SUMMARY OF DATA FOR CHEMICAL SELECTION

Bilberry Fruit Extract
84082-34-8

BASIS OF NOMINATION TO THE NTP

Bilberry fruit extract is presented to the CSWG as part of a review of botanicals used as dietary supplements. Ranked number eight in top-selling herbal supplements in 1998-99 with 3.9 million units purchased, bilberry produced sales in food, drug, and mass market retail outlets in the US of $4.6 million in 1997.

Herbalists have long valued bilberry berries and leaves for treatment of eye fatigue and other problems, such as glaucoma, cataracts, and macular degeneration. Some claim that bilberry protects the arteries by reducing deposits that can lead to heart attacks and strokes. The healing effects of bilberry probably stem from anthocyanosides. No information on the effects of long-term administration of bilberry or its anthocyanosides was found in a review of the available literature. Bilberry leaf received a negative evaluation by German Commission E and is listed as an unapproved herb because its efficacy was not demonstrated and, with higher dosages or on prolonged use, it may cause chronic intoxication.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

According to Dr. John Walker of the US Environmental Protection Agency (EPA), the Interagency Testing Committee has deferred action on bilberry fruit extract.

Ms. Kara Dinda, Director of Education for the American Botanical Society, provided information on their monograph program as it relates to bilberry.

SELECTION STATUS

ACTION BY CSWG: 12/16/99

Studies requested:

Ames *Salmonella* assay

Mouse lymphoma assay

Chromosome aberrations (*in vitro*)

Micronuclei (*in vivo*)

Followup: Based on the results of the battery of genotoxicity tests, reconsider for additional testing

Priority: The CSWG does not assign priority to genotoxicity testing

Rationale/Remarks:

Widespread human exposure based on use as a popular dietary supplement for eye strain

Low suspicion of carcinogenicity based on negative results for keracyanin, a flavonoid structurally related to an active ingredient in bilberry

Marginal genotoxic activity predicted on basis of structural analysis of flavonoids

NCI is conducting Ames and mouse lymphoma assays

CHEMICAL IDENTIFICATION

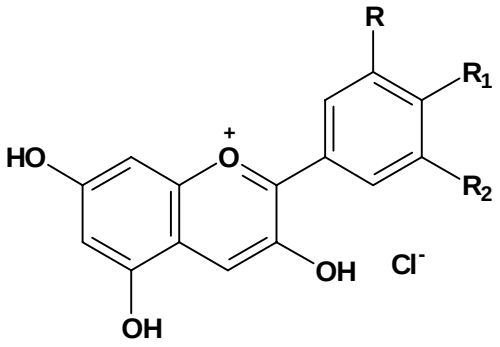
CAS Registry Number:	84082-34-8
Synonyms:	Myrtocyan; whortleberry extract
Botanical Names:	*Myrtilli fructus*; dried, ripe fruit of *Vaccinium myrtillus L.*
Description:	Prepared from the fruit of the bilberry shrub native to mainland Europe, Britain, and Siberia, bilberry extract used in dietary supplements is standardized to 25% anthocyanosides (Nuova Linnea, 1999).

Chemical Composition: The chemical definition of bilberry extract (*Vaccinium myrtillus*) prepared from the fruit of the bilberry shrub is a mixture of natural glycosides of the aglycone anthocyanins, cyanidin, delphinidin, and malvidin (Nuova Linnea, 1999).

R_2 = H, R = R_1 = OH: Cyanidin

R = R_1 = R_2 = OH: Delphinidin

R_1 = OH, R = R_2 = OMe: Malvidin



Technical Products and Impurities: Bilberry extract standardized to 25 percent anthocyanosides (glycoside form of anthocyanins) is available from Nuova Linnea (1999).

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EXPOSURE INFORMATION

Production and Producers: According to the OPD Chemical Buyers Directory, bilberry extract is manufactured or distributed by Allchem Industries, Inc., American Ingredients, Inc., Anmar International, Ltd., CPB International, Inc., DNP International Co., Inc., Extractsplus; Fabrichem, Inc., G.C.I. Nutrients; Infinity Marketing Group, Inc., Maypro Industries, Inc., Mini Star International Inc., Motherland Herb-Pharm Inc., Pharmline, Inc., QBI (Quality Botanical Ingredients, Inc.); Paul Schueller International Inc., Schweizerhall, Inc., Storchem Inc., and P.L. Thomas & Co., Inc. (Tilton, 1998).

Bilberry extracts are widely available to consumers in dietary supplements sold in health food stores and pharmacies. Some bilberry supplements marketed through the Internet are listed in Table 1 below.

