GRAS ASSOCIATES

Food Safety Regulatory Services, A Nutrasource Company

nutrasource

Pharmaceutical and Nutraceutical Services

GRAS Conclusion

of

Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder

Food Usage Conditions for General Recognition of Safety

on behalf of

Crush Dynamics, Inc.

102-9206 Shale Ave., Summerland BC V0H 1Z2

4/21/23

CONFIDENTIAL

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FOREWORD

Crush Dynamics, Inc. based our Generally Recognized as Safe (GRAS) assessment of the Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder, primarily on the composite safety information, i.e., scientific procedures with corroboration from history of use. The safety/toxicity of Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder, history of use of grape pomace and grape-derived products, and compositional details, specifications, and method of preparation of the subject ingredient were reviewed. In addition, a search of the scientific and regulatory literature was conducted through March 20, 2023, with particular attention paid to adverse reports, as well as those that supported conclusions of safety. Those references that were deemed pertinent to this review are listed in Part 7. The composite safety/toxicity studies, in concert with dietary exposure information, ultimately provide the specific scientific foundation for the GRAS conclusion.

At Crush Dynamics, Inc.'s request, GRAS Associates, LLC (GA) convened an Expert Panel to complete an independent safety evaluation of Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder products. Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder are prepared by fermenting grape pomace from red or white grapes with food grade *Saccharomyces cerevisiae* yeast to yield the finished products. The purpose of the evaluation is to ascertain whether Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder are generally recognized as safe, i.e., GRAS, under the intended conditions of use. In addition, Crush Dynamics, Inc. has asked GA to act as Agent for the submission of this GRAS notification.

PART 1. SIGNED STATEMENTS AND CERTIFICATION

Crush Dynamics, Inc. has concluded that our Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder, which meets the specifications described below, is GRAS in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). This determination was made in concert with an appropriately convened panel of experts who are qualified by scientific training and experience. The GRAS determination is based on scientific procedures as described in the following sections. The evaluation accurately reflects the intended conditions of food use for the designated Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder preparations.

This signed statement and certification has been prepared in accordance with the requirements of 21 CFR 170.225.

(a) This certification is signed by a responsible official of GRAS Associates, LLC acting as agent for Crush Dynamics, Inc.

(b) Part 1 of this GRAS notification does not include any confidential information.

(c) (1) This Independent GRAS Assessment was conducted in accordance with Subpart E of 21 CFR Part 170.

(c) (2) Names and addresses of organizations;

Sponsoring Party:
Crush Dynamics, Inc.
102-9206 Shale Ave.
Summerland, BC V0H 1Z2

As the Responsible Party, Crush Dynamics, Inc. accepts responsibility for the GRAS conclusion that has been made for Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder preparation, as described in the subject safety evaluation.

Agent:
GRAS Associates, LLC
11810 Grand Park Avenue
Suite 500
North Bethesda, MD 20852

(c) (3) The name of the ingredient is; Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder.

(c) (4) The ingredient will be used as a flavoring agent and flavor enhancer in candy containing chocolate, condiments, meatless products, yogurt, and beverages, including carbonated drinks, fruit drinks, sports drinks, coffee, tea, nutritional drinks and nutritional powders.

(c) (5) The statutory basis for our conclusion of GRAS status is through scientific procedures in accordance with § 170.30(a) and (b).

(c) (6) It is our view that the ingredient is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on our conclusion that the notified substance is GRAS under the conditions of its intended use.

(c) (7) If FDA were to ask to see the data and information that are the basis for our conclusion of GRAS status, either during or after FDA evaluation of this notice, we agree to:

(i) make the data and information available to FDA; and

(ii) agree to both of the following procedures for making the data and information available to FDA:

(A) Upon FDA's request, we will allow FDA to review and copy the data and information during customary business hours at our address specified where these data and information will be available; and

(B) Upon request by FDA, we will provide FDA with a complete copy of the data and information either in an electronic format that is accessible for their evaluation or on paper.

(c) (8) None of the data and information in Parts Part 2 through Part 7 of this GRAS notice are exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552 (e.g., as trade secret or as commercial or financial information that is privileged or confidential).

(c) (9) We certify that, to the best of our knowledge, this GRAS Assessment is a complete, representative, and balanced review that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of the substance.

(c) (10) Crush Dynamics, Inc. does not intend to add Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder to any meat and/or poultry products that come under FSIS/USDA jurisdiction. Therefore, 21 CFR 170.270 does not apply.

(c) (11) Signature

[INSERT SIGNATURE]

Agent for Crush Dynamics, Inc.

William J. Rowe Date:
President
GRAS Associates, LLC
11810 Grand Park Ave
Suite 500
North Bethesda, MD 20852

PART 2. IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT

A. Identity of Ingredient

Fermented grape pomace is the common or usual name of Ruby Purée and Gold Purée and their corresponding dried powders (Ruby Powder and Gold Powder). The compositional features of the Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder are described in more detail in this section. The ingredients are marketed as Ruby Purée and Ruby Powder and Gold Purée and Gold Powder.

Common or Usual Name: Fermented grape puree and powder
Chemical Name: N/A
Synonyms: N/A
CAS Number: N/A
Molecular Formula: N/A
Molecular Weight (MW): N/A

1. Botanical Identification

Ruby and Gold Fermented Grape Puree and Powder are produced from the pomace of red and white *Vitis vinifera* grapes (Table 1), respectively, harvested in the Okanagan Valley region of British Columbia, Canada.

Table 1. Classification of *Vitis vinifera* L.[a]

Rank	Scientific Name
Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Rhamnales
Family	Vitaceae Juss.
Genus	*Vitis* L.
Species	*Vitis vinifera* L.

[a] From: https://plants.usda.gov/home/plantProfile?symbol=VIVI5

Ruby Fermented Grape Pomace is produced from the red *V. vinifera* varietals that may include Cabernet Franc, Cabernet Sauvignon, Malbec, Merlot, Pinot Noir, Syrah, and Petit Verdot. Gold Fermented Grape Pomace is produced from white varietals that may include Chardonnay, Gewurztraminer, Pinot Gris, Riesling, Pinot Blanc, Sauvignon Blanc, Semillon, and Viognier.

2. Chemistry of Grapes and Grape Pomace

Grape pomace (Figure 1) is a by-product of processing of grapes for wine and juice. It is generated during the process of pressing to extract the grape juice, and includes the skin, seeds, and pulp of the grape (Chakka and Babu, 2022; Teixeira et al., 2014). The resulting grape pomace contains carbohydrates, dietary fiber, vitamins and minerals, as well as a variety of phenolic compounds (Chakka and Babu, 2022; Machado and Domínguez-Perles, 2017). The phenolic compounds in grape pomace can be broadly categorized into flavonoid and non-flavonoid phenolics. Non-flavonoid phenolics include phenolic acids (hydroxycinnamic acids and hydroxybenzoic acids) and stilbenes, including resveratrol. Flavonoids include flavanols or flavan-3-ols (catechin, epicatechin, gallocatechin), flavonols (quercetin, kaempferol, myricetin), anthocyanins, and tannins. Proanthocyanidins (PAC) are oligomers and polymers formed by the condensation of flavan-3-ol monomers, and are the main polyphenolics in grape seeds (Machado and Domínguez-Perles, 2017; Yang et al., 2022). The total concentrations of phenolic compounds in grape seed, skin, and pulp have been reported to be around 2178 mg/g, 375 mg/g, and 23.8 mg/g gallic acid equivalents (GAE), respectively (Xia et al., 2010).

The phenolic content varies depending on grape variety; while some studies have found that red grape varieties have a higher phenolic content, other analyses have have found no significant difference in total polyphenol content in pomace derived from red and white grapes (Onache et al., 2022; Kammerer et al., 2004; Chedea et al., 2022). The flavanol monomers frequently found in grape pomace are catechin and epicatechin, while the most common flavonols are typically quercetin, isorhamnetin, kaempferol, and syringenin, as well as their glycoside derivatives. With respect to phenolic acids in pomace, hydroxybenzoic acids are typically found in higher concentrations than hydroxycinnamic acids. Proanthocyanidin B1 and B2 are the main dimers found in grape pomace, in both red and white varieties, with comparatively lower concentrations of B3 detected (Machado and Domínguez-Perles, 2017). A recent analysis of grape pomace from several red and white cultivars (including Muscat Ottonet, Cabernet Sauvignon, Merlot, and Pinor Noir) reported a total polyphenol content ranging from 17.06 mg to 25.58 mg GAE/100 g dry weight, with phenolic compounds including catechin, quercetin, epicatechin, gallic acid, syringic acid, and isorhamnetin detected across all varieties. Quercetin was found to be higher in red grape pomaces compared to white grape pomaces (Onache et al., 2022).

Dietary fiber also makes up a large proportion of grape pomace, which can contain up to 85% depending on the grape variety (Antonić et al., 2020).

Figure 1. Red Grape Pomace

3. Chemical Composition of Ruby and Gold Puree Fermented Grape Pomace

Ruby and Gold Fermented Grape Pomace are produced from the pomace of red and white *Vitis vinifera* grapes (Table 1), respectively. Two representative lots of Ruby and Gold Fermented Grape Pomace were analyzed for a panel of polyphenols, and the results are summarized in Table 2. The analytical method and data are found in **Error! Reference source not found.**. These results are in l ine with typical phenolic compounds detected in grape pomace from red and white cultivars (Onache et al., 2022).

Table 2. Polyphenolic Content of Representative Lots of Ruby and Gold Fermented Grape Pomace

Compound[1]	mg/kg (Dry Weight)			
	Ruby Fermented Grape Pomace		Gold Fermented Grape Pomace	
	Lot # RP1-23048	Lot # RP1-HF-221104	Lot # WG1-21350	Lot # WG1-HF-211126
Flavan-3-ols				
Catechin	1.637	0.413	ND	ND
Gallocatechin	0.059	0.036	0.082	0.110
Flavonols				
Kampferol	0.109	0.062	0.046	0.046
Myricetin	0.086	0.023	ND	ND
Quercetin	1.998	1.041	0.653	0.675
Isorhamnetin	0.162	0.101	0.045	0.047
Phenolic Acids				
Gallic Acid	ND	ND	1.393	1.816
Vanillic Acid	0.519	0.398	0.106	0.167
3,4-Dihydroxybenzoic Acid	0.267	0.096	0.646	0.607
Other				

Compound[1]	mg/kg (Dry Weight)			
	Ruby Fermented Grape Pomace		Gold Fermented Grape Pomace	
	Lot # RP1-23048	Lot # RP1-HF-221104	Lot # WG1-21350	Lot # WG1-HF-211126
Naringenin	0.013	0.008	0.014	0.023
Pungenol (3,4-dihydroxyacetophenone)	2.065	0.448	6.396	2.476
Protocatechuic aldehyde (3,4-Dihydroxybenzaldehyde)	ND	ND	0.0336	ND

[1] Analysis carried out using liquid chromatography tandem mass spectrometry (LC-MS/MS).
Kg – Kilograms; mg – Milligrams; ND – Not detected

Apigenin, caffeic acid, ferulic acid, p-coumaric acid, piceol, taxifolin, and vanillin were below the limit of detection for all samples tested. The proanthocyanidin (PAC) dimer content of representative lots of Ruby and Gold Fermented Grape Pomace was measured as described by Pico et al. (2019) and Pico et al. (2020). Ruby Fermented Grape Pomace contained 1.42 mg/kg of procyanidin B1 dimer, 1.34 mg/kg of procyanidin B2 dimer, and 0.69 mg/kg of procyanidin B3 dimer, while none was detected in the Gold Pomace product.

The phenolic content of Ruby and Gold Fermented Grape Pomace compared to commercial grape-derived products (expressed as percent on a dry basis (w/w)), as well as the flavonoid and dimeric PAC content of edible grapes, is shown in Table 3. exGrape® Total grape pomace extract was the subject of GRN 446 (FDA, 2013), while MegaNatural™ Gold Grape Seed Extract (GSE) and Grape Skin Extract (GSKE) were the subject of GRN 125 (FDA, 2003b). MegaNatural™ Gold GSKE is produced from both the skin and seeds of grapes and is referred to by FDA as grape pomace extract (GPE) in the response letter. The products described in GRN 125 and GRN 446 are water extracts that are selectively concentrated by column chromatography, and as such contain much higher proportions of polyphenolic compounds compared to the Ruby and Gold Fermented Grape Pomace. As Ruby and Gold Fermented Grape Pomace are not extracts, but rather whole pomace that also contains grape solids, the proportions of detectable polyphenolic compounds are closer to those reported in edible grapes (USDA, 2020; USDA, 2021b).

Table 3. Polyphenolic Content of Ruby and Gold Fermented Grape Pomace Compared to Commercial Grape-Derived Products and Edible Grapes

Polyphenolic Compound	mg/kg (Dry Weight)					Mean Flavonoid and PAC Dimer Content of Grapes[5] (mg/100 g Edible Portion)	
	Ruby Fermented Grape Pomace[1]	Gold Fermented Grape Pomace[2]	GRN 446[3]	GRN 125 (GSKE)[4]	GRN 125 (GSE)[4]	Grapes (Red)	Grapes (White or Green)
Total Polyphenols	36,700[6]	40,800[7]	734,200	945,700	951,700	NR	NR
Catechin	1.025	ND	11,200	26,400	29,200	0.82	3.73

Polyphenolic Compound	mg/kg (Dry Weight)					Mean Flavonoid and PAC Dimer Content of Grapes[5] (mg/100 g Edible Portion)	
	Ruby Fermented Grape Pomace[1]	Gold Fermented Grape Pomace[2]	GRN 446[3]	GRN 125 (GSKE)[4]	GRN 125 (GSE)[4]	Grapes (Red)	Grapes (White or Green)
PAC Dimers	3.45[8]	ND	204,400	36,200	43,700	2.37	1.91
Gallocatchin	0.048	0.096	NR	NR	NR	ND	0.01
Kampferol	0.086	0.046	NR	200	3.8	ND	0.06
Myricetin	0.055	ND	3,400	100	20	0.01	0.22
Quercetin	1.519	0.664	17,500	2,300	40	1.04	1.12
Gallic Acid	ND	1.604	890	18,700	950	N/A	N/A
Caffeic Acid	ND	ND	300	300	100	N/A	N/A

[1]Average values for lots RP1-23048 and RP1-HF-221104 as reported in Table 2.
[2]Average values for lots WG1-21350 and WG1-HF-211126 as reported in Table 2.
[3]GRN 446, exGrape® Red grape pomace extract (FDA, 2013).
[4]GRN 125, MegaNatural™ Gold grape seed extract (GSE) and grape pomace extract (GSKE) (FDA, 2003b).
[5]USDA Database for the Flavonoid Content of Selected Foods (USDA, 2021b) and USDA Database for the Proanthocyanidin Content of Selected Foods (USDA, 2020).
[6]Highest value from representative lots in Table 8, converted to mg/kg.
[7]From Table 11, converted to mg/kg.
[8]Sum of PAC B1, B2, and B3 as measured by method described by Pico et al. (2019) and Pico et al. (2020).
g – Grams; GSE – Grape seed extract; GSKE – Grape skin extract; mg – Milligrams; N/A – Not applicable; ND – Not detected; NR – Not reported; PAC – Proanthocyanidin; USDA – US Department of Agriculture

4. Nutritional Profile

The typical nutritional data for Ruby and Gold Fermented Grape Pomace Purees and Powders are shown in Table 4 and Table 5, respectively. Individual results are also shown in Appendix 2.

Table 4. Typical Nutritional Profiles for Ruby and Gold Puree

Analysis	Results per 100 g	
	Ruby Puree	Gold Puree
Calories (Cal)	69	51
Total Fat as Triglycerides (g)	1.37	1.33
Saturated Fatty Acids (g)	0.25	0.24
Cis-Monounsaturated Fatty Acids (g)	0.24	0.21
Cis-Polyunsaturated Fatty Acids (g)	0.8	0.81
Omega-6 Fatty Acids (g)	0.78	0.79
Omega-3 Fatty Acids (g)	0.02	0.02
Trans Fatty Acids (g)	<0.01	<0.01
Conjugated Linoleic Acid (g)	<0.01	<0.01
Cholesterol (mg)	<1.0	<1.0
Sodium (mg)	4.7	1.4
Potassium (mg)	374	282
Carbohydrates (g)	12.2	8.4
Total Dietary Fiber (g)	9.5	6.6
Total Sugars (g)	1.3	<1.6

Analysis	Results per 100 g	
	Ruby Puree	Gold Puree
Fructose (g)	0.68	<0.2
Glucose (g)	0.66	<0.2
Sucrose (g)	<0.2	<0.2
Maltose (g)	<0.5	<0.5
Lactose (g)	<0.5	<0.5
Protein (F=6.25) (g)	2	1.3
Calcium (mg)	69.3	63.8
Iron (mg)	1.5	1
Ash (g)	0.87	0.75
Moisture (g)	83.56	88.19

g – Grams; mg - Milligrams

Table 5. Typical Nutritional Profiles for Ruby and Gold Powder

Analysis	Results per 100 g	
	Ruby Powder	Gold Powder
Calories (Cal)	397	398
Total Fat as Triglycerides (g)	10.66	11.1
Saturated Fatty Acids (g)	1.67	1.61
Cis-Monounsaturated Fatty Acids (g)	1.79	1.75
Cis-Polyunsaturated Fatty Acids (g)	6.72	7.25
Omega-6 Fatty Acids (g)	6.58	7.10
Omega-3 Fatty Acids (g)	0.14	0.15
Trans Fatty Acids (g)	0.02	0.01
Conjugated Linoleic Acid (g)	<0.01	<0.01
Cholesterol (mg)	<1.0	<1.0
Sodium (mg)	7.4	8.1
Potassium (mg)	2580	2140
Carbohydrates (g)	66.1	66.1
Total Dietary Fiber (g)	54.5	60.4
Total Sugars (g)	2.47	<10
Fructose (g)	<0.2	<0.1
Glucose (g)	1.6	<0.2
Sucrose (g)	0.21	<0.1
Maltose (g)	<0.5	<0.4
Lactose (g)	<0.5	<0.4
Protein (F=6.25) (g)	9.2	11.34
Calcium (mg)	529	488
Iron (mg)	11.9	90.2
Ash (g)	6.59	6
Moisture (g)	7.43	5.48

g – Grams; mg - Milligrams

B. Manufacturing Processes

Crush Dynamics has attested that all raw materials, processing aids and food contact substances used in the manufacture are used in accordance with existing US regulations, are the subjects of effective food contact notifications, or were concluded to be GRAS for their respective uses and that

Ruby and Gold Fermented Grape Pomace (Puree and Powder) is produced in accordance with current Good Manufacturing Practices (cGMP) (Appendix 3).

