

Evaluation of
Benzylcarbinol
For Use as an Ingredient in
Tobacco Products

January 2009

INTRODUCTION

Benzylcarbinol (CAS # 60-12-8) is currently used worldwide at levels up to **100 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 benzylcarbinol abstracted from online toxicity databases.

Overview^a

The following information was generated from the MICROMEDEX database tool <http://csi.micromedex.com> on January 21st 2009, unless otherwise indicated.

Benzylcarbinol appears as a colourless, viscous liquid with a characteristic rose-like odour. It is used as a fragrance in cosmetics and detergents, and as a flavouring agent in foods.

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 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, 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.

TOXICITY DATA ON UNBURNT MATERIAL

Non-human Toxicity Excerpts

The following information was generated from the HSDB – Hazardous Substances Data Bank (last revision November 2002), a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on January 21st 2009.

^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.

1. A more potent anesthetic than benzyl alcohol. ... Injected in mice, it causes muscular weakness & incoordination, exophthalmos, coma & death. [**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-118]
2. Drying of the corneal tear film in rabbits is hastened by 0.3% soln. /Phenylethyl alcohol/ [**PEER REVIEWED**] [Grant, W.M. *Toxicology of the Eye*. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 725]
3. Tests on rabbits eyes indicate that...irritation of conjunctiva & transient clouding of corneal epithelium were induced by application of 1% soln. [**PEER REVIEWED**] [Grant, W.M. *Toxicology of the Eye*. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 725]
4. When admin orally to rats, mice & guinea pigs, ld50 values of synthetic flavoring substances, incl phenylethanol, ranged between 2.5 & 6.2 g/kg. [**PEER REVIEWED**] [zaitsev an et al; vopr pitan ISS 5: 48 (1974)]
5. When instilled into the rabbit eye, 0.005 ml of undiluted material or 0.5 ml of 5 or 15% soln in propylene glycol caused severe corneal irritation and iritis ... /2-Phenylethanol/ [**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. 4642]
6. The material was slightly irritating to the skin of guinea pigs and rabbits. /2-Phenylethanol/ [**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. 4642]
7. An 8-hr exposure of rats to an atmosphere essentially saturated with vapors failed to cause any deaths. /2-Phenylethanol/ [**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. 4643]
8. beta-Phenylethyl alcohol has been found to obstruct genetic transformation in *B. subtilis* by rendering competent *B. subtilis* organisms unable to irreversibly incorporating transforming DNA. [**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. 4643]
9. ... beta-Phenylethyl alcohol stimulates or recovers the cell division ability in UV-irradiated cells of *E. coli* beta by selectively suppressing the initiation of DNA replication. [**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. 4643]
10. Similar threshold conc (0.5%) for conjunctival irritation were noted for phenethyl alcohol in humans and rabbits /Phenethyl alcohol/ [**PEER REVIEWED**] [Marzulli, F.N., H.I. Maibach. *Dermatotoxicology* 4th ed. New York, NY: Hemisphere Publishing Corp., 1991., p. 762]

Human Toxicity Excerpts

1. Phenethyl alcohol 0.5% in 0.9% sodium chloride applied as eyedrops to pt is reported to cause sensation of smarting in about 3 of 4 pt, but to produce only occasional slight conjunctival hyperemia. [**PEER REVIEWED**] [Grant, W. M. Toxicology of the Eye. 2nd ed. Springfield, Illinois: Charles C. Thomas, 1974., p. 806]
2. A patch test using phenyl ethyl alcohol full strength for 24 hr produced no irritation in 20 human subjects. A skin sensitization test carried out on 25 volunteers at a conc of 8% in petrolatum produced no sensitization reactions. [**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. 4643]
3. Similar threshold conc (0.5%) for conjunctival irritation were noted for phenethyl alcohol in humans and rabbits ... /Phenethyl alcohol/ [**PEER REVIEWED**] [Marzulli, F.N., H.I. Maibach. Dermatotoxicology 4th ed. New York, NY: Hemisphere Publishing Corp., 1991., p. 762]

Health Hazard Data

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances (last revision February 2006), a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on January 21st 2009.

