ORIGINAL SUBMISSION

GRN 000606

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October 29, 2015

BY MESSENGER

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

Subject: **GRAS Notification for the Intended Use of Vinyl acetate-Vinyl laurate Copolymers (VINNAPAS® B 500/20 VL and VINNAPAS® B 500/40 VL) in Chewing Gum Base**

Dear Dr. Gaynor:

Pursuant to the proposed rule outlined at 62 Fed. Reg. 18939 (April 17, 1997), we hereby submit, on behalf of Wacker Chemie AG ("Wacker"), this notification that the intended use of the vinyl acetate-vinyl laurate copolymers ("PVAcVL copolymers"), marketed under the tradenames VINNAPAS® B 500/20 VL and VINNAPAS® B 500/40 VL, as components 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.

To facilitate your review, this notification is submitted in the format suggested under proposed 21 C.F.R. § 170.36 (c) (see 62 Fed. Reg. at 18961). Three copies of the "GRAS Exemption Claim" and the "Additional Information" documents are enclosed. Also included is an electronic copy of the documents.

If you have any questions concerning this submission, please do not hesitate to contact me.

Sincerely,

(b) (6)

Diane B. McColl

Enclosures

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GRAS EXEMPTION CLAIM

We hereby claim that the intended use of the vinyl acetate-vinyl laurate copolymers ("PVAcVL copolymers") as components of chewing gum base is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (FDC Act) because we have determined that such use of the PVAcVL copolymers is generally recognized as safe (GRAS).

(1) Name and address of the notifier:

Thomas Wimmer, PhD
Senior Technical Manager, Service Gum
Wacker Chemie AG
Hanns-Seidel-Platz 4, 81737 München, Germany

(2) Common or usual name of the substance that is the subject of the GRAS exemption claim:

Vinyl acetate-vinyl laurate copolymer
CAS name: Dodecanoic acid, ethenyl ester, polymer with ethenyl acetate
CAS number: 26354-30-3
Trade names:

"VINNAPAS® B 500/20 VL" Copolymer (consists of ~80% vinyl acetate and ~20% vinyl laurate (wt/wt))
"VINNAPAS® B 500/40 VL" Copolymer (consists of ~60% vinyl acetate and ~40% vinyl laurate (wt/wt))

(3) Applicable conditions of use of the notified substances:

(a) Foods in which PVAcVL copolymers are to be used:

The PVAcVL copolymers are intended to be used as components of chewing gum base.

(b) Maximum levels of use of PVAcVL copolymers in chewing gum:

PVAcVL copolymer(s) may be included in chewing gum base at levels ranging from about 5% to 26%. The gum base accounts for about 20% to 35% of the weight of a formulated chewing gum. Thus, in practice, the PVAcVL

copolymer(s) may account for no more than about 9% (wt./wt.) of the finished chewing gums as consumed.

(c) Purpose for which PVAcVL copolymers are to be used:

PVAcVL copolymers will be used in chewing gum base to reduce or eliminate the use for additional softeners.

(d) Description of the population expected to consume PVAcVL:

Individuals who consume chewing gum.

(4) Basis for the GRAS determination:

The basis of the GRAS determination is through scientific procedures.

(5) Review and Copying Statement:

The data and information that are the basis for Wacker's GRAS determination are available for review and copying by Food and Drug Administration (FDA) personnel at reasonable times at the following location:

Hyman, Phelps & McNamara, P.C.
700 Thirteenth St. NW, Suite 1200
Washington, DC 20005

or will be sent to FDA upon request.

(b) (6)

Thomas Wimmer, PhD
Senior Technical Manager, Service Gum
Wacker Chemie AG
Hanns-Seidel-Platz 4, 81737 München, Germany

ADDITIONAL INFORMATION

(1) Identity of the notified substance

(a) Chemical name

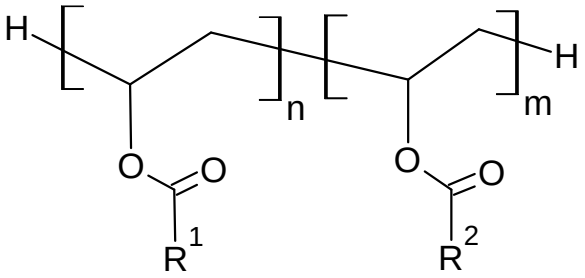
Dodecanoic acid, ethenyl ester, polymer with ethenyl acetate

