Toxicological profile for

Raisin extract, juice, concentrate

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

Not applicable.

1.2. Synonyms

Oils, raisin; Raisin extract (ChemIDplus)

1.3. Molecular formula

Unspecified (ChemIDplus)

1.4. Structural Formula

No data available to us at this time.

1.5. Molecular weight (g/mol)

No data available to us at this time.

1.6. CAS registration number

68915-86-6

1.7. Properties

1.7.1. Melting point

(°C): 38.91 (estimated) (EPISuite, 2017)

1.7.2. Boiling point

(°C): 265 (EPISuite, 2017)

1.7.3. Solubility

393.9 mg/L at 25°C (estimated) (EPISuite, 2017)

1.7.4. pKa

No data available to us at this time.

1.7.5. Flashpoint

(°C): No data available to us at this time.

1.7.6. Flammability limits (vol/vol%)

No data available to us at this time.

1.7.7. (Auto)ignition temperature

(°C): No data available to us at this time.

1.7.8. Decomposition temperature

(°C): No data available to us at this time.

1.7.9. Stability

No data available to us at this time.

1.7.10. Vapor pressure

0.000552 mmHg at 25°C (estimated) (EPISuite, 2017)

1.7.11. log Kow

2.54 (estimated) (EPISuite, 2017)

2. General information

2.1. Exposure

No data available to us at this time.

2.2. Combustion products

This ingredient was investigated in a pyrolysis study. Results are given in JTI Study Report (s).

Compound	Two stage heating		One stage heating	
	Abundance	Area%	Abundance	Area%
furfural	73034803	9.67	52949453	8.87
4,5-dimethylfurfural	24311393	3.22	12741637	2.13
2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one	27753766	3.67	21430208	3.59
5-formyl-2-furfurylmethanoate + unknown	5307296	0.70	7241778	1.21
5-hydroxymethylfurfural	554383267	73.37	397277787	66.53
levoglucosan	28298537	3.75	63657059	10.66
1,6-anhydro-beta-D-glucofuranose	21439975	2.84	30714636	5.14
Total ion chromatogram	755727000	100	597096345	100

This ingredient was investigated in a pyrolysis study. Results are given in Baker and Bishop (2005) J. Anal. Appl. Pyrolysis 74, pp. 145–170.

Ingredient	Max. cig.	Composition of pyrolysate	Max.

Name & CAS Number	appln. level (ppm)	(Compound, %)	level in smoke (µg)
Raisin extract	10,000	Hydroxymethylfurfural (22.8)	1,100
68915-86-6		Furfural (12.4)	620
		Benzene? And/or isovaleraldehyde (12.0)	600
		Acetic acid (5.3)	270
		Toluene (3.4)	170
		Phenol + cyclohexenone?	100
		Styrene (1.6)	80
		Benzofuran (0.5)	25
		Cresol (0.5)	25
		2-Butanone (0.4)	20
		Pyridine (0.2)	10
		2-Butenal (0.1)	5

2.3. Ingredient(s) from which it originates

No data available to us at this time.

3. Status in legislation and other official guidance

CAS RN 68915-86-6 is neither registered nor pre-registered under REACH (ECHA).

Marc de raisin, pepin de raisin, pulpe de raisin and pépins de raisin are all pre-registerd under REACH (“envisaged registration deadline 30 November 2010”; no CAS RNs given).

Tourteau de pépins de raisins is also pre-registered under REACH (“envisaged registration deadline 31 May 2013”; no CAS RN given) (ECHA, 2018).

CAS RN 68915-86-6 is not classified for packaging and labelling under Regulation (EC) No. 1272/2008 (ECHA, 2019).

Oils, raisin are listed in the US EPA Toxic Substances Control Act (TSCA) inventory, available at: https://iaspub.epa.gov/sor_internet/registry/substreg/searchandretrieve/searchbylist/search.do

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

No data available to us at this time.

4.2. Absorption, distribution and excretion

No data available to us at this time.

4.3. Interactions

“Resveratrol (RESV), present at concentrations of about 10 microM in red wine, has been found to inhibit events associated with tumor initiation, promotion and progression. The mechanism involved could be the inhibition of activities catalyzed by cytochromes P450 (CYPs), which activate procarcinogens. This led us to investigate the inhibitory effect of RESV on CYP1A, CYP2E1 and CYP3A enzymatic activities and to compare it to that of non volatile compounds present in red wine. Red wine solids (RWS) were prepared by evaporating one volume of red wine to dryness followed by reconstitution with five volumes of buffer (20% natural strength). CYP activities were determined in microsomes from rat liver, human liver or cells containing cDNA-expressed CYPs. Testosterone, chlorzoxazone, and ethoxyresorufin were used as selective substrates for CYP3A, CYP2E1 and CYP1A1/1A2, respectively. RESV and RWS were found to be irreversible (probably mechanism-based) inhibitors for CYP3A4 and non competitive reversible inhibitors for CYP2E1. Their inhibitory potency was assessed using IC(50) values that were found within

4-150 microM for RESV and 0.3-9% natural strength for RWS. Non volatile compounds of other beverages such as white wine, grape juice or Xtra Old Cognac(R) displayed lower inhibitory effect on CYP activities than RWS. When considering the concentration of RESV in red wine (2 microM for 20% natural strength), it appears that RSW inhibitory effect was not only due to RESV, but also to other compounds whose identification would prove to be worthwhile because of their possible chemopreventive properties." As taken from Piver B et al. Toxicol Lett. 2001 Dec 15; 125(1-3):83-91. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/11701226

"[...] Grape juice and prune juice had profound inhibitory effects on iron bioavailability. These inhibitory effects were likely due to high levels of polyphenolic compounds that bind and thereby prevent absorption of soluble Fe." As taken from Boato F et al. J Agric Food Chem. 2002 Nov 6; 50(23):6935-8. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12405800&query_hl=18&itool=pubmed_DocSum

"BACKGROUND: Grape and blueberry extracts are known to protect against age-related cognitive decline. However, beneficial effects achieved by mixing grape and blueberry extracts have yet to be evaluated in dogs, or their bioavailability assessed. Of concern to us were cases of acute renal failure in dogs, after their ingestion of grapes or raisins. The European Pet Food Industry Federation (2013) considers only the grape or raisin itself to be potentially dangerous; grape-seed extracts per-se, are not considered to be a threat. Our aim was therefore to evaluate the renal and hepatic safety, and measure plasma derivatives of a polyphenol-rich extract from grape and blueberry (PEGB; from the Neurophenols Consortium) in dogs. Polyphenol expression was analyzed by UHPLC-MS/MS over 8 hours, for dogs given PEGB at 4 mg/kg. Safety was evaluated using four groups of 6 dogs. These groups received capsules containing no PEGB (control), or PEGB at 4, 20, or 40 mg/kg BW/d, for 24 weeks. Blood and urine samples were taken the week prior to study commencement, then at the end of the 24-wk study period. Routine markers of renal and liver damage, including creatinine (Creat), blood urea nitrogen, albumin, minerals, alkaline phosphatase (ALP), and alanine transaminase (ALT) were measured. Biomarkers for early renal damage were also evaluated in plasma (cystatin C (CysC), and neutrophil gelatinase-associated lipocalin (NGAL)), and urine (CysC, clusterin (Clu), and NGAL). Ratios of urinary biomarkers to Creat were calculated, and compared with acceptable maximal values obtained for healthy dogs, as reported in the literature. RESULTS: While several PEGB-specific polyphenols and metabolites were detected in dog plasma, at the end of the PEGB consumption period, our biomarker analyses presented no evidence of either renal or liver damage (Creat, BUN, ionogram, albumin and ALT, ALP). Similarly, no indication of early renal damage could be detected. Plasma CysC, urinary CysC/Creat, Clu/Creat, and NGAL/Creat ratios were all beneath reported benchmarked maximums, with no evidence of PEGB toxicity. CONCLUSIONS: Long-term consumption of a pet specific blend of a polyphenol-rich extract from grape and blueberry (PEGB; from the Neurophenols Consortium), was not associated with renal or hepatic injury, and can therefore be considered safe. " As taken from Martineau AS et al. 2016. BMC Vet. Res. 12(1), 162. PubMed, 2017 available at: https://www.ncbi.nlm.nih.gov/pubmed/27487916

5. Toxicity

5.1. Single dose toxicity

No data available to us at this time.