Crush Dynamics has conducted a Hazard Analysis and Risk Assessment to identify Critical Control Points (CCP) steps and carries out routine analysis throughout the manufacturing process to monitor biological, chemical, and physical contaminants. Crush Dynamics's Food Safety Plan/Preventative Control Plan can be found in Appendix 4.

1. Incoming Raw Material Quality

The incoming grape pomace from red and white grapes is tested for the presence of pesticide residues by a multi-residue pesticide analysis (Fruit and Vegetable Pesticide Scan) including testing for approximately 500 pesticide residues. Pesticide results must conform to the maximum residue limits (MRL) for foods as established by Health Canada and the U.S. Department of Agriculture (USDA) MRL Database and 40 CFR 180.

Crush Dynamics's Pesticide Control Procedure, and representative pesticide residue analysis results and report can be found in Appendix 5.

2. Manufacturing Process for Ruby Puree and Gold Puree Fermented Grape Pomace

The manufacturing process for Ruby and Gold Fermented Grape Puree and Powder is summarized in

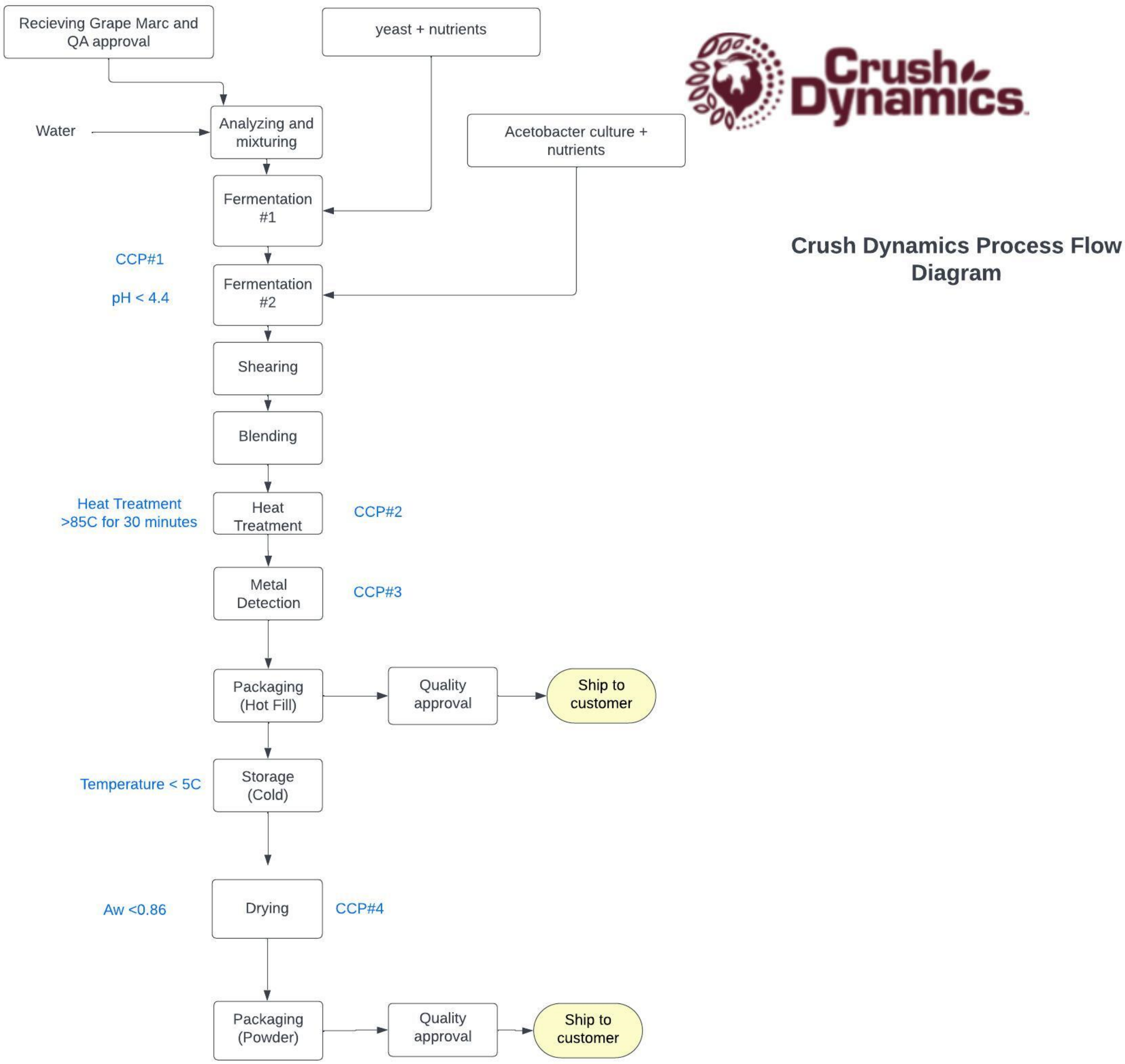

Figure 2 .

Destemmed grape pomace, obtained by pressing red or white grapes, is used as the starting material for Ruby and Gold Fermented Grape Puree. After harvesting, sorting, cleaning, and removal of stems, grapes are pressed to extract the juice. The remaining material, including pulp, skin, and seeds (pomace) is used as the starting material for Ruby and Gold Fermented Grape Puree.

a. Fermentation and Raw Materials

Grape pomace (from red or white grapes) undergoes a two-step fermentation process using yeast, vinegar bacteria (Acetobacter) and nutrients that are either food-grade or safe and suitable for the intended use, produced in accordance with cGMP.

Fermentation is carried out using food grade *Saccharomyces cerevisiae*, along with food grade nutrient blends that include a combination of minerals, vitamins, and inactivated *S. cerevisiae*. Fermentation step 1 is carried out using a commercial blend of nutrients containing di-ammonium phosphate, magnesium sulfate, inactivated yeast, and thiamine, niacin, folic acid and calcium pantothenate, added at a rate of 0.3 g/L. Fermentation step 2 is carried out using vinegar bacteria (acetobacter) CFR????? and a commercial blend of nutrients containing ammonium and potassium phosphate, magnesium sulfate, yeast extract, and a vitamin mineral mix, added at a 1% usage rate. The vinegar or acetic acid bacteria is naturally cultivated from the grape pomace itself and the active dry yeast meets applicable standards for food for human consumption, has not been genetically modified, and is safe for the intended use. Dried yeasts (including *Saccharomyces cerevisiae*) are GRAS for direct addition to food per 21 CFR 172.896. The nutrients used are obtained from US- and Canadian-based companies[1] providing nutrient pre-mixes for vinegar and wine production and are suitable for human consumption and safe for their intended use.

Granulated sugar (sucrose, cane, or beet sugar), used during the fermentation process, is GRAS per 21 CFR 184.1854 when used in accordance with cGMP, and provided the ingredient is of a purity suitable for its intended use. The sugar used is produced from raw cane sugar that has not been genetically modified or bioengineered.

Water used during manufacturing is from a municipal water source and is treated and tested per city requirements and supported by routine monitoring via an environmental monitoring program.

b. Blending and Drying

Following fermentation, water is added to maintain a moisture content of ≤ 90% and the fermented grape pomace is blended, sheared, and heat-treated (> 85°C for 30 minutes) to produce Ruby and Gold Fermented Grape Purees. No additional processing aids are used. The Ruby and Gold Fermented Grape Purees are dried and milled to produce Ruby and Gold Fermented Grape Powders, respectively, with a moisture content of ≤ 9%.

[1]Yeast nutrients obtained from: Nutrients Inc.: http://nutrientsinc.com/; LALLEMAND: https://www.lallemandwine.com/en/south-africa/products/catalogue/nutrients-protectors/

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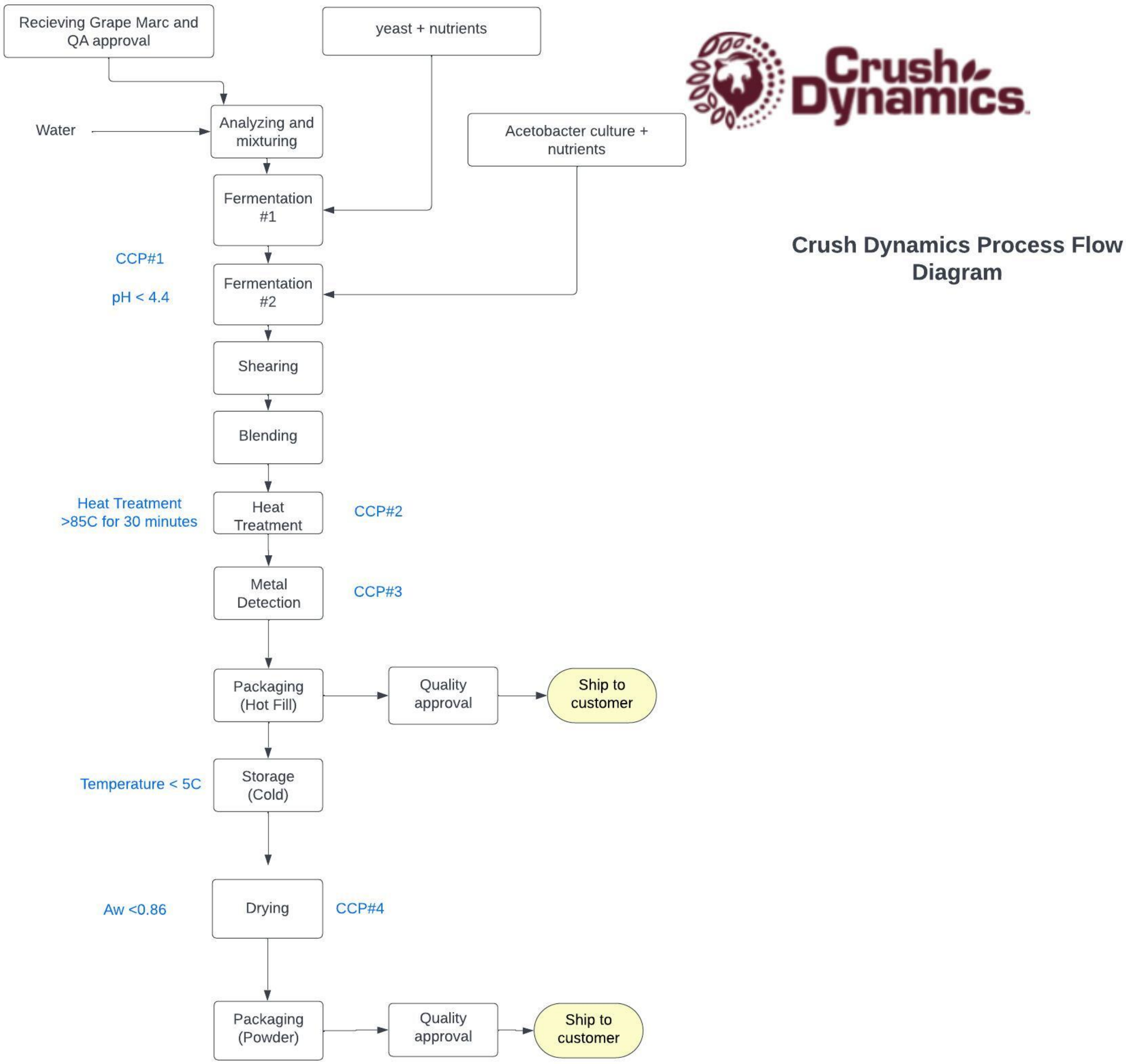

Figure 2. Flow Chart of Manufacturing Process for Ruby and Gold Fermented Grape Puree and Powder

C. Product Specifications

1. Specifications for Ruby and Gold Fermented Grape Puree and Powder and Supporting Methods

Food grade specifications for Ruby and Gold Fermented Grape Purée and Powder have been established by Crush Dynamics and are shown in Table 6 and

Table 7. Specification sheets for Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder are found in Appendix 6.

Table 6. Specifications for Ruby and Gold Fermented Grape Puree

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Ruby Puree	Crush Dynamics, Inc.'s Specifications for Gold Puree	Method of Analysis
Sensory Characteristics			
Appearance	Deep red to dark purple puree or slurry	Golden brown puree or slurry	Visual
Flavor and Aroma	Sharp and acidic slight sweet fruitiness	Sharp and acidic slight sweet fruitiness	Gustatory & Olfactory
Particle Size	Fine free flowing puree	Fine free flowing puree	Visual
Foreign Material	None	None	Visual
Analytical Characteristics			
Total Polyphenols (%)	Report Only	Report Only	FC/UV-Vis
Moisture (%)	≤ 90[1]	≤ 90[1]	Loss on drying
pH	≤ 4.4	≤ 4.4	USP <791>
Ethanol (%)	≤ 0.5	≤ 0.5	GC-FID
Microbiological Characteristics			

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Ruby Puree	Crush Dynamics, Inc.'s Specifications for Gold Puree	Method of Analysis
Total Aerobic Plate Count (CFU/g)	≤ 10,000	≤ 10,000	MFHPB-18
Yeast and Molds (CFU/g)	≤ 1,000	≤ 1,000	MFHPB-22
Total Coliforms (CFU/g)	< 10	< 10	MFHPB-34
***Salmonella* spp. (/25 g)**	Negative	Negative	MFHPB-24
***Escherichia coli* (CFU/g)**	< 10	< 10	MFHPB-34
***Staphylococcus aureus* (CFU/g)**	< 25	< 25	MFHPB-21
Heavy Metals			
Arsenic (ppm)	≤ 0.10	≤ 0.10	ICP-MS
Cadmium (ppm)	≤ 0.01	≤ 0.01	ICP-MS
Lead (ppm)	≤ 0.05	≤ 0.05	ICP-MS
Mercury (ppm)	≤ 0.01	≤ 0.01	ICP-MS
Other Contaminants			
Ochratoxin A (ppb)	≤ 2	≤ 2	CFIA BFCL-050
Aflatoxin (ppb)	≤ 2	≤ 2	CFIA BFCL-050
Pesticides	Conforms to cGAP standards	Conforms to cGAP standards	AOAC 2007.01

[1]Target range is 87-89%.

AOAC - Association of Official Agricultural Chemists; CFIA – Canadian Food Inspection Agency; CFU – Colony Forming Units; cGAP – Current Good Agricultural Practices; FC/UV-Vis – Folin Ciocalteu/ultraviolet-visible; GC-FID – Gas-chromatography flame-ionization-detector; ICP-MS – Inductively coupled plasma-mass spectrometry; g – Gram(s); MFHPB – Microbiology Food Health Protection Branch; ppb – Parts per billion; ppm – Parts per million; USP – United States Pharmacopoeia

Table 7. Specifications for Gold Fermented Grape Powder

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Ruby Powder	Crush Dynamics, Inc.'s Specifications for Gold Powder	Method of Analysis
Sensory Characteristics			
Appearance	Deep red to dark purple fine powder	Golden fine powder	Visual
Flavor and Aroma	Sharp and acidic slight sweet fruitiness	Sharp and acidic slight sweet fruitiness	Gustatory & Olfactory
Particle Size	100% through 80 mesh	100% through 80 mesh	Sieve Analysis
Foreign Material	None	None	Visual
Analytical Characteristics			
Total Polyphenols (%)	Report Only	Report Only	FC/UV-Vis
Moisture (%)	≤ 9.0	≤ 9.0	Loss on drying
Water Activity	≤ 0.86	≤ 0.86	AOAC 978.18
Ethanol (%)	≤ 0.5	≤ 0.5	GC-FID
Microbiological Characteristics			
Total Aerobic Plate Count (CFU/g)	≤ 10,000	≤ 10,000	MFHPB-18
Yeast and Molds (CFU/g)	≤ 1,000	≤ 1,000	MFHPB-22
Total Coliforms (CFU/g)	< 10	< 10	MFHPB-19
***Salmonella* spp. (/25 g)**	Negative	Negative	MFHPB-24
***Escherichia coli* (CFU/g)**	< 10	< 10	MFHPB-19
***Staphylococcus aureus* (CFU/g)**	< 25	< 25	MFHPB-21
Heavy Metals			
Arsenic (ppm)	≤ 0.10	≤ 0.10	ICP-MS
Cadmium (ppm)	≤ 0.01	≤ 0.01	ICP-MS
Lead (ppm)	≤ 0.05	≤ 0.05	ICP-MS
Mercury (ppm)	≤ 0.01	≤ 0.01	ICP-MS
Other Contaminants			
Ochratoxin A (ppb)	≤ 2	≤ 2	CFIA BFCL-050
Aflatoxin (ppb)	≤ 2	≤ 2	CFIA BFCL-050
Pesticides	Conforms to cGAP standards	Conforms to cGAP standards	AOAC 2007.01

AOAC - Association of Official Agricultural Chemists; CFIA – Canadian Food Inspection Agency; CFU – Colony Forming Units; cGAP – Current Good Agricultural Practices; FC/UV-Vis - Folin Ciocalteu/ultraviolet-visible; g – Gram; GC-FID - Gas-chromatography flame-ionization-detector; ICP-MS

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Ruby Powder	Crush Dynamics, Inc.'s Specifications for Gold Powder	Method of Analysis

- Inductively coupled plasma-mass spectrometry; MFHPB - Microbiology Food Health Protection Branch; ppb – Parts per billion; ppm – Parts per million

The results of analysis of five non-consecutive lots of Ruby Puree, three non-consecutive lots of Gold Puree, and one representative lot each of Gold Powders, demonstrating that the ingredients consistently meet these specifications, are shown in Table 8, Table 9, Table 10, and Table 11, respectively. Certificates of Analysis for the lots are found in Appendix 7.