Table 1. Some bilberry fruit extracts sold to consumers as dietary supplements

Name	Supplier	Recommended Dose	Description
Bilberry	Natrol	no dosage given	capsule containing 40 mg bilberry extract (25% anthocyanoside content)
Bilberry	Vitamin Shoppe	no dosage given	bilberry is available as tinctures, fluid extract, dried leaves, and berries
Bilberry 60	Vitanet	3-8 capsules/day	capsule containing 80 mg bilberry extract standardized to contain 25% anthocyanosides
Bilberry Extract	Vitamin USA	80-160 mg/day	no details available
Bilberry Extract	Nature's Way	1 capsule 3 x d	capsule containing 80 mg bilberry fruit extract standardized to 25% anthocyanidins
Bilberry Extract	Life Extension Foundation	no data	standardized bilberry extract (25% anthocyanin) from bilberries harvested in northern Sweden
Bilberry-Power	Reach4Life	no data	extract standardized to 25% anthocyanosides; also quercetin, citrus bioflavonoid & rutin

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Eye Formula	Life Plus	1-2 tablets 3 x d	100 mg bilberry extract/tablet plus rutin, hesperidin, β-carotene & glutathione, among others
Mega Multiple III - Tablets	Pro Health, Inc.	not given	bilberry extract 25 mg, and many other ingredients
LifePath® Chewies	Enrich International	1 gumdrop/15 lb bw/day	antioxidant gumdrops for children containing bilberry, grapeseed extract, bioflavonoids, EnriDole 3-C®, bee pollen, *Ginkgo biloba*, rutin, quercetin & milk thistle
OptimEyes	Body Wise International	3 caplets/day	bilberry fruit extract (25% anthocyanidins) plus taurine, selenium, vitamins C & E, lutein, *N*-acetylcysteine, mixed carotenoids & ginkgo biloba

Sources: Natrol, 1996; Life Extension, 1997; Vitamin Shoppe, 1998; Body Wise, 1999; Enrich, 1999; Life Extension, 1999; Life Plus, 1999; Netrition, 1999; Pro Health, 1999; Reach4Life, 1999; Vitamin USA, 1999; Vitanet, 1999

Bilberry fruit is not listed in the EPA's Toxic Substances Control Act (TSCA) Inventory.

Use Pattern: Bilberry fruit extract is commonly used to relieve eye fatigue, reduce eye irritation, and aid night vision. It also has reported applications in the treatment of vascular retinal disturbances, cataract, and diabetic-induced glaucoma and myopia. Bilberry extract has been indicated in the treatment of hemorrhoids and mild intestinal infections (colibacillosis), atherosclerosis, arteriosclerosis, and coldness of hands and feet. It is also reported to have vasoprotective activity (Nuova Linnea, 1999).

Bilberry is viewed as a phytopharmaceutical in Europe where it is credited with antioxidant and blood vessel reinforcing properties. In skin creams, bilberry extract is used to soften broken capillaries under the skin surface and to protect the epidermis from the harmful effects of free radicals, chemicals, and drugs. Bilberry extract is also cited in treatments to help prevent and treat bruising or purpura, and may relieve inflammations such as those which occur in osteoarthritis, rheumatoid arthritis, and gum disease (Nuova Linnea, 1999).

Bilberry leaf is used for diabetes mellitus, for prevention and treatment of complaints of the

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gastrointestinal tract, kidney and urinary tract, for arthritis, gout, dermatitis, hemorrhoids, poor circulation, and heart problems (Blumenthal, 1998).

Proanthocyanidins, such as those found in bilberry extract, have been described as potent free radical scavengers, possessing an antioxidant effect up to 50 times more potent than vitamin E (Vitanet, 1999).

Human Exposure: Exposure of humans to bilberry fruit extract occurs through its use as a dietary supplement. Daily dosage as dried fruit is 20 to 60 g (internal), which corresponds to 240 to 280 mg of extract standardized to 25% anthocyanoside, and 10 percent decoction (external) (Blumenthal, 1998; Herbalgram, 1999).

No listing was found for bilberry fruit extract in the National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983.

Environmental Occurrence: Bilberry belongs to the *Vaccinium myrtillus* L. family and is closely related to the North American blueberry. Bilberry grows in mainland Europe, Britain, and Siberia (HealthNotes, 1998; Nuova Linnea, 1999).

Regulatory Status: Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). For dietary supplements, such as bilberry extract, which were on the market before October 15, 1994, DSHEA requires no proof of safety in order for them to remain on the market. The labeling requirements for supplements allow warnings and dosage recommendations as well as substantiated "structure or function" claims. All claims must prominently note that they have not been evaluated by the FDA, and they must bear the statement "This product is not intended to diagnose, treat, cure, or prevent any disease" (Croom & Walker, 1995).

