distillers grains on a dry weight basis. The daily feed intake of broiler chickens may include up to 15% by weight dry distillers grains.³⁷

The Distillers Grain Technology Council has stated that DG can be used in daily feed for the food-producing target animals as presented in Table 1 below.³⁸ Weights and intakes of feed are nominal, meaning that they are representative of populations of animals generally, and may not be specific to particular categories of food-producing animals raised under specific conditions.³⁹ The quantity of food consumed per day per animal may not be representative of

³⁶ $71.1 \text{ ppm} \div 0.40 = 178 \text{ ppm}$.

³⁷ Using Distillers Grains in the U.S. and International Livestock and Poultry Industries, *see* http://www.matric.iastate.edu/DGbook/distillers_grain_book.pdf.

³⁸ Distillers Grains Technology Council, University of Louisville, Lutz Hall Room 435, Louisville, Kentucky 40292: www.distillersgrains.org.

³⁹ SAX'S Dangerous Properties of Industrial Materials. Ninth Edition (1996). Table 2. Van Nostrand Reinhold Company. New York.

food intakes for a specific period of time during growth, but rather reflect an average that approximates intakes over an expected lifetime.

TABLE 1. Feeding Data for Food-Producing Target Animals

Target Animal Species	Weight (kg)	Food Consumed (g/day)	Distillers Grains (dry weight basis) Consumed per Day		
			(%)	(g/day)	g/kg bw/day
Beef Cattle	500	10,000	30%	3,000	6
Dairy Cattle	500	10,000	30%	3,000	6
Poultry ⁴⁰ (broiler)	2.5	232.5	15%	34.9	14
Sheep	60	2,400	30%	720	12
Swine	60	2,400	30%	720	12

The amount of distillers grains consumed on a dry basis for each animal is calculated as follows for cattle:

$$(10,000 \text{ g-food}/500 \text{ kg bw}) \times (0.3 \text{ g-distillers grains/g-food}) \\ = 6 \text{ g-distillers grains/kg bw}$$

The maximum distillers grains consumed by beef cattle, on a dry weight basis, is 6 g/kg bw/day. With a maximum residual level of 45 mg/kg of polyethylene glycol (400) dioleate in distiller's grains on a dry weight basis, a maximum dietary intake for beef cattle is calculated as follows:

$$6 \text{ g-distillers grain/kg bw} \times (45 \text{ mg-PEGDO/kg-distillers grains}) \times (\text{kg}/1000 \text{ g}) \\ = 0.27 \text{ mg PEGDO/kg bw/day}$$

The dietary intake of polyethylene glycol (400) dioleate by other food-producing target animals is similarly calculated and presented in the table below:

⁴⁰ The feed consumption for broiler chickens is reported to be 93 mg/kg bw/day – Predicting Feed Intake of Food-Producing Animals, Subcommittee on Feed Intake, Committee on Animal Nutrition, Board on Agriculture, National Research Council, National Academy Press, Washington, D.C., 1987.

TABLE 2. EDIs for Target animals

Target Animal Species	EDI (mg/kg-bw/day) for Polyethylene Glycol (400) Dioleate
Beef Cattle	0.27
Dairy Cattle	0.27
Poultry (Broiler)	0.63 ⁴¹
Sheep	0.5 ⁴²
Swine	0.5 ⁴³

Poultry consume the highest amount of DG per body weight per day among all the food-producing target animals, thus providing a worst-case dietary intake of 0.59 mg/kg bw/day for polyethylene glycol 400 dioleate for all food-producing target animals. As shown above, a very conservative ADI of 25 mg/kg-bw/day has been established for polyethylene glycol (400) dioleate for the target animals. Accordingly, we conclude that the residual polyethylene glycol (400) dioleate that may be present in the animal feed as an impurity, as a result of the use of polyethylene glycol (400) dioleate in the Notifier's defoamer, as described above, is safe for the target animals.

⁴¹ 14 g-distillers grain/kg bw x (45 mg-PEGDO/kg-distillers grains) x (kg/1000 g) = 0.63 mg PEGDO/kg bw/day.

⁴² 12 g-distillers grain/kg bw x (45 mg-PEGDO/kg-distillers grains) x (kg/1000 g) = 0.5 mg PEGDO/kg bw/day.

⁴³ 12 g-distillers grain/kg bw x (45 mg-PEGDO/kg-distillers grains) x (kg/1000 g) = 0.5 mg PEGDO/kg bw/day

VII. Dietary Exposure Assessment for Humans of Polyethylene Glycol (400) Dioleate

Table 3. EDI Summary for Polyethylene Glycol (400) Dioleate

Dietary Exposure	EDI (mg/kg bw/day)
Animal Dietary Exposure to Polyethylene Glycol (400) Dioleate	0.63 mg/kg bw/day
Human Dietary Exposure to Polyethylene Glycol (400) Dioleate	0.02 mg/kg bw/day

As described above, PEG fatty acid esters are rapidly hydrolyzed to their respective fatty acid and polyethylene glycol moieties upon ingestion. Fatty acids are naturally present in a wide variety of foods, are naturally present in the body, and are readily absorbed and metabolized. The polyethylene glycol moieties, on the other hand, are not well-absorbed by the body and do not become a component of the animal products intended for consumption. Further, any absorbed polyethylene glycol moieties have generally been shown to be excreted in the urine and feces in unmetabolized form. Since PEG fatty acid esters do not remain PEG fatty acid esters *per se* upon ingestion by the animal, there is no potential exposure to PEG fatty acid esters (*e.g.*, polyethylene glycol (400) dioleate) based on the consumption of any component of the animal, which include but are not limited to meat (*e.g.*, muscle and organ tissue), eggs and milk.