Table 8. Specifications and Representative Lots for Ruby Fermented Grape Puree

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Ruby Puree	Ruby Puree Representative Lots				
		RP1-HF-210424-1	1911	RP1-21329	RP2-221101-1	RP1-23048
Sensory Characteristics						
Appearance	Deep red to dark purple puree or slurry	Conforms	Conforms	Conforms	Conforms	Conforms
Flavor and Aroma	Sharp and acidic slight sweet fruitiness	Conforms	Conforms	Conforms	Conforms	Conforms
Particle Size	Fine free flowing puree	Conforms	Conforms	Conforms	Conforms	Conforms
Foreign Material	None	Conforms	Conforms	Conforms	Conforms	Conforms
Analytical Characteristics						
Total Polyphenols (%)	Report Only	3.67[1]	2.71[1]	NR	NR	0.23[2]
Moisture (%)	≤ 90	88.3	87.1	89.9	88.1	87.5
pH	≤ 4.4	4.1	4.2	3.9	3.97	4.07
Ethanol (%)	≤ 0.5	0.19	0.27	0.19	0.47	0.33
Microbiological Characteristics						
Total Aerobic Plate Count (CFU/g)	≤ 10,000	150	1,500	< 100	140	340
Yeast and Molds (CFU/g)	≤ 1,000	< 10	< 10	< 5	< 10	< 10
Total Coliforms (CFU/g)	< 10	< 10	< 10	< 10	< 10	< 10
***Salmonella* spp. (CFU/25 g)**	Negative	Negative	Negative	Negative	Negative	Negative
***Escherichia coli* (CFU/g)**	< 10	Negative	Negative	< 10	< 10	< 10
***Staphylococcus aureus* (CFU/g)**	< 25	Negative	Negative	< 25	< 10	< 10
Heavy Metals						
Arsenic (ppm)	≤ 0.10	0.0135	0.0133	0.0059	< 0.01	0.011

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Ruby Puree	Ruby Puree Representative Lots				
		RP1-HF-210424-1	1911	RP1-21329	RP2-221101-1	RP1-23048
Cadmium (ppm)	≤ 0.01	< 0.0050	< 0.0050	< 0.0050	< 0.01	< 0.010
Lead (ppm)	≤ 0.05	0.0086	0.0135	0.0064	< 0.01	< 0.010
Mercury (ppm)	≤ 0.01	0.0013	0.0011	< 0.0010	< 0.005	< 0.0010
Other Contaminants						
Ochratoxin A (ppb)	≤ 2	< 0.04	< 0.04	< 0.04	ND	ND
Aflatoxin (ppb)	≤ 2	NR	NR	NR	ND	ND
Pesticides	Conforms to cGAP standards	Conforms	Conforms	Conforms	Conforms	Conforms

[1]Reported on a dry weight basis.
[2]Reported on an "as-is" basis.
CFU – Colony Forming Units; g – Gram(s); ND – Not detected; NR – Not reported; ppm – Parts per million

Table 9. Specifications and Representative Lots for Gold Fermented Grape Puree

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Gold Purée	Gold Purée Representative Lots		
		WG1-21350	WG2-221109-1	WG1-HT-211015-B1
Sensory Characteristics				
Appearance	Golden slurry	Conforms	Conforms	Conforms
Flavor and Aroma	Sharp and acidic slight sweet fruitiness	Conforms	Conforms	Conforms
Particle Size	Fine free flowing puree	Conforms	Conforms	Conforms
Foreign Material	None	Conforms	Conforms	Conforms
Analytical Characteristics				
Total Polyphenols (%)	Report Only	0.44[1]	NR	NR
Moisture (%)	≤ 90	88.9	88.6	88.01
pH	≤ 4.4	3.92	3.97	3.92
Ethanol (%)	≤ 0.5	< 0.01	< 0.01	NT
Microbiological Characteristics				
Total Aerobic	≤ 10,000	35	6,100	50

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Gold Purée	Gold Purée Representative Lots		
		WG1-21350	WG2-221109-1	WG1-HT-211015-B1
Plate Count (CFU/g)				
Yeast and Molds (CFU/g)	≤ 1,000	< 5	< 10	< 5
Total Coliforms (CFU/g)	< 10	< 10	< 10	< 10
***Salmonella* spp. (/25 g)**	Negative	Negative	Negative	Negative
***Escherichia coli* (CFU/g)**	< 10	< 10	< 10	< 10
***Staphylococcus aureus* (CFU/g)**	< 25	< 25	< 10	< 25
Heavy Metals				
Arsenic (ppm)	≤ 0.10	0.0069	0.011	0.008
Cadmium (ppm)	≤ 0.01	< 0.0050	< 0.01	< 0.0050
Lead (ppm)	≤ 0.05	< 0.0050	< 0.01	< 0.0050
Mercury (ppm)	≤ 0.01	< 0.001	< 0.005	< 0.0010
Other Contaminants				
Ochratoxin A (ppb)	≤ 2	NR	NR	NR
Aflatoxin (ppb)	≤ 2	NR	NR	NR
Pesticides	Conforms to cGAP standards	Conforms	Conforms	Conforms

[1]Measured on an "as-is" basis, average of duplicate measurements (0.42% and 0.47% (w/w)).

CFU – Colony Forming Units; cGAP – Current Good Agricultural Practices; g – Gram(s); NR – Not reported; NT – Not tested; ppb – Parts per billion; ppm – Parts per million

Table 10. Specifications and Representative Lot for Ruby Fermented Grape Pomace Powder

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Ruby Powder	Ruby Powder Representative Lot RP3-21329-33222-RD
Sensory Characteristics		
Appearance	Deep red to dark purple fine powder	Conforms
Flavor and Aroma	Sharp and acidic slight sweet fruitiness	Conforms
Particle Size	100% through 80 mesh	Conforms
Foreign Material	None	Conforms
Analytical Characteristics		
Total Polyphenols (%)	Report Only	NR
Moisture (%)	≤ 9.0	7.4
Water Activity	≤ 0.86	0.46
Ethanol (%)	≤ 0.5	0.19
Microbiological Characteristics		
Total Aerobic Plate Count (CFU/g)	≤ 10,000	180
Yeast and Molds (CFU/g)	≤ 1,000	< 10
Total Coliforms (CFU/g)	< 10	< 10
***Salmonella* spp. (/25 g)**	Negative	Negative
***Escherichia coli* (CFU/g)**	< 10	< 10
***Staphylococcus aureus* (CFU/g)**	< 25	< 10
Heavy Metals		
Arsenic (ppm)	≤ 0.10	0.06
Cadmium (ppm)	≤ 0.01	< 0.01
Lead (ppm)	≤ 0.05	0.05
Mercury (ppm)	≤ 0.01	0.01
Other Contaminants		
Ochratoxin A (ppb)	≤ 2	NR
Aflatoxin (ppb)	≤ 2	NR

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Ruby Powder	Ruby Powder Representative Lot
		RP3-21329-33222-RD
Pesticides	Conforms to cGAP standards	Conforms

CFU – Colony Forming Units; cGAP – Current Good Agricultural Practices; g – Gram; NR – Not reported; ppb – Parts per billion; ppm – Parts per million

Table 11. Specifications and Representative Lots for Gold Fermented Grape Pomace Powder

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Gold Powder	Gold Powder Representative Lot
		WG3-21350-33422-2
Sensory Characteristics		
Appearance	Golden fine powder	Conforms
Flavor and Aroma	Sharp and acidic slight sweet fruitiness	Conforms
Particle Size	100% through 80 mesh	Conforms
Foreign Material	None	Conforms
Analytical Characteristics		
Total Polyphenols (%)	Report Only	4.08[1]
Moisture (%)	≤ 9.0	8.1
Water Activity	≤ 0.86	0.47
Ethanol (%)	≤ 0.5	< 0.01
Microbiological Characteristics		
Total Aerobic Plate Count (CFU/g)	≤ 10,000	5,200
Yeast and Molds (CFU/g)	≤ 1,000	100
Total Coliforms (CFU/g)	< 10	< 10
***Salmonella* spp. (/25 g)**	Negative	Negative

Physical & Chemical Parameters	Crush Dynamics, Inc.'s Specifications for Gold Powder	Gold Powder Representative Lot
		WG3-21350-33422-2
***Escherichia coli* (CFU/g)**	< 10	< 10
***Staphylococcus aureus* (CFU/g)**	< 25	< 10
Heavy Metals		
Arsenic (ppm)	≤ 0.10	0.08
Cadmium (ppm)	≤ 0.01	< 0.01
Lead (ppm)	≤ 0.05	0.029
Mercury (ppm)	≤ 0.01	< 0.0095
Other Contaminants		
Ochratoxin A (ppb)	≤ 2	NR
Aflatoxin (ppb)	≤ 2	NR
Pesticides	Conforms to cGAP standards	Conforms

[1]Average of duplicate measurements (4.19% and 3.96% (w/w)).
CFU – Colony Forming Units; cGAP – Current Good Agricultural Practices; g – Gram; NR – Not reported; ppb – Parts per billion; ppm – Parts per million

2. Specifications for Ruby and Gold Fermented Grape Puree and Powder Compared to Commercial Grape-Derived Products

Specifications for Ruby and Gold Fermented Grape Puree and Powder compared to specifications of other grape-derived products that have been the subject of GRAS notices and have received letters of no question from FDA are shown in Table 12. The total polyphenols in the Fermented Grape Puree and Powder are lower when compared to the other products, which is to be expected as all other products are extracts containing selectively concentrated polyphenols. While certain microbial specifications for the Ruby and Gold Fermented Grape Pomace are higher than other grape-derived products, similar acceptance criteria have been reported in GRNs for other fruit-derived ingredients. For example, GRN 805 (Apple peel powder), which includes a total aerobic plate count specification of <10,000 CFU/g, and yeast and mold specification of <10,000 CFU/g (FDA, 2019), which are similar to, and higher than, those for Ruby and Gold Fermented Grape Pomace, respectively. Similarly, another pomace-derived ingredient (GRN 972) includes *E. coli* specification limits of <10 CFU/g (FDA, 2022), similar to Ruby and Gold Fermented Grape Pomace.

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Table 12. Specifications for Ruby and Gold Fermented Grape Puree amd Powder Compared to other Commercial Grape-Derived Products

Physical and Chemical Parameters	Crush Dynamics' Ruby Puree	Crush Dynamics' Gold Puree	Crush Dynamics' Ruby Powder	Crush Dynamics' Gold Powder	GRN 446[4]	GRN 125 (GSKE)[5]	GRN 125 (GSE)[5]	GRN 124[7]
Appearance	Deep red to dark purple puree or slurry	Golden brown puree or slurry	Deep red to dark purple fine powder	Golden fine powder	Fine purple powder	Red purple powder	Rose beige powder	NS
Analytical Characteristics								
Moisture (%)	≤ 90	≤ 90	≤ 9.0	≤ 9.0	≤ 6.0	≤ 8.0	≤ 8.0	< 8.0
Residual Ethanol (%)	≤ 0.5	≤ 0.5	≤ 0.5	≤ 0.5	≤ 0.01	NS	NS	NS
Total Polyphenols (%)	3.67[1]	0.44[2]	NR	4.08[3]	≥ 55	80	90	≥ 78
Procyanidins (%)	NS	NS	NS	NS	≥ 15	NS	NS	NS
Anthocyanins (%)	NS	NS	NS	NS	≥ 2.0	1.5	NS	NS
Resveratrol (mg/kg)	NS	NS	NS	NS	≥ 100	NS	NS	NS
Heavy Metals								
Arsenic (ppm)	≤ 0.10	≤ 0.10	≤ 0.10	≤ 0.10	≤ 3	NS	NS	≤ 5
Mercury (ppm)	≤ 0.01	≤ 0.01	≤ 0.01	≤ 0.01	≤ 1	NS	NS	≤ 0.20
Cadmium (ppm)	≤ 0.01	≤ 0.01	≤ 0.01	≤ 0.01	≤ 1	NS	NS	≤ 1.0
Lead (ppm)	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05	≤ 2	NS	NS	≤ 1.0
Microbiological Characteristics								
Total Aerobic Plate Count (CFU/g)	≤ 10 000	≤ 10 000	≤ 10 000	≤ 10 000	≤ 1000	≤ 1000	≤ 1000	≤ 1000
Total Coliforms (CFU/g)	< 10	< 10	≤ 10	≤ 10	None/1 g	≤ 10	≤ 10	≤ 3
Salmonella	Negative/25 g	Negative/25 g	Negative/25 g	Negative/25 g	None/10 g	Negative/30 g	Negative/30 g	Negative[7]
Escherichia coli	< 10 CFU/g	< 10 CFU/g	< 10 CFU/g	< 10 CFU/g	None/10 g	Negative/10 g	Negative/10 g	≤ 3 CFU/g
Staphylococcus aureus	< 25 CFU/g	< 25 CFU/g	< 25 CFU/g	< 25 CFU/g	NS	NS	NS	≤ 10 CFU/g
Yeast and Mold (CFU/g)	≤ 1,000	≤ 1,000	≤ 1,000	≤ 1,000	≤ 100	≤ 1,000	≤ 1,000	≤ 100 CFU
Other Contaminants								
Ochratoxin A	≤ 2	≤ 2	≤ 2	≤ 2	Values reported for 3 lots: 4.7,	NS	NS	NS

Physical and Chemical Parameters	Crush Dynamics' Ruby Puree	Crush Dynamics' Gold Puree	Crush Dynamics' Ruby Powder	Crush Dynamics' Gold Powder	GRN 446[4]	GRN 125 (GSKE)[5]	GRN 125 (GSE)[5]	GRN 124[7]
					4.5, and 1.9 µg/kg[8]			
Aflatoxin	≤ 2	≤ 2	≤ 2	≤ 2	NS	NS	NS	NS
Pesticides	Conforms to cGAP standards	Conforms to cGAP standards	Conforms to cGAP standards	Conforms to cGAP standards	Conforms with USP 561	Meets FDA tolerances for grapes	Meets FDA tolerances for grapes	NS

CFU - Colony forming units; cGAP – Current Good Agricultural Practices; FDA – U.S. Food and Drug Administration; g - Gram; GAE – Gallic acid equivalent; GRN - GRAS Notice; GSE - Grape seed extract; GSKE - Grape skin extract; kg – Kilogram; mg – Milligrams; MRL – Maximum Residue Limits; NMT – Not More Than; NS - Not Specified; ppm – Parts per million; USP – United States Pharmacopoeia

[1]Highest value from representative lots in Table 8.
[2]From Table 9.
[3]From Table 11.
[4]GRN 446, exGrape® Red grape pomace extract (FDA, 2013).
[5]GRN 125, MegaNatural™ Gold grape seed extract (GSE) and grape pomace extract (GSKE) (FDA, 2003b).
[6]GRN 124, ActiVin® grape seed extract (FDA, 2003a).
[7]Negative for *S. typhimurium*.
[8]Measured values of three lots, no specification limits established.

D. Physical or Technical Effect

Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder will be added as a flavoring agent and flavor enhancer in conventional foods.

E. Stability

1. Stability Data for Crush Dynamics, Inc.'s Ruby Fermented Grape Pomace (Puree)

Crush Dynamics conducted a 12-month ambient storage stability study on a representative lot of Ruby Fermented Grape Puree, stored at 21°C. A 12-month shelf-life validation study and 3-month shelf-life extension study was also carried out on a second representative lot of Ruby Puree stored at 4°C. Ruby Puree was observed to be stable over the course of the stability study, as demonstrated in Table 13 and Table 14. Certificates of Analysis and study reports are found in Appendix 8.

Table 13. Ruby Fermented Grape Puree One-Year Ambient Storage Stability Data

Physical / Chemical Parameter Measured	Specifications	Lot # 1911-2					
		T = 0	T = 9.5 weeks	T = 3 months	T = 4 months	T = 6 months	T = 12 months
Moisture (%) (w/w)	≤ 90	84.22	84.50	83.64	84.16	NR	NR
pH	≤ 4.4	4.04	3.68	3.83	3.75	3.90	4.5
Appearance	Puree or slurry	Thick slurry	Thick slurry	Thick slurry	Thick slurry	Thick slurry	Thick slurry
Aroma	Strong fermented and acidic	Strong fermented and acidic	Strong fermented and acidic	Strong fermented and acidic	Strong fermented and acidic	Strong fermented and acidic	Strong fermented and acidic
Color	Deep red to dark purple	Reddish purple	Reddish purple	Reddish purple	Reddish purple	Reddish purple	Reddish purple
Flavor	Sharp and acidic slight sweet fruitiness	Strong fermented and acidic, moderate to strong sour, slight grape	Strong fermented and acidic, moderate to strong sour, slight grape	Strong fermented and acidic, moderate to strong sour, slight grape	Strong fermented and acidic, moderate to strong sour, slight grape	Strong fermented and acidic, strong sour, very slight grape	Strong fermented and acidic, strong sour, no grape, slight bitter
Titratable Acidity (%) (w/w)	NS	2.29	3.57	3.34	3.52	2.95	1.18
Aerobic Colony Count (CFU/g)	≤ 10,000	690	370	270	740	150 est.	2,600 est.
Yeast (CFU/g)	≤ 1,000	< 10	< 10	< 10	< 10	< 10	< 10
Mold (CFU/g)	≤ 1,000	< 10	< 10	< 10	< 10	< 10	< 10

CFU – Colony forming units; est. – Estimated; g – Grams; NR – Not reported; T – Time; w/w – Weight/weight

To further validate the 12-month shelf-life and determine stability beyond one year, a shelf-life validation study and three-month shelf-life extension study was carried out a separate lot of Ruby Puree which had been stored in cold storage (at 4°C) for 12 months. The product was evaluated at 12 months for microbiological parameters, analytical parameters as well as Ochratoxin A and polyphenol content, and at 15 months for analytical and microbiological parameters. Results are shown in Table 14.

