ANGELICA ROOT OIL

SYNONYMS

Angelica seed oil
Angelica [Italian]
Angelica archangelica root oil
Angelica root oil
Angelica root solid extract
Angelica root oil (Angelica archangelica L.)
Angelica seed oil (Angelica archangelica L.)
Angelica stem oil (Angelica archangelica L.)
Angelika oel [German]
Arcangelique [Spanish]
Archangelique [French]
Echt engelwurz [German]
Oils, angelica
Oils, angelica archangelica
Oils, angelica root

CHEMICAL STRUCTURE

Ill defined (complex mixture)

CHEMICAL FORMULA

A complex mixture of compounds, the oil is composed mainly of limonene, α-pinene, d-α-phellandrene, β carophyllene, linalool, borneol acetaldehyde and four macrocyclic lactones and various coumarins.

From a GC-MS analysis of the essential oil, 111 compounds were identified, the contents of which made up 90.61% of the total essential oil. The main constituents were found to be 3-carene (12.70%), beta-elemene (6.20%), beta-terpinene (3.53%), beta-myrcene (1.97%), gamma-elemene (1.82%), beta-phellandrene (1.65%), and beta-maaliene (1.61%), et al. In addition, suberosin (0.16%), a coumarins compound, was also determined. [Zhao *et al*., 2011].

IDENTIFIER DETAILS

CAS Number	:	8015-64-3, 8015-60-3
CoE Number	:	56
FEMA	:	2088
EINECS Number	:	283-871-1
E Number	:	-

CLP CLASSIFICATION

Ingredient CLP Classification: No

Endpoint	Classification	Category
Acute Oral Toxicity	-	-
Acute Dermal Toxicity	-	-
Acute Inhalation Toxicity	-	-
Skin Corrosive/irritant	-	-
Eye Damage/Irritation	-	-
Respiratory Sensitisation	-	-
Skin Sensitisation	-	-
Mutagenicity/Genotoxicity	-	-
Carcinogenicity	-	-
Reproductive Toxicity	-	-
Specific Target Organ Toxicity	-	-
Aspiration Toxicity	-	-

SPECIFICATIONS

Melting Point: undefined (complex mixture)

Boiling point: undefined (complex mixture)

PURPOSE

Flavouring compound.

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
-	-	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
-	-	-	-

FDA Status:[CFR21]

Section Number	Comments
GRAS182.20&182.1010	Essential oils, oleoresins (solvent-free), and natural extractives (including distillates)

HUMAN EXPOSURE

Natural Occurrence: Angelica is a herbaceous plant about 1.5m high, cultivated in Europe, especially France, Belgium, and Germany. The plant is characterized by spindle shaped, fleshy roots, an erect stalk, alternate leaves,

and greenish-yellow flowers with an inferior ovary; the seeds are oblong with an off-white colour. The plants blooms from June to August [Fenaroli, 2005].

Reported Uses: Angelica root oil is reportedly used in baked goods at 38.68 ppm, frozen dairy at 26.82 ppm, soft candy at 37.42 ppm, gelatin pudding at 35.81 ppm, non-alcoholic beverages at 13.31 ppm, alcoholic beverages at 41.29 ppm [Fenaroli, 2005].

Angelica root oil is reportedly used in the medicinal, pharmaceutical and cosmetic products and includes a fragrance for soaps, detergents, perfumes and creams. Angelica root oil has been reportedly used for centuries to treat bronchial and stomach ailments, arthritic insomnia and nervous conditions [Leung *et al.,* 1996].

TOXICITY DATA

Carmines (2002), Rustemeier *et al*., (2002), Roemer *et al*., (2002) and Vanscheeuwijck *et al.,* (2002) reported on a testing program designed to evaluate the potential effects of 333 ingredients added to typical commercial blended test cigarettes on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], determination of smoke chemical constituents and a 90-day rat inhalation study. Based on the findings of these studies, the authors concluded that the addition of the combined ingredients, including angelica root oil at levels up to 2 ppm, "did not increase the overall toxicity of cigarette smoke" [Carmines, 2002].

