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October 9, 2019



Paulette Gaynor
GRAS Notification Program
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5100 Campus Drive
College Park, Maryland 20740-3835

Subject: GRAS Notification for the Intended Use of Vinyl Acetate-Vinyl Laurate Copolymer (5 to 40% VL) in Chewing Gum Base.

Dear Dr. Gaynor:

In accordance with 21 C.F.R. Part 170, Subpart E - Generally Recognized As Safe (GRAS) Notice, we hereby submit, on behalf of Wacker Chemie AG (Wacker), this notification that the intended use of the vinyl acetate-vinyl laurate copolymers (VAVLP) (5 to 40% VL), as a component of chewing gum base is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because Wacker has determined that such use is “generally recognized as safe” (GRAS) based on scientific procedures.

As noted herein, this GRAS notice incorporates by reference the data and information in Wacker’s GRN 606, and also includes an updated literature search for

Paulette Gaynor
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publications pertinent to safety of the intended use (the latest search was conducted on August 19, 2019) as well as an updated estimated dietary intake (EDI) assessment.

To facilitate your review, this notification is submitted in the format required under 21 C.F.R. §§ 170.220-255. Enclosed is one paper and one electronic copy of the GRAS notice documents. If you have any questions concerning this submission, please do not hesitate to contact me.

Sincerely,

A rectangular grey box redacting the signature of Riëtte L. van Laack.

Riëtte L. van Laack

Counsel to Wacker Chemie AG

RVL/ced

**Notification of a Generally Recognized As Safe (GRAS)
Conclusion for the Use of Vinyl Acetate-Vinyl Laurate
Copolymers (VAVLP) as Components of Chewing Gum
Base**

SUBMITTED BY:

Service Gum Wacker Chemie AG ,
Johannes-Hess-Strasse 24,
84489 Burghausen,
Germany

SUBMITTED TO:

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
5001 Campus Drive
College Park, MD 20740

CONTACT FOR TECHNICAL OR OTHER INFORMATION:

Riëtte L. van Laack
Hyman, Phelps & McNamara, PC,
700 Thirteenth St. NW, Suite 1200,
Washington DC 20005.

Oct. 9, 2019

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Figure 1. Chemical structure of vinyl acetate-vinyl laurate (VAVLP)

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List of Acronyms

ADI	Acceptable Daily Intake
bw	Bodyweight
CASRN	Chemical Abstracts Service Registry Number
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
GMP	Good Manufacturing Practice
COA	Certificate of Analysis
ECHA	European Chemical Agency
EDI	Estimated Daily Intake
EPA	U.S. Environmental Protection Agency
EFSA	European Food Safety Authority
FARE®	Foods And Residue Evaluation Program®
FCC	Food Chemicals Codex
FDA	U.S. Food and Drug Administration
g	Gram
GRAS	Generally Recognized As Safe
IRIS	Integrated Risk Information System
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	Kilogram
LOAEL	Lowest-Observed-Adverse-Effect Level
mg	Milligram
NCHS	National Center For Health Statistics
NHANES	National Health and Nutrition Examination Survey
NOAEL	No-Observed-Adverse-Effect-Level
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
ppm	parts per million
RfD	Reference Dose
USDA	U.S. Department of Agriculture
WWEIA	What We Eat in America
µg	Microgram

Part 1: Signed Statements and Certification

Wacker Chemie AG submits to the U.S. Food and Drug Administration (FDA) this generally recognized as safe (GRAS) notice in accordance with 21 CFR part 170, subpart E.

Name and Address of Notifier

Thomas Wimmer, PhD Senior Technical Manager, Service Gum Wacker Chemie AG ,
Johannes-Hess-Strasse 24, 84489 Burghausen, Germany.

Name of GRAS Substance

The substance that is the subject of this GRAS notice is vinyl acetate-vinyl laurate (VAVLP) copolymer (5 to 40% VL), using either acetaldehyde or isopropanol as a chain transfer agent during the polymerization process.

Intended Use and Consumer Exposure

The copolymers (singly or in combination) are intended to be used in chewing gum base, the maximum concentration of the copolymer in gum as consumed will not exceed 9% by weight.

Basis for Conclusion of GRAS Status

Wacker Chemie AG's conclusion of GRAS status for the intended use of VAVLP copolymers (5 to 40% VL) for use in chewing gum base is based on scientific procedures in accord with 21 CFR §170.30(a) and (b).

Pre-Market Approval Exclusion Claim

The intended use of VAVLP copolymer (5 to 40% VL), using either acetaldehyde or preferred isopropanol as a chain transfer agent during the polymerization process, is not subject to the pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act because Wacker Chemie AG has concluded that such use is generally recognized as safe (GRAS) through scientific procedures.

Availability of Information

The data and information that serve as the basis for this GRAS conclusion, as well as the information that has become available since the GRAS conclusion, will be sent to the FDA upon request, or are available for the FDA's review and copying during customary business hours at

the office of Hyman, Phelps & McNamara, PC, 700 Thirteenth St. NW, Suite 1200, Washington DC 20005.

Exemptions from Disclosure

It is our view that none of the data and information in Parts 2 through 7 of the GRAS notice are exempt from disclosure under the Freedom of Information Act (FOIA).

Certification Statement

On behalf of Wacker Chemie AG, I hereby certify that, to the best of my knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, known to me and pertinent to the evaluation of the safety and GRAS status of the use of the substance.



Name: Thomas Wimmer, PhD
Senior Technical Manager,
Service Gum Wacker Chemie AG

Oct. 3rd, 2019
Date

Part 2. Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

Identity

The substance that is the subject of this GRAS notice is VAVLP copolymer (5 to 40% VL), using either acetaldehyde or preferred isopropanol as a chain transfer agent during the polymerization process. The safety of the intended use of vinyl acetate-vinyl laurate (VAVLP) copolymers sold under the trade names VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL was previously determined as detailed in a notice submitted to the U.S. Food and Drug Administration (FDA) and filed as GRN 606. The copolymers that are the subject of GRN 606 are specified as approximately 20% or 40% (w/w) vinyl laurate (VL) in the VAVLP. This documentation expands the specifications for the copolymers intended for use in chewing gum base to include VAVLP with VL accounting for 5 to 40% (w/w).

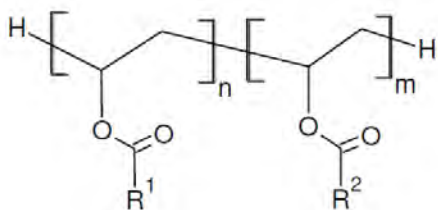
VAVLP copolymers are white to pale-yellowish, odorless, and tasteless solids at ambient temperature (softening occurs at above ~85°C). They are insoluble in water but soluble in certain organic solvents such as acetone and chloroform.

VAVLP is identified by the Chemical Abstracts Services Registry Number (CASRN) of 26354-30-3 with associated names of dodecanoic acid, ethenyl ester, and polymer with ethenyl acetate. The International Union of Pure and Applied Chemistry (IUPAC) name is poly(vinyl acetate-co-vinyl laurate).

The empirical formula of VAVLP copolymers is $[C_{14}H_{26}O_2]_m [C_4H_6O_2]_n H_2$ and the chemical structure is shown in Figure 1. In VINNAPAS[®] B 500/20 VL and in VINNAPAS[®] B 500/40 VL, $n = 10$ and $m = 2.54$ or 0.95 , respectively. At a value of $n = 10$, the value of $m = 0.20$ to 2.54 reflects the range of molar ratios of VA/VL in the expanded range copolymer product, i.e., VAVLP copolymers (5 to 40% VL). The maximum value of 40% VL is already covered by VINNAPAS[®] B 500/40 VL.

The molecular weight (MW) of VINNAPAS[®] B 500/20 VL is 450,000 g/mol, the MW of VINNAPAS[®] B 500/40 VL is 240,000 g/mol and the MW of VAVLP copolymers (5 to 40% VL) is >70,000 g/mol measured by gel permeation chromatography (GPC). Per 21 C.F.R. § 172.615, the minimum molecular weight for polyvinyl acetate is 2000 g/mol.

Figure 1. Chemical structure of vinyl acetate-vinyl laurate (VAVLP)



R1 = methyl; R2 = undecyl,

Manufacturing and Production Process

The VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL copolymers that are the subject of GRN 606 are produced by a chain-growth polymerization process from vinyl acetate (VA) and vinyl laurate (VL) of high purity (>99.8 and 98%, respectively) mixed in appropriate proportions. Tert-butylperoxy-2-ethylhexanoate (CAS 3009-82-4) and 2,2-Di(tert-butylperoxy)butane (CAS 2167-23-9) are used as radical initiators. Acetaldehyde serves as a chain transfer agent during the polymerization process. After polymerization, the remaining chain transfer agent, unreacted monomers, and decomposition products of the radical initiators are removed by evaporation at elevated temperature and vacuum and by steam stripping the polymer with water.

VAVLP copolymer (5 to 40% VL) addressed in this GRAS notice is made using the same production process, but the process is optimized to decrease the amount of residual vinyl laurate monomer content. Either acetaldehyde or preferred isopropanol may serve as a chain transfer agent during the polymerization process.

Details on the starting materials used in the production of VAVLP copolymers are summarized in

Table 1 below.

Table 1. Materials Used in the Production of VAVLP copolymers

Material	Purity	Regulatory Status
Vinyl acetate	VA used for the production of the VAVLP s has a high purity of >99.8%.	Polyvinyl acetate with a minimum molecular weight of 2000 Da is permitted as a chewing gum base (21CFR §172.615)
Vinyl laurate	VL which is used for the production of VAVLP copolymers has a high purity of about 98%.	VL is recognized by the FDA as a safe starting material for the manufacture of food-grade sucrose fatty acid esters (FDA, 2008a,b).
Acetaldehyde	Acetaldehyde is used as the chain transfer agent during polymerization. Residual acetaldehyde in the final product is limited to below 1 ppm.	Acetaldehyde is generally recognized as safe for use in foods as a synthetic flavoring substance and adjuvant (21CFR §182.60).
Isopropanol	Isopropanol is an alternative chain transfer agent in the manufacturing of VAVLP copolymers (5 to 40% VL). Residual isopropanol in the final product is limited to below 50 ppm.	Isopropanol (also known as isopropyl alcohol) is a food additive permitted for direct addition to food as a synthetic flavoring substances and adjuvants (21CFR §172.515).
tert-Butylperoxy-2-ethylhexanoate	Under the temperature conditions of this (exothermic) polymerization reaction, it decomposes completely. Its decomposition products are expected to be removed quantitatively in the distillation and purification steps of synthesized VAVLP copolymer.	-
2,2-Di(tert-butylperoxy)butane	Under the conditions of VAVLP copolymer production, the primary radicals predominantly initiate the desired polymerization reactions. Traces of potential by-products (methane, carbon dioxide, ethane, acetone, tert-butanol, methyl ethyl ketone and small amounts of propionic acid methyl ester, acetic acid methyl ester and tert-butyl methyl ether) would be removed in the evaporation steps and steam stripping at the end of the production process.	-

Specifications for the VAVLP Copolymers

Specifications for the vinyl acetate-vinyl laurate (VAVLP) copolymers sold under the trade names VINNAPAS® B 500/20 VL and VINNAPAS® B 500/40 VL previously determined to be GRAS are presented in Table 2 along with specifications for VAVLP copolymers with the expanded range of 5 to 40% VL.

Specifications for the VAVLP copolymers (5 to 40% VL) on parameters of free acetic acid, residual vinyl laurate monomer and residual vinyl acetate monomer are identical to the specifications for VINNAPAS® B 500/20 VL and VINNAPAS® B 500/40 VL. Specifications for viscosity and saponification number for VAVLP copolymers (5 to 40% VL) are comparable to specifications for VINNAPAS® B 500/20 VL and VINNAPAS® B 500/40 VL.

As noted in GRN 606, specifications for the VAVLP copolymers do not include limits for microbial purity because the water content of the copolymers is low and the conditions of the manufacturing process preclude microbial proliferation. The specifications also do not include limits for heavy metals; however, routine analyses of heavy metals show that heavy metals are below the limit of detection of 1 mg/kg for all elements.

Table 2. Product Specifications

Parameter	This GRAS Notification	GRN 606	
	VAVLP copolymers (5 to 40% VL)	VINNAPAS® B 500/40 VL	VINNAPAS® B 500/20 VL
Percentage (w/w) vinyl laurate (VL) in the VAVLP	5-40%	~40%	~20%
Viscosity	3-13 mPa s	8-12 mPa s	8-12 mPa s
Free acetic acid	≤ 0.05% (≤ 500 ppm)	≤0.05% (≤ 500 ppm)	≤0.05% (≤ 500 ppm)
Saponification number	475-630 mg KOH/g	475-495 mg KOH/g	555-575 mg KOH/g
Residual vinyl acetate monomer (VAM)	≤ 5 mg/kg	≤ 5 mg/kg	≤ 5 mg/kg
Residual vinyl laurate monomer (VLM)	≤ 1000 mg/kg	≤ 1000 mg/kg	≤ 1000 mg/kg
Isopropanol (if used as chain transfer agent)	≤ 50 mg/kg	Not applicable	Not applicable

See Appendix A for Certificates of Analysis

Wacker Chemie AG (Wacker) demonstrated compliance of VINNAPAS® B 500/20 VL and VINNAPAS® B 500/40 VL with product specifications as shown in analyses from multiple batches of each product and reported in GRN 606. By definition, products meeting

specifications for VINNAPAS® B 500/20 VL or VINNAPAS® B 500/40 VL will also meet specifications for the expanded 5 to 40% VL copolymers.

