

Evaluation of
Angelica Root Oil
For Use as a Cigarette Ingredient

April 2005

INTRODUCTION

Angelica Root Oil (CAS # 8015-64-3) is currently used worldwide at levels below **1 ppm** in selected cigarette brands manufactured and/or distributed by Philip Morris International. This document is a review of current published toxicology information on Angelica Root Oil abstracted from online toxicity databases.

TOXICITY DATA ON UN-BURNED MATERIAL

The following information was generated from the MICROMEDEX database tool <http://csi.micromedex.com> on April 20th 2005, unless otherwise indicated.

Overview

Preparations of the plant *Angelica archangelica* have been used for centuries in herbal medicine and as a culinary flavour. Extracts of the root predominantly contain simple terpenes (components include: borneol, linalool, bergaptene, limonene, phellandrene, pinene, angelic acid, various sesquiterpenes and phenolic acids, coumarins and furocoumarins such as angelicin), and are used as a bitter to stimulate the appetite, diaphoretic and expectorant properties have been attributed.

As a food flavouring additive, the material has been assessed under the provisions of the *Federal Food, Drug and Cosmetic Act, section 201(s)*, by the Expert Committee of the USA Flavour and Extract manufacturers' Association (FEMA), to be generally recognised as safe (GRAS) under current conditions of use.

As an ingredient in cosmetic preparations, there are no legislative limitations on the usage of Angelica Root Oil, however the fragrance industry (International Fragrance Association) has recommended the restriction of use in leave-on formulations to 0.78% and wash-off formulations to 3.9%. This is due to phototoxic effects (genotoxicity) associated with the potential presence in the oil of UV-reactive furocoumarins¹.

This material appears on the list of "Permitted Additives to Tobacco Products in the United Kingdom" (Department of Health, 2003) at a maximum level permitted for inclusion in cigarettes of 0.1 % w/w tobacco.

The material has low acute toxicity and low potential to evoke irritation or sensitisation responses.

As a herbal remedy, the American Herbal Products Association has stated that large oral doses should not be taken during pregnancy due to anecdotal reports of potential stimulating effects on uterine muscles².

The following information was generated from the HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on April 20th 2005.

¹ Papadopoulo D. Averbeck D. Genotoxic effects and DNA photoadducts induced in Chinese hamster V79 cells by 5-methoxypsoralen. *Mutation Research*.151: 281-291, 1985

² McGuffin M.C. Hobbs R. Upton A. American Herbal Product Association's *Botanical Safety Handbook*. Boca Raton. CRC Press. 1997. 10

Non-Human Toxicity Excerpts

1. Undiluted angelica seed oil applied to the backs of hairless mice was not irritating. Applied full strength to intact or abraded rabbit skin for 24 hr under occlusion, it was mildly irritating. /seed oil/ [**PEER REVIEWED**] [Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 96]
2. Angelica root oil applied undiluted to the backs of hairless mice or to intact or abraded rabbit skin for 24 hr under occlusion was not irritating. ... Phototoxic effects were reported for undiluted angelica root oil tested on hairless mice and swine. Various concn of angelica root oil in methanol...also tested for phototoxicity in mice, applications of 20 ul/5 sq cm of skin being exposed to simulated sunlight for 1 hr. Positive reactions were obtained with concentrations of 3.125, 6.25, 12.5 25, 50 and 100%, while 1.56% evoked a doubtful reaction and 0.78% showed no phototoxic effect. /root oil/ [**PEER REVIEWED**] [Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 94]
3. Vapor of angelica root oil showed antibacterial activity against Myobacterium avium... Angelica root oil exhibited in vitro antifungal activity against 14 out of 15 fungi tested. /root oil/ [**PEER REVIEWED**] [Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 94]

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on April 20th 2005.

Health hazard data

Acute toxicity

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

Rat

LD50 - ROUTE: Oral; DOSE: 11160 mg/kg [Pharmazie. (VEB Verlag Volk und Gesundheit, Neue Gruenstr. 18, Berlin DDR-1020, Ger. Dem. Rep.) V.1- 1946- (14,435,1959)]

TOXIC EFFECTS:

Behavioral - Somnolence (general depressed activity)

Liver - Other changes

Kidney, Ureter, and Bladder - Other changes

Mouse

LD50 - ROUTE: Oral; DOSE: 2200 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (13,713,1975)]

Rabbit

LD50 - ROUTE: Skin; DOSE: >5 gm/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (13,713,1975)]

Irritation

SKIN - STANDARD DRAIZE TEST

Rabbit

ROUTE: Skin; DOSE: 500 mg/24H; REACTION: Mild [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (12,821,1974)]

TOXICITY DATA ON BURNT MATERIAL

Data on the toxicity of angelica root oil as a cigarette ingredient has been evaluated in a series of studies. The results of these studies may be found in the following references:

R.R. Baker et al., 2004, "An overview of the effects of tobacco ingredients on smoke chemistry and toxicity", Food and chemical toxicology, 42S:53-83. **PEER REVIEWED**

E.L. Carmines, 2002, "Evaluation of the Potential Effects of Ingredients Added to Cigarettes. Part I: Cigarette Design, Testing Approach and Review of Results," Food and Chemical Toxicology, 40:77-91. **PEER REVIEWED**

K. Rustemeier et al, 2002, "Evaluation of the Potential Effects of Ingredients Added to Cigarettes Part II. Chemical Smoke Composition," Food and Chemical Toxicology, 40:93 - 104. **PEER REVIEWED**

Roemer et al, 2002, "Evaluation of the Potential Effects of Flavor Ingredients Added to Cigarettes. Part 3. In Vitro Genotoxicity and Cytotoxicity," Food and Chemical Toxicology, 40:105-111. **PEER REVIEWED**

P.M. Vanscheeuwijck et al, 2002, "Toxicological Evaluation of Cigarettes without and with the Addition of Flavor Ingredients to the Tobacco. Part 4. Subchronic Inhalation Toxicity," Food and Chemical Toxicology, 40:113-131. **PEER REVIEWED**

These studies indicate that ingredients used in the production of cigarettes do not increase the overall toxicity of cigarette smoke.

DATA ON THE EFFECTS ON HUMAN HEALTH

The following information was generated from the HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on April 20th 2005.

Tested at 1% in petrolatum, it produced no irritation after a 48-hr closed-patch test on human subjects. A Kligman maximization test was carried out on 21 volunteers. The material was tested at a concn of 1% in petrolatum and produced no sensitization reactions. /root oil/ [**PEER REVIEWED**] [Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 94]

CONCLUSION

Cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases in smokers. Smokers are far more likely to develop diseases, like lung cancer, than non-smokers. There is no 'safe' cigarette. Government health warnings about smoking apply to all cigarettes, regardless of the ingredients added, including those containing only tobacco and paper.

While Philip Morris International has not conducted human studies on the health effects of ingredients used in cigarette manufacture, studies have been conducted using scientifically accepted *in vitro* and *in vivo* toxicity assays with various ingredient mixtures (see Toxicity Data on Burnt Material above). These studies show there is no meaningful difference in the composition or toxicity of smoke when the smoke from cigarettes with added ingredients is compared to the smoke from cigarettes without added ingredients. These findings are supported by similar studies from the published literature. It is our scientific judgement, based on the best available data, that angelica root oil used in our cigarettes does not increase the overall toxicity of cigarette smoke.