5.2. Repeated dose toxicity

Bioactive component	Model	Dose used	Dose duration	End point	Reference
Red wine, grape juice	Anesthetized dogs	4 mL/kg intragastric	≈2 h	Improved coronary blood flow	[45]
Purple grape juice	Coronary artery disease patients	≈640 mL/d orally	14 d	Improved FDM, ↓ LDL oxidation	[29]
Purple grape juice	Human subjects	5-7 mL/kg/day orally	1 wk	↓platelet aggregation	[7]
Purple grape juice	Human subjects	7 mL/kg/day orally	14 d	↓platelet aggregation, ←NO release and ↓superoxide production	[6]
Grape extract	Sprague-Dawley rat	≥100 mk/kg/day orally	3 wk	←cardiac free radical scavenging	[14]
Concord grape juice	Hypertensive patients	5.5 mL/kg/day orally	8 wk	↓systolic BP 7.2 mm Hg and diastolic BP 6.2 mm Hg	[39]
Grape powder	ApoE° mice	150 µg total polyphenolsper day orally	10 wk	↓antherosclerotic lesions 41% ↓LDL oxidation	[31]
Red grape juice	HepG2 and HL60 cells	≈5 mL/L in culture medium	Up to 20h	Disrupt LDL trafficking in cells	[66]
Red grape juice	Hemodialysis patients	100 mL/d orally	14 d	↓MCP1, LDL and ApoB	[17]
Polyphenolic grape extract	Human platelets in vitro	Incubation of platelets in PEG up to 50 µg/mL	Up to 60 min	↓ platelet aggregation ↓ stimulated-[Ca^{2+}] Activation of PECAM-1	[47]

Grape-seed proanthocyanidin	Rats	100 mg/kg/day orally	3 wk	↓myocardial infarct size	[50]
Grape-seed proanthocyanidin	Rats	Up to 100 mg/kg/day orally	3 wk	↓ischemia/reperfusion injury ↓VF 70% free radical intensity ↓75%	[8]
Grape-seed proanthocyanidin	Hypercholesterolemic subjects	200 mg/d orally	8 wk	↓oxidized LDL in humans, ↓VF and tachycardia	[9]
Grape-seed proanthocyanidin	Antherosclerotic hamsters	Up to 100 mg/kg/day orally	10 wk	↓foam cells 50-63% ↓ plasma cholesterol 25%	[33]
Concord grape seed extract	Rat aortic rings	Up to 0.25 µg/mL in bath	Minutes	← EDR	[34]
Grape seed extract	Hamsters, aortic rings	18.4 mg/kg/day up to 70 µg/mL in bath	12 wk 60 min	↓ plasma cholesterol 25% ↓ antherosclerosis 68% ← EDR >70%	[38]
Grape seed extract	Human subjects	2g/d orally	4 wk	Improved FMD	[19]
Grape skin and seed extract	Dogs	Up to 25 mg/kg/day orally	8 d	↓ platelet aggregation	[22]
Grape flesh and skin	Rats	2.5 mg/lg/day orally	30 d	↓ ischemia/reperfusion ←ROS scavenging ↓myocardial infaret size 34%	[21]
Grape skin and seed extract	Hyperlipidemic rabbits	≈2 g/d orally	15 wk	↓ abdominal aortic atherosclerosis	[32]
Resveratrol	Isolated platelets	Up to 1.2 µg/L	Minutes	↓platelet aggregation 42%	[48]
Resveratrol	Rat aortic smooth muscle cells	50 µmol/L in medium	30 min	↓angiotensin II-induced vascular smooth muscle cell hypertrophy ↓ phosohorylationof PI_3K and p70 ^{S6k}	[60]
Resveratrol	Isolated rat heart	10 µmol/L in perfusate	Minutes	↓myocardial infaret size/apoptosis/NO dependent Improved aortic flow	[35]

				←iNOS mRNA	
Resveratrol, oleanoic acid	COX enzyme	100 µmol/L in medium	5 min	↓COX-1 activity 98% (resveratrol) ↓COX-2 activity (oleanoic acid)	[62]
Resveratrol	tsA201 cells	77 µmol/L in medium	Minutes	Blocked cardiac Na^+ and Ca^+ ion channels ↓stimulated-diastolic $[Ca^{2+}]i$	[55]
Resveratrol	Rat and guinea pigs Isolated cardoimyocytes	Up to 45 mg/kg intravenous Up to 100 µmol/L in medium	Minutes Minutes	↓arrythymia duration, VT, and mortality ↓APD, inhibit I_{Ca}	[51]

ADP indicates action potential duration; ApoB, apolipoprotein B; EDR, endothelium-dependant relaxation; $I_{Ca,}$ calcium current; iNOS, inducible NO synthase; MCP1, monocyte chemoatrractant protein-1; PGE, polyphenolic grape extract; VT, ventricular tachycardia; VF ventricular fibrillation; increase←; decrease↓.

As taken from Leifert WR, Abeywardena MY. Nutr Res. 2008 Nov; 28 (11):729-37. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19083481

“The study was designed to test whether the ingestion grape juice (GJ) could modulate monocrotaline (MCT)-induced Cor pulmonale resulting from antioxidant properties. Three-week-old male Wistar rats received GJ (10 mL/kg/day) by gavage for 6 weeks. A single injection of MCT (60 mg/kg body weight intraperitoneally) was administered at the end of the third week. Animals were divided in four groups: control, MCT, GJ, and GJ + MCT. MCT promoted a significant increase in right ventricle (36%) and lung (70%) weight to body weight ratio. There was an increase in the right systolic (38%) as well as in the end diastolic (70%) ventricular pressures. MCT caused a significant decrease in lung endothelial nitric oxide synthase (20%) but increase in lipid peroxidation (13%) and catalase (43%). MCT-induced decrease in the endothelial nitric oxide synthase and increase in the right ventricular end diastolic pressure were prevented by GJ, whereas right systolic ventricular pressure and lung weight to body weight ratio were corrected only partially. MCT-induced increase in heart and right ventricle to body weight ratios was not changed by GJ. GJ blunted MCT-induced increase in lipid peroxidation but had no effect on the changes in catalase and superoxide dismutase activities. GJ appears to offer some protection against MCT-induced Cor pulmonale and right ventricle function changes.” As taken from Ludke AR et al. J Cardiovasc Pharmacol. 2010 Jan; 55 (1):89-95. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19904214

5.3. Reproduction toxicity

No data available to us at this time.

5.4. Mutagenicity

The Ames test was used to evaluate the mutagenicity of a number of neat complex flavour mixtures. Studies in which Raisin juice concentrate was part of the test mixture include EMT960820 and EMT000226 (CD-ROM 1, JTI Submission, 2002). The results show that these mixtures were not mutagenic.