Table 14. Ruby Fermented Grape Pomace (Puree) Shelf-Life Validation and Extension Stability Study

Physical / Chemical Parameter Measured	Specifications	Lot # RP1-21204		
		T = 0 months	T = 12 months	T = 15 months
Moisture (%) (w/w)	≤ 90	86.62	89.59	87.93
pH	≤ 4.4	3.84	3.83	3.82
Polyphenols (%)[1]	Report only	0.39	0.36	NR
Titratable Acidity (%) (w/w)	NS	2.085	2.070	2.063
Aerobic Colony Count (CFU/g)	≤ 10,000	5800	4848	5000
Coliforms (CFU/g)	< 10	< 10	< 10	< 10
***E. coli* (CFU/g)**	< 10	< 10	< 10	< 10
Yeast (CFU/g)	≤ 1,000	< 100	< 100	< 100
Mold (CFU/g)	≤ 1,000	< 100	< 100	< 100
Ochratoxin A (ppb (w/w))	< 2 ppb	< 0.04	< 0.04	NR

CFU – Colony forming units; est. – Estimated; g – Grams; ppb – Parts per billion; NR – Not reported; NS – Not specified; w/w – Weight/weight
[1]Measured on an "as-is" basis by UV/Vis spectrophotometry using Folin-Ciocalteu methodology

These shelf-life stability studies demonstrate that Ruby Fermented Grape Puree is stable for 15 months when stored at 4°C in bulk packaging (pail). There were no changes in organoleptic parameters over the 12 months and product continued to pass internal sensory evaluation at 15 months. Product continued to meet analytical and microbiological (aerobic colony count, coliforms, *E. coli*, yeast, and mold) specifications after 12 and 15 months of storage. Moreover, ochratoxin A continued to meet limits established by Crush Dynamics' control procedures, indicating no growth of ochratoxin A-producing organisms had occurred during storage. Crush Dynamics' Food Safety Plan/HACCP Plan (Appendix 4) includes steps to ensure the Fermented Grape Pomace products meet established parameters (including pH and temperature) to control microbial growth and meet the intended shelf life. Based on the established Food Safety Plan and control steps, the representative shelf-life data for Ruby Fermented Grape Puree would be expected to be similar to that of the Gold Fermented Grape Puree. *Aspergillus carbonarius*, and to a lesser extent *A. niger*, are the strains most commonly associated with ochratoxin A production in grapes (Mondani et al., 2020; JECFA, 2001). Ochratoxin A production by *A. carbonarius* and *A. niger* isolates has been reported to occur at a water activity (a_w) range from 0.95-0.99 a_w (Bragulat et al., 2019; Mondani et al., 2020; Abarca et al., 2019). Crush Dynamics' Food Safety Plan ensures that the a_w of Gold Fermented Grape Powders is below 0.86, which would further limit microbial growth and ochratoxin A production.

PART 3. DIETARY EXPOSURE

Crush Dynamics, Inc.'s Ruby and Gold Fermented Grape Puree and Powder are intended to be used interchangeably in candy containing chocolate, condiments, meatless products, yogurt, and beverages, including carbonated drinks, fruit drinks, sports drinks, coffee, tea, nutritional drinks and nutritional powders. The intended use levels will vary by actual food category, ranging from 1% to 5% for Purees (higher use level due to moisture content) and 0.1% to 0.5% for Powders.

The amounts of Crush Dynamics, Inc.'s Ruby and Gold Fermented Grape Puree and Powder to be added to foods will not exceed the amounts reasonably required to accomplish the intended technical effect in foods. Ruby and Gold Puree and Powder are intended for interchangeable use; depending on the finished product application, Ruby or Gold Puree or Powder may be used in a food product. Only a single ingredient (Ruby Puree or Gold Puree, or Ruby Powder or Gold Powder) is intended to be used in a given food. It is intended that Ruby and Gold Fermented Grape Puree may be used as an alternative to other grape-derived ingredients, where applicable.

1. Estimate of Dietary Exposure to the Substance

Crush Dynamics, Inc proposes to use their Ruby and Gold Fermented Grape Powder at a maximum of 0.5% and their Ruby and Gold Fermented Grape Puree at a maximum of 5% in the intended categories.

The estimated daily intake was calculated using the Creme Food Safety® model (https://www.cremeglobal.com). The model includes food consumption data included in the NHANES (NHANES) 2017-2020 survey (CDC, 2021). Calculations for this intake analysis were completed using deterministic (single points) input data, and the maximum intended use level of the ingredient(s). Output calculation types include daily average intakes, acute exposures, as well as population statistics such as mean, percentiles, standard errors, and confidence intervals. Results are output for "Consumers Only" (i.e., consumers of the food / substance of interest). Results of the exposure assessment are given in absolute terms (g/day) as well as relative to the consumer's body weight (g/kg body weight /day) at the mean and 90th percentile. The per unit of body weight exposure is calculated on a subject level using the body weight recorded by the NHANES data. The results for estimated "Consumers Only" daily intake for Ruby and Gold Powder are shown in Table 15 and Ruby and Gold Puree in Table 16. A detailed estimated daily intake analysis report is provided in Appendix 9.

Table 15. Summary of Estimated Daily Intake for Crush Dynamics, Inc.'s Ruby and Gold Fermented Grape Powder in the US Based on National Health and Nutrition Examination Survey (NHANES) [2017-2020]

Population Group	N	Intake (g/day)		Intake (g/kg bw/day)	
		Mean ± SE	90th Percentile ± SE	Mean ± SE	90th Percentile ± SE
Children, female (< 2 yr)	94	0.61 ± 0.08	1.51 ± 0.17	0.053 ± 0.006	0.120 ± 0.018

Population Group	N	Intake (g/day)		Intake (g/kg bw/day)	
		Mean ± SE	90th Percentile ± SE	Mean ± SE	90th Percentile ± SE
Children, male (< 2 yr)	137	0.48 ± 0.05	1.39 ± 0.15	0.043 ± 0.004	0.125 ± 0.012
Children, female (2-5 yr)	330	0.68 ± 0.04	1.56 ± 0.14	0.040 ± 0.002	0.089 ± 0.006
Children, male (2-5 yr)	343	0.83 ± 0.04	1.92 ± 0.12	0.047 ± 0.003	0.116 ± 0.006
Children, female (6-11 yr)	547	1.15 ± 0.04	2.37 ± 0.12	0.034 ± 0.001	0.072 ± 0.004
Children, male (6-11 yr)	555	1.49 ± 0.06	3.45 ± 0.14	0.044 ± 0.002	0.101 ± 0.006
Teenage, female (12-18 yr)	581	1.73 ± 0.06	3.65 ± 0.17	0.029 ± 0.001	0.061 ± 0.005
Teenage, male (12-18 yr)	604	2.28 ± 0.08	4.24 ± 0.30	0.036 ± 0.001	0.077 ± 0.003
Adults, female	3081	1.83 ± 0.03	4.30 ± 0.09	0.024 ± 0.001	0.055 ± 0.001
Adults, male	2870	2.79 ± 0.06	6.39 ± 0.15	0.031 ± 0.001	0.075 ± 0.002
All Ages	9142	2.09 ± 0.03	4.99 ± 0.08	0.030 ± 0.000	0.071 ± 0.001

bw – Body weight; kg – Kilograms; g – Grams; SE – Standard error; yr – Year

The estimated mean and 90th percentile consumption of Ruby and Gold Powder for all ages is 2.09 g/day (0.030 g/kg bw/day) and 4.99 g/day (0.071 g/kg bw/day), respectively. In the population with the highest consumption in terms of g/day (adult males), the mean and 90th percentile estimated dietary intakes at the proposed maximum intended use levels of Ruby and Gold Powder are 2.79 g/day (0.031 g/kg bw/day) and 6.39 g/day (0.075 g/kg bw/day), respectively. In terms of intake relative to body weight, female infants and toddlers less than 2 years old have the highest estimated consumption at the mean (0.053 g/kg bw/day), and male infants and toddlers less than 2 years old have the highest estimated consumption at the 90th percentile (0.125 g/kg bw/day), primarily due to juice consumption.

Based on an average (per dry weight basis) total polyphenol content of approximately 3.5% in the Ruby and Gold Fermented Grape Purees and Powders, this would equate to an approximate mean and 90th percentile intake of 73.2 mg/day and 174.6 mg/day of total polyphenols in the “all ages” group, and an approximate mean and 90th percentile intake of 97.6 mg/day and 223.6 mg/day of total polyphenols in the population with the highest consumption in terms of g/day (adult males). In infants and toddlers less than 2 years of age, the estimated mean and 90th percentile intake of polyphenols equates to approximately 16.8 mg/day and 48.7 mg/day in males, and 21.4 mg/day and 52.8 mg/day in females, respectively.

Table 16. Summary of Estimated Daily Intake for Crush Dynamics, Inc.'s Ruby and Gold Fermented Grape Puree in the US Based on National Health and Nutrition Examination Survey (NHANES) [2017-2020]

Population Group	N	Intake (g/day)		Intake (g/kg bw/day)	
		Mean ± SE	90th Percentile ± SE	Mean ± SE	90th Percentile ± SE
Children, female (< 2 yr)	94	6.09 ± 0.79	15.07 ± 1.67	0.534 ± 0.059	1.204 ± 0.185
Children, male (< 2 yr)	137	4.85 ± 0.55	13.87 ± 1.49	0.430 ± 0.043	1.253 ± 0.118
Children, female (2-5 yr)	330	6.80 ± 0.39	15.59 ± 1.43	0.401 ± 0.024	0.888 ± 0.062
Children, male (2-5 yr)	343	8.31 ± 0.45	19.18 ± 1.23	0.467 ± 0.027	1.161 ± 0.055
Children, female (6-11 yr)	547	11.55 ± 0.40	23.70 ± 1.16	0.339 ± 0.015	0.725 ± 0.041
Children, male (6-11 yr)	555	14.93 ± 0.56	34.47 ± 1.39	0.443 ± 0.019	1.010 ± 0.060
Teenage, female (12-18 yr)	581	17.34 ± 0.62	36.46 ± 1.67	0.288 ± 0.011	0.606 ± 0.049
Teenage, male (12-18 yr)	604	22.82 ± 0.81	42.38 ± 2.97	0.360 ± 0.013	0.767 ± 0.033
Adults, female	3081	18.27 ± 0.34	43.04 ± 0.90	0.242 ± 0.006	0.552 ± 0.015
Adults, male	2870	27.85 ± 0.57	63.85 ± 1.50	0.312 ± 0.006	0.748 ± 0.016
All Ages	9142	20.94 ± 0.25	49.90 ± 0.82	0.300 ± 0.004	0.711 ± 0.011

bw – Body weight; kg – Kilograms; g – Grams; SE – Standard error; yr – Year

As would be expected, the estimated mean and 90th percentile consumption of Ruby and Gold Puree for all ages is 20.94 g/day (0.300 g/kg bw/day) and 49.90 g/day (0.711 g/kg bw/day), respectively, in line with the 10-fold higher usage level accounting for up to 90% moisture in the Puree. In the population with the highest consumption in terms of g/day (adult males), the mean and 90th percentile estimated dietary intakes at the proposed maximum intended use levels of Ruby and Gold Puree are 27.85 g/day (0.312 g/kg bw/day) and 63.85 g/day (0.748 g/kg bw/day), respectively. In terms of intake relative to body weight, female infants and toddlers less than 2 years old have the highest estimated consumption at the mean (0.534 g/kg bw/day), and male infants and toddlers less than 2 years old have the highest estimated consumption at the 90th percentile (1.253 g/kg bw/day).

B. Estimate of Dietary Exposure to Polyphenols

Polyphenols are ubiquitous in foods and are regularly consumed as part of the diet (Gu et al., 2004; Del Bo et al., 2019), and the USDA has published databases of the flavonoid content of 506 different foods (USDA, 2021b) and the PAC content of 285 different foods (USDA, 2020). As cited in GRN 125, earlier reports estimated the typical daily intake of polyphenols in the average US diet to be approximately 1 g/day (FDA, 2003b). A meta-analysis by Del Bo et al. (2019) estimated the total polyphenol intake for the overall population to be around 900 mg/day, with the main sources of polyphenols represented by tea, coffee, red wine, fruit, and vegetables. Huang et al. (2020) estimated a usual dietary intake of polyphenols of approximately 884 mg per 1000 kcal/day in adults in the U.S., with phenolic acids (around 1006 mg/day) and flavonoids (around 379 mg/day) being the main classes consumed. The authors reported that foods and beverages contributed 99.8% of polyphenol intake, with coffee, beans, and tea as major dietary contributors. In the United Kingdom, the mean total polyphenol intake was estimated to range from 266.6±166.1 mg/day in children aged 1.5-3 years to 1035.1±544.3 mg/day in adults aged 65 years and over, with flavan-3-ols and hydroxycinnamic acids being the most consumed polyphenols across all age groups (Ziauddeen et al., 2019).

C. Estimated Dietary Exposure to Any Other Substance That is Expected to be Formed In or On Food

This section is not applicable to Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder product, which would be chemically stable under the proposed conditions of use.

D. Dietary Exposure to Contaminants or Byproducts

Potential contaminants of Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder include microbes and heavy metals. The specifications set for Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder (Table 6 and Table 6) place limits on the maximum permissible levels of these impurities to assure an acceptable final product. The batch data for five different lots of Ruby Fermented Grape Pomace Puree, three different lots of Gold Fermented Grape Pomace Puree, and one lot of each of Ruby and Gold Fermented Grape Pomace Powders document quality control of the final product such that it meets these specifications (Table 8, Table 9, Table 10, and Table 11). Crush Dynamics also tests for pesticide residues in incoming raw grape pomace and results must conform to MRLs set by Health Canada and USDA. Representative pesticide results are found in Appendix 4. The fermented grape pomace also undergoes a Fruit and Vegetable Product multiple mycotoxin scan at an accredited third-party laboratory, and results must conform to the Maximum Limits for Canada as per Health Canada's Maximum Limits and guidance values for ochratoxin A in foods and FDA guidance levels for foods. Crush Dynamics's Mycotoxin Control Procedure and representative mycotoxin results and report are found in Appendix 10.

PART 4. SELF-LIMITING LEVELS OF USE

There are no known self-limiting levels of use. It is possible that the use levels of Crush Dynamics, Inc.'s Ruby and Gold Fermented Grape Purée and Powder products would be limited by taste attributes.

PART 5. EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

The statutory basis for the conclusion of GRAS status of Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder in this document is based on scientific procedures in accordance with 21 CFR 170.30(a)(b). Therefore, experience based on common use in food before 1958 does not apply.

PART 6. NARRATIVE

A. Introduction

B. History of Safe Consumption of Grapes and Grape-Derived Products

Grapes are one of the world's oldest crops, and evidence for the use of grapes, including as foods, juices, and wines dates back as far as 6000 BC (Chedea et al., 2022). Similarly, domestication of grape species, most commonly *Vitis vinifera*, has been suggested to have occurred around the same time period. At present, there are more than 60 species of grapes in the genus *Vitis* (Guzmán-Ardiles et al., 2022).

Grapes, including seeded grapes, have been consumed for millennia and are one of the most frequently consumed raw fruits in the U.S., following apples and bananas (USDA, 2021a). Globally, 78 megatonnes (Mt) of grapes were produced in 2020, with Asia as the largest producer (29.8 Mt), followed by Europe (28.2 Mt) and the Americas (13.2 Mt) (FAO, 2022).

Approximately 75% of grapes produced are used for winemaking (Antonić et al., 2020). The grape skin, pulp, seeds, and stems of the grape remaining after pressing are referred to as grape pomace. Grape must, freshly crushed fruit juice, also contains solids from the skin, seeds and stems of the fruit, depending on press pressure used. Wines are typically made from first-press fractions, and subsequent fractions (using increased pressure) result in musts that are increasingly rich in grape solids (from seed, stems, skins) (Moreno and Peinado, 2012). Concentrated grape must, also called grape molasses, petimezi (Greek style molasses syrup) or pekmez (Turkish and Italian molasses), saba or defrutum, is made from cooking down the must or the leftover grapes from winemaking to obtain a thick syrup. Concentrated grape musts have been used since ancient times as a food ingredient (Kochilas, 2011; McMahon, 2022; Monaco, 2018; Moreno and Peinado, 2012). The Food and Agriculture Organization of the United Nations (FAO) defines pekmez as "a molasses-like syrup obtained after condensing juices of fruit must, especially grape by boiling it with a coagulant agent" (FAO, 2018b). Grape must is also included in the FAO online thesaurus and is considered a commodity that is included in pesticide residues testing by FAO (FAO, 2017; FAO, 2018a). The United States Department of Agriculture (USDA) defines grape must as "a mixture of grape juice, grape pulp and grape skin that is fermented into wine" (USDA, 2006). Grape must is also a component of cooking sauces, condiments (e.g. Balsamic vinegar) and salad dressings. Balsamic vinegars are typically made with cooked grape must that is fermented by yeast and acetic acid bacteria, yielding a dense, dark-brown aged vinegar (Giudici et al., 2009).

1. United States

A search of FDA's GRAS Notice Inventory website[2] on February 10, 2023, using the search terms "grape", "vitis", "vinifera", or "pomace" identified four notifications that received "no questions" letters from FDA. These GRNs are summarized in Table 17.

