

**Evaluation of  
alpha-Pinene  
for Use as a Cigarette Ingredient**

**October 2005**

## **INTRODUCTION**

Alpha-pinene (CAS # 80-56-8) is currently used worldwide at levels below **5 ppm** in selected cigarette brands manufactured and/or distributed by Philip Morris International. This document is a review of current published toxicology information on alpha-pinene 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 October 27<sup>th</sup> 2005, unless otherwise indicated.

### ***Overview***

Alpha-pinene is a monoterpene that gives off a pine scent. It can be obtained from the oil of turpentine which contains 58-65%  $\alpha$ -pinene along with 30% of  $\beta$ -pinene.  $\alpha$ -Pinene is commonly used in the manufacture of insecticides, solvents, plasticizers, perfume bases and synthetic pine oil<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.

The Joint FAO/WHO Expert Committee on Food Additives has assessed alpha-pinene as presenting no safety concerns at current levels of intake when used as a flavouring agent<sup>2</sup>. It 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 40 mg/kg in foods.

Alpha-pinene is a common cosmetic ingredient.

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 0.15 % w/w tobacco.

The following information was generated from the HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on October 27<sup>th</sup> 2005.

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

1. Turpentine treatment incr the affinity of liver microsomal cytochrome P450 to alpha-pinene (the main component of turpentine). [\*\*PEER REVIEWED\*\*] [Jarvisalo J, Vainio H; Acta Pharmacol Toxicol 46 (1): 32 (1980)]
2. Camphor, alpha-pinene (the major component of turpentine), and thujone (a constituent in the liqueur called absinthe) produced an increase in porphyrin production in primary

<sup>1</sup> The Merck index, eleventh edition, 1991.

<sup>2</sup>Joint FAO/WHO Expert committee on food additives, sixty-third meeting: Summary and conclusions, Geneva 2004 [http://www.who.int/ipcs/publications/jecfa/en/summary\\_final.pdf](http://www.who.int/ipcs/publications/jecfa/en/summary_final.pdf)

cultures of chick embryo liver cells. In the presence of desferrioxamine (an iron chelator which inhibits heme synthesis and thereby mimics the effect of the block associated with acute porphyria), the terpenes enhanced porphyrin accumulation 5 to 20 fold. They also induced synthesis of the rate-controlling enzyme for the pathway, 5-aminolevulinic acid synthase. These effects are shared by well-known porphyrogenic chemicals such as phenobarbital and glutethimide. Camphor and glutethimide alone led to the accumulation of mostly uro- and heptacarboxylporphyrins, whereas alpha-pinene and thujone resulted in lesser accumulations of porphyrins which were predominantly copro- and protoporphyrins. In the presence of desferrioxamine, plus any of the three terpenes, the major product that accumulated was protoporphyrin. The terpenes tested are porphyrogenic and hazardous to patients with underlying defects in hepatic heme synthesis. [**\*\*PEER REVIEWED\*\***] [Bonkovsky HL et al; Biochem Pharmacol 43 (11): 2359-68 (1992)]

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) October 27<sup>th</sup> 2005.

### ***Health hazard data***

#### *Acute toxicity*

LDLO/LCLO - LOWEST PUBLISHED LETHAL DOSE/CONC

##### ***Rat***

LCLo - ROUTE: Inhalation; DOSE: 625 ug/m3 [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (16,853,1978)]

TOXIC EFFECTS:

*Brain and Coverings* - Recordings from specific arc-as of CNS

*Sense Organs and Special Senses (Nose, Eye, Ear, and Taste)* - Other

*Lung, Thorax, or Respiration* - Other changes

##### ***Guinea Pig***

LCLo - ROUTE: Inhalation; DOSE: 572 ug/m3 [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (16,853,1978)]

TOXIC EFFECTS:

*Brain and Coverings* - Recordings from specific arc-as of CNS

*Sense Organs and Special Senses (Nose, Eye, Ear, and Taste)* - Other

*Lung, Thorax, or Respiration* - Other changes

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

##### ***Rat***

LD50 - ROUTE: Oral; DOSE: 3700 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (16,853,1978)]

TOXIC EFFECTS:

*Brain and Coverings* - Recordings from specific arc-as of CNS

*Behavioral* - Somnolence (general depressed activity)

*Lung, Thorax, or Respiration* - Other changes

LD50 - ROUTE: Unreported; DOSE: 3700 mg/kg [Handbook of pesticide toxicology. Robert Krieger ed, Academic press, 2001 (1,826,2001)]

## 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) (4,232,1952)]

### *Irritation*

#### SKIN - STANDARD DRAIZE TEST

### **Rabbit**

ROUTE: Skin; DOSE: 500 mg/24H; REACTION: Moderate [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (16,853,1978)]

## **TOXICITY DATA ON BURNT MATERIAL**

Data on the toxicity of alpha-pinene 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\*\*

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 the 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 October 27<sup>th</sup> 2005.

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

1. Irritates skin, mucous membranes. Causes skin eruption, gi irritation, delirium, ataxia, kidney damage, coma. Inhalation causes palpitation, dizziness, nervous disturbances, chest pain, bronchitis, nephritis. Benign skin tumors from chronic contact. [\*\*PEER REVIEWED\*\*] [Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 1545]
2. Fatal dose about 180 g orally as turpentine /which contains 58-65% alpha-pinene/. [\*\*PEER REVIEWED\*\*] [The Merck Index. 9th ed. Rahway, New Jersey: Merck & Co., Inc., 1976., p. 969]
3. Symptomatology: 1. Burning pain in mouth & throat, abdominal pain, nausea, vomiting & occasionally diarrhea. 2. Mild respiratory tract symptoms are often noted.... Coughing, choking, dyspnea & even cyanosis. Aspiration or ... systemic absorption may lead to pulmonary edema & pneumonitis. /turpentine/ [\*\*PEER REVIEWED\*\*] [Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. III-395]
4. Symptomatology: 3. Transient excitement, ataxia, confusion & finally stupor, which is commonest severe symptom. Convulsions occur occasionally, usually not until several hr after ingestion, when they may interrupt a deep coma. /turpentine/ [\*\*PEER REVIEWED\*\*] [Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. III-394]
5. Symptomatology: 4. Occasionally painful urination, albuminuria, hematuria, urine may have odor resembling ... violets ... renal lesion is usually transient. 5. Odor of turpentine on breath & in vomitus. 6. Fever & tachycardia are common. 7. Death is usually due to respiratory failure. /turpentine/ [\*\*PEER REVIEWED\*\*] [Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. III-394]
6. ... /It has/ essentially the same toxicity as turpentine. [\*\*PEER REVIEWED\*\*] [Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. II-259]
7. As little as 15 ml (1/2 oz) has proved fatal to a child, but a few children have survived 2 & even 3 oz. Mean lethal dose in adult probably lies between 4 & 6 oz. /turpentine/ [\*\*PEER REVIEWED\*\*] [Gosselin, R.E., R.P. Smith, H.C. Hodge. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. III-393]

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) October 27<sup>th</sup> 2005.

### ***Health hazard data***

#### *Irritation*

SKIN - STANDARD DRAIZE TEST

#### ***Man***

ROUTE: Skin; DOSE: 100%; REACTION: Severe [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (16,853,1978)]

### **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 judgment, based on the best available data, that alpha-pinene used in our cigarettes does not increase the overall toxicity of cigarette smoke.