In Vivo Toxicity Status

Species	Test Type	Route	Reported Dosage
Rat	LD_{50}	Oral	11000mg/kg
Mouse	LD_{50}	Oral	2200mg/kg
Rabbit	LD_{50}	Oral	>5000mg/kg

[Lewis, 2000]

Carcinogenicity and Mutagenicity

In a group of nine DDY mice given 640 mg/kg of aqueous Angelica radix both two week prior to and two weeks after transplantation of Ehrlich tumours, there was reported to be increased survival rate and tumour growth was inhibited [Haranaka *et al.,* 1985].

Dermal Toxicity

Angelica root oil when applied neat to the backs of hairless mice or applied covered to abraded or intact rabbit skin for 24 hours was reported to be non irritating [Urbach *et al.,* 1974]. However, neat angelica root oil was reported to

have caused phototoxic effects in mice and swine skin at concentrations above 3.125% in methanol, with the concentration of 1.56% producing a doubtful response when followed by irradiation with artificial sunlight [BIBRA, 1993].

When tested at 1% in petrolatum there was reportedly no effect of angelica root oil after a 48 hour closed patch test on an unspecified number of human subjects [Opdyke 1975]. When tested at 1% in petrolatum on 24 human volunteers there was reported to be no sensitisation reactions [Epstein, 1974].

There was reported photosensitisation of both hairless mice and swine exposed to neat Angelica root oil [Urbach *et al.,* 1974]. Positive photosensitisation reactions were found for applications of 20μl/ per $5cm^2$ exposed to stimulated sunlight for 1 hour at concentrations above 3.125%, whilst a concentration of 1.56% produced a doubtful reaction, a concentration of 0.78% showed no phototoxic reaction [Urbach *et al.,* 1974].

Reproductive / Developmental Toxicity

No data identified

Inhalation Toxicity

A recent study investigated the effect of cigarettes, containing various additives in three combinations, in a 90-day nose-only smoke inhalation study in rats. These ingredients included angelica root oil at 2 ppm, a level described as a multiple of its typical use in a US cigarette. The data from this study along with that from a number of other biological and chemical studies indicate that the addition of the combined ingredients "did not increase the inhalation toxicity of the smoke, even at the exaggerated levels used" [Vanscheeuwijck *et al.*, 2002].

The addition of angelica root oil at 12 ppm to reference cigarettes, used in a 90 day-sub-chronic inhalation exposure in rats, led to a series of pathological changes to smoke exposure that were indistinguishable from those changes caused by the control cigarettes. This indicated that addition of angelica root oil to a reference cigarette had no discernable effect upon the type or severity of the treatment related pathological changes associated with tobacco smoke exposure [Baker *et al.,* 2004].

Roemer (2014) and Schramke (2014) reported on a testing program designed to evaluate the potential effects of 350 ingredients added to an experimental kretek cigarette on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], Mouse Lymphoma assay, determination of smoke chemical constituents, a 4-day in vivo micronucleus assay and a 90-day rat inhalation study. Based on the results of these studies, the authors concluded that the addition of ingredients commonly used in the manufacture of kretek cigarettes, including Angelica

root oil at levels up to 9 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other relevant studies

When angelica root oil was administered orally to rats at 0, 0.5, 1.0, 2.0, or 3.0 g/kg for 8 weeks the tolerated dose was reported to be, 1.5 g/kg. Doses of 2.0 and 3.0 g were reported to be associated with inactivity and death of some animals with an associated weight loss, those animals that died [the numbers of deaths and animals per group were not specified], were reported to have severe kidney and liver damage. However, it was also reported that rats dosed at 0.5 and 1.0 g gained less weight than control animals and were not truly unaffected by treatment [Opdyke, 1975].

When an i.v. injection of an aqueous root extract of 'Dang gui' (*Angelica sinesis*) at a dose level of 20 g/kg in rats [strain an number not specified] was reported to have inhibited platelet aggregation. The i.v. administration to mice of 16 g/kg was reported to have caused an enhancement of macrophages [BIBRA 1993].