Analytical data from batches of the copolymer meeting the expanded range for the percentage (w/w) vinyl laurate (VL) in the VAVLP copolymer (~5-20% VL), sold under CAPIVA® S08, are summarized in **Table 3**. The certificates of analysis (COAs) are provided in Appendix A.

Table 3: Analytical data of the VAVLP copolymer (sold under CAPIVA® S08)

Parameter	Specifications	Method	Batch Number				
			1503277	1503288	1503297	1503307	1503314
Vinyl laurate in copolymer	5-40%	Calculated from saponification number	9.1 %	8.5 %	9.8 %	10.1 %	10.3 %
Viscosity	3.2-4 mPa s	ASTM D445-06	3.4	3.4	3.4	3.6	3.5
Free acetic acid	≤ 0.05% (500 ppm)	Gas chromatography (GC)	0.023%	0.020%	0.020%	0.020%	0.020%
Saponification Number	475-630 mg KOH/g	Titration	615	617	612	611	610
Residual VAM	≤ 5 mg/kg	GC	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0
Residual VLM	≤ 1000 mg/kg	GC	20	20	20	20	20
Isopropanol	≤ 50 mg/kg	GC	3	4	3	3	5

Stability

The VAVLP copolymers are shelf stable. As demonstrated in documentation supporting GRN 606, the manufacturer guarantees a shelf life of two years under proper storage and handling conditions. Analytical data demonstrating stability from batches of the copolymer meeting the expanded range for 5 to 40% VL in the VAVLP copolymer are provided below in Table 4.

Table 4. Batch analysis/shelf life of VAVLP copolymer (sold under CAPIVA® S08)

Batch	Analysis Date	Vinyl laurate in copolymer (% w/w)	Viscosity (mPa s)	Saponification number (mg KOH/g)	Residual VAM (ppm)	Residual VLM (ppm)	Free acetic acid (ppm)
Specifications		5-40	3.2-4.0	475-630	≤ 5	≤ 1000	500
1503277	March 2015	9.1	3.41	615	< 1	< 20	230
	Sept. 2017	9.6	3.38	613	< 1	< 20	< 200
1503297	March 2015	9.8	3.41	612	< 1	< 20	< 200
	Sept. 2017	11.3	3.38	606	< 1	< 20	< 205
1503307	March 2015	10.1	3.41	611	< 1	< 20	< 200
	Sept. 2017	10.6	3.38	609	< 1	< 20	< 200
1503314	March 2015	10.3	3.41	610	< 1	< 20	< 200
	Sept. 2017	11.1	3.38	607	< 1	< 20	210

* VAM=Vinyl Acetate Monomer

** VLM=Vinyl Laurate Monomer

Part 3. Dietary Exposure

Proposed Use and Level

The VAVLP copolymer (5 to 40% VL) is intended for use as a component of chewing gum base at a level of up to 26% (which corresponds to a maximum of 9% in chewing gum as consumed) to reduce or eliminate the use of additional softeners.

Although the maximum technically feasible use level of VAVLP copolymers in chewing gum base is 35% by weight, corresponding to 17% by weight in chewing gum as consumed (GRN 606), due to excessive hardness of the gum that results from such concentrations of the copolymers (see Self-Limiting Use Section page 10), more realistically VAVLP will account for no more than 26% in chewing gum base, corresponding to no more than 9% by weight in the final product.

Estimated Daily Intakes

Data Source and Population

The estimated intake of VAVLP copolymers in gum base as reported in GRN 606 were derived from data reported in a previously filed GRAS notification (GRN 374), and data collected in a Market Facts Mail Panel Survey conducted in 1995. For adults at the 90th percentile intake of chewing gum, the maximum per user intake of VAVLP copolymers, assuming 17% in gum as chewed (i.e., maximum technically feasible use level as the worst-case scenario),¹ was 0.877 g VAVLP/ day, or approximately 15 mg/kg bw/day assuming a 60 kg body weight. Using data from mail panel survey, children ages 2-5 years were estimated to have the highest intake of VAVLP copolymers on a body weight basis; the estimated intake for a “heavy” consumer of chewing gum was estimated at 48 mg/kg bw/day. More recent data are available to estimate intake of chewing gum and in turn intake of VAVLP.

For this notice, estimates of daily intake of VAVLP copolymers (and residues) based on the maximum technically feasible use level of the copolymers in chewing gum base were calculated from reported intakes of chewing gum collected in the What We Eat in America (WWEIA) component of the National Health and Nutrition Examination Survey (NHANES) in the combined survey periods from 2011 to 2014 (WWEIA, NHANES 2011-2014). This continuous survey uses a complex multistage probability sample designed to be representative of the civilian

¹ The maximum technically feasible use of VAVLP copolymers in gum base is 35%by weight, corresponding to 17% by weight in chewing gum as consumed (GRN 606). However, due to excessive hardness of the gum that results from such concentrations of the copolymers, more realistically VAVLP will account for no more than 9% in the final product.

U.S. population (CDC, 2014 & 2017). The NHANES datasets provide nationally representative nutrition and health data and prevalence estimates for nutrition and health status measures in the United States.

As part of the examination, trained dietary interviewers collected detailed information on all foods and beverages consumed by respondents in the previous 24-hour time period (midnight to midnight). A second dietary recall was administered by telephone three to ten days after the first dietary interview, but not on the same day of the week as the first interview. The sample population for this analysis was limited to the children 2 years of age and older with two days of dietary recall.

Analysis

Food codes corresponding to any chewing gum were identified in the WWEIA, NHANES 2011-2014. A total of three codes were identified: 91800100 Chewing gum, NFS; 91801000 Chewing gum, regular; 91802000 Chewing gum, sugar free. To estimate intake of VAVLP copolymers and potential residues from the proposed use in chewing gum base, each reported intake of chewing gum was multiplied by the maximum technically feasible use level of VAVLP (i.e., 17% by weight in chewing gum as consumed). Contributions from all reported intakes of chewing gum were summed across both days of dietary recall and the resulting value was divided by two to create an estimate of 2-day average VAVLP copolymer intake for each participant. Intakes of VAVLP copolymers derived on a body weight basis were calculated using each participant's measured body weight.

Estimates of intake were calculated on a *per user* basis in units of mg VAVLP copolymers per day (mg/day) and mg VAVLP copolymers per kg body weight per day (mg/kg bw/day) for age groups 2-5 years, 6-12 years, 13-19 years, 20 years and older, and 2 years and older. In this analysis, a "user" is anyone who reported consuming chewing gum on either of the survey days. The resulting values represent estimates of VAVLP copolymer intake assuming the maximum technically feasible use level of VAVLP copolymers in chewing gum base.

Results

As shown in **Error! Reference source not found.** below, per user mean and 90th percentile intakes of chewing gum ranged from 2.2 and 4.2 g/day for children ages 2-5 years, respectively, to 3.0 and 6.0 g/day for adults ages 20 years and older, respectively. On a body weight basis adults ages 20 years and older and teenagers ages 19 years and older had the lowest intakes of chewing gum with mean and 90th percentile intakes in each age group of 0.04 and 0.07 g/kg bw/day, respectively, while children ages 2-5 years had the highest per user mean and 90th percentile intakes at 0.14 and 0.25 g/kg bw/day.

Based on these estimated intakes of chewing gum (Table 5), the highest and worst-case estimated daily intake of VAVLP copolymers per user of chewing gum would occur in children ages 2-5 years, with mean and 90th percentile intakes of 23.0 and 42.7 mg/kg bw/day respectively assuming the maximum technically feasible use level.

Table 5. 2-day average estimated daily intake of VAVLP from use in chewing gum base

Age, years	N	% User	per user intake of Chewing Gum				per user intake of VAVLP*			
			Mean	90th percentile	Mean	90th percentile	Mean	90th percentile	Mean	90th percentile
			-- g/day --		-- g/kg-bw/day --		-- mg/day --		-- mg/kg-bw/day --	
2-5	45	2.7	2.2	4.2	0.14	0.25	380	708	23.0	42.7
6-12	118	4.8	2.7	5.0	0.08	0.14	464	844	13.3	23.6
13-19	86	3.1	2.7	5.6	0.04	0.07	456	956	6.6	12.5
≥ 20	244	2.6	3.0	6.0	0.04	0.07	511	1018	6.3	11.7
≥ 2	493	2.9	2.9	6.0	0.05	0.09	491	1015	8.2	15.6

*Based on maximum technically feasible use level (17% w/w in chewing gum). Due to excessive hardness of the gum that results from such concentrations of the copolymers, VAVLP will typically be no more than 9% w/w in chewing gum.

Updated EDIs Compared with EDIs in GRN 606

As noted above, estimated intakes of VAVLP copolymers were 15 mg/kg bw/day at the per user 90th percentile for adults, and 48 mg/kg bw/day among children representative of “heavy” consumers of gum as reported in GRN 606.

Based on the more recent NHANES, WWEIA data, the per user 90th percentile intake of VAVLP copolymers is 15.6 mg/kg bw/day for adults ages 20 years and older and 42.7 mg/kg bw/day for children ages 2-5 years. Estimates of VAVLP copolymer intake based on recent food consumption data and assuming the worst-case maximum technically feasible use level for VAVLP (17% w/w in finished chewing gum), are therefore comparable to estimates relied upon in GRN 606. It follows that based on current data estimated exposures to residual vinyl acetate and vinyl laurate monomers based on current data would support the same safety conclusion.

Part 4. Self-Limiting Levels of Use

The highest technically feasible concentration of VAVLP in chewing gum is 17% in the final product, i.e., 35% in the gum base (GRN 606). However, due to excessive hardness of the gum that results from such concentrations of the copolymers, more realistically VAVLP will account for not more than 9% of the chewing gum in practice (26% in the gum base). Therefore, the maximum concentration of the copolymer in gum as consumed will not exceed 9% by weight.

Part 5. Experience Based on Common Use in Food before 1958

The conclusion of GRAS status of the use of VAVLP copolymer (5 to 40% VL) as a component of chewing gum base is based upon scientific procedures.

Part 6. Narrative

Approach for Assessing Safety

The safety of the intended use of vinyl acetate-vinyl laurate (VAVLP) copolymer sold under the trade names VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL was previously concluded to be GRAS by an Expert Panel as detailed in a notice to FDA and filed as GRN 606. The percentage (w/w) of vinyl laurate (VL) in the VAVLP copolymers specified in GRN 606 is approximately 20% and 40% in VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL, respectively. This GRAS notification expands the identity for the VAVLP copolymer to include copolymers with 5 to 40% VL (w/w).

The safety determination for the use of VAVLP copolymers in chewing gum base as previously concluded by Wacker and filed as GRN 606 is incorporated herein. The current assessment, which considers the safety of copolymers in the range of 5 to 40% (w/w) VL builds on the previous determination of safety established in GRN 606, includes an update of the literature on which that safety assessment was completed, and evaluates the safety of potential residuals resulting from use of isopropanol as a transfer agent.

A review of the recent literature was conducted to identify literature bearing on the safety of the vinyl acetate-vinyl laurate copolymer and the vinyl laurate and vinyl acetate monomers subsequent to the 2015 GRAS determination. The latest search was conducted on August 19, 2019. The following resources were searched: European Chemical Agency (ECHA), Joint FAO/WHO Executive Committee on Food Additives (JECFA), European Food Safety Authority (EFSA), PubMed, and Google Scholar. Search terms used were as follows: “vinyl laurate,” “vinyl acetate,” “26354-30-3,” “toxicity,” and “safety.”

Available Safety Information for VA, VL, and VAVLP

No new safety information for VL or VAVLP was found in the updated literature search on August 19, 2019.

The available safety information for VAVLP, VA, and VL that were relied upon in GRN 606 to assess the safety of VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL Copolymers included published pre-clinical data on the safety of VAVLP copolymers (Messinger and Bär 2014a), published pre-clinical data on the safety of VL (van Acker et al., 2015, Lina et al., 2015; Messinger and Bär 2014b) and authoritative reviews as well as published information on the safety of VA (Albertini 2013; JECFA, 2011; Environment Canada/Health Canada 2008a, 2008b). Unpublished data on the lack of digestion of VAVLP copolymers also provided corroborative evidence to support the safety assessment (Hergeth, 2007).

A guideline-compliant, prenatal developmental toxicity study on VA conducted in rabbits was summarized by ECHA in 2019. Briefly, 22 pregnant female rabbits/group were treated via gavage with 0, 10, 30, or 100 mg/kg bw/day from gestation day 6 to 28. No effects were observed at any dose. Thus, the NOAEL was set at the highest dose, 100 mg/kg bw/day (ECHA 2019 – Developmental toxicity/teratogenicity 003 Key). These doses were selected based on the results from two preliminary, dose range-finding studies where systemic effects (clinical signs, gastrointestinal effects, body weight/food consumption deficits) were observed at doses \geq 200 mg/kg bw/day (ECHA 2019 – Developmental toxicity/teratogenicity 004 Supporting, 005 Supporting). No developmental or reproductive effects were reported in the preliminary study with pregnant rabbits (ECHA 2019 – Developmental toxicity/teratogenicity 005 Supporting).

