

GRAS Extension Expert Statement

Determination of GRAS Extension For MegaNatural™ Grape Seed Extract (GSE) And MegaNatural™ Grape Pomace Extract (GSKE) For Use In Beverage Products at an Increased Incorporation Rate

The Chairman of the initial GRAS Panel, an independent Expert qualified by scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was requested by Polyphenolics Incorporated, a subsidiary of Constellation Wines US, to determine the expanded Generally Recognized as Safe (GRAS) status of MegaNatural™ Grape Seed Extract (GSE) and MegaNatural™ GSKE Grape Pomace Extract.

MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract, composed primarily of polyphenolic proanthocyanidin (PAC) compounds, have previously been self-affirmed to be Generally Recognized as Safe (GRAS) food ingredients for largely interchangeable use in fruit juices, fruit flavored beverages, fruit flavored beverage mixes, and carbonated fruit flavored beverages at the intended concentration of approximately 210 ppm (w/v) or 50 mg per 8 fluid ounce serving.

The initial GRAS determination for MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract was supported by the evaluation of an independent panel of recognized experts, hereinafter referred to as the Expert Panel, qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients. A comprehensive search of the scientific literature for safety and toxicological information on grape seed extract and grape pomace extract, constituent proanthocyanidins, and related polyphenols was conducted through August 2001, summarized, and included in an initial Report to the Expert Panel. The results and conclusions of a mutagenicity [Erexson, 2003]¹ and a 90-day safety study [Bentivegna and Whitney, 2002]², undertaken by Polyphenolics on MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract,

¹ Erexson GL. 2003. Lack of in vivo clastogenic activity of grape seed and grape pomace extracts in a mouse micronucleus assay. *Food and Chem. Toxicol.* 41(3):347-350.

² Bentivegna SS, Whitney KM. 2002. Subchronic 3-month oral toxicity study of grape seed and grape pomace extracts. *Food and Chem. Toxicol.* 40:1731-1743.

were also included therein. This report was subsequently made available to the members of Expert Panel to assist and facilitate the deliberation of MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract GRAS status.

The Expert Panel independently evaluated the material submitted, as well as other materials deemed appropriate or necessary. Following a critical evaluation, the Expert Panel conferred and unanimously agreed that MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract, meeting the specifications cited, be considered Generally Recognized as Safe (GRAS) by scientific procedures when used in fruit juice and fruit flavored beverages as an antioxidant to retard deterioration, provided it is used in accordance with current Good Manufacturing Practice (21 CFR §182.1(b)) in a composite amount not to exceed 210 ppm (w/v) in the finished beverage products.

The U.S. Food and Drug Administration (FDA) has been notified of this opinion and, after review, has issued an Agency Response Letter (GRN 000125) that was not in disagreement.

Subsequent expansions of MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract self-affirmed these products to be Generally Recognized as Safe (GRAS) food ingredients for use in hot and cold breakfast cereals, nutrition bars, yogurt, and frozen dairy desserts and mixes (frozen yogurt) for use as an antioxidant added to foods for which no defined standard of identity exists, so as to provide 100 mg per serving of composite GSE / GSKE product in order to better retard deterioration and for incorporation into additional food categories: frozen dairy desserts and mixes (ice cream and other frozen milk desserts), grain products and pastas (frozen multicourse grain-based meals, macaroni and noodle products, rice and other cereal grains, and uncooked cereal grains), and milk and milk products (buttermilk, cream, evaporated, condensed and dry milks, flavored milk drinks, milk-based meal replacements, reduced- or non-fat milks, and sour cream). In addition, uses in baked goods and baking mixes, cheeses, chewing gum, condiments and relishes, confections and frostings, dairy product analogs, gelatins, puddings and fillings, gravies and sauces, hard candy, jams and jellies, soft candy, and sweet sauces, toppings and syrups were included.

As in the earlier GRAS expansion, the constituent MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract proanthocyanidins (PACs) were proposed for use as an antioxidant added to foods for which no defined standard of identity exists, so as to provide not more than 100 mg per serving of composite MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract product, depending on specific food category, in order to better retard deterioration.

The GRAS determination by the Polyphenolics Inc. Division of the Constellation Wine Company Inc. and subsequent GRAS Notification to the FDA and GRAS expansions were therefore based on the weight of currently available scientific information and grounded upon generally available scientific data. Those GRAS determinations were the direct result of a consensus among a panel of qualified Experts that there was reasonable certainty that these products, MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract, under the intended conditions of use, would not be harmful.

Polyphenolics is now interested in increasing the incorporation rate of MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract in the fruit juices, fruit flavored beverages, fruit flavored beverage mixes, and carbonated fruit flavored beverages from 50 mg GSE Grape Seed Extract or GSKE Grape Pomace Extract/serving to 200 mg GSE or GSKE per serving (840 ppm/8 fluid ounce serving). No new research or literature was presented for expert review in seeking to establish expanded GRAS status for the newly proposed food use applications as the previous material was of a quantity and breadth that remained more than adequate to provide a reasonable certainty of no additional risk to the consumer for MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract.

Significant portions of these previous reports to the Expert Panel, particularly those regarding polyphenolic chemistry and antioxidant capacity, polyphenolic GSE/GSKE chemistry and stability, production methodology, ADME, preclinical toxicological safety, and clinical safety, were reviewed for the current extension by the Chairman of the Expert Panel. The scientific data and information summarized in the previous Reports

to the Expert Panel represented a thorough review of the relevant literature dealing with PACs, related polyphenolic compounds, and reflects the published results of non-clinical laboratory studies of GSE and GSKE, conducted in accordance with generally accepted scientific procedures.

