

Evaluation of
Benzyl Benzoate
For Use as an Ingredient in
Tobacco Products

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INTRODUCTION

Benzyl benzoate (CAS # 120-51-4) 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 benzyl benzoate abstracted from online toxicity databases.

Overview^a

The following information was generated from the MICROMEDEX database tool <http://csi.micromedex.com> on February 23rd 2009, unless otherwise indicated.

Benzyl benzoate which is commonly used as an acaricide, naturally occurs in oils of Ylang-ylang and tolu balsam. It is readily metabolized to benzoic acid, which is endogenous in humans^[1]. It is used as food flavouring in preparations such as non-alcoholic beverages, baked goods and also as a 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 benzyl benzoate as presenting no safety concerns at current levels of intake when used as a flavouring agent. The daily intake is estimated at 70 µg/kg bw/day in the USA and 32 µg/kg bw/day in Europe^[1]. 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 0.5 mg/kg in foods.

The use of benzyl benzoate 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 HSDB – Hazardous Substances Data Bank (last revision March 2003), a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on February 23rd 2009.

Non-human Toxicity Excerpts

1. If applied over too wide an area or too frequently /to small animals/ it can induce toxic effects which are sometimes fatal. Signs of toxicity incl nausea, vomiting & diarrhea, with depression of respiration & of the heart. Cats are particularly susceptible to this action... Most prominent feature is nervous excitability. **[**PEER REVIEWED**]** [Humphreys, D.J. Veterinary Toxicology. 3rd ed. London, England: Bailliere Tindell, 1988., p. 131]
2. In animals, /benzyl benzoate/ has been reported to cause progressive incoordination, central nervous system excitation, convulsions, and death. **[**PEER REVIEWED**]** [American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994., p. 1615]
3. Cats receiving 33% benzyl benzoate in isopropyl alcohol (two doses of 22,420 mg each), ethyl alcohol (two doses of 22,420 mg each), or water (three doses of 22,420 mg each) locally died at 43, 46, and 69 hr after treatment, respectively. **[**PEER REVIEWED**]** [Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 3. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 1506]
4. Signs of poisoning manifested by animals receiving toxic oral doses of benzyl benzoate included salivation, piloerection, muscular incoordination, tremors, progressive paralysis of hind limbs, prostration, violent convulsions, dyspnea, and death, which usually was preceded by respiratory paralysis. Death of rabbits treated with a large single dermal dose of benzyl benzoate was delayed, and the animals died without exhibiting prior symptoms of systemic effects. Cats receiving a lethal dermal dose of benzyl benzoate exhibited excessive salivation and twitching of the treated areas of their backs. Generalized tremors, muscular incoordination, paralysis of hind limbs, convulsions, respiratory failure, and death followed. In some instances, the cats remained prostrate following the convulsive seizures for many hours prior to death. All of the cats that died lost from 200 to 400 g in wt, probably as a result of decreased intakes of food and water. **[**PEER REVIEWED**]** [Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 3. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 1506]
5. Pregnant rats were fed benzyl benzoate in their diet at 10,000 ppm from the beginning of gestation to 21 days postparturition. No external, skeletal, or visceral abnormalities in the fetuses were observed. **[**PEER REVIEWED**]** [Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 3. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 1507]
6. Dermally applied benzyl benzoate was nontoxic to the pig, sheep, heifer, or horse, even after five or six daily applications, but was toxic to the cat. **[**PEER REVIEWED**]** [Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982., p. 2308]
7. Concn of benzyl benzoate repelling 90% of *Hyalomma excavatum* nymphs from caged gerbils was 2.0%. LC50 values of benzyl benzoate for nymphs was 1.1%. **[**PEER REVIEWED**]** [Hadani A et al; Entomol exp appl 22 (1): 53 (1977)]