Table 6. Safety Data for VAVLP and VL from GRN 606 as well as New VA Data

Compound	Study	Key Findings	Reference ^a
VAVLP	Digestibility	Resistant to digestive fluids (saliva, gastric juice, intestinal fluid)	Hergeth, 2007
VAVLP	13-week oral toxicity in Sprague-Dawley rats	NOAEL = 3783 mg/kg bw/day for males; 4396 mg/kg bw/day for females (highest dose tested)	Messinger and Bär 2014a
VA monomer	authoritative body reviews; published review	Dietary exposure at levels resulting in formation of acetaldehyde at physiologic levels has no adverse effects	Albertini 2013; JECFA, 2011; Environment Canada/Health Canada 2008a, 2008b
VA monomer	Prenatal developmental study	NOAEL = 100 mg/kg bw/day in pregnant rabbits treated during gestation (highest dose tested)	ECHA 2019
VL monomer	Ames assay	No mutagenic activity	van Acker et al., 2015
VL monomer	mouse lymphoma HPRT gene mutation assay	Not mutagenic in mammalian cells	van Acker et al., 2015
VL monomer	<i>in vitro</i> CHO chromosome aberration assay	Negative in the absence of metabolic activation with S9-mix, inconsistent results in the presence of S9 mix	van Acker et al., 2015
VL monomer	<i>in vivo</i> mammalian micronucleus test	No treatment-related effect with 2000 mg/kg bw/day (high dose)	van Acker et al., 2015
VL monomer	90-day oral toxicity in Sprague-Dawley rats	NOAEL = 1000 mg/kg bw/day (highest dose tested)	Lina et al., 2015
VL monomer	reproduction toxicity study	No treatment-related effects	Messinger and Bär 2014b
VL monomer	prenatal developmental toxicity study	No treatment-related effects	Messinger and Bär 2014b

^a as cited in GRN 606

Safety Information 2- Propanol (Isopropanol)

The safety of 2-propanol (isopropanol) (CAS RN 67-63-0), has been reviewed by several agencies and authoritative bodies. The following resources were searched for information bearing on the safety of 2-propanol: the Organisation for Economic Co-operation and Development (OECD), US FDA 21 Code of Federal Regulations (CFR), Joint FAO/WHO Expert Committee on Food Additives (JECFA), European Food Safety Authority (EFSA), National Toxicology Program (NTP), Environmental Protection Agency (EPA) and EPA's Integrated Risk Information System (IRIS). Search terms included the names 2-propopropanol and isopropanol, as well as the Chemical Abstracts Service Registry Number (CAS RN) where appropriate. The search was also updated in October 2018 and in August 2019; no new studies were identified. An OECD Screening Information Dataset (SIDS) summary report published in March 1997 was located for the 2-propanol. The information referenced in this SIDS report is summarized below in addition to references identified in the search which were not summarized in the OECD report.

The majority of data for isopropanol have been submitted to OECD are from studies conducted by industry for the purposes of generating and providing the safety data of high production volume chemicals (HPVCs) including isopropanol (OECD, 2007). The large database of information on HPVCs is the result of industry cooperation with government and authoritative bodies since the 1980s to evaluate, register, and document the safety of HPVCs such as isopropanol. This cooperative relationship provides an extensive historical collection of toxicology and chemistry information for HPVCs.

The purpose of the OECD Screening Information Data Sets (SIDS) is part of a larger cooperative effort of OECD member countries to evaluate, report, and provide access to the safety data of all HPVCs (one metric ton or more produced annually) manufactured or imported by European countries. Similar reporting and inventory are maintained in the USA under the Toxic Substances Control Act (TSCA) by the US EPA. As a consequence of the need to track and register HPVCs and other industrial chemicals, safety data generated by industry are provided to regulatory and authoritative bodies for review. The authoritative bodies publish the study information and assess and report to the public regarding the quality and validity of data. Thus, studies generated by industry that are deemed by OECD to be of a high or acceptable quality can be cited with confidence, and OECD SIDS review activities provide an additional check on the conclusions reported by the study authors. Studies from industry submitted to ECHA are evaluated and reported in a similar manner.

In case where the data submitted to and published by authoritative or regulatory bodies also is published in scientific journals, the data summarized in the present notification are cited both as journal articles, and as publications by the authoritative bodies. In cases where the data are only available in publications by authoritative bodies (industry data) and are not also published separately in scientific journals, the authoritative body publication is cited in this notification.

All studies pivotal to the safety determination described herein are published as journal articles and also appear in publications by authoritative bodies. Studies that appear only in publications by authoritative bodies and are not also published as journal articles are considered supportive.

Absorption, Distribution, Metabolism, and Excretion

Numerous studies on the absorption, distribution, metabolism, and excretion of 2-propanol have been performed. Results from these studies indicate that 2-propanol is readily absorbed in animals and man through the lungs, skin and gastrointestinal (GI) tract. There is evidence for a delay in absorption through the GI tract at high dose levels and an extension in half-life suggesting limited metabolic capability. 2-Propanol is rapidly distributed throughout the body and has been shown to cross the blood/brain barrier. Elimination from the blood follows first order kinetics (OECD, 1997).

The ADME of 2-propanol was studied in male and female F344 rats. Rats were exposed by gavage to single and multiple 300 and 3000 mg/kg bw doses. Approximately 81-89% of the administered dose was exhaled (as acetone, CO₂, and unmetabolized 2-propanol) (Slauter et al., 1994). Approximately 3-8% of the administered dose was excreted in urine as 2-propanol, acetone, and a metabolite tentatively identified as isopropyl glucuronic acid. Small amounts of radiolabel were found in feces and in the carcass. There were no major differences in the rates or routes of excretion reported between males and females. Additionally, repeated exposure had no effect on excretion (Slauter et al., 1994; Teramoto et al., 1987).

In a study with three human volunteers, acetone was produced following 2-propanol ingestion. There was a correlation between blood levels of 2-propanol and acetone, with the initial peak of 2-propanol recorded half an hour after dosing and declined as the acetone levels increased over a 24-hour period (Lacouture et al., 1987 as cited in OECD, 1997).

A physiologically-based pharmacokinetic (PBPK) model for 2-propanol, and its major metabolite, acetone, has been developed and published (Clewell et al., 2001). The model can be used to predict rat or human kinetics for exposures to 2-propanol by multiple routes of entry (intravenous, intraperitoneal, oral, inhalation and dermal). This model was subsequently applied to derive an oral RfD for 2-propanol (Gentry et al, 2002).

Acute Oral Toxicity

The OECD SIDS report (OECD, 1997) summarized several acute oral toxicity studies of 2-propanol in different animal species. The species, sample size, clinical parameters monitored and additional study details were not provided. The oral LD₅₀ was in the range of 4710 mg/kg bw – 5840 mg/kg bw in rats, 4475 mg/kg bw in mice, 5030 mg/kg bw in rabbits, and 4830 mg/kg bw in dogs. The acute oral toxicity studies are summarized below. These values are

supported by additional acute toxicity values found in the literature (ChemIDPlus Lite, accessed October 2018).

Table 7. Acute Oral Toxicity Studies of 2-Propanol (CAS No. 67-63-0) (as cited in OECD, 1997)

Reference	Species	LD50 (mg/kg bw)
Kimura et al., 1971	Rat	4710
Lehman & Chase, 1944	Rat	5280
Guseinov, 1985 (not available in English language, as cited in OECD 2007)	Rat	5500
Smyth & Carpenter, 1948	Rat	5840
Guseinov, 1985 (not available in English language, as cited in OECD 2007)	Mouse	4475
Lehman & Chase, 1944	Rabbit	5030
Munch, 1972	Rabbit	7990
Lehman & Chase, 1944	Dog	4830

Short-Term Toxicity

Studies of short-term animal toxicity of 2-propanol were not identified in the OECD SIDS report.

Subchronic Toxicity

The systemic (non-cancer) toxicity of repeated exposure to 2-propanol has been evaluated in rats by the oral route. Pilegaard and Ladefoged (1993) tested the subchronic oral toxicity of 2-propanol in male rats. Male rats were continuously administered 2-propanol in drinking water at levels of 0, 1, 2, 3, and 5% for 12 weeks. The relative organ weights of liver, kidneys, and adrenals were significantly increased in a dose-dependent manner. No histological alterations were attributable to the treatment, except a dose-dependent increase in formation of hyaline casts and droplets in the proximal tubules of the kidneys. There was no indication of neurotoxicity as evident by the fact that dorsal hippocampal glial fibrillary acidic protein (GFAP) was unaffected after treatment. Therefore, the NOEL (NOAEL) was determined to be 1% (equivalent to 870 mg/kg bw/day) and the LOEL (LOAEL) was 2% (equivalent to 1280 mg/kg bw/day) based on the kidney effects.

Lehman and Chase, (1944) tested the subchronic oral toxicity of 2-propanol in male and female rats. Rats were continuously administered 2-propanol in drinking water at doses of 0, 600, or 2300 mg/kg bw/day for male rats and 0, 1000, or 3900 mg/kg bw/day for female rats for 27 weeks. The rat strain and sample size were not provided. Decreased body weight gains were reported in male rats during the first thirteen weeks of the study, and then increased body weight gain for the remainder of the study. In contrast, female rats showed decreased body weight gain throughout the study. No gross or microscopic abnormalities were reported. A NOEL (NOAEL)

of 600 mg/kg bw/day for males and 1000 mg/kg bw/day for females was derived from this study, with a LOEL (LOAEL) of 2300 mg/kg bw/day for males and 3900 mg/kg bw/day for females.

Reproductive Toxicity

The reproductive toxicity of 2-propanol has been investigated in two one-generation reproduction studies and one two-generation reproduction study. All studies were GLP-compliant.

One-Generation Study

Male and female Wistar rats (sample size not provided) were administered 2-propanol in drinking water continuously at doses of 0, 0.5, 1.0 or 2.0%. The pre-mating exposure period was 21 days for females and 70 days for males. The exposure period occurred through weaning (Day 21 after birth). Parental rats dosed with 2% 2-propanol had decreased body weight gain with corresponding reduced pup weight gain and decreased survival compared with controls. A dose-related increase in relative liver weights of the F1 animals was also reported. No effect on reproductive parameters was reported. No macroscopic or histopathological changes were associated with 2-propanol treatment. The parental and F1 offspring NOEL (NOAEL) was 1%, equivalent to 825 and 625 mg/kg bw/day for females and males respectively (British Industrial Biological Research Ass., Report 0570/3/86, as cited in OECD, 1997).

Gallo et al., (1977) also tested the effects of 2-propanol in a one-generation reproduction study. Male and female Wistar rats (sample size not provided) were administered 2-propanol in drinking water continuously at doses of 0, 2 or 3%. The pre-mating exposure period was 8 weeks for both males and females. The rats were exposed prior to mating and through lactation and weaning of the F1 generation. Reduced parental body weight gain and reduced food and water consumption were reported in the treated animals compared with controls. In addition, fertility, litter size, and pup weights at postnatal Days 4 and 21 were reduced in the 3% treatment group compared with the controls. This dose was reduced to 2% and the parental animals were re-mated to provide litters for a developmental toxicity evaluation. No parental toxicity or reproductive toxicity was noted. The parental and F1 offspring NOEL (NOAEL) was 2% (equivalent to 2000 mg/kg bw/day as calculated by Exponent using conversion factors as in Derelanko, 2000).

Two-Generation Study

Bevan et al. (1995) tested the effects of 2-propanol in a two-generation reproduction study. Male and female Sprague-Dawley rats (n=30/sex/dose) (P1) were dosed with 2-propanol once daily by oral gavage with 0, 100, 500 or 1000 mg/kg bw/day for at least 10 weeks prior to mating. The exposure period was prior to mating, through lactation and weaning of F1 and F2 generations. Findings in the parental animals included increased lactation body weight gain in the 500 and 1000 mg/kg bw/day females, increased liver and kidney weights in the 500 and 1000 mg/kg

bw/day groups of both sexes, and centrilobular hepatocyte hypertrophy in some P2 males. There were microscopic findings in the kidneys from the mid- and high-dose P1 males and from all treated groups of the P2 males. Exposure to 1000 mg/kg bw/day and to a lesser extent 500 mg/kg bw/day resulted in a reduction in postnatal survival in both F1 and F2 litters. Body weights of the offspring were also reduced during the early postnatal period in the 1000 mg/kg bw/day F1 males and in the 1000 mg/kg bw/day F2 pups of both sexes. In the 1000 mg/kg bw/day group, 18/70 F1 weanlings were euthanized prior to P2 selection. No treatment-related postmortem findings were reported in the offspring from either generation.

A statistically significant reduction was reported in the male mating index of the 1000 mg/kg bw/day treated P2 males compared to controls. The change in this reproductive parameter was considered to be possibly treatment related and significant, although the mechanism of this effect could not be discerned from the results of the study. However, the lack of a significant effect on the female mating index in either generation, the absence of any adverse effect on litter size, and the lack of histopathological findings of the testes of the high-dose males suggested that the observed reduction in male mating index may not be biologically relevant. Additional support for this conclusion was provided by the fact that most of the females became pregnant. Furthermore, male and female fertility, and female fecundity indices of rats dosed with 2-propranol were not different from those of controls by statistical analysis and were within, or relatively close to, historical control values. No treatment-related microscopic changes in reproductive tissues or biologically meaningful differences in other reproductive parameters were reported. In addition, no reproductive effects were noted in other studies in which rats were dosed up to 2% in the drinking water (OECD SIDS, 1997).