("Vinyl acetate-vinyl laurate copolymer")

(b) Chemical Abstracts Service (CAS) Registry Number

26354-30-3

(c) Chemical structure and properties



R1 = methyl; R2 = undecyl,

n = 10; m = 0.95 – 2.53

VINNAPAS® B 500/20 VL Copolymer: Vinyl acetate ~80% (wt/wt)
Vinyl laurate ~20% (wt/wt)
n:m ~10:0.95 (molar ratio)
Molecular weight (M_w) ~240,000

VINNAPAS® B 500/40 VL Copolymer: Vinyl acetate ~60% (wt/wt)
Vinyl laurate ~40% (wt/wt)
n:m ~10:2.53 (molar ratio)
Molecular weight (M_w) ~450,000

(e) Method of manufacture of PVAcVL copolymers

The PVAcVL copolymers that are the subject of this GRAS Notification are produced by a chain-growth polymerization process from vinyl acetate (VAc) and vinyl laurate (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.

(f) Characteristic properties

At ambient temperature the PVAcVL copolymers are white to pale-yellowish, odorless and tasteless solids and are insoluble in water but soluble in certain organic solvents (acetone, chloroform).

The PVAcVL copolymers are shelf stable. The manufacturer guarantees a shelf life of two years under proper storage and handling conditions.

(g) Any content of potential human toxicants

None.

(h) Specifications for food-grade material

A specially convened Panel of independent experts qualified by training and experience to evaluate the safety of food ingredients reviewed the analytical results of several non-consecutive representative batches of PVAcVL and concluded that the products complied with appropriate specifications for food-grade PVAcVL. The specifications are provided in Table 1 below.

Table 1: Specifications of PVAcVL copolymers

	Specification
VINNAPAS® B 500/40 VL	
Viscosity	8-12 mPas
Free acetic acid	≤0.05 %
Saponification number	475-495 mgKOH/g
Residual vinyl acetate monomer	≤5 mg/kg
VINNAPAS® B 500/20 VL	
Viscosity	8-12 mPas
Free acetic acid	≤0.05 %
Saponification number	555-575 mgKOH/g
Residual vinyl acetate monomer	≤5 mg/kg

The specifications do not include limits for microbial purity because the water content of the PVAcVL copolymers is low and the conditions of the manufacturing process preclude microbial proliferation. In addition, no limitations for heavy metals are included but routine analyses of heavy metals invariably show that heavy metals are below the limit of detection of 1 mg/kg for all elements.

(2) Information on any self-limiting levels of use

The highest technically feasible concentration of PVAcVL copolymers in chewing gum is 17% in the final product, i.e., 35% in the gum base. However, because of the excessive hardness of the gum that results from such concentrations of the copolymer, realistically PVAcVL copolymers will account for not more than about 9% of the chewing gum in practice.

(3) Probable Consumption of the Substance

For calculating the exposure to the VINNAPAS® PVAcVL copolymers from their use in chewing gum, Wacker started with the value of 1.72 g/day as the average daily intake of chewing gum in the U.S. per an unpublished report by Leatherhead Food International cited and relied on in GRAS Notice No. 374 (FDA, 2011). The estimated daily intake of chewing gum by the 90th percentile

consumer was calculated by multiplying the average chewing gum intake of 1.72 g/day by a factor of three (3) (JECFA, 1989), to yield an estimated daily intake of 5.16 g chewing gum per day at the 90th percentile. At the highest possible but unrealistic use level of 17% PVAcVL copolymer in the chewing gum (i.e. 35% in the gum base), this corresponds to 0.877 g PVAcVL/person/day.

Although chewing gum is typically not swallowed, the copolymers themselves are not absorbed or degraded by the enzymes in the gastrointestinal tract. To the extent that any impurities are present in the copolymers, the impurities may leach from the gum based and be ingested.[1] Because the pure PVAcVL copolymer accounts for at least 99.9% of the VINNAPAS® copolymer products, as per the specifications, the maximum systemic exposure to any impurities, i.e. 0.1%, would be less than 14.2 µg/kg bw/day for the heavy user consumer (average bw = 60 kg).

