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February 21, 2022

Via FedEx

Dr. Paulette Gaynor
Office of Food Additive Safety
CFSAN
Food and Drug Administration
5100 Campus Drive
College Park, MD 20740

**Re: GRAS Notification for NABACO LLC's Use of Polyvinyl Alcohol
(PVOH) as a Component of Coatings for Fruits and Vegetables**

Dear Dr. Gaynor:

On behalf of NABACO LLC, I hereby submit the enclosed GRAS Notification for the use of polyvinyl alcohol (PVOH) as a component of fruit and vegetables coatings. The attached GRASN provides the information required under 21 CFR 170.220 *et seq.* Enclosed is both a paper copy and an electronic version on a thumb drive. The thumb drive has been scanned with Webroot and was found not to contain any electronic virus.

Should you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

A solid gray rectangular box used to redact the signature of Mark L. Itzkoff.

Mark L. Itzkoff

GRAS Notification for Polyvinyl Alcohol

Prepared for: U.S. Food and Drug Administration
Office of Food Additive Safety
CFSAN
5001 Campus Drive
College Park, MD 20740

Prepared by: Soni & Associates Inc.
749 46th Square
Vero Beach, FL 32968, USA

And

Mark L. Itzkoff
Attorney
1629 K St., NW
Suite 300
Washington, DC 20006

Date: February 14, 2022

Table of Contents

PART 1 – SIGNED STATEMENTS AND CERTIFICATION.....	4
1.1. Applicability of 21 CFR Part 170, Subpart E	4
1.2. Name and Address of Notifier	4
1.3. Name of the Substance.....	4
1.4. Intended Conditions of Use.....	4
PART II - IDENTITY AND TECHNICAL INFORMATION.....	7
2.1. Description.....	7
2.2. Specifications and Identity.....	7
2.3. Manufacturing Process.....	8
PART III - DIETARY EXPOSURE	10
3.1. Estimated Daily Intake from the Proposed Uses.....	10
3.2. Cumulative Intake from Existing and Proposed Uses.....	13
3.3. Consumption Summary.....	14
PART IV - SELF LIMITING LEVELS OF USE	15
PART V - EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958	16
PART VI - NARRATIVE.....	17
6.1. Data Pertaining to Safety	17
6.2. Toxicological Studies.....	17
6.2.1. Toxicokinetics	17
6.2.2. Acute Toxicity.....	18
6.2.3. Subchronic Toxicity	18
6.2.4. Mutagenicity Genotoxicity	18
6.2.5. Chronic Toxicity and Carcinogenicity	19
6.2.6. Reproduction and Developmental Toxicity	19
6.3. National and International Regulatory Agencies Assessments.....	20
6.3.1. GRAS Notification on Polyvinyl alcohol.....	20
6.3.2. JECFA Evaluation	22

6.3.3. European Commission Evaluation22

6.3.4. Additional Regulatory Citations and Uses.....23

6.4. Safety of Other Constituents23

6.5. Summary, Discussion and Conclusion 24

Part VII- SUPPORTING LITERATURE AND REFERENCES27

Appendix I29

PART 1 – SIGNED STATEMENTS AND CERTIFICATION

1.1.Applicability of 21 CFR Part 170, Subpart E

We submit this GRAS Notice in accordance with 21 CFR Part 170, Subpart E.

1.2.Name and Address of Notifier

Company: NABACO LLC
Name: Dr. Gary Beall, CEO
Address: 5040 SH 123
Bldg. 500
San Marcos, Texas 78666

1.3.Name of the Substance

The name of the substance of this GRAS assessment is polyvinyl alcohol (PVOH), CAS Number 9002-89-5. It is also known as vinyl alcohol polymer. The Notifier intends to use the substance as a component of the NABACO fruit and vegetable coating products marketed under the tradename NatuWrap PA™.

1.4.Intended Conditions of Use

NABACO intends to use polyvinyl alcohol as a surface-finishing agent and/or texturizer as defined at 21 CFR 170.3 (o)(30) and (32). Under the intended conditions of use the polymer will be one component of a product that will create a thin edible film that will function as a physical barrier on fruits and vegetables. This barrier will reduce moisture loss and oxidation to protect the freshness and extend the shelf-life of agricultural products. It will be applied to the surface of fruits (e.g., berries, grapes, stone fruit, citrus, bananas, mangoes, avocados) and vegetables (e.g., legumes, roots, tubers) at levels consistent with current Good Manufacturing Practice and is self-limiting for technological reasons. The maximum application will be 0.133 grams per pound of food.

1.5.Statutory Basis for GRAS Determination

This GRAS determination for the use of polyvinyl alcohol is based on scientific procedures in accordance with 21 CFR 170.30(a) and 170.30(b).

1.6.Exemption from Premarket Approval Requirements

GRAS Notice for Polyvinyl Alcohol
Submitted by NABACO LLC

It is the view of NABACO LLC that under the intended conditions of use, polyvinyl alcohol is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on our conclusion that polyvinyl alcohol, meeting the specifications cited herein, and when used as a food ingredient and as a nutrient, is GRAS and is therefore exempt from the premarket approval requirements.

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

1.7.Availability of Data and Information

The data and information that are the basis for this GRAS conclusion will be made available to the FDA upon request by contacting Mark Itzkoff, Counsel for NABACO, at the below address. The data and information will be made available to the FDA in a form in accordance with that requested under 21 CFR 170.225(c)(7)(ii)(A) or 21 CFR 170.225(c)(7)(ii)(B).

Mark L. Itzkoff
Counsel for NABACO, Inc.
1629 K St., NW
Suite 300
Washington, D.C. 20006

Tel: 202-600-7704
Email: Mark@Itzkofflaw.com

1.8.Applicability of FOIA exemptions

Parts 2 through 7 of the GRASN do not contain any privileged or confidential information such as trade secrets and/or commercial or financial information that would be exempt from disclosure under the Freedom of Information Act.

1.9.Certification

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

GRAS Notice for Polyvinyl Alcohol
Submitted by NABACO LLC

1.10. Name, position/title of responsible person who signs dossier and signature:



~~Dr. Gary Beall, CEO~~
~~CEO, NABACO~~

02/15/2022
Date

Please address correspondence to NABACO Counsel:

Mark Itzkoff
1629 K St., NW
Suite 300
Washington, DC 20006

Phone: 202-600-7704
Email: Mark@Itzkofflaw.com

1.11. USDA/FSIS

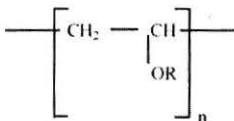
NABACO does not intend to use polyvinyl alcohol in any meat and/or poultry applications. Therefore, 21 CFR 170.270 does not apply.

PART II - IDENTITY AND TECHNICAL INFORMATION

2.1. Description

The subject of this GRAS assessment, polyvinyl alcohol, occurs as an odorless translucent, white, or cream-colored granular powder. The Food Chemicals Codex (FCC 2019; 11th Edition Third Supplement) has updated the monograph on polyvinyl alcohol and provides its description and specifications. Polyvinyl alcohol 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. Physical and chemical properties of polyvinyl alcohol vary and depends on the degree of polymerization. Polyvinyl alcohol insoluble in aliphatic and aromatic hydrocarbons, esters, ketones, and oils. The general descriptive properties of polyvinyl alcohol, along with structural formula is provided in Table 1.

