

**Evaluation of
d,l-Citronellol
for Use as a Cigarette Ingredient**

December 2005

INTRODUCTION

d,l-Citronellol (CAS # 106-22-9) 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 d,l-citronellol 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 19th 2005, unless otherwise indicated.

Overview

The d-form of citronellol occurs in Ceylon and Java citronella oils whereas the l-form is a constituent of rose and geranium oils. d,l-Citronellol is commonly used in perfumery¹.

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 also assessed citronellol; a group ADI of 0–0.5 mg/kg bw, expressed as citral, was established for citral, citronellol, geranyl acetate, linalool, and linalyl acetate by the Committee at its twenty-third meeting. The daily intake is estimated at 13 µg/kg bw/day in the USA and 6.2 µg/kg bw/day in Europe².

d,l-Citronellol 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 RTECS – Registry of Toxic Effects of Chemical Substances, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on December 19th 2005.

Health hazard data

Acute toxicity

TDLO/TCLO - LOWEST PUBLISHED TOXIC DOSE/CONC

¹ The Merck Index, an encyclopedia of chemicals, drugs, and biologicals ; 11th edition ; Merck & Co., Inc., 1989

² Safety evaluations of certain food additives and contaminants, WHO Food Additive Series 52: Aliphatic branched-chain saturated and unsaturated alcohols, aldehydes, acids, and related esters. <http://www.inchem.org/documents/jecfa/jecmono/v52je15.htm>

Rat

TCLo - ROUTE: Inhalation; DOSE: 1.3 mg/m³/4H ['Vrednie chemichescie veshestva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,289,1998)]

TCLo - ROUTE: Inhalation; DOSE: 1.3 mg/m³/4H ['Vrednie chemichescie veshestva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,289,1998)]

TOXIC EFFECTS:

Behavioral - Alteration of classical conditioning

TDLo - ROUTE: Oral; DOSE: 5 gm/kg ['Vrednie chemichescie veshestva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,289,1998)]

TOXIC EFFECTS:

Liver - Changes in liver weight

Kidney, Ureter, and Bladder - Changes in kidney weight

Mouse

TDLo - ROUTE: Intraperitoneal; DOSE: 100 mg/kg [Life Sciences. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.1-8, 1962-69; V.14- 1974- (72,91,2002)]

TOXIC EFFECTS:

Behavioral - Antianxiety

LD50/LC50 - LETHAL DOSE/CONC 50% KILL**Rat**

LD50 - ROUTE: Oral; DOSE: 3450 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (13,757,1975)]

LD50 - ROUTE: Oral; DOSE: 5 gm/kg ['Vrednie chemichescie veshestva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,289,1998)]

TOXIC EFFECTS:

Brain and Coverings - Other degenerative changes

Skin and Appendages - Dermatitis, other

Mouse

LD50 - ROUTE: Intramuscular; DOSE: 4 gm/kg [Journal of Scientific and Industrial Research, Section C: Biological Sciences. (New Delhi, India) V.14-21, 1955-62. For publisher information, see IJEB A6. (21,342,1962)]

LD50 - ROUTE: Subcutaneous; DOSE: 880 mg/kg [Sapporo Igaku Zasshi. Sapporo Medical Journal. (Sapporo Igaku Daigaku, Nishi-17-chome, Minami-1-jo, Chuo-ku, Sapporo 060, Japan) V.3- 1952- (3,73,1952)]

TOXIC EFFECTS:

Peripheral Nerve and Sensation - Spastic paralysis with or without sensory change

Rabbit

LD50 - ROUTE: Skin; DOSE: 2650 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (13,757,1975)]

Irritation

SKIN - STANDARD DRAIZE TEST

Rabbit

ROUTE: Skin; DOSE: 100 mg/24H; REACTION: Severe [Cosmetics and Toiletries. (Allured Pub. Corp., POB 318, Wheaton, IL 60189) V.91- 1976- (94(8),41,1979)]

Guinea Pig

ROUTE: Skin; DOSE: 100 mg/24H; REACTION: Severe [Cosmetics and Toiletries. (Allured Pub. Corp., POB 318, Wheaton, IL 60189) V.91- 1976- (94(8),41,1979)]

Other multiple dose toxicity data

Rat

TCLo - ROUTE: Inhalation; DOSE: 0.3 mg/m³/4H/3D intermittent ['Vrednie chemichescie veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,289,1998)]

TOXIC EFFECTS:

Behavioral - Alteration of classical conditioning

TCLo - ROUTE: Inhalation; DOSE: 2.8 mg/m³/24H/100D continuous ['Vrednie chemichescie veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,289,1998)]

TOXIC EFFECTS:

Sense Organs and Special Senses (Nose, Eye, Ear, and Taste) - Change in sensation of smell

Behavioral - Alteration of classical conditioning

Biochemical - True cholinesterase

TOXICITY DATA ON BURNT MATERIAL

Data on the toxicity of d,l-citronellol as a cigarette ingredient 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. 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 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 RTECS – Registry of Toxic Effects of Chemical Substances, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on December 19th 2005.

Health hazard data

Irritation

SKIN - STANDARD DRAIZE TEST

Man

ROUTE: Skin; DOSE: 16 mg/48H; REACTION: Moderate [Cosmetics and Toiletries. (Allured Pub. Corp., POB 318, Wheaton, IL 60189) V.91- 1976- (94(8),41,1979)]

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 d,l-citronellol used in our cigarettes does not increase the overall toxicity of cigarette smoke.