Angelica root oil has been reported to have calcium antagonist like action *in vitro ,* in a number of *Angelica* species. Calcium antagonists have apparently been investigated in cardiovascular disease where relaxation of the cardiac muscle is desirable [Leung et al., 1996]. Angelica sinensis has been reported to have cardiovascular properties. An injectible aqueous extract of the root was reported as being 91% effective in the treatment of 111 human patients with ischemic cerebrovascular disease [Xiao *et al.,* 1987].

In an immunotoxicity assay angelica root oil failed to modulate the cell mediated or humoral immune response of female CD1 mice, when it was administered intragastrically for five days at doses up to 2500 mg/kg/day [Gaworski *et al.*, 1994].

Rats administered [Strain and number not specified] 1.5 or 3 g/kg of a methanolic extraction of Japanese angelica root for 21 days by oral gavage, were reported to have increased serum cholesterol, increased activity of CP450 activity in the liver and kidneys, a decrease in unspecified serum enzymes and non specified changes in the lungs [BIBRA 1993]. In a study which angelica root oil was administered to rats at 2 or 3 g/kg/day for 8 weeks deaths were reported to be associated with severe liver and kidney damage. Rats dosed at 0.5 or 1 g/kg/day were reported to be associated with lower mean body weights compared to the controls [BIBRA, 1993].

A separate study reported that the growth rates of mice exposed to approximately 5% [7.5 g/kg/day] of Chinese Dang gui angelica root in the diet for 15 weeks, was reported to be unaffected. However, there was reported to be an increase in the rate of glutamic oxidation in the liver [BIBRA, 1993].

There was reported to be an increase in the levels of glutathione s-transferase levels in the stomach, kidney and small intestine mucosa of mice treated with

30 mg [1.5 g/kg/bw], angelica oil on three occasions two days apart [Lam *et al.,* 1991].

Angelica sinensis has been reported to have cardiovascular effects, with an aqueous injectible extract of the root was reported to be 91% effective in treating 111 patients with acute ischemic cerebrovascular disease. Angelicin has been reported to have a relaxant activity on a wide variety of smooth muscle preparations form various animal species [Leung *et al.,* 1996].

No significant side effects were reported for 40 human patients [suffering from acute ischemic apoplexy] injected *i.v.* for 15-30 days with 200-240 ml/day [which approximates to 1g/kg/bw/day] of a 25% solution of Chinese Dang gui root [BIBRA, 1993].

In a recent review by the SCCNFP (2001) [Scientific Committee on Cosmetic products and Non Food Products, intended for consumers], they state that Angelica root oil may be used in cosmetic products, provided that the total concentration of furocoumarin-like substances in the finished cosmetic product does not exceed 1 ppm. Angelica root oil application has been reported to be positive in 2% of 86 human subjects tested [the concentration was not specified] [Rudziki *et al.,* 1982].

In the present study, the effect of essential oil of the root of Angelica *archangelica Linn*. was evaluated against electrically and chemically induced seizures. The seizures were induced in mice by maximal electroshock and pentylenetetrazol. The effect of essential oil of the root of Angelica archangelica on seizures was compared with standard anticonvulsant agents, phenytoin and diazepam. The essential oil of the root of Angelica archangelica suppressed duration of tonic convulsions and showed recovery in maximal electroshock induced seizures while it delayed time of onset of clonic convulsions and showed mortality protection in pentylenetetrazol induced seizures. The essential oil of the root of Angelica archangelica also produced motor impairment at the antiseizure doses. The study indicated that the essential oil exhibited antiseizure effect. The antiseizure effect may be attributed to the presence of terpenes in the essential oil [Pathak *et al*., 2010].