As there is no expectation of accumulation of polyethylene glycol (400) dioleate in the tissues of the food-producing target animals, there is little likelihood of any significant human exposure as a result of consuming food products derived from the target animals. Nevertheless, for the sake of conservatism, we will assume, as worst-case, that at slaughter, polyethylene glycol (400) dioleate may be present in the edible portions of the carcass at levels equal to the

amount of the compound consumed on that day.⁴⁴ We will also conservatively assume that the compound is equally distributed throughout the carcass and in any milk or eggs that may be produced by the target animals.

To determine the dietary intake of polyethylene glycol (400) dioleate by the consumption of edible parts of a species of target animals, FDA assigns consumption values for different edible products of each species, based on the relative amount of each organ or tissue that is consumed by individuals.⁴⁵ Specifically, according to FDA's Guidance for Industry: *General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals*, FDA assumes that these consumption values (*i.e.*, grams consumed per person per day) are applied to all species of the target animals, as it is assumed that when an individual consumes a full portion⁴⁶ of a meat product from one species, that individual will not also consume a full portion of a meat product from another species. Additionally, FDA assumes that on a daily basis an individual consumes a full portion of milk in addition to a full portion of eggs⁴⁷ in addition to the full portion of edible muscle and organ tissue (from one animal species). These values are used to determine the exposure of polyethylene glycol (400) dioleate, based on the level of polyethylene glycol (400) dioleate in each edible portion of the target animal. The consumption values and the polyethylene glycol (400) dioleate levels are summarized in the table below, based on the assumptions that (1) the maximum daily intake of polyethylene glycol (400)

⁴⁴ This is a conservative assumption in that the polyethylene glycol (400) dioleate is not readily absorbed through the intestinal tract and any fatty acids and polyoxyethylene components that may be absorbed are readily metabolized or directly excreted, respectively and not stored in animal tissues and organs. As the majority of the polyethylene glycol (400) dioleate will pass directly through the digestive system, this clearly provides a worst-case for human dietary exposure.

⁴⁵ See *FDA's Guidance for Industry: General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals*; <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052180.pdf>.

⁴⁶ According to FDA's guidance on *General Principles for Evaluating the Safety of Compounds used in Food-Producing Animals*, a full portion of meat consists of 300 g of muscle tissue, 100 g of liver, 50 g of kidney, and 50 g of fat.

⁴⁷ According to FDA, the estimated daily intake is 1.5 liters for milk and 100 grams for eggs.

dioleate of 0.59 mg/kg bw/day is evenly distributed throughout the muscle tissues, organs, milk, and eggs of the food-producing target animals and (2) the polyethylene glycol (400) dioleate is metabolized on a daily basis:

TABLE 4. Consumption Values for Polyethylene Glycol (400) Dioleate

Edible Product	Consumption (g food/day)	Polyethylene Glycol (400) Dioleate Level (µg/g tissue)
Muscle	300 g	0.63
Liver	100 g	0.63
Kidney	50 g	0.63
Fat	50 g	0.63
Milk	1.5 L	0.63
Eggs	100 g	0.63

To estimate the dietary exposure of polyethylene glycol (400) dioleate, the Notifier considered each edible portion of cattle. In addition, based on FDA's assumptions discussed above, the Notifier assumed that a full portion of milk and eggs are consumed in addition to a full portion of edible muscle or organ tissues. Based on this, the Notifier calculated the relative level of polyethylene glycol (400) dioleate in each edible product to obtain, in essence, a dietary exposure for individual human consumers. The exposures due to milk and eggs, as well as the sum of all the exposure values (to obtain a cumulative dietary exposure level) are calculated as follows:

Muscle:

$$(0.63 \mu\text{g PEGDO} / 1 \text{ g muscle}) \times (300 \text{ g muscle/person/day}) \\ = 189 \text{ PEGDO/person/day}$$

Liver:

$$(0.63 \mu\text{g PEGDO} / 1 \text{ g liver}) \times (100 \text{ g liver/person/day}) \\ = 63 \mu\text{g PEGDO/person/day}$$

Kidney:

$$(0.63 \mu\text{g PEGDO} / 1 \text{ g kidney}) \times (50 \text{ g kidney/person/day}) \\ = 32 \mu\text{g PEGDO/person/day}$$

Fat:

$$(0.63 \mu\text{g PEGDO} / 1 \text{ g fat}) \times (50 \text{ g fat/person/day}) \\ = 32 \mu\text{g PEGDO/person/day}$$