Table 1. General Descriptive Characteristics of Polyvinyl Alcohol*

Parameter	Description
Common name	Polyvinyl alcohol
Synonyms	Vinyl alcohol polymer; Poly(vinyl alcohol); Ethenol homopolymer; PVOH; Hydroxyethene
CAS Number	9002-89-5
EC Number	209-183-3; 618-340-9
Chemical/Molecular formula	$(C_2H_3OR)_n$ where R=H or COCH ₃ (randomly distributed)
Structural formula	
Molecular weight	Ranges from 37,000 to 150,000 g/mol
Degree of Hydrolysis	Between 86.5 and 89%
Color	White or cream
Physical form	Granular powder
Solubility	Water; sparingly soluble in ethanol
Uses/Technical effects	Coating binder; sealing agent; surface finishing agent

*Based on publicly available information and provided by NABACO (2021)

2.2. Specifications and Identity

Food grade specifications for the polyvinyl alcohol used by NABACO have been established and are presented in Table 2. Where applicable these specifications comply with the polyvinyl alcohol monograph published in FCC (2019).¹ The functional use of polyvinyl alcohol in the food industry includes, among other uses, as a coating, binder, sealing agent, and surface finishing agent where polyvinyl alcohol is ingested (FCC, 2019).

¹ In the NABACO application, the polymer will dissolve in an aqueous solution. Therefore, the particle size is not relevant and is not measured in the quality control testing.

GRAS Notice for Polyvinyl Alcohol
Submitted by NABACO LLC

In addition to FCC, the chemical and physical characteristics of polyvinyl alcohol have also been reviewed in several other national and international official monographs, including the United States Pharmacopeia (USP, 2004) and the JECFA (2003; 2007). All analytical methods are validated for their intended use. Analytical results of three independently produced, representative batches are attached in Appendix I. The PVOH manufacturer, Kuraray, does not test every lot for lead levels. Rather, they monitor the lead level in their products on an ongoing basis and have determined that the level remains below 1 part per million.

Table 2. Specifications of Polyvinyl Alcohol

Parameter	Characteristics	Reference/Test Methodology
Description	Translucent, white or cream-colored granular powder	Visual inspection
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	4.8–5.8 mPa·s (4% aqueous solution at 20°C)	FCC
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; ppm = part per million

2.3. Manufacturing Process

Polyvinyl alcohol is manufactured according to current good manufacturing practices (cGMP) and is essentially the same as the process described in GRAS Notice 767. PVOH is manufactured by polymerizing vinyl acetate monomer (VAM) to polyvinyl acetate and subsequent controlled hydrolysis (saponification) of the polyvinyl acetate to PVOH.

Polymerization of VAM takes place in methanol with a proprietary agent to initiate the polymerization reaction.

The saponification process is passed on the partial replacement of ester groups in vinyl acetate with hydroxyl groups using sodium hydroxide. Both the degree of polymerization and degree of saponification are controlled by modifying reaction conditions such as residence time, concentration of reaction agent and reaction temperature.

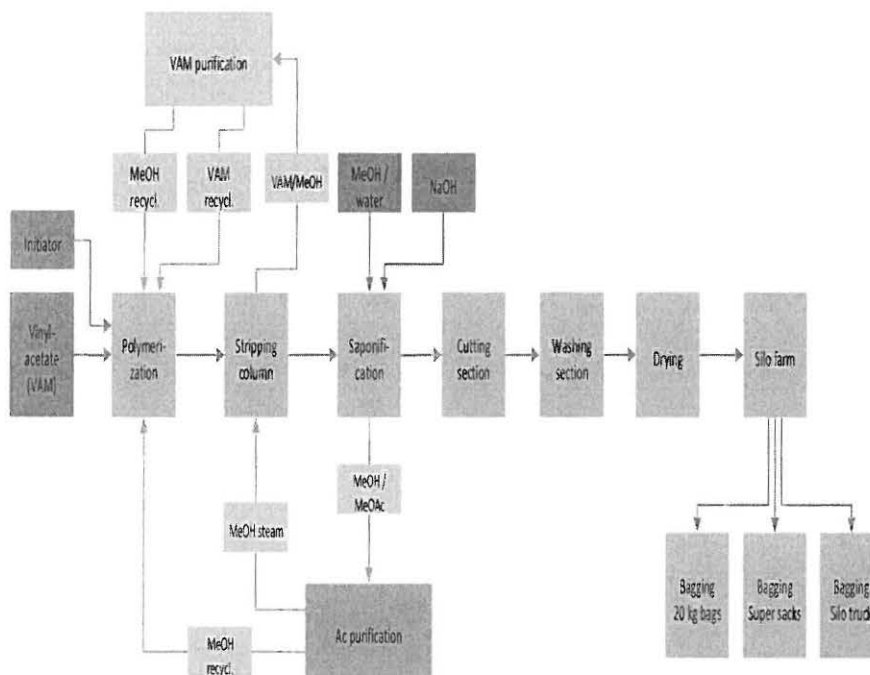
GRAS Notice for Polyvinyl Alcohol
Submitted by NABACO LLC

During saponification, the resulting PVOH precipitates from the methanol solution and forms a gel. The gel is subsequently cut into granules. Following this the PVOH is washed and dried.

In the production process two major solvent mixtures are generated. First, a mixture of VAM and methanol, and secondly, a mixture of methyl acetate in methanol. Both mixtures are recycled in separate distillation processes. The purified solvents are then reused in the production process.

Primary side components are sodium acetate, methanol and methyl acetate which are removed during the washing and drying production step. The final product is tested for compliance with Kuraray specifications.

The manufacturing process is set forth in Figure 1, below.



Effective as of November 2021

PART III - DIETARY EXPOSURE

3.1. Estimated Daily Intake from the Proposed Uses

Under the intended conditions of use, NABACO's NatuWrap PA™ containing polyvinyl alcohol will be used as a coating on fruits and vegetables. When used as directed, NatuWrap PA™ will be applied to the outside of the peel of fruits and vegetables. The quantity of NatuWrap PA™ recommended for use varies with the specific application, however the maximum application rate will result in a maximum of 0.133 g polyvinyl alcohol per pound of food (0.29 g/kg).

A. Fruit

NatuWrap PA™ will be applied to the peels of fruits that may be consumed with peels or without peels. Fruits where the peel or rind is removed or discarded before the food is consumed include bananas, citrus fruit, squash, and watermelon. The polyvinyl alcohol component of the NatuWrap PA™ coating is not expected to migrate through the fruit skin into the edible portions of these foods. While NatuWrap PA™ may be used on apples, oranges or grapes, it is expected that the product will remain on the peel and not present in juice extracted from these or other fruits. The primary source of consumer exposure to NatuWrap PA™ will be raw fruit with edible peels (RFEP).

In a recent report, Kimmons et al. (2009) reviewed data from the 2003-2004 National Health and Nutrition Examination Survey (NHANES) and determined the dietary contribution of fruits and vegetables from multiple sources. As shown in Table 3, below, the study reported on the ten most reported fruit and vegetable sources for adolescents, men over 19 years of age, and women over 19 years of age.

Table 3. Reported RFEP Fruit Sources as Percentage of Total Fruit Intake

Fruit	Adolescents Age 12 – 18 Years	Men Age ≥ 19 Years	Women Age ≥ 19 Years
Apples, raw	9.9	9.7	8.5
Grapes, raw	3.8	3.5	3.4
Strawberries, raw	Not Reported	1.6	2.2
Total	13.7	14.8	14.1
% total fruit intake represented by top 10	72.4	66.9	61.6
Percent RFEP in top 10	18.9	22.1	22.8

It is reasonable to assume that the percentage of RFEP in the total fruit intake is close to the percentage of RFEP in the top 10 fruit sources, *i.e.*, less than 25%. Thus, for the purpose of this estimate, we will use 25% as the percentage of RFEP in the diet.

The US Department of Agriculture (USDA) has reported the results on the intake of various fruits and vegetables (Smiciklas-Wright et al., 2002). The reported intake for apples, strawberries, and grapes among consumers who reported eating these fruits are presented in Table 4, below.