Human Toxicity Excerpts

1. Benzyl benzoate is relatively nontoxic but may irritate the skin and eyes. Increased pruritus and irritation (manifested by burning and stinging, particularly of the genitalia and scalp) are common and may be severe in hot humid climates. [**PEER REVIEWED**] [American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994., p. 1615]
2. Liq is irritating to eyes on direct contact, but no damage has been reported... [**PEER REVIEWED**] [Grant, W. M. Toxicology of the Eye. 2nd ed. Springfield, Illinois: Charles C. Thomas, 1974., p. 185]
3. A 2-month-old boy weighing 4.2 kg, who was hospitalized for scabies, was bathed over the body, except for the face, with a solution containing benzyl benzoate (43%), soap (20%), ethyl alcohol (20%), and distilled water (17%). Convulsions appeared 2.5 hr later and were controlled with diazepam. About 1.5 hr later, convulsions recurred requiring even stronger doses of diazepam. There was no hyperthermia, hypocalcemia, or hypoglycemia. The cerebrospinal fluid was normal, as were X-rays of the head. All organic causes and subdural hematoma were eliminated. It was highly probable that the condition was iatrogenic and that the etiological agent was the benzyl benzoate. However, this could not be proved, since benzyl benzoate was not found in the urine and since the quantity of urine was too small for analysis of metabolites such as hippuric acid. The boy apparently fully recovered and was in good health when last examined at 6 months of age. [**PEER REVIEWED**] [Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 3. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 1507]
4. ... A 7 year old boy died following a transplant for aplastic bone marrow. The etiology of his condition was not established with certainty. However, the month preceding diagnosis he was bathed over the body every other day with Ascabiol, a scabicide which contained benzyl benzoate (10%) and disulfiram (2%) in addition to ethyl alcohol, water, and polysorbate. It seemed likely that the condition resulted from chronic overdosage with the scabicide. [**PEER REVIEWED**] [Hayes, W.J., Jr., E.R. Laws, Jr., (eds.). Handbook of Pesticide Toxicology. Volume 3. Classes of Pesticides. New York, NY: Academic Press, Inc., 1991., p. 1507]

Health Hazard Data

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances (last revision August 2007), a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on February 23rd 2009.

Acute toxicity

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

Rat

LD50 - ROUTE: Oral; DOSE: >1 gm/kg [Encyclopedia of Toxicology: Reference Book, Elsevier, 2005 (-,264,2005)]

LD50 - ROUTE: Oral; DOSE: 1700 uL/kg [Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10- (93,26,1948)]

LD50 - ROUTE: Skin; DOSE: 4 mL/kg [Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10- (93,26,1948)]

Mouse

LD50 - ROUTE: Intraperitoneal; DOSE: >500 mg/kg ['Industrial Hygiene and Toxicology,' 2nd ed., Patty, F.A., ed., New York, John Wiley & Sons, Inc., 1958-63 (2,1897,1963)]

LD50 - ROUTE: Oral; DOSE: 1400 uL/kg [Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10- (93,26,1948)]

Rabbit

LD50 - ROUTE: Oral; DOSE: 1680 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (11,1015,1973)]

LD50 - ROUTE: Skin; DOSE: 4 gm/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (11,1015,1973)]

Guinea Pig

LD50 - ROUTE: Oral; DOSE: 1 mL/kg [Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10- (93,26,1948)]

Dog

LD50 - ROUTE: Oral; DOSE: >22440 mg/kg [Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10- (84,358,1945)]

Cat

LD50 - ROUTE: Oral; DOSE: 2240 mg/kg [Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10- (84,358,1945)]

TOXIC EFFECTS:

Behavioral - Tremor

Behavioral - Muscle weakness

Gastrointestinal - Changes in structure or function of salivary glands

Other Multiple Dose Toxicity Data**Rabbit**

TDL₀ - ROUTE: Skin; DOSE: 180 mL/kg/13W intermittent [Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10- (93,26,1948)]

TOXIC EFFECTS:

Behavioral - Muscle weakness

Nutritional and Gross Metabolic - Weight loss or decreased weight gain

Others - Death

TOXICITY DATA ON BURNT MATERIAL

Data on the toxicity of benzyl benzoate 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. 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**

Renne R.A. *et al.* 2006, “Effects of Flavoring and Casing Ingredients on the Toxicity of Mainstream Cigarette Smoke in Rats,” *Inhalation Toxicology*, 18:685-706. **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 benzyl benzoate as an ingredient, at the levels used in our brands, does not increase the overall toxicity of tobacco smoke.

References

1. JECFA. *WHO Food Additives Series 48: Safety Evaluation of Certain Food Additives and Contaminants: Benzyl Derivatives*. **2001**.