SUMMARY OF DATA FOR CHEMICAL SELECTION

Bladderwrack

BASIS OF NOMINATION TO THE CSWG

The lack of toxicity testing coupled with a strong suspicion that adverse events may occur in humans exposed to bladderwrack is brought to the attention of the CSWG.

Although bladderwrack is not thought to be one of the highest volume dietary supplements, it is widely promoted, especially to women, for weight loss. Bladderwrack is a source of iodine, and it is this iodine that provides the theoretical basis for bladderwrack's activity. If iodine levels in bladderwrack are sufficiently high to cause weight loss, however, they would also be high enough to cause a hyperthyroid condition.

Although there is information in the FDA's Adverse Event Monitoring System that raises concerns about the safety of bladderwrack, the presence of other diet aids, especially ephedra, make it difficult to ascertain the role, if any, of bladderwrack. Thus, it is recommended that special tests be conducted on pure bladderwrack to determine if the iodine concentrations present in dietary supplements provide sufficient thyroid stimulation to pose a risk to consumers.

SELECTION STATUS

ACTION BY CSWG: 12/12/00

Studies requested:

Subacute toxicity

Chemical analysis (iodine content of diet aides vs natural bladderwrack)

Priority: None assigned

Rationale/Remarks:

Effectiveness of bladderwrack as a diet aide appears to be based, at least in part, on iodine Content

Concern about the safety of dietary supplements containing bladderwrack if weight loss is caused by hyperthyroidism from excessive iodine intake

Concerns regarding possible additive or synergistic toxicities from several components in diet aides containing bladderwrack

CHEMICAL IDENTIFICATION

CAS Registry Name and Number:	*Fucus vesiculosus* - 68917-51-1 *Fucus vesiculosus*, ext. - 84696-13-9
Botanical Name:	*Fucus vesiculosus*
Synonyms:	Bladderwrack: black-tang; bladder fucus; blasentang; cut-weed; fucus; kelpware; quercus marina; sea-wrack; seetang; tang; Varech vesiculeux (Blumenthal, 1998; Budavari, 1996; Felter & Lloyd, 2000; Grieve, 1995) *Fucus vesiculosus* oil: algae extract; algarol; algarol superessence; fucus absolute; fucus oil; seaweed absolute; seaweed extract; seaweed oil; seaweed resinoid (NLM, 2000) *Fucus vesiculosus* extract: bladderwrack extract; fucus extract; fucus vesiculosus extract (NLM, 2000)
Structural Class:	Family *Fucoideae*
Description:	Preparations of bladderwrack consist of the dried thallus of *Fucus vesiculosus* L. or *Ascophyllum nodosum* Le Jolis or of both species (Blumenthal, 1998); constituents are algin, ~0.01% iodine, and some bromine mannite (Budavari, 1996)

Technical Products and Impurities: As found in commerce, *Fucus vesiculosus* is hard and brittle, forming a wrinkled mass, blackish or with a whitish efflorescence or incrustation. It acquires a cartilaginous consistency when slightly moistened. It has a strong, seaweed-like odor and a saline and mucilaginous taste. The powder is reddish brown with numerous fragments of epidermal tissue (Grieve, 1995).

Bladderwrack is available to consumers as a dietary supplement for weight loss, often with ephedra (ma huang), chromium picolinate, or other herbals used for weight loss. Some products that have been or are being sold to consumers are listed below in Table 1.

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Table 1. Some dietary supplements containing bladderwrack