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to bilberry extract and cancer risks in humans were identified in the available literature.

The German Commission E monograph on bilberry fruit indicates that no contraindications, side effects, or interactions with other drugs are known. Bilberry leaf extract received a negative evaluation by Commission E because efficacy has not been documented and with higher dosages or on prolonged use, chronic intoxication may arise (Blumenthal, 1998).

The FDA's Special Nutritionals Adverse Event Monitoring System reported five illnesses or injuries associated with the use of special nutritional products and dietary supplements containing bilberry (FDA, 1998). No mention of possible preexisting conditions was made, and there is no certainty that a reported adverse event can be attributed to a particular product or ingredient.

According to Williamson and Wyandt (1998), herbal preparations of bilberry should never be recommended as an alternative to diabetic medications. Potential interactions of bilberry supplements with over-the-counter and prescription medications are unknown.

European clinical trials have reportedly shown the effectiveness of bilberry extract for treating the symptoms of varicose veins in the lower limbs in 18- to 75-year-old subjects. These trials revealed no significant side effects, even at 50 percent over the normal dose (Jacobs & Reed, 1999).

Bilberry extract has been described as safe for use during pregnancy (Herbalgram, 1999). In two clinical trials, a standardized bilberry extract given to 115 women with venous insufficiency and hemorrhoids following pregnancy resulted in improvements of symptoms, including pain, burning, and pruritus (Jacobs & Reed, 1999).

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Animal Data: *Acute Studies.* No information on the acute toxicity of bilberry fruit extract was identified in the available literature. The acute toxicities of some active ingredients of bilberry, as listed in RTECS, are presented below (NLM, 1999).

Table 2: Acute toxicities of bilberry extract components

Chemical	Species	Route	LD_{50} Dose
Cyanidin	rat	ip	1500 mg/kg
	dog	oral	>3000 mg/kg
	mammal (NOS)	oral	>6000 mg/kg
Malvidin chloride	mouse	iv	18 mg/kg

Subacute/Subchronic Studies. No information on the subacute or subchronic toxicity of bilberry fruit extract was found in the available literature. The symptoms of intoxication from bilberry leaf in animal experiments were initially cachexia, anemia, icterus, acute excitation, and disturbances of tonus, which, after long-term administration of 1.5 g/kg/day, could finally end in death (Blumenthal, 1998).

Chronic/Carcinogenicity Studies. No 2-year carcinogenicity studies of bilberry, bilberry extract, bilberry fruit extract, or bilberry leaf extract were identified in the available literature.

Short-Term Tests: No information on the mutagenic potential of any bilberry extract was identified in the available literature.

At dosages of 100 to 200 µg/ml, cyanidin chloride produced a statistically significant increase in sister chromatid exchanges and micronuclei in human lymphocyte cultures. Lower doses were ineffective (Popp & Schimmer, 1991).

Cyanidin (dose unspecified) was negative in Chinese hamster V-79 cells when assayed by

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an *in vitro* chromosome aberration test without metabolic activation (Kojima, 1985).

Metabolism: No information on the metabolism of any bilberry extract was found in the available literature.

Other Biological Effects: *Anti-ulcer activity*. Bilberry extract possesses antiulcer activity in various experimental models. The anthocyanidin pigment, 3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-1-benzopyrylium chloride (IdB 1027), isolated from the extract, appears to account at least in part for these antiulcer properties (Magistretti *et al.,* 1988). Mertz-Nielsen and coworkers (1990) concluded that a marked increase in gastric mucosal release of prostaglandin E_2 seen in human volunteers may explain the antiulcer and gastroprotective effects of IdB 1027. Cristoni and coworkers (1989) suggested that the gastroprotective activity of IdB 1027 is mediated by an increase in the efficiency of the gastric mucosal barrier.

Antimutagenic and Anticarcinogenic Activity. Bilberry fruit extracts were screened for anticarcinogenic activity by *in vitro* assays measuring ability to induce the Phase II detoxification enzyme quinone reductase and to inhibit the induction of ornithine decarboxylase. Crude extracts containing the anthocyanin and proanthocyanidin fractions showed little activity. However, further fractionation produced an extract that induced quinone reductase (Bomser *et al.*, 1996).

Cyanidin chloride inhibited the liver S-9-mediated mutagenicity in *S. typhimurium* TA98 of the heterocyclic amines, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx) and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) (Malaveille *et al.*, 1996)

In contrast, cyanidin, malvidin, and delphinidin were inactive in preventing the S-9-mediated mutagenicity in *S. typhimurium* TA98 of the heterocyclic amines, 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ) and 3-amino-1-methyl-*5H*-pyrido[4,3-*b*]indole (Trp-P-

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2) from cooked food. The authors noted that anthocyanidins lacking the keto group at carbon atom 4 of the flavane nucleus were inactive while flavones, flavonols, and flavanones bearing the 4-keto group exerted high antimutagenic activity (Edenharder *et al.*, 1993).