The total dietary exposure to polyethylene glycol (400) dioleate for a individual consumer not consuming eggs and milk is calculated as follows:

$$189 \mu\text{g PEGDO/person/day (muscle)} + 63 \mu\text{g PEGDO/person/day (liver)} + 32 \mu\text{g} \\ \text{PEGDO/person/day (kidney)} + 32 \mu\text{g PEGDO/person/day (fat)} \\ = 316 \mu\text{g PEGDO/person/day}$$

The dietary exposure to polyethylene glycol (400) dioleate for a individual consumer who does consume eggs and milk is calculated as follows:

Milk:

$$(0.63 \text{ mg PEGDO} / 1.0 \text{ L milk}) \times (1.5 \text{ L milk/person/day}) \\ = 0.95 \text{ mg PEGDO/person/day}$$

Eggs:

$$(0.63 \mu\text{g PEGDO} / 1 \text{ g egg}) \times (100 \text{ g egg/person/day}) \\ = 63 \mu\text{g PEGDO/person/day}$$

Thus, the cumulative exposure to polyethylene glycol (400) dioleate from the consumption of all animal (cattle) products (*i.e.*, muscle tissue, organ tissue (liver and kidney), and fat), and milk and eggs (poultry) provides us with the estimated daily intake (EDI) for the GRAS substance as follows:

$$0.316 \text{ mg} + 0.95 \text{ mg} + 0.063 \text{ mg} = 1.3 \text{ mg PEGDO/person/day}$$

Assuming an individual consumes 3 kg of food per day, this results in a dietary concentration of $1.3 \text{ mg}/3 \text{ kg} = 0.4 \text{ ppm}$ per day. Assuming that an average individual weighs 60 kg, the EDI for polyethylene glycol (400) dioleate also may be expressed as $1.3 \text{ mg/p/d} \div 60 \text{ kg bw} = 0.02 \text{ mg/kg bw/d}$.

VIII. Conclusion

Based on the dossier of information provided in this GRAS notification, and on the scientific procedures discussed herein, the Notifier has concluded that polyethylene glycol (400) dioleate (CAS Reg. No. 9005-07-6), a component of the Notifier's FoamBlast® FMT defoamer, is Generally Recognized As Safe (GRAS) when present as an impurity, at levels up to 64 ppm, in the feed for the food-producing target animal species, as a result of the use of the defoamer as a processing aid in the production of dried and wet distillers grains with added solubles.

Furthermore, the Notifier has concluded that the publicly available information on polyethylene glycol fatty acid esters as a class and the relevant data on polyethylene glycol stearates, which we believe is directly relevant considering the substance will be metabolized to PEG and to a fatty acid very similar in toxicological profile to oleic acid, fully support the Notifier's conclusion.

APPENDIX 1



February 28, 2011

U.S. Food and Drug Administration
Center for Veterinary Medicine
Division of Animal Feeds (HFV-224)
7519 Standish Place
Rockville, Maryland 20855

Re: Authorization to Act as Agent for Carolina Chemical LLC

Dear Sir or Madam:

This is to advise that the law firm of Keller and Heckman LLP, its employees, associates, and agents, specifically including, but not limited to Devon Wm. Hill, are authorized to act as agents on behalf of Carolina Chemical LLC (a subsidiary of Emerald Performance Materials, LLC) with regard to its Generally Recognized as Safe (GRAS) Notification for Polyethylene Glycol (400) Dioleate (CAS Reg. No. 9005-07-6), submitted to the U.S. Food and Drug Administration, Center for Veterinary Medicine.

This letter is our authorization to you to permit said firm to undertake appropriate communications relevant to making submissions or inquiring as to the status of the above referenced GRAS Notification filed by or on behalf of Carolina Chemical LLC, including examination of all relevant information including confidential business, proprietary, and trade secret information submitted or developed under the Federal Food, Drug and Cosmetic Act.

Sincerely,

A handwritten signature in cursive script that reads "Barry Ferguson".

Barry Ferguson
Sales/Export Manager

Emerald Carolina Chemical, LLC

8309 Wilkinson Blvd / Charlotte, NC, 28214 / Phone: 704-393-0089 / Fax: 704-391-7340

www.emeraldmaterials.com

APPENDIX 2

CERTIFICATE OF ANALYSIS

Customer: Emerald

Date: October 1, 2010

PO#: K011837-18

Product: Mulsifan 400 DO

Lot #: (b) (4)

Quantity: 12,150 lbs

(b) (4)

Parameter (Dimension)	Specifications	Analysis Value
pH @ 5% distilled	5.5 -7.0	6.2
Moisture content % (KF)	1.0 % max.	0.17
Saponification value	105 - 115	114
Hydroxyl value	40 max	20
Acid Value	7.0 max	2.6
Color (Gardner)	5 max	1

This product complies with the specifications listed above. This certificate does not relieve our customers of their obligation to inspect the goods upon receipt and does not establish any warranties to third parties, to whom it might be passed on. No additional warranty of any kind, expressed or implied, is linked hereto.

