

**Evaluation of  
Camphene  
for Use as a Cigarette Ingredient**

**December 2005**

## **INTRODUCTION**

Camphene (CAS # 79-92-5) 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 camphene 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 December 6<sup>th</sup> 2005, unless otherwise indicated.

### ***Overview***

Camphene, a terpene hydrocarbon, naturally occurs in many essential oils, such as turpentine (levo & dextro forms), in cypress oil (dextro form), in camphor oil from species of Lauraceae (dextro), in bergamot oil, in oil of citronella, neroli, ginger, valerian. Camphene has also been identified as an emission from numerous tree species and other plants<sup>1</sup>.

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 manufacturer's Association (FEMA), to be generally recognized as safe (GRAS) under current conditions of use<sup>2</sup>.

Camphene has also been defined as a flavouring substance which may be used as foodstuffs by the *Council of Europe Committee of Experts on Flavouring Substances* at an upper level of 20 mg/kg in foods.

Camphene is a common cosmetic ingredient.

The following information was generated from the HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on December 6<sup>th</sup> 2005.

### ***Non-Human Toxicity Excerpts***

1. /Laboratory animals: Acute Exposure/ Camphene applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was slightly irritating. [\*\*PEER REVIEWED\*\*] [Opdyke, D.L.J. (ed.). *Monographs on Fragrance Raw Materials*. New York: Pergamon Press, 1979., p. 171]
2. / Laboratory animals: Acute Exposure/ Oral administration of camphene (260 mmol/kg) to rats increased bile flow 50% 4 hours after administration. [\*\*PEER REVIEWED\*\*] [Opdyke, D.L.J. (ed.). *Monographs on Fragrance Raw Materials*. New York: Pergamon Press, 1979., p. 172]
3. / Laboratory animals: Acute Exposure/ Camphene applied to rabbit eyes was irritating with a risk of serious damage to eyes. [\*\*PEER REVIEWED\*\*] [European Chemicals Bureau; IUCLID

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<sup>1</sup> The Merck index, an Encyclopedia of chemicals, drugs, and biologicals, eleventh edition, 1989

<sup>2</sup>Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives [http://www.inchem.org/documents/jecfa/jecval/jec\\_319.htm](http://www.inchem.org/documents/jecfa/jecval/jec_319.htm)

Dataset, Camphene (79-92-5) (2000 CD-ROM edition). Available from the database query page: <http://ecb.jrc.it/esis/esis.php> as of February 4, 2004. ]

4. / Laboratory animals: Acute Exposure/ ...The spring extract was the least toxic (LD50: 1200 mg/kg bw) and contained lower levels of camphor (7.7%), alpha,beta-thujone (1.3%) and camphene (3.1%). [\*\*PEER REVIEWED\*\*] [Farhat GN et al; *Toxicol* 39 (10): 1601-5 (2001) ]
5. / Laboratory animals: Subchronic or Prechronic Exposure/ Male Wistar rats were used in a 14-day feeding study with daily administration of 0.5% and 1% concentration of camphene in food. ...Camphene at 1% concentration in the diet slightly reduced body weight gain. No effect on the food intake. Relative liver weights slightly increased. [\*\*PEER REVIEWED\*\*] [OECD; Screening Information Dataset for Camphene (100-44-7) (1998). Available from: <http://www.chem.unep.ch/irptc/sids/volume1/79-92-5.pdf> as of February 6, 2004. ]
6. / Laboratory animals: Developmental or Reproductive Toxicity/ Pregnant Sprague-Dawley rats were administered doses of 250-1000 mg/kg bw camphene from the 6th to 15th day of gestation by oral gavage. ...No toxic effect observed in treated dams nor in the fetuses at the dose of 250 mg/kg bw for 10 days. In the 1000 mg/kg bw/day dosage group some mild and transient effects: salivation and reduced motor activity were observed in 6 of the treated dams, 5-20 minutes after first exposure and in two of the treated dams after the second exposure and lasted from 20 minutes up to 6 hours. In the high dose treated dams there was a transient decline of the food consumption: 6%, 22% and 10% respectively on days 7, 8 and 9th of pregnancy. No other clinical signs observed in the high dose group. No substance-related pathological changes /in the dams/ were detected at autopsy. Camphene at 1000 mg/kg bw/day... caused slight but not significant ( $p < 0.01$ ) increase of the resorption rate, and consequently of the implantation loss /(11.5% versus 5.2% in controls)/. No further influence on the prenatal development was detected. [\*\*PEER REVIEWED\*\*] [OECD; Screening Information Dataset for Camphene (100-44-7) (1998). Available from: <http://www.chem.unep.ch/irptc/sids/volume1/79-92-5.pdf> as of February 6, 2004. ]
7. /Genotoxicity/ Negative in the Ames test of *Salmonella typhimurium* TA 98, TA 100 with and without activation. [\*\*PEER REVIEWED\*\*] [European Chemicals Bureau; IUCLID Dataset, Camphene (79-92-5) (2000 CD-ROM edition). Available from the database query page: <http://ecb.jrc.it/esis/esis.php> as of February 4, 2004. ]
8. /Alternative in vitro tests/ The chemical composition of the essential oil from *Artemisia iwayomogi* Kitamura was analyzed. ...Camphor (19.31%), 1,8-cineole (19.25%), borneol (18.96%), camphene (4.64%), and beta-caryophyllene (3.46%) were found to be the major components. The oil exhibited antibacterial activity against six Gram-(+) and six Gram-(-) bacteria in tests using the broth dilution method. [\*\*PEER REVIEWED\*\*] [Yu HH et al; *Planta Med* 69 (12): 1159-62 (2003) ]
9. /Other toxicity information/ An ointment containing camphene, menthol, and essential oils was found to have broncholytic effects in animals. [\*\*PEER REVIEWED\*\*] [Schafer D et al; *Arzneim Forsch* 31 (1):82-86 (1981) ]