Table 4. Average Daily Intake of Apples, Strawberries, and Grapes Among Consumers Reporting (Grams)

	All Consumers	2-5	6-11	12 – 19		20 – 39		40 – 59		60 and Over	
				M	F	M	F	M	F	M	F
Apples	14	19	18	11	10	13	11	14	14	19	14
Grapes*	12	27	17	9	13	10	9	11	9	12	10
Strawberry*	3	2	3	2	3	2	4	4	4	8	7

* - Study reported only combined intake for raw fruit and fruit juice

As noted above, NatuWrap PA™ is intended to be applied to the raw fruit at levels so that the polyvinyl alcohol concentration will not exceed 0.29 g/kg of fruit or 29 g/100 kg. According to the USDA data presented above, the average daily consumption for apples, grapes, and strawberries was 14, 12 and 3 grams, respectively, with 60-year-old males reporting the highest average consumption level for both apples and strawberries at 19 and 8 grams, respectively.

Using 14 g per day of apples, 12 g per day of grapes, and 3 g per day of strawberries as the average daily consumption, the intake of the polyvinyl alcohol from the coating is calculated as follows:

- i. Apples:
(14 g apples/day) (29 g polyvinyl alcohol/100 kg apples) = 4.1 mg/day
- ii. Grapes
(12 g grapes/day) (29 g polyvinyl alcohol/100 kg grapes) = 3.5 mg/day
- iii. Strawberries
(3 g strawberries/day) (29 g polyvinyl alcohol/100 kg strawberries) = 0.9 mg/day

The total intake from these sources would be 8.5 mg per day.

As shown in Table 3, these three fruits represent RFEP in the top 10 fruit sources and that the top 10 represent between 61.6% and 72.4% of daily fruit consumption. It is reasonable to assume that the percentage of RFEP in all fruit consumed is similar to the percentage in the top 10 sources. Using 61.6% as the minimum concentration of the top 10 sources, the daily intake of NatuWrap PA™ from all fruit would be:

$$(8.5 \text{ mg/day}) / (61.6\%) = 14 \text{ mg/day}$$

Assuming that a high end consumer eats twice as much fruit as the average consumer, the daily intake for the high end consumer would be:

$$2 \times (14 \text{ mg/day}) = \underline{28 \text{ mg/day}}$$

B. Vegetables

A similar calculation can be used to determine the intake of polyvinyl alcohol from the use of NatuWrap PA™ on vegetables with edible peels (VEP). The Kimmons et al. (2009) report cited in Table 3 also includes data on the 10 most common vegetable sources. This information is set forth in Table 5, below.

Table 5. Reported VEP Vegetable Sources as Percentage of Total Vegetable Intake

Vegetables	Adolescents Age 12 – 18 Years	Men Age ≥ 19 Years	Women Age ≥ 19 Years
White potato, baked/boiled	13.1	8.8	8.6
Beans, various	4.6	5.3	3.7
Beans, string	Not Reported	2.0	2.3
Total	17.7	16.1	14.6
% total vegetable intake represented by top 10	70.1	57.4	54.9
Percent VEP in top 10	25.2	28.0	26.6

Thus, the top 10 vegetables represent 55% to 70% of the total amount of vegetables in the diet. Using an analogous assumption as was used to calculate the intake of polyvinyl alcohol due to the use of NatuWrap PA™ on fruit, it is reasonable to estimate that VEP will represent 30% of vegetable intake.

The USDA has also published data on the consumption of vegetables (Smiciklas-Wright et al., 2002). For potatoes and string (i.e., green) beans, the consumption levels are listed in Table 6 below.

Table 6. Average Daily Intake of Baked/Boiled Potatoes, String Beans, Among Consumers Reporting (Grams)

	All Consumers	2-5	6-11	12 – 19 M F		20 – 39 M F		40 – 59 M F		60 and Over M F	
Baked Potatoes	8	3	4	7	5	10	8	9	10	12	10
Boiled Potatoes	5	2	1	3	2	4	2	7	5	11	8
String Beans	7	5	5	4	3	7	6	9	7	10	9
Total	20	10	10	14	10	21	16	25	22	33	27

Using the same polyvinyl alcohol concentration used in the calculations for fruit exposure (29 g polyvinyl alcohol/100 kg vegetable) the average consumer's intake would be as follows:

$$(20 \text{ g vegetables/day}) (29 \text{ g polyvinyl alcohol/100 kg vegetables}) = 5.8 \text{ mg/day}$$

Assuming that the top 10 reported vegetables are 55% of the total vegetables consumed and that the percentage of VEP in the diet is the same as the percentage of VEP in the top 10, then the amount of polyvinyl alcohol that may be consumed from its use on vegetables would be:

$$(5.8 \text{ mg/day})/(55\%) = 10.5 \text{ mg/day}$$

It is important to note that this estimate is very conservative since the use of NatuWrap PA™ on potatoes accounts for more than half of the amount consumed through vegetable consumption, and this estimate assumes that consumers eat the entire potato,

GRAS Notice for Polyvinyl Alcohol
Submitted by NABACO LLC

including the peel. In practice, the peel is often removed before or after frying or boiling potatoes and many consumers do not eat the peel when eating baked potatoes.

Assuming that a high end consumer would eat twice as much vegetables coated with NatuWrap PA™ as the average consumer, the quantity of polyvinyl alcohol per day for the high end consumer would be:

$$2 \times (10.5 \text{ mg/day}) = \underline{21 \text{ mg/day}}$$

C. Total

The total amount of polyvinyl alcohol NatuWrap PA™ consumed by a high end consumer from both fruit and vegetable applications would be:

$$(28 \text{ mg/day}) + (21 \text{ mg/day}) = \underline{49 \text{ mg/day}}$$

For a 60 kg consumer, the dietary intake would be:

$$(49 \text{ mg/day})/(60 \text{ kg}) = \underline{0.82 \text{ mg/kg.}}$$

3.2. Cumulative Intake from Existing and Proposed Uses

In addition to the proposed uses by NABACO, in three previous GRAS notices estimates of the polyvinyl alcohol from proposed and existing uses were provided. In the first GRAS notice (GRN 000141), Colorcon reported that the total maximum daily intake of polyvinyl alcohol from its intended use in dietary supplements and from its existing use in pharmaceutical products would be 360 mg/person/day, equivalent to 6 mg/kg bw/day for a 60 kg person. In the second GRAS notice (GRN 000767), Monosol estimated the dietary exposure to polyvinyl alcohol using consumption data from the USDA's 1994-1996 CSFII and reported that the cumulative dietary exposure, including that from GRN 000141, of polyvinyl alcohol for the total users only U.S. population is 45.16 mg/kg bw/day at the 90th percentile. In the subsequent GRAS notice (GRN, 927), Adept reported that there is no dietary exposure to polyvinyl alcohol or its constituents. Adept also noted that considering a worst-case scenario its intended use in edible film would result in the estimated daily intake of polyvinyl alcohol of 5.8 mg/person/day (0.1 mg/kg bw/day for a 60 kg individual) and the cumulative new estimated daily intake of polyvinyl alcohol of 45.26 mg/kg/day. As described above the proposed use of polyvinyl alcohol from its uses in fruits and vegetables will result in 49 mg/person/day. For a 60 kg consumer, the dietary intake of polyvinyl alcohol would be 0.82 mg/kg bw/day. The total cumulative intake from the proposed uses and previous existing uses will be 46.08 mg/kg bw/day.²

² We note that in its response to GRASN 886 submitted by Apeel for "a mixture of mono-and diglycerides derived from grape seed" or "MDAG", the agency performed an independent estimate of the dietary exposure. FDA estimated that the daily exposure for high end consumers to be 281 mg/p/d.

