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March 14, 2018

Via FedEx

Dr. Paulette Gaynor
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Campus Drive
College Park, MD 20740

Re: GRAS Notification for MonoSol's Use of Polyvinyl Alcohol (PVOH) as a Component in Edible Film

Dear Dr. Gaynor:

We respectfully submit the enclosed (new) GRAS notification (in electronic format, *i.e.*, CD)[1] on behalf of our client, MonoSol LLC, for polyvinyl alcohol (PVOH) for use as a component of water-soluble, edible film, which, in turn, may be used to form pouches containing pre-portioned aliquots of (1) certain dry ingredients (*i.e.*, instant tea, instant coffee, hot chocolate mix, flavored drink powder, and whey protein supplement powder) to be used by the consumer in preparing ready-to-serve foods and beverages, (2) colors to be used by processing plants in manufacturing flavored beverages (non-dairy and non-alcohol), and (3) dry ingredients to be used by commercial establishments in making pizza dough. The enclosed GRAS notification provides detailed information related to the intended uses, manufacturing, and safety of the PVOH.

[1] All electronic files included in this submission have been checked and found to be virus free.

We look forward to FDA's review of this submission and would be happy to answer any questions. Thank you for your attention to this matter.

Sincerely,

(b) (6)

Melvin S. Drozen

Enclosure

GRAS Notification for Polyvinyl Alcohol

Prepared for: U.S. Food and Drug Administration
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740-3835

Prepared by: Keller and Heckman LLP
1001 G Street, NW
Suite 500 West
Washington, DC 20001

Date: March 14, 2018

Table of Contents

GRAS NOTICE FOR POLYVINYL ALCOHOL

SUBMITTED BY MONOSOL, LLC

Part 1 – Signed statements and certification

1.1 Applicability of 21 C.F.R. part 170, subpart E

We submit this GRAS notice in accordance with 21 C.F.R. part 170, subpart E.

1.2 Name and address of the notifier

Company: MonoSol, LLC
Name: Thomas J. Yogan
Address: 707 E. 80th Place, Suite 301
Merrillville, IN 46410
Phone: 219-762-3165 Ext 341
Fax: 219-755-4062

1.3 Name of the notified substance

Polyvinyl alcohol

1.4 Applicable conditions of use of the notified substance

MonoSol, LLC (MonoSol) has developed a film (trade name: Vivos™ Edible Film) with a proprietary composition that contains polyvinyl alcohol (PVOH) in combination with other edible food grade ingredients and is sealed with heat and/or by using a custom sealing solution which comply with FDA regulations. Water-soluble, edible film made with PVOH as intended will be used to form pouches containing pre-portioned aliquots of (1) certain dry ingredients (*i.e.*, instant tea, instant coffee, hot chocolate mix, flavored drink powder, and whey protein supplement powder) to be used by the consumer in preparing ready-to-serve foods and beverages, (2) colors to be used by processing plants in manufacturing flavored beverages (non-dairy and non-alcohol), and (3) dry ingredients to be used by commercial establishments in making pizza dough. When pouches formed from the PVOH film are added to a liquid, the film will dissolve and ultimately be ingested along with the finished food or beverage made with the dry ingredients inside the pouches. Foods that are intended for infants and toddlers, such as infant formulas or foods formulated for babies or toddlers, and meat and poultry products are excluded from the list of intended food uses of PVOH.

The amount of PVOH in the film (*i.e.*, 56%) has been optimized for package integrity with respect to containing dry food ingredients and colors until ready for use and, at that time, dissolving when the entire pouch is added to liquid. The latter feature of the film increases the speed and convenience of incorporating dry ingredients to prepare a serving or batch of food or beverage for consumption.

1.4.1. Consumer Products

The maximum level of PVOH in a serving of the resulting food or beverage was calculated for each category of product to be prepared by consumers based on the amount of PVOH in the film (56%), the maximum amount of film used in making the pouch for any product within each category, and the preparation and serving instructions on the relevant food labels. The maximum amount of PVOH in a serving and the serving size associated with the maximum potential amount of PVOH in the food or beverage for each intended use category is tabulated in Table 1 below.

Table 1. Maximum potential level of PVOH in consumer products.

Finished Food	Serving Size (grams)	PVOH (grams/serving)	PVOH in Finished Food (%)
Instant Tea	239.3	0.0672	0.028
Instant Coffee	239.3	0.0672	0.028
Hot Chocolate	177	0.2016	0.114
Flavored Drink	502	0.0560	0.011
Whey Protein Supplement	515.5	0.734	0.142

1.4.2. Color Packs

Polyvinyl alcohol is also intended for use as a food ingredient in the edible film to deliver prepackaged water-soluble sealed pouches containing powdered color for use during manufacture of flavored beverages, except for dairy and alcohol. The size of the pouch in each case is the smallest feasible for containing the amount of powdered color required for the batch-size of beverage. Beverage formulations are held proprietary with respect to the precise level of color added. Independent analyses, however, indicate the levels in some popular beverages. DyeDiet (May 16, 2011) reports that certain flavors of carbonated soft drinks were found to contain color at levels of up to 57 milligrams per liter (mg/L). DyeDiet (May 13, 2011) reports that certain non-carbonated sports drinks were found to contain color at levels of up to 70 mg/L. Conservatively assuming a flavored beverage is made with powdered color at a concentration of 132 mg/L, and based on the amount of film needed to contain this amount of powdered color for a batch size of 1000 gallons, a single (12 ounce) serving of flavored beverage would contain 0.0006 grams PVOH, or 0.000176%.

1.4.3. Pizza Dough Packs

Polyvinyl alcohol is also intended for use as an ingredient in the edible film to deliver prepackaged water-soluble sealed pouches containing dry ingredients for use in making batches of pizza dough. Each pouch (dough pack) would contain approximately 300 grams of ingredients to be mixed with flour and water to prepare one batch of pizza dough. The dough would contain 1.26 grams PVOH/batch, which can be used to make approximately 21 pizzas. Assuming 8 slices (servings)/pizza, each slice (serving) would contain approximately 0.0075 grams PVOH.

1.5 Basis for the GRAS determination

The statutory basis for our conclusion of GRAS status is through scientific procedures in accordance with 21 C.F.R. §§ 170.30(a) and (b).

1.6 Exclusion from premarket approval

The notified substance is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) based on our conclusion that the notified substance is GRAS under the conditions of its intended use.

1.7 Availability of data and information

If the Food and Drug Administration (FDA) asks to see the data and information that are the bases for our conclusion of GRAS status, either during or after FDA's evaluation of our notice, we agree to make the data and information available to FDA. Further, upon FDA's request, we will allow the Agency to review and copy the data and information during customary business hours at the above address, and will provide FDA with a complete copy of the data and information, either in an electronic format that is accessible for the Agency's evaluation, or on paper.

1.8 Applicability of FOIA exemptions

This GRAS notice does not contain confidential business information (CBI) exempt from disclosure under the Freedom of Information Act per 5 U.S.C. § 552(b)(4).

1.9 Certification

We certify that, to the best of our knowledge, our GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of the substance.

(b) (6)

13 MAR 2018

Name: Thomas J. Yogan
Date

Title: Senior Vice President & Chief Technologist

Please address correspondence to MonoSol's counsel:

Melvin S. Drozen
Keller and Heckman LLP
1001 G Street, N.W., Suite 500 West
Washington, DC 20001
Phone: (202) 434-4222
Email: drozen@khlaw.com

Part 2 – Identity, method of manufacture, specifications, and physical or technical effect

2.1 Scientific data and information that identifies the notified substance

As described in the Food Chemicals Codex (FCC 2016), polyvinyl alcohol occurs as an odorless translucent, white or cream-colored granular powder. It is soluble in water and sparingly soluble in ethanol. Commercially produced polyvinyl alcohol is a mixture of synthetic polymers produced by the polymerization of vinyl acetate and partial hydrolysis of the resulting esterified polymer. Depending on the degree of polymerization, physical and chemical properties of polyvinyl alcohol vary. Polyvinyl alcohol is soluble in water and insoluble in aliphatic and aromatic hydrocarbons, esters, ketones, and oils (Handbook of Pharmaceutical Excipients, 1994). The structural formula of polyvinyl alcohol is presented in Figure 1. The PVOH used in MonoSol's edible film contains no additives.