Behavioural Data

Min et al., (2005) monitored the behavioural effects of angelica essential oil in the social interaction test of anxiety and the hole-board test of exploration and locomotor activity in rats. In the social interaction test, angelica essential oil decreased aggressive behaviours at the doses of 21 and 42 mg/kg, while the doses of 21 and 42 mg/kg significantly increased social interaction time of the high light, unfamiliar test condition and 21 mg/kg could also prolong social interaction time of the high light, familiar test condition. In the hole-board test, angelica essential oil at 10.5 mg/kg significantly increased head-dipping counts and duration. The authors concluded that their findings suggest the potential usefulness of angelica essential oil against various types of anxiety-related disorders and social failure. [Min *et al*., 2005]

In vitro Toxicity Status

Carcinogenicity and Mutagenicity

The mutagenicity of the smoke condensate was assayed in the *Salmonella* plate incorporation [Ames] assay with the tester strain TA98 in the presence of an S9 metabolic activation system. The cytotoxicity of the cigarette condensate was determined in the neutral red uptake assay and the (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium, inner salt assay (MTS assay) with the human hepatocellular liver carcinoma cell line, HEP-G2. It was concluded that the *in vitro* mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients, which included angelica root oil at levels up to 1 ppm.

In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-21).

Roemer *et al.,* (2002) reported on a study in which cigarettes containing various additives in three different combinations were produced. Smoke condensates prepared from these cigarettes were then tested in two different *in vitro* assays. The mutagenicity of the smoke condensate was assayed in the *Salmonella* plate incorporation [Ames] assay with tester strains TA98, TA100, TA102, TA1535 and TA1537 in the presence and absence of an S9 metabolic activation system. The cytotoxicity of the gas/vapour phase and the particulate phase was determined in the neutral red uptake assay with mouse embryo BALB/c 3T3 cells. The authors concluded that the *in vitro* mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients which included angelica root oil at levels up to 2 ppm [a multiple of its typical use in a US cigarette] [Roemer *et al.,* 2002].

Baker *et al.,* [2004]; examined the effects of the addition of 482 tobacco ingredients upon the biological activity and chemistry of mainstream smoke. The ingredients, essentially different groups of flavourings and casings, were added in different combinations to reference cigarettes. The addition of angelica root oil at 12 ppm was determined not to have affected the mutagenicity of the total particulate matter (TPM) of the smoke in either the Ames, *in vitro* micronucleus assay or the neutral red assay when compared with that of the control cigarettes [Baker *et al.,* 2004].

Additional information concerning the *in vitro* mutagenicity of this material can be found in “An Interim report on data originating from Imperial Tobacco Limited’s Genotoxicity testing programme” September 2003.

Angelica root oil was found to be negative in the Ames assay when tested with *Salmonella* strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations up to 1000 mg/plate both with and without metabolic activation [Heck *et al.,* 1989].

Roemer (2014) and Schramke (2014) reported on a testing program designed to evaluate the potential effects of 350 ingredients added to an experimental

kretek cigarette on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], Mouse Lymphoma assay, determination of smoke chemical constituents, a 4-day in vivo micronucleus assay and a 90-day rat inhalation study. Based on the results of these studies, the authors concluded that the addition of ingredients commonly used in the manufacture of kretek cigarettes, including Angelica root oil at levels up to 9 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other Relevant Studies

Angelica root oil vapour has been reported to have antibacterial activity against *Mycobacterium avium*, but not *E. Coli*, *Bacillus subtilis*, *Streptococcus aureus*, *Streptococcus fecalis* or *Salmonella typhosa*. Angelica root oil vapour was reported to have *in vitro* activity against 14/15 fungi tested [strains and concentrations not specified] [Opdyke, 1975].

Thirteen essential oils were examined for their antioxidant activity using three different assay systems. Scavenging abilities of the oils for the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical ranged from 39% for angelica seed oil to 90% for jasmine oil at a level of 200 microg/mL.[Wei, 2007].

PYROLYSIS AND TRANSFER STUDIES

In an extension to the Baker and Bishop (2004) study, a further 159 ingredients were analysed. Under pyrolysis of Angelica root oil breakdown product included phellandrene (19.9%), α-pinene (16.7%), δ-carene (14.6%), sabinene (5.9%) and β-mycrene (3.8%) [Baker and Bishop, 2005].

REFERENCES

Baker RR, *et al.,* (2004) An overview of the effects of tobacco ingredients on smoke chemistry and toxicity. *Food Chem Toxicol*. **42** Suppl: S53-83.