Based on data from a Market Facts Mail Panel Survey in which 1044 households reported their one-day intake of regular and sugarfree chewing gum by mail, the average consumption of chewing gum varies between 2.1 pieces for preschoolers and 3.8 pieces for teenagers (Environ International Corp. unpublished results) (FDA, 2001). Applying maximum figures for the weight per piece of gum (3 g), the maximum but unrealistic use level of PVAcVL in the gum base as consumed (17%) and the maximum level of total impurities in PVAcVL (0.1%), the highest possible estimated daily intake of any such impurities on a per kg bodyweight basis would occur in children aged 2 to 5 years (~48 µg/kg bw/day based on an average 1.6 pieces of chewing gum in this age group and an average body weight of 17 kg).

(4) Detailed summary of the basis for the notifier's determination that a particular use of the notified substance is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because such use is GRAS

Due to their high molecular weights and their chemical structures, the PVAcVL copolymers are resistant to the action of digestive enzymes, and any unintentionally ingested copolymer from swallowed chewing gum would pass

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[1] Unpublished evidence from a hydrolytic stability test with digestive fluid simulants supports that the copolymers are not absorbed or degraded by the digestive enzymes in the alimentary tract (Hergeth, 2007).

through the gastrointestinal tract unchanged.[2] The safety assessment of the two PVAcVL copolymers therefore focused on the presence of potential impurities, including unreacted monomers, the transfer agent (acetaldehyde), and the residues or breakdown products of the two radical initiators.

The safety of VAc has been examined by a number of authoritative bodies, including FDA, Health Canada and JECFA over the years, each of which concluded that the dietary exposure to VAc at levels that result in the formation of acetaldehyde at physiological or usual background levels has no adverse consequences in terms of genotoxic events, neither directly nor indirectly via acetaldehyde (FDA, 2008; Environment Canada/Health Canada, 2008a & 2008b; JECFA, 2011; Albertini, 2013). This view is supported also by more recent studies (van Acker et al., 2015).

The safety of VL has been examined in studies on genotoxicity, reproduction and developmental toxicity as well as in a standard 13-week oral toxicity study (van Acker et al., 2015). The results of the *in-vitro* genotoxicity tests should be interpreted in a similar way to the results of corresponding tests with VAc as they are homologues. Results from the *in-vivo* studies demonstrated no adverse effects were observed at doses of up to 1000 mg/kg bw/day, the highest dose tested (Lina et al., 2015).

The degradation products of the radical initiators, which are used in only small amounts in the copolymerization process, are well known, fully characterized, and expected to be removed efficiently during the down-stream processing of the copolymers. Moreover, their chemical structures lack characteristics that raise toxicological concerns.

Taken together, the available safety data of the monomers, VAc and VL, the non-digestibility of the PVAcVL copolymers, and the existing knowledge and safety data available on the by-products that would result from the processing aids (radical initiators, acetaldehyde) coupled with the efficacy of the final purification steps in the production process demonstrate that the PVAcVL copolymers are safe under their intended conditions of use based on scientific procedures.

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[2] The safety of finely powdered Vinnapas® B 500/40 VL was confirmed in a 4-week and a 13-week oral toxicity study in rats (Messinger and Bär, 2014).

(5) Basis for concluding, in light of the data and information described above, that there is consensus among experts qualified by scientific training and experience to evaluate the safety of substances added to food that there is reasonable certainty that the substance is not harmful under the intended conditions of use.

A specially-convened panel of independent experts (Expert Panel), qualified by scientific training and experience to evaluate the safety of food ingredients, independently and collectively critically evaluated the published and unpublished scientific information and data deemed appropriate or pertinent to the safety of PVAcVL copolymers under the conditions of intended use in chewing gum base. The Expert Panel also evaluated data and information concerning the method of manufacture, the chemical and physical properties of the product, the product specifications and analytical data, and the specific conditions of intended use of PVAcVL in chewing gum base.

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. A copy of the Expert Panel's GRAS opinion is provided in Appendix 1 (attached).

References

Albertini RJ. (2013). Vinyl acetate monomer (VAM) genotoxicity profile: relevance for carcinogenicity. Crit. Rev. Toxicol., 43(8):671-706.