A benchmark dose analysis has been conducted for reproductive and developmental toxicity observed after exposure to 2-propranol (Allen et al., 1998). The benchmark dose level (BMDL) values of interest lie between the study dosages of 100 and 500 mg/kg bw/day, for which there are conflicting no-effect interpretations. The U.S. EPA (1992, as cited in EPA, 2009 and OECD, 1997) and Tyl (1996, as cited in OECD, 1997) concluded the reductions were treatment- and dose-related, a conservative interpretation that supports a NOAEL of 100 mg/kg bw/day.

Alternatively, Bevan et al. (1995) deemed the observations not to be biologically significant and concluded the NOAEL to be 500 mg/kg bw/day. In addition, the reduction reported in the male mating index of the 1000 mg/kg bw/day P2 males compared to controls, though statistically significant, was not considered biologically significant. In order to clarify these issues, a benchmark dose (BMD) assessment was conducted for the developmental and reproductive findings with 2-propranol (Allen et al., 1998). For the offspring developmental effects, the BMDLs of 449 and 418 mg/kg bw/day were estimated for the F1 and F2 generations for Day 4 survival, respectively. Based upon the decrease in male mating index observations in the P2 males, a BMDL₁₀ of 416 mg/kg bw/day was estimated for reproductive effects.

Developmental Toxicity and Teratogenicity

The developmental toxicity of 2-propanol has been characterized in two rat developmental toxicity studies and one rabbit developmental toxicity study. These studies were all GLP-compliant.

Rat

Female Wistar rats (sample size not provided) were dosed continuously with 2-propanol in drinking water at doses of 0, 0.5, 1.25 and 2.5% from gestational Day 6 through 16. Maternal body weights were significantly decreased from gestational Days 7 through 16. Animals in the 1.25% and 2.5% dose groups exhibited reduced food and water consumption during the treatment period. Fetal body weights were reduced on a per fetus basis, but not on a per litter basis in the 1.25% and 2.5% dose groups. No teratogenic effects were observed; however, delayed ossification of the skeleton was reported in the 1.25% and 2.5% dose groups, consistent with retarded development as a result of maternal toxicity. The NOEL (NOAEL) was determined to be 0.5 % (equivalent to 500 mg/kg bw/day as calculated by Exponent using the dose conversion assumptions of Derelanko, 2000) for both maternal toxicity and teratogenicity (British Industrial Biological Research Assoc., Report no. 0570/2/86, as cited in OECD, 1997).

Female Sprague-Dawley rats (sample size not provided) were dosed by oral gavage at 0, 400, 800 or 1200 mg/kg bw/day from gestational Day 6 through 15. This study was conducted in accordance with US EPA TSCA Test guidelines. No dams aborted or delivered early. Two dams died at 1200 mg/kg bw/day and one dam died at 800 mg/kg bw/day. Reduced maternal gestational weight gain on gestational Days 0 to 20 associated with significantly reduced gravid uterine weights were reported in the high-dose animals. All gestational parameters were equivalent across groups. Fetal body weights per liter were significantly reduced at the two highest doses. No adverse maternal or developmental effects were reported at 400 mg/kg bw/day. The NOAEL for maternal toxicity and developmental toxicity was 400 mg/kg bw/day. No evidence of increased teratogenicity was reported at any dose tested. Therefore, 2-propanol was not teratogenic to SD rats (Tyl et al., 1994).

Rabbit

Female New Zealand rabbits (sample size not provided) were dosed by oral gavage at 0, 120, 240 or 480 mg/kg bw/day from gestational Day 6 through 18. No does aborted or delivered early. Four does died at 480 mg/kg bw/day. Maternal body weights were significantly reduced during treatment and clinical signs of toxicity were observed at 480 mg/kg bw/day. No adverse maternal effects were reported at 120 or 240 mg/kg bw/day. All gestational parameters were equivalent across groups. The NOAEL for maternal toxicity was determined to be 240 mg/kg bw/day due to reduction in maternal body weight and mortality at the high dose level. No

evidence of increased teratogenicity was reported at any dose tested. 2-propanol was not teratogenic to New Zealand rabbits. The NOAEL for developmental toxicity was determined to be 480 mg/kg bw/day due to reduction in maternal body weight (Tyl et al., 1994).

Developmental Neurotoxicity

2-propanol has also been tested for developmental neurotoxicity in female Sprague Dawley rats via oral gavage. The rats were dosed at 0, 200, 700 and 1200 mg/kg bw/day from gestational Day 6 through 21. This study was specifically designed to investigate developmental neurotoxicity. One high-dose dam died on postnatal Day 15, but no other clinical observations or effects on maternal weight, food consumption, or gestation length were reported. Pup survival, weight, sex ratio, and sexual maturation were unaffected. There were no biologically significant findings in the behavioral tests, no changes in organ weights, and no pathological findings attributable to 2-propanol exposure. The NOEL (NOAEL) for maternal toxicity was determined to be 700 mg/kg bw/day based on mortality reported at the high dose. No exposure-related effects were noted on motor activity, weights of the four regions of the brain, developmental landmarks, or morphological changes to the tissues of the central nervous tissue. These data suggest the developmental neurotoxicity NOAEL for rats is 1200 mg/kg bw/day (Bates et al., 1994).

Genotoxicity

Characterization of the genotoxicity hazard for 2-propanol is provided by both *in vitro* and *in vivo* mutation and chromosomal studies.

Florin et al. (1980) tested the mutagenic potential of 2-propanol in *Salmonella typhimurium* reverse mutation assay. 2-Propanol was tested at a concentration of 180 mmol/plate in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537, with and without metabolic activation (S9 mix). No increase in the number of revertant colonies was reported in the four test strains at the tested concentration, in the presence or absence of the S9 mix. Zeiger et al. (1992) tested the mutagenic potential of 2-propanol in a GLP compliant *Salmonella typhimurium* reverse mutation assay. 2-Propanol was tested at a concentration of 100 mmol/plate in *Salmonella typhimurium* strains TA 97, TA 98, TA 100, TA 102, TA 104, TA 1535, TA1537, and TA 1538, with and without S9 mix. No increase in the number of revertant colonies was reported in all test strains at the tested concentrations, with and without the S9 mix.

2-Propanol was also tested for its genotoxicity potential in four *in vitro* non-bacterial test systems. In the sister chromatid exchange assay using Chinese hamster V79 fibroblasts, 2-propanol did not induce sister chromatids at concentrations of 3.3, 10, 33.3 and 100 mmol/L in the presence or absence of S9 mix (von der Hude et al., 1987). 2-Propanol did not induce aneuploidy in the meiotic nondisjunction assay using *Neurospora crassa* (strain I x I) in the absence of S9 mix (Griffith, 1980, as cited in OECD, 1997). The concentration used in this study

was not provided. In the cell transformation assay using SA7/Syrian Hamster Embryo cells, 2-propanol at concentrations of 62-1000 µg/ml did not induce transformation in the absence of S9 mix (Casto & Hatch, 1978, as cited in OECD, 1997). In the GLP compliant, Hypoxanthine-Guanine Phosphoribosyl Transferase (HGPRT) assay using Chinese Hamster Ovary (CHO) cells, 2-propanol at concentrations of 0.5-5.0 mg/ml did not induce mutations at the HGPRT locus of CHO cells in the presence or absence of the S9 mix (Kapp et al., 1993).

The potential for 2-propanol to induce structural chromosomal aberrations was also investigated in an *in vivo* micronucleus assay, conducted in accordance with US EPA TSCA test guidelines according to GLP. Male and female ICR mice were injected intraperitoneally (IP) with a single dose of 350, 1173 or 2500 mg/kg bw, and the bone marrow examined after 24, 48 and 72 hours. No other information such as positive control used in the study and minimum number of cells scored per treatment group was available in this report. The injection of the 2-propanol did not induce a statistically significant increase in micronuclei in polychromatic erythrocytes (PCEs) (Kapp et al., 1993).

Overall, the genotoxic potential of 2-propanol has been investigated in six *in vitro* assays (two *Salmonella typhimurium* assays and four non-bacterial test systems) and in one *in vivo* micronucleus assay. All genotoxicity assays reported for 2-propanol were negative.

Mutagenicity studies showed that 2-propanol was not mutagenic in two Ames assays both in the presence or absence of an S9 metabolic activation system. *In vitro* sister chromatid exchange (SCE) assays using cultured V79 cells both with and without S9 activation, were also negative. 2-Propanol did not induce transformation in Syrian hamster embryos infected with Simian SA7 virus. 2-Propanol was found to be negative in an *in vitro* CHO/HGPRT assay, was negative *in vitro* for aneuploidy in *Neurospora crassa* and did not increase micronuclei in an *in vivo* micronuclei assay in mice. These studies demonstrate that 2-propanol is not genotoxic. These studies are summarized in below.

Table 8. Genotoxicity Studies of 2-Propanol (as cited in the OECD, 1997)

Reference	Study Design	Study Concentration	Results
Florin et al., 1980	<i>Salmonella typhimurium</i> TA 98, TA 100, TA 1535 and TA 1537, with and without S9 mix	180 mmol/plate	Negative
Zeiger et al., 1992	<i>Salmonella typhimurium</i> strains TA 97, TA 98, TA 100, TA 102, TA 104, TA 1535, TA 1537, and TA 1538, with and without S9 mix.	100 mmol/plate	Negative
Von der Hude et al., 1987	Sister chromatid exchange assay using Chinese hamster V79 fibroblasts with and without S9 mix.	3.3, 10, 33.3 and 100 mmol/ plate	Negative

Griffith, 1980	Meiotic nondisjunction assay using <i>Neurospora crassa</i> (Strain I x I) without S9 mix	No data provided	Negative
Casto & Hatch, 1978 [as cited in OECD, 1997]	Cell transformation assay using SA7/Syrian Hamster Embryo without S9 mix	62-1000 µg/mL	Negative
Kapp et al., 1993	Hypoxanthine-Guanine Phosphoribosyl Transferase (HGPRT) assay using Chinese hamster ovary (CHO) cells with and without S9 mix	0.5-5.0 mg/mL	Negative
Kapp et al., 1993	<i>In vivo</i> micronucleus assay (male & female ICR mice; IP injection; bone marrow examined after 24, 48 and 72 hours)	Single dose of 350, 1173 or 2500 mg/kg bw	Negative
Adapted from studies summarized in OECD SIDS 1997 report.			

Chronic Toxicity and Carcinogenicity Studies

Two carcinogenicity studies, one in Fischer 344 rats and the other in mice (CD-1 and C3H), were identified in the OECD SIDS report (1997); however, the route of administration in both studies was inhalation. Nevertheless, the results from these inhalation studies demonstrate that 2-propanol does not exhibit carcinogenic potential relevant to humans. Gentry et al. (2002) in their determination of an oral RfD based on PBPK modeling and the toxicological outcomes in several studies, concluded that the toxicity of 2-propanol is similar regardless of the route of exposure.

Human Studies

A number of cases of poisoning due to the intentional ingestion of 2-propanol especially among alcoholics or suicide victims, and intoxications following ingestion have been reported. Signs of intoxication were CNS depression, leading to coma, respiratory arrest and death. Gastrointestinal effects (nausea, vomiting) and hypothermia may occur. Cardiac effects included severe hypotension, shock and cardiac arrest with tachycardia as a secondary effect. The lowest dose that has been reported to be life threatening was 170 mL in an 18-month old child. If a weight of 13.7 kg is assumed for a child of approximately 2 years of age and a density of 0.785 g/mL for 2-propanol is applied (ChemIDPlus Lite, accessed October 2018), an intake of 170 mL is approximately equal to a dose of 9.74 g/kg bw. Acetone can be detected in the blood, breath and urine after intoxication with 2-propanol, but acidosis did not usually occur (WHO, 1990).

Occasional reports of allergic reaction via skin contact to 2-propanol have appeared in the literature (WHO, 1990).

Oral administration of 2-propanol in syrup at dose level of 2.6 or 6.4 mg /kg bw/day 2-propanol for 6 weeks was well tolerated by human male volunteers, with no adverse effects on hematology, blood chemistry, urinalysis, or ophthalmoscopy (WHO, 1990).

The manufacture of 2-propanol by the strong-acid process has been associated with an excess of upper respiratory tract cancer in workers and the IARC has concluded that there is sufficient evidence for carcinogenicity to humans relating to this manufacturing process. However, the carcinogenic risks among workers were related to exposures to sulfuric acid and manufacturing by-products such as dialkyl sulfates (inhalation and/or dermal exposure) rather than from exposure to 2-propanol itself (WHO, 1990). A single study was reported showing that 2-propanol was associated with a higher risk of breast cancer. However, there was a combined exposure with freon and solder flux and aspects of lifestyle (such as smoking habits and alcohol consumption), which were not taken into account in the evaluation (Spiritas et al., 1991).