Two notices in particular pertained to grape pomace extracts. GRN 446 (FDA, 2013) was submitted for an aqueous extract produced from red grape pomace (pulp, skin, and seeds) that is subjected to a short fermentation period by naturally occurring *Saccharomyces*, and is intended for use as an antioxidant in fruit juices (except those for which a standard of identity exists) and fruit-flavored beverages at concentrations of up to 210 mg/kg (corresponding to up to 154 mg/kg total polyphenols). GRN 125 (FDA, 2003b) was submitted for two grape-derived extracts, one of which (grape skin extract; GSKE) is referred to by FDA as a grape pomace extract. GSKE is an aqueous extract of grape pomace (seeds and skin) and is also intended for use in fruit juices and fruit-flavored beverages at concentration of up to 210 ppm (corresponding to up to approximately 199 mg/kg total polyphenols). Both were determined by FDA to be GRAS under the intended conditions of use. The phenolic content of these two grape pomace extracts, as well grape seed extract (GRN 125 (GSE)) compared to Ruby and Gold Fermented Grape Pomace products is shown in Table 3. Both GRN 446 and 125 estimated a maximum (90th percentile) daily intake of 130 mg/day, which would correspond to approximately 95 mg/day and 123 mg/day of total polyphenols from extracts in GRN 446 and GRN 125 (GSKE), respectively).

Table 17. Summary of Grape-Derived Ingredients in FDA GRAS Inventory

Substance	GRN # / Closure Date	Intended Use	Use Rate	Company/ Reference	FDA Response
Monoacylglycerides from Grape Seed	GRN 886 July 13, 2020	As a component of a surface finishing agent to protect the freshness and extend the shelf life of fresh produce at levels not to exceed GMP.	At a level up to 1.52 g/kg of produce. Approximate intake of 218 mg/day.	Apeel Sciences FDA (2020)	FDA had no questions
Red Grape Pomace Extract	GRN 446 Apr. 15, 2013	As an antioxidant in fruit juices (except those for which a standard of identity exists), fruit flavored beverages, fruit flavored beverage mixes and carbonated fruit flavored beverages	Up to 210 mg/kg (alone or in combination with other safe and appropriate antioxidant substances). Maximum (90th percentile) intake of 130 mg/day, or 4 mg/kg bw/day.	Groupe GRAP'SUD FDA (2013)	FDA had no questions, and noted that some uses may require a color additive listing
Grape Seed Extract and Grape Pomace Extract	GRN 125 Aug. 18, 2003	As an antioxidant in fruit juices, fruit flavored beverages, fruit flavored beverage mixes and	At a concentration of 210 ppm (alone or in combination with other	Polyphenolics , Inc. FDA (2003b)	FDA had no questions, and noted that some

[2] GRAS Notice Inventory. Available online at: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices

Substance	GRN # / Closure Date	Intended Use	Use Rate	Company/ Reference	FDA Response
		carbonated fruit flavored beverages	safe and appropriate antioxidant substances). Maximum (90th percentile) intake of 130 mg/day, or 4 mg/kg bw/day.		uses may require a color additive listing
Grape Seed Extract	GRN 124 Aug. 1, 2003	As an antioxidant or emulsifier in beverages and beverage bases, breakfast cereals, fats and oils, frozen dairy desserts and mixes, grain products, milk (whole and skim), milk products, processed fruits and fruit juice	At levels ranging from 0.01 to 0.08% Maximum (90th percentile) intake of 291 mg/day, or 6.09 mg/kg bw/day.	San Joaquin Valley Concentrates FDA (2003a)	FDA had no questions

bw - Body weight; g - Grams; GMP - Good Manufacturing Practice; GRN - GRAS notice; kg - Kilogram; mg – Milligrams; ppm - Parts per million

Several whole grape extracts have also been the subject of independent GRAS conclusions[3], including Ethical Natural's ORAC-15™ and VinCare®[4] (both containing 80% polyphenols) extracts, and Cyvex Nutritions BioVin[5], which are produced from the skin, seed, and pulp of grapes.

A search of FDA's New Dietary Ingredient Notification (NDIN) list[6] using the search terms "grape", "vitis", "vinifera", or "pomace" identified two notifications for grape-derived extracts to which FDA had no objections. NDIN 732 (FDA, 2011) was submitted by SEPPIC in 2011 for Provinols™, an extract derived from wine of red grapes (Cabernet Sauvignon). The recommended daily dose of the extract is 100-300 mg/day, containing an equivalent of 95-285 mg of polyphenols. NDIN 572 (FDA, 2009) was submitted by CODE (Conseil Organisation Distribution Ergonomie) in 2009 for polyphenols from grapeseed extract (Grapemax Extra-Pure), with a suggested dose of 242 mg of polyphenols per serving and 484 mg of polyphenols per day.

a. Code of Federal Regulations / Food Chemicals Codex

According to 21 CFR §73.170 and 21 CFR §73.169, grape skin extract and grape color extract are approved for use as color additives by FDA. Grape skin extract (enocianina) is prepared by aqueous extraction (steeping) of the deseeded grape marc (or pomace) remaining after pressing to produce grape juice or wine and undergoes fermentation during the steeping process. Grape skin extract contains common grape components including anthocyanins, tartaric acid, tannins, and minerals. Grape color extract is an aqueous solution of anthocyanin grape pigments produced from Concord

[3] AIBMR Independent GRAS Conclusion Inventory Database. Available online at: https://aibmr.com/natural-products-industry-compliance-consultation/gras-self-determination-gras-independent-conclusions-generally-recognized-as-safe-safety-studies/
[4] Information available at: https://www.ethicalnaturals.com/products/signature-ingredients/vincare-patented-whole-grape-extract (Accessed April 7, 2023)
[5] Information available at: https://www.nutraingredients-usa.com/Article/2010/07/23/Grape-extracts-get-GRAS# (Accessed April 7, 2023)
[6] NDIN Inventory. Available online at: https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/submitted-75-day-premarket-notifications-new-dietary-ingredients

grapes (or a dehydrated water-soluble powder prepared from the aqueous solution). Neither product may be used in foods for which a standard of identity exists, and both must meet specifications for pesticide residues as per Section 408 of the FD&C Act.

The Food Chemicals Codex (FCC) has also published a monograph for grape skin extract, which is similarly described as being produced by aqueous extraction of grape marc following pressing to extract juice, which undergoes fermentation during the steeping (extraction) process, and contains anthocyanidins, and other naturally present compounds such as tartrates, malates, tannins, and minerals.

b. Flavor and Extract Manufacturers Association

Grape seed extract (synonym oligomeric proanthocyanidins) is considered GRAS by the Flavor and Extract Manufacturers Association (FEMA), as FEMA number 4045. Reported uses range from 100-200 ppm in beverages, cheeses, condiments and relishes, frozen dairy, gelatins and puddings, imitation dairy, instant coffee and tea, milk products, seasonings and flavors, soups, and sugar substitutes (Smith et al., 2003).

2. Europe

The European Food Safety Authority (EFSA) has published scientific opinions related to health claims for grape seed extract (EFSA, 2011; EFSA, 2012c; EFSA, 2012b; EFSA, 2012a; EFSA, 2021), however they have not reviewed the safety of grape pomace, seed, or skin. EFSA reviewed data on anthocyanins (E 163) as a food additive, including data obtained from studies using aqueous grape skin extract (GSKE), and concluded that there was insufficient data to determine an Acceptable Daily Intake (ADI) (EFSA, 2013). The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) has also published scientific opinions on the safety of dry grape extract for use in animal feed. They concluded that dry grape extract may be used in and on feed without specific authorization at up to 100 mg/kg complete feed for all species except dogs, which have no safe intake level (FEEDAP et al., 2016a), and was safe in drinking water at up to 50 mg/L for all species except dogs (FEEDAP et al., 2016b).

3. Canada

Red wine extract, grape seed extract, and grape skin extract (as a color additive) are listed in Health Canada’s Natural Health Products Database. Red wine extract may be used as a source of antioxidants, at a dose not to exceed 1 g per day (and not to exceed 95% polyphenols) (Health Canada, 2018b). Grape seed extract may be used as a source of antioxidants and to helps relieve symptoms related to non-complicated chronic venous insufficiency, with doses of up to 475 mg of extract per day, standardized to 70-85% oligomeric proanthocyanidins (OPCs) (Health Canada, 2018a).

4. Australia/New Zealand

The Food Standards Australia-New Zealand (FSANZ) Novel Food Reference Group of the Advisory Committee on Foods includes grape pomace extract and grape seed extract as non-traditional, not novel foods and no concerns regarding composition or safety were noted (FSANZ, 2023). The safe dose, however, was not stated by FSANZ.

C. Absorption, Distribution, Metabolism & Excretion (ADME) Studies

In general, dietary phenolics have been reported to have low absorption rates in the small intestine and are metabolized in the large intestine by gut microflora into metabolites that are either absorbed or excreted (Rodriguez-Lopez et al., 2022; Yang et al., 2022). Once absorbed, flavonoids are metabolized into their glucuronate and sulfate conjugates, which may or may not be methylated across the catechol functional group. This occurs by Phase II drug-metabolizing enzymes, specifically uridine-5′-diphosphate glucuronosyl-transferases, sulfotransferases and catechol-O-methytransferases (D Archivio et al., 2007; Donovan et al., 2001; O'Leary et al., 2003). Metabolism increases the solubility of phenolic aglycones and facilitates their excretion in the bile and urine.

Animal studies have shown that the bioavailability of grape polyphenols and flavanols is low due to limited absorption, extensive metabolism in the gastrointestinal tract, and rapid excretion. Absorbed polyphenols and their metabolites have low potential for bioaccumulation in tissues or placental transport. Polyphenol and flavanol absorption or metabolism may be influenced by age, sex or diet.

Margalef et al. (2016a) compared the kinetics of flavanols in young (8-weeks) and old (adult, 24-weeks) rats, and found that adult rats treated with the grape seed PAC extract (1,000 mg/kg bw) showed decreased flavanol absorption and Phase II flavanol metabolism compared with younger rats.

In another study, 8- to 10-week-old male and female rats received a 1,000 mg/kg bw dose of grape seed polyphenol extract (by oral gavage) and were euthanized at 1, 2 or 4 hours (h) post administration. Both male and female rats reached peak maximum plasma concentrations of flavanols and their metabolites by 1 to 2 h post-administration. The maximum concentration of unconjugated flavanols occurred at 1 h post-administration. Similar amounts of total metabolites in the liver were measured for both males and females. In mesenteric white adipose tissue, primarily non-conjugated flavanols were detected, with relatively low concentrations of Phase I metabolites, and only glucuronide and methyglucuronide forms present. No difference in the total concentration of flavanols and flavanol metabolites in mesenteric white adipose tissue was observed between the sexes. Similarly, there was no difference between sexes in the kinetics of flavanols and their metabolites in brain tissue. However, female rats had twice the number of total metabolites in plasma than male rats. Male rats had a greater proportion of methyl-glucuronidated metabolites in the plasma than females and a lower proportion of methyl-sulfated metabolites than female rats after 2 h, and the accumulation of free flavanols in mesenteric white adipose tissue occurred over a longer period of time in males. In the brain tissue of female rats, the primary metabolites were PAC dimers, while in males the primary metabolite was methylated epicatechins, which were not found in female rats. Males also had a higher quantity of flavanol metabolites in brain tissue. These results suggest that there may be sex-related variability in the metabolism and distribution of grape seed flavanols (Margalef et al., 2016b).

The distribution of flavanol metabolites in tissues was examined in Wistar rats (17-20 weeks of age) administered grape seed extract at doses of 0, 125, 250, 375, or 1000 mg/kg bw (n=1 for control group; n=3 for each experimental dose group). Tissue-specific distribution of flavanol metabolites was observed that was not dose-related. Most of the metabolites were found in the kidney with lesser amounts present in the liver. The predominant metabolites were glucuronidated metabolites in the kidneys, methyl-glucuronidated metabolites in the liver, free flavanols in mesenteric white adipose tissue and methylated metabolites in the brain (Margalef et al., 2015a).

In another study, male Wistar rats (8-weeks old) were fed 100 mg/kg bw grape seed polyphenol extract in a standard diet or a high-fat cafeteria-diet that included bacon, sausage, biscuits with paté, cheese, ensaimada (sweetened pastry), carrots, and sweetened milk for 12 weeks. Each group also had a control group which was not fed grape seed extract. No flavanol metabolites were measured in the plasma and few were detected in the liver, aorta, brain or mesenteric white adipose tissue 21 h after administration of the last dose of grape seed extract. The authors suggested that long-term administration of the polyphenol extract did not result in tissue accumulation of flavanols (Margalef et al., 2015b).

The bioavailability and distribution of flavanols and flavanol metabolites was compared in pregnant rats and female virgin rats (n=6/group). Animals received 1000 mg/kg bw of grape seed flavanols by oral gavage on day 19 of pregnancy. The distribution of the extract and metabolites to rat plasma, liver, white adipose tissue, brain, amniotic fluid, placenta and fetuses were assessed 1 and 2 h after administration. After 1 h, some phenolic compounds were present in plasma, and maximal plasma concentrations were attained at 2 h post-administration. The authors concluded that metabolism in the liver appeared to be reduced during pregnancy, and placental transport is inefficient for flavanols and metabolites of flavanols (Arola-Arnal et al., 2013).

Molinar-Toribio et al. (2018) examined the effect of diet on polyphenol metabolism. Adult female Wistar-Kyoto rats were fed a standard diet or a high-fat high-sucrose diet with or without grape seed extract (containing 30 mg/kg bw/day of PACs) for 16 weeks. Lower concentrations of PAC metabolites were observed in the urine and feces of the high fat-high high sucrose diet group than in the standard diet grape seed extract group, suggesting that substances in the high fat-high high sucrose diet may have inhibited absorption of polyphenols. There also was a tendency toward the formation of conjugated epicatechin metabolites in the high fat-high sucrose diet group (Molinar-Toribio et al., 2018).

Martineau et al. (2016) examined the effect of a polyphenol-rich grape and blueberry extract in beagle dogs (5 males and 1 female/treatment group). Animals were administered capsules containing no extract (control), or 4, 20, or 40 mg/kg bw/day of polyphenol-rich grape and blueberry extract for 24 weeks. Plasma metabolites of the extract were measured, including hydroxy- and dihydroxyphenyl-γ-valerolactone, metabolites of flavan-3-ols, derivatives of resveratrol, resveratrol glucuronide, dihydroresveratrol sulfate and glucuronide, quercetin, isorhamnetin sulfate, and the anthocyanin metabolite, malvidin. Peak concentrations of resveratrol metabolites were reached after 30 minutes, but peak concentrations of flavan-3-ol and flavanol metabolites were measured at 8 h post-administration. The authors also concluded that there was no evidence of renal or liver damage after 24 weeks of administration.

ADME studies have been carried out using a variety of grape-derived polyphenols. While studies have not been carried out specifically with Ruby or Gold Fermented Grape Pomace (Puree or Powder), the polyphenols in these products would be expected to follow a similar ADME as those described in the following studies.

D. Safety of Grape-derived Products

Safety studies have not been specifically carried out using whole grape pomace; however, a number of safety and toxicology studies have been carried out using other grape-derived products, primarily extracts with high polyphenol content, and are discussed here as evidence for safety of grape polyphenols in the diet.

1. Acute Toxicity Studies

A summary of acute toxicity studies using grape and grape seed extracts is shown in Table 18. The results support oral LD_{50} values of > 4,000 mg/kg bw/day in rats. In male mice, the oral LD_{50} value of a grape extract prepared from the edible portion of grape was >10,000 mg/kg (Zeghad et al., 2016). In female rats, the oral LD_{50} of a grape pomace extract was >2000 mg/kg (Mossa et al., 2015).

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Table 18. Summary of Acute Toxicity Studies Using Grape-Derived Extracts

Species / Sex	Test Article	Dose / Duration	Result / LD_{50}	Reference
Weanling Female Rats (Strain Not Reported)	Hydroethanolic grape pomace extract	2000 mg/kg bw by gavage; Single dose, 14-day observation	No toxicity seen; LD_{50} > 2000 mg/kg bw	Mossa et al. (2015)
Male Wistar Rats	Hydroethanolic grape seed extract (Containing 598.8 mg polyphenols/g)	0, 3000, 4630, 6380, 9000, or 12 650 mg/kg bw by gavage; Single dose, 14-day observation	Reduced feed intake & increased mortality at doses ≥ 6380 mg/kg bw; LD_{50} (probit analysis) = 6300 mg/kg bw	El-Adawi et al. (2006)
Male and Female F344 Rats	Grape seed water/ethanol extract (Gravinol Super™)	0, 2000, or 4000 mg/kg bw by gavage; Single dose, 14-day observation	No toxicity seen; LD_{50} > 4000 mg/kg bw	Yamakoshi et al. (2002)
Male and Female Albino Rats (Strain Not Reported)	ActiVin® grape seed extract	5000 mg/kg bw by gavage; Single dose, 14-day observation	LD_{50} > 5000 mg/kg bw One female animal died on day of dosing	Bagchi et al. (2001)
Adult Male Albino Mice	Methanol/water grape extract	0, 500, 2500, 5000 and 10,000 mg/kg bw by gavage; Single dose, 14-day observation	No toxicity seen; LD_{50} > 10,000 mg/kg bw	Zeghad et al. (2016)

bw – Body weight; g – Grams; kg – Kilograms; LD_{50} - Median (50%) lethal dose; mg - Milligrams

2. Subchronic Toxicity Studies

A summary of the subchronic toxicity studies is shown in Table 19. NOAELs from the studies in terms of polyphenol intake are provided if information about polyphenol content was mentioned in the studies.

Oral subchronic toxicity studies have been conducted using grape powder, and extracts of grape pomace, seeds and skin. The no observed adverse effect levels (NOAEL) in rats range from 0.5% (432 mg/kg bw/day) to 2.5% in the diet (1780 mg/kg bw/day in male rats and 2150 mg/kg bw/day in female rats, respectively). In one study in rats administered 5% grape pomace extract in feed, effects noted included histopathological changes in the parotid glands and proximal tubules of the kidney, increased platelets and decreased weight of adipose tissue (Inoue et al., 2013). The NOAEL in both genders was 1.0% (600 mg/kg bw/day in males and 700 mg/kg bw/day in females; corresponding to 552 mg/kg and 644 mg/kg bw/day of total polyphenols, respectively). In one study in dogs, administration of 15.0% (estimated 2000 mg/kg bw/day) grape color powder in feed was associated with decreased weight gain but no other adverse effects (Becci et al., 1983b). A recent study using wine extract in male rats found no effects when administered the equivalent of 25 mg/kg bw/day of grape polyphenols in drinking water (Tekos et al., 2023).