MDAG is intended for use in the same applications as the polyvinyl alcohol in this Notice. However, polyvinyl alcohol will be used at a much lower concentration, 0.29 mg/kg of produce versus 1.52 mg/kg for MDAG. Using the FDE estimate, the daily exposure to polyvinyl alcohol from this application would be: $((0.29 \text{ mg/kg polyvinyl alcohol})/(1.52 \text{ mg/kg MDAG}))(281 \text{ mg/p/d MDAG}) = 54 \text{ mg/p/d polyvinyl alcohol}$
For the 60 kg consumer, this would be:

3.3. Consumption Summary

In summary, the proposed use of polyvinyl alcohol as a coating on fruits and vegetables for a high end consumer will result in 49 mg/person/day or 0.82 mg/kg bw/day for an individual weighing 60 kg. The existing uses of polyvinyl alcohol from dietary supplement products, pharmaceutical products, conventional food products, and from its use in abattoirs will result in a cumulative intake of 45.26 mg/kg bw/day. Thus the total intake of polyvinyl alcohol from the proposed uses by NABACO and the existing uses will be 46.08 mg/kg bw/day. For safety assessment purposes maximum intake of polyvinyl alcohol from all sources of 46.08 mg/kg bw/day is considered.

$$(54 \text{ mg/p/d}) / (60 \text{ kg}) = 0.90 \text{ mg/kg/day}$$

The cumulative intake of polyvinyl alcohol using the FDA exposure estimate would be 46.16 mg/kg/day.

PART IV - SELF LIMITING LEVELS OF USE

The proposed use of polyvinyl alcohol on fresh (i.e., unprocessed) agricultural produce is self-limiting for technological reasons, such as appearance on produce and/or the effect on the produce's flavor profile, either of which could affect consumer acceptability. The quantity of polyvinyl alcohol to achieve the technical function is also inherently self-limiting given the unique characteristics of each fruit and vegetable and varies with the specific application. For example, over application of the substance may damage the fruit or vegetable, while under application will prohibit the maximum shelf life benefits from being achieved.

PART V - EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

The statutory basis for the conclusion of the GRAS status of polyvinyl alcohol in this document is not based on common use in food before 1958. The GRAS assessment is based on scientific procedures.

PART VI - NARRATIVE

6.1. Data Pertaining to Safety

The safety of polyvinyl alcohol has been extensively investigated and reported in the published literature. The safety of polyvinyl alcohol has been studied in different species following both oral and non-oral routes, such as rectal, intra-vaginal, subcutaneous, intravenous, intra-peritoneal and dermal. As polyvinyl alcohol is very poorly absorbed following oral administration, the findings from non-oral studies are considered not to be predictive of oral toxicity. Given this, for the safety assessment of polyvinyl alcohol, emphasis is placed on the oral studies. The available safety related information on polyvinyl alcohol includes metabolism, genotoxicity, acute toxicity, subchronic toxicity and reproductive and developmental toxicity. Additionally, the carcinogenicity of polyvinyl alcohol has been studied following intra-vaginal administration to female mice. Additionally, polyvinyl alcohol has been approved for use in coatings applied to pharmaceutical products. Several national and international regulatory and other agencies have extensively evaluated the safety of polyvinyl alcohol. All these evaluations have concluded that polyvinyl alcohol is safe for use as a food or dietary supplement ingredient at the levels described in those assessments.

In a critical evaluation of the available safety data on polyvinyl alcohol, DeMerlis and Schoneker (2003) reported that orally administered polyvinyl alcohol is relatively harmless. The safety of polyvinyl alcohol is based on the following: (1) the acute oral toxicity of polyvinyl alcohol is very low, with LD₅₀ in the range of 15-20 g/kg bw; (2) orally administered polyvinyl alcohol is very poorly absorbed from the gastrointestinal tract; (3) polyvinyl alcohol does not accumulate in the body when administered orally; (4) polyvinyl alcohol is not mutagenic or clastogenic; and (5) NOAELs of orally administered polyvinyl alcohol in male and female rats were 5000 mg/kg bw/day in the 90-day dietary study and 5000 mg/kg bw/day in the two-generation reproduction study, which was the highest dose tested.

6.2. Toxicological Studies

6.2.1. Toxicokinetics

Orally administered polyvinyl alcohol is poorly absorbed from the gastrointestinal tract (EFSA, 2005; Sanders and Matthews, 1990). Based on findings from animal study, Sanders and Matthews (1990) reported that greater than 98% of the radioactivity associated with a single oral dose of 0.01 mg/kg ¹⁴C-labeled polyvinyl alcohol administered to 3 male rats was recovered in the feces within 48 hours of administration. In the urine, less than 0.2% of the total radioactivity was detected.

In an attempt to further assess potential for absorption and subsequent bioaccumulation, Sanders and Matthews (1990) administered 0.1 mg/kg ¹⁴C-labeled polyvinyl alcohol by gavage to 3 male F344 rats for 10 consecutive days. The almost 100% recovery of orally dosed radioactivity in fecal materials supports the conclusion of Sanders and Matthews (1990), that polyvinyl alcohol is very poorly absorbed. These observations suggest that there is minimal amount of polyvinyl alcohol available for distribution to body tissues and only trace amounts are likely to be absorbed. This is not unexpected for a

degradation-resistant, high-molecular weight polymer. Thus, 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 in feces essentially intact and unabsorbed.

6.2.2. Acute Toxicity

In several studies, acute toxicity of polyvinyl alcohol has been investigated in rats, mice and dogs, following oral administration. As described in JECFA (2004) and EFSA (2005) assessment reports, the LD₅₀ 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. The oral LD₅₀ of polyvinyl alcohol in different species has been reported as follows: mouse- >4000 mg/kg bw; rat- >21500 mg/kg bw; and dog- >20000 mg/kg bw, respectively. The findings from these studies suggest that polyvinyl alcohol is practically nontoxic following oral administration.

6.2.3. Subchronic Toxicity

In the 90-day oral toxicity study, Kelly et al. (2003) investigated the potential systemic and neurotoxic effects of polyvinyl alcohol in rats. In this GLP-compliant feeding study, male Sprague-Dawley rats (20/sex/group) were fed a diet containing polyvinyl alcohol that resulted in a dose level of 0, 2000, 3500 and 5000 mg/kg bw/day for 90 days. Rats in control group received untreated standard laboratory diet. Dose levels were selected on the basis of a preliminary 14-day range finding toxicity study. During the course of study and at termination rats were assessed for clinical observations, ophthalmology, body weight and feed consumption, hematology, coagulation, clinical chemistry, urinalyses, motor activity and functional observational battery, and gross and microscopic pathology. The only readily apparent polyvinyl alcohol treatment-related effect noted during the course of study was unformed stool with brown/black anogenital staining in rats fed polyvinyl alcohol at levels of 3500 and 5000 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 observations in these rats. The presence of loose stools and anogenital staining was considered to be the result of the large amount of unabsorbed polyvinyl alcohol in the stool. As a result, water is likely retained within the stool. The investigators concluded that this was a physiological process and not a toxic effect per se.

Besides above mentioned observations, 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 2000, 3500 and 5000 mg/kg/day for up to 90 days did not result in any adverse, toxicological effects. The findings from this study suggest the no-observed-adverse-effect-level (NOAEL) of 5000 mg/kg bw/day.

6.2.4. Mutagenicity Genotoxicity

In addition to above described subchronic study, Kelly et al. (2003) also investigated the genotoxic potential of polyvinyl alcohol in a series of investigations as evaluated by: bacterial reverse mutation assay in *Salmonella typhimurium* and

Escherichia coli (Ames assay); *in vitro* forward mutation assay in a sub-line of mouse lymphoma L5178Y cells; and *in vivo* mouse micronucleus assay.

In the bacterial reverse mutation assay (Ames assay), polyvinyl alcohol at concentrations of up to 5000 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 WP2uvrA/pKM101 (CM 891) (Kelly et al., 2003). In the *in vitro* mouse lymphoma assay, polyvinyl alcohol at concentrations up to 5000 µg/mL, in the presence and absence of metabolic activation (S9 mix), 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 2000 mg/kg bw did not show any evidence of causing chromosome damage or bone marrow cell toxicity at 24 to 48 hours following administration.