Reference Doses (RfD)

Gentry et al. (2002) applied an interspecies PBPK model (as described above by Clewell et al., 2001) to perform route to route (using inhalation and oral data) and cross-species dosimetry to derive a reference dose (RfD) for 2-propanol. Adult PBPK models for rats and humans were extended to simulate exposure to 2-propanol during pregnancy and used to estimate internal dose metrics in the mother and fetus during development. The principal structural change to the Clewell et al. (2001) PBPK model was the addition of separate compartments for the uterus, mammary tissue, placenta, and fetus.

Endpoints from chronic, developmental, and reproductive toxicity studies were considered for the derivation of the RfD. These studies included subchronic and chronic repeated dose inhalation toxicity studies with 2-propanol. In the Burleigh-Flayer et al. (1994, 1998, as cited in Gentry et al., 2002) studies rats and mice were exposed to 2-propanol at concentrations of 0, 100, 500, 1500 or 3500 ppm for 6h/day 5/day per week for 13 weeks by inhalation. The NOAEL in this study was 500 ppm in males based on the occurrence of hyaline droplets and 2500 ppm in females based on body weight, clinical pathology and motor activity effects (LOAEL 5000 ppm). In an additional 13 week inhalation study in rats by Burleigh-Flayer et al. (1998, as cited in Gentry et al., 2002), the NOAEL for motor activity effects was 1500 ppm. A combined inhalation chronic toxicity and carcinogenicity study (Burleigh-Flayer et al., 1997, as cited in Gentry et al., 2002) was conducted with CD-1 mice and F344 rats (75/sex/dose). In this study mice and rats were exposed to 2-propanol at concentrations of 0, 500, 2500 or 5000 ppm via inhalation for 6h/day, 5 days/week for at least 78 weeks (mice) or 104 weeks (rats). Renal effects were noted in males and females with a NOAEL in males of 500 ppm and females of 2500 ppm. Three studies were used to evaluate the potential reproductive and developmental toxicity of 2-propanol (Bevan et al., 1995, and Tyl et al., 1994, and Nelson et al. 1988, as cited in Gentry et al., 2002). In the study conducted by Tyl et al. (1994), the NOAEL was 400 mg/kg bw/day based on

decreased fetal body weight. The studies conducted by Tyl et al. (1994) and Bevan et al. (1995) were oral gavage administration of 2-propanol, while the study conducted by Nelson et al. (1988) was inhalation exposure. In the Nelson et al. (1988, as cited in Gentry et al., 2002) study, decreases in fetal weight were observed following exposure to all three concentrations of 2-propanol (3500, 7000, and 10,000 ppm). However, the authors noted that these effects were observed in the presence of maternal toxicity, and the fetal body weight effects observed following exposure to the lowest concentration were very slight and assigned a LOAEL of 3500 ppm. Bevan et al. (1995) conducted a two-generation reproduction study in rats and noted increased mortality in the F1 offspring and reduced F1 (males) and F2 (males and females) body weights with a NOAEL of 500 mg/kg bw/day as well as decreased a male mating index with a NOAEL of 420 mg/kg bw/day based on bench mark dose level modeling (BMDL). Table 4 below summarizes the NOAELs considered for the derivation of the RfD by Gentry et al. (2002).

The dose metric used for most responses was the total area under the curve (AUC) for the combination of 2-propanol and its major metabolite, acetone. Peak blood concentration of 2-propanol was the dose metric for neurobehavioral effects because short-term, rapidly reversible toxic effects, such as the acute neurobehavioral effects of 2-propanol, are more likely to result from the current concentration of the chemical in the tissue. In such cases, the likelihood of toxicity from a particular exposure scenario can be estimated by the maximum concentration. The recommended RfD was 11 mg/kg bw/day based on the most conservative endpoint of decreased fetal body changes. All of the RfD values derived from the PBPK model for various endpoints are within a factor of 3, regardless of route of exposure in the animal study.

Table 9. NOAELs Considered in the Derivation of the RfD by Gentry et al. (2002)

Study	NOAEL	Endpoint	Route and Duration of Exposure	Citation
Chronic Inhalation Toxicity	500 ppm (males) 2500 ppm (females)	Chronic renal disease	Inhalation 6h/day, 5 days/week, 104 weeks	Burleigh- Flayer et al. (1997, as cited in Gentry et al., 2002)
Developmental Effects	3500 ppm (LOAEL)	Decreased fetal body weight	Inhalation 7d/day for 19 days	Nelson et al. (1988, as cited in Gentry et al., 2002)
Developmental Effects	400 mg/kg bw/day	Decreased fetal body weight	Oral gavage daily Days 6-15 of gestation	Tyl et al. (1994)
Developmental Effects	500 mg/kg bw/day	Decreased fetal body weight	Oral gavage daily for 10 weeks prior to mating and during gestation in P1 generation	Bevan et al. (1995)
Reproductive Effects	420 mg/kg bw/day (BMDL)	Decreased male mating index	Oral gavage daily for 10 weeks	Bevan et al. (1995)

Study	NOAEL	Endpoint	Route and Duration of Exposure	Citation
Neurobehavioral effects	1500 ppm	Increased motor activity	Inhalation 6h/day, 5 days/week, 13 weeks	Burleigh- Flayer et al. (1994, 1998, as cited in Gentry et al., 2002)

Acceptable Daily Intake (ADI)

In 2005, the EFSA Scientific Committee for Food (SCF) reviewed the safety of 2-propanol for its use as a carrier solvent for flavorings. Based on the results of genotoxicity studies, the SCF considered 2-propanol as non-mutagenic, non-clastogenic and did not require additional genetic toxicity studies for this compound. From its review of the range of subchronic, reproductive and developmental studies in various species, the SCF considered the NOAEL for subchronic oral toxicity study to be 870 mg/kg bw/day in rats, the NOAEL for developmental toxicity to be 400 mg/kg bw/day in rats and the NOAELs for maternal and developmental toxicity in rabbits to be 240 and 480 mg/kg bw/day, respectively. The Panel noted the particular sensitivity of the rabbit to 2-propanol; however, in absence of mechanistic information about the species differences, the SCF derived a full ADI of 2.4 mg/kg bw/day based on the NOAEL of 240 mg/kg/day for maternal toxicity in rabbits (EFSA, 2005).

2-Propanol Safety Summary

The mammalian and human toxicological properties of 2-propanol have been well characterized in multiple animal species and humans for a variety of exposure durations and toxicity endpoints. High quality studies have been conducted that evaluate acute toxicity, subchronic and chronic toxicity, reproductive toxicity, developmental and developmental neurotoxicity, subchronic neurotoxicity, genotoxicity and carcinogenic potential. In addition, studies are available that characterize the pharmacokinetics of 2-propanol in mammals. Taken together, these data support the conclusion that 2-propanol is not genotoxic, not carcinogenic, does not have neurotoxic potential, and is not a selective developmental toxin upon ingestion.

NOAELS for repeated dose studies of 2-propanol (oral) are in the range of 600 to 870 mg/kg bw/day and LOAELS are in the range of greater than 1000 mg/kg bw/day from subchronic testing reported in the publically available literature (Pilegaard and Ladefoged, 1993, Lehman and Chase, 1944). Effects noted included body weight effects and effects in the kidneys.

Reproductive and developmental NOAELS from the publically available literature are slightly lower than those reported for subchronic toxicity studies. NOAELS for developmental effects were 400 and 480 mg/kg bw/day in rats and rabbits, respectively, and the lowest NOAEL for maternal toxicity was determined to be 240 mg/kg bw/day in rabbits (Tyl et al., 1994).

Developmental neurotoxicity NOAEL in rats was slightly higher at 1200 mg/kg bw/day (Bates et al., 1994).

Bevan et al. (1995) tested the effects of 2-propanol in a two-generation reproduction study, however, conflicting interpretations of the toxicological endpoints observed between the doses of 100 and 500 mg/kg bw/day exist. This resulted in reanalysis and benchmark dose modeling by several investigators. Benchmark dose analysis by Allen et al., 1998 resulted in the estimation of a BMDL₁₀ of 416 mg/kg bw/day for reproductive effects, while the U.S. EPA (1992, as cited in EPA, 2009, and OECD, 1997) and Tyl, (1996, as cited in OECD, 1997) concluded that body weight reductions observed were treatment- and dose-related in reproductive studies, and conservatively interpreted a NOAEL of 100 mg/kg bw/day. Alternatively, Bevan et al. (1995) deemed the observations not to be biologically significant and concluded the NOAEL to be 500 mg/kg bw/day.

Based on endpoints from various studies and utilizing the most conservative endpoint of fetal body weight changes (NOAEL of 420 mg/kg bw/day), Gentry et al. (2002) identified a reference dose (RfD) of 11 mg/kg bw/day for 2-propanol using an interspecies physiologically- based pharmacokinetic (PBPK) model. The Scientific Committee for Food (SCF, EFSA, 2005) noted the particular sensitivity of the rabbit to 2-propanol; however, in absence of mechanistic information about the species differences, the SCF derived a full ADI of 2.4 mg/kg bw/day based on the NOAEL of 240 mg/kg/day for maternal toxicity in rabbits. The latest derived ADI by EFSA is relied upon for the safety assessment of isopropanol in this notification.

Safety Evaluation for VAVLP copolymers (5 to 40% VL)

The safety of the intended use of VAVLP copolymers (5 to 40% VL) can be assessed from the safety of VAVLP copolymers previously determined to be GRAS for their intended use in chewing gum base and the safety of the isopropanol transfer agent that may be used to manufacture these copolymers. VAVLP copolymers (20% and 40% VL) sold under the trade names VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL were previously determined to be GRAS for their intended use in chewing gum base based on a comprehensive review of the safety of VAVLP copolymers as well as the potential residuals in the copolymers.

GRN 606 presents the safety determination for the intended use of copolymers VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL as a component in chewing gum base. As previously noted, the complete GRAS notification, which includes a synopsis developed by the GRAS Expert Panel and the signed Expert Panel opinion that the intended use is GRAS, is incorporated herein by reference. The notification was filed by FDA and FDA responded with a letter indicating the agency had no concerns about the GRAS conclusion. The Expert Panel relied on data summarized in Table 6 above, as well as product characterization data and estimates of potential intake. Based on the data summarized from GRN 606 above, the Expert Panel concluded:

Based on a critical review of the scientific evidence, the Expert Panel unanimously concluded that under the conditions of intended use in chewing gum base, Wacker's PVAcVL copolymers meeting appropriate food grade specifications and manufactured in accordance with current good manufacturing practice, is safe. Further, the Expert Panel unanimously concluded that the intended use of the two PVAcVL copolymers, singly or combined, at levels up to 26% of chewing gum base, is GRAS based on scientific procedures.

Specifications for residual monomers in VAVLP copolymers (5 to 40% VL) are identical to the specifications for the residual monomers in the VAVLP copolymers (20% and 40% VL) previously determined to be GRAS (GRN606). It therefore follows that potential exposure to residuals in the VAVLP copolymers (5 to 40% VL) is also safe. The expanded range of VL in the copolymers may also contain residue from use of isopropanol as a transfer agent. On a bodyweight basis, children consumers of chewing gum may have the highest intake of the copolymer, with a per user 90th percentile intake of 42.7 mg/kg bw/day. Assuming the maximum isopropanol concentration in the copolymer that is manufactured with isopropanol as a transfer agent (up to 50 ppm), the maximum potential exposure to isopropanol by children ages 2 to 5 years is 0.002 mg/kg bw/day, which is well below the ADI of 2.4 mg/kg bw/day. The intended use of the VAVLP copolymers (5 to 40% VL) and produced with isopropanol as a transfer agent can therefore be concluded to be safe.

GRAS Criteria

The regulatory framework for determining whether the use of a substance in food for animals can be considered GRAS in accordance with section 201(s) of the Federal Food, Drug, and Cosmetic Act ("the Act"), is set forth at 21 CFR 170.30, which states:

General recognition of safety may be based only on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.

General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies, which may be corroborated by unpublished studies and other data information.

In the preamble to the final rule for GRAS notifications, FDA stated that a GRAS conclusion, based on scientific procedures may be supported by scientific data (such as human, animal,

analytical or other scientific studies), information, methods and principles, published or unpublished, appropriate to establish the safety of a substance under the conditions of intended use (FDA, 2016). The safety standard requires that there be a reasonable certainty of no harm under the conditions of intended use of the substance. To be eligible for a GRAS conclusion based on scientific procedures, there must be evidence of a consensus among qualified experts that the proposed use is safe and the pivotal data and information supporting the safety of the ingredient's intended use must be publicly available.

GRAS Panel Conclusions

Wacker Chemie AG determined that VAVLP copolymers (5 to 40% VL) produced using either acetaldehyde or isopropanol as the transfer agent, when used at a level up to 26% in chewing gum base, which corresponds to a maximum of 9% in chewing gum as consumed, is safe. This GRAS conclusion was based on information in the generally available public domain relevant to the safety of VAVLP copolymers as discussed herein. An independent panel of experts, qualified by their scientific training and national and international experience to evaluate the safety of food and food ingredients (the "GRAS Panel"), was specially convened to evaluate the safety and GRAS status of the intended use and reached a GRAS conclusion. The GRAS panelists were: Richard Kraska, Ph.D. (GRAS Associates, LLC); Stanley M. Tarka, Jr., Ph.D. (The Tarka Group, Inc. and The Pennsylvania State University College of Medicine), and John A. Thomas, Ph.D. (Indiana University School of Medicine). The GRAS Panel critically evaluated safety documentation and other available data and information that the members of the Panel believed to be pertinent to the safety of the intended use of VAVLP copolymers (5 to 40% VL) in chewing gum base. The GRAS Panel concluded that other qualified experts evaluation the same data and information would concur with their conclusions. The Opinion of the GRAS Panel is presented in Appendix B.