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Messinger H., Bär A. (2014). Oral 4-week and 13-week toxicity studies of polyvinyl acetate vinyl laurate copolymer in rats. Regul. Toxicol. Pharmacol., 70: 1-6.

Van Acker, F., Messinger H., Bär A. (2015). Evaluation of vinyl laurate in a battery of in vitro and in vivo tests for genotoxicity. Regul. Toxicol. Pharmacol., 72(1): 77-84.

APPENDIX 1

Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Status of Two Vinyl Acetate/Vinyl Laurate Copolymers (Vinnapas® B 500/20 VL and Vinnapas® B 500/40 VL) as Components of Gum Base for Use in Chewing Gum

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Prepared for:

Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street NW, Suite 1200
Washington, D.C. 20005

August 21, 2015

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 “Expert Panel”), was specially convened by Hyman, Phelps & McNamara, P.C. on behalf of Wacker Chemie AG, Munich, Germany ("Wacker"), and asked to conduct a critical and comprehensive evaluation of the available and pertinent data and information on two vinyl acetate/vinyl laurate copolymers ("PVAcVL copolymers"), and to determine whether, under the intended conditions of use as components of chewing gum base is Generally Recognized as Safe ("GRAS") based on scientific procedures. The Expert Panel consisted of the below-signed qualified scientific experts: Robert J. Nicolosi, Ph.D. (University of Massachusetts-Lowell), John A. Thomas, Ph.D. (Indiana School of Medicine), and Stanley M. Tarka Jr., Ph.D. (The Tarka Group Inc., and The Pennsylvania State University). For purposes of the Expert Panel’s evaluation, “safe” or “safety” that there is a reasonable certainty of no harm under the intended conditions of use of the ingredient in foods, as stated in 21 CFR § 170.3(i) (U.S. FDA, 2014). Curricula vitae evidencing their expert qualifications for evaluating the safety of food ingredients are available upon request.

The Expert Panel, independently and collectively, critically evaluated a supporting dossier [Documentation in Support of the Safety and Generally Recognized as Safe (GRAS) Status of VINNAPAS® B 500/20 VL and VINNAPAS® B 500/40 VL for Use as Components of Chewing Gum Base] of publicly available scientific materials compiled from the literature and other public sources by Albert Bär, Ph.D. and Horst Messinger, Ph.D. of Bioresco Ltd. The dossier includes information derived from a comprehensive search of the scientific literature conducted through August 01, 2015 and also contains a comprehensive package of data and information pertaining to the method of manufacture, product specifications and analytical data, stability, and dietary consumption estimates for the conditions of intended use of the two PVAcVL copolymers that are produced by Wacker in Burghausen, Germany, from vinyl acetate (VAc) and vinyl laurate (VL) by chain-growth polymerization, and dietary consumption estimates for the intended use. These PVAcVL copolymers have been sold for many years to producers of chewing gum bases and chewing gums in the European Union under the tradenames Vinnapas® B 500/20 VL and Vinnapas® B 500/40 VL. The panel also considered any additional data and information that we deemed pertinent to the safety of the two PVAcVL copolymers under the conditions of intended use.

Following an independent, critical and collaborative evaluation of the data and information, the Expert Panel convened via

telephone conference on August 21, 2015 and unanimously concluded that the intended use described herein of Vinnapas® B 500/20 VL and Vinnapas® B 500/40 VL as components of chewing gum base at levels of up to 26%, meeting appropriate food-grade specifications and manufactured consistent with current Good Manufacturing Practices (cGMP), is GRAS based on scientific procedures. A summary of the basis for the Expert Panel's conclusion is provided in the following section.

Summary and Basis for GRAS Determination

- The two PVAcVL copolymers which are the subject of this safety evaluation are produced by a chain-growth polymerization process from VAc 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, 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.

- The final copolymer products comply with appropriate food grade specifications that are publicly available. The specifications include purity criteria (content of free acetic acid, residual VAc and VL monomers) as well as physicochemical characteristics (viscosity, saponification number) designed to result in constant quality and purity. At ambient temperature these two PVAcVL copolymers are white to pale-yellowish, odorless and tasteless solids and are insoluble in water but soluble in certain organic solvents (acetone, chloroform).