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 December 6<sup>th</sup> 2005.

### **Health hazard data**

#### *Acute toxicity*

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

##### **Rat**

LC50 - ROUTE: Inhalation; DOSE: 17100 mg/m<sup>3</sup>/4H ['Vrednie chemichescie veshestva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,298,1998)]

TOXIC EFFECTS:

*Behavioral* - Excitement

*Lung, Thorax, or Respiration* - Dyspnea

LC50 - ROUTE: Inhalation; DOSE: 17100 mg/m<sup>3</sup>/5M ['Vrednie chemichescie veshestva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,298,1998)]

TOXIC EFFECTS:

*Behavioral* - Somnolence (general depressed activity)

*Behavioral* - Muscle contraction or spasticity

*Behavioral* - Alteration of classical conditioning

LC50 - ROUTE: Inhalation; DOSE: 17100 mg/m<sup>3</sup>/1H ['Vrednie chemichescie veshestva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,298,1998)]

TOXIC EFFECTS:

*Peripheral Nerve and Sensation* - Flaccid paralysis without anesthesia (usually neuromuscular blockage)

*Behavioral* - Ataxia

*Behavioral* - Irritability

LD50 - ROUTE: Oral; DOSE: >5 gm/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (13,735,1975)]

##### **Rabbit**

LD50 - ROUTE: Skin; DOSE: >2500 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (13,735,1975)]

OTHER LD/LC - OTHER LETHAL DOSE/CONC

##### **Mouse**

LD - ROUTE: Intraperitoneal; DOSE: >500 mg/kg ['Summary Tables of Biological Tests,' National Research Council Chemical-Biological Coordination Center. (National Academy of Science Library, 2101 Constitution Ave., NW, Washington, DC 20418) (4,376,1952)]

#### *Genetic effects*

BODY FLUID ASSAY

##### **Rat**

CELL TYPE: Salmonella typhimurium; DOSE: 2500 mg/kg [Nutrition and Cancer. (Franklin Institute Press, POB 2266, Philadelphia, PA 19103) V.1- 1978- (1,10,1979)]

*Other multiple dose toxicity data*

***Mammal - Unspecified Species***

TCLo - ROUTE: Inhalation; DOSE: 3.6 mg/m<sup>3</sup>/24H/90D continuous ['Vrednie chemichescie veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,298,1998)]

**TOXIC EFFECTS:**

*Behavioral* - Alteration of classical conditioning

*Lung, Thorax, or Respiration* - Respiratory stimulation

*Lung, Thorax, or Respiration* - Other changes

TCLo - ROUTE: Inhalation; DOSE: 32.2 mg/m<sup>3</sup>/24H/90D continuous ['Vrednie chemichescie veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,298,1998)]

**TOXIC EFFECTS:**

*Liver* - Fatty liver degeneration

*Liver* - Other changes

*Blood* - Hemorrhage

**TOXICITY DATA ON BURNT MATERIAL**

Data on the toxicity of camphene after combustion has been evaluated in a series of studies. The results of these studies may be found in the following references:

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. Vanscheuwijck 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\*\***

Gaworski et al, 1998, "Toxicological evaluation of flavor ingredients added to cigarette tobacco: 13-week inhalation exposure in rats" Inhalation Toxicology, 10:357-381. **\*\*PEER REVIEWED\*\***

Gaworski et al, 1999, "Toxicological evaluation of flavor ingredients added to cigarette tobacco: skin painting bioassay of cigarette smoke condensate in SENCAR mice" Toxicology, 139 1-17. **\*\*PEER REVIEWED\*\***

These studies indicate that chemicals 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 December 6<sup>th</sup> 2005.

### ***Human Toxicity Excerpts***

1. /Human exposure studies/ Tested at 4% in petrolatum, /camphene/ ... produced no irritation after a 48-hour closed-patch test on human subjects. ... In a study of the sensitizing properties of 17 terpenes and related compounds present in essential oils, camphene was found not to be a sensitizer for human skin. [\*\*PEER REVIEWED\*\*] [Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 171]
2. /Other toxicity information/ Camphene dissolved in dimethylformamide and water at 1, 10, and 100 ug/mL showed no cytotoxic effects on HeLa cells in monolayer culture. [\*\*PEER REVIEWED\*\*] [Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 172]

## **CONCLUSION**

Cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases in smokers. Smokers are far more likely to develop serious 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 camphene used in our cigarettes does not increase the overall toxicity of cigarette smoke.