Common or Usual Name: Polyvinyl alcohol; Vinyl alcohol polymer; PVOH

Chemical Name: Polyvinyl alcohol; Ethenol homopolymer

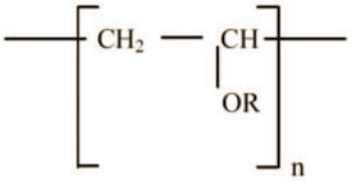
Chemical Abstracts Service Registry Number (CASRN): 25213-24-5. A different CASRN (*i.e.*, 9002-89-5) is referenced in a 2003 review of PVOH for use as a coating agent, binder, sealant or surface-finishing agent by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at the 61st meeting. Likewise, the U.S. Pharmacopeia & National Formulary (27th Ed.) and WHO Food Additive Series 52 on PVOH reference CASRN 9002-89-5. However, these reports are not consistent in their use of the nomenclature. Strictly speaking, CASRN 90002-89-5 describes super- or fully-hydrolyzed polyvinyl alcohol, also called homopolymer, polyvinyl alcohol. In these same reports, the degree of hydrolysis is listed to be between 85% and 89%, which refers to a slightly different structure known as partially-hydrolyzed polyvinyl alcohol. CASRN 25213-24-5 refers to partially-hydrolyzed polyvinyl alcohol and fits the degree of hydrolysis specified in the JECFA, USP, and WHO documents. For example, based on the WHO's specific statement on the degree of hydrolysis (*i.e.*, 85%-89%), the PVOH is partially hydrolyzed and not fully hydrolyzed; hence, CASRN 25213-24-5 is appropriate. Therefore, with respect to the PVOH intended for use in edible film, MonoSol uses CASRN 25213-24-5 as the correct and relevant CASRN and believes PVOH described by CASRN 25213-24-5 is the substance addressed in the JECFA, USP, and WHO reference documents.

Chemical Formula: $(C_2H_3OR)_n$ where R=H and $COCH_3$ (randomly distributed)

Degree of Hydrolysis: The degree of hydrolysis is between 86.5% and 89%

Molecular weight: Ranges from 37,000 to 150,000 g/mol

Figure 1. Structural formula of polyvinyl alcohol, where R=H and $COCH_3$ (randomly distributed).

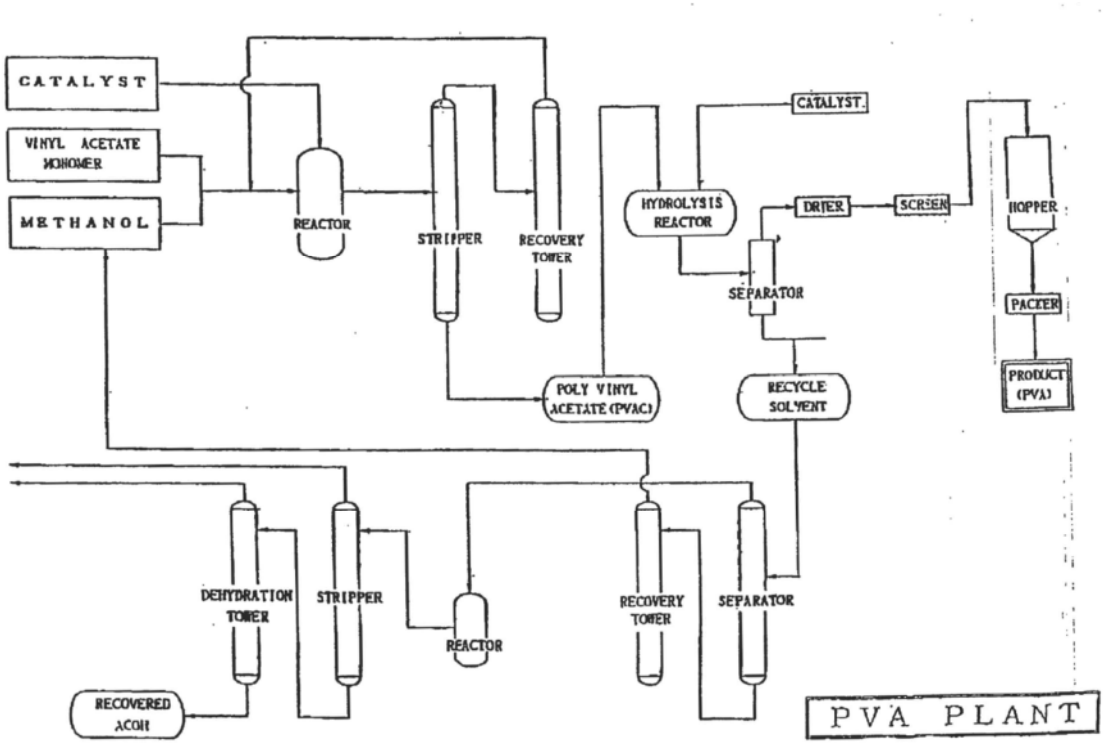


2.2 Description of the method of manufacture of PVOH

PVOH is manufactured from vinyl acetate monomer and subsequent controlled hydrolysis (saponification) of polyvinyl acetate. A proprietary agent is used to initiate the polymerization process. The process is based on the partial replacement of ester groups in vinyl acetate with hydroxyl groups. The manufacturing process for the PVOH is essentially the same as is described in GRAS notice (GRN) 000141. Following polymerization, the material is saponified (hydrolysis) with sodium hydroxide. The process of hydrolysis results in the partial replacement of ester groups in the vinyl acetate with hydroxyl groups. Following gradual addition of the saponification agent, PVOH is precipitated, washed, and dried. The degree of hydrolysis depends on the time at which the saponification reaction is stopped. The final product is assayed for conformity with the specifications. The residual vinyl acetate in the PVOH is not detectable (limit of detection 1.5 ppm of vinyl acetate). Sodium acetate, methanol, and methyl acetate are the primary expected side products. As the resulting product is washed, most of the side products are expected to be removed in the aqueous solution. The sodium acetate is a reaction byproduct that is monitored by the residue-on-ignition test. The residual methanol and methyl acetate are monitored by process control, individual specifications and analytical methods. The manufacturer has provided assurance regarding the maximum potential presence of residual substances associated with starting materials, including the initiator, and based on this information MonoSol has determined that the final PVOH is safe and suitable for the intended use.

The manufacturing flow chart provided in GRN 000141, and copied in Figure 2 below, accurately represents the steps used in manufacturing the PVOH used in MonoSol's edible film.

Figure 2. Manufacturing process for polyvinyl alcohol



2.3 Specifications for food-grade PVOH

Food grade specifications for the PVOH used in the preparation of edible film have been established by MonoSol and are presented in Table 2. These specifications comply with those in the Food Chemicals Codex (FCC 2016) except for the viscosity. The viscosity of the PVOH at the middle and upper ends of the range of molecular weight (*i.e.*, 37,000 to 150,000 g/mol) is different (higher) than specified in the FCC monograph because the molecular weight is different (higher). In this regard, FDA has stated that it is appropriate to consider dietary exposure to only the low molecular weight (< 1,000 Daltons) oligomers, as this weight typically corresponds to a molecular size that is capable of absorption by the digestive tract, and is understood to be of potential toxicological significance. All PVOH that may be used in MonoSol's film has the same profile as grades that meet the FCC specification for viscosity in terms of the low molecular weight fraction (LMWF) of the polymer. The chemical and physical characteristics of PVOH have also been reviewed in several other national and international official monographs, including the United States Pharmacopeia (USP, 2004) and the JECFA (2007). Analytical results of multiple independently produced, representative batches (Appendix I) demonstrate that the PVOH consistently meets the specifications.

Table 2. Specifications for PVOH

Parameter	Characteristics	Reference/Test Methodology
Description	Translucent, white or cream-colored granular powder	Visual inspection
Identification		
Color reaction A	Blue color	FCC
Color reaction B	Dark red to blue color	FCC
Infrared absorption	Pass (*i.e.*, same maxima at the same wavelengths as reference standard)	FCC
Precipitation reaction	White turbid precipitate	FCC
Specific tests		
Acid value	NMT 3	FCC
Ester value	Between 125 and 153 mg KOH/g	FCC
Degree of hydrolysis	Between 86.5 and 89.0%	FCC
Loss on drying	NMT 5%	FCC
pH	5.0 - 6.5	FCC
Residue on ignition	NMT 1%	FCC
Viscosity	85% -115% of viscosity value referenced by vendor (4% aqueous solution at 20°C)*	FCC/USP
Water insoluble substances	NMT 0.1%	FCC
Heavy metals		
Lead	NMT 2 ppm	FCC
Organic impurities		
Methanol	NMT 1%**	FCC
Methyl acetate	NMT 1%**	FCC

NMT = Not more than;

*Per USP monograph the pass/fail criteria is 85% to 115% of viscosity value mentioned on the label. The testing of viscosity was per FCC (2016) but utilizing USP pass/fail criteria;

** FCC (2016) includes an *incorrect* equation for calculating the results for methanol and methyl acetate. The variable for Ru in the equation should be reflective of the peak areas for methanol or methyl acetate and not of methanol only. The USP monograph for polyvinyl alcohol has different wording and allows for their individual contributions when calculating the results for methanol or methyl acetate concentration. Hence, the methodology followed was as per the FCC monograph but the formula used was as per the USP monograph.