Acute toxicity

TDLO/TCLO - LOWEST PUBLISHED TOXIC DOSE/CONC

Rat

TCLo - ROUTE: Inhalation; DOSE: 120 mg/m³/4H ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,135,1984)]

TOXIC EFFECTS:

Behavioral - Somnolence (general depressed activity)

Blood - Normocytic anemia

Blood - U28

Mouse

TDL_o - ROUTE: Intraperitoneal; DOSE: 200 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

LDLO/LCLO - LOWEST PUBLISHED LETHAL DOSE/CONC

Mouse

LDLo - ROUTE: Subcutaneous; DOSE: 1640 mg/kg [Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428 E. Preston St., Baltimore, MD 21202) V.1- 1909/10- (14,211,1920)]

TOXIC EFFECTS:

Behavioral - General anesthetic

Behavioral - Ataxia

Behavioral - Coma

Rabbit

LDLo - ROUTE: Oral; DOSE: 2 gm/kg [Journal of Economic Entomology. (Entomological Soc. of America, 4603 Calvert Rd., College Park, MD 20740) V.1- 1908- (48,139,1955)]

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

Rat

LC50 - ROUTE: Inhalation; DOSE: >500 mg/m³ [Gigiena i Sanitariya. For English translation, see HYSAAV. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1- 1936- (52(10),83,1987)]

TOXIC EFFECTS:

Behavioral - Somnolence (general depressed activity)

Blood - Normocytic anemia

Blood - U28

LC50 - ROUTE: Inhalation; DOSE: >500 mg/m³ ['Vrednie chemichescie veshestva, galogen I kislород sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,135,1984)]

LD50 - ROUTE: Oral; DOSE: 1790 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (2,327,1964)]

TOXIC EFFECTS:

Behavioral - Coma

Gastrointestinal - Gastritis

LD50 - ROUTE: Oral; DOSE: 1800 mg/kg ['Vrednie chemichescie veshestva, galogen I kislород sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,135,1984)]

TOXIC EFFECTS:

Brain and Coverings - Other degenerative changes

Mouse

LD50 - ROUTE: Oral; DOSE: 800 mg/kg ['Vrednie chemichescie veshestva, galogen I kislород sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,135,1984)]

TOXIC EFFECTS:

Brain and Coverings - Other degenerative changes

LD50 - ROUTE: Oral; DOSE: 2540 mg/kg [Voprosy Pitaniya. Problems of Nutrition. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1-10, 1932-41; V.11- 1952- (33(5),48,1974)]

Rabbit

LD50 - ROUTE: Skin; DOSE: 790 uL/kg [Toxicology and Applied Pharmacology. (Academic Press, Inc., 1 E. First St., Duluth, MN 55802) V.1- 1959- (28,313,1974)]

Guinea Pig

LD50 - ROUTE: Intraperitoneal; DOSE: 200 mg/kg ['Patty's Industrial Hygiene and Toxicology,' 3rd rev. ed., Clayton, G.D., and F.E. Clayton, eds., New York, John Wiley & Sons, Inc., 1978-82. Vol. 3 originally pub. in 1979; pub. as 2nd rev. ed. in 1985. (2C,4642,1982)]

LD50 - ROUTE: Oral; DOSE: 400 mg/kg ['Vrednie chemichescie veshstva, galogen I kislород sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., Chimia, 1994. (-,135,1984)]

TOXIC EFFECTS:

Brain and Coverings - Other degenerative changes

LD50 - ROUTE: Oral; DOSE: 2540 mg/kg [Voprosy Pitaniya. Problems of Nutrition. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1-10, 1932-41; V.11- 1952- (33(5),48,1974)]

OTHER LD/LC - OTHER LETHAL DOSE/CONC

Mouse

LD30 - ROUTE: Skin; DOSE: 100 pph ['Vrednie chemichescie veshstva, galogen I kislород sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., Chimia, 1994. (-,135,1984)]

Irritation

SKIN - STANDARD DRAIZE TEST

Rabbit

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

ROUTE: Skin; DOSE: 100%; REACTION: Mild [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (13,903,1975)]

EYE - STANDARD DRAIZE TEST

Rabbit

ROUTE: Eyes; DOSE: 750 ug/24H; REACTION: Severe ['Prehled Prumyslove Toxikologie; Organicke Latky,' Marhold, J., Prague, Czechoslovakia, Avicenum, 1986 (-,215,1986)]

ROUTE: Eyes; DOSE: 12 gm/10M; REACTION: Mild [Arzneimittel-Forschung. Drug Research. (Editio Cantor Verlag, Postfach 1255, W-7960 Aulendorf, Fed. Rep. Ger.) V.1-1951- (9,349,1959)]

Reproductive effects

Rat

TDLo - ROUTE: Oral; DOSE: 43 mg/kg; DURATION: female 6-15D of pregnancy [Journal of Toxicology and Environmental Health. (Hemisphere Pub., 1025 Vermont Ave., NW, Washington, DC 20005) V.1- 1975/76- (12,235,1983)]

TOXIC EFFECTS:

Specific Developmental Abnormalities - Eye, ear

Specific Developmental Abnormalities - Craniofacial (including nose and tongue)

Effects on Newborn - Growth statistics (e.g