Using grape pomace and grape seed extracts, Bentivegna and Whitney (2002) determined a NOAEL in male and female rats of 2.5% in the diet, corresponding to approximately 1554 and 1877 mg/kg bw/day of total polyphenols (from pomace), and 1611 and 1946 mg/kg bw/day polyphenols (from seed), in males and females, respectively.

Table 19. Summary of Subchronic Toxicity Studies Using Grape-Derived Products

Study Setup and Details	Animal Study Details and Results	Reference
Material: Wine extract (containing 26.7% polyphenolic compounds) **Duration:** 14 days **Animals:** Male Wistar rats (6/group) **Dose:** 0 or 93.2 mg/kg bw (providing 25 mg/kg polyphenols), in drinking water	**Outcome Measurements:** • Clinical observations, body weight, growth rate, hematology, clinical chemistry, pathology, and histopathology. **Results and Significance:** • No effect of wine polyphenols was seen on body weight or growth rate, clinical signs, clinical chemistry, or pathology. • Histopathological examination revealed lesions in lungs in both treatment and control groups, which was determined to have occurred before start of study and was not related to treatment with wine extract. • NOAEL: 93.2 mg/kg bw/day (equivalent to 25 mg/kg bw/day polyphenols).	Tekos et al. (2023)
Material: Grape skin/pomace extract (containing 87.3% total phenols, 67.3% oligomers, 15.9% polymers, 16.7% monomers, 2.6% total anthocyanins) (MegaNatural™ GSKE) **Duration:** 90 days **Animals:** Crl:CD (Sprague-Dawley) IGS BR rats (20/sex/group) **Dose/Concentration:** 0 or 2.5%, in feed	**Outcome Measurements:** • FDA Redbook. Clinical observations, ophthalmology, feed consumption, body weight, hematology, clinical chemistry, organ weight, pathology. **Results and Significance:** • No deaths, abnormal clinical signs or effects of GSE were seen on ophthalmology, and no toxicologically significant effects of GSE hematology, clinical chemistry, organ weights, or pathology. • Decreased absolute and relative heart weights in females and increased occurrence of mild renal cortical inflammation in males receiving 2.5% in feed that were not considered to be related to treatment. • Increased feed consumption in males receiving 2.5% in feed that did not result in increased body weight. • NOAEL: 2.5% in the diet (1780 mg/kg bw/day in male rats and 2150 mg/kg bw/day in female rats, corresponding to approximately 1554 mg/kg bw/day and 1877 mg/kg bw/day of total polyphenols in male and female rats, respectively).	Bentivegna and Whitney (2002)
Material: Grape powder (containing 3830 mg/kg total polyphenols, 709.8 mg/kg anthocyanins, 22.06 mg/kg catechins) **Duration:** 6 weeks **Animals:** Young (1 month) and old (21 month) male F344 rats (7-8/group) **Dose/Concentration:** 0 or 1.5%, in water	**Outcome Measurements:** • Biomarkers of kidney toxicity and oxidative stress. **Results and Significance:** • NOAEL: 1.5% (estimated 1537 and 952 mg/kg bw/day, for young and old rats, respectively, corresponding to approximately 5.9 and 3.6 mg/kg bw/day of total polyphenols).	Pokkunuri et al. (2016)

Study Setup and Details	Animal Study Details and Results	Reference
Material: Grape pomace extract (containing >92% total polyphenols, >15% PAC, and >2% anthocyanins) exGrape®) **Duration:** 13 weeks **Animals:** F344/DuCrj rats (10/sex/group) **Dose/Concentration:** 0, 0.2%, 1.0%, 5.0%, in feed	**Outcome Measurements:** • Clinical observations, feed consumption, body weight, hematology, clinical chemistry, organ weight, pathology. Study was carried out according to OECD Guidelines. **Results and Significance:** • No effect of pomace extract on clinical signs, body weight, mean feed intake, hematology or clinical chemistry. • Diffuse hypertrophy and basophilia in the glandular epithelial cells of the parotid glands was observed in all male and female animals receiving 5.0% extract. • Number of renal proximal tubules with calcification was higher in the 5.0% group based on a semi-morphometric analysis. • Based on the histopathological changes in the parotid glands and proximal tubules of the kidney in the 5% group, the NOAEL in both genders was 1.0% (600 mg/kg bw/day in males and 700 mg/kg bw/day in females; corresponding to a minimum of 552 mg/kg and 644 mg/kg bw/day of total polyphenols, respectively). • An additional 4-week study in male F344 rats was carried out to examine the effect of 5.0% of grape pomace extract on the parotid gland and found it was an adaptive non-adverse effect that was reversible upon removal of the grape seed extract from the diet for two weeks (Inoue et al., 2014). Similar changes in the parotids were not observed in rats given the same dose of the grape seed extract by gavage but were observed in rats given 5.0% tannic acid in the diet, which suggested to the authors that the effect may have been due to astringency of the test material.	Inoue et al. (2013)
Material: Grape Seed Hydroethanolic Extract (89.3% PAC and 6.6% monomeric flavanols) (Gravinol Super™) **Duration:** 90 days **Animals**: F344/DuCrj rats (10/sex/dose) **Dose/Concentration:** 0%, 0.02%, 0.2% or 2%, in feed	**Outcome Measurements:** • Clinical observations, feed consumption, water intake, body weight, urinalysis, hematology, clinical chemistry, organ weight, pathology. **Results and Significance:** • No deaths or abnormal clinical signs. • No effect of GSE on body weight, water consumption, mean total food consumption, hematology, clinical chemistry, or urinalysis, and no effect on organ weights or pathology. • NOAEL: 2% in the diet (1410 mg/kg bw/day in males and 1501 mg/kg bw/day in females).	Yamakoshi et al. (2002)
Material: Grape Seed Extract (containing 90.5% total phenols, 74.9% oligomers, 14.7% polymers, 10.4% monomers) (MegaNatural™ GSE) **Duration:** 90 days **Animals**: Crl:CD (Sprague-Dawley) IGS BR rats (20/sex/group) **Dose/Concentration:** 0, 0.625, 1.25, or 2.5%, in feed	**Outcome Measurements:** • FDA Redbook. Clinical observations, ophthalmology, feed consumption, body weight, hematology, clinical chemistry, organ weight, pathology. **Results and Significance:** • No deaths or effects of GSE on ophthalmology, and no toxicologically relevant effect of GSE on hematology, clinical chemistry, organ weights, pathology. • Mild head tilt on the last two observation days (days 84 and 91) in 6/20 females given 2.5% grape seed extract that was of questionable relationship to test material administration. • Increased feed consumption in 2.5% group males that did not result in increased body weight.	Bentivegna and Whitney (2002)

Study Setup and Details	Animal Study Details and Results	Reference
	• NOAEL: 2.5% in the diet (1780 mg/kg bw/day in male rats and 2150 mg/kg bw/day in female rats, corresponding to 1611 mg/kg bw/day and 1946 mg/kg bw/day of total polyphenols in males and females, respectively).	
Material: Grape Seed Extract (containing 76.3% oligomeric polyphenols, 2.8% monomeric PAC, 0.5% phytosterols) (ActiVin®) **Duration:** 90 days **Animals:** Sprague-Dawley rats (20/sex/group) **Dose/Concentration:** 0, 0.5%,1.0% or 2.0%, in feed	**Outcome Measurements:** • Clinical observations, ophthalmology, feed consumption, body weight, hematology, clinical chemistry, organ weight, pathology. **Results and Significance:** • No deaths or abnormal clinical signs, and no toxicologically relevant effect of GSE on ophthalmology, hematology, clinical chemistry, organ weights, pathology. • Increased feed consumption in male and female rats fed GSE, particularly in male rats consuming 2.0%, but no effect on body weight. • NOAEL: 2% in the diet (1586 mg/kg bw/day for males and 1928 mg/kg bw/day for females, corresponding to approximately 1237 mg/kg bw/day and 1504 mg/kg bw/day in males and females, respectively).	Wren et al. (2002)
Material: Grape Color Powder (3% anthocyanins) **Duration:** 90 days **Animals:** Beagle dogs (4/sex/group) **Dose/Concentration:** 0, 7.5, or 15% of a grape powder containing 40% grape extract, in feed	**Outcome Measurements:** • Clinical observations, feed consumption, body weight, ophthalmology, urinalysis, hematology, clinical chemistry, organ weight, pathology. **Results and Significance:** • Decreased body weight gain at 15.0% but NOAEL assigned to this dose in GRN 446 (estimated 2000 mg/kg bw/day in terms of extract).	Becci et al. (1983b)
Material: Grape Seed Extract (composition not specified); *Vitis vinifera* from northern Tunisia **Duration:** 8 weeks **Animals: M**ale Wistar rats (6/group) **Dose/Concentration:** 0, 0.5%, 5.0%, 10%, 20%, in feed	**Outcome Measurements:** • Feed intake, body weight, relative weight of the brain, hippocampus, heart, liver, kidney and adipose tissue, standard hematology, plasma glucose, triglycerides, cholesterol, creatinine, urea, uric acid, ALT, AST, lactate dehydrogenase, and a number of inflammatory and antioxidant parameters. **Results and Significance**: • No significant effect of GSE on food consumption or body weight. • Red blood cell distribution width increased in all groups, but the effect was slight and not dose dependent. No effect of GSE on other red blood cell parameters. Increase in platelets in rats given ≥ 5% of the extract, which was also not dose dependent. • Increase in weight of the hippocampus in the 20% group and a significant decrease in the weight of adipose tissue in rats given ≥ 5% of the extract. • NOAEL: 0.5% in the diet (432 mg/kg bw/day).	Charradi et al. (2018)

ALT – Alanine tranaminase; AST – Aspartate aminotransferase; bw – Body weight; FDA – Food and Drug Administration; GRN – GRAS Notice; GSE – Grape seed extract; kg – Kilograms; NOAEL – No observable adverse effect level; OECD - Organisation for Economic Co-operation and Development; mg – Milligrams; PAC – proanthocyanidins

3. Chronic Toxicity Studies

Chronic toxicity studies carried out using grape seed extracts have shown that grape-derived polyphenols are well tolerated over repeated daily exposure of up to two years. NOAELs from the studies in terms of polyphenol intake are provided if information about polyphenol content was mentioned in the studies.

The chronic toxicity of grape seed extract (ActiVin®) was examined in male B6C3F1 mice (15-20 g). Grape seed extract was added to the diet to provide a dose of approximately 100 mg/kg bw/day of grape seed extract for 12 months, and mice were observed daily. The authors reported that there were no unusual deaths, and no significant changes in body weight or physical appearance. There was also no significant effect of the grape seed extract on weight or histopathology of the organs examined in the study (brain, heart, intestine, kidney, liver, lung, and spleen), no significant changes in serum enzymes (blood urea nitrogen (BUN), alanine transaminase (ALT), and creatinine kinase (CK) activity), and no hepatic DNA fragmentation (an index of oxidative damage) was observed by Ray et al. (2001). These results suggest a NOAEL for chronic toxicity of grape seed extract of at least 100 mg/kg bw/day, or approximately 78 mg/kg bw/day of polyphenols (based on a minimum total polyphenol content of 78% reported in GRN 124 (FDA, 2003a)).

In the same study, Ray et al. (2001) also evaluated the effect of grape seed extract in female B6C3F1 mice administered doses of 0, 100, 250, or 500 mg/kg bw/day in the diet, for 6 months. No significant differences in body weights or physical appearance were observed, and there was no effect of the grape seed extract on clinical chemistry parameters or organ histopathology, suggesting a NOAEL of at least 500 mg/kg bw/day, or approximately 390 mg/kg bw/day of total polyphenols.

Another study examined the effect of grape seed extract (Gravinol Super™) on UVB-induced photocarcinogenesis in 7-week-old SKH-1 hairless mice. The grape seed extract used contained 89.3% PAC (74.8% oligomers, 6.6% dimers, 5.0% trimers and 2.9% tetramers), 6.6% monomeric flavanols (2.5% (+)-catechin, 2.2% (-)-epicatechin, and 1.4% (-)-epigallocatechin), and 0.5% (-)-epigallocatechin-3-gallate). While not designed specifically to assess safety, mice were fed grape seed extract at concentrations of 0, 0.2%, or 0.5% (w/w) in the diet for 30 weeks, and an additional group was fed 1.0% (w/w) extract but not subjected to irradiation protocol to assess the effect of the grape seed extract alone. On day 15, control mice and mice receiving 0.2% and 0.5% extract were irradiated every day with UVB for a total of 10 days. One week after the last UVB exposure, mice were irradiated three times a week for a total of 30 weeks from the last exposure (which served at the tumor promoter). Endpoints monitored included weekly food consumption, biweekly body weight, physical characteristics of spleen, liver and kidney, total body mass, total bone mineral density, total bone mineral content, tumor incidence and tumor multiplicity. Administration of grape seed extract resulted in a dose-dependent decrease in photocarcinogenesis compared to control irradiated mice, and there were no adverse effects of grape seed extract on any other parameter measured in the study. No tumors were observed in mice fed 1.0% extract. There was no effect on body weight gain or loss in mice fed grape seed extract. Grape seed extract (0.2% or 0.5%) significantly decreased tissue fat levels without changing the total body mass of animals compared to control animals. Grape seed extract also had no effect on organ weights (liver, spleen, kidney). These results suggest that long-term feeding of 1.0% grape seed extract alone did not induce a carcinogenic effect, and no adverse effects were observed in irradiated mice fed 0.2% or 0.5%. Based on estimated initial body weight and feed consumption of 23 g and 2.88 g/day, respectively (Dinkova-Kostova et al., 2008), the estimated dose of the grape seed extract is estimated to be 1252 mg/kg bw/day (Mittal et al., 2003).

4. Reproductive and Developmental Toxicity Studies

A study in Sprague-Dawley rats was carried out by Becci et al. (1983a) to examine the effect of grape color extract (Welch's Special Grape Color Powder Type BW-AT) on reproductive performance of two generations of animals, and was described in detail in GRN 446 (FDA, 2013). The test article used contained 40% (w/w) grape color extract in a maltodextrin carrier, no further information on phenolic content was specified. Groups of male and female Sprague-Dawley rats (n=25/sex; 160-180 g) were provided feed containing 0, 7.5, or 15% grape color powder. A fourth group of 15 rats/sex received feed containing 9% maltodextrin. After 3 weeks of feeding the respective diets, all F0-generation rats were paired, one male to one female within groups. Female F0 rats were fed test diets throughout mating, gestation, and lactation, and selected F1-generation male and female rats continued on a 13-week subchronic feeding study, receiving the same test diet as the parents. Grape color extract at 7.5% or 15% in the diet had no adverse effects on reproductive performance. Body weights for F0 and F1 generation pups at both dose levels were significantly lower than those of control pups at 21 days after birth. Body weight gain of F1-generation female rats in the 15% dose group was also reduced compared to the control group. The authors suggested that since there was no significant difference in food-conversion data between groups, the decrease in body-weight gain may have been the result of the lower calorific value of the feed supplemented with the grape color powder compared with the control diet. The authors concluded that there was no evidence of toxicity of pathological effects in rats fed grape powder through two generations (Becci et al., 1983a). While a NOAEL for the study was not determined by the authors, a NOAEL of 15% of the diet, or 10,000 mg/kg bw/day (4000 mg/kg bw/day in terms of the extract) was assigned for both reproductive effects and subchronic toxicity in GRN 446 (FDA, 2013).

Althali et al. (2019) examined the effect of grape seed extract on maternal and developmental toxicity of zearalenone in pregnant Swiss albino mice. Mice were treated orally by gavage with grape seed extract (150 mg/kg bw/day), zearalenone (25 mg/kg bw/day), or grape seed extract and zearalenone. Untreated and vehicle-treated (corn oil) groups were also included. The PAC content of the extract was not reported, however it included gallic acid (2.02 ± 0.13 mg/g), vanillin (1.31 ± 0.05 mg/g), coumaric acid (0.07 ± 0.01 mg/g), and quercetin (0.2 ± 0.02 mg/g). The zearalenone and the grape seed extract were provided by gavage during days 6-13 and 0-19 of gestation, respectively. The dams were terminated by cervical dislocation on day 19 of gestation and uterine horns were removed. The numbers of implants, resorptions, hematoma, and live/dead fetuses in each uterus were counted. Live fetuses were removed from the uterus, weighed, measured for body length, and examined for gross malformations. Dams and fetuses were further evaluated for various maternal and developmental parameters. Half of the fetuses were weighed and examined for length and soft tissue anomalies and other fetuses were placed in ethanol (95%) followed by alizarin red staining for evaluation of skeletal anomalies. No adverse effects of grape seed extract alone were observed compared to control animals, and the extract did not exacerbate the adverse effects of zearalenone in dams and fetuses (Althali et al., 2019).

Another recent study in male albino rats (200-250 g, 8/group) examined the effect of grape seed extract on cadmium-induced testicular toxicity. Animals were administered saline (control), cadmium (5 mg/kg bw/day), grape seed extract (100 mg/kg bw/day), or cadmium plus grape seed extract, orally by gavage for 30 days. To prevent interactions, cadmium was given in the morning and grape seed extract in the afternoon. At the end of the study, animals were euthanized, and the testes were removed, weighed, and sectioned and stained with hematoxylin and eosin. They also were stained immunohistochemically for detection of expression of proliferating cell nuclear antigen (PCNA). Both negative control and grape seed extract-only groups showed a normal testicular architecture. In these two groups, positive nuclear PCNA immunoreactivity was observed in the vast majority of the spermatogenic cells of almost all seminiferous tubules, while negative immunoreactivity was observed in the cadmium group (Morsi et al., 2020).

