

SUMMARY OF DATA FOR CHEMICAL SELECTION

Echinacea

BASIS OF NOMINATION TO THE CSWG

Echinacea is presented to the CSWG as part of a review of botanicals being used as dietary supplements in the United States. Alternative herbal medicines are projected to be a \$5 billion market by the turn of the century. Echinacea is an extremely popular herbal supplement; sales are nearly \$300 million a year according to the last figures available.

Sweeping deregulation of botanicals now permits echinacea to be sold to the public without proof of safety or efficacy if the merchandiser notes on the label that the product is not intended to diagnose, treat, cure, or prevent any disease. The literature on echinacea clearly showed that it is being used for the treatment of viral and bacterial infections although virtually no information on safety was found.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

According to the Center for Food Safety and Applied Nutrition, FDA does not have information about the safety or purported benefits of echinacea.

SELECTION STATUS

ACTION BY CSWG: 4/28/98

Studies requested:

- Toxicological evaluation, to include 90-day subchronic study
- Carcinogenicity, depending on the results of the toxicologic evaluation
- Micronucleus assay

Priority: Moderate

Rationale/Remarks:

- Potential for widespread human exposure.
- Most popular herbal supplement in the US, used to stimulate immune system
- Test material should be standardized to 2.4% β -1,2-*d*-fructofuranoside
- NCI will conduct Ames *Salmonella* assay

CHEMICAL IDENTIFICATION

<u>Chemical Abstract Service Names:</u>	<u>CAS Registry Numbers:</u>
<i>Echinacea angustifolia</i> , ext.	84696-11-7
<i>Echinacea purpurea</i> , ext.	90028-20-9
<i>Echinacea pallida</i> , ext.	97281-15-7
<i>Echinacea angustifolia</i> , tincture	129677-89-0

Description: Echinacea are herbaceous perennials of the daisy family. Echinacea may have either simple or branched stems. The flowers are large and daisy-like and are sometimes known as coneflowers because of the raised capitulum containing disc florets to which are attached ray florets. The color of ray flowers ranges from white, through pink and rose, to deep purple with yellow reserved for *E. paradoxa* var. *paradoxa*. Disc flowers may be red brown to green. The leaf shape varies from lanceolate to ovate. Roots are either a single taproot or fibrous in form (Awang & Kindack, 1991; Houghton, 1994).

E. angustifolia with a typical height of up to 2 feet is shorter than *E. purpurea* (1.5 to 5 feet) and *E. pallida* (1 to 3 feet) (Herbal Resources, Inc., 1995).

Chemical Composition: The pharmacologically important constituents of echinacea can be grouped as follows:

- *Polysaccharides.* A number of immunostimulatory and mildly anti-inflammatory polysaccharides have been isolated including inulin, found at 5.9% in *E. angustifolia* root. The most potent immune-enhancing polysaccharides are the water-soluble, acidic, branched-chain heteroglycans composed of many types of sugars rather than the polyfructose rich inulin.
- *Flavonoids.* The leaves and stems of *E. angustifolia* and *E. purpurea* contain numerous flavonoids with rutoside being most abundant. Total flavonoid content (calculated as quercetin) in the two species was 0.48% and 0.38%, respectively.
- *Caffeic Acid Derivatives.* Echinacoside, a caffeic acid derivative believed to be

unique to echinacea, has been identified in the roots of *E. angustifolia* and *E. pallida* at concentrations of 0.3-1.3% and 0.4-1.7%, respectively. *E. purpurea* has been assumed to have similar levels. Cichoric acid, chlorogenic acid, and cynarin are also pharmacologically important caffeic acid derivatives found in echinacea.