10/5/10
QF

CERTIFICATE OF ANALYSIS

Customer: Emerald

Date: October 1, 2010

PO#: K011837-18

Product: Mulsifan 400 DO

Lot #: (b) (4)

Quantity: 23,850 lbs

Parameter (Dimension)	Specifications	Analysis Value
pH @ 5% distilled	5.5 -7.0	6.3
Moisture content % (KF)	1.0 % max.	0.18
Saponification value	105 - 115	112
Hydroxyl value	40 max	20
Acid Value	7.0 max	3.3
Color (Gardner)	5 max	2.5

This product complies with the specifications listed above. This certificate does not relieve our customers of their obligation to inspect the goods upon receipt and does not establish any warranties to third parties, to whom it might be passed on. No additional warranty of any kind, expressed or implied, is linked hereto.

10/5/10
Jf

(b) (4)

CERTIFICATE OF ANALYSIS

Customer: Emerald

Date: July 30, 2010

PO#: K011837-17

Product: Mulsifan 400 DO

Lot #: (b) (4)

Quantity: 1,800 lbs

Parameter (Dimension)	Specifications	Analysis Value
pH @ 5% distilled	5.5 -7.0	6.5
Moisture content % (KF)	1.0 % max.	0.12
Saponification value	105 - 115	114
Hydroxyl value	40 max	17
Acid Value	7.0 max	3.3
Color (Gardner)	5 max	2.5

This product complies with the specifications listed above. This certificate does not relieve our customers of their obligation to inspect the goods upon receipt and does not establish any warranties to third parties, to whom it might be passed on. No additional warranty of any kind, expressed or implied, is linked hereto.

8.4.10
PY

(b) (4)

CERTIFICATE OF ANALYSIS

Customer: Emerald

Date: July 30, 2010

PO#: (b) (4)

Product: Mulsifan 400 DO

Lot #: 101391053

Quantity: 29,250 lbs

<u>Parameter (Dimension)</u>	<u>Specifications</u>	<u>Analysis Value</u>
pH @ 5% distilled	5.5 -7.0	6.7
Moisture content % (KF)	1.0 % max.	0.14
Saponification value	105 - 115	112
Hydroxyl value	40 max	26
Acid Value	7.0 max	2.2
Color (Gardner)	5 max	1

This product complies with the specifications listed above. This certificate does not relieve our customers of their obligation to inspect the goods upon receipt and does not establish any warranties to third parties, to whom it might be passed on. No additional warranty of any kind, expressed or implied, is linked hereto.

8.4.10

PF

(b) (4)

CERTIFICATE OF ANALYSIS**Customer:** Emerald**Date:** April 14, 2010**PO#:** K011837-15**Product:** Mulsifan 400 DO**Lot #:** (b) (4)**Quantity:** 4,500 lbs

Parameter (Dimension)	Specifications	Analysis Value
pH @ 5% distilled	5.5 -7.0	6.3
Moisture content % (KF)	1.0 % max.	0.1
Saponification value	105 - 115	113
Hydroxyl value	40 max	15.4
Acid Value	7.0 max	2.2
Color (Gardner)	5 max	1

This product complies with the specifications listed above. This certificate does not relieve our customers of their obligation to inspect the goods upon receipt and does not establish any warranties to third parties, to whom it might be passed on. No additional warranty of any kind, expressed or implied, is linked hereto.

4/14/10
J

APPENDIX 3

(b) (4)



Sept 30, 2010

Steve Chaffin
Emerald Carolina Chemical, LLC
8309 Wilkinson Blvd
Charlotte, NC 28214

Dear Mr. Chaffin,

This letter is in reference to the following (b) (4) products:

Mulsifan 400 DO & Mulsifan 400 MO

I can confirm that Mulsifan 400 MO is compliant with both 21 CFR 573.800 & 173.340 (3) requirements. As to Mulsifan 400 DO, our product is compliant with all 21 CFR 173.340 (3) requirements however it does not meet the 21 CFR 573.800 requirements with regard to the Saponification value.

Sincerely,

(b) (4)



(b) (4)



(b) (4)



APPENDIX 4

(b) (4)



January 17, 2011

Barry Ferguson
Sales/Export Manager
Emerald Performance Materials

Dear Mr. Ferguson,

The stability of our product, Mulsifan 400 DO is guaranteed for at least one year if properly stored.

Sincerely,

(b) (4)



(b) (4)



1001 G Street, N.W.
Suite 500 West
Washington, D.C. 20001
tel. 202.434.4100
fax 202.434.4646

Writer's Direct Access
Devon Wm. Hill
(202) 434-4279
hill@khlaw.com

February 16, 2012

Via Electronic Mail and Federal Express

Dr. Andrea Krause, Ph.D.
Food and Drug Administration
Division of Animal Feeds (HFV-224)
Office of Surveillance and Compliance
Center for Veterinary Medicine
7519 Standish Place
Rockville, Maryland 20855

Re: Amendment to AGRN 000-006; GRAS Notification for Polyethylene Glycol (400) Dioleate; Our File No. EM13458-01

Dear Dr. Krause:

On behalf of our client, Emerald Carolina Chemicals, LLC (the Notifier), we hereby respectfully submit the enclosed Amendment to the Generally Recognized as Safe (GRAS) notification for polyethylene glycol (400) dioleate, designated AGRN 000-006, filed on April 8, 2011. As discussed in detail in AGRN 000-006, the Notifier's defoamer product is added to the condensed distillers solubles (*i.e.*, thin stillage concentrate) to assist in separating out corn oil during processing of grain from ethanol distillation. Accordingly, the polyethylene glycol (400) dioleate defoamer component may be present at minute levels as an impurity in distillers grains fed to the food-producing animals.