5. Mutagenicity and Genotoxicity Studies

Genotoxicity studies that have been carried out using grape skin and grape seed extracts are summarized in Table 20 and have been uniformly negative. These include studies for both mutagenicity and clastogenicity.

Table 20. Summary of Genotoxicity Studies Using Grape Extracts

Study Type / Details	Test Material / Dose	Result	Reference
Study Design: *In vitro* **Study Type:** Ames **Strains:** *S. typhimurium* TA97, TA98, TA100, and TA1535 **Controls: W**ater; 2-Aminoanthracene, Sodium Azide, 9-Aminoacridine, 4-Nitro-O-Phenylenediamine	**Test Material:** Grape seed extract (constituents not specified). **Dose Levels:** 0, 100, 333, 1,000, 3,333, and 10,000 µg/plate, with and without S9.	Negative	NTP (2003)
Study Design: *In vitro* **Study Type:** Ames **Strains:** *S. typhimurium* TA97, TA98, TA100, and TA102 **Controls:** Water; 4-Nitroquinoline 1-oxide, 2-Nitrofluorene, Sodium Azide, Mitomycin C, 2-Aminofluorene, 2-Aminoantracene, and Benzo[*a*]pyrene	**Test Material:** *V. labrusca* (Isabel varietal) Grape skin water/ethanol extract, containing 10.% total phenolics, 5.5% PAC. **Dose Levels:** 0, 0.1, 1, 10, and 100 µg/mL, with and without S9.	Negative	Aiub et al. (2004)
Study Design: *In vitro* **Study Type:** Ames **Strains:** *S. typhimurium* TA98, TA100, TA1535, and TA1537 **Controls:** Water; Benzo[*a*]pyrene, 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide, 2-aminoanthracene, Sodium Azide, 9-Aminoacridine hydrochloride monohydrate	**Test Material:** Grape seed water/ethanol extract (Gravinol Super™), containing 89.3% total phenolics, 6.6% monomeric flavonols. **Dose Levels:** TA98 and TA100: 0, 19, 39, 78, 156, 313, 625, and 1250 µg/plate TA1535 and TA1537: 0, 156, 313, 625, 1250, 2500, and 5000 µg/plate.	Negative	Yamakoshi et al. (2002)

Study Type / Details	Test Material / Dose	Result	Reference
Study Design: *In vitro* **Study Type:** Chromosome Aberration Assay **Strains:** *E. coli* PQ35, PQ37, PQ65, OG40, and OG100 **Controls:** Water; Aflatoxin B1 and 4-Nitroquinoline 1-oxide	**Test Material:** *V. labrusca* (Isabel varietal) grape skin water/ethanol extract, containing 10.% total phenolics, 5.5% PAC. **Dose Levels:** 0, 0.1, 1, 10, and 100 µg/mL, with and without S9.	No increase in induction of the SOS function sfiA (Negative)*	Aiub et al. (2004)
Study Design: *In vitro* **Study Type:** Comet Assay **Cells:** 3T3 fibroblasts from Balb/c mice **Controls: W**ater; Hydrogen peroxide	**Test Material:** *V. labrusca* (Isabel varietal) Grape skin water/ethanol extract, containing 10.% total phenolics, 5.5% PAC. **Dose Levels:** 0, 0.1, 1, 10, and 100 µg/mL, with and without S9.	Negative	Aiub et al. (2004)
Study Design: *In vitro* **Study Type:** Chromosome Aberration Assay **Cells:** Chinese hamster lung cells **Controls: W**ater; Benzo[*a*]pyrene, 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide, 2-aminoanthracene, Sodium Azide, 9-Aminoacridine hydrochloride monohydrate	**Test Material:** Grape seed water/ethanol extract (Gravinol Super™), containing 89.3% total phenolics, 6.6% monomeric flavonols. **Dose Levels:** 0, 18.8, 37.5, and 75 µg/mL in the 6-hour incubation without S9; 0, 9.4, 18.8, and 37.5 µg/mL in the 24 and 48-hour incubation without S9; 0, 18.8, 37.5, 75, 150, and 300 µg/mL in the 6-hour incubation with S9.	Negative	Yamakoshi et al. (2002)
Study Design: *In vivo* **Study Type:** Micronucleus Test **System:** Male ddY mice **Controls: W**ater; Mitomycin C	**Test Material:** Grape seed water/ethanol extract (Gravinol Super™), containing 89.3% total phenolics, 6.6% monomeric flavonols. **Dose Levels:** 2 doses of 0, 500, 1000, or 2000 mg/kg bw separated by 24 hours.	Negative	Yamakoshi et al. (2002)
Study Design: *In vivo* **Study Type:** Micronucleus Test **System:** Male Crl:CD-1® (ICR) BR mice **Controls:** 0.5% aqueous carboxymethylcellulose; Cyclophosphamide dissolved in sterile deionized water	**Test Material:** MegaNatural™ grape seed extract, containing 90.5% total phenolics. **Dose Levels:** 0, 500, 1000, and 2000 mg/kg bw in the 24-hour incubation without S9; 0 and 2000 mg/kg bw in the 48-hour incubation without S9.	Negative	Erexson (2003)
Study Design: *In vivo* **Study Type:** Micronucleus Test **System:** Male Crl:CD-1® (ICR) BR mice **Controls:** 0.5% aqueous carboxymethylcellulos; Cyclophosphamide dissolved in sterile deionized water	**Test Material:** MegaNatural™ grape seed extract, containing 87.3% total phenolics, 2.6% anthocyaninins. **Dose Levels:** 0, 500, 1000, and 2000 mg/kg bw in the 24-hour incubation without S9; 0 and 2000 mg/kg bw in the 48-hour incubation without S9.	Negative	Erexson (2003)

bw – Body weight; C – Celsius; GSE – Grape seed extract; h – Hours; kg – Kilograms; mg – Milligrams; mL – Milliliters; NaCl – Sodium chloride; PAC – Proanthocyanidin; W – Watt; µg – Micrograms

* A positive result was observed for PQ37 at 100 µg/ml in the presence of S9. The authors noted that the PQ37 strain used in the SOS Chromotest lacked the ability for nucleoside excision repair and did not consider the positive result in this strain at a high concentration to be relevant and concluded that that the results suggest that grape skin extract is not mutagenic.

6. Studies in Humans

Results of human studies providing safety information are summarized in the following sections. Clinical studies have been carried out using grape juice, grape skin, and grape and grape seed extracts.

a. Reviews

Numerous clinical studies have been carried out using grape powder, grape pomace, grape juice, and whole grape, grape seed, and grape skin extracts, at doses ranging from 22.4 mg to 2547 mg/day, and as high as 92 g/day of grape powder.

Zamani et al. (2022) conducted a systematic review and meta-analysis of 11 clinical studies to assess the effect of grape products on liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), in adults. While the studies were not carried out to assess safety, the authors concluded that supplementation with grape products had no adverse effects on ALT, AST, and ALP when administered for durations longer than 12 weeks. Another meta-analysis of 8 clinical studies including 291 participants concluded that grape products had no adverse effect on liver enzymes. Studies included used grape seed extract, grape extract, and grape powder, at doses of 200-400 mg/day, 350-2,000 mg/day, and 60-92 g/day (Ghaffar et al., 2022).

While these studies were not designed to assess safety, the large number of participants and lack of reported adverse events help support a conclusion of safety.

b. Uncontrolled Clinical Studies

Safety studies have been carried out using various grape-derived preparations, including grape juice, grape skin, and grape and grape seed extracts, and have shown good tolerability. Increasing doses of up to 4000 mg/day of grape skin extract for over more than 19 months, and up to 2500 mg/day of grape seed extract for 4 weeks, have been reported with good safety profiles. A grape extract containing 1600 mg/day of total phenolics was shown to be safe and well-tolerated when used for a median duration of 8 weeks (29% of patients continued longer than 16 weeks) in cancer patients.

A Phase I study was carried out to examine the safety, tolerability, and dose determination of powdered muscadine grape skin extract in 14 men (median age 61 years) with prostate cancer. Each 500 mg capsule of grape skin extract contained approximately 1.2 mg of ellagic acid, 9.2 μg of quercetin, and 4.4 μg of resveratrol. Using a modified continual reassessment method with 2 patients per cohort, dose escalation continued from 500 mg/day through 1000 mg/day, 2000 mg/day, and 3000 mg/day up to the maximum dose of 4000 mg/day (n=6). Treatment cycles consisted of once daily oral dosing of powdered grape skin on days 1 through 28. No patient experienced dose limiting toxicities and all patients were escalated to the highest dose level of 4000 mg/day. All adverse events were reported as grade 1 events, and patients continued on therapy for a median of 19.8 months with no tolerability issues. No serious adverse events were reported with the study. Grade 1 events were primarily gastrointestinal (36%), such as flatulence, soft stools, abdominal distension, and eructation. The authors concluded that the safety and dose-finding study demonstrates that powdered muscadine grape skin is safe and tolerable up to a dose of 4000 mg/day (Paller et al., 2015).

Another Phase I study was carried out to assess the safety and maximum tolerated dose of muscadine grape extract (MGE) in cancer patients. Twenty-three patients (mean age 72 years) received MGE at five dose levels, corresponding to 320 to 1600 mg total phenolics per day. The major compounds found in the extract included epicatechin (22.0 ± 0.7 ng/g), gallic acid (13.5 ± 0.6 mg/g), procyanidin B (7.1 ± 0.3 mg/g), ellagic acid (4.7 ± 0.4 mg/g), catechin (2.7 ± 0.1 mg/g) and catechin gallate (1.8 ± 0.1 mg/g); other phenolics including resveratrol, quercetin and myricetin were below the detection limit (< 0.1 mg/g). Safety and maximum tolerated dose (MTD) were assessed at 4 weeks. Adverse events were assessed at each study visit and were considered attributable to MGE if possibly, probably, or definitely related. Dose-limiting toxicity (DLT) was defined as grade 3 gastrointestinal side effects possible, probably, or definitely attributable to treatment or any grade 4 or 5 adverse event attributable to treatment. The MTD was defined as the dose level immediately below the dose level that induced a DLT in ≥ 2 patients. The expected adverse events with MGE administration were flatulence, diarrhea, nausea, dyspepsia, and abdominal cramping. After 4 weeks, possibly attributable adverse events grade 2 or higher were fatigue (n=1), decreased lymphocyte count (n=1), and constipation (n=2), including one dose limiting toxicity for grade 3 constipation. The MTD was not reached. The median time on therapy was 8 weeks, and 29% of patients were treated beyond 16 weeks. The authors concluded that grape extract was safe and well-tolerated in older cancer patients at all doses tested (Bitting et al., 2021).

A four-week safety assessment of a PAC-rich grape seed extract (Gravinol-S; containing 80% PAC) was carried out in healthy subjects. Twenty-nine healthy Japanese subjects were randomized into three groups and received either 1,000, 1,500, or 2,500 mg GSE (corresponding to 800, 1,200, and 2,000 mg PAC) for 4 consecutive weeks, followed by an additional 2-week follow-up. Parameters measured included blood platelet count, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red blood cells, white blood cells, ALT, albumin, albumin/globulin ratio (A/G ratio), ALP, AST, BUN, calcium, chloride, creatinine, creatinine phosphokinase (CPK), iron (Fe), ferritin, gamma-glutamyl transpeptidase, glucose, HbA1c, high-density lipoprotein cholesterol, inorganic phosphorus, potassium, lactate dehydrogenase (LDH), LDL cholesterol, sodium, total bilirubin, total cholesterol, total protein, triglycerides and uric acid. Adverse events and changes to body weight, blood pressure and pulse rate were also monitored. None of the subjects had any significant adverse events, abnormal physical signs, or abnormal biological measurements during the study, based on the physicians' evaluation. Six subjects experienced mild AEs including nausea, constipation, diarrhea, and headache. These AEs were experienced by one of the ten subjects in the 1,000 mg group, three of the nine subjects in the 1,500 mg group, and two of the ten subjects in the 2,500 mg group. However, the AEs were mild and transient, and participants continued in the study. The lack of a placebo group in the study complicated assignment of the AEs to GSE administration. One male subject in the 1,000 mg group had elevated CPK in post-week 2, which was considered by the investigator to be due to intense physical exercise on the previous day. In addition, two male subjects in the 2,500 mg group had increased CPK and LDH above normal range on week 4, which had returned to normal range in the

2-week follow-up. The investigators concluded that neither increase was clinically significant nor related to GSE intake. The authors also reported that 2 of the male subjects in the 2,500 mg group had baseline serum Fe levels above the normal range that decreased to below the normal range on Week 2 and returned to baseline levels at the 2 week follow up visit. However, since no effect of GSE intake was observed on other parameters related to serum Fe, the authors concluded that the effect was not clinically relevant. The authors concluded that daily GSE consumption of up to 2,500 mg is generally safe and well tolerated in healthy subjects when taken orally but may possibly induce mild inhibition of iron absorption in some people (Sano, 2017).

Another small study examined the safety, tolerability, and MTD of a standardized grape seed extract (GSE) complexed with soy phospholipids (standardization not reported). Eight subjects (ages 46-68 years) with lung cancer (heavy active and former smokers) were treated with increasing doses of GSE for 3 months. Subjects received 450 mg/day for week 1,900 mg/day for week 2, 1,350 mg/day for week 3, and 1,800 mg/day for the rest of the treatment duration (3 months) as tolerated. No significant changes were observed in blood pressure, heart rate, or lipid panels. One of the 6 subjects had an isolated, mild (grade 1) increase in AST at the month 3 visit (last scheduled blood draw), which returned to within normal limits upon retest a week later. The authors concluded that the GSE was well tolerated at the maximum dose of 1,800 mg/day (Mao et al., 2019).

c. Controlled Clinical Studies

Results of twelve human clinical studies that included safety endpoints are summarized below. Two acute studies used high doses: Garcia-Diez et al. (2021) treated 25 subjects with 46 grams of grape powder, and Shin et al. (2015) treated 20 subjects with 1,050 mg grape polyphenols. In longer-term studies, treatment periods ranged from 14 days to 24 months, with doses including 2 g/day of grape extract for 8 weeks (Hokayem et al., 2013), and 12 g of grape powder (containing 500 mg polyphenols) for 5 weeks (Janiques et al., 2014), with no adverse events reported. Annunziata et al. (2019) reported the use of 800 mg/day of polyphenol-rich grape pomace extract for 8 weeks with no adverse events reported.

These studies are included here to provide supporting evidence that grape products and grape-derived polyphenols have no harmful effects on humans at the doses tested.

A summary of these studies is shown in Table 21.

Table 21. Summary of Controlled Clinical Trials with Grape-derived Products

Substance Tested and Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
Grape skin extract 800 mg/day (anthocyanin oligomers)	108 patients with mild-to-moderate dry eye disease	Randomized, double-blind, placebo-controlled study; 12 weeks	Grape skin extract had no adverse effects on dry eye symptoms. No significant difference in safety parameters monitored (liver function markers AST and ALT) between groups. One AE (epigastric pain)	Fan et al. (2023)

Substance Tested and Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
			reported in the test group and patient withdrew from study.	
Grape seed extract 100 mg/day	42 adolescents with metabolic syndrome	Randomized, double-blind, placebo-controlled, parallel group study; 16 weeks	GSE had no adverse effects on insulin concentration and insulin resistance. No AEs were reported.	Mohammad et al. (2021)
Grape seed extract 300 mg/day (285 mg PAC)	80 healthy subjects with mild hypertension	Randomized, double-blind, placebo-controlled, parallel group study; 16 weeks	GSE did not increase blood pressure. Test material was very well tolerated. In the placebo group, two SAEs were reported and occurred accompanied with hospitalization, but no SAEs were reported in GSE group. None of the AEs observed were related to the treatment. No safety issues were identified checking the routine blood parameters.	Schon et al. (2021)
Grape pomace extract 800 mg/day	213 healthy subjects	Randomized, double-blind, placebo-controlled, 2-arm-parallel group study; 8 weeks	Treatment had no adverse effects on parameters measured (serum trimethylamine-N-oxide and oxidative stress biomarkers). No AEs were reported.	Annunziata et al. (2021)
Grape seed extract 300 mg/day (255 mg polyphenols)	40 obese or overweight subjects	Randomized, double-blind, placebo-controlled study; 12 weeks	GSE had no adverse effects on blood lipid profile when accompanied by a restricted-calorie diet. No AEs were reported.	Yousefi et al. (2021)
Grape seed PAC extract 150 mg/day	124 patients with non-proliferative diabetic retinopathy	Randomized, multi-center, double-blind, placebo-controlled study; 12 months	GSE had no adverse effects on hard exudates, a feature of diabetic macular edema. AEs between groups were not statistically significant. No statistically or clinically relevant evidence of difference among the treatment groups with regard to vital signs and laboratory results.	Moon et al. (2019)
Grape extract 250 mg/day	111 healthy older adults	Randomized, double-blind, placebo-controlled, parallel study; 12 weeks	No adverse effects of grape extract on cognitive parameters. No AEs were reported.	Calapai et al. (2017)
Grape powder 12 g/day (500 mg polyphenols)	34 clinically stable hemodialysis patients	Randomized, double-blind, placebo-controlled study; 5 weeks	No adverse effects of Grape powder on parameters measured (CRP and glutathione peroxidase). No AEs were reported.	Janiques et al. (2014)

Substance Tested and Dose	Population Characteristics	Study Design and Duration	Noted Effects Safety Parameter Results	Reference
Grape extract 2 g/day	38 healthy overweight/obese first-degree relatives of type 2 diabetic patients, fed fructose during last 6 days of study	Randomized, double-blind, placebo-controlled study; 8 weeks	Eight weeks of grape extract had no effect on CRP, AST, ALT, γ-glutamyl transpeptidase, triglycerides, cholesterol, fasting glucose or insulin levels, blood GSH/GSSG ratio, erythrocyte SOD, muscle enzymatic activities of catalase, glutathione peroxidase, SOD, plasma cytokines (IL-1α, IL-1β, IL-6, IL-4, TNF-α, and interferon-γ), adipokines (adiponectin, leptin, and resistin), or ghrelin compared to the placebo group. No AEs were reported.	Hokayem et al. (2013)
Grape seed extract 200 mg/day (190 mg PAC)	51 patients with seasonal allergic rhinitis and skin prick test sensitivity to ragweed	Randomized, double-blind, placebo-controlled study; 8 weeks	No adverse events were related to test material and no significant laboratory abnormalities were reported.	Bernstein et al. (2002)
Grape powder 46 g/day	25 metabolically healthy obese subjects	Randomized, double-blind, placebo-controlled, acute trial; 1 day	An acute dose of grape powder did not affect postprandial glucose and lipid elevations. No AEs were reported.	Garcia-Diez et al. (2021)
Grape extract derived from red and white grape seeds and skins 500 or 1500 mg/day (350 and 1050 mg polyphenols)	20 healthy, non-obese men	Randomized, double blind, placebo-controlled, three arm, cross-over design; 1 day	Grape extract had no effect on postprandial hunger or fullness. Test material was well tolerated with no reports of gastrointestinal symptoms or other AEs during the study.	Shin et al. (2015)

AE – Adverse event; ALT - Alanine transaminase; AST - Aspartate aminotransferase; CRP – C-reactive protein; g – Grams; GSE – Grape seed extract; IL – Interleukin; mg – Milligrams; mL – Milliliters; PAC – Proanthocyanidins; SAE – Serious adverse event; SOD – Superoxide dismutase; TNF – Tumor necrosis factor

E. GRAS Criteria

FDA defines "safe" or "safety" as it applies to food ingredients as:

> "…reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."[7]

[7] See 21 CFR 170.3 (e)(i) and 81 FR 54959 Available at: https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe

Amplification is provided in that the conclusion of safety is to include probable consumption of the substance in question, the cumulative effect of the substance and appropriate safety factors. It is FDA's operational definition of safety that serves as the framework against which this evaluation is provided.