- The Expert Panel reviewed batch analyses data from 5 non-consecutive batches of VINNAPAS® B 500/20 VL and VINNAPAS® B 500/40 VL, demonstrating that the ingredient is manufactured in a reproducible manner and a consistent product is produced that conforms to the established physical and chemical specifications established by Wacker. Additionally, the Expert Panel reviewed data demonstrating that no undesirable substances were present in the monomer at levels of toxicological concern in regards to acetaldehyde, acetone, propionaldehyde, methyl acetate, residual vinyl acetate, ethyl acetate, vinyl propionate, free acetic acid, vinyl decanoate, residual vinyl laurate, lauric acid, unsaturated C14-acid vinyl ester and vinyl myristate. Quantitative analyses using gas chromatography confirms this.

- The shelf life of VINNAPAS® B 500/20 VL and VINNAPAS® B 500/40 VL has been investigated between November 2006 and December 2014. In total, eight batches were examined. All relevant parameters, such as viscosity (K-value), saponification number, residual monomers and free acetic acid remained unchanged, demonstrating the chemical stability of these two

PVAcVL copolymers under storage conditions. The manufacturer guarantees a shelf life of two years.

- Vinnapas® B 500/20 VL and Vinnapas® B 500/40 VL are intended to be used as ingredients of chewing gum base at concentrations singly or combined of 5 – 26%. Their use reduces or even eliminates the need for softeners and renders the chewing gum less sticky or non-sticky. The highest feasible level of use due to hardness of the copolymer is 26% (singly or combined) in the gum base. Therefore the concentration in the formulated chewing gum as consumed will not exceed 17%. Typically, however, the PVAcVL copolymers will account for no more than 9% (wt/wt) of the chewing gum as consumed.

- Being insoluble in water and having weight average molecular weights of about 240 kDa and 450 kDa for Vinnapas® B 500/20 VL and Vinnapas® B 500/40 VL, respectively, it is expected that neither copolymer is absorbed or degraded by the digestive enzymes in the alimentary tract. Unpublished evidence from a hydrolytic stability test with digestive fluid simulants supports this (Hergeth, 2007).

- Nonetheless, the safety of finely powdered Vinnapas® B 500/40 VL was examined in a 4-week and a 13-week oral toxicity study in Sprague-Dawley rats. The highest dose level tested was 5% in admixture to a standard rat chow diet which corresponds to an intake of 3.8 and 4.4 g/kg bw/d in the male and female rats of the 13-week study, respectively. There were no treatment-related effects on mortality, bodyweight gains, feed efficiency, ophthalmoscopic findings, hematological and clinical chemical parameters, neurobehavorial observations as well as gross and histopathological changes of standard organs and tissues in either study. The highest dose tested in the 13-week study (3783 and 4396 mg/kg bw/d for male and female rats, respectively) proved to be a NOAEL (Messinger and Bär, 2014a).

- The main impurity in the PVAcVL copolymers is unreacted VL with a maximum level of 1000 ppm as per Wacker's specifications. Residual VAc, however, is present at not more than 5 ppm as per specifications. A full range of safety studies was therefore performed with VL, i.e. Ames tests (OECD Guideline 471), a mouse lymphoma HPRT gene mutation assay (OECD Guideline 476 (1997)), an *in vitro* CHO chromosome aberration assay (OECD Guideline 473), an *in-vivo* mammalian micronucleus test (OECD Guideline 474 (1997)), a 90-day repeated oral toxicity study in rats (OECD Guideline

408), a combined repeated dose and reproduction/development toxicity screening study (OECD 421) and a prenatal developmental toxicity study (OECD 414). The experimental details and results of these studies have been published (Messinger & Bär, 2014b, Lina et al., 2015, van Acker et al., 2015).

- VL exhibited no mutagenic activity in the Ames tests. It also was not mutagenic in mouse lymphoma cells (HPRT mutation assay) with and without metabolic activation. The *in vitro* chromosome aberration test was negative in the absence of metabolic activation with S9-mix but produced inconsistent results in the presence of S9-mix. In the in-vivo mammalian micronucleus test with a high-dose VL level of 2000 mg/kg bw, there was no treatment-related increase in the mean frequency of micronucleated polychromatic erythrocytes of the bone marrow (van Acker et al., 2015).