The above described observations from the genotoxicity studies of polyvinyl alcohol are further supported by the studies described in the JECFA (2004) and mentioned in EFSA (2005) evaluation of polyvinyl alcohol. As described in the JECFA and EFSA reports, negative results were noted in several strains of *S. typhimurium* in both the presence and absence of metabolic activation (Shibuya et al., 1985; Schweikl et al., 1996), as well as in an *in vitro* Chinese hamster V79 chromosomal aberration assay and *in vivo* in a female mouse bone marrow micronucleus test (Shibuya et al., 1985).

6.2.5. Chronic Toxicity and Carcinogenicity

No chronic toxicity or carcinogenicity studies were found following oral administration of polyvinyl alcohol, in the published literature. However, in a 2-year chronic toxicity study conducted by National Toxicology Program (NTP), intra-vaginal administration of polyvinyl alcohol to female B6C3F1 mice did not reveal compound-related neoplastic or non-neoplastic lesions (NTP, 1998). In this study, three groups (i.e., an untreated control, a vehicle control, and a dose group receiving 20 µL 25% polyvinyl alcohol [PVA] in de-ionized water) of 100 female B6C3F1 mice were administered polyvinyl alcohol. The only clinical finding noted in this study was vaginal irritation. The NTP report concluded that “under the conditions of this 2-year study, there was no evidence of carcinogenic activity...”

Based on the low absorption rate of polyvinyl alcohol through the mucosa of the gastrointestinal tract, the absence of genotoxicity concerns, and the results of the NTP study showing no neoplastic lesions in the internal and external organs of the intra-vaginally exposed mice, including on the directly exposed vaginal mucosal surface, it is concluded that there is no evidence that polyvinyl alcohol is carcinogenic and that polyvinyl does not pose a carcinogenic risk following dietary exposures.

6.2.6. Reproduction and Developmental Toxicity

In a 2-generation reproductive toxicity study, Rodwell et al. (2003) investigated the effects of polyvinyl alcohol on fertility, early embryonic development, growth and

GRAS Notice for Polyvinyl Alcohol
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subsequent development in rats. In this GLP-compliant study, groups of P₀ and F₁ parental Sprague-Dawley rats (26/sex/group) were fed diets containing polyvinyl alcohol at levels providing doses of 2000, 3500, or 5000 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 on their respective dietary exposure during the 14-day mating period, gestation, and lactation. Females were generally euthanized on lactation day 21.

Polyvinyl alcohol exposure via diet did not induce any treatment-related effects on P₀ or F₁ male reproductive performance, as evaluated by mating and fertility indices and sperm counts. 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 P₀ or F₁ 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 F₁ or F₂ generation were observed. Similarly, polyvinyl alcohol treatment in both F₁ and F₂ generations did not affect absolute organ weights, or organ to body weights and organ to brain weight ratios. Macroscopic and microscopic observations performed on the P₀ and F₁ parental animals and on the F₁ and F₂ pups did not reveal any adverse effects from polyvinyl alcohol exposure. The findings from this well-designed reproductive study suggest a NOAEL of 5000 mg/kg bw/day for both parental and offspring, the highest dose tested (Rodwell et al., 2003).

6.3. National and International Regulatory Agencies Assessments

6.3.1. GRAS Notification on Polyvinyl alcohol

Based on FDA GRAS Notices inventory website, the FDA has received three GRAS notices (Table 7) for use of polyvinyl alcohol as a food ingredient in a variety of conventional foods, all of which have received “no question” letters from the FDA. These GRAS notices include GRN 000141 (FDA, 2004), GRN 000767 (FDA, 2018) and GRN 000927 (FDA, 2021).

Table 7. GRAS Notices on Polyvinyl Alcohol Submitted to FDA and Received No Questions*

GRN No.	Substance	Date of closure	FDA's Letter
927	Polyvinyl alcohol	Feb 26, 2021	FDA has no questions (in PDF) (206 kB)
767	Polyvinyl alcohol	Sep 7, 2018	FDA has no questions (in PDF) (57 kB)
141	Polyvinyl alcohol	Apr 28, 2004	FDA has no questions

*Additional details of the complete GRAS notice and the FDA response letter is available by ‘click’ on the substance of the notice or FDA’s no question letter.

The first GRAS notice (GRN 000141) on polyvinyl alcohol was submitted by Colorcon (2003). In this notice, 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 that a person consumes a maximum of ten 1

GRAS Notice for Polyvinyl Alcohol
Submitted by NABACO LLC

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.

As regards safety of polyvinyl alcohol, 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 NOAEL for polyvinyl alcohol of 5000 mg/kg bw/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.

In the second GRAS notice by Monosol (2018) the Notifier determined that polyvinyl alcohol is GRAS, through scientific procedures, for use as a component of water-soluble, edible film that 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 at a level up to 0.734 g polyvinyl alcohol/serving, (2) approved color additives to be used in manufacturing flavored beverages (non-dairy and non-alcohol) at a level up to 0.0006 g polyvinyl alcohol/serving, and (3) dry ingredients to be used by commercial establishments in making pizza dough at a level up to 0.0075 g polyvinyl alcohol/serving.

In this second GRAS notice, the total maximum daily intake (90th percentile) of polyvinyl alcohol from its intended use in edible film was estimated for the total users only U.S. population as 45.16 mg/kg bw/day. The notifier discussed the safety of polyvinyl alcohol using the same published studies that were discussed in GRN 141. These published studies included animal toxicity studies (a subchronic toxicity study in rats and a two generation reproductive study), in which the authors reported no treatment-related effects at a dose of 5000 mg/kg bw/day. The notifier reported that a literature search was conducted through January 2018 and did not report any new data or information that would contradict their GRAS conclusion. In a September 19, 2018 response letter to the notifier, the FDA did not question the conclusion that polyvinyl alcohol is GRAS under the intended conditions of use.

The most recent and third GRAS notice was submitted by Adept Limited (2020) for the use of polyvinyl alcohol as a component of water-soluble anus plugs for use in abattoirs to block fecal material during processing of sheep, lambs, and hogs at levels up to 59% of the plug formulation. The notifier discussed publicly available data and

GRAS Notice for Polyvinyl Alcohol
Submitted by NABACO LLC

information supporting the safety of the intended use of polyvinyl alcohol, noting the previous GRAS conclusions from GRNs 000141 and 000767. In this GRAS notice, Adept Limited discussed published absorption, distribution and elimination studies of ¹⁴C-labeled polyvinyl alcohol in rats and concludes that polyvinyl alcohol is not broken down or absorbed to any significant extent. Adept discussed a published subchronic study evaluating potential systemic or neurotoxic effects of dietary administration of polyvinyl alcohol to rats, concluding that there were no adverse effects up to the highest doses of 5000 mg/kg bw/day for 90 days. The notifier also discussed a published two generation dietary study in rats and concluded that there were no effects on reproductive or developmental parameters evaluated up to the highest dose of 5000 mg/kg bw/day. Based on the published results from a standard battery of three genotoxicity studies, Adept concluded that polyvinyl alcohol is not genotoxic. Adept further describes the safety conclusions of polyvinyl alcohol by the JECFA and EFSA. Following its review, on February 26, 2021, the FDA responded to the notifier that the agency did not question the conclusion that polyvinyl alcohol is GRAS under the intended conditions of use.

6.3.2. JECFA Evaluation

In an extensive evaluation, The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2004) reviewed number of studies related to the toxicity of polyvinyl alcohol following administration by different routes to a number of 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, taken as a whole, the 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 on the basis of the maximum dose tested in both the 90-day and the two-generation toxicity studies in rats. The Committee established an acceptable daily intake (ADI) for polyvinyl alcohol of 50 mg/kg bw/day, on the basis of the NOEL of 5000 mg/kg bw/day from the subchronic toxicity and two-generation studies in rats, with a safety factor of 100 (JECFA, 2004). These studies considered by JECFA were subsequently published and are described earlier in this GRAS document.

6.3.3. European Commission Evaluation

In 2005, the Scientific Panel of the European Food Safety Authority (EFSA, 2005) 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 from the proposed and existing food uses is not of safety concern.