Pursuant to our telephone conference on February 3, 2012, you asked us to provide (1) an explanation as to why the saponification number of the Notifier's polyethylene glycol (400) dioleate exceeds the range set forth in 21 C.F.R. § 573.800 ("Polyethylene glycol (400) mono- and dioleate"); (2) a description for how the polyethylene glycol (400) dioleate functions as a defoamer; (3) a revised GRAS Status Claim which specifies the food-producing target animal species that are subject to the notification; and (4) a description of why turkeys, egg laying hens and goats should be included among the types of food-producing target animal species subject to this GRAS notification.

Accordingly, the enclosed Amendment to AGRN 000-005 includes the following:

- (1) An explanation as to why saponification number of the Notifier's polyethylene glycol (400) dioleate exceeds the range set forth in 21 C.F.R. § 573.800. Namely, as detailed in

KELLER AND HECKMAN LLP

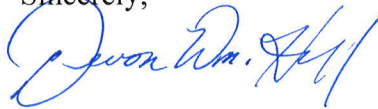
Food and Drug Administration
February 16, 2012
Page 2

the attached Amendment, the saponification number range provided in the regulation applies only to polyethylene glycol (400) monooleate and not to the dioleate.

- (2) A detailed description of polyethylene glycol (400) dioleate's chemical and physical properties that enable it to function as a defoamer (*i.e.*, its defoaming mechanism).
- (3) A detailed description and dietary intake calculations demonstrating why turkeys, egg laying hens and goats should be included among the types of food-producing target animal species subject to this GRAS notification.
- (4) A revised GRAS Status Claim which states that the polyethylene glycol (400) dioleate is GRAS when present as an impurity in animal feed for the following food-producing target animal species: beef cattle, dairy cattle, poultry (turkey, broiler chickens and egg laying hens), sheep, goat and swine.

The enclosed Amendment to AGRN 000-006 is provided in triplicate. We trust that this Amendment satisfies the Agency's needs, and will be deemed accepted and complete. Should any questions arise, please contact us, preferably by telephone or e-mail, so that we can promptly respond.

Sincerely,



Devon Wm. Hill

Cc: Geoffrey Wong, Ph.D.

Enclosure

**Amendment to AGRN 000-006
Generally Recognized as Safe (GRAS) Notification for
Polyethylene Glycol (400) Dioleate
(CAS Reg. No. 9005-07-6)**

Prepared for:

U.S. Food and Drug Administration
Center for Veterinary Medicine
Division of Animal Feeds (HFV-224)
7519 Standish Place
Rockville, MD 20855

Notifier:

Emerald Carolina Chemical, LLC
8309 Wilkinson Boulevard
Charlotte, NC 28214-9052

February 16, 2012

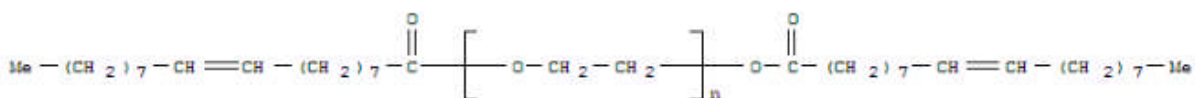
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I. Saponification Number

As provided in AGRN 000-006, the saponification number for the Notifier's polyethylene glycol (400) dioleate defoamer component exceeds the specification provided in 21 C.F.R. § 573.800. For the reasons set forth herein, that saponification specification applies only to polyethylene glycol (400) monooleate, and not to polyethylene glycol (400) dioleate. As discussed below, the presence of an additional oleate ester in the dioleate increases the overall molecular weight of the substance compared to the monooleate. The saponification number, in turn, is related to molecular weight and to the number of bonds that can be saponified. Thus, it is technically impossible for polyethylene glycol (400) dioleate to meet the saponification number range (80-88) provided in the regulation. However, as discussed below, the larger saponification number (105-115) is consistent with what would be expected for the dioleate. The larger saponification number also has no bearing with respect to the safety of the substance.

The reason the saponification number for the dioleate version of the substance, the "Mulsifan DO 400," exceeds the range in the regulation is because the specification set forth in Section 573.800 necessarily only applies to the monoester. We note, for example, that the average molecular weight range provided in Section 573.800 is 640-680, which corresponds to the polyoxyethylene glycol 400 monooleate, which is an oleic acid/polyoxyethylene glycol 400 ester. More specifically, the molecular weight of the oleate carbonyl portion of the monooleate is approximately 265 Daltons¹ and the molecular weight of the polyoxyethylene portion is, by definition, 400 Daltons, resulting in a total molecular weight of 666 Daltons² (variations in the degree of ethoxylation result in the 640-680 molecular weight range provided in the regulation). It is chemically impossible for the dioleate version of the substance to have a molecular weight within the range specified in the regulation as the presence of the second oleate ester would bring the total molecular weight of the polyoxyethylene glycol (400) dioleate to approximately 946 Daltons as shown in the structure below (where the (O-CH₂-CH₂) repeat unit has a molecular weight of 400 Daltons):