- Thus VL exhibits overall a similar safety profile as VAc in these mutagenicity tests. This is due to the fact that VL, much like VAc, is hydrolyzed by ubiquitous carboxylesterases in living systems and thereby becomes a source of acetaldehyde, though to a lesser extent than VAc (Chahinian et al., 2002, 2010). However, with regard to safety, it is generally accepted that the exposure to VAc (and thus VL) at doses which result in the formation of acetaldehyde at physiological or usual background levels has no adverse consequences in terms of genotoxic events, neither directly nor indirectly via acetaldehyde (FDA, 2008b; Environment Canada/Health Canada, 2008a; JECFA, 2011; Albertini, 2013).

- The safety of VL was examined in a 13-week oral toxicity test in Wistar rats (OECD Guideline 408). VL was administered daily by gavage (in corn oil) to four groups of rats (10 animals/sex/group) at doses of 0, 50, 250 and 1000 mg/kg bw/d. There were no statistically significant differences between the test groups and the controls in body weight, feed or water intake, clinical or ophthalmological observations, functional observational battery and motor activity assessment. Also standard hematological parameters, clinical chemistry variables, as well as renal or urinary parameters remained unaffected by the treatment. All animals survived to the end of the study. Gross examination at necropsy at the end of the treatment did not reveal any macroscopic changes that could be attributed to the treatment. There were no statistically significant differences in absolute or relative organ weights. Microscopic examination of the sampled organs and tissues did not reveal treatment-related

histopathological changes. In particular, there were no histopathological changes in the digestive tract (esophagus, stomach, jejunum, ileum, cecum, colon, rectum), i.e. the tissues with potential direct exposure to orally administered VL. There was no effect of the test substance on estrus cyclicity, epididymal sperm motility, epididymal sperm counts, testicular sperm counts and the epididymal sperm morphology. Accordingly, the no-observed-adverse-effect level (NOAEL) for VL was determined to be 1000 mg/kg bw/d, i.e. the highest dose level tested (Lina et al., 2015).

- The potential effects of oral VL on systemic and reproduction parameters were examined in a reproduction toxicity study in HanRcc:WIST (SPF) rats (OECD Guideline 422). VL was administered by gavage (in corn oil) at doses of 0, 50, 250 and 1000 mg/kg bw/d. The VL treatment was well tolerated and there were no effects of the treatment on food consumption and body weight gains during the 14-day pairing period, the gestation or the lactation period. There were no changes in the hematological and biochemical parameters that could be attributed to the VL treatment. There were no effects observed on functional observational parameters and motor activity. No changes were noted on organ weights or on the completeness of spermatogenesis stages or cell populations of the testes. Macroscopic and histopathologic examination of selected organs and tissues observed no changes that could be associated with the VL treatment. The male mating performance was not affected by the VL treatment. The sperm stages and cell populations were all within the range of normal background alterations. The reproductive performance remained unaffected by the treatment. The post-implantation loss was significantly increased in the low-dose group mainly due to one dam which had 12 post-implantation losses. In the absence of a dose/response relationship, this observation was considered to be incidental. The sex ratio, viability and body weight gain of the litters were not affected by the VL treatment and there were no macroscopic findings (Messinger & Bär, 2014b).

- The developmental toxicity was examined in HanRcc:WIST (SPF) rats following OEC Guideline 414. Ten pregnant, 11-weeks old rats per group received VL from day 6-20 *post coitum* at daily doses of 50, 250 and 1000 mg/kg bw/d by gavage (in corn oil). The VL treatment was well tolerated. Body weight and food intake were similar among all treatment groups. Necropsy of the maternal rats at termination of the study did not reveal any abnormalities in any dose group. All females had litters with viable fetuses. Gravid uterus weights did not differ

significantly between treated groups and controls. The VL treatment had no effect on any parameter of reproduction including post-implantation loss and mean number of fetuses per dam. Group mean fetal body weights and the sex ratio were normal. Minor visceral and skeletal alterations and variations were considered to be incidental. Skeletal malformations did not occur in any fetus. Bone and cartilage variations were found but their distribution among the control and VL groups did not suggest a treatment-related effect (Messinger & Bär, 2014b).