In Vivo: Antioxidant and antigenotoxic activities of purple grape juice--organic and conventional--in adult rats (Abstract). Oxidative damage to biomolecules occurs by the accumulation of molecular damage due to free radicals and/or a diminution of antioxidant protection. The aim of this study was to evaluate the protection of organic and conventional purple grape juices in brain, liver, and plasma from adult Wistar rats (7 months old) against the oxidative damage provoked by carbon tetrachloride (CCl(4)). Adult rats were divided into three groups (control, conventional purple grape juice, and organic purple grape juice). Half of the rats received CCl(4), and the other half received the vehicle (vegetable oil). The chemical analytical determination showed that the highest levels of total phenolic, resveratrol, and catechins were seen in organic purple grape juices. Considering the treatment groups, it was observed that in all tissues (brain structures and liver) and plasma, CCl(4) treatment increased the lipid peroxidation (LP) levels. Both grape juices were capable to reduce LP levels in cerebral cortex and hippocampus; however, in the striatum and substantia nigra only the organic grape juice reduced LP level. CCl(4) caused an increase in catalase activity in cerebral cortex, hippocampus, and substantia nigra and in superoxide dismutase activity in substantia nigra. This increase was reduced by both juices in substantia nigra and hippocampus structures ($P < .05$). In the alkaline version of the comet assay performed on whole blood, it was observed that CCl(4) was capable of inducing mainly DNA damage class 4 and 3 frequencies, which was significantly reduced in groups that received both purple grape juices. This implies that both grape juices have an important antigenotoxic activity. As taken from Dani C et al. J Med Food. 2009 Oct; 12(5):1111-8.PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19857077

5.5. Cytotoxicity

No data available to us at this time.

5.6. Carcinogenicity

“Many popular dietary supplements are enriched in polyphenols such as the soy isoflavones, tea catechins, and resveratrol (from grape skins), each of which has been shown to have chemopreventive activity in cellular models of cancer. The proanthocyanidins, which are oligomers of the catechins, are enriched in grape seeds and form the basis of the dietary supplement grape seed extract (GSE). Evidence suggests that the proanthocyanidins may be metabolized to the monomeric catechins. This study was carried out to determine whether GSE added to rodent diets protected against carcinogen-induced mammary tumorigenesis in rats and whether this was affected by the composition of the whole diet. Female rats were begun on 5%, 1.25%, or 0% (control) GSE-supplemented diets at age 35 d. At age 50 d they were administered 7,12-dimethylbenz[a]anthracene (DMBA) in sesame oil at 80 mg/kg body weight. They were weighed and monitored weekly for tumor development until 120 d after DMBA administration. Administration of GSE in AIN-76A diet did not show any protective activity of GSE against DMBA-induced breast cancer. However, administration of GSE in a laboratory dry food diet (Teklad 4% rodent diet) resulted in a 50% reduction in tumor multiplicity. In similar experiments, genistein administered in AIN-76A diet also failed to show chemopreventive activity against the carcinogen N-methyl-N-nitrosourea; however, when administered at the same dose in the Teklad 4% rodent diet, genistein exhibited significant chemopreventive activity (44-61%). These results demonstrate that GSE is chemopreventive in an animal model of breast cancer; moreover, the diet dependency of the chemopreventive activity for both GSE and genistein suggests that whether or not a compound is chemopreventive may depend on the diet in which the agent is administered.” As taken Kim H et al. from J Nutr. 2004 Dec; 134(12 Suppl):3445S-3452S. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15570052&query_hl=4&itool=pubmed_docsum

“Grape contains flavonoids with antioxidant properties which are believed to be protective against various types of cancer. This antioxidative protection is possibly provided by the effective scavenging of reactive oxygen species (ROS), thus defending cellular DNA from oxidative damage and potential mutations. This study of healthy adults tested whether a daily regimen of grape juice supplementation could reduce cellular DNA damage in peripheral lymphocytes and reduce the amount of free radicals released. Sixty-seven healthy volunteers (16 women and 51 men) aged 19-57 years were given 480 ml of grape juice daily for 8 weeks in addition to their normal diet, and blood samples were drawn before and after the intervention. The DNA damage was determined by using the single cell gel (comet) assay with alkaline electrophoresis and was quantified by measuring tail length (TL). Levels of free radicals were determined by reading the lucigenin-perborate ROS generating source, using the Ultra-Weak Chemiluminescence Analyzer System. Grape juice consumption resulted in a significant decrease in lymphocyte DNA damage expressed by TL (before supplementation: 88.75 +/- 1.55 microm versus after supplementation: 70.25 +/- 1.31 microm; P=0.000 by paired t-test). Additionally, grape juice consumption for 8 weeks reduced the ROS/photon count by 15%, compared to the beginning of the study. The preventive effect of grape juice against DNA damage was simultaneously shown in both sexes. These results indicate that the consumption of grape juice may increase plasma antioxidant capacity, resulting in reduced DNA damage in peripheral lymphocytes achieved at least partially by a reduced release of ROS. Our findings support the hypothesis that polyphenolic compounds contained in grape juice exert cancer-protective effects on lymphocytes, limiting oxidative DNA damage possibly via a decrease in free radical levels.”

As taken from Park YK. Mutat Res. 2003 Aug 28; 529(1-2):77-86. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12943921&query_hl=34&itool=pubmed_docsum

5.7. Irritation/immunotoxicity

"Reports of immunoglobulin E (IgE)-mediated allergic reactions to grapes and wine are limited in the literature. Nevertheless, grapes are widely grown and consumed in Mediterranean countries. The object of this prospective study was to present clinical features, in vivo and in vitro allergy testing, and human leukocyte antigen (HLA) serotyping in patients with recurring reactions to grapes and grape products. Eleven unrelated Greek patients, six men and five women (aged 16-44 years; mean, 26.9 years) were enrolled based on a documented history of IgE-mediated reactions to grapes, wine, or other grape products. Their evaluation included full history, reaction severity, clinical examination, skin-prick tests with food allergens and molds, serum IgE, specific IgEs to the same allergen battery, and HLA typing. Patients reported 35 grape-induced anaphylaxis episodes ranging from moderate (more than one system involved but not prominent respiratory or cardiovascular symptoms; 45.5%) to severe (serious respiratory obstruction and/or hypotension and loss of consciousness; 54.5%). A causative agent was identified: wine, 10/35 (28.6%); red grapes, 9/35 (25.7%); stuffed vine leaves, 8/35 (22.9%); raisins, 3/35 (8.6%); white grapes, 2/35 (5.7%); wine vinegar, 2/35 (5. 7%); and grape juice, 1/35 (2.9%). Other foods that induced anaphylaxis were apples (54.5%), cherries (18.6%), peaches (18.6%), and bananas (9.3%). Specific IgE values were in accordance with skin-prick tests reactivity. Concerning HLA typing, 9/11 possessed HLA-DR11(5) and -DQ7(3) and the remaining two possessed HLA-DR17(3) and -DQ2 antigens. Grapes, wine and other grape products might cause serious allergic reactions in sensitized individuals. The cosensitization and reaction incidence to other fruit allergens could be a basis for further investigation of panallergens of fruits. HLA class II antigens may contribute in genetic predisposition to these allergic reactions." As taken from Kalogeromitros DC. Allergy Asthma Proc. 2005 Jan-Feb; 26(1):53-8. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15813289&query_hl=18&itool=pubmed_docsum

"Grape allergy is particularly rare in spite of the vast extension of Vitis vinifera cultivation on all continents. We report on the case of a 28-year-old woman who presented with allergic systemic reaction after eating white grapes (Vitis vinifera). She complained of two severe episodes of anaphylaxis after eating grapes, with generalized pruritus, acute generalized urticaria, facial swelling, lip and oropharingeal angioedema, and dysphagia. Both the episodes were treated at the Emergency Room level, with parenteral administration of corticosteroids and antihistamines. Skin prick tests with commercial extract of grapes provided a negative result, while prick by prick procedure performed with white grapes and white grape juice yielded a positive result. Grape-specific serum IgE were also detected. We conclude that in the diagnosis of grape allergy the currently available commercial extracts might not be completely reliable and the prick-by-prick procedure with fresh grapes should always be performed." As taken from Caiaffa MF. J Investig Allergol Clin Immunol.