Baker and Bishop, (2005). The pyrolysis of non-volatile tobacco ingredients using a system that simulates cigarette combustion conditions. *J. Anal. Appl. Pyrolysis.* **74**: 145-170.

BIBRA (1993) Toxicity profile Angelica.

Carmines, (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 1: Cigarette design, testing approach, and review of results. *Food and Chemical Toxicology* **40**, 77-91.

Fenaroli, (2005). Fenaroli's Handbook of Flavour Ingredients, 5th Edition. CRC Press, Boca Raton, USA.

Gaworski *et !l.*, (1994). An imlunotoxicity assessment of food flavouring ingredients. *Fd. Chem. Toxicol.*, **3"**, 409.

Haranaia *et al.,* (1985) Antitumour activities and tumour necrosis factor producibility of traditional Chinese medicines and crude drugs. *Cancer Immunol. Immunother*. **20(1):** 1-5.

Heck *et al.,* (1989) An evaluation of food flavour ingredients in a genetic toxicity screening battery. *The Toxicologist* **9(1):** 257.

In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-21).

Lam *et al.,* (1991) Effects of essential oils on the glutathione s-transferase activity in mice. *J. Agric. Food Chem.* **(39):** 660-662.

Leung *et al.,* (1996) Encyclopaedia of common natural ingredients used in food, drugs and cosmetics. John Wiley & Sons New York.

Lewis, (2000) Sax's Dangerous Properties of Industrial Chemicals. 3,10th Edition John Wiley & Sons New York.

Min *et al.*, (2005) The effects of angelica essential oil in social interaction and hole-board tests. *Pharm. Biochem. Behav.* **81(8)**: 838-42

Opdyke, (1975) Fragrance raw materials monographs Angelica root oil. *Fd Cosmet Toxicol.* **13:** 713-714.

Pathak *et al*., (2010). Evaluation of antiseizure activity of essential oil from roots of angelica archangelica linn. In mice. *Indian J Pharm Sci.* **72(3)**: 371-5.

Roemer *et al.,* (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 3: *In vitro* genotoxicity and cytotoxicity. *Fd Chem Toxicol* **40**, 105-111.

Roemer (2014) Toxicological assessment of kretek cigarettes: Part 1: background, assessment approach, and summary of findings. Regul Toxicol Pharmacol.; **70** Suppl 1: 2-14

Roemer (2014) Toxicological assessment of kretek cigarettes Part 6: the impact of ingredients added to kretek cigarettes on smoke chemistry and in vitro toxicity. Regul Toxicol Pharmacol.; **70** Suppl 1: 66-80

Rudzki *et al.,* (1982) Allergy to perfume mixture. *Contact Dermatitis* **43** 115-116.

Rustemeier *et al.,* (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 2: Chemical composition of mainstream smoke. *Fd Chem Toxicol* **40**, 93-104.

Schramke (2014) Toxicological assessment of kretek cigarettes. Part 7: the impact of ingredients added to kretek cigarettes on inhalation toxicity. Regul Toxicol Pharmacol; **70** Suppl 1: 81-9.

SCCNFP (2001) Opinion of the scientific committee on cosmetic products and non food products intended for consumers concerning an initial list of perfumery materials which must not form part of cosmetic products except subject to the restrictions and conditions laid down. Adopted by the SCCNFP during the 18th plenary meeting of 25 September 2001.

Urbach *et al.,* (1974) Report to RIFM 15 May [As cited in Opdyke 1975].

Vanscheeuwijck *et al.,* (2002). Evaluation of the potential effects of ingredients added to cigarettes. Part 4: Subchronic inhalation toxicity. *Fd Chem Toxicol* **40**, 113-131.

Wei *et al,* (2007) Antioxidant activities and volatile constituents of various essential oils. *J. Agr. Food Chem.* **55(5):** 1737-42

Xiao *et al.,* (1987) *Phytotherapy Res*. **1**: 53. As cited in Leung *et al.,* (1996).

Zhao *et al*., (2011). GC-MS analysis of essential oil from root of Angelica dahurica cv. Qibaizhi. *Zhongguo Zhong Yao Za Zhi*. **36(5):** 603-7.