2.4 Information on the technical effect of PVOH

PVOH has multiple applications in food, food packaging, pharmaceuticals, medical products, and cosmetics (CIR, 1998; 21 C.F.R. §175.105, §175.300, §175.320, §176.170, §176.180, §177.1200, §177.1670, §177.2260, §177.2800, §178.3910, §181.30). The physical characteristics of PVOH, such as good film strength and adhesion qualities, make it a useful film-coating agent. Because of these properties, polyvinyl alcohol can be used as edible film to deliver prepackaged sealed pouches containing food products and food colors that can be consumed along with the film. PVOH is intended for use in

an amount not to exceed the amount required to achieve its technological effect as part of the film formulation.

Part 3 – Dietary exposure

The quantity of PVOH in an edible pouch depends on the amount of film used to make the pouch, which varies according to the composition of the dry ingredients and the mass of ingredients inside the pouch. The estimated daily intake (EDI) of PVOH for each intended use is based on assuming foods chosen always have the maximum amount of PVOH per serving as described in Part 1.4 above.

For the instant tea, instant coffee, pizza dough pack, and color pack applications, estimates of the intake of PVOH are based on the maximum level of PVOH in tea, coffee, pizza, and soft drinks, respectively, as described in Part 1.4 above, in conjunction with the relevant 90th percentile intake level for each type of food in the United States Department of Agriculture's (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII 1994-1996) (Smiciklas-Wright et al., 2002) for quantities of foods consumed daily. The FDA commonly uses the estimated daily intake for the 90th percentile consumer of a food additive as a measure of high chronic dietary intake.

For the intended use of edible film made with PVOH for color packs, soft drinks adequately represent the intake of any flavored beverage (non-dairy and non-alcohol) that could be made using a color pack with PVOH, including carbonated beverages and non-carbonated beverages such as sports drinks, because only one type of flavored beverage is expected to be consumed per eating occasion, and the EDI for PVOH is calculated by assuming the bottled (or canned) beverage selected is always one with the highest expected use level of color (corresponding to the highest amount of PVOH per serving as described in Part 1.4 above). Based on the 90th percentile intakes reported by Smiciklas-Wright (2002) for users of tea (947 g), coffee (1,167 g), and soft drinks (1,115 g), along with the maximum levels of PVOH in prepared tea (0.028%), coffee (0.028%), and soft drinks (0.000176%), the maximum potential EDIs of PVOH from these foods are calculated to be 0.265 g, 0.327 g, and 0.00196 g, respectively. Regarding the cumulative intake of PVOH from the intended use of the edible film, tea and coffee are not both expected to be consumed at the same time. Therefore, the EDI of PVOH from the intended use of the edible film packs for tea and coffee is assumed to be 0.327 g, *i.e.*, the calculated EDI of PVOH for coffee, which is higher than the calculated EDI of PVOH for tea (0.265 g). For pizza, Smiciklas-Wright (2002) reported the 90th percentile intake by users to be 351 g. Based on the weight of a single slice (71 g), the 90th percentile intake is approximately 5 slices of pizza per day. Thus, based on the intended use level of PVOH (0.0075 g/slice), the EDI of PVOH for the intended use of the edible film for pizza dough packs is 0.0375 g.

Intake data for a matching food category are not available in the USDA CSFII database for hot chocolate, flavored drinks (made by consumers from instant powder), and whey protein supplements. Because a person has finite hydration needs, it is unlikely that an individual consumes more than one beverage at the 90th percentile daily intake levels for each beverage. In this regard, as it relates to the intended use of PVOH, hot chocolate would not likely be consumed daily by those who also consume coffee at the 90th percentile daily intake level of 1,167 g. Likewise, a flavored drink from instant powder

would not likely to be consumed daily by those who also consume soft drinks at the 90th percentile daily intake level of 1,115 g. As a conservatism, however, hot chocolate, flavored drinks from instant powder, and whey protein supplements are each assumed to be consumed in addition to the 90th percentile daily intake levels of soft drinks and coffee/tea made with the edible film containing PVOH. The intake of hot chocolate, flavored drinks from instant powder, and whey protein is assumed to be two servings of each per day. Thus, based on the amounts of PVOH in a serving for hot chocolate (0.2016 g), flavored drinks from instant powder (0.0560 g), and whey protein supplements (0.734 g), as described in Part 1.4 above, the EDIs of PVOH from consumption of these foods are calculated to be 0.4032 g, 0.112 g, and 1.468 g, respectively.

Based on a body weight of 60 kg, the proposed use of PVOH at levels ranging from 0.0006 g to 0.734 g/serving in instant tea powder mix, instant coffee, mix for flavored water drinks, whey protein supplements (includes pre- and post-training supplements and mass gainers), hot chocolate (cocoa) mix, and dry ingredients for pizza dough, and use for packaged powder colors for the manufacture of beverages (non-dairy and non-alcohol), will result in a conservative EDI of 39.16 mg PVOH/kg bw/day. In addition to the proposed use of PVOH as a food ingredient, PVOH may be used in dietary supplement products and in pharmaceutical products. In GRN 000141, a very conservative estimate of exposure to PVOH from its use in dietary supplements and from its existing use in pharmaceutical products was determined to be 6 mg/kg bw/day. Thus, the cumulative EDI of PVOH will be 45.16 mg/kg bw/day.

The EDI of PVOH for each intended food/beverage category, calculated in the manner described above (and by assuming a body weight of 60 kg) are shown in Table 3 below, along with the EDI from existing pharmaceutical and dietary supplement (capsule) applications and the total EDI from all uses.

Table 3. EDI of PVOH from the intended use in edible film.

Food/beverage category	**EDI (mg/kg bw/day)**
Instant Tea/Instant Coffee	5.45
Hot Chocolate	6.72
Flavored Drinks	1.87
Whey Protein Supplements	24.47
Color Packs	0.03
Pizza Dough Packs	0.625
Pharmaceuticals and Dietary Supplements	6
Total:	**45.16**

Part 4 – Self-limiting levels of use

Pouches containing dry ingredients are made with the minimum amount of film necessary to achieve pouch performance. Using more film than necessary would entail undesirable material costs and could potentially implicate concerns with misleading package sizes in comparison to the quantity of dry food ingredients inside the pouch. Further, the composition of the edible film, including the amount of PVOH used in the film (*i.e.*, 56%), was developed to provide the best performance with respect to package integrity while containing dry food ingredients and colors until ready for use and, at that time, dissolving when the entire pouch is added to liquid. The level at which PVOH would cause food to become unpalatable, while unknown, is necessarily higher than the amount of PVOH in food under the intended conditions of use because products made with MonoSol's edible film have been deemed acceptable by olfactory measures.

Part 5 – Experience based on common use in food before 1958

N/A

Part 6 – Narrative

In the published literature, several studies of polyvinyl alcohol are reported in different species following both oral and non-oral routes, such as rectal, intra-vaginal, subcutaneous, intravenous, intra-peritoneal and dermal. The findings from non-oral studies are considered not to be predictive of oral toxicity, as polyvinyl alcohol is very poorly absorbed following oral administration. Hence, in the following section, emphasis is placed on the oral studies. The safety assessment of polyvinyl alcohol is based on metabolic, mutagenicity, and toxicological data in general, and on the resulting exposure to polyvinyl alcohol from its proposed and existing uses. As indicated earlier, polyvinyl alcohol has been approved for use in coatings applied to pharmaceutical products. Polyvinyl alcohol has also been evaluated for safety-in-use by national and international regulatory and other agencies. In these comprehensive safety evaluations, polyvinyl alcohol has been extensively reviewed and demonstrated to be safe for use as a food or dietary supplement ingredient at the levels described in those assessments.