Conclusion of GRAS Status

The intended use of VAVLP copolymers (5 to 40% VL) is up to 26% in chewing gum base, which corresponds to a maximum of 9% in chewing gum as consumed. The copolymers may be produced with acetaldehyde or isopropanol used as a transfer agent. As previously concluded in GRN 606, the intake of VAVLP copolymers containing 20% or 40% VL and made with acetaldehyde as a transfer agent is safe. Intake of VAVLP copolymers containing 5 to 40% VL and made with acetaldehyde as a transfer agent provides a comparable exposure to residuals and therefore also can be concluded to be safe. Intake of VAVLP copolymers (5 to 40% VL) and made with isopropanol as a transfer agent provides a maximum potential intake of isopropanol by children ages 2 to 5 years of 0.002 mg/kg bw/day, which is well below the ADI of 2.4 mg/kg bw/day. Therefore, use of isopropanol as a transfer agent in the production of the substance does

not present a safety concern. The intended use of the VAVLP copolymers (5 to 40% VL) produced with isopropanol as a transfer agent therefore can be concluded to be safe.

In summary, VAVLP copolymers (5 to 40% VL), produced with acetaldehyde or isopropanol as a transfer agent, can be concluded to be safe. Therefore, it can be concluded that the proposed use of VAVLP copolymers (5 to 40% VL) in chewing gum base is safe within the meaning of the FD&C Act, i.e., meets the standard of reasonable certainty of no harm.

Discussion of Information Inconsistent with GRAS Determination

No information has been identified that would be inconsistent with a finding that the proposed use of VAVLP copolymers (5 to 40% VL), meeting appropriate specifications specified herein and used according to current Good Manufacturing Practices (cGMP), is GRAS.

Basis for Conclusion that there is Consensus Regarding Safety

The intended use of VAVLP copolymers (5 to 40% VL) has been determined to be safe through scientific procedures as set forth in 21 CFR§170.30(b), thus satisfying the so-called “technical” element of the GRAS determination. Because this safety evaluation was based on generally available and widely accepted data and information, it also satisfies the so-called “common knowledge” element of a GRAS determination.

Determination of the safety and GRAS status of VAVLP copolymers (5 to 40% VL) up to 26% in chewing gum base, which corresponds to a maximum of 9% in chewing gum as consumed, under its intended conditions of use has been made through the deliberations of an Expert Panel of individuals qualified by scientific training and experience to evaluate the safety of substances intended to be added to food. They have critically reviewed and evaluated the publicly available information summarized in this document and have individually and collectively concluded that VAVLP copolymers (5 to 40% VL) produced consistent with Good Manufacturing Practice and meeting the specifications described herein, is safe under its intended conditions of use. The Panel further unanimously concludes that these uses of VAVLP copolymers (5 to 40% VL) are GRAS based on scientific procedures, and that other experts qualified to assess the safety of foods and food ingredients would concur with these conclusions. The Panel’s GRAS opinion is included as Appendix B to this document.

Part 7. List of Supporting Data and Information in GRAS Notice

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Appendices

Appendix A. Batch Analyses

Date of delivery

Delivery note

Requisition No.

Date of requisition

/

Order No.

Customer No. Fax

/ 000000 /

Wacker Chemie AG Werk Burghausen Postfach D-84489 Burghausen

CAPIVA® S08

date of issue: 25.01.2018

Material	60083703	Batch	1503277	NET	0,000	Date of manufacture	24.03.2015	Best use before end	23.03.2018
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Technical data	Test method/Inspection condition	Unit	Measured value	Lower limit	Upper limit
Viscosity	ASTM D 445-06 10%, ethyl acetate, 20°C	mPa.s	3,4	3,2	4,0
METTLER softening point	ASTM 3104	°C	103,7	102,0	110,0
Free acetic acid	GC gas-chromatographic	%	0,023	-	0,050
Residual vinyl acetate monomer	GC gas-chromatographic	mg/kg	< 1,0	-	5,0
Content of vinyl laurate monomer	GC gas-chromatographic	ppm	20	-	100

Wacker Chemie AG, Werk Burghausen
 Qualitätskontrolllabor, Dr. Klaus Hegemann
 Telefax +49 (8677) 83-3318

This certificate was issued by machine and is valid without a signature.

This data does not absolve the purchaser from checking the quality of all supplies immediately on receipt, particularly regarding the possible influences of transport and intermediate storage conditions over which we have no control.
 All sales of this product shall be subject to our General Conditions of Sale.

Date of delivery

Delivery note

Requisition No.

Date of requisition

/

Order No.

Customer No. Fax

/ 000000 /

Wacker Chemie AG Werk Burghausen Postfach D-84489 Burghausen

CAPIVA® S08

date of issue: 25.01.2018

Material	60083703	Batch	1503288	NET	0,000	Date of manufacture	25.03.2015	Best use before end	24.03.2018
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Technical data	Test method/Inspection condition	Unit	Measured value	Lower limit	Upper limit
Viscosity	ASTM D 445-06 10%, ethyl acetate, 20°C	mPa.s	3,4	3,2	4,0
METTLER softening point	ASTM 3104	°C	104,8	102,0	110,0
Free acetic acid	GC gas-chromatographic	%	0,020	-	0,050
Residual vinyl acetate monomer	GC gas-chromatographic	mg/kg	< 1,0	-	5,0
Content of vinyl laurate monomer	GC gas-chromatographic	ppm	20	-	100

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 All sales of this product shall be subject to our General Conditions of Sale.

Date of delivery

Delivery note

Requisition No.

Date of requisition

/

Order No.

Customer No. Fax

/ 000000 /

Wacker Chemie AG Werk Burghausen Postfach D-84489 Burghausen

CAPIVA® S08

date of issue: 25.01.2018

Material	60083703	Batch	1503297	NET	0,000	Date of manufacture	26.03.2015	Best use before end	25.03.2018
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Technical data	Test method/Inspection condition	Unit	Measured value	Lower limit	Upper limit
Viscosity	ASTM D 445-06 10%, ethyl acetate, 20°C	mPa.s	3,4	3,2	4,0
METTLER softening point	ASTM 3104	°C	103,7	102,0	110,0
Free acetic acid	GC gas-chromatographic	%	0,020	-	0,050
Residual vinyl acetate monomer	GC gas-chromatographic	mg/kg	< 1,0	-	5,0
Content of vinyl laurate monomer	GC gas-chromatographic	ppm	20	-	100

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Date of delivery

Delivery note

Requisition No.

Date of requisition

/

Order No.

Customer No. Fax

/ 000000 /

Wacker Chemie AG Werk Burghausen Postfach D-84489 Burghausen

CAPIVA® S08

date of issue: 25.01.2018

Material	60083703	Batch	1503307	NET	0,000	Date of manufacture	07.09.2017	Best use before end	06.09.2020
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Technical data	Test method/Inspection condition	Unit	Measured value	Lower limit	Upper limit
Viscosity	ASTM D 445-06 10%, ethyl acetate, 20°C	mPa.s	3,6	3,2	4,0
METTLER softening point	ASTM 3104	°C	104,4	102,0	110,0
Free acetic acid	GC gas-chromatographic	%	0,020	-	0,050
Residual vinyl acetate monomer	GC gas-chromatographic	mg/kg	< 1,0	-	5,0
Content of vinyl laurate monomer	GC gas-chromatographic	ppm	20	-	100

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Date of delivery

Delivery note

Requisition No.

Date of requisition

/

Order No.

Customer No. Fax

/ 000000 /

Wacker Chemie AG Werk Burghausen Postfach D-84489 Burghausen

CAPIVA® S08

date of issue: 25.01.2018

Material	60083703	Batch	1503314	NET	0,000	Date of manufacture	28.03.2015	Best use before end	27.03.2018
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Technical data	Test method/Inspection condition	Unit	Measured value	Lower limit	Upper limit
Viscosity	ASTM D 445-06 10%, ethyl acetate, 20°C	mPa.s	3,5	3,2	4,0
METTLER softening point	ASTM 3104	°C	105,1	102,0	110,0
Free acetic acid	GC gas-chromatographic	%	0,020	-	0,050
Residual vinyl acetate monomer	GC gas-chromatographic	mg/kg	< 1,0	-	5,0
Content of vinyl laurate monomer	GC gas-chromatographic	ppm	20	-	100

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Appendix B. GRAS Panel Opinion

Report of the GRAS Panel Concerning the Generally Recognized As Safe (GRAS) Status of Vinyl Acetate-Vinyl Laurate (VAVLP) Copolymers as Components of Chewing Gum Base

Introduction

The undersigned, an independent panel of experts, qualified by their scientific training and national and international experience to evaluate the safety of food and food ingredients (the “GRAS Panel”), was specially convened by Hyman, Phelps & McNamara, to evaluate the safety and “generally recognized as safe” (“GRAS”) status of the intended use of vinyl acetate-vinyl laurate (VAVLP) copolymers with 5 to 40% (w/w) vinyl laurate (VL), singly or in combination, intended to be used in chewing gum base at a maximum concentration of 26%, corresponding to a maximum concentration of 9% by weight in chewing gum as consumed. The GRAS panelists were: Richard Kraska, Ph.D. (GRAS Associates, LLC); Stanley M. Tarka, Jr., Ph.D. (The Tarka Group, Inc. and The Pennsylvania State University College of Medicine), and John A. Thomas, Ph.D. (Indiana University School of Medicine).

For the purpose of this review, “safe” or “safety” means that there is “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use,” as defined by the U.S. Food and Drug Administration (FDA or the “Agency”) in 21 C.F.R. § 570.3(i).

The safety of the intended use of VAVLP copolymer with 20% VL (sold under the trade name VINNAPAS® B 500/20 VL) and VAVLP copolymer with 40% VL (sold under the trade name VINNAPAS® B 500/40 VL) in chewing gum base at a maximum concentration of 26%, corresponding to a maximum concentration of 9% by weight in chewing gum as consumed (finished products), was previously concluded to be safe and GRAS as detailed in a notice to FDA filed by FDA as GRN 606. FDA responded with a letter indicating the Agency had no concerns about the GRAS conclusion. This review expands the specifications for the VAVLP copolymers intended for use in chewing gum base to include copolymers with VL ranging from 5 to 40% (w/w). Both of the VAVLP copolymers specified in GRN 606 fall within the range of copolymers addressed in this review. Throughout this document the VAVLP with VL accounting for 5 to 40% (w/w) is referred to as VAVLP copolymers (5 to 40% VL).

Exponent, Inc. (“Exponent”) performed an updated search of the scientific literature, through July 24, 2018, relating to the safety of VAVLP copolymers and impurities such as residual monomers of VL and vinyl acetate (VA), and residual chain transfer agents, i.e. acetaldehyde and isopropanol. Exponent summarized the results of the literature search and prepared a safety dossier, “Documentation in Support of the Generally Recognized As Safe (GRAS) Conclusion for Vinyl Acetate-Vinyl Laurate (VAVLP) Copolymers as Components of Chewing Gum Base (Nov. 2, 2018) for consideration by the convened GRAS Panel.

The GRAS Panel (Drs. Tarka, Thomas, and Kraska) independently critically evaluated Exponent's safety documentation (the dossier), and other available data and information that the members of the Panel believed to be pertinent to the safety of the intended use of VAVLP copolymers (5 to 40% VL) in chewing gum base. In particular, the Panel reviewed the following: identity of the expanded range of VAVLP, updated information on the manufacture of the expanded range of copolymers, specifications for the expanded range of copolymers, updated estimates of potential intakes of residues from use of the VAVLP copolymers in chewing gum base that are based on recent food consumption data, the safety of VAVLP copolymers as previously described in GRN 606, an updated safety literature for VAVLP copolymers since completion of the previous GRAS assessment, and the safety of 2-Propanol (isopropanol), a chain transfer agent used in the production of VAVLP copolymers (5 to 40% VL).

On Nov. 15, 2018, the Expert Panel convened via teleconference, and independently, jointly, and unanimously concluded that VAVLP copolymers (5 to 40% VL), produced consistent with current good manufacturing practice (cGMP) and meeting the stated specifications, is safe and suitable for its intended use in chewing gum base at a maximum concentration of 26%, corresponding to a maximum concentration of 9% by weight in chewing gum as consumed. The Panel further concluded unanimously that the intended use of VAVLP copolymers (5 to 40% V) in chewing gum base at a maximum concentration of 26%, corresponding to a maximum concentration of 9% by weight in chewing gum as consumed is GRAS based on scientific procedures. It is also the unanimous consensus opinion of this GRAS Panel that other qualified experts would concur with these conclusions.

Summarized below are the data, information, and interpretive analysis supporting the GRAS Panel's conclusions.