GRAS Notice for Polyvinyl Alcohol
Submitted by NABACO LLC

The available evidence shows that polyvinyl alcohol is only minimally absorbed following oral administration. The Panel noted that the NOAEL of 5000 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. 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. The Panel concluded that the consumption of the polyvinyl alcohol through its use as a coating agent for food supplement tablets and/or capsules at its intended use level is not of safety concern.

6.3.4. Additional Regulatory Citations and Uses

In addition to food uses, polyvinyl alcohol is commonly used in pharmaceutical industry as part of film coating agents for ingestible tablets and capsules. As mentioned earlier, it is also used for coating ingestible dietary supplements as described in GRN 000141. Polyvinyl alcohol is approved for use as an indirect food additive in products that are intended for use in contact with food (21 CFR 177.1670), as a diluent in color additive mixtures for coloring shell eggs [21 CFR 73.1 (b)(2)] and for ophthalmic drug products for over the counter human use (21 CFR 349.12). It is also approved for use in cosmetic products (CIR, 1998) as well as in pharmaceutical products (Rothschild, 2004). In Europe, the specifications for the use of pharmaceutical grade polyvinyl alcohol are published in the European Pharmacopoeia (PhEur, 2002). In the UK, polyvinyl alcohol is allowed for use in non-parenteral licensed medicines (EFSA, 2005).

There exists an established history of use of polyvinyl alcohol in cosmetics and medical applications, as well as a component of food packaging materials (CIR, 1998; 21 CFR §175.105, §175.300, §175.320, §176.170, §176.180, §177.1200, §177.1670, §177.2260, §177.2800, §178.3910, §181.30).

6.4. Safety of Other Constituents

The subject of this GRAS polyvinyl alcohol contains residual solvents and by-products. Although the product used in toxicity studies also contains these constituents, the available additional information on some of these by-products generated during manufacturing is discussed here. The levels of these by-products and their levels are monitored by process control, individual specifications and analytical methods. The specifications of methanol and methyl acetate establish a limit of 1%. Considering that maximum cumulative intake of polyvinyl alcohol from all uses as 50 mg/kg bw/day, 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 (30 mg for an individual weighing 60 kg).

The residual solvent levels of methanol are permitted (21 CFR 173.250) from its use as secondary direct food additive in certain food for human consumption. As per this regulation, methanol may be present 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 ppm. (b) In hops extract as a residue from the extraction of hops, at a level not to exceed 2.2% 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. Methanol uses are also recognized in the following 21 CFR citations with limits in parenthesis: 175.105 as an indirect food additive for use only as a component of adhesives; 172.589 for sucrose fatty acid esters (10 ppm); 172.560 for Modified hop extract (100 ppm); 173.250 for spice oleoresins (50 ppm); 172.867 for Olestra (300 ppm); and 73.615 for Turmeric oleoresin.

The available information also shows 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 a good example of fruit juice that contains approximately 500 mg methanol/liter. Thus, a typical serving of orange juice (200 ml or 6 oz) results in consumption of 100 mg of methanol. These observations suggest that the resulting intake of methanol (30 mg/day) from all the uses (cumulative) of polyvinyl alcohol is safe.

As per 21 CFR 172.515, methyl acetate, the other processing by-product, is a food additive permitted for direct addition to food for human consumption as a synthetic flavoring substance and adjuvant in accordance with the following conditions: 1) 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. According to 21 CFR 175.105, methyl acetate is an indirect food additive for use only as a component of adhesives. The Flavor and Extract Manufacturer's Association (FEMA) has also approved food uses of methyl acetate (FEMA No. 2676) as a flavoring agent in beverages, ice cream, candy and baked goods at levels ranging from 11 to 29 ppm.

In summary, these regulatory citations for the by-products, and other safety related-information on methanol and methyl acetate, suggest that the resulting cumulative intake of these manufacturing by-products from the proposed and existing uses of polyvinyl alcohol is safe.

6.5. Summary, Discussion and Conclusion

NABACO Inc., intends to market NatuWrap PA™ containing polyvinyl alcohol as a food ingredient for use as a surface-finishing agent and/or texturizer as defined at 21 CFR 170.3 (o)(30) and (32).³ When used in accordance with product instructions NatuWrap PA™ will be applied to the exterior of produce to form a thin and edible physical barrier against moisture loss and oxidation to protect the freshness and extend the shelf-life of agricultural products such as fruits (e.g., berries, grapes, stone fruit, citrus, bananas, mangoes, avocados) and vegetables (e.g., legumes, roots, tubers). It will be used at levels consistent with current Good Manufacturing Practice but not to exceed 0.29 g PVOH/kg

³*Surface-finishing agents:* Substances used to increase palatability, preserve gloss, and inhibit discoloration of foods, including glazes, polishes, waxes, and protective coatings. *Texturizers:* Substances which affect the appearance or feel of the food.

GRAS Notice for Polyvinyl Alcohol
Submitted by NABACO LLC

of food and is self-limiting for technological reasons. The intended use of polyvinyl alcohol on fruits and vegetables is estimated to result in a maximum daily (90th percentile) intake of 49 mg/person/day or 0.82 mg/kg bw/day (for an individual weighing 60 kg). The cumulative intake of polyvinyl alcohol from the proposed uses and the existing uses is estimated as 46.08 mg/kg bw/day. The polyvinyl alcohol, subject of this GRAS assessment, meets appropriate food grade specifications, and is manufactured in compliance with current Good Manufacturing Practices.

For the present GRAS assessment, a comprehensive search of the scientific literature for safety and toxicity information on polyvinyl alcohol was conducted through September 2021 and used in the preparation of this dossier. The available information suggest that polyvinyl alcohol is commonly used in film coating formulations for pharmaceutical tablets and capsules. Similarly, it is also used for coating dietary supplements. Polyvinyl alcohol is also permitted for use in cosmetic products. As per FDA regulations, polyvinyl alcohol is approved for use as an indirect food additive in products that are in contact with food. In response to three GRAS Notification for polyvinyl alcohol use as a film coating for dietary supplements, as a component of water-soluble edible film, and as a component of water-soluble anus plugs, the FDA did not question the conclusion that the polyvinyl alcohol is GRAS for these intended conditions of use. The EFSA Panel evaluated the use of polyvinyl alcohol as a food additive film coating agent for food supplements and concluded that the consumption of the polyvinyl alcohol as a coating agent is safe. Similarly, JECFA also evaluated the safety of polyvinyl alcohol for use as a coating, binder, sealing or surface-finishing agent and established an ADI of 50 mg/kg bw for polyvinyl alcohol. There is no evidence that the existing uses of polyvinyl alcohol have resulted in any adverse effects in humans.

The safety of polyvinyl alcohol is supported by toxicity studies that include GLP-compliant studies (i.e., a subchronic oral toxicity study, a 2-generation reproductive toxicity study, and *in vitro* and *in vivo* genotoxicity assays). The available evidence suggests that following oral administration, polyvinyl alcohol is only minimally absorbed. The acute oral toxicity studies in rats, mice and dogs suggest that polyvinyl alcohol possesses a low order of acute toxicity. In the 90-day subchronic toxicity study, there was no evidence of systemic toxicity following dietary administration of polyvinyl alcohol at doses up to 5000 mg/kg bw/day, the highest dose tested. Similarly, in a 2-generation reproductive toxicity study, no adverse effects of polyvinyl alcohol administration occurred in parental, or first or second-generation rats. In this study also, the highest dose level of polyvinyl alcohol tested was 5000 mg/kg bw/day. The findings from a series of *in vitro* and *in vivo* mutagenicity and genotoxicity assays suggest that polyvinyl alcohol is neither mutagenic nor genotoxic. No oral chronic toxicity and carcinogenicity studies were available, however, in a topical carcinogenicity study, intravaginal administration of polyvinyl alcohol to female mice did not indicate any carcinogenic activity. The cumulative intake of polyvinyl alcohol of 46.08 mg/kg bw/day from all sources, including current proposed uses, is over 100 fold compared to the NOAEL of 5000 mg/kg bw/day determined from subchronic oral toxicity and 2-generation reproductive toxicity studies. The cumulative intake is also lower as compared to the JECFA established ADI of 50 mg/kg bw/day.