- *Essential Oils*. The essential oil content of the three common species ranges from 0.1% in *E. purpurea* root to up to 2% in *E. pallida* root. Components of the essential oils include borneol, α -pinene, humulene, caryophyllene and its epoxide, germacrene D, and methyl-p-hydroxycinnamate.
- *Polyacetylenes*. A number of polyacetylenes have been identified from the roots of all three commercial species. Echinolone, isolated from *E. angustifolia*, has shown insecticidal activity. At least 13 other polyacetylenes have been isolated.
- *Alkylamides*. Isobutylamides, held responsible for echinacea's local anesthetic effect, are major constituents of the roots of *E. angustifolia* and *E. purpurea*. The amides of *E. purpurea* root have mainly a 2,4-dienoic unit such as dodeca-2E, 4E, 8Z, 10E-tetraenoic acid isobutylamide, whereas those of *E. angustifolia* root favor a monoenoic structure such as dodeca-2E-ene-8, 10-dienoic acid isobutylamide.
- *Miscellaneous*. Other compounds isolated from echinacea species include: resins, glycoproteins, sterols, minerals, and the alkaloids, tussilagine and isotussilagine (Awang & Kindack, 1991; Bauer & Wagner, 1991; Houghton, 1994; Muller-Jakic *et al.*, 1994; Herbal Resources, Inc., 1995; Hoffman, 1998).

Sesquiterpene cinnamoyl esters which were originally identified in commercial samples of *E. purpurea* have since been shown to be due to an adulterant *Parthenium integrifolium*; it has been postulated that the polyacetylenes are artifacts formed during storage, since they are found in dried but not fresh roots of *E. pallida* (Awang & Kindack, 1991; Hoffman, 1998). Bauer and Wagner (1991) have reviewed the chemical composition of echinacea.

Technical Products and Impurities: Echinacea is available at health food stores and pharmacies as well as through direct-mail companies. Preparations include dried root or herb, liquid extract, powder, capsules, tablets, creams and gels. Injectable preparations, popular in Germany, are not available in North America (Awang & Kindack, 1991; Herbal Resources, Inc., 1995; Herb Research Foundation, 1997). Croom and Walker (1995) note that a problem plaguing the interpretation of much of the echinacea clinical literature is that the active constituents are not unequivocally identified and most studies have utilized preparations that are not standardized with respect to active ingredients.

The following products are representative of the many echinacea preparations available.

Extracts or Tinctures: Liquid extracts or tinctures may be alcohol- or glycerine-based. EchinaCare Liquid, imported from Switzerland, is the fresh-pressed juice of *E. purpurea* stems, leaves, and flowers stabilized in 22% alcohol. The juice is standardized on a fixed content of 2.4% soluble 6-1, 2-D-fructofuranosides. Eclectic Echinacea, a Canadian firm, offers an extra strength tincture. Echinacea is macerated in a menstruum of absolute alcohol and distilled water to yield a 1:2 tincture corresponding to 1 kg of plant material to 2 liters of menstruum (Herbal Resources, Inc., 1995; Herb Research Foundation, 1997; Eclectic Echinacea Corp., 1998).

Capsules or Tablets: Echinacea capsules or tablets may contain root powder or herb. EchinaCare capsules from Switzerland contain a powder concentrate from the fresh-pressed juice of *E. purpurea* stems, leaves, and flowers standardized to 2.4% 6-1,2-D-fructofuranoside. The 50 mg capsules are also standardized at a 50:1 ratio (50 pounds of plant material to yield one pound of powder). Vitamin Connection, a catalog company, offers five different capsule products ranging in strength from 226 to 500 mg (Herbal Resources, Inc., 1995; Herb Research Foundation, 1997; Vitamin Connection, 1998).

Tea: The root and/or herb may be brewed as a tea. The herb tea offered by Eclectic Echinacea uses the dried flowering tops of the echinacea plant (Herb Research Foundation, 1997; Eclectic Echinacea, 1998).

Cream: A skin cream from Eclectic Echinacea contains 10% fresh echinacea formulated in bees wax with benzoin as a fixative (Eclectic Echinacea, 1998).

Echinacea is also found in combination herbal products, such as in capsules with astragalus and reishi mushroom, or with goldenseal. Absorbine Jr., a rub for muscle aches, contains echinacea combined with marigold, wormwood, and menthol (Awang & Kindack, 1991).

EXPOSURE INFORMATION

Production and Producers: The genus *Echinacea* is native to the North American prairies.

Nearly all parts of the plant are used for therapeutic preparations including the root, leaves, flowers, and seeds. Echinacea products may be derived from cultivated or wild stocks. European products rely on cultivated plants, mainly *E. purpurea*. Some European preparations are derived from cell cultures of echinacea species (Awang & Kindack, 1991; Houghton, 1994; Herbal Resources, Inc., 1995; Herb Research Foundation, 1997; Eclectic Echinacea, 1998).

