

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

February 2006

INTRODUCTION

Geraniol (CAS # 106-24-1) 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 geraniol 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 February 10th 2006, unless otherwise indicated.

Overview

Geraniol is an acyclic terpene alcohol. Along with linalool and citronellol, it is the most important terpene alcohol used as a fragrance and flavour substance. It is a colourless liquid with a flowery rose-like odour. It can be used in all flowery rose-like compositions and does not discolour soaps. In flavour compositions, geraniol is used in small quantities to accentuate citrus notes. It is an important intermediate in the manufacture of geranyl esters, citronellol, and citral¹.

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 geraniol as presenting no safety concerns at current levels of intake when used as a flavouring agent. The daily intake is estimated at 5.2 µg/kg bw/day in the USA and 11 µg/kg bw/day in Europe².

Geraniol is a common cosmetic ingredient. The presence of the substance must be indicated in the list of ingredients referred to in Article 6(1)(g) when its concentration exceeds: 0.001% in leave-on products, 0.01% in rinse-off products³.

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.

An LD50 of 4800 mg/kg bw was found after testing male and female rats with geraniol².

Groups of five male and five female weanling Osborne-Mendel rats were given diet containing geraniol extra, a mixture of 3,7-dimethyl-2,6-octadienol and 3,7-dimethyl-1,6-octadienol, at a concentration of 10 000 mg/kg of diet, calculated (Food & Drug Administration, 1993) to provide

¹ *Ullmann's Encyclopedia of Industrial Chemistry* Copyright © 2002 by Wiley-VCH Verlag GmbH & Co. KGaA. All rights reserved. DOI: 10.1002/14356007.a11_141 Article Online Posting Date: January 15, 2002

² WHO Food Additives Series: 52: Aliphatic branched-chain saturated and unsaturated alcohols, aldehydes, acids, and related esters. <http://www.inchem.org/documents/jecfa/jecmono/v52je15.htm>

³ EU - Cosmetics Directive (76/768/EEC) - Annex III - Other Limitations/Requirement

an average daily intake of 500 mg/kg bw, for 16 weeks. In a second study, the same strain and number of animals were given diet containing geraniol extra at a concentration of 1000 mg/kg of diet, calculated (Food & Drug Administration, 1993) to provide an average daily intake of 50 mg/kg bw, for 27–28 weeks. In both studies, no treatment-related effects on growth, haematological parameters or organ weights, or on macroscopic or microscopic changes in the tissues were observed. The NOELs for geraniol were 500 and 50 mg/kg bw per day in the first and second study, respectively, the highest doses tested (Hagan et al., 1967)².

No evidence of mutagenicity was reported in standard or modified (preincubation method) Ames assays when geraniol (up to 889 µg/plate) was incubated with *Salmonella typhimurium* strains TA92, TA94, TA97a, TA98, TA100, TA102, TA1535, and/or TA1537 with and without metabolic activation (Rockwell & Raw, 1979; Eder et al., 1980; Florin et al., 1980; Kasamaki et al., 1982; Lutz et al., 1982; Ishidate et al., 1984; Zeiger et al., 1987; Creutziger, 1989; Gomes-Carneiro et al., 1998; National Toxicology Program, 2003)².

Geraniol did not induce sister chromatid exchanges in Chinese hamster ovary cells in the absence of metabolic activation at concentrations up to 333 µmol/l (51.4 µg/ml) (Sasaki et al., 1989). In a non-standard assay designed to maximize the frequency of chromosomal aberrations in a Chinese hamster B241 cell line, there was no evidence of an increase in chromosomal aberrations at concentrations of up to 125 µg/ml in the absence of metabolic activation (Ishidate et al., 1984), although there was an 8% increase in polyploidy².

Rec assays for DNA repair in *Bacillus subtilis* strains M45 and H17 have been performed with geraniol. In one study, geraniol gave negative results at concentrations of 16 or 17 µg/disc (Oda et al., 1979). Rec assays performed with lower concentrations of test substance gave negative results for geraniol².

Geraniol neither induced sister chromatid exchanges nor chromosomal aberrations in a non-standard assay for chromosomal aberrations².

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 February 10th 2006.

Health hazard data

Acute toxicity

TDLO/TCLO - LOWEST PUBLISHED TOXIC DOSE/CONC

Rat

TCLo - ROUTE: Inhalation; DOSE: 0.5 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:

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

TCLo - ROUTE: Inhalation; DOSE: 0.5 mg/m³/4H ['Vrednie chemichescie veshestva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,289,1998)]

LDLO/LCLO - LOWEST PUBLISHED LETHAL DOSE/CONC

Rabbit

LDLo - ROUTE: Intravenous; DOSE: 50 mg/kg [Nippon Yakurigaku Zasshi. Japanese Journal of Pharmacology. (Nippon Yakuri Gakkai, c/o Kyoto Daigaku Igakubu Yakurigaku Kyoshitsu, Konoe-cho, Yoshida, Sakyo-ku, Kyoto 606, Japan) V.40- 1944- (58,394,1962)]

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

Rat

LD50 - ROUTE: Oral; DOSE: 3600 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (2,327,1964)]

TOXIC EFFECTS:

Behavioral - Somnolence (general depressed activity)

Behavioral - Coma

Skin and Appendages - Hair

LD50 - ROUTE: Oral; DOSE: 2.1 gm/kg ['Vrednie chemichescie veshstva. 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

LD50 - ROUTE: Oral; DOSE: 4.5 gm/kg ['Vrednie chemichescie veshstva. Prirodnie organicheskie soedinenia' (Hazardous substances. Nature products.) Volkova N.V. et al., Sankt-Peterburg, 1998. (-,285,1998)]

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 IJEBA6. (21,342,1962)]

LD50 - ROUTE: Oral; DOSE: 3.5 gm/kg ['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

LD50 - ROUTE: Subcutaneous; DOSE: 1090 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: >5 gm/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (12,881,1974)]

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)]

TOXICITY DATA ON BURNT MATERIAL

Data on the toxicity of geraniol 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 HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on February 10th 2005.

Human Toxicity Excerpts

See oil of citronella... Vomiting, shock, cyanosis & convulsions preceded death in chills who consumed unknown quantity of commercial preparation consisting largely of oil of citronella /shich contains 93% geraniol/. Gastric mucosa was found to be severely damaged. /Oil of citronella/ [**PEER REVIEWED**] [Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-168]

Minimum/Potential Fatal Human Dose

3(?). 3= Moderately toxic: probable oral lethal dose (human) 0.5-5 g/kg, between 1 oz and 1 pint (or 1 lb) for 70 kg person (150 lb). [**PEER REVIEWED**] [Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-168]

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 February 10th 2006.

Health hazard data

Irritation

SKIN - STANDARD DRAIZE TEST

Man

ROUTE: Skin; DOSE: 16 mg/24H; REACTION: Severe [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 geraniol used in our cigarettes does not increase the overall toxicity of cigarette smoke.