GRAS Notice for Polyvinyl Alcohol
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In summary, on the basis of scientific procedures⁴ and common knowledge of exposure from existing uses, the consumption of polyvinyl alcohol as a food ingredient component when used as part of an edible film coating on fruits is considered safe at levels up to 50 mg/kg bw/day. The intended uses are compatible with current regulations, *i.e.*, polyvinyl alcohol-containing films will be used as a coating on fruits. Polyvinyl alcohol used in these applications is produced according to current good manufacturing practices (cGMP). The intended uses of the film along with other existing uses from all uses is estimated to result in maximum intake of 50 mg polyvinyl alcohol/kg bw/day using. Such exposure to polyvinyl alcohol is considered safe on the basis of the totality of the evidence, including the above described safety studies.

Based on a critical evaluation of the publicly available data, summarized herein, NABACO Inc. has concluded that polyvinyl alcohol, meeting the specifications cited herein, and when used as a surface-finishing agent and/or texturizer [21 CFR 170.3 (o)(30) and (32)], creating a thin and edible physical barrier against moisture loss and oxidation to protect the freshness and extend the shelf at levels consistent with current Good Manufacturing Practice as described in this monograph, and resulting in maximum cumulative estimated intake of 46.08 mg/kg bw/day, is safe. It is also the opinion of NABACO Inc. that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that polyvinyl alcohol, when used as described, is Generally Recognized As Safe (GRAS) based on scientific procedures.

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

Part VII- SUPPORTING LITERATURE AND REFERENCES

- Adept Limited. 2020. GRAS Notification to FDA for Use of Polyvinyl Alcohol (PVOH) in Plugs to Block Fecal Material During Meat Processing. Adept Limited. GRN 000927. Complete GRAS notice available at FDA GRAS inventory website.
- CIR. 1998. Final report on the safety assessment of polyvinyl alcohol - Safety assessment of cosmetic ingredients (36th Report of the Cosmetic Ingredient Review Expert Panel). *Int. J. Toxicol.* 17:67-92.
- Colorcon. 2003. GRAS Notification to FDA on Polyvinyl Alcohol use in aqueous film coatings applied to dietary supplements (tablets/capsules). Colorcon. GRN 000141. Complete GRAS notice available at FDA GRAS inventory website.
- DeMerlis, C.C., Schoneker, D.R. 2003. Review of the oral toxicity of polyvinyl alcohol (PVA). *Food Chem Toxicol.* 41(3):319-326.
- EFSA. 2005. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to the use of polyvinyl alcohol as a coating agent for food supplements. *The EFSA Journal* 294:1-15.
- FCC. 2019. Monograph on Polyvinyl alcohol The Food Chemicals Codex (11th Edition Third Supplement).
- FDA. 2004. Agency Response Letter GRAS Notice No. GRN 000141. Polyvinyl Alcohol. U.S. Food and Drug Administration (FDA). April 28, 2004.
- FDA. 2018. Agency Response Letter GRAS Notice No. GRN 000767. Polyvinyl Alcohol. U.S. Food and Drug Administration (FDA). September 07, 2018.
- FDA. 2021. Agency Response Letter GRAS Notice No. GRN 000927. Polyvinyl Alcohol. U.S. Food and Drug Administration (FDA). February 26, 2021.
- JECFA. 2003. The Joint FAO/WHO Expert Committee on Food Additives (JECFA). 61st Meeting. Chemical and Technical Assessment (CTA). Pages 3. Publisher FAO.
- JECFA. 2004. The Joint FAO/WHO Expert Committee on Food Additives (JECFA). 61st Meeting. World Health Organization (WHO), Geneva. WHO Technical Report Series 922, pp. 35-37.
- JECFA. 2007. Joint FAO/WHO Expert Committee on Food Additives Sixty-Eight Meeting and published in FAO JECFA Monographs 4, Geneva, Switz. Food and Agriculture Organization of the United Nations (FAO) / World Health Organization (WHO), Geneva,
- Kelly, C.M., DeMerlis, C.C., Schoneker, D.R., Borzelleca, J.F. 2003 Subchronic toxicity study in rats and genotoxicity tests with polyvinyl alcohol. *Food Chem Toxicol.* 41:719-727.
- Kimmons, J., Gillespie, C., Seymour, J., Serdula, M., Blanck, H.M. 2009. Fruit and vegetable intake among adolescents and adults in the United States: Percentage

GRAS Notice for Polyvinyl Alcohol
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- meeting individualized recommendations. Medscape J Med. 11(1):26. Epub 2009 Jan 26. PMID: 19295947; PMCID: PMC2654704.
- Monosol LLC. 2018. GRAS Notification to FDA for Use of Polyvinyl Alcohol (PVOH) as a Component in Edible Film. MonoSol LLC. GRN 000767. Complete GRAS notice available at FDA GRAS inventory website.
- NABACO. 2021.
- NTP. 1998. Toxicology and Carcinogenesis Studies of Polyvinyl Alcohol (Molecular Weight ~24,000) (CAS NO. 9002-89-5) in B6C3F1 Mice (Intravaginal Studies). National Toxicology Program (NTP), Research Triangle Park, North Carolina. NTP Technical Report Series, No 474.
- PhEur. 2002. Poly(vinyl Alcohol). In: European Pharmacopoeia, 4th Edition. Council of Europe (COE), Strasbourg. European Treaty Series, No. 50, pp 1779-1780.
- Rodwell, D.E., Kelly, C.M., DeMerlis, C.C., Schoneker, D.R., Borzelleca, J.F. 2003. Effects of polyvinyl alcohol administered in the diet to rats on fertility, early embryonic development, growth and development. Food Chem Toxicol 41:729-737.
- Rothschild, D.L. Jr. 2004. Polyvinyl alcohol. In: The Food Chemical News Guide to the Current Status of Food Additives and Color Additives. FCN Publishing, Washington, DC.
- Sanders, J.M., Matthews, H.B. 1990. Vaginal absorption of polyvinyl alcohol in Fischer 344 rats. Hum Exp Toxicol 9:71-77.
- Schweikl, H., Schmalz, G., Gottke, C. 1996. Mutagenic activity of various dentine bonding agents. Biomaterials 17:1451-1456.
- Shibuya, T., Tanaka, N., Katoh, M., Matsuda, Y.T., Morita, K. 1985. Mutagenicity testing of STfilm with the Ames test, chromosome test *in vitro* and micronucleus test in female mice. J Toxicol Sci 10:135-141.
- Smiciklas-Wright, H., Mitchell, D.C., Mickle, S.J., Cook, A.J., Goldman, J.D. 2002. Foods Commonly Eaten in the United States: Quantities Consumed Per Eating Occasion and in a Day, 1994-1996. U.S. Department of Agriculture NFS Report No. 96-5, pp. 252.
- USP. 2004. Polyvinyl alcohol. In: U.S. Pharmacopeia & National Formulary (27th Ed.). U.S. Pharmacopeia (USP) Convention Inc., Rockville, Maryland, p. 1509.

Appendix I

Analytical results from three non-consecutive lots along with Data for Lead

Kuraray Europe GmbH
Philipp-Reis-Straße 4
65795 Hattersheim am Main

CERTIFICATE OF ANALYSIS

Page 1 of 1

Order No.:
Delivery No.:
Cust Order No.:
Date of Print: 31.01.2022

These data do not release the customer from the obligation to carry out an inspection of goods received. All sales of this product shall be subject to our Standard Terms and Conditions of Sale.