6.1 Regulatory Assessments

6.1.1 GRN 141 for use of PVOH in coating for dietary supplement capsules

In GRN 000141, the notifier informed the FDA that polyvinyl alcohol is GRAS, through scientific procedures, for use in aqueous film coating formulations applied to dietary supplement products (*i.e.*, tablets or capsules), where the coating formulation is up to 4% (by weight) of the tablet or capsule, and polyvinyl alcohol is up to 45% (by weight) of the coating formulation. Assuming a person consumes a maximum of ten 1 g dietary supplement tablets or capsules and ten 1 g pharmaceutical tablets or capsules with polyvinyl alcohol film coating formulations per day, the maximum daily intake of polyvinyl alcohol was estimated as 180 mg/person/day from dietary supplements and 180 mg/person/day from its use in film coatings applied to pharmaceutical products. The total maximum daily intake of polyvinyl alcohol from its intended use in dietary supplements and from its use in pharmaceutical products was estimated as 360 mg/person/day, equivalent to 6 mg/kg bw/day for a 60-kg person.

Regarding safety, the notifier reported that acute and subchronic oral toxicity studies conducted in animals including rats, mice, and dogs as well as a two-generation reproductive toxicity study conducted in rats fed polyvinyl alcohol showed no adverse toxicological or reproductive effects. *In vitro* and *in vivo* genotoxicity studies with polyvinyl alcohol also did not reveal any evidence of mutagenic or clastogenic effects. These studies suggest that polyvinyl alcohol is not mutagenic, genotoxic, or carcinogenic by the oral route. The notifier concluded that animal toxicology data (subchronic toxicity and reproductive toxicity study) support a no-observed-adverse-effect-level (NOAEL) for polyvinyl alcohol of 5,000 mg/kg body weight/day, the highest dose tested. In a response letter to the notifier, the FDA did not question the conclusion that the ingredient polyvinyl alcohol is GRAS under the intended conditions of use.

6.1.2 JECFA review

In 2004, the Joint FAO/WHO Expert Committee on **Food Additives** (**JECFA**) evaluated a large database of studies regarding the toxicity of polyvinyl alcohol after administration by various routes to several species. The Committee concluded that polyvinyl alcohol was very poorly absorbed following oral administration, that the acute oral toxicity was generally very low, and that the overall results were consistent with very low toxicity and showed no evidence for carcinogenicity. No adverse effects were noted in a two-generation reproductive toxicity study and a subchronic toxicity study in rats. There was no evidence for genotoxicity in a battery of tests undertaken with preparations of polyvinyl alcohol. The Committee identified a No-Observed-Effect-Level (NOEL) of 5000 mg/kg bw/day for polyvinyl alcohol based on the maximum dose tested in both the 90-day and the two-generation studies in rats. The Committee established an acceptable daily intake (ADI) for polyvinyl alcohol of 50 mg/kg bw/day, based on the NOEL of 5000 mg/kg bw/day from the subchronic toxicity and two-generation studies in rats, with a safety factor of 100.

6.1.3 European Commission Evaluation

The Scientific Panel of the European Food Safety Authority (EFSA) reviewed the safety of polyvinyl alcohol as a food additive when used as film coating agent for food supplements. Following a critical review of the relevant polyvinyl alcohol data, including physical/chemical properties, specifications, manufacturing process, proposed use levels, exposure, safety-related studies, etc., the EFSA Panel concluded that the consumption of polyvinyl alcohol, through its use as a coating agent for food supplement tablets and/or capsules at its intended use level and resulting in a total (cumulative) intake of 4.8 mg/kg bw/day from the proposed and existing food uses is not of safety concern. The Panel noted that the NOAEL of 5,000 mg/kg bw/day (the highest dose tested) derived from the 90-day (subchronic) and two-generation reproductive dietary toxicity studies with polyvinyl alcohol indicates a low order of toxicity. Polyvinyl alcohol is only minimally absorbed following oral administration. The maximum assumed combined intakes of 4.8 mg/kg bw/day from the proposed uses plus existing uses from pharmaceutical products was over 1000-fold below the established NOAEL.

6.2. Toxicological Studies

6.2.1. ADME

Following oral administration, polyvinyl alcohol was found to be poorly absorbed from the gastrointestinal tract (EFSA, 2005; Sanders and Matthews, 1990). In an experiment in the rat, over 98% of the radioactivity associated with a single oral dose (0.01 mg/kg ^{14}C-labeled) of polyvinyl alcohol was excreted in the feces within 48 hours of administration (Sanders and Matthews, 1990). In this study, < 0.2% of the total radioactivity was detected in the urine. To further characterize absorption and subsequent bioaccumulation, Sanders and Matthews (1990) administered 0.10 mg/kg ^{14}C-labeled polyvinyl alcohol to rats via gavage for 10 consecutive days. The majority (~ 100%) of the radioactivity was found in fecal matter, suggesting that polyvinyl alcohol is

very poorly absorbed by the oral route (Sanders and Matthews, 1990). The Panel concluded that as polyvinyl alcohol is very poorly absorbed, there is minimal amount available for distribution to body tissues and only trace amounts are likely to be absorbed.

6.2.2. Acute Toxicity

Acute oral toxicity of polyvinyl alcohol has been evaluated in rats, mice and dogs. The LD_{50} values of polyvinyl alcohol for mice, rats and dogs following oral administration have been reported to range from > 1.5 to approximately 22 g/kg bw (JECFA, 2003; EFSA, 2005). The oral LD_{50} of polyvinyl alcohol in mouse, rat and dog studies were reported as > 4000, >21500 and > 20000 mg/kg bw, respectively. These observations suggest that polyvinyl alcohol is practically nontoxic following oral administration.

6.2.3. Subchronic Toxicity

Kelly et al. (2003) investigated the potential systemic and neurotoxic effects of polyvinyl alcohol in a GLP-compliant rat study. In this study, male and female Sprague-Dawley rats (20/sex/group) were fed a diet providing dose levels of 0, 2,000, 3,500 and 5,000 mg/kg/day for 90 days. Control rats (20/sex) were given untreated standard laboratory diet. Assessments included clinical observations, ophthalmology, body weight and food consumption, hematology, coagulation, clinical chemistry, urinalyses, motor activity and functional observational battery evaluations and gross and microscopic pathology. The only overt polyvinyl alcohol treatment-related finding observed during the study was unformed stool with brown/black anogenital staining in rats fed 3,500 and 5,000 mg/kg/day. This finding was attributed to the consumption and excretion of high levels of polyvinyl alcohol. It was not accompanied by macroscopic or microscopic changes in these rats. No treatment-related changes were noted in mortality, ophthalmology, body weight and food consumption data, hematology, clinical chemistry, urinalysis data, functional observational assessments, motor activity, organ weight data and macroscopic and microscopic examinations. The investigators concluded that administration of polyvinyl alcohol as a dietary admixture to rats at doses of 2,000, 3,500 and 5,000 mg/kg/day for up to 90 days did not result in any adverse, toxicological effects. The results of this study suggest a NOAEL of 5,000 mg/kg/day. The polyvinyl alcohol used in the Kelly et al. (2003) study was 85-89% hydrolyzed, like the polyvinyl alcohol that is the subject of the present GRAS assessment.

6.2.4. Mutagenicity Genotoxicity

In a series of experiments, Kelly et al. (2003) also investigated the genotoxic potential of polyvinyl alcohol: (1) in a bacterial reverse mutation assay in *Salmonella typhimurium* and *Escherichia coli* (Ames assay); (2) in an *in vitro* forward mutation assay in a sub-line of mouse lymphoma L5178Y cells; and (3) in an *in vivo* mouse micronucleus assay. In the Ames assay, polyvinyl alcohol at concentrations of up to 5,000 μg/plate, both in the presence and absence of liver preparations from Aroclor 1254-induced rats (S9 mix), was not mutagenic to *S. typhimurium* strains TA1535, TA1537, TA98 and TA100, or to a tryptophan-dependent mutant of *E. coli* strain WP2*uvr*A/pKM101 (CM 891) (Kelly et al., 2003). Similarly, in the mouse lymphoma assay, in the presence and absence of metabolic

activation (S9 mix), polyvinyl alcohol at concentrations up to 5,000 μg/mL did not increase the incidence of forward mutations at the thymidine kinase locus (TK+/-). In the *in vivo* mouse micronucleus assay, administration of single doses of polyvinyl alcohol via oral gavage to male and female Swiss mice at doses of up to 2,000 mg/kg bw did not show any evidence of causing chromosome damage or bone marrow cell toxicity at 24 to 48 hours following administration. These observations are further supported by the studies described in the JECFA evaluation of polyvinyl alcohol (JECFA, 2003). As described in the JECFA report, negative results were noted in several strains of *S. typhimurium* in both the presence and absence of metabolic activation, as well as in an *in vitro* Chinese hamster V79 chromosomal aberration assay and *in vivo* in a female mouse bone marrow micronucleus test.