2003; 13(3):211-2. PubMed, 2010 available http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14635473&query_hl=18&itool=pubmed_DocSum

“Background: An IgE-mediated allergy against a lipid-transfer protein of grapes was the cause of repeated severe anaphylaxis in a patient after consumption of grapes, wine, and raisins. Objective: Although the patient was aware of her grape allergy, avoidance proved difficult and accidental anaphylaxis occurred. Furthermore, wine allergy in a wine-growing district means a non-negligible restriction of quality of life. Methods: Although there is little data on specific oral tolerance induction (SOTI) in lipid-transfer protein (LTP) allergy, SOTI with increasing doses starting from approximately 20 mg of grapes was done. For follow-up, skin tests, grape-specific IgE and IgG4, basophil activation tests, and immunoblotting were performed. Results: Within 3 days the patient reached tolerance to the daily maintenance dose of 20 g of grapes (about 3 grape pieces) without anaphylaxis symptoms. Two months later, a controlled challenge with a total of 66.5 mL of white wine was tolerated. Grape-specific IgE stayed stable at 2.37 kU/L (class 2) and grape-specific IgG4 was first detectable 21 months after SOTI. Prick-to-prick skin tests continued to be positive to grapes, to raisins, and to white and red wine. The basophil activation test still showed strong IgE-mediated activation of basophils after stimulation with grape extract. Immunoblotting still detected IgE binding to a 8-kDa protein. Conclusions: We performed SOTI in a patient with severe IgEmediated allergy against the LTP Vit v 1 of grapes and reduced the risk of anaphylaxis because of accidental intake of any kind of grapes. However, underlying mechanisms of SOTI and maintenance of the established tolerance are still not known.” As taken from Schäd SG et al. 2010. World Allergy Organ. J. 3(1), 1-5. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23282379

"Raisins (Vitis vinifera L.) are dried grapes largely consumed as important source of nutrients and polyphenols. Several studies report health benefits of raisins, including anti-inflammatory and antioxidant properties, whereas the anti-inflammatory activity at gastric level of the hydro-alcoholic extracts, which are mostly used for food supplements preparation, was not reported until now. The aim of this study was to compare the anti-inflammatory activity of five raisin extracts focusing on Interleukin (IL)-8 and Nuclear Factor (NF)-κB pathway. Raisin extracts were characterized by High Performance Liquid Chromatography-Diode Array Detector (HPLC-DAD) analysis and screened for their ability to inhibit Tumor necrosis factor (TNF)α-induced IL-8 release and promoter activity in human gastric epithelial cells. Turkish variety significantly inhibited TNFα-induced IL-8 release, and the effect was due to the impairment of the corresponding promoter activity. Macroscopic evaluation showed the presence of seeds, absent in the other varieties; thus, hydro-alcoholic extracts from fruits and seeds were individually tested on IL-8 and NF-κB pathway. Seed extract inhibited IL-8 and NF-κB pathway, showing higher potency with respect to the fruit. Although the main effect was due to the presence of seeds, the fruit showed significant activity as well. Our data suggest that consumption of selected varieties of raisins could confer a beneficial effect against gastric inflammatory diseases." As taken from Di Lorenzo C et al. 2016. Int. J. Mol. Sci. 17(7), E1156. PubMed, 2017 available at: https://www.ncbi.nlm.nih.gov/pubmed/27447609

5.8. All other relevant types of toxicity

Anti-Oxidative Effect:

The total antioxidant activity of 12 fruits and 5 commercial fruit juices was measured in this study using automated oxygen radical absorbance capacity (ORAC) assay. On the basis of the wet weight of the fruits (edible portion), strawberry had the highest ORAC activity (micromoles of Trolox equivalents per gram) followed by plum, orange, red grape, kiwi fruit, pink grapefruit, white grape, banana, apple, tomato, pear, and honeydew melon. On the basis of the dry weight of the fruits, strawberry again had the highest ORAC activity followed by plum, orange, pink grapefruit, tomato, kiwi fruit, red grape, white grape, apple, honeydew melon, pear, and banana. Most of the antioxidant capacity of these fruits was from the juice fractions. The contribution of the fruit pulp fraction (extracted with acetone) to the total ORAC activity of a fruit was usually less than 10%. Among the commercial fruit juices, grape juice had the highest ORAC activity followed by grapefruit juice, tomato juice, orange juice, and apple juice. As taken from Hong Wang H et al. 1996. J. Agric. Food Chem. 44, 701-705 available at http://pubs.acs.org/doi/abs/10.1021/jf950579y

Other “In Vitro Test”: Indeed, resveratrol isolated from grape skin was shown to inhibit the COX-1 enzyme by 98% at 100 µg/mL, but resveratrol was without effect against the closely related COX-2 enzyme [62]. In addition, viniferin and catechin (also from grape skin) inhibited COX-1 and COX-2 [62] and are therefore somewhat comparable to the pharmacological agents aspirin, naproxen, and ibuprofen in terms of their selectivity for inhibition of different isoforms of COX. Peroxisome proliferator-activated receptors regulate transcription of various genes involved in cholesterol metabolism in the liver and other organs [63,64]. In a study by Ma et al [65], the grape seed proanthocyanidins were antiinflammatory in human umbilical vein endothelial cells by a mechanism involving activation of PPARβ expression [65]. Thus, in addition to their cardioprotective effects, grape seed proanthocyanidins appear to reduce the inflammatory processes (see Fig. 2), which might partly explain the mechanism(s) for the amelioration of other chronic inflammatory conditions such as inflammatory bowel disease, cancer, and diabetes. As taken from Leifert WR, Abeywardena MY. Nutr Res. 2008 Nov; 28 (11):729-37. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19083481

6. Functional effects on

6.1. Broncho/pulmonary system

No data available to us at this time.

Cardioprotective actions of grape polyphenols (Abstract). The aim of this review is to discuss the accumulating evidence that suggests that grape extracts and purified grape polyphenols possess a diverse array of biological actions and may be beneficial in the prevention of some inflammatory-mediated diseases including cardiovascular disease. The active components from grape extracts, which include the grape seed, grape skin, and grape juice, that have been identified thus far include polyphenols such as resveratrol, phenolic acids, anthocyanins, and flavonoids. All possess potent antioxidant properties and have been shown to decrease low-density lipoprotein-cholesterol oxidation and platelet aggregation. These compounds also possess a range of additional cardioprotective and vasoprotective properties including antiatherosclerotic, antiarrhythmic, and vasorelaxation actions. Although not exclusive, antioxidant properties of grape polyphenols are likely to be central to their mechanism(s) of action, which also include cellular signaling mechanisms and interactions at the genomic level. This review discusses some of the evidence favoring the consumption of grape extracts rich in polyphenols in the prevention of cardiovascular disease. Consumption of grape and grape extracts and/or grape products such as red wine may be beneficial in preventing the development of chronic degenerative diseases such as cardiovascular disease. As taken from Leifert WR, Abeywardena MY. Nutr Res. 2008 Nov; 28 (11):729-37. As taken from PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19083481