Echinacea is available from American Ingredients, Maypro Industries, and Pharmline. Echinacea extract is available from Acta Pharmacal, American Ingredients, Ashland Chemical Co., Bio-Botanica, CPB International, Extractsplus, Frutarom Meer Corp., G.C.I. Nutrients, Mini Star Int., Motherland Herb-Pharm, NF Formulas, QBI and RIA, Int. Echinacea powder is available from American Ingredients and Ashland Chemical Co. Echinacea root is available from American Ingredients, Botanicals Int., Herbarium, and Mini Star, Int. (McCoy, 1997). There are many additional distributors of echinacea products who sell through direct marketing.

The popularity of echinacea has grown in the US in the past decade, and in 1995 it was one of the leading sellers in health food stores (Croom & Walker, 1995). In 1996, sales of herbal supplements were close to \$3 billion and, with a market share of 9.6%, echinacea was the largest seller. Herbal supplements are projected to become a \$5 billion market by the turn of the century (Anon., 1997; Tanaka, 1997).

The Port Import/Export Reporting Service (PIERS) reported echinacea imports of 140,602 pounds over the 13-month period from November 1996 to December 1997 (Dialog Information Services, 1998).

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

Use Pattern: Of the nine Echinacea species, *E. angustifolia*, *E. purpurea*, and *E. pallida* are the most commonly used. Recently both *E. simulata* and *E. paradoxa* have also been collected for the botanical market (Awang & Kindack, 1991; Bauer & Foster, 1991; Herbal Resources, Inc., 1995). Echinacea was widely used by the Plains Indians of North America for a variety of purposes including treatment of snake bite and relief of fever. From 1887, the plant was incorporated into a variety of patent medicines and by the 1920s echinacea was the largest selling patent medicine in North America. Echinacea was included in the National Formulary of the United States from 1916 to 1950; however, after years of debate over its effectiveness, use declined in the 1930s. As interest in echinacea waned in North America it increased in Europe. A German firm (Madaus) imported *E. purpurea* seeds from the US and this species is the subject of almost all research on the genus conducted in Europe over the last fifty years. Today, more than 280 echinacea-containing products are manufactured in Germany alone (Awang & Kindack, 1991; Houghton, 1994; Eclectic Echinacca, 1998).

Echinacea is regarded as effective in treating certain viral and bacterial infections as well

as wounds and inflammation, while stimulating the immune system. Its ability to potentiate the immune system and to reduce inflammation provide the basis for many of its suggested uses including treatment of colds, coughs, flu, other upper respiratory infections, enlarged lymph glands, sore throat, urinary tract infections, herpes and candida, wounds, skin infections, eczema and psoriasis (Awang & Kindack, 1991; Brown, 1996; Herb Research Foundation, 1997).

Echinacea has been used in conjunction with cyclophosphamide and thymostimulin for immunostimulation in patients with advanced cancers (Lersch *et al.*, 1990; 1992).

Echinacea is also used in toothpastes and cosmetics (Awang & Kindack, 1991).

Some recommended usage levels for echinacea are as follows: extracts or tincture (0.5-5 ml 3/day), capsules or tablets (0.5-2 g 3/day), and tea (0.5-2 g 3/day). With long-term use, echinacea appears to lose effectiveness and the recommended period of maximum continuous use is 6 to 8 weeks (Herb Research Foundation, 1997).

Human Exposure: The primary exposure of humans to echinacea occurs through its widespread use as an herbal supplement. Approximately one third of the US adult population or approximately 60 million consumers, have increasingly utilized alternative pharmaceutical preparations to prevent or treat illnesses (Tanaka, 1997).

There is potential for worker exposure to echinacea during the growing, harvesting, and processing of the plants. For the purposes of quantifying the costs of food labeling regulations, the FDA (1997) estimated that there were 250 herbal/botanical firms (lower bound estimate).

No listing was found for echinacea 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: The genus *Echinacea* is indigenous only to North America. *E. angustifolia* (narrow-leaved coneflower) grows from Saskatchewan to Texas and it is also found in Tennessee. *E. purpurea* (purple coneflower) is found in the area circumscribed by Michigan, Ohio, Georgia, Louisiana, Oklahoma, and Iowa. *E. pallida* grows in the prairies and glades from Arkansas to Wisconsin, Minnesota, Oklahoma, Kansas, and Nebraska. *E. simulata* and *E. paradoxa* are endemic in the Ozarks of Missouri and Arkansas (Bauer & Foster, 1991; Herbal Resources, Inc., 1995; Medicinal Herbs Online, 1996; TimeLife Books, 1998).