6.2.5. Chronic Toxicity and Carcinogenicity

In the published literature, no chronic toxicity or carcinogenicity studies were found following oral administration of polyvinyl alcohol. In a well-designed 2-year National Toxicology Program (NTP) study, intra-vaginal administration of polyvinyl alcohol to female B6C3F1 mice did not reveal compound-related neoplastic or non-neoplastic lesions. The only clinical finding observed in this study was vaginal irritation (NTP, 1998). The NTP concluded that "under the conditions of this 2-year study, there was no evidence of carcinogenic activity...."

6.2.6. Reproduction and Developmental Toxicity

In a GLP-compliant study, Rodwell et al. (2003) investigated the effects of polyvinyl alcohol on fertility, early embryonic development, growth and subsequent development in rats. In this 2-generation study, groups of P_0 and F_1 parental Sprague-Dawley rats (26/sex/group) were fed diets containing polyvinyl alcohol at dose levels providing dose levels of 2,000, 3,500, or 5,000 mg/kg bw/day for at least 70 consecutive days prior to mating. The treatment of male rats was continued during the 14-day mating period and throughout the post-mating period until euthanized. Female rats continued their respective treatments during the 14-day mating period, gestation, and lactation. Females were generally euthanized on lactation day 21. As evaluated by mating and fertility indices and sperm counts, polyvinyl alcohol did not induce any treatment-related effects on P_0 or F_1 male reproductive performance. Similarly, as assessed by mating, fertility and pregnancy indices, and estrous cycling data, there were no biologically significant effects attributable to polyvinyl alcohol treatment on P_0 or F_1 female reproductive performance. No polyvinyl alcohol related effects on litter parameters (litter size, pup sex distribution, pup survival, clinical observations, and body weights) in either the F_1 or F_2 generation were noted. Absolute organ weights, or organ to body weights and organ to brain weight ratios were unaltered by polyvinyl alcohol treatment in both F_1 and F_2 generations. Macroscopic and microscopic observations performed on the P_0 and F_1 parental animals and of the F_1 and F_2 pups did not reveal any adverse effects from polyvinyl alcohol exposure. The results of this study suggest a NOAEL 5,000 mg/kg bw/day for both parental and offspring in this reproductive study, the highest dose tested (Rodwell et al., 2003).

6.3. Basis for GRAS Conclusion for Intended Use of PVOH

The safety of polyvinyl alcohol is supported by toxicity studies, including several GLP-compliant studies (i.e., a 90-day oral toxicity study, a 2-generation reproductive toxicity study, and *in vitro* and *in vivo* genotoxicity assays). Following oral administration, PVOH is only minimally absorbed. The acute oral toxicity studies in rats, mice and dogs suggest that PVOH is of a low order of acute toxicity. In the subchronic toxicity study, there was no evidence of systemic toxicity following dietary administration of PVOH. The highest dose level of PVOH tested was 5,000 mg/kg bw/day. The only notable finding in this study consisted of loose stools that appear to be related to the high content of non-absorbed PVOH in the dietary admixture. Similarly, in a 2-generation reproductive toxicity study in the rat, no adverse effects of PVOH administration occurred in parental (p-generation), or first or second-generation animals. In this study, the highest dose level of polyvinyl alcohol tested was also 5000 mg/kg bw/day. The results of a series of *in vitro* and *in vivo* mutagenicity and genotoxicity assays performed with prokaryotic and mammalian test systems suggest that polyvinyl alcohol is neither mutagenic nor genotoxic. No oral long-term toxicity and carcinogenicity studies were available. In a topical carcinogenicity study, intravaginal administration of polyvinyl alcohol to female mice did not indicate any carcinogenic activity.

MonoSol's GRAS conclusion is based on the conservative EDI of PVOH under the intended conditions of use (*i.e.*, 39.16 mg/kg bw/day) and the cumulative EDI for PVOH from all known food (including dietary supplements) and pharmaceutical uses (*i.e.*, 45.16 mg/kg bw/day) being below the ADI of 50 mg/kg bw/day that was determined by JECFA.

6.4. Safety of Constituents

As noted in product specifications (Table 2), polyvinyl alcohol contains methanol and methyl acetate at levels up to 1%. As described in Part 2.2, these are the side products and their levels are monitored by process control, individual specifications and analytical methods. The resulting estimated daily intake of these manufacturing by-products (methanol as well as for methyl acetate) from the intended uses of polyvinyl alcohol as a food ingredient will be below 0.5 mg/kg bw/day (*i.e.*, less than 30 mg per day for an individual weighing 60 kg).

Per 21 C.F.R. § 173.250, methanol residues are permitted from its use as a solvent in the following foods under the conditions specified: (a) In spice oleoresins as a residue from the extraction of spice, at a level not to exceed 50 parts per million. (b) In hops extract as a residue from the extraction of hops, at a level not to exceed 2.2 percent by weight; Provided, that: (1) The hops extract is added to the wort before or during cooking in the manufacture of beer. (2) The label of the hops extract specifies the presence of methyl alcohol and provides for the use of the hops extract only as prescribed by paragraph (b)(1) of this section. Additionally, other clearance permit methanol residues with limits in parenthesis as follows: 21 C.F.R. §§ 175.105 ("Adhesives"); 172.859 ("Sucrose fatty acid esters") (10 ppm); 172.560 ("Modified hop extract") (250 ppm, 100 ppm, or 50 ppm,

depending upon the extraction method); 172.867 (“Olestra”) (300 ppm, per FCC monograph); and 73.615 (“Turmeric oleoresin”) (50 ppm).

It is also important to recognize that dietary methanol can arise from fresh fruits and vegetables, where it occurs as free alcohol, methyl esters of fatty acids or methoxy group on polysaccharides such as pectin. Orange juice is also a good example of fruit juice that contains methanol. A typical serving of orange juice (6 ounces or 200 ml) with the reported methanol level of 500 mg/liter in orange juice results in consuming 100 mg of methanol. Based on this example for orange juice alone, it would be appropriate to assume that the resulting intake of methanol (< 30 mg/day) from the proposed uses of polyvinyl alcohol is safe.

The other processing by-product, methyl acetate is among the listed synthetic flavoring substances and adjuvants permitted under 21 C.F.R. § 172.515 for use in accordance with the following conditions: a) they are used in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice, and 2) they consist of one or more of the following, used alone or in combination with flavoring substances and adjuvants generally recognized as safe in food, prior-sanctioned for such use, or regulated by an appropriate section in this part. The Flavor and Extract Manufacturer’s Association has also approved food uses of methyl acetate as a flavoring agent (FEMA No. 2676) in beverages, ice cream, candy and baked goods at levels ranging from 11 to 29 ppm.

Part 7 – List of supporting data and information

7.1 References

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7.2 Tables

Table 1 Maximum potential level of PVOH in consumer products.

Table 2. Specifications for PVOH

Table 3. EDI of PVOH from the intended use in edible film.

7.3 Figures

Figure 1 Structural formula for of polyvinyl alcohol, where R=H and $COCH_3$ (randomly distributed).

7.4 Appendices

Appendix 1 Product specifications from different non-consecutive lots.

APPENDIX I. Product specifications from different non-consecutive lots.