Furthermore, in discussing GRAS criteria, FDA notes that:[7]

> "…General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances directly or indirectly added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use."
>
> "'Common knowledge' can be based on either "scientific procedures" or on experience based on common use of a substance in food prior to January 1, 1958."

FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called "common knowledge element," in terms of the two following component elements:

- Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and
- There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of expert panels or opinions from authoritative bodies, such as JECFA and the National Academy of Sciences.

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. General recognition of safety through scientific procedures shall be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods.

The apparent imprecision of the terms "appreciable," "at the time," and "reasonable certainty" demonstrates that the FDA recognizes the impossibility of providing absolute safety in this or any other area (Lu, 1988; Renwick, 1990; Rulis and Levitt, 2009).

As noted below, this safety assessment to ascertain GRAS status for Ruby and Gold Fermented Grape Puree and Powder for the specified food uses meets FDA criteria for reasonable certainty of no harm by considering both the technical and common knowledge elements.

F. Expert Panel Findings on Safety of Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder

An evaluation of the safety and GRAS status of the intended use of Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder has been conducted by an Expert Panel convened by GRAS Associates; the Panel consisted of Name, Credentials; Name, Credentials; and Name, credentials, as Panel Chair. The Expert Panel reviewed Crush Dynamics, Inc.'s dossier as well as other publicly available information available to them. The individuals who served as Expert Panelists are qualified to evaluate the safety of foods and food ingredients by merit of scientific training and experience.

The GRAS Expert Panel report is provided in Appendix 11.

G. Common Knowledge Elements for GRAS Conclusions

The first common knowledge element for a GRAS conclusion requires that data and information relied upon to establish safety must be generally available; this is most commonly established by utilizing studies published in peer-reviewed scientific journals. The second common knowledge element for a GRAS conclusion requires that consensus exists within the broader scientific community.

1. Public Availability of Scientific Information

The majority of the studies reviewed have been published in the scientific literature as summarized in Part 6. These include studies using a variety of grape-derived products, including pomace and grape extracts. In addition, previous GRAS notices for grape-derived products, including grape pomace extracts, have received "no questions" letters from FDA, including GRN 124, GRN 125 and GRN 446.

2. Scientific Consensus

The second common knowledge element for a GRAS conclusion requires that there be a basis to conclude that consensus exists among qualified scientists about the safety of the substance for its intended use.

Crush Ruby and Gold Fermented Grape Puree and Powder are produced by fermentation of grape pomace that is produced during the winemaking process and is produced according to Current Good Manufacturing Practices (cGMP) using food grade materials. Crush Dynamics, Inc. has established sufficient rigorous product specifications and has demonstrated batch-to-batch consistency against these specifications.

A number of well-respected regulatory agencies, including Health Canada and FSANZ, have indicated that grape- and grape pomace-derived products and polyphenols are safe for human consumption (FSANZ, 2023; Health Canada, 2018b; Health Canada, 2018a). Four grape-derived extracts, including two grape pomace extracts, have been notified as GRAS to FDA, and have consistently yielded "no questions" letters.

Ruby and Gold Fermented Grape Puree and Powder contain whole pomace, including grape solids (carbohydrates and dietary fiber), thus the relative content of polyphenolic compounds (on a dry weight basis) is lower than that reported for grape-derived extracts (e.g., as described in GRN 125 and GRN 446) which have been selectively concentrated. However, safety studies have been carried out showing the safe use of various grape-derived polyphenolic extracts containing specified amounts of total polyphenols which allow for comparison to the total polyphenols provided by Ruby and Gold Fermented Grape Puree and Powder.

A number of toxicity studies have been carried out with grape products, including grape powder and grape pomace and seed extracts. A study on the reproductive effects of a grape color powder in rats used grape color extract at 0, 7.5, or 15% in the diet, and found no evidence of toxicity or pathological effects through two generations of animals. Based on this study, the authors of GRN 446 (exGrape® Total grape pomace extract) assigned a NOAEL of 15% in the diet, or 10 000 mg/kg bw/day for both reproductive effects and subchronic toxicity for the grape powder. In a 90-day subchronic toxicity study in rats, Bentivegna and Whitney (2002) determined the NOAEL for grape pomace extract and grape seed extract to be 2.5% in the diet of rats, corresponding to up to 1611 and 1946 mg/kg bw/day polyphenols in male and female rats, respectively. Based on the results of this study, and application of an uncertainty factor of 100, an ADI of 16.1 mg/kg bw/day and 19.5 mg/kg bw/day can be determined for male and female humans, respectively, corresponding to approximately 1128 mg/day and 1362 mg/day of grape polyphenols for a 70-kg male and female human, respectively. Similarly, using a safety factor of 400, an ADI for infants and toddlers up to 2 years of age of 4.03 mg/kg bw/day and 4.9 mg/kg bw/day can be estimated for males and females, respectively. This would correspond to a maximum ADI of approximately 60.6 mg/day for males and 72.0 mg/day for females (at the 98th percentile body weight[8]).

A large number of human clinical studies have also been carried out with grape extracts, powders, pomace, and polyphenols, with doses including 500 mg/day of total polyphenols and have reported no adverse effects.

The mean and 90th percentile estimated daily intakes of Ruby and Gold Fermented Grape Pomace Powder from the intended use in foods for "all ages" is 2.09 g/day and 4.99 g/day (0.030 and 0.071 g/kg bw/day) respectively. Based on an average (per dry weight basis) total polyphenol content of approximately 3.5% in the Ruby and Gold Fermented Grape Purees and Powders, this would equate to an approximate mean and 90th percentile intake of 73.2 mg and 174.6 mg of total polyphenols in the "all ages" group. The mean and 90th percentile estimated daily intakes of Gold Fermented Grape Powder for adult males (the group with the highest estimated consumption) is 2.79 g/day and 6.39 g/day, respectively (corresponding to an estimated 97.6 mg/day and 223.6 mg/day of total polyphenols). The mean and 90th percentile estimated intakes of Ruby and Gold Fermented Grape Pomace Puree from the intended use in foods for "all ages" is 20.94 g/day and 49.90 g/day (0.300 and 0.711 g/kg bw/day), due to the 10-fold higher use level in Ruby and Gold Puree compared to

[8] Based on CDC/WHO growth chart data. Available at: https://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts (Accessed April 6, 2023)

Ruby and Gold Powder from the higher moisture content. However, on a dry weight basis this would not be expected to change the total polyphenol content, and estimated total polyphenol intakes would be similar to those described for the Ruby and Gold Powder. The 90th percentile intake is an overestimate of consumption and is based on the assumption that all of the foods would be consumed at the maximum consumption level each day. It is unlikely that consumers would consume all products containing Ruby or Gold Puree and Powders. The values for the 90th percentile intakes of polyphenols are below the ADI for polyphenols as estimated from the study by Bentivegna and Whitney (2002) of up to 1128 mg/day and 1362 mg/day of polyphenols, for 70-kg male and female adults, respectively. In male infants and toddlers less than 2 years of age the mean and 90th percentile estimated daily intakes of Ruby and Gold Fermented Grape Pomace Powder is 0.48 g/day and 1.39 g/day, respectively (0.0.043 and 0.125 g/kg bw/day). In female infants and toddlers less than 2 years of age the mean and 90th percentile estimated daily intakes of Ruby and Gold Fermented Grape Pomace Puree is 0.61 g/day and 1.51 g/day, respectively (0.053 and 0.120 g/kg bw/day). This corresponds to mean and 90th percentile polyphenol intakes of 16.8 and 48.7 mg/day in males, and 21.4 and 52.8 mg/day in females, respectively. These values are below the maximum ADIs of 60.6 mg/day and 72.0 for male and female infants/toddlers up to 2 years of age. Moreover, these values are below the amounts of grape products and polyphenols that have been used in human clinical studies without reported adverse events.

In summary, a compelling case can be made that scientific consensus exists regarding the safety of Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder.

H. Discussion of Information Inconsistent with GRAS Conclusion

The authors of this GRAS dossier are not aware of information that would be inconsistent with a finding that the proposed use of Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder in food is generally recognized as safe.

The regulatory framework for determining whether a substance is generally recognized as safe (GRAS) is in 21 CFR 170.30, which states that GRAS status through scientific procedures shall ordinarily be based upon published studies, which may be corroborated by unpublished studies and other data and information. These criteria have been applied to the existing data for Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder.

I. Conclusion

In consideration of the aggregate safety information available, Crush Dynamics, Inc. concludes that Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder as defined in the subject notification is safe for use in candy containing chocolate, condiments, meatless products, yogurt, and beverages, including carbonated drinks, fruit drinks, sports drinks, coffee, tea, nutritional drinks and nutritional powders. Ruby and Gold Fermented Grape Pomace (Puree and Powder) is not intended for use in infant formulas and meat and poultry products.

An ADI for whole grape pomace has not been established. An ADI for grape-derived polyphenols based on the NOAEL from a 90-day repeat dose oral toxicity study in male and female rats was determined to be 1128 mg/day and 1362 mg/day for a 70 kg male or female human, respectively. The dietary levels of total polyphenols from anticipated food consumption are not likely to exceed the ADI when Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder is used as proposed in this notification.

The weight of the publicly available evidence from studies with grape-derived products and grape polyphenols provide a basis upon which to conclude that the proposed uses of Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder as described in this dossier satisfy the safety standard of Reasonable Certainty of No Harm and are safe. Based on the pivotal, published data and information that are generally available, one may conclude that the proposed uses of Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder as produced consistent with current Good Manufactory Practice (cGMP) and meeting the food grade specifications presented above, are Generally Recognized As Safe (GRAS) based on scientific procedures. Support for these conclusions by a consensus of qualified experts in the general scientific community is provided in Appendix 11 (Expert Panel Report).

Accordingly, Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder as produced by Crush Dynamics, Inc. in accordance with FDA Good Manufacturing Practices and when it meets those specifications declared within the subject notification meets FDA's definition of safety in that there is "reasonable certainty of no harm under the intended conditions of use" as described herein and, therefore, is generally recognized as safe (GRAS).

PART 7. LIST OF SUPPORTING DATA AND INFORMATION IN THE GRAS NOTICE.

A. References

1. List of Acronyms

ADI	Average daily intake
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AOAC	Association of Official Agricultural Chemists
AST	Aspartate aminotransferase
a_w	Water activity
bw	Body weight
C	Celsius
CCP	Critical Control Points
cGMP	Current Good Manufacturing Practices
CPK	Creatinine phosphokinase
DLT	Dose-limiting toxicity
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
FCC	Food Chemicals Codex

FD&C	Food Drug and Cosmetic
FD&C Act	Federal Food Drug and Cosmetics Act
FDA	Food and Drug Administration
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
FEMA	Flavor Extract Manufacturers Association
FSANZ	Food Standards Australia-New Zealand
g	Grams
GA	GRAS Associates
GAE	Gallic acid equivalent
GMP	Good manufacturing practices
GPE	Grape pomace extract
GRAS	Generally Recognized as Safe
GRN	GRAS notification
GSE	Grape seed extract
GSKE	Grape skin extract
h	Hours
kg	Kilograms
L	Liters
LDH	Lactate dehydrogenase
mg	Milligrams
MGE	Muscadine grape extract
MRL	Maximum Residue Limits
Mt	Megatonnes
MTD	Maximum tolerated dose
MW	Molecular weight
NDIN	New Dietary Ingredient Notification
ng	Nanograms
NHANES	National Health and Nutrition Examination Survey
NOAEL	No-observed-adverse-effect level
NOAEL	No adverse effect level
OECD	Organisation for Economic Co-operation and Development
OPCs	Oligomeric proanthocyanidins
PAC	Proanthocyanidin
PCNA	Proliferating cell nuclear antigen
ppm	Parts per million
USDA	United States Department of Agriculture
USP	United States Pharmacopoeia
w/w	Weight/weight
µg	Micrograms

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B. Appendices

Appendix 1 Polyphenol Analysis

Appendix 1.1 Polyphenol Data

[Insert]

Appendix 1.2 Methodology

[Insert]

Appendix 2 Nutritional Analyses

See attached PDF.

Appendix 3 Attestation

[Insert]

Appendix 4 Food Safety Plan/HACCP Plan

[Insert]

Appendix 5 Pesticide Analysis

See attached PDF.

Appendix 6 Specifications

See attached PDF.

Appendix 7 Certificates of Analysis for Multiple Lots

See attached PDF.

Appendix 8 Stability Study Data

See attached PDF.

Appendix 9 Intake Analysis Report

[Insert]

Appendix 10 Mycotoxin Analysis

See Attached PDF

Appendix 11 GRAS Associates Expert Panel Report

The Generally Recognized as Safe (GRAS) Status of the Proposed Uses of Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder

Month Day, Year

Foreword

An independent panel of experts ("Expert Panel") was convened by GRAS Associates, LLC on behalf of their client, Crush Dynamics, Inc., to evaluate the safety and Generally Recognized as Safe (GRAS) status of Crush Dynamics, Inc.'s proposed uses of Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder in conventional foods. The members of this Expert Panel[†] are qualified to serve in this capacity by qualification of scientific training and experience in the safety of food and food ingredients.

GRAS Associates and [Company Name] ensured that all reasonable efforts were made to identify and select a balanced Expert Panel with expertise in food safety, toxicology, and nutrition. The Expert Panel was selected and convened in accordance with the Food and Drug Administration (FDA)'s guidance for industry on "Best Practices for Convening a GRAS Panel"[9]. Efforts were placed on identifying conflicts of interest or relevant "appearance issues" that could potentially bias the outcome of the deliberations of the Expert Panel and no such conflicts of interest or "appearance issues" were identified. The Expert Panel members received a reasonable honorarium as compensation for their time; the honoraria provided to the Expert Panel members were not contingent upon the outcome of their deliberations.

Discussion

A significant amount of safety information is generally available and has been discussed in Part 6 of this dossier. First, there is a history of safe consumption when used as an ingredient in food products in the U.S., Canada, South America, Europe, Asia, and Australia and New Zealand. Second, a number of experimental studies have investigated the safety. The composite evidence from historical safe consumption and experimental studies collectively demonstrate the safety of Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder for human food consumption.

Discuss safety summary as appropriate – history or use, previous GRNs, agency opinions, ADME, clinical studies, ADI/EDI, margin of safety, toxicity, etc.

[†] ADD brief experience summary of panelists, e.g. --- Dr. Emmel, Chair of the Expert Panel, is a chemist with substantial food safety experience in addressing steviol glycosides and other food ingredients. Dr. Kapp is a toxicologist with over 35 years of experience. He is a Fellow of the Academy of Toxicological Sciences, a Fellow of the Royal Society of Biology, and a European Registered Toxicologist.

[9] Available at: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm583856.htm

Estimated intake and safety discussion as appropriate. Therefore, Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder is expected to be safe within established allowable limits.

In summary, sufficient qualitative and quantitative scientific evidence in the composite is available to support the safety-in-use of Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder preparation given the following conditions:

Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder preparation continues to meet the designated specifications; and

Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder preparation is produced in accordance with Current Good Manufacturing Practices (CGMPs).

Conclusion

The Expert Panel critically reviewed the data provided by Crush Dynamics, Inc. for their Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder preparation, as well as publicly available published information obtained from peer-reviewed journals and other safety assessments prepared by other Expert Panels and well-respected international regulatory bodies.

The ingestion of Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder from the intended uses results in intakes that are safe within the limits of established historical use and published safety studies…EDI/ADI, etc. discussion

The Expert Panel unanimously concluded that the proposed uses of Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder preparation, manufactured as described in Part 2.B. of their dossier, and declared within the subject notification meets the FDA definition of safety in that there is "reasonable certainty of no harm under the intended conditions of use" as described herein, and Crush Dynamics, Inc.'s Ruby Fermented Grape Puree and Gold Fermented Grape Puree and Powder preparation is generally recognized as safe (GRAS).

It is also our opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, we have also concluded that [Ingredient name], when used as described in this dossier, is GRAS based on scientific procedures [or change to history of use if applicable].

Insert Signature Image

[NAME], [Credentials]
Chair

Insert Signature Image

[NAME], [Credentials]

Insert Signature Image

[NAME], [Credentials]

END