Regulatory Status: Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). For dietary supplements on the market prior to October 15, 1994, the 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).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

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

There have been no reports of serious adverse effects associated with the administration of echinacea. Occasionally the injection of echinacea extracts has resulted in a feverish reaction. Skin rashes and insomnia have also been reported. Due to cross hypersensitivity, echinacea should not be taken by persons allergic to flowers of the daisy family. Echinacea is contraindicated in individuals with autoimmune illnesses and other progressive systemic diseases such as tuberculosis, multiple sclerosis, and HIV infection and AIDS related illnesses (Avedikian, 1994; Houghton, 1994; Brown, 1996).

Claims of the effectiveness of echinacea as a non-specific stimulator of the immune system are based mainly on European studies, mostly German, conducted over the last 20 years (Awang & Kindack, 1991). Two recent placebo-controlled, double-blind trials examined the effects of daily oral doses of echinacea on the course and severity of colds and flu. In one study of 108 patients with increased susceptibility, doses of 2-4 ml of an *E. purpurea* liquid preparation resulted in a decreased frequency of colds and flu as measured by the number of patients remaining healthy (35.2% with echinacea, 25.9% placebo) as well as the length of time between infections (40 days with echinacea, 25 days placebo). A second study, using a root preparation of *E. purpurea*, studied 180 subjects with influenza. At 900 mg daily, echinacea significantly reduced flu symptoms when compared to placebo or lower (450 mg) echinacea dose groups (Croom & Walker, 1995; Brown, 1996).

Animal Data: The acute toxicity values for the expressed juice of *E. purpurea* are shown in Table 1. There were no deaths produced by the doses shown; the researchers noted that the doses used were the largest which could be feasibly administered (Mengs *et al.*, 1991).

Table 1. Acute toxicity data for echinacea

Route	Species	LD ₅₀ (mg/kg)	Clinical Signs
Oral	Rat	>15,000	none
	Mouse	>30,000	none
Intravenous	Rat	>5,000	sedation, dyspnea
	Mouse	>10,000	sedation, dyspnea

There was no evidence of toxic effects in groups of 18 male and 18 female Wistar rats given the expressed juice of *E. purpurea* by gavage in doses of 0, 800, 2,400, or 8,000 mg/kg a day for 4 weeks (Mengs *et al.*, 1991).

No 2-year carcinogenicity studies of echinacea were identified in the available literature.

Short-Term Tests: Echinacin Liquidum, a commercial preparation of *E. purpurea*, was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 when tested both with and without S-9 at doses up to 5,000 µg/plate (Mengs *et al.*, 1991). Schimmer and coworkers (1994) also reported negative results for up to 400 µl of *E. purpurea* extract tested in strains TA98 and TA100 both with and without S-9. However, two commercial extracts of *E. angustifolia* at the same dose levels were positive in strains TA98 and TA100 while a third extract prepared by the researchers was negative. Histidine was the source of a positive effect in one extract but the cause of the remaining activity was not established.

At doses up to 5,000 µg/ml, Echinacin Liquidum did not induce mutations at the HPRT locus of mouse lymphoma L5178Y cells both in the absence and presence of S-9 (Mengs

et al., 1991).

Echinacin Liquidum treatment up to 5,000 $\mu\text{g/ml}$ did not induce chromosome aberrations (CAs) in human lymphocytes. A small but significant increase in CAs observed at 5,000 $\mu\text{g/ml}$ without activation was not considered biologically significant since the frequency of CAs fell within the historical control range and the increase also coincided with an increase in osmality of the treatment medium. No significant differences were seen in the presence of S-9 (Mengs *et al.*, 1991).

A single oral dose of 25,000 mg/kg of Echinacin Liquidum did not increase the number of micronucleated polychromatic erythrocytes in the bone marrow of male and female mice (Mengs *et al.*, 1991).

Concentrations of 5-55 $\mu\text{g/ml}$ of Echinacin Liquidum did not produce any morphological transformation of Syrian hamster embryo (SHE) cells (Mengs *et al.*, 1991).