67,000 g/mol PVOH

Galbraith ID #		234-165-A	234-165-B	234-165-C	234-165-E	234-165-F
Lot #		DE13016507	DE13018038	DE13004286	DE13017868	DE13017868
Identification						
Color reaction A	Blue color	Pass	Pass	Pass	Pass	Pass
Color reaction B	Dark red to blue color	Pass	Pass	Pass	Pass	Pass
Infrared absorption per reference USP Polyvinyl alcohol	Pass	Pass	Pass	Pass	Pass	Pass
Precipitation reaction	White turbid precipitate	Pass	Pass	Pass	Pass	Pass
Specific tests						
Acid value	NMT 3	1.32	1.93	1.42	1.16	1.06
Ester value	Between 125 and 153 mg KOH/g	144.6	140.6	143.8	144.8	145
Degree of hydrolysis	Between 86.5 and 89.0%	86.99%	87.43%	86.9%	87.07%	87.04%
Loss on drying	NMT 5%	1.13%	0.44%	2.21%	0.66%	0.64%
pH	5.0 - 6.5	5.06	5.03	5.26	5.04	5.11
Residue on ignition	NMT 1%	0.62%	0.85%	0.86%	0.71%	0.74%
Viscosity	85 -115% of viscosity value referenced by vendor (4% aqueous solution at 20 C)*	8.034 mPa·s	7.517 mPa·s	7.816 mPa·s	7.484 mPa·s	7.482 mPa·s
Water insoluble substances	NMT 0.1%	0.04%	0.09%	0.03%	0.06%	0.01%
Heavy metals						
Lead	NMT 2 ppm	NMT 2 mg/kg	NMT 2 mg/kg	NMT 2 mg/kg	NMT 2 mg/kg	NMT 2 mg/kg
Organic impurities						
Methanol	NMT 1%	0.65%	0.79%	0.43%	0.94%	0.95%
Methyl acetate	NMT 1%	0.11%	0.19%	0.29%	0.18%	0.19%

150,000 g/mol PVOH

Galbraith ID #		234-165-G	234-165-H	234-165-I	234-165-J	234-165-K	234-165-L
Lot #		DE13017786	DE13018266	DE13018403	DE13016996	DE13017786	DE13016983
Identification							
Color reaction A	Blue color	Pass	Pass	Pass	Pass	Pass	Pass
Color reaction B	Dark red to blue color	Pass	Pass	Pass	Pass	Pass	Pass
Infrared absorption per reference USP Polyvinyl alcohol	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Precipitation reaction	White turbid precipitate	Pass	Pass	Pass	Pass	Pass	Pass
Specific tests							
Acid value	NMT 3	1.51	1.58	1.32	0.9	1.45	0.88
Ester value	Between 125 and 153 mg KOH/g	140.9	140.8	138.9/139.4	139.8	139.9	141.8
Degree of hydrolysis	Between 86.5 and 89.0%	87.37%	87.37%	87.5/87.45%	87.48%	87.47%	87.25%
Loss on drying	NMT 5%	0.92%	0.90%	1.54%	1.27%	0.91%	1.53%
pH	5.0 - 6.5	5.05	5.01	5.06	5.08	5.05	5.27
Residue on ignition	NMT 1%	0.44%	0.35%	0.41%	0.30%	0.43%	0.72%
Viscosity	85 -115% of viscosity value referenced by vendor (4% aqueous solution at 20 C)*	21.567 mPa·s	19.946 mPa·s	20.163 mPa·s	20.736 mPa·s	21.465 mPa·s	21.168 mPa·s
Water insoluble substances	NMT 0.1%	0.02%	0.10%	0.01%	<0.01%	0.03%	<0.01%
Heavy metals							
Lead	NMT 2 ppm	NMT 2 mg/kg	NMT 2 mg/kg	NMT 2 mg/kg	NMT 2 mg/kg	NMT 2 mg/kg	NMT 2 mg/kg
Organic impurities							
Methanol	NMT 1%	0.82%	0.82%	1.00%	0.51%	0.79%	0.54%
Methyl acetate	NMT 1%	0.36%	0.22%	0.22%	0.10%	0.34%	0.28%

* Per USP monograph for PVOH the pass/fail criterion is 85% to 115% of viscosity value mentioned on bottle. For the PVOH with a molecular weight of 67,000 g/mol, the target viscosity is 8 mPa·s, and for the PVOH with a molecular weight of 150,000, the target viscosity is 23 mPa·s. Hence, we would "pass" per this pass/fail criteria. The methodology per Galbraith is similar, with one change being that a filtration step is included in the viscosity test per the PVOH USP monograph.

From: Drozen, Melvin S.
To: Morissette, Rachel
Cc: Alsobrook, Lisa P.
Subject: Questions for GRN 000767 (PVOH)
Date: Wednesday, June 20, 2018 1:49:42 PM
Attachments: image014.png
Letter to FDA (response to questions on GRN 767) .pdf
GRN 767, Part 6.2 - revised.pdf
6-8-18 GRN767 Questions for Notifier.pdf

Dear Dr. Morissette,

Please find the attached letter and revised Section 6.2 that we are submitting on behalf of our client, MonoSol LLC, to address the list of questions posed by FDA(in the attached June 8 list of questions) regarding MonoSol's Generally Recognized as Safe (GRAS) notice, designated GRN 767, for the use of polyvinyl alcohol (PVOH) as a component of water-soluble, edible film intended for use to form pouches containing pre-portioned aliquots of dry ingredients. We look forward to the Agency's continued review of GRN 767, and receipt of a "no questions" letter in the foreseeable future. Please let us know if you need any further information.

Sincerely,

Mel Drozen.

Melvin S. Drozen
Partner
tel: +1 202.434.4222 | fax: +1 202.434.4646 | drozen@khlaw.com
1001 G Street NW, Suite 500 West | Washington, DC 20001

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Friday, June 8, 2018 11:58 AM
To: Drozen, Melvin S. <Drozen@khlaw.com>
Subject: questions for GRN 000767 (PVOH)

Dear Mel,

Please see attached our list of questions for GRN 000767 as we discussed over the phone yesterday. Please let me know if you have further questions.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

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June 20, 2018

Via Electronic Mail

Rachel Morissette, Ph.D.
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Campus Drive
College Park, MD 20740

Re: Response to FDA's Questions Regarding MonoSol's GRN 767

Dear Dr. Morissette:

We are writing on behalf of our client, MonoSol LLC, to address a list of questions posed by the Food and Drug Administration (FDA) regarding the Generally Recognized as Safe (GRAS) notice that we submitted on March 14, 2018 for the use of polyvinyl alcohol (PVOH) as a component of water-soluble, edible film intended for use to form pouches containing pre-portioned aliquots of dry ingredients. As elaborated upon in our June 7, 2018 teleconference, there are three categories of dry ingredients that may be packaged in the edible film: (1) instant tea, instant coffee, hot chocolate mix, flavored drink powder, and whey protein supplement powder to be used by the consumer to prepare a single serving of the food or beverage for personal consumption, (2) colors to be used by processing plants to make large batches of flavored beverages (non-dairy and non-alcohol) for bottling, and (3) dry ingredients to be used by commercial establishments to make large batches of pizza dough for making pizzas in a restaurant or fast food setting.[1] FDA's questions, from your June 8, 2018 letter, are listed below and followed by our responses.

Question 1. Section 6.2 of the notice contains discussions on toxicological studies used to support MonoSol's GRAS conclusion. In those individual study discussions, MonoSol does not indicate whether they concur or disagree with the findings of the studies and whether those studies support their independent GRAS conclusion. Please provide

[1] *See* GRN 767 at Section 1.4 (Applicable conditions of use of the notified substance) on pages 3 – 4.

statements for each study discussed indicating if MonoSol concurs with the study findings and whether these findings support the GRAS conclusion. Please provide a revised Section 6.2 highlighting the changes made.

Response

We have revised Section 6.2 to indicate that MonoSol concurs with the findings of each study summarized and has determined that these findings support MonoSol's conclusion that PVOH is GRAS for the intended uses described in GRN 767. The revised Section 6.2 is attached, and changes are highlighted as requested by FDA. Further, we reviewed the available data and information on PVOH prior to submitting GRN 767, and we are not aware of any data and information that are, or may appear to be, inconsistent with MonoSol's conclusion of GRAS status.

Question 2. The notice does not clearly indicate MonoSol's GRAS conclusion. Please provide a statement indicating that based on the data and information presented in the notice, MonoSol concludes that PVOH is GRAS for its intended use.