“Red wine and purple grape juice contain polymeric flavonoids with antioxidant properties believed to be protective against cardiovascular events but the alcohol and sugar content of these beverages has curtailed their medicinal use. Acute cardiac events are also associated with enhanced inflammation and thrombosis. In this study, the extracts from grape skins or seeds were examined for their anti-inflammatory properties and effect on platelet release of reactive oxygen intermediates. Incubation of platelets with seed or skin extract led to a decrease in platelet aggregation from 68.8+/-19.8% to 45+/-3.6% for seeds and to 27+/-7.2% for skin, respectively ($P<0.05$). Platelet incubation with grape skin or seed extracts led to a marked decrease in superoxide release from 73+/-6.2 to 2+/-3.4 for grape seeds and to 0.33+/-0.57 for grape skin (chemilum. units; $P<0.05$) as well as a significant increase in radical-scavenging activity, decrease in reactive oxygen species release by confocal microscopy, and enhanced platelet NO was measured using an NO-sensitive microelectrode. These effects were dose dependent for both grape extracts. Coincubation with seeds and skins led to additive inhibition of platelet aggregation, enhanced NO release, and prevented superoxide production. Incubation with seed or skin extracts led to an immediate attenuation of release of the inflammatory mediator, soluble CD40 ligand. Thus, the extracts from purple grape skins and seeds inhibit platelet function and platelet-dependent inflammatory responses at pharmacologically relevant concentrations. These findings suggest potentially beneficial platelet-dependent antithrombotic and anti-inflammatory properties of purple grape-derived flavonoids.” As taken from Vitseva O et al. J Cardiovasc Pharmacol. 2005 Oct; 46(4):445-51. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16160595&query_hl=18&itool=pubmed_docsum

“In vitro, the flavonoid components of red wine and purple grape juice are powerful antioxidants that induce endothelium-dependent vasodilation of vascular rings derived from

rat aortas and human coronary arteries. Although improved endothelial function and inhibition of LDL oxidation may be potential mechanisms by which red wine and flavonoids reduce cardiovascular risk, the in vivo effects of grape products on endothelial function and LDL oxidation have not been investigated. This study assessed the effects of ingesting purple grape juice on endothelial function and LDL susceptibility to oxidation in patients with coronary artery disease (CAD). METHODS AND RESULTS: Fifteen adults with angiographically documented CAD ingested 7.7+/-1.2 mL. kg(-1). d(-1) of purple grape juice for 14 days. Flow-mediated vasodilation (FMD) was measured using high-resolution brachial artery ultrasonography. Susceptibility of LDL particles to oxidation was determined from the rate of conjugated diene formation after exposure to copper chloride. At baseline, FMD was impaired (2.2+/-2. 9%). After ingestion of grape juice, FMD increased to 6.4+/-4.7% (P=0.003). In a linear regression model that included age, artery diameter, lipid values, and use of lipid-lowering and antioxidant therapies, the effect of grape juice on FMD remained significant (mean change 4.2+/-4.4%, P<0.001). After ingestion of grape juice, lag time increased by 34.5% (P=0.015). CONCLUSIONS: Short-term ingestion of purple grape juice improves FMD and reduces LDL susceptibility to oxidation in CAD patients. Improved endothelium-dependent vasodilation and prevention of LDL oxidation are potential mechanisms by which flavonoids in purple grape products may prevent cardiovascular events, independent of alcohol content." As taken from Stein JH et al. Circulation. 1999 Sep 7; 100(10):1050-5. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10477529&query_hl=18&itool=pubmed_DocSum

"In the dog, monkey, and human we have shown that 5 ml/kg of red wine or 5-10 ml/kg of purple grape juice but not orange or grapefruit juice inhibits platelet activity, and protects against epinephrine activation of platelets. Red wine and purple grape juice enhances platelet and endothelial production of nitric oxide (Fitzpatrick et al., 1993, Parker et al., 2000). This is thought to be one of the mechanisms whereby purple grape juice significantly improved endothelial function in 15 patients with coronary artery disease. The consumption of purple grape juice by the patients also offered increased protection against LDL cholesterol oxidation, even though all the patients were also taking another antioxidant vitamin E, 400 IU/day. The number of people and animals in these studies was small; however, each one acted as their own control as measurements were made in each before, and then after consumption of red wine or purple grape juice. Thus these studies are thought to be significant. We feel that the results of these studies are encouraging and justify further research on larger numbers of subjects. This suggests that the flavonoids in purple grape juice and red wine may inhibit the initiation of atherosclerosis by one or more of the mechanisms described above. It will take years to fully characterize the potential benefits of daily consumption of red wine or purple grape juice for maintaining a healthy heart. Based on the existing evidence of antiplatelet and antioxidant benefits and improved endothelial function from red wine and purple grape juice, it seems reasonable to suggest that moderate amounts of red wine or purple grape juice be included among the 5-7 daily servings of fruits and vegetables per day as recommended by the American Heart Association to help reduce the risk of developing cardiovascular disease." As taken from Folts JD. Adv Exp Med Biol. 2002; 505:95-111. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12083471&query_hl=34&itool=pubmed_DocSum

6.3. Nervous system

Monoamine oxidase (MAO) is a mitochondrial enzyme involved in the oxidative catabolism of neurotransmitters and xenobiotic amines, including vasopressor and neurotoxic amines, and a current target for antidepressant and neuroprotective drugs. Raisin extracts and homogenates exhibited reversible in vitro inhibition of MAO isozymes, particularly MAO-A, suggesting the presence of MAO-inhibiting substances. Chromatographic and spectrometric studies showed the occurrence of aromatic beta-carboline alkaloids in raisins, and norharman and harman were identified as the key contributors to MAO inhibition. On average, harman ranged from 6 to 644 ng/g and norharman from 2 to 120 ng/g. Several technological variables appeared to determine the presence of these compounds in raisins. Dark-brown raisins (i.e., sun-dried) contained much higher levels than golden raisins. Tetrahydro-beta-carboline-3-carboxylic acid compounds that are direct precursors of aromatic beta-carbolines were also identified in raisins and appeared in a higher amount, reaching up to 50 microg/g. beta-Carbolines were isolated from raisins and acted as good competitive inhibitors of MAO-A (harman) and MAO-B (norharman) isozymes. These results suggest that beta-carboline alkaloids and perhaps raisins containing a high level of beta-carbolines might exhibit potential activity as MAO inhibitors. The results also show that some raisins can be a source of dietary exposure to bioactive beta-carbolines. As taken from Herraiz T. J Agric Food Chem. 2007, Oct 17; 55(21):8534-40. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&list_uids=17883257&dopt=AbstractPlus

"In this study, we investigated the effects of grape seed extract (GSE) on the expression of osteopontin (OPN) and cyclooxygenase-2 (COX-2) in a rat model of spinal cord ischemia-reperfusion injury (SC-IRI). Fifty male rats were divided into 5 groups: control (CON); control + GSE (CON + GSE) (received GSE for 28 days); sham operated (Sham); IRI; and IRI + GSE. SC-IRI was induced by clamping the aorta just above the bifurcation for 45 min, and then the clamp was released for 48 h for reperfusion. IRI + GSE group received GSE for 28 days before SC-IRI. Sensory, motor, and placing/stepping reflex assessment was performed. Prostaglandin E2 (PGE2), thiobarbituric acid reactive substances (TBARs), and total antioxidant capacity (TAC) were measured in spinal cord homogenate. Immunohistochemical examination of the spinal cord for OPN and COX-2 were carried out. SC-IRI resulted in significant increase in plasma nitrite/nitrate level and spinal cord homogenate levels of TBARs and PGE2, and OPN and COX-2 expression with significant decrease in TAC. GSE improves the sensory and motor functions through decreasing OPN and COX-2 expression with reduction of oxidative stress parameters. We conclude a neuroprotective effect of GSE in SC-IRI through downregulating COX-2 and OPN expression plus its antioxidants effects." As taken from Sakr HF et al. 2016. Can. J. Physiol. Pharmacol. 94(7), 719-27. PubMed, 2017 available at: https://www.ncbi.nlm.nih.gov/pubmed/27135919