Saponification is the alkaline hydrolysis of an alkyl fatty acid ester to a carboxylate salt and an alcohol. A saponification number is the number of milligrams of potassium hydroxide required to saponify one gram of a given alkyl fatty ester by completely hydrolyzing the ester

¹ The oleic carbonyl portion of the molecule (which is esterified with polyoxethylene glycol and has a molecular structure of CH₃-(CH₂)₇-CH=CH-(CH₂)₇-C=O). The molecular weight of the oleic carbonyl functionality is 18 x 12 (carbon) + 33 x 1 (hydrogen) + 1 x 16 (oxygen) = 265 Daltons.

² When the oleic carbonyl functionality is esterified with a ethoxylate polyethylene glycol with a molecular weight of 400, and terminated with a hydrogen atom, the total molecular weight is 265 + 400 + 1 = 666 Daltons.

groups present in the fatty acid ester. Saponification values can be used to determine the molecular weight of the ester containing the alkyl fatty moiety based on the following equation: (where the molecular weight of potassium hydroxide is 56.1 g/mol):

$$\text{MW (g/mol)} = [(56.1 \text{ g-KOH/mol}) \div \text{SN (mg-KOH/g-fatty ester)}] \times (1000 \text{ mg/g}) \times (\# \text{ of ester linkages})$$

Inserting an average molecular weight of 670 into this formula for the polyethylene glycol (400) monooleate (which contains one ester linkage) results in a saponification number (SN) of 84, precisely within the range provided in Section 573.800. Similarly, if we use the theoretical molecular weight of 946 for the polyethylene glycol (400) dioleate (which contains two ester linkages) we calculate a SN of approximately 119, which is close to the range provided by the supplier (keeping in mind that the molecular weight will vary slightly depending on carbon length impurities that may be present in the oleic acid and as well as the degree of ethoxylation).

We believe that the saponification number range set forth in Section 573.800 is intended to apply only to polyoxyethylene glycol (400) monooleate. Because of the additional oleate moiety, it would be physically impossible for polyoxyethylene glycol (400) dioleate to meet the saponification range identified in the regulation. Therefore, the range of 105-115 provided in AGRN 000-006 appropriately identifies that the Mulsifan DO 400 product meets the saponification range expected for a polyoxyethylene glycol (400) dioleate.

Furthermore, we note that the higher saponification number for the dioleate does not in any way indicate a safety concern when compared to the monooleate. We note that the saponification number is also used to determine the purity level of a fatty alkyl ester compound. This is because the presence of different alkyl carbon chain lengths and non-saponifiable matter in a substance will cause the measured saponification number to vary from the theoretical value. The closer a measured saponification number is to the theoretical value determined for that compound, the more pure the compound. As the range of the saponification number provided by our supplier for polyethylene glycol (400) dioleate (105-115) is very close to the calculated saponification number (119), we can conclude that there is no purity or safety concerns associated with the Notifier's polyethylene glycol (400) dioleate.

The higher saponification number also reflects the presence of two (2) ester linkages in the polyoxyethylene glycol (400) dioleate that need to be saponified (or hydrolyzed) into its alcohol and carboxylic acid components compared to the one (1) ester linkage in the polyoxyethylene glycol (400) monooleate. Both products give rise to oleic acid (carboxylic acid) and polyoxyethylene glycol 400 (alcohol). As the polyoxyethylene glycol (400) dioleate contains a higher percentage by weight of oleic acid, it will release a higher percent by weight of oleic acid compared to polyoxyethylene glycol (400) monooleate. As fatty acids, including oleic acid, and polyoxyethylene glycol 400 are considered GRAS for direct addition to food (see 21 C.F.R. §§ 172.860 and 172.820, respectively), and oleic acid is a common metabolism product of many food oils, the higher saponification number only identifies that the structure of the oleic acid/polyoxyethylene glycol 400 ester is a dioleate, and has no bearing on safety.

II. Polyethylene Glycol (400) Dioleate Defoaming Mechanism

Polyoxyethylene glycol (400) dioleate is used as a component of a defoamer that is added to condensed distillers solubles (CDS) prior to processing in a mechanical centrifuge that separates corn oil from the aqueous CDS. A defoamer is a chemical additive that functions to reduce and inhibit the formation of foam in industrial process liquids. This action eliminates problems that occur with the presence of surface foam or entrapped air that can lead to reduced efficiency in industrial processes such as pumping, separation, and centrifugation.

Foam is frequently produced in hydrophilic-hydrophobic mixtures, and is expected to be formed during the separation of hydrophobic corn oil from aqueous concentrated stillage or CDS in the production of distillers grains at ethanol production plants. Generally a defoamer is insoluble in the foaming medium and has surface active properties such that it has an affinity to the air-liquid surface where it destabilizes foam lamellas (foam film) causing the rupture of air bubbles and breakdown of surface foam.