Moreover, the increased intake of additional polyphenolic substances arising from this higher incorporation rate of MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract in fruit juices, fruit flavored beverages, fruit flavored beverage mixes, and carbonated fruit flavored beverages, in addition to all previous GRAS applications, were estimated using data contained in the USDA CSFII (1994-1996, 1998) and provided for Expert review. The Amended Intake report has been attached as Appendix 1.

Published values cited in the previous Addendum Report to the Expert Panel indicate estimated dietary intake of flavonoids, catechins, and proanthocyanidins by the average American consumer is in the range of 460-1,000 mg/day. Intake arose from the common occurrence of these substances in fruits, juices, tea, chocolate, vegetables, and in many other foods and beverages. Revised all-user mean and 90th percentile composite MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract intake based on the current GRAS expansion is approximately 799 and 1,350 mg/person/day, respectively, for the total population, within or slightly above the normal range consumed.

As noted in previous GRAS assessments, quercetin is a minor component of both the MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract products. Following chemical analysis, the mean of six lots of MegaNatural™ GSKE Grape Pomace Extract was determined contain 0.23 g of quercetin per 100 g of grape pomace extract or 0.23% quercetin. As this relates to the composite consumption of one serving of 200 mg grape pomace extract, comprising the newly proposed food use applications, quercetin intake would therefore be approximately 0.46 mg/application, while intake from all other food categories would be 0.23 mg of quercetin/application.

As indicated in Appendix 1, the heaviest consumers of GSKE in the population, male teenagers in the 90th percentile of intake, would consume 1890 mg/day of grape

pomace extract. This would equate to a worst-case quercetin intake of 4.35 mg/day. This degree of quercetin intake is a fraction of the estimated 25 mg/day average background intake by an individual in the United States [NTP, 1992]³.

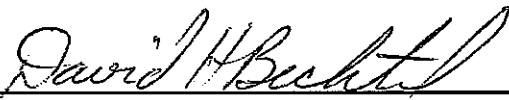
If MegaNatural™ Grape Seed Extract were exclusively substituted for MegaNatural™ Grape Pomace Extract, quercetin intake would be substantially less. Chemical analysis of six MegaNatural™ Grape Seed Extract lots determined quercetin content to be approximately 0.0045 g of quercetin per 100 g of Grape Seed Extract or 0.0045% quercetin. As this relates to the composite consumption of one serving of 200 mg grape seed extract, quercetin intake from the newly proposed food use application would therefore be approximately 0.0090 mg/application, while intake from all other food categories would be 0.0045 mg of quercetin/application.

As indicated in Appendix 1, the heaviest consumers of GSE in the population, male teenagers in the 90th percentile of intake, would consume 1890 mg/day of grape seed extract. This would equate to a worst-case quercetin intake of 0.09 mg/day. Conservatively estimating the average body weight of a male teenager to be approximately 50 kg would result in a daily dose of quercetin exposure from exclusive worst-case consumption of GSE to be approximately 0.0018 mg/kg/day. This amount is only a fraction of the 1,900 mg/kg (40,000 ppm) dose of dietary quercetin associated with an increase in the occurrence of tumors in the kidney of male F344 rats in the 2-year NTP dietary bioassay [NTP, 1992]. Importantly, the previous Expert Panel noted that the increase in tumors was small, confined to male rats in the highest treatment group, not observed in the females, and not reproduced in a second comparable and contemporary 2-year study employing an even higher 5% dietary treatment (50,000 ppm) [Ito, N *et al.*, 1989]⁴. Based on these considerations, MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract are not carcinogenic under the combined conditions of use when consumed in the existing GRAS applications and the newly proposed increase use level in beverages.

³ National Toxicology Program. 1992. Toxicology and carcinogenesis studies of quercetin in F344/N rats. U.S. Department of Health and Human Services.

⁴ Ito N, Hagiwara A, Tamano S, Kagawa M, Shibata MA, Kurata Y, Fukushima S. 1989. Lack of carcinogenicity of quercetin in F344/DUCRJ rats. *Jpn. J. Cancer Res.* 80(4):317-325. Cited In: National Toxicology Program. 1992. Toxicology and carcinogenesis studies of quercetin in F344/N rats. U.S. Department of Health and Human Services.

Based on the critical evaluations of the previous Expert panel and the newly calculated intake assessment of MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract in the expanded list of applications in food products and proposed increased use levels of MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract, the undersigned qualified Expert has determined that, MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract meeting the specifications cited, is Generally Recognized As Safe (GRAS) by scientific procedures. The constituent MegaNatural™ Grape Seed Extract and MegaNatural™ GSKE Grape Pomace Extract are therefore GRAS for use in accordance with current Good Manufacturing Practice (21CFR§182.1(b)) as an antioxidant added to the specified foods for which no defined standard of identity exists, so as to provide 100 mg per serving of composite Grape Seed Extract and GSKE Grape Pomace Extract product and at a level of 200 mg GSE or GSKE/serving in fruit juices, fruit flavored beverages, fruit flavored beverage mixes, and carbonated fruit flavored beverages in order to better retard deterioration.

 7/18/07
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