Metabolism: No studies on the metabolism of echinacea were identified in the available literature.

Other Biological Effects: A number of studies have examined the oncolytic, immunostimulating, and anti-inflammatory activities of echinacea and its constituents.

At 400 mg/kg the pentane-soluble root oil from *E. angustifolia* and (Z)-1,8-pentadecadiene, a constituent of the oil, showed inhibitory activity in the *in vivo* mouse P-388 lymphocytic leukemia and the rat Walker carcinosarcoma 256 tumor systems. An extract of *E. pallida* was inhibitory to the latter tumor type (Voaden & Jacobson, 1972).

In a series of *in vitro* studies, acidic arabinogalactan, a purified polysaccharide from *E.*

purpurea, was shown to be effective in activating mouse macrophages to cytotoxicity against tumor cells (WEHI 164 fibrosarcoma) and micro-organisms (*Leishmania enriettii*). Arabinogalactan induced peritoneal macrophages to produce tumor necrosis factor (TNF- α) and interleukin-1 (IL-1). Interferon- β_2 was secreted by bone marrow macrophages in a dose-dependent manner after arabinogalactan activation. Arabinogalactan did not activate B cells but it did induce a slight increase in T cell proliferation. Arabinogalactan enhanced oxygen radical release by macrophages both *in vitro* and *in vivo* (Luettig *et al.*, 1989).

Polysaccharides (xyloglucanes and arabinogalactane) isolated from *E. purpurea* restored the resistance of immunosuppressed mice against lethal infections with *Listeria monocytogenes* and *Candida albicans* (Steinmuller *et al.*, 1993). These same polysaccharides were also tested for their ability to activate human phagocytes *in vitro* and *in vivo*. They enhanced the spontaneous motility of polymorphonuclear leucocytes (PMN) and increased the ability of these cells to kill staphylococci. Monocytes were activated to secrete TNF- α , IL-6, and IL-1. Intravenous administration of 5 mg of the polysaccharides to test subjects induced both the adherence of PMN to blood vessels and the migration of PMN and monocytes from bone marrow into the peripheral blood (Roesler *et al.*, 1991).

Extracts of *E. purpurea* enhanced the cellular immune function of peripheral blood mononuclear cells from normal individuals and patients with either chronic fatigue syndrome or acquired immunodeficiency syndrome. At concentrations $\geq 0.1 \mu\text{g/ml}$ *in vitro*, echinacea significantly enhanced natural killer (NK) cell function of all groups; concentrations $\geq 1 \mu\text{g/ml}$ significantly increased antibody-dependent cellular cytotoxicity (ADCC) of peripheral mononuclear cells from all groups (See *et al.*, 1997).

Intravenous administration of an aqueous extract of *E. angustifolia* inhibited carrageenan-induced hind paw edema in rats and dermal administration reduced croton oil-induced

inflammation in the mouse ear. In a follow-up study, the polysaccharide fraction of *E. angustifolia* roots was found to be about 100 times more potent than the aqueous extract in reducing carrageenan-induced paw edema. The polysaccharide fraction was also a stronger inhibitor of croton oil-induced edema (Tragni *et al.*, 1985; Tubaro *et al.*, 1987).

Extracts of *E. angustifolia* roots were tested *in vitro* for antihyaluronidase activity. Hyaluronidases, which depolymerize or hydrolyze hyaluronic acid and chondroitin sulfates, are thought to play a key role in the etiology of inflammatory disease. Antihyaluronidase activity was associated with all the solvent-extractable components of *E. angustifolia*, most prominently with the acidic constituents of medium-high polarity (the caffeoyl conjugates) (Facino *et al.*, 1993).

The n-hexane extract of *E. angustifolia* root was shown to possess inhibitory activity in *in vitro* cyclooxygenase (sheep seminal microsomes) and 5-lipoxygenase (porcine leucocytes) assays. Cyclooxygenase and 5-lipoxygenase are the key enzymes of arachidonic acid metabolism. Nine alkaloids were identified in the n-hexane extract (Muller-Jakic *et al.*, 1994).

Structure Activity Relationships: Echinacea consists of a complex mixture of natural products which does not lend itself to traditional structure activity analysis.

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