The properties of a defoamer which facilitate the rupture of the foam film include (1) insolubility in the foam medium, (2) facile dispersibility in the foam medium, (3) chemical inertness, and (4) a lower surface tension than the foam medium. Insolubility is important because if a defoamer was soluble in a foam film, its surfactant properties would lead to reinforced foam formation. Easy dispersibility allows the defoamer to be dispersed in the medium quickly with agitation. Chemical inertness is important to ensure that a defoamer will not react with any components in the medium.

Polyoxyethylene glycol (400) dioleate with its hydrophobic and hydrophilic moieties in its structure is easily dispersed in the CDS medium from which it is transferred to the air-liquid surface. Once it reaches the air-liquid surface it enters the foam interface forming micelles with its hydrophobic moieties that disrupt the foam film structure, thereby inhibiting foaming.

III. Inclusion of Turkey, Egg Laying Hens and Goat to List of Target Animal Species

AGRN 000-006 provides that, although the animal species tested were predominantly rats, the toxicology data is equally applicable to the following food-producing target animal species: beef cattle, dairy cattle, poultry (broiler chickens), sheep and swine. For the reasons set forth herein, **turkeys, egg laying hens and goats** should be included in the list of food-producing target animals subject to this notification. The calculations below demonstrate that the maximum dietary intake of polyoxyethylene glycol (400) dioleate for each of the new target animal species is below the conservative Acceptable Daily Intake (ADI) of 25 mg/kg-bw/day.

First, we calculate the amount of distillers grains consumed on a dry basis for each animal. Next, using the maximum residual level of 45 mg/kg of polyoxyethylene glycol (400) dioleate in the distillers grains on a dry basis, we calculate the maximum amount of polyoxyethylene glycol (400) dioleate consumed (*i.e.*, the maximum dietary intake) for each target animal species. This value is then compared to the very conservative ADI for polyoxyethylene glycol (400) dioleate for the target animal species.

a. Amount of Distillers Grains Consumed by Target Animal Species

An egg laying hen has an average body weight of 4.2 lb (1.9 kg) and consumes 52 g of dry feed per day for a food consumption of $52 \text{ g}/1.9\text{kg} = 27 \text{ g/kg bw/day}$ ³. Assuming that egg laying hens consume no more than 15% by weight dry distillers grains in feed⁴, the maximum daily consumption of distillers grains for egg laying hens is $27 \text{ g/kg bw/day} \times 15\% = 4.1 \text{ g/kg bw/day}$.

A female turkey is reported to have an average body weight of 8.1 kg and consumes 2.23 kg of dry feed per week ($2.23 \text{ kg/wk} \times 1000 \text{ g/kg} \div 7 \text{ days/wk} = 320 \text{ g/day}$) or 320 g/day for a daily feed intake of $320 \text{ g/day} \div 8.1 \text{ kg bw} = 39.5 \text{ g/kg bw/day}$ ⁵. Additionally, a male turkey is reported to have an average body weight of 12.8 kg and consumes 3.6 kg of dry feed per week or 514 g of feed per day ($3.6 \text{ kg} \times 1,000 \text{ g/kg} \div 7 \text{ days/wk} = 514 \text{ g}$) for a daily intake of $514 \text{ g}/12.8 \text{ kg bw} = 40 \text{ g/kg bw/day}$. Assuming that female turkeys consume no more than 15% by weight of dry distillers grains⁶, and male turkeys consume no more than 20% by weight dry distillers grains⁷, the maximum daily amount of distillers grains consumed is 6 g/kg bw/day ⁸ for female turkeys and 8 g/kg bw/day for male turkeys.⁹

The maximum daily dry feed intake for goats is 4% of their body weight or 40 g/kg bw/day ($0.04 \text{ kg/kg bw/day} \times 1000 \text{ g/kg} = 40 \text{ g/kg bw/day}$).¹⁰ Assuming a goat consumes no

³ “Revisions of Feedstuffs in Table 1 of OPPTS Test Guideline 860.100 and Guidance on Constructing Maximum Reasonably Balanced Diets (MRBD),” United States Environmental Protection Agency, Jan. 30, 2008, page 5, available at: <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0155-0003>.

⁴ Using Distillers Grains in the U.S. and International Livestock and Poultry Industries, *see* http://www.card.iastate.edu/books/distillers_grains/pdfs/distillers_grains_book.pdf.

⁵ J.D. Furman. Nutrient Requirements of Chickens and Turkeys. 8th ed. 1984. National Academy Press. Washington, D.C., *see* <http://www.afn.org/~poultry/flkman9.htm>.

⁶ B.A. Babcock, D.J. Hayes, J.D. Lawrence. Using Distillers Grains in the U.S. and International Livestock and Poultry Industries. The Midwest Agribusiness Trade Research and Information Center. 2008. p.128, available at http://www.card.iastate.edu/books/distillers_grains/pdfs/distillers_grains_book.pdf.

⁷ See “Value-added Feed Source for Beef, Dairy Beef, Dairy, Poultry, Swine, Sheep,” National Corn Growers Association (NCGA), September 9, 2008, available at http://www.ethanol.org/pdf/contentmgmt/NCGA_Distillers_Grain_908-1.pdf.