Product Name	Manufacturer	Other Ingredients
Bio-Mark Weight Control System	Bio-Mark International	Ma-huang, guarana, hawthorn berry, cascara sagrada, goldenrod, parsley, bai-zhu, fo-ti, uva-ursi, fumitory, others
Cellasene	Sundown	Ginkgo biloba, sweet clover, grape seed bioflavonoids, evening primrose oil, soya lecithin combined with fish oil
Dermalife Derma Patch	Dermalife	Principal extract is *Fucus vesiculosus*
Lee Causey's Slim n' Up	First Fitness, Inc.	Cola nut, ephedra, dandelion root, guarana, kelp, Mg & K gluconate, green tea, L-carnitine, α-keto-glutarate, coenzyme Q-10, valerian root, others
Megawatt	Shaperite Concepts Ltd	Ephedra, camillia sinesis, willow, ginger, astragalus, saw palmetto, licorice root, Ni-Chrome™
Natural Trim	Starlight International	Fumitory, licorice root, goldenrod, fo-ti, parsley, uva-ursi, bai-zhu, hawthorn berry, cascara sagrada, chromium picolinate, others
Nature's Nutrition Formula One	Affiliated Consultants International/Alliance USA	Ma-huang, cola nut, willow, ginkgo biloba, fo-ti, hawthorn berry, saw palmetto, chromium picolinate, boron proteinate, others
Slim NRG+	Momentum Marketing	Ephedra sinica, willow, gotu kola, ginger, ginkgo biloba, choline bitartrate, hawthorn berry, L-carnitine, chromium nicotinate, boron proteinate, others
Thermojetics Green	Herbalife International of America, Inc.	Ma-huang, yerba mate, valerian root, willow, others
Thigh Cream	Alpha Worldwide Marketing	Aloe vera, ivy, glycerine, avocado, theophylline, others
Tri-Chromaleane	Achiever's Unlimited	Chromium picolinate, ephedra, guarana, willow bark, gotu kola, Siberian ginseng, astragalus, licorice root, others
ThermAslim	Thermaslim	Guarana, ma huang, citrimax, white willow bark extract, chromium nicotinate, pancreatin, fo-ti, hawthorne berry extract, saw palmetto berry extract, others

Source: Dermalife, 2000; FDA, 1998; Feel21, 2000; Thermaslim, 1999

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EXPOSURE INFORMATION

Production:

Manufacturing process. The entire living plant is gathered from the rocks about the end of June and dried rapidly in the sun. When it becomes brittle it is easily reduced to a coarse powder. When thrown up on the shore, the seaweed is not suitable for medicinal purposes (Grieve, 1995).

Production/import/export levels. *Fucus vesiculosus* oils are listed in the TSCA Inventory (NLM, 2000).

Producers and Importers: Bladderwrack extract is available from AF Pharma LLC, Bio-Botanica Inc., Pharmaline, Inc., and Westco Fine Ingredients, Inc. Bladderwrack is available from California Energy Nutriceuticals (Tilton, 2000).

Fucoidan [9072-19-9], which is prepared from *Fucus vesiculosus*, is a polysaccharide composed predominantly of sulfated fucose. Fucoidan is available from Sigma-Aldrich (2000).

Use Pattern:

Preparations of bladderwrack are used for diseases of the thyroid, obesity, arteriosclerosis, and digestive disorders, as well as for "cleansing the blood" (Blumenthal, 1998).

In the United States, products such as Cellasene, Medex, and Bioslim diet patches are sold as non-prescription weight loss supplements. The proposed action is that the iodine in bladderwrack increases thyroid hormone production leading to increased metabolism. This increased metabolism has the potential to initiate weight loss without a change in a dieter's eating habits (Egger *et al.*, 1999; Morrison, 2000).

Bladderwrack is a valuable manure for crops along the British coast. It has also been evaluated for making paper and alcohol, and for kelp burning as a source of iodine, but these uses were not cost effective (Grieve, 1995).

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Many different seaweeds are used in several perfumery products to impart a green herbaceous, phenolic woody and dry odor (The Good Scents Company, 2000).

Human Exposure:

The charcoal derived from kelp burning has been used since the 1700s in the treatment of goiter and scrofulous swellings, but iodine from other sources led to the neglect of kelp products for such purposes. In 1862, Duchesne-Duparc observed weight reduction in chronic psoriasis patients he was treating with bladderwrack, and he subsequently used infusions or extracts in pill form for this purpose (Felter & Lloyd, 2000; Grieve, 1995).

Dosages of charcoal are 10 grains to 2 drachms; of extract, 3 to 10 grains; of liquid extract (often with sodium and potassium iodides added), 1 to 2 fluid drachms; of decoction, 2 fluid ounces three times daily; of infusion, 1 wine glassful (Grieve, 1995).

Elusan® Cleanser, an herbal dietary supplement containing bladderwrack and used to promote regularity of the digestion process, contains 60 µg of iodine per capsule (Plantes & Medecines, 1998).

Environmental Occurrence: *Fucus vesiculosis* is a perennial sea-weed found on submerged rocks on both coasts of North America, and in Europe north of the Mediterranean, where it drifts in from time to time through the Strait of Gibralter (Felter & Lloyd, 2000; Grieve, 1995).

Regulatory Status: Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). The DSHEA requires no proof of safety for dietary supplements on the market prior to October 15, 1994. Labeling requirements for dietary 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” (FDA, 1995).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

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

Animal Data:

Chronic/carcinogenicity studies. No 2-year carcinogenicity studies of bladderwrack in animals were identified in the available literature.