Reproductive Effects. Malvidin chloride inhibited spermatogenesis in langur monkeys fed 50 mg/kg for 60 days. The weights of testes and epididymides were reduced and atrophy of the Leydig cells was observed. In the epididymis, epithelial cell heights were reduced after malvidin chloride treatment. Conspicuous shrinkage of seminiferous tubules and Leydig cell nuclei was evident. Depletion of total proteins, RNA, sialic acid, alkaline/acid phosphatase activity in testes and epididymides with the elevation of testicular levels of cholesterol and glycogen also occurred (Bhargava, 1990).

Effects on Arteriolar Vasomotion. Intravenously injected *Vaccinium Myrtillus* anthocyanosides (VMA) induced vasomotion in cheek pouch arterioles and terminal arterioles of hamsters. In the skeletal muscle arteriolar networks, VMA increased vasomotion frequency and amplitude in all vessel orders. Thus, VMA was effective in promoting and enhancing arteriolar rhythmic diameter changes that play a role in the redistribution of microvascular blood flow and interstitial fluid formation (Colantuoni *et al.*, 1991).

Effects of Leaf Extracts on Low Density Lipoproteins (LDL). A dried extract of *Vaccinium myrtillus L*. leaf administered orally to streptozotocin-diabetic rats for four days consistently caused a drop in plasma glucose and triglyceride levels. Both *Vaccinium myrtillus L*. leaf extracts and ciprofibrate, a positive control, were effective in lowering triglyceride level in rats on hyperlipidaemic diets, in ethanol-treated normolipidaemic animals, and in genetically hyperlipidaemic Yoshida rats (Cignarella *et al.*, 1996).

Antioxidative activity. Cyanidin 3-*O*-β-D-glucoside and cyanidin isolated from the seed

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coat of red beans had antioxidative activity when examined by using linoleic acid autoxidation, liposome, rabbit erythrocyte membrane, and rat liver microsomal systems. These data suggested that these anthocyanin pigments may play an important role in the prevention of lipid peroxidation of cell membranes induced by active oxygen radicals (Tsuda *et al.*, 1994;Tsuda *et al.*, 1996).

Anthocyanins and the aglycon, cyanidin, isolated from tart cherries, also exhibited *in vitro* antioxidant activities comparable to those of *tert*-butylhydroquinone and butylated hydroxytoluene and superior to vitamin E. Cyanidin exhibited anti-inflammatory activity (Wang *et al.*, 1999).

Structure-Activity Relationships:

The suspected active ingredients in bilberry are red-blue pigments, the anthocyanins. In addition to bilberry, anthocyanins are found in blueberry, cranberry, and lingonberry. No information on the genotoxic or carcinogenic potential of these other fruit extracts was found in the available literature.

Anthocyanins are members of the flavonoids, a group of more than 4000 naturally occurring polyphenols sharing a similar chemical structure (Boik, 1996).

Perhaps the most widespread of the flavonoids is the flavonol aglycone quercetin. Extensive information suggests that quercetin is a frameshift mutagen. Quercetin has consistently shown mutagenic activity in *S. typhimurium* strains TA97, TA98, TA100, and TA102 without metabolic activation. Responses with metabolic activation have also tended to be positive, but somewhat dependent on the activation system used and other conditions of the experiment. The genotoxic potential of quercetin has also been demonstrated in several other assays. Quercetin has been examined for carcinogenic activity in 10 different tests, all but two of which were negative. A thorough discussion of these results can be obtained in the Summary Sheet for *Ginkgo biloba* extract, which

was presented to the CSWG on April 29, 1998.

A more closely related flavonoid is the anthocyanin, keracyanin (3-rhamnoglucoside of cyanidin chloride, $C_{27}H_{31}ClO_{15}$). In a chronic oral toxicity study, male and female Wistar rats given 0, 1.5, or 3.7 g/kg of keracyanin a day in the diet for two years did not develop an increase in cancer (Tsubura *et al.*, 1983). Keracyanin was tested for mutagenicity in the chromosome aberration test with or without metabolic activation using Chinese hamster V79 cells, and by the micronucleus test using bone marrow of BDF_1 male mice. The incidence of cells with chromosome aberrations was elevated by 13 to 27 percent when V79 cells were exposed at 2 mg/ml keracyanin for 48 hours without metabolic activation. Keracyanin was nonmutagenic in other test systems (Kojima, 1985).

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