

Evaluation of
beta-Caryophyllene
For Use as an Ingredient in
Tobacco Products

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INTRODUCTION

beta-Caryophyllene (CAS # 87-44-5) is currently used worldwide at levels below **5 ppm** in selected brands of tobacco products manufactured and/or distributed by Philip Morris International, including cigarettes and fine-cut tobacco. This document is a review of the published toxicology information on *beta*-caryophyllene abstracted from online toxicity databases.

Overview^a

The following information was generated from the MICROMEDEX database system <http://csi.micromedex.com> on February 6th 2009, unless otherwise indicated.

beta-Caryophyllene is isolated from the oil of clove stems and separated from eugenol. It occurs naturally in lime peel oil, guava fruit, carrot, celery seeds, cinnamon bark and many other plants^[1]. *beta*-Caryophyllene is a common cosmetic ingredient.

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.

The Joint FAO/WHO Expert Committee on Food Additives has assessed *beta*-caryophyllene as presenting no safety concerns at current levels of intake when used as a flavouring agent. The daily per capita intake is estimated at 8 µg/kg bw/day in the USA and 6 µg/kg bw/day in Europe^[2]. 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 5 mg/kg in foods.

The use of this ingredient on tobacco products is regulated in several countries worldwide. It is approved for use in tobacco products as an additive or flavouring in several countries with Tobacco Product Regulations, including e.g. Belgium, Croatia, Czech Republic, Egypt, Finland, France, Germany, Great Britain, Hungary, Lithuania, Macedonia, Romania, Slovak Republic, Spain and Switzerland. Apart from countries that approve its use, there is no country, regardless of the extent to which tobacco products are regulated therein, that affirmatively prohibits the use of this ingredient on tobacco products.

^a **Note:** Philip Morris International shares the concerns of regulators and the public health community about the proliferation of certain cigarette brands that have a predominantly candy-like or fruity flavour and are particularly appealing to minors, and we support legislation that would ban such cigarettes. However, there is currently no consistent terminology used by regulators and the public health community to describe such cigarettes. This can lead to confusion and potential for misinterpretation. In this document, any references to flavours or "smoke aroma" or flavour perceptions such as "sweet", "fruity", etc. are not meant to describe a flavour, taste or aroma that would dominate the taste of the final product, let alone dominate it in a way that is appealing to minors. Rather, such references are only used to explain the differences and nuances between the various flavours described in this and related documents.

TOXICITY DATA ON UNBURNT MATERIAL

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances (last revision February 2008), a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on February 6th 2009.

Health Hazard Data

Acute toxicity

TDLO/TCLO - LOWEST PUBLISHED TOXIC DOSE/CONC

Mouse

TDLo - ROUTE: Oral; DOSE: 50 mg/kg [Journal of Ethnopharmacology. (Elsevier Scientific Pub. Ireland Ltd., POB 85, Limerick, Ireland) V.1- 1979- (110,323,2007)]

TOXIC EFFECTS:

Biochemical - Effect on inflammation or mediation of inflammation

Rabbit

TDLo - ROUTE: Ocular; DOSE: 7.5 ug/kg [Farmaco. (Societa Chimica Italiana, Corso Strada Nova, 86, Casella Postale 227, 27100 Pavia, Italy) V.44- 1989- (56,387,2001)]

TOXIC EFFECTS:

Peripheral Nerve and Sensation - *Local anesthetic*

OTHER LD/LC - OTHER LETHAL DOSE/CONC

Rat

LD - ROUTE: Intratracheal; DOSE: >48 mg/kg [Archives of Toxicology. (Springer-Verlag, Heidelberger Pl. 3, D-1000 Berlin 33, Fed. Rep. Ger.) V.32- 1974- (59,78,1986)]

TOXIC EFFECTS:

Lung, Thorax, or Respiration - *Pulmonary emboli*

Irritation

SKIN - STANDARD DRAIZE TEST

Rabbit

ROUTE: Skin; DOSE: 500 mg/24H; REACTION: Not Reported [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (11,1059,1973)]

TOXICITY DATA ON BURNT MATERIAL

Data on the toxicity of *beta*-caryophyllene as a cigarette ingredient has been evaluated in a series of studies. The results of these studies may be found in the following references:

Baker R.R. *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**

Carmines E.L., 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**

Rustemeier K. *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 E. *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**

Vanscheeuwijck P.M. *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**

CONCLUSION

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 by Philip Morris International and/or others using scientifically accepted *in vitro* and *in vivo* toxicity assays with various ingredient mixtures. These studies show there is no meaningful difference in the composition or toxicity of smoke when the smoke from cigarettes with the added ingredient is compared to the smoke from cigarettes without this added ingredient. Based on a review of current published toxicological information, it is our scientific judgement that the addition of *beta*-caryophyllene as an ingredient, at the levels used in our brands, does not increase the overall toxicity of tobacco smoke.

References

1. Burdock, G. A. *Fenaroli's Handbook of Flavor Ingredients*. CRC Press, **2005**.
2. JECFA. *WHO Food Additive Series 54: Aliphatic and Alicyclic Hydrocarbons*. **2006**.