Acute, subacute, and subchronic studies. No information on acute, subacute, or subchronic toxicity of bladderwrack as it relates to carcinogenic potential was identified in the available literature. Other concerns, e.g., induction of hyperthyroidism or exacerbation of existing hyperthyroidism, is discussed in the section on other biological effects.

Short-Term Tests: No information on the genotoxicity of bladderwrack was identified in the available literature.

Metabolism: No information on products produced from the metabolism of bladderwrack ingredients was identified in the available literature. The potential effects of iodine on metabolism are described in the section on other biological effects.

Other Biological Effects: Bladderwrack preparations are used for weight loss. According to German Commission E, the effectiveness for this application is not verified. However, above the daily dosage of 150 µg of iodine, there is danger that hyperthyroidism may be induced or existing hyperthyroidism may be made worse (Blumenthal, 1998).

Hyperthyroidism is a condition in which the overactive thyroid gland leads to symptoms of nervousness, irritability, increased perspiration, thinning of the skin, fine brittle hair, weight loss despite a good appetite, amenorrhea, and muscular weakness (Morrison, 2000).

The human thyroid gland can tolerate wide fluctuations in iodine levels and no evidence exists to support the assumption that increasing iodine intake in non-thyroid-deficient individuals has any effect on weight loss (Egger *et al.*, 1999). Because of the lack of unbiased clinical research on bladderwrack as a weight-loss agent, whether the amount of iodine in dietary supplements is significant enough to produce a noticeable effect on metabolism is unknown (Morrison, 2000).

In a case study reported in the literature, a young woman who had been taking 400 mg tablets of *Fucus vesiculosus* (three tablets three times a day) developed kidney disease that may have been associated with high levels of arsenic (21.3 mg/kg) and other metals in the tablets (Conz *et al.*, 1998).

According to German Commission E, in rare cases allergic reactions to bladderwrack preparations involving serious overall reactions may occur (Blumenthal, 1998).

The FDA's Special Nutritionals Adverse Event Monitoring System reported 108 matches for bladderwrack dietary supplements in 104 adverse event reports (AER) as of October 20, 1998. Some effects reported that would be consistent with stimulation of the thyroid gland were as follows: numbness in hands, disorientation and sweating; severe headaches, elevated heart rate, dizziness, blurred vision, nausea; developed jitteriness and palpitations; dizziness, nervousness and cramps; palpitations, tachycardia, tremors of hands and legs and insomnia; hands were shaking, heart pounding, nervousness and depression; "hypersensitive," jittery, and nervous; exhausted, shaky, legs weak; heaviness in chest, hair loss; abnormal liver and thyroid function tests; heart palpitations, chest pains; loss of menstrual cycle; "heat flashes," heart palpitations, sleeplessness, thyroid condition; shaking, nervousness; and rapid pulse. Since no information on preexisting conditions was available and most of the 108 cases were exposed to other herbal diet aids, including ephedra alkaloids, there is no certainty that the reported adverse events can be attributed to bladderwrack. A recent review of 140 AERs related to the use of dietary supplements containing ephedra alkaloids considered 62 percent to be definitely, probably, or possibly related. Adverse events associated with use of ephedra alkaloids included hypertension, palpitations, tachycardia, stroke, and seizures (FDA, 1998; Haller & Benowitz, 2000).

Fucoidan, a complex sulfated polysaccharide derived from *Fucus vesiculosus*, has been shown to mediate a variety of biological effects on mammalian cells, including blocking of sperm-egg binding in diverse species and blocking the infection of human cell lines with several viruses, including HIV, herpes, and cytomegalovirus (Patankar *et al.*, 1993). Commercial crude fucoidan from *Fucus vesiculosus* showed potent anticoagulant activity (Nishino *et al.*, 1994). Fucoidan has also been described as having antitumor and immunomodulating activities (D'Adamo, 1998) and to be toxic to *Neisseria meningitidis* and some strains of *Escherichia coli* (Criado & Ferreirós, 1984).

Ethanol extracts of *Fucus vesiculosus* at doses of 5-20 g/kg administered intragastrically to fasted New Zealand rabbits produced no dose-related influence on glycemia or triglyceridemia (Lamela *et al.*, 1989)

Structure-Activity Analysis: Bladderwrack is a natural product containing, among other things, the gelatinous substance, algin; mannitol; and small amounts of iodine. Thus, a traditional analysis of activity based on structural correlations was not attempted.

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