- The safety of VAc which occurs in Vinnapas® B 500/20 VL and Vinnapas® B 500/40 VL at levels of not more than 5 ppm as per Wacker's specifications, has been the subject of previous extensive reviews because of the significant use of VAc in the production of many chemicals (Environment Canada/Health Canada, 2008 a, b; BAuA, 2008; JECFA, 2011; Albertini et al., 2013). It was concluded that "the genotoxicity data … are in line with the hypothesis that vinyl acetate genotoxicity is mediated by acetaldehyde" and that "the genotoxicity of acetaldehyde only becomes evident after the cellular defense mechanisms are overloaded" (Environment Canada/Health Canada, 2008a). In other words, there exists a threshold dose-response for the mutagenicity of vinyl acetate in human cultured cells (Albertini et al., 2013).

- In consideration of these data, the very low solubility of VL in water (243 µg/L) and the fact that exposure to acetaldehyde from regular foods is much higher than that which may result indirectly from the tautomerisation of vinyl laurate (and vinyl acetate) ingested with PVACL (see van Acker et al., 2015 at p. 84), it is concluded that residual traces of vinyl laurate and vinyl acetate in Vinnapas® B 500/20 VL and Vinnapas® B 500/40 VL present no risk to human health.

- For the consideration of the safety of Vinnapas® B 500/20 VL and Vinnapas® B 500/40 VL, it is further recognized that these PVAcVL copolymers serve as (partial) substitutes for PVAc. Since the maximum permissible level of residual VAc in PVAc is also 5 ppm (FCC, 2008/9), its partial substitution by PVAcVL copolymers that may contain up to 5 ppm VL remains without consequence for the total content of acetaldehyde precursors in the gum base as consumed.

- The decomposition products of the radical initiators which are used, in only small amounts, in the PVAcVL

copolymerization process are known from experiments in model systems in which there are no other substances (monomers, polymers) present and in which therefore only the primary breakdown to radicals and their interactions can be studied. 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 will occur much more rarely than in the reported model systems. Yet, even if formed during the production of PVAcVL, such breakdown products are expected to be removed efficiently during the down-stream processing of Vinnapas® B 500/20 VL and Vinnapas® B 500/40 VL. Moreover, their chemical structures lack characteristics that would raise toxicological concerns.

- For the average consumption of chewing gum in the US, intakes of 1.43 and 1.72 g/person/d have been reported (FDA, 2011). Assuming a use of PVAcVL in all of this chewing gum at the highest technologically feasible level (17% in the chewing gum) and further assuming that the so-called heavy consumer eats three times more chewing gum than the average, the PVAcVL would be 0.729 – 0.877 g/person/d. Data of a Market Facts Mail Panel Survey indicates that chewing gum consumption is higher in children. Applying a high weight of 3g per gum, a 3-times higher intake of the heavy consumer than the mean consumer and a maximum PVAcVL content of 17% in all chewing gum consumed, the PVAcVL exposure on a per body weight basis is highest in 2 – 5 year old children with an exposure of 48 mg/kg bw/d.

- Since the sum of all impurities in PVAcVL is less than 1000 ppm, the exposure to total impurities is ≤48 µg/kg bw/d in the heavy consumer of this youngest age group. About 20 – 50% of these impurities are acetic acid as shown by batch analyses and about one- to two-thirds of this amount, i.e. 16 – 32 µg/kg bw/d, is VL which also has a known safety profile. Hydrolysis of this amount of VL, if it leached from the gum base, would produce 3.1 – 6.2 µg/kg bw/d acetaldehyde which is negligible compared to the exposure from food and endogenous formation.

CONCLUSION

We, the Expert Panel, independently and collectively critically evaluated the published and unpublished data and information summarized above, as well as any other data and information that we deemed pertinent to the safety of the intended use of the two PVAcVL copolymers described above. We unanimously conclude that the intended use of the two PVAcVL copolymers, 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 the two PVAcVL copolymers, singly or combined, at levels up to 26% of chewing gum base, is GRAS based on scientific procedures.

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

(b) (6)

25 August 2015

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CONCLUSION

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SUBMISSION END