6.4. Other organ systems, dependent on the properties of the substance

“Red grape juice (RGJ) polyphenols have been shown to reduce circulating levels of LDL cholesterol and to increase LDL receptor activity. To explore the effect of RGJ-derived polyphenols on intracellular cholesterol homeostasis, human hepatocarcinoma HepG2 and promyelocytic HL-60 cell lines were incubated in serum-free medium, with or without LDL, in the presence or absence of RGJ. In the presence of LDL, RGJ increased both the activity and cell surface expression of the LDL receptor, and increased the cell total cholesterol content. In cells exposed to LDL, RGJ also increased levels of the active form of sterol regulatory element-binding protein-1 and mRNA expression of the LDL receptor and hydroxymethylglutaryl-CoA reductase. In contrast, RGJ caused a marked reduction in the expression of CYP7A1, apolipoprotein B, ABCA1, and ABCG5. Experiments using the acyl-CoA cholesterol acyltransferase inhibitor S-58035 indicated that no measurable free cholesterol from endocytosed LDL reaches the endoplasmic reticulum in cells treated with RGJ. Finally, fluorescence microscopy revealed that in RGJ-treated cells, DiI-labeled LDL did not colocalize with CD63, a protein localized at steady state in the internal vesicles of late endosomes. These results indicate that RGJ polyphenols disrupt or delay LDL trafficking through the endocytic pathway, thus preventing LDL cholesterol from exerting regulatory effects on intracellular lipid homeostasis.” As taken from Dávalos A et al. J Nutr. 2006 Jul; 136(7):1766-73. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/16772435

“This study examines whether the beneficial antioxidant effects of red wine can be reproduced by nonalcoholic red grape juice concentrate. Seven subjects consumed 125 ml concentrate daily for 7 days. Following first ingestion there was a rise in serum total antioxidant capacity (TAC) from 441 to 478 mumol/l at 60 min ($p < 0.005$). On day 8, TAC was 50 mumol/l higher than at baseline ($p < 0.05$). There was reduced susceptibility of low-density lipoprotein (LDL) to oxidation. Red grape juice concentrate ingestion results in increased serum antioxidant capacity and protection of LDL from oxidation and thus nonalcoholic red grape extract may have similar beneficial effects to red wine.” As taken from Day AP. Ann Nutr Metab. 1997; 41(6):353-7. PubMed, 2001 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9491190&query_hl=10&itool=pubmed_docsum$

“Grape juice and skin and seed extracts of Vitis vinifera var. Ribier black table grapes were found to be highly inhibitory towards Listeria monocytogenes. This grape juice was also active against all other Listeria species tested but not against Bacillus cereus, Salmonella Menston, Escherichia coli, Staphylococcus aureus or Yersinia enterocolitica. Fractionation of the extracts showed that the antilisterial activity was strongest in the polymeric phenolic fractions. Two different types of active compounds were identified: the red-pigmented polymeric phenolics from juice and skin showed pH-dependent antilisterial activity, while the unpigmented polymeric phenolics from the seed showed antilisterial activity which was independent of pH.” As taken from Rhodes PL. Int J Food Microbiol. 2006 Apr 1; 107(3):281-6. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16386816&query_hl=34&itool=pubmed_docsum

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

This ingredient was considered as part of an overall safety assessment of ingredients added to tobacco in the manufacture of cigarettes. An expert panel of toxicologists reviewed the open literature and internal toxicology data of 5 tobacco companies to evaluate a composite list of ingredients used in the manufacture of cigarettes. The conclusion of this report was that these ingredients did not increase the inherent biological activity of tobacco cigarettes, and are considered to be acceptable under conditions of intended use (Doull et al., 1994 & 1998).

Tobacco smoke condensates from cigarettes containing Raisin juice, concentrate and an additive free, reference cigarettes were tested in a battery of *in vitro* and/or *in vivo* test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the condensate was not changed by the addition of Raisin juice, concentrate. Table below provides tested level(s) and specific endpoint(s).

Endpoint	Tested level (ppm)	Reference
Smoke chemistry	47,925	Carmines, 2002 & Rustemeier et al., 2002
	600	Baker et al., 2004a
	15,000 (No CAS)	JTI KB Study Report(s)

	86,400	Gaworski et al., 2011 & Coggins et al., 2011a
In vitro genotoxicity	47,925	Carmines, 2002 & Röemer et al., 2002
	11,400 (extract) 600 (juice/concentrate, no CAS)	Baker et al., 2004c
	15,000 (No CAS)	JTI KB Study Report(s)
	86,400	Gaworski et al., 2011 & Coggins et al., 2011a
In vitro cytotoxicity	47,925	Carmines, 2002 & Röemer et al., 2002
	11,400 (extract) 600 (juice/concentrate, no CAS)	Baker et al., 2004c

	15,000 (No CAS)	JTI KB Study Report(s)
	86,400	Gaworski et al., 2011 & Coggins et al., 2011a
Inhalation study	47,925	Carmines, 2002 & Vanscheeuwijck et al., 2002
	11,400 (extract) 600 (juice/concentrate, no CAS)	Baker et al., 2004c
	15,000 (No CAS)	JTI KB Study Report(s)
	86,400	Gaworski et al., 2011 & Coggins et al., 2011a
Skin painting	15,000 (No CAS)	JTI KB Study Report(s)

9. Heated/vapor emissions toxicity

No data available to us at this time.

10. Ecotoxicity

10.1. Environmental fate

The Canadian authority is “Uncertain” whether raisin oils are persistent in the environment.

Data accessed June 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

EPISuite provides the following data:

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:

Bond Method :	1.26E-006 atm-m3/mole (1.28E-001 Pa-m3/mole)
Group Method:	1.14E-009 atm-m3/mole (1.16E-004 Pa-m3/mole)
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:	HLC: 3.214E-007 atm-m3/mole (3.256E-002 Pa-m3/mole) VP: 0.000552 mm Hg (source: MPBPVP) WS: 394 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:

Log Kow used:	2.54 (KowWin est)
Log Kaw used:	-4.288 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate):	6.828
Log Koa (experimental database):	None

Probability of Rapid Biodegradation (BIOWIN v4.10):

Biowin1 (Linear Model):	0.6394	
Biowin2 (Non-Linear Model) :	0.4821	
Biowin3 (Ultimate Survey Model):	2.7619	(weeks)
Biowin4 (Primary Survey Model) :	3.5723	(days-weeks)
Biowin5 (MITI Linear Model) :	0.6200	
Biowin6 (MITI Non-Linear Model):	0.7317	
Biowin7 (Anaerobic Linear Model):	0.3600	
Ready Biodegradability Prediction:	YES	

Hydrocarbon Biodegradation (BioHCwin v1.01):

Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:

Vapor pressure (liquid/subcooled):	0.0984 Pa (0.000738 mm Hg)
Log Koa (Koawin est):	6.828
Kp (particle/gas partition coef. (m3/ug)): Mackay model: Octanol/air (Koa) model:	3.05E-005 1.65E-006

Fraction sorbed to airborne particulates (phi):

Junge-Pankow model:	0.0011
Mackay model:	0.00243
Octanol/air (Koa) model:	0.000132

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant =	17.0414 E-12 cm3/molecule-sec
Half-Life =	0.628 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =	7.532 Hrs

Ozone Reaction:	No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi): 0.00177 (Junge-Pankow, Mackayavg) 0.000132 (Koa method) Note: the sorbed fraction may be resistant to atmospheric oxidation	

Soil Adsorption Coefficient (KOCWIN v2.00):

Koc :	10 L/kg (MCI method)
Log Koc:	1.000 (MCI method)
Koc :	32.15 L/kg (Kow method)
Log Koc:	1.507 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:

Rate constants can NOT be estimated for this structure!