Response

MonoSol concludes that PVOH is GRAS for use as a component of water-soluble, edible film intended for use to form pouches containing pre-portioned aliquots of (1) certain dry ingredients (*i.e.*, instant tea, instant coffee, hot chocolate mix, flavored drink powder, and whey protein supplement powder) to be used by the consumer in preparing ready-to-serve foods and beverages, (2) colors to be used by processing plants in manufacturing flavored beverages (non-dairy and non-alcohol), and (3) dry ingredients to be used by commercial establishments in making pizza dough. This conclusion is based on the data and information presented in GRN 767, including the results of the subchronic toxicity and two-generation studies in rats discussed in Sections 6.3.3 and 6.2.6, respectively, which are published in peer-reviewed scientific journals, together with the estimated daily intake (EDI) of PVOH of 45.16 mg/kg bw/day, which represents the cumulative EDI for all uses described in GRN 767 and the EDI for existing pharmaceutical and dietary supplement (capsule) applications for PVOH that was calculated in GRN 141. MonoSol concludes that the toxicological data support an acceptable daily intake (ADI) for polyvinyl alcohol of 50 mg/kg bw/day, as discussed at Section 6.2.6, as compared to the conservatively calculated EDI of PVOH of 45.16 mg/kg bw/day (*i.e.*, below the ADI).

Question 3. We note that there are discrepancies between Table 1 (Maximum potential level of PVOH in consumer products) and Table 3 (EDI of PVOH from the intended use in edible film). In our phone conversation, you clarified this difference between the tables as follows: "color packs" and "'pizza dough packs" are not included in Table 1 due to their use in a manufacturing setting. Specifically, you noted that color packs would be

used in the manufacturing of beverages; these color packs would be used in large quantities of beverage solution that would then be bottled for sale. Additionally you stated that the color packs and the flavored drinks would not be used in the same beverage serving, because the use of PVOH in flavored drinks is intended for end-consumer use in a single serve size, and color packs are intended for use in the manufacturing of beverages; therefore, the consumer should not be exposed to PVOH by both of these uses in one beverage serving. You stated that the pizza dough packets refer to dry ingredients, such as yeast, spices, and salt, that would be further added to flour and water to make pizza dough. Please concur if this is an accurate description of your intended use of PVOH in the notice.

Response

We concur with FDA's description above of the intended uses of PVOH in GRN 767. Table 1 (Maximum potential level of PVOH in consumer products) provides the maximum amount of PVOH in a serving and the serving size that is associated with the maximum potential amount of PVOH in single-serving sizes of instant tea, instant coffee, hot chocolate mix, flavored drink powder, and whey protein supplement powder prepared by a consumer as described in Section 1.4.1. Table 3 (EDI of PVOH from the intended use in edible film), in addition to providing the EDIs for single-serving consumer products made with PVOH, also provides the EDIs for PVOH from colors to be used by processing plants in manufacturing flavored beverages (non-dairy and non-alcohol) and dry ingredients to be used by commercial establishments in making pizza dough, as described in Sections 1.4.2 and 1.4.3, respectively, as well as the EDI for PVOH from pharmaceutical and dietary supplement applications (capsule), as described in GRN 141.

Question 4. In the notice's discussion of the subchronic study by Kelly et al. (2003), it is stated that the anogenital staining was observed in rats. However, in the study text, the authors state that the anogenital staining was observed in male rats only. Further, the reasoning for the anogenital staining (which occurred in the middle and the highest dose) is stated in the notice as "This finding was attributed to the consumption and excretion of high levels of polyvinyl alcohol." This statement only confirms that this is a treatment-related effect, but does not provide an explanation of why this treatment-related effect is not toxicologically relevant. Please clarify the sex of the rats found to have adverse effects in this study. Also, please provide an explanation for why this treatment-related effect is not toxicologically relevant, i.e., why this is not an adverse effect.

Response

Revisions to the attached Section 6.2, discussed above with respect to our response to FDA's Question 1, also include clarification regarding the sex of the rats observed to have

anogenital staining (*i.e.*, male) in the subchronic study by Kelly et al. (2003), and an explanation of why the anogenital staining is not toxicologically relevant.

* * *

We hope and trust that the information above and in the attached, revised Section 6.2 responds fully to FDA's questions regarding MonoSol's GRN 767. We look forward to the Agency's continued review of the Notice and we would be happy to provide you with any further information you may need.

Sincerely,

Melvin S. Drozen
Counsel to MonoSol LLC

Attachment

6.2. Toxicological Studies

6.2.1. ADME

Following oral administration, polyvinyl alcohol was found to be poorly absorbed from the gastrointestinal tract (EFSA, 2005; Sanders and Matthews, 1990). In an experiment in the rat, over 98% of the radioactivity associated with a single oral dose (0.01 mg/kg ^{14}C-labeled) of polyvinyl alcohol was excreted in the feces within 48 hours of administration (Sanders and Matthews, 1990). In this study, < 0.2% of the total radioactivity was detected in the urine. To further characterize absorption and subsequent bioaccumulation, Sanders and Matthews (1990) administered 0.10 mg/kg ^{14}C-labeled polyvinyl alcohol to rats via gavage for 10 consecutive days. The majority (~ 100%) of the radioactivity was found in fecal matter, suggesting that polyvinyl alcohol is very poorly absorbed by the oral route (Sanders and Matthews, 1990). The EFSA Expert Panel concluded that ~~as~~ polyvinyl alcohol is very poorly absorbed, ~~there is minimal amount~~ from the gastrointestinal tract and is, thus, unavailable for distribution through the bloodstream to the internal ~~body~~ tissues and organs of the body ~~and only trace amounts are likely to be absorbed~~ (EFSA, 2005). MonoSol agrees with the Panel's conclusion that the data reported by Sanders and Matthews (1990) show that only trace amounts of polyvinyl alcohol can be absorbed in the digestive tract. MonoSol notes that a substance or its breakdown products must be absorbed from the gastrointestinal tract and reach the internal organs and tissues in sufficient amounts to have the potential to exert systemic effects in the body. MonoSol concurs with the determinations of Sanders and Matthews (2009) and the EFSA Panel (EFSA, 2005) that polyvinyl alcohol is not broken down or absorbed systemically to any significant extent in the gastrointestinal tract and that it passes through and is excreted from the gastrointestinal tract essentially intact and unabsorbed. MonoSol determines that these observations support MonoSol's conclusion that polyvinyl alcohol is GRAS when used as intended as a component of edible film for (1) certain dry ingredients (*i.e.*, instant tea, instant coffee, hot chocolate mix, flavored drink powder, and whey protein supplement powder) to be used by the consumer in preparing ready-to-serve foods and beverages, (2) colors to be used by processing plants in manufacturing flavored beverages (non-dairy and non-alcohol), and (3) dry ingredients to be used by commercial establishments in making pizza dough.

6.2.2. Acute Toxicity

Acute oral toxicity of polyvinyl alcohol has been evaluated in rats, mice and dogs. The LD_{50} values of polyvinyl alcohol for mice, rats and dogs following oral administration have been reported to range from > 1.5 to approximately 22 g/kg bw (JECFA, 2003; EFSA, 2005).[1] The oral LD_{50} of polyvinyl alcohol in mouse, rat and dog studies were

[1] JECFA and EFSA cited unpublished studies, *i.e.*, Burford and Chappel (1968) and Hazleton Laboratories (1959), and one published study, *i.e.*, Zaitsev, N.A., Skachkova, I.N., Sechenov, I.M. Substantiation of hygienic norms in water media of some polymer compounds

reported as > 4000, >21500 and > 20000 mg/kg bw, respectively. MonoSol notes that the acute oral LD_{50} of polyvinyl alcohol exceeds the greatest of the very high doses tested in acute toxicity studies, which is consistent with the very poor absorption of this ingredient in the gastrointestinal tract. MonoSol determines that polyvinyl alcohol is practically nontoxic following acute oral administration, which supports MonoSol's GRAS conclusion for the intended use of this ingredient.