⁸ $40 \text{ g/kg bw/day} \times 15\% = 6 \text{ g/kg bw/day}$.

⁹ $40 \text{ g/kg bw/day} \times 20\% = 8 \text{ g/kg bw/day}$.

¹⁰ M. Rashid, “Goats and their Nutrition,” Manitoba Goat Association, *see* <http://www.gov.mb.ca/agriculture/livestock/goat/pdf/bta01s08.pdf>.

more than 30% by weight dry distillers grains in their feed¹¹, the maximum daily consumption of distillers grains is $40 \text{ g/kg bw/day} \times 30\% = 12 \text{ g/kg bw/day}$.

b. Maximum Dietary Intake of Polyethylene Glycol 400 Dioleate for each Target Animal Species

As the concentration of polyethylene glycol (400) dioleate in distillers grains is 45 mg-polyethylene glycol (400) dioleate/kg-distillers grains, the maximum dietary intake of the substance in turkey, egg laying hens, and goats are presented in the following revised tables:

TABLE 1. Feeding Data for Food-Producing Target Animals

Target Animal Species	Weight (kg)	Food Consumed (g/day)	Distillers Grains (dry weight basis) Consumed per Day		
			(%)	(g/day)	g/kg bw/day
Beef Cattle	500	10,000	30%	3,000	6
Dairy Cattle	500	10,000	30%	3,000	6
Poultry ¹²					
(broiler)	2.5	232.5	15%	34.9	14
Egg laying hen	1.9	52	15%	7.8	4.1
Female turkey	8.1	320	15%	48	6
Male turkey	12.8	514	20%	102.8	8
Sheep	60	2,400	30%	720	12
Swine	60	2,400	30%	720	12
Goat	-	4% (maximum of body weight)	30%		12 ¹³

With a maximum residual level of 45 mg/kg of polyethylene glycol 400 dioleate in distiller's grains on a dry weight basis, a maximum dietary intake for laying hens is calculated as follows:

¹¹ T. Hutchens and R. Harmon. Adding Value to Kentucky Products by Feeding Distillers Dried Grains (Report Summer 2005). Goat Producer's Newsletter. University of Kentucky. November 2005. Available at http://www.distillersgrains.org/files/feedsource/Hutchens_11_05.pdf

¹² The feed consumption for broiler chickens is reported to be 93 mg/kg bw/day – Predicting Feed Intake of Food-Producing Animals, Subcommittee on Feed Intake, Committee on Animal Nutrition, Board on Agriculture, National Research Council, National Academy Press, Washington, D.C., 1987.

¹³ $40 \text{ g/kg bw/day} \times 30\% = 12 \text{ g/kg bw/day}$.

$$4.1 \text{ g-distillers grain/kg bw} \times (45 \text{ mg-PEGDO/kg-distillers grains}) \times (\text{kg}/1000 \text{ g}) \\ = 0.18 \text{ mg PEGDO/kg bw/day}$$

The dietary intake of polyethylene glycol (400) dioleate by the other food-producing target animals is similarly calculated and presented in the table below:

TABLE 2. EDIs for Target Animals

Target Animal Species	EDI (mg/kg-bw/day) for Polyethylene Glycol 400 Dioleate
Beef Cattle	0.27
Dairy Cattle	0.27
Poultry (Broiler)	0.63
(Egg Laying Hen)	0.18 ¹⁴
(Turkey - Female)	0.27 ¹⁵
(Turkey - Male)	0.36 ¹⁶
Sheep	0.5
Swine	0.5
Goat	0.5 ¹⁷

IV. Revised GRAS Status Claim

Polyoxyethylene glycol (400) dioleate is GRAS based on scientific procedures, when present at levels up to 64 ppm in the defoamer, as an impurity in animal feed for food-producing target animal species (*e.g.*, beef cattle, dairy cattle, poultry (turkey, broiler chickens and egg laying hens), sheep, goat and swine) as a result of its use as an emulsifier in the production of wet and dried distillers grain with added solubles (WDGS and DDGS, respectively). Polyoxyethylene glycol (400) dioleate serves no technical purpose in the animal feed itself. Accordingly, the GRAS substance that is the subject of this notification is only present as a potential impurity in the WDGS and DDGS due to its use in the processing of the CDS.

¹⁴ 4.1 g-distillers grain/kg bw x (45 mg-PEGDO/kg-distillers grains) x (kg/1000 g) = 0.18 mg PEGDO/kg bw/day.

¹⁵ 6 g-distillers grain/kg bw x (45 mg-PEGDO/kg-distillers grains) x (kg/1000 g) = 0.27 mg PEGDO/kg bw/day.

¹⁶ 8 g-distillers grain/kg bw x (45 mg-PEGDO/kg-distillers grains) x (kg/1000 g) = 0.36 mg PEGDO/kg bw/day.

¹⁷ 12 g-distillers grain/kg bw x (45 mg-PEGDO/kg-distillers grains) x (kg/1000 g) = 0.5 mg PEGDO/kg bw/day.

The use of polyoxyethylene glycol (400) dioleate in this manner as a component of the Notifier's defoamer product has been determined to be exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 301 *et. seq.*).