Volatilization from Water:

Henry LC: 1.26E-006 atm-m3/mole (estimated by Bond SAR Method)

Half-Life from Model River:	614.8 hours (6.926 days)
Half-Life from Model Lake:	6818 hours (79.41 days)

Removal In Wastewater Treatment:

Total removal:	3.28 percent
Total biodegradation:	0.10 percent
Total sludge adsorption:	3.11 percent
Total to Air:	0.07 percent

(using 10000 hr Bio P,A,S)

Level III Fugacity Model:

	Mass Amount(percent)	Half-Life(hr)	Emissions(kg/hr)
Air	1.59	15.1	1000
Water	39.3	360	1000
Soil	59.1	720	1000
Sediment	0.0884	3.24e+003	0

Persistence Time: 384 hr

10.2. Aquatic toxicity

According to Canadian categorization criteria, raisin oil is not expected to be inherently toxic to aquatic organisms because it is considered to be of “low ecotoxicological concern” [no further data available].

Data accessed June 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

ECOSAR version 1.11 reports the following aquatic toxicity data for CAS RN 68915-86-6:

Values used to Generate ECOSAR Profile

Log Kow: 2.545 (EPISuite Kowwin v1.68 Estimate)

Wat Sol: 393.9 (mg/L, EPISuite WSKowwin v1.43 Estimate)

ECOSAR v1.11 Class-specific Estimations
Neutral Organics

ECOSAR Class	**Organism**	**Duration**	**End Pt**	**Predicted mg/L (ppm)**
Neutral Organics :	Fish	96-hr	LC50	46.426

Neutral Organics	:	Daphnid	48-hr	LC50	27.720
Neutral Organics	:	Green Algae	96-hr	EC50	25.421
Neutral Organics	:	Fish		ChV	4.815
Neutral Organics	:	Daphnid		ChV	3.109
Neutral Organics	:	Green Algae		ChV	7.446
Neutral Organics	:	Fish (SW)	96-hr	LC50	58.637
Neutral Organics	:	Mysid	96-hr	LC50	30.134
Neutral Organics	:	Fish (SW)		ChV	8.876
Neutral Organics	:	Mysid (SW)		ChV	2.216

10.3. Sediment toxicity

No data available to us at this time.

10.4. Terrestrial toxicity

ECOSAR version 1.11 reports the following terrestrial toxicity data for CAS RN 68915-86-6:

Values used to Generate ECOSAR Profile

Log Kow: 2.545 (EPISuite Kowwin v1.68 Estimate)

Wat Sol: 393.9 (mg/L, EPISuite WSKowwin v1.43 Estimate)

ECOSAR v1.11 Class-specific Estimations
Neutral Organics

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Neutral Organics :	Earthworm	14-day	LC50	266.065

10.5. All other relevant types of ecotoxicity

The Canadian authority is “Uncertain” whether raisin oils are bioaccumulative in the environment.

Data accessed June 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

EPISuite provides the following data:

Bioaccumulation Estimates (BCFBAF v3.01):

Log BCF from regression-based method:	1.346 (BCF = 22.18 L/kg wet-wt)
Log Biotransformation Half-life (HL):	-0.8969 days (HL = 0.1268 days)
Log BCF Arnot-Gobas method (upper trophic):	1.317 (BCF = 20.74)
Log BAF Arnot-Gobas method (upper trophic):	1.317 (BAF = 20.74)
Log Kow used:	2.54 (estimated)

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12. Other information

No data available to us at this time.

13. Last audited

June 2019

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1 Identification

· **Product identifier**

· **Trade name: Raisin Extract natural**

· **Product number:** 6060
· **Application of the substance / the mixture** Food flavorings

· **Details of the supplier of the safety data sheet**
· **Manufacturer/Supplier:**
Advanced Biotech
10 Taft Road
Totowa, NJ 07512 USA

· **Information department:**
Product safety department
sarfa@adv-bio.com
· **Emergency telephone number:**
1(800)535-5053 (Info Trac)
1(352)323-3500 (International)
During normal business hours: 1(973)339-6242

2 Hazard(s) identification

· **Classification of the substance or mixture**
The product is not classified according to the Globally Harmonized System (GHS).

· **Label elements**
· **GHS label elements**
Pictograms on label shall be in the shape of a square set at a point and shall include a black hazard symbol on a white background with a red frame sufficiently wide to be clearly visible.
· **Hazard pictograms** Not Applicable
· **Signal word** Not Applicable
· **Hazard statements** Not Applicable
· **Classification system:**
· **NFPA ratings (scale 0 - 4)**

Health = 0
Fire = 1
Reactivity = 0

· **HMIS-ratings (scale 0 - 4)**

Health = 0
Fire = 1
Reactivity = 0

· **Other hazards**
· **Results of PBT and vPvB assessment**
· **PBT:** Not applicable.
· **vPvB:** Not applicable.

3 Composition/information on ingredients

· **Description:** Mixture of the substances listed below with nonhazardous additions.

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· **Dangerous components:** Not Applicable

4 First-aid measures

· **Description of first aid measures**
· **General information:** No special measures required.
· **After inhalation:** Supply fresh air; consult doctor in case of complaints.
· **After skin contact:** Generally the product does not irritate the skin.
· **After eye contact:** Rinse opened eye for several minutes under running water.
· **After swallowing:** If symptoms persist consult doctor.
· **Information for doctor:**
· **Most important symptoms and effects, both acute and delayed**
No further relevant information available.
· **Indication of any immediate medical attention and special treatment needed**
No further relevant information available.

5 Fire-fighting measures

· **Extinguishing media**
· **Suitable extinguishing agents:**
CO2, powder or alcoholresistant foam.
Use fire fighting measures that suit the environment.
· **Special hazards arising from the substance or mixture** No further relevant information available.
· **Advice for firefighters**
· **Protective equipment:** No special measures required.
· **Additional information**
Cool endangered receptacles with water spray.
Collect contaminated fire fighting water separately. It must not enter the sewage system.

6 Accidental release measures

· **Personal precautions, protective equipment and emergency procedures** Not required.
· **Environmental precautions:** Dilute with plenty of water.
· **Methods and material for containment and cleaning up:**
Absorb with liquid-binding material (sand, diatomite, acid binders, universal binders, sawdust).
· **Reference to other sections**
See Section 7 for information on safe handling.
See Section 8 for information on personal protection equipment.
See Section 13 for disposal information.

7 Handling and storage

· **Handling:**
· **Precautions for safe handling** No special measures required.
· **Information about protection against explosions and fires:** No special measures required.

· **Conditions for safe storage, including any incompatibilities**
· **Storage:**
· **Requirements to be met by storerooms and receptacles:** No special requirements.
· **Information about storage in one common storage facility:** Not required.