Description

The safety of the intended use of VAVLP copolymer with 20% VL (VINNAPAS® B 500/20 VL) and VAVLP copolymer with 40% VL (VINNAPAS® B 500/40 VL) was previously determined as detailed in a notice to the FDA filed as GRN 606. These VAVLP copolymers are produced by a chain-growth polymerization process from VA and VL of high purity (>99.95 and 98%, respectively) mixed in appropriate proportions. Tert-butylperoxy-2-ethylhexanoate (CAS 3009-82-4) and 2,2-Di(tert-butylperoxy)butane (CAS 2167-23-9) are used as radical initiators. Acetaldehyde serves as a chain transfer agent during the polymerization process. After polymerization, the remaining chain transfer agent, unreacted monomers, and decomposition products of the radical initiators are removed by evaporation at elevated temperature and vacuum and by washing of the polymer with water.

This GRAS review expands the identity for the VAVLP copolymers to include copolymers with 5 to 40% VL. VAVLP copolymers (5 to 40% VL) addressed in this review are made using the same production process, but the process is optimized by lower usage of VA to reduce further residual VL monomer content. Either acetaldehyde or isopropanol may serve as a chain transfer

agent during the polymerization process. Specifications for the VAVLP copolymers (5 to 40% VL) on parameters of free acetic acid, residual VL monomer, and residual VA monomer are identical to the specifications for VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL. Specifications for viscosity and saponification number for VAVLP copolymers (5 to 40% VL) are comparable to specifications for VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL

Intended Use

VAVLP copolymers (5 to 40% VL) are intended to be used, singly or in combination, in chewing gum base at a maximum concentration of 26%, corresponding to a maximum concentration of 9% by weight in chewing gum as consumed.

The highest technically feasible concentration of VAVLP copolymers in chewing gum base is 35% (corresponding to 17% in the final product, see GRN 606). However, due to excessive hardness of the gum that results from such concentrations of the copolymers, the maximum use level of VAVLP copolymers in chewing gum base is realistically no more than 26%. Therefore, the maximum concentration of the copolymer in finished product, that is, gum as consumed, will not exceed 9% by weight.

Estimated Daily Intake (EDI)

For this review, the EDIs for VAVLP copolymers (and impurities) were calculated based on the maximum technically feasible use level¹ of the copolymers in chewing gum base and intakes of chewing gum collected in the What We Eat in America (WWEIA) component of the National Health and Nutrition Examination Survey (NHANES) in the combined survey periods from 2011 to 2014 (WWEIA, NHANES 2011-2014). The per user 90th percentile EDI of VAVLP copolymers is 15.6 mg/kg bw/day for adults ages 20 years and older and 42.7 mg/kg bw/day for children ages 2-5 years.

Previously, in GRN 606, the EDIs of VAVLP copolymers, also based on the maximum technically feasible use level² in chewing gum base but with older food consumption data, were 15 mg/kg bw/day at the per user 90th percentile for adults, and 48 mg/kg bw/day among children representative of “heavy” consumers of chewing gum. Intake estimates of VAVLP copolymers based on recent food consumption data are therefore comparable to estimates relied upon in

¹ The maximum technically feasible use of VAVLP copolymers in gum base is 35% by weight, corresponding to 17% by weight in chewing gum as consumed (GRN 606).

² *Ibid.*

GRN 606. It follows that estimated exposures to impurities based on current data would support the same safety conclusion in GRN 606.

Safety Information

The safety of the intended use of VAVLP copolymer with 20% VL (sold under the trade name VINNAPAS® B 500/20 VL) and VAVLP copolymer with 40% VL (sold under the trade name VINNAPAS® B 500/40 VL) in chewing gum base at a maximum concentration of 26%, corresponding to a maximum concentration of 9% by weight in chewing gum as consumed, was previously determined to be GRAS as detailed in a notice to FDA and filed as GRN 606. This review expands the identity for the VAVLP copolymer to include copolymers with 5 to 40% VL (w/w).

The current assessment, which considers the safety of copolymers in the range of 5 to 40% (w/w) VL builds on the previous determination of safety established in GRN 606, includes an update of the literature on which that safety assessment was completed, and evaluates the safety of potential residues resulting from the use of isopropanol as a transfer agent.

No new safety information for VA, VL, or VAVLP copolymers was found in the updated literature search. The available safety information for VAVLP, VA, and VL copolymers that were relied upon in GRN 606 included published pre-clinical data on the safety of VAVLP copolymers (Messinger and Bär 2014a), published pre-clinical data on the safety of VL (van Acker et al., 2015, Lina et al., 2015; Messinger and Bär 2014b), and authoritative reviews as well as published information on the safety of VA (Albertini 2013; JECFA, 2011; Environment Canada/Health Canada 2008a, 2008b). Unpublished data on the lack of digestion of VAVLP copolymers also provided corroborative evidence to support the safety assessment (Hergeth, 2007).

The mammalian and human toxicological properties of 2-propanol have been well characterized in multiple animal species and humans for a variety of exposure durations and toxicity endpoints. Taken together, these data support the conclusion that 2-propanol is not genotoxic, not carcinogenic, does not have neurotoxic potential, and is not a selective developmental toxin when ingested. Based on endpoints from various studies and utilizing the most conservative endpoint of fetal body weight changes (NOAEL of 420 mg/kg bw/day), Gentry et al. (2002) identified a reference dose (RfD) of 11 mg/kg bw/day for 2-propanol using an interspecies, physiologically-based pharmacokinetic (PBPK) model. The Scientific Committee for Food (SCF; EFSA, 2005) noted the particular sensitivity of the rabbit to 2-propanol; however, in the absence of mechanistic information about the species differences, the SCF derived a full ADI of 2.4 mg/kg bw/day based on the NOAEL of 240 mg/kg/day for maternal toxicity in rabbits. The latest derived ADI by EFSA is relied upon for the safety assessment of isopropanol in this review.

Safety Assessment

The safety of the intended use of VAVLP copolymers (5 to 40% VL) can be assessed from the safety of VAVLP copolymers previously determined to be GRAS and the safety of the isopropanol transfer agent that may be used to manufacture the copolymers. VAVLP copolymers (20% and 40% VL) sold under the trade names VINNAPAS[®] B 500/20 VL and VINNAPAS[®] B 500/40 VL were previously determined to be GRAS based on a comprehensive review of the safety of VAVLP copolymers as well as potential residues of vinyl laurate monomer and vinyl acetate monomer in the copolymers.

Specifications for residues in VAVLP copolymers (5 to 40% VL) are identical to specifications for residues in the VAVLP copolymers (20% and 40% VL) determined to be GRAS (GRN 606). It, therefore, follows that potential exposure to residues of vinyl laurate monomer and vinyl acetate monomer in the VAVLP copolymers (5 to 40% VL) is also safe. The expanded range of VL in the copolymers may also contain residue from use of isopropanol as a transfer agent. On a body weight basis, children consumers of chewing gum may have the highest intake of the copolymer, with a per user 90th percentile intake of 42.7 mg/kg bw/day. Assuming the maximum isopropanol concentration in the copolymer that is manufactured with isopropanol as a transfer agent (up to 50 ppm), the maximum potential exposure to isopropanol by children ages 2 to 5 years is 0.002 mg/kg bw/day, which is well below the ADI of 2.4 mg/kg bw/day. The intended use of the VAVLP copolymers (5 to 40% VL) and produced with isopropanol as a transfer agent can therefore be concluded to be safe.

Summary and Conclusion

The intended use of VAVLP copolymers (5 to 40% VL) is up to 26% in chewing gum base, which corresponds to a maximum of 9% in chewing gum as consumed. The copolymers may be produced using either acetaldehyde or isopropanol as the transfer agent. As previously concluded in GRN 606, the intake of VAVLP copolymers containing 20% or 40% VL and made with acetaldehyde as a transfer agent is safe. Intake of VAVLP copolymers containing 5 to 40% VL and made with acetaldehyde as a transfer agent provides a comparable exposure to residues and therefore also can be concluded to be safe. Intake of VAVLP copolymers (5 to 40% VL) and made with isopropanol as a transfer agent provides a maximum potential intake of isopropanol by children ages 2 to 5 years of 0.002 mg/kg bw/day, which is well below the ADI of 2.4 mg/kg bw/day. Therefore, the use of isopropanol as a transfer agent in the production of the substance does not present a safety concern. The intended use of the VAVLP copolymers (5 to 40% VL) produced with isopropanol as a transfer agent therefore can be concluded to be safe.

In summary, VAVLP copolymers (5 to 40% VL), produced using either acetaldehyde or isopropanol as the transfer agent, can be concluded to be safe. Therefore, it can be concluded that the proposed use of VAVLP copolymers (5 to 40% VL) in chewing gum base is safe within the meaning of the Federal Food, Drug, and Cosmetic Act, i.e., meets the standard of reasonable certainty of no harm.

Conclusion of the GRAS Panel

We, the undersigned qualified GRAS panel members, have, both individually and collectively, critically evaluated published and unpublished data and information pertinent to the safety of the intended use of VAVLP copolymers (5 to 40 % VL) described above. We unanimously conclude that the intended use of VAVLP copolymers (5 to 40% VL), manufactured in accordance with current good manufacturing practice (cGMP), and meeting appropriate food grade specifications, is safe.

We further unanimously conclude that the intended use of VAVLP copolymers (5 to 40% VL), simply or combined, at levels up to 26% by weight of chewing gum base, corresponding to 9% by weight of the chewing gum as consumed, manufactured in accordance with cGMP, and meeting appropriate food grade specifications is Generally Recognized as Safe (GRAS) based on scientific procedures.

It is our opinion that other qualified experts would concur with our conclusions.

By:



Stanley M. Tarka, Jr., Ph.D.
Fellow, ATS
President
The Tarka Group, Inc. and
The Pennsylvania State University College of Medicine

20 November 2018

Date

John A. Thomas, Ph.D.
Fellow, ATS
Adjunct Professor
Department of Pharmacology and Toxicology
Indiana University School of Medicine

Date

Richard Kraska, Ph.D.
Executive Vice President
GRAS Associates, LLC

Date

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Indiana University School of Medicine

23 Nov. 2018

Date

Richard Kraska, Ph.D.
Executive Vice President
GRAS Associates, LLC

Date

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We further unanimously conclude that the intended use of VAVLP copolymers (5 to 40% VL), simply or combined, at levels up to 26% by weight of chewing gum base, corresponding to 9% by weight of the chewing gum as consumed, manufactured in accordance with cGMP, and meeting appropriate food grade specifications is Generally Recognized as Safe (GRAS) based on scientific procedures.

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Date



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11/26/2018

Date

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U.S. Food and Drug Administration

February 11, 2020

GRN 885 VAVLP Copolymers - Validation of the analytical methods

Herewith we confirm that the analytical methods used for measuring the parameters for the specification of VAVLP Copolymers discussed in GRN 885 are all validated.

Wacker Chemie AG



Dr. Cornelia Ciosto
Senior Manager Quality Assurance & Regulatory Affairs
QUALITY MANAGEMENT

Sitz: München
Amtsgericht: München HRB 159705
Vorstand:
Rudolf Staudigl (Vorsitzender)
Christian Hartel
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Auguste Willems
Vorsitzender des Aufsichtsrats:
Peter-Alexander Wacker

From: [Riette van Laack](#)
To: [Downey, Jason](#)
Subject: RE: GRN 885 - Responses to Follow-up Questions
Date: Wednesday, February 12, 2020 12:10:10 PM
Attachments: [image001.png](#)
[GRN 885 Validation of analytical methods_20200211_\(00627239\).pdf](#)
[tables 02 12 2020_\(00627238\).pdf](#)

Dear Jason:

On behalf of Wacker, I hereby provide the responses to the requests in your e-mail from Monday February 3, 2020.

For purposes of clarity, I repeat the requests. To avoid any problems with the tables, I have attached a document which includes copies of the tables incorporated in this message. Please, let me know if you would like the responses in a different format.

1. In Part 3 (Dietary Exposure), Wacker provided an estimated daily intake (EDI) of chewing gum and vinyl acetate-vinyl laurate copolymer (VAVLP) from its use in chewing gum base. However, Wacker did not address the exposure to potential impurities from the proposed use of VAVLP. Wacker should discuss the exposure for any expected impurities (e.g., residual monomers, radical initiators, chain transfer agents, reagents) in the VAVLP under the intended conditions of use.

RESPONSE:

As indicated in GRN 885, Table 2 (Specifications), the limits for the impurities vinyl acetate monomer (raw material monomer), vinyl laurate monomer (raw material monomer), acetic acid (thermal decomposition product of the polymer) and isopropanol (chain transfer agent) are 5 ppm, 1000 ppm, 500 ppm and 50 ppm respectively. The maximum limit for the radical initiator impurities, based on calculation, is 0.1 ppm. A summary of the impurities, source, and limits in VAVLP is presented in Table A. The potential exposure to these impurities was calculated based on the 2-day average estimated daily intake of VAVLP from use in chewing gum base (GRN 885, Table 5), and is summarized in Table B.