6.2.3. Subchronic Toxicity

Kelly et al. (2003) investigated the potential systemic and neurotoxic effects of polyvinyl alcohol in a GLP-compliant rat study. In this study, male and female Sprague-Dawley rats (20/sex/group) were fed a diet providing dose levels of 0, 2,000, 3,500 and 5,000 mg/kg/day for 90 days. Control rats (20/sex) were given untreated standard laboratory diet. Assessments included clinical observations, ophthalmology, body weight and food consumption, hematology, coagulation, clinical chemistry, urinalyses, motor activity and functional observational battery evaluations and gross and microscopic pathology. The only overt polyvinyl alcohol treatment-related finding observed during the study was unformed stool with brown/black anogenital staining in male rats fed 3,500 and 5,000 mg/kg bw/day. This finding was attributed to the consumption and excretion of high levels of polyvinyl alcohol. It was not accompanied by macroscopic or microscopic changes in these rats. MonoSol agrees with Kelly et al. (2003) that unformed stool and anogenital staining observed in the males exposed to the two highest doses of polyvinyl alcohol in this study was caused by the large amount of unabsorbed polyvinyl alcohol in the stool of these animals. MonoSol notes, in agreement with the authors of this study, that the unabsorbed polyvinyl alcohol in the colon of these animals is conducive to water retention in the stool, resulting in soft stools and staining of the anogenital area from the excretion of softened, potentially watery stools. MonoSol concurs with the authors that this is a physiological process, not a toxic effect. (This laxative effect is not expected in consumers at the ADI derived for polyvinyl alcohol (*i.e.*, 50 mg/kg bw/day), which is much lower (*i.e.*, 40 times lower) than the dose that did not produce the effect in the male or female rats in this study (*i.e.*, 2000 mg/kg bw/day). No treatment-related changes were noted in mortality, ophthalmology, body weight and food consumption data, hematology, clinical chemistry, urinalysis data, functional observational assessments, motor activity, organ weight data and macroscopic and microscopic examinations. The investigators concluded that administration of polyvinyl alcohol as a dietary admixture to rats at doses of 2,000, 3,500 and 5,000 mg/kg/day for up to 90 days did not result in any adverse, toxicological effects. The results of this study suggest a NOAEL of 5,000 mg/kg/day. The polyvinyl alcohol used in the Kelly et al. (2003) study was 85-89% hydrolyzed, like the polyvinyl alcohol that is the subject of the present GRAS assessment. MonoSol concurs with the findings and interpretation of the results of the study Kelly et al. (2003) study, as reported by the authors of this study, and determines that the data support MonoSol's GRAS conclusion for the intended use of polyvinyl alcohol.

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using "stage-by-stage" principle = [Substantiation of hygienic standards for some polymeric compounds in water with the use of gradual standardization]. Gig Sanit 10, 75-76, 1986.

6.2.4. ~~Mutagenicity~~ Genotoxicity

In a series of experiments, Kelly et al. (2003) also investigated the genotoxic potential of polyvinyl alcohol: (1) in a bacterial reverse mutation assay in *Salmonella typhimurium* and *Escherichia coli* (Ames assay); (2) in an *in vitro* forward mutation assay in a sub-line of mouse lymphoma L5178Y cells; and (3) in an *in vivo* mouse micronucleus assay. In the Ames assay, polyvinyl alcohol at concentrations of up to 5,000 µg/plate, both in the presence and absence of liver preparations from Aroclor 1254-induced rats (S9 mix), was not mutagenic to *S. typhimurium* strains TA1535, TA1537, TA98 and TA100, or to a tryptophan-dependent mutant of *E. coli* strain WP2*uvr*A/pKM101 (CM 891) (Kelly et al., 2003). Similarly, in the mouse lymphoma assay, in the presence and absence of metabolic activation (S9 mix), polyvinyl alcohol at concentrations up to 5,000 µg/mL did not increase the incidence of forward mutations at the thymidine kinase locus (TK+/-). In the *in vivo* mouse micronucleus assay, administration of single doses of polyvinyl alcohol via oral gavage to male and female Swiss mice at doses of up to 2,000 mg/kg bw did not show any evidence of causing chromosome damage or bone marrow cell toxicity at 24 to 48 hours following administration. These observations are further supported by the studies described in the JECFA evaluation of polyvinyl alcohol (JECFA, 2003). As described in the JECFA report, negative results were noted in several strains of *S. typhimurium* in both the presence and absence of metabolic activation, as well as in an *in vitro* Chinese hamster V79 chromosomal aberration assay and *in vivo* in a female mouse bone marrow micronucleus test.

MonoSol concludes from the publicly available data that polyvinyl alcohol is not genotoxic, which supports MonoSol's GRAS conclusion.

6.2.5. Chronic Toxicity and Carcinogenicity

In the published literature, no chronic toxicity or carcinogenicity studies were found following oral administration of polyvinyl alcohol. In a well-designed 2-year National Toxicology Program (NTP) study, intra-vaginal administration of polyvinyl alcohol to female B6C3F1 mice did not reveal compound-related neoplastic or non-neoplastic lesions. The only clinical finding observed in this study was vaginal irritation (NTP, 1998). The NTP concluded that "under the conditions of this 2-year study, there was no evidence of carcinogenic activity...." MonoSol concludes that the absence of carcinogenic activity reported in a lifetime bioassay conducted by the NTP in exposed intra-vaginally to polyvinyl alcohol indicates that polyvinyl alcohol is not carcinogenic, does not pose a carcinogenic risk from dietary exposures to this ingredient and, thus, supports MonoSol's GRAS conclusion.

6.2.6. Reproduction and Developmental Toxicity

In a GLP-compliant study, Rodwell et al. (2003) investigated the effects of polyvinyl alcohol on fertility, early embryonic development, growth and subsequent development in rats. In this 2-generation study, groups of P_0 and F_1 parental Sprague-Dawley rats (26/sex/group) were fed diets containing polyvinyl alcohol at dose levels providing dose levels of 2,000, 3,500, or 5,000 mg/kg bw/day for at least 70 consecutive days prior to

mating. The treatment of male rats was continued during the 14-day mating period and throughout the post-mating period until euthanized. Female rats continued their respective treatments during the 14-day mating period, gestation, and lactation. Females were generally euthanized on lactation day 21. As evaluated by mating and fertility indices and sperm counts, polyvinyl alcohol did not induce any treatment-related effects on P_0 or F_1 male reproductive performance. Similarly, as assessed by mating, fertility, and pregnancy indices, and estrous cycling data, there were no biologically significant effects attributable to polyvinyl alcohol treatment on P_0 or F_1 female reproductive performance. No polyvinyl alcohol related effects on litter parameters (litter size, pup sex distribution, pup survival, clinical observations, and body weights) in either the F_1 or F_2 generation were noted. Absolute organ weights, or organ to body weights and organ to brain weight ratios were unaltered by polyvinyl alcohol treatment in both F_1 and F_2 generations. Macroscopic and microscopic observations performed on the P_0 and F_1 parental animals and of the F_1 and F_2 pups did not reveal any adverse effects from polyvinyl alcohol exposure. The results of this study suggest a NOAEL 5,000 mg/kg bw/day for both parental and offspring in this reproductive study, the highest dose tested (Rodwell et al., 2003 MonoSol concurs that 5,000 mg/kg bw/day is an appropriate NOAEL for parental rats and offspring based on the data published by Rodwell et al. (2003).

In addition, MonoSol concurs with the ADI of 50 mg/kg bw/day established by JECFA for polyvinyl alcohol, which was calculated by applying a safety factor of 100 (*i.e.*, 10 for interspecies difference and 10 for intraspecies variability) to the NOAEL of 5000 mg/kg bw/day obtained from the two-generation study in rats as well as the subchronic toxicity study discussed in Section 6.2.3. above.

From: Drozen, Melvin S.
To: Morissette, Rachel
Cc: Alsobrook, Lisa P.
Subject: RE: question on literature search for GRN 767
Date: Friday, June 29, 2018 3:53:00 PM
Attachments: image002.png

Dear Rachel,

The last full literature search we did for GRN 767 was January 10, 2018 which we reconfirmed yesterday. We trust that this is satisfactory. Regards. Mel.

Melvin S. Drozen
Partner
tel: +1 202.434.4222 | fax: +1 202.434.4646 | drozen@khlaw.com
1001 G Street NW, Suite 500 West | Washington, DC 20001

From: Drozen, Melvin S.
Sent: Thursday, June 28, 2018 1:43 PM
To: 'Morissette, Rachel' <Rachel.Morissette@fda.hhs.gov>
Cc: Alsobrook, Lisa P. <alsobrook@khlaw.com>
Subject: RE: question on literature search for GRN 767

Hello Rachel,

OK. Let me check.

Regards,

Mel.

Melvin S. Drozen
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tel: +1 202.434.4222 | fax: +1 202.434.4646 | drozen@khlaw.com
1001 G Street NW, Suite 500 West | Washington, DC 20001

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Thursday, June 28, 2018 12:46 PM
To: Drozen, Melvin S. <Drozen@khlaw.com>
Subject: question on literature search for GRN 767

Hi Mel,

Can you please confirm the date through which a literature search was conducted for GRN 000767? I did not see it listed in the notice. We have been including that information in our No Questions letters, and I realized that I was missing that information.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
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