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· **Further information about storage conditions:** None.
· **Specific end use(s)** No further relevant information available.

8 Exposure controls/personal protection

· **Additional information about design of technical systems:** No further data; see item 7.

· **Control parameters**
· **Components with limit values that require monitoring at the workplace:**
The product does not contain any relevant quantities of materials with critical values that have to be monitored at the workplace.
· **Additional information:** The lists that were valid during the creation were used as a basis.

· **Exposure controls**
· **Personal protective equipment:**
· **General protective and hygienic measures:**
The usual precautionary measures for handling chemicals should be followed.
· **Breathing equipment:** Not required.
· **Protection of hands:**
The glove material has to be impermeable and resistant to the product/ the substance/ the preparation.
Due to missing tests no recommendation to the glove material can be given for the product/ the preparation/ the chemical mixture.
Selection of the glove material should be based on consideration of the penetration times, rates of diffusion and the degradation
· **Material of gloves**
The selection of the suitable gloves does not only depend on the material, but also on further marks of quality and varies from manufacturer to manufacturer. As the product is a preparation of several substances, the resistance of the glove material can not be calculated in advance and has therefore to be checked prior to the application.
· **Penetration time of glove material**
The exact break through time has to be determined by the manufacturer of the protective gloves and has to be observed.
· **Eye protection:** Goggles recommended during refilling.

9 Physical and chemical properties

· **Information on basic physical and chemical properties**	
· **General Information**	
· **Appearance:**	
Form:	Liquid
Color:	Brown
· **Odor:**	Raisin
· **Odour threshold:**	Not determined.
· **pH-value:**	Not determined.
· **Change in condition**	
Melting point/Melting range:	Undetermined.
Boiling point/Boiling range:	Undetermined.
· **Flash point:**	> 110 °C (> 230 °F)
· **Flammability (solid, gaseous):**	Not applicable.

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· **Ignition temperature:**	
Decomposition temperature:	Not determined.
· **Auto igniting:**	Product is not selfigniting.
· **Danger of explosion:**	Product does not present an explosion hazard.
· **Explosion limits:**	
Lower:	Not determined.
Upper:	Not determined.
· **Vapor pressure:**	Not determined.
· **Density:**	Not determined.
· **Relative density**	Not determined.
· **Vapour density**	Not determined.
· **Evaporation rate**	Not determined.
· **Solubility in / Miscibility with**	
Water:	Fully miscible.
· **Partition coefficient (n-octanol/water):**	Not determined.
· **Viscosity:**	
Dynamic:	Not determined.
Kinematic:	Not determined.
· **Solvent content:**	
Organic solvents:	0.0 %
· **Other information**	No further relevant information available.

10 Stability and reactivity

· **Reactivity**
· **Chemical stability**
· **Thermal decomposition / conditions to be avoided:**
No decomposition if used according to specifications.
· **Possibility of hazardous reactions** No dangerous reactions known.
· **Conditions to avoid** No further relevant information available.
· **Incompatible materials:** No further relevant information available.
· **Hazardous decomposition products:** No dangerous decomposition products known.

11 Toxicological information

· **Information on toxicological effects**
· **Acute toxicity:**
· **Primary irritant effect:**
· **on the skin:** No irritant effect.
· **on the eye:** No irritating effect.
· **Sensitization:** No sensitizing effects known.

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· **Additional toxicological information:**
The product is not subject to classification according to internally approved calculation methods for preparations:
When used and handled according to specifications, the product does not have any harmful effects according to our experience and the information provided to us.

· **Carcinogenic categories**

· **IARC (International Agency for Research on Cancer)**
None of the ingredients is listed.

· **NTP (National Toxicology Program)**
None of the ingredients is listed.

· **OSHA-Ca (Occupational Safety & Health Administration)**
None of the ingredients is listed.

12 Ecological information

· **Toxicity**
· **Aquatic toxicity:** No further relevant information available.
· **Persistence and degradability** No further relevant information available.
· **Behavior in environmental systems:**
· **Bioaccumulative potential** No further relevant information available.
· **Mobility in soil** No further relevant information available.
· **Additional ecological information:**
· **General notes:** Not known to be hazardous to water.
· **Results of PBT and vPvB assessment**
· **PBT:** Not applicable.
· **vPvB:** Not applicable.
· **Other adverse effects** No further relevant information available.

13 Disposal considerations

· **Waste treatment methods**
· **Recommendation:** Smaller quantities can be disposed of with household waste.

· **Uncleaned packagings:**
· **Recommendation:** Disposal must be made according to official regulations.
· **Recommended cleansing agent:** Water, if necessary with cleansing agents.

14 Transport information

· **UN-Number**	
· **DOT, ADR, ADN, IMDG, IATA**	Not Regulated

· **UN proper shipping name**	
· **DOT, ADR, ADN, IMDG, IATA**	Not Regulated

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· **Transport hazard class(es)**	
· **DOT, ADR, ADN, IMDG, IATA**	
· **Class**	Not Regulated
· **Packing group**	
· **DOT, ADR, IMDG, IATA**	Not Regulated
· **Environmental hazards:**	
· **Marine pollutant:**	No
· **Special precautions for user**	Not applicable.
· **Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code**	Not applicable.
· **Transport/Additional information:**	Not dangerous according to the above specifications.
· **UN "Model Regulation":**	-

15 Regulatory information

· **Safety, health and environmental regulations/legislation specific for the substance or mixture**
· **Sara**

· **Section 355 (extremely hazardous substances):**
None of the ingredients is listed.

· **Section 313 (Specific toxic chemical listings):**
None of the ingredients is listed.

· **TSCA (Toxic Substances Control Act):**
None of the ingredients is listed.

· **Proposition 65**

· **Chemicals known to cause cancer:**
None of the ingredients is listed.

· **Chemicals known to cause reproductive toxicity for females:**
None of the ingredients is listed.

· **Chemicals known to cause reproductive toxicity for males:**
None of the ingredients is listed.

· **Chemicals known to cause developmental toxicity:**
None of the ingredients is listed.

· **Carcinogenic categories**

· **EPA (Environmental Protection Agency)**
None of the ingredients is listed.

· **TLV (Threshold Limit Value established by ACGIH)**
None of the ingredients is listed.

· **NIOSH-Ca (National Institute for Occupational Safety and Health)**
None of the ingredients is listed.

· **GHS label elements** Not Applicable

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· **Hazard pictograms**
Pictograms on label shall be in the shape of a square set at a point and shall include a black hazard symbol on a white background with a red frame sufficiently wide to be clearly visible.
· **Signal word** Not Applicable
· **Hazard statements** Not Applicable
· **Chemical safety assessment:** A Chemical Safety Assessment has not been carried out.

16 Other information

This information is based on our present knowledge. However, this shall not constitute a guarantee for any specific product features and shall not establish a legally valid contractual relationship.

· **Department issuing SDS:** Product safety department
· **Contact:** Sidney Arfa
· **Date of preparation / last revision** 06/25/2015 / -
· **Abbreviations and acronyms:**
ADR: Accord européen sur le transport des marchandises dangereuses par Route (European Agreement concerning the International Carriage of Dangerous Goods by Road)
IMDG: International Maritime Code for Dangerous Goods
DOT: US Department of Transportation
IATA: International Air Transport Association
ACGIH: American Conference of Governmental Industrial Hygienists
EINECS: European Inventory of Existing Commercial Chemical Substances
ELINCS: European List of Notified Chemical Substances
CAS: Chemical Abstracts Service (division of the American Chemical Society)
NFPA: National Fire Protection Association (USA)
HMIS: Hazardous Materials Identification System (USA)