PRODUCT QUALITY CONTROL DATA

Material: PV001245 KURARAY POVAL# 5-88 FA 500kg Big bag

Batch Number	Test Method	Value	Unit	Min	Max
Characteristics	Test Method Description				
N122015126					
Methanol content		0,52	%	0,00	0,99
Viscosity 4% (DIN 53015)		5,2	mPa.s	4,8	5,8
pH		5,1		5,0	6,5
Degree of Hydrolysis		87,7	mole%	86,5	89,0
Ash Content		0,08	%	0,00	0,37
Solid content 105°C, 3h		98,3	%	95,0	100,0
Volatile Matter		1,7	%	0,0	5,0
Methylacetat content		0,02	%	0,00	0,99
Insoluble Matter POVAL		0,02	%	0,00	0,10

"This report is computer generated and valid without signature."

Kuraray Europe GmbH
Philipp-Reis-Straße 4
65795 Hattersheim am Main

CERTIFICATE OF ANALYSIS

Page 1 of 1

Order No.:
Delivery No.:
Cust Order No.:
Date of Print: 31.01.2022

These data do not release the customer from the obligation to carry out an inspection of goods received. All sales of this product shall be subject to our Standard Terms and Conditions of Sale.

PRODUCT QUALITY CONTROL DATA

Material: PV001245 KURARAY POVAL# 5-88 FA 500kg Big bag

Batch Number

Characteristics	Test Method	Value	Unit	Min	Max
Test Method Description					
N122015118					
Methanol content		0,60	%	0,00	0,99
Viscosity 4% (DIN 53015)		5,2	mPa.s	4,8	5,8
pH		5,2		5,0	6,5
Degree of Hydrolysis		87,6	mole%	86,5	89,0
Ash Content		0,12	%	0,00	0,37
Solid content 105°C, 3h		98,4	%	95,0	100,0
Volatile Matter		1,6	%	0,0	5,0
Methylacetat content		0,02	%	0,00	0,99
Insoluble Matter POVAL		0,00	%	0,00	0,10

"This report is computer generated and valid without signature."

Kuraray Europe GmbH
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65795 Hattersheim am Main

CERTIFICATE OF ANALYSIS

Page 1 of 1

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Delivery No.:
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These data do not release the customer from the obligation to carry out an inspection of goods received. All sales of this product shall be subject to our Standard Terms and Conditions of Sale.

PRODUCT QUALITY CONTROL DATA

Material: PV001245 KURARAY POVAL# 5-88 FA 500kg Big bag

Batch Number

Characteristics	Test Method	Value	Unit	Min	Max
Test Method Description					
N122015117					
Methanol content		0,53	%	0,00	0,99
Viscosity 4% (DIN 53015)		5,3	mPa.s	4,8	5,8
pH		5,2		5,0	6,5
Degree of Hydrolysis		87,4	mole%	86,5	89,0
Ash Content		0,12	%	0,00	0,37
Solid content 105° C, 3h		98,4	%	95,0	100,0
Volatile Matter		1,6	%	0,0	5,0
Methylacetat content		0,02	%	0,00	0,99
Insoluble Matter POVAL		0,04	%	0,00	0,10

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Priifbericht

Auftraggeber Frau Dr. Shu-Hsien Li
D581, PVA/PVB - R&TS / PVB-Film
Eingangsdatum 28.10.2021

08.11.2021

Labor-Auftrags-Nr.: 2111252

bei Nachfragen bitte unbedingt angeben !!

Proben-Nr. Parameter	Probenbezeichnung sample designation	Unit	analysis result	GW
2111252-006	Poval 5-88 FA N121085317 Probenahme: 28.10.2021 Probenfreigabe: 05.11.2021 15:25			

Determination of the original sample

Aufschlussart*	DIN EN ISO 15587-2: 2002-07 Water quality - Information for the determination of selected elements in water - Part 2: nitric acid digestion (CEM)		
Blei*	Lead*	mg/kgOS	< 1,0

Freigabe Priifbericht <lurch: Dr. Christoph Waller Fachlicher Leiter in Abteilung Umwelt- und Prozessanalyt

The present test results relate exclusively to the tested sample material.

The publication and reproduction of our test reports and their use for advertising purposes - even in part - require our written approval.

Telefonische Rlickfragen bitte an:

Dr. Kaltz 069/305-13801 (Achim.Kaltz@Infraserv.com)

Dr. Waller 069/305-35056 (Christoph.Waller@Infraserv.com) Dr. Alt 069/305-6774 (Christopher.Alt@Infraserv.com)

You are welcome to give us feedback about our performance to the above-mentioned people.

This test report was created by an EDI system and is also valid without a signature!

test procedure

DIN EN ISO 17294-2

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Priifbericht

Auftraggeber Frau Dr. Shu-Hsien Li
D581, PVA/PVB - R&TS / PVB-Film
Eingangsdatum 28.10.2021

08.11.2021

Labor-Auftrags-Nr.: 2111252

bei Nachfragen bitte unbedingt angeben !!

Proben-Nr. Parameter	Probenbezeichnung	Einheit	Analysenergebnis	GW
2111252-007	Poval 5-88 FA N120075080 Probenahme: 28.10.2021 Probenfreigabe: 05.11.2021 15:26			

Bestimmung der Originalprobe

Aufschlussart*

DIN EN ISO 15587-2: 2002-07
Wasserbeschaffenheit - Aufschluss for die
Bestimmung ausgewählter Elemente in
Wasser - Teil 2:
Salpetersäure- Aufschluss (CEM)

Blei*

mg/kgOS

< 1,0

Freigabe Priifbericht durch: Dr. Christoph Waller Fachlicher Leiter in Abteilung Umwelt- und Prozessanalytik

Die vorliegenden Priifergebnisse beziehen sich ausschlieBlich auf das untersuchte Probenmaterial.

Die Veröffentlichung und Vervielfältigung unserer Priifberichte sowie deren Verwendung zu Werbezwecken bedürfen - auch auszu

Telefonische Rückfragen bitte an:

Dr. Kaltz 069/305-13801 (Achim.Kaltz@Infraserv.com)

Dr. Waller 069/305-35056 (Christoph.Waller@Infraserv.com) Dr. Alt 069/305-6774 (Christopher.Alt@Infraserv.com)

Gerne können Sie uns eine Rückmeldung über unsere Leistung an die oben genannten Personen geben.

Dieser Priifbericht wurde durch ein EDY-System erstellt und ist auch ohne Unterschrift gültig!

Prüfverfahren

DIN EN ISO 17294-2

ik

igswweise - unserer schriftlichen Genehmigung.

Report Translation

Client: Dr. Shu-Hsien Liaaa
D581, PVA/PVB – R&TS/PVB Film
Date Received: 10/28/2021

Order # 2111252
Nov. 8, 2021

Sample No: 2111252-006
Sample Designation: Proval 5-88 FA N121085317
Sample received: 10/28/2021
Sample released: 11/05/2021 15:25

Determination of the original sample

Sample Preparation Method: ISO 15587-2:2002-07 *Water Quality – Information for the determination of selected elements in water – Part 2: nitric acid digestion.*

Analytical Test Method: ISO 17294-2

Results: Lead <1.0 mg/kg OS Test method ISO 17294-2

Test Report released by Dr. Christopher Waller

This test report was created by an EDI system and is valid without a signature

Report Translation

Client: Dr. Shu-Hsien Liaaa
D581, PVA/PVB – R&TS/PVB Film
Date Received: 10/28/2021

Order # 2111252
Nov. 8, 2021

Sample No: 2111252-007
Sample Designation: Proval 5-88 FA N120075080
Sample received: 10/28/2021
Sample released: 11/05/2021 15:25

Determination of the original sample

Sample Preparation Method: ISO 15587-2:2002-07 *Water Quality – Information for the determination of selected elements in water – Part 2: nitric acid digestion.*

Analytical Test Method: ISO 17294-2

Results: Lead <1.0 mg/kg OS Test method ISO 17294-2

Test Report released by Dr. Christopher Waller

This test report was created by an EDI system and is valid without a signature