Table A. Impurities and Limits in VAVLP

Impurity	Source	Limit in VAVLP	Comment
Vinyl acetate monomer	raw material - monomer	Max. 5 ppm	GRN 885, Table 5, specification limits established based on batch analyses
Vinyl laurate monomer	raw material - monomer	Max. 1000 ppm	
Acetic acid	Thermal decomposition product of the polymer	Max. 500 ppm	
Isopropanol	Chain transfer agent	Max. 50 ppm	
Tert-Butylperoxy-2-ethylhexanoate 2,2-di-(tert-butylperoxy)-butane	Radical initiators	Max 0.1 ppm	Limits established based on calculation: Usage max. 250 ppm, at 116°C in 1 h 50% is decomposed. Distillation and stripping: > 12 h at 145 °C

			=> reduction by 1/2 Max. Concentration in VAVLP: = 250 ppm/4096 = 0.06 ppm Limits set by rounding up to 0.1ppm
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Table B. Estimated Daily Intake of Impurities in VAVLP

Age, years	per user intake of VAVLP		per user intake of acetic acid		per user intake of VAM		per user intake of VLM		per user intake of isopropanol		per user intake of radical initiators	
	Mean	90th	Mean	90th	Mean	90th	Mean	90th	Mean	90th	Mean	90th
	mg/kg-bw/day		-- mg/kg-bw/day --		-- mg/kg-bw/day --		-- mg/kg-bw/day --		-- mg/kg-bw/day --		-- mg/kg-bw/day --	
2 to 5	23	42.7	0.0115	0.0214	0.000115	0.000214	0.023	0.0427	0.00115	0.00214	0.0000023	0.0000043
6 to 12	13.3	23.6	0.0067	0.0118	0.000067	0.000118	0.0133	0.0236	0.00067	0.00118	0.0000013	0.0000024
13-19	6.6	12.5	0.0033	0.0063	0.000033	0.000063	0.0066	0.0125	0.00033	0.00063	0.0000007	0.0000013
= 20	6.3	11.7	0.0032	0.0059	0.000032	0.000059	0.0063	0.0117	0.00032	0.00059	0.0000006	0.0000012
= 2	8.2	15.6	0.0041	0.0078	0.000041	0.000078	0.0082	0.0156	0.00041	0.00078	0.0000008	0.0000016

- On p. 19, Wacker discusses the updated EDIs for chewing gum and VAVLP as compared to the EDIs in GRN 606. However, Wacker did not address if the proposed use of VALVP in GRN 885 could be considered substitutional for the use in GRN 606. If the notified use (under the CAPIVA® brand) is in addition to the current VINNAPAS® brand (Wacker GRN 606), there could be an increase in exposure to VAVLP. If the notified use is not substitutional for the current use, Wacker should address whether there would be an increase in the dietary exposure to VAVLP and provide a cumulative exposure to VAVLP.

RESPONSE:

The proposed use of VAVLP in GRN 885 is substitutional for the use in GRN 606; therefore, there is no increase in exposure to VAVLP.

- Wacker discusses specifications for the VAVLP copolymer, including the percentage of vinyl laurate (VL), residual monomers, isopropanol, acetic acid, and other physical properties (viscosity and saponification number). However, Wacker did not address potential by-products in the VAVLP copolymer. Wacker should provide a narrative to address any breakdown products of the processing aids, including any of the radical initiators that may be carried over into the VAVLP and are present at detectable levels.

RESPONSE:

VAVLP copolymers (5 to 40% VL) are produced by a chain-growth polymerization process from vinyl acetate (VA) and vinyl laurate (VL) of high purity (>99.8 and 98%, respectively) mixed in appropriate proportions. Tert-butylperoxy-2-ethylhexanoate (CAS 3009-82-4) and 2,2-Di(tert-butylperoxy)butane (CAS 2167-23-9) are used as radical initiators. Isopropanol serves as a chain transfer agent during the polymerization process. After polymerization, the remaining chain transfer agent, unreacted monomers, and decomposition products of the radical initiators are removed by evaporation at elevated temperature and vacuum and by steam stripping the polymer with water.

Under the temperature conditions of this (exothermic) polymerization reaction, the radical initiator,

tert-butylperoxy-2-ethylhexanoate, decomposes completely. Its decomposition products are expected to be removed in the distillation and purification steps of synthesized VAVLP copolymer.

Under the conditions of VAVLP copolymer production, 2,2-Di(tert-butylperoxy)butane, the primary radical initiator, predominantly initiates the desired polymerization reactions. Traces of potential volatile by-products (methane, carbon dioxide, ethane, acetone, tert-butanol, methyl ethyl ketone and small amounts of propionic acid methyl ester, acetic acid methyl ester and tert-butyl methyl ether) would be removed in the evaporation steps and steam stripping at the end of the production process.

As previously documented in GRN 606, the decomposition products and the decomposition kinetics of the radical initiators, which are used in only small amounts ($\Sigma \leq 250$ ppm) in the VAVLP copolymerization, are known from experiments in model systems in which there are no other substances present. The use of these radical initiators in a polymerization process will, in contrast, result mainly in the radical-mediated propagation of the chain elongation of the polymer. Thus, interactions between breakdown products of the radical initiators are statistically less likely than in the reported model systems. Yet, even if products are formed during the production of VAVLP, such breakdown products are expected to be removed efficiently during the downstream processing of VAVLP.

4. Wacker should provide a statement indicating that all analytical methods are validated for their particular purpose.

RESPONSE:

Attached to this e-mail, is the requested statement by Wacker.

Please let me know if you have any questions or comments regarding our responses.

Regards,

Riëtte

Riëtte van Laack
Director
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202-737-9329 (fax)
www.hpm.com
Visit the HPM blog at: www.fdalawblog.net

From: Downey, Jason <Jason.Downey@fda.hhs.gov>

Sent: Monday, February 3, 2020 8:32 AM
To: Riette van Laack <RvanLaack@hpm.com>
Subject: GRN 885 - Follow-up Questions

Dear Dr. van Laack,

During our review of GRAS Notice number 885 (intended use of VAVLP in chewing gum base), which you submitted on behalf of Wacker Chemie AG (Wacker), we noted the following requests that are needed to complete our review of the notice:

1. In Part 3 (Dietary Exposure), Wacker provided an estimated daily intake (EDI) of chewing gum and vinyl acetate-vinyl laurate copolymer (VAVLP) from its use in chewing gum base. However, Wacker did not address the exposure to potential impurities from the proposed use of VAVLP. Wacker should discuss the exposure for any expected impurities (e.g., residual monomers, radical initiators, chain transfer agents, reagents) in the VAVLP under the intended conditions of use.
2. On p. 19, Wacker discusses the updated EDIs for chewing gum and VAVLP as compared to the EDIs in GRN 606. However, Wacker did not address if the proposed use of VALVP in GRN 885 could be considered substitutional for the use in GRN 606. If the notified use (under the CAPIVA® brand) is in addition to the current VINNAPAS® brand (Wacker GRN 606), there could be an increase in exposure to VALVP. If the notified use is not substitutional for the current use, Wacker should address whether there would be an increase in the dietary exposure to VAVLP and provide a cumulative exposure to VAVLP.
3. Wacker discusses specifications for the VAVLP copolymer, including the percentage of vinyl laurate (VL), residual monomers, isopropanol, acetic acid, and other physical properties (viscosity and saponification number). However, Wacker did not address potential by-products in the VAVLP copolymer. Wacker should provide a narrative to address any breakdown products of the processing aids, including any of the radical initiators that may be carried over into the VAVLP and are present at detectable levels.
4. Wacker should provide a statement indicating that all analytical methods are validated for their particular purpose.

I am expecting a second set of clarifying questions soon, which I will send to you as soon as possible.

Please provide responses to the above requests within **10 business days**. If you are unable to complete the response within that time frame, please contact me to discuss further options. If you have questions or need further clarification, please feel free to contact me. Thank you in advance for your attention to our comments.

Regards,

Jason

Jason Downey, PhD

Staff Fellow (Biologist)

Division of Food Ingredients

Center for Food Safety and Applied Nutrition

Office of Food Additive Safety

U.S. Food and Drug Administration

jason.downey@fda.hhs.gov



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Downey, Jason

From: Riette van Laack <RvanLaack@hpm.com>
Sent: Wednesday, February 12, 2020 12:10 PM
To: Downey, Jason
Subject: RE: GRN 885 - Responses to Follow-up Questions
Attachments: GRN 885 Validation of analytical methods_20200211 (00627239).pdf; tables 02 12 2020 (00627238).pdf

Dear Jason:

On behalf of Wacker, I hereby provide the responses to the requests in your e-mail from Monday February 3, 2020.

For purposes of clarity, I repeat the requests. To avoid any problems with the tables, I have attached a document which includes copies of the tables incorporated in this message. Please, let me know if you would like the responses in a different format.

1. In Part 3 (Dietary Exposure), Wacker provided an estimated daily intake (EDI) of chewing gum and vinyl acetate-vinyl laurate copolymer (VAVLP) from its use in chewing gum base. However, Wacker did not address the exposure to potential impurities from the proposed use of VAVLP. Wacker should discuss the exposure for any expected impurities (e.g., residual monomers, radical initiators, chain transfer agents, reagents) in the VAVLP under the intended conditions of use.

RESPONSE:

As indicated in GRN 885, Table 2 (Specifications), the limits for the impurities vinyl acetate monomer (raw material monomer), vinyl laurate monomer (raw material monomer), acetic acid (thermal decomposition product of the polymer) and isopropanol (chain transfer agent) are 5 ppm, 1000 ppm, 500 ppm and 50 ppm respectively. The maximum limit for the radical initiator impurities, based on calculation, is 0.1 ppm. A summary of the impurities, source, and limits in VAVLP is presented in Table A. The potential exposure to these impurities was calculated based on the 2-day average estimated daily intake of VAVLP from use in chewing gum base (GRN 885, Table 5), and is summarized in Table B.

Table A. Impurities and Limits in VAVLP

Impurity	Source	Limit in VAVLP	Comment
Vinyl acetate monomer	raw material - monomer	Max. 5 ppm	GRN 885, Table 5, specification limits established based on batch analyses
Vinyl laurate monomer	raw material - monomer	Max. 1000 ppm	
Acetic acid	Thermal decomposition product of the polymer	Max. 500 ppm	
Isopropanol	Chain transfer agent	Max. 50 ppm	
Tert-Butylperoxy-2-ethylhexanoate	Radical initiators	Max 0.1 ppm	Limits established based on calculation:

2,2,di-(tert-butylperoxy)-butane			Usage max. 250 ppm, at 116°C in 1 h 50% is decomposed. Distillation and stripping: > 12 h at 145 °C => reduction by 1/2 ¹² Max. Concentration in VAVLP: = 250 ppm/4096 = 0.06 ppm Limits set by rounding up to 0.1ppm
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Table B. Estimated Daily Intake of Impurities in VAVLP

Age, years	per user intake of VAVLP		per user intake of acetic acid		per user intake of VAM		per user intake of VLM		per user intake of isopropanol		per user intake of radical initiators	
	Mean	90th	Mean	90th	Mean	90th	Mean	90th	Mean	90th	Mean	90th
	mg/kg-bw/day		-- mg/kg-bw/day --		-- mg/kg-bw/day --		-- mg/kg-bw/day --		-- mg/kg-bw/day --		-- mg/kg-bw/day --	
2 to 5	23	42.7	0.0115	0.0214	0.000115	0.000214	0.023	0.0427	0.00115	0.00214	0.0000023	0.0000043
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RESPONSE:

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Under the temperature conditions of this (exothermic) polymerization reaction, the radical initiator, tert-butylperoxy-2-ethylhexanoate, decomposes completely. Its decomposition products are expected to be removed in the distillation and purification steps of synthesized VAVLP copolymer.

Under the conditions of VAVLP copolymer production, 2,2-Di(tert-butylperoxy)butane, the primary radical initiator, predominantly initiates the desired polymerization reactions. Traces of potential volatile by-products (methane, carbon dioxide, ethane, acetone, tert-butanol, methyl ethyl ketone and small amounts of propionic acid methyl ester, acetic acid methyl ester and tert-butyl methyl ether) would be removed in the evaporation steps and steam stripping at the end of the production process.

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RESPONSE:

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Please let me know if you have any questions or comments regarding our responses.

Regards,

Riëtte

Riëtte van Laack
Director
Hyman, Phelps, & McNamara, P.C.
700 Thirteenth Street N.W.
Suite 1200
Washington, DC 20005
202-737-9637
202-737-9329 (fax)
www.hpm.com
Visit the HPM blog at: www.fdalawblog.net

From: Downey, Jason <Jason.Downey@fda.hhs.gov>
Sent: Monday, February 3, 2020 8:32 AM
To: Riette van Laack <RvanLaack@hpm.com>
Subject: GRN 885 - Follow-up Questions

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Regards,

Jason

Jason Downey, PhD

Staff Fellow (Biologist)

Division of Food Ingredients

Center for Food Safety and Applied Nutrition

Office of Food Additive Safety

U.S. Food and Drug Administration

jason.downey@fda.hhs.gov



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U.S. Food and Drug Administration

February 11, 2020

GRN 885 VAVLP Copolymers - Validation of the analytical methods

Herewith we confirm that the analytical methods used for measuring the parameters for the specification of VAVLP Copolymers discussed in GRN 885 are all validated.

Wacker Chemie AG



Dr. Cornelia Ciosto
Senior Manager Quality Assurance & Regulatory Affairs
QUALITY MANAGEMENT

Sitz: München
Amtsgericht: München HRB 159705
Vorstand:
Rudolf Staudigl (Vorsitzender)
Christian Hartel
Tobias Ohler
Auguste Willems
Vorsitzender des Aufsichtsrats:
Peter-Alexander Wacker

Attachment to E-mail Re GRN 885
Feb. 12, 2020

Tables Referenced in Response to Request No. 1

Table A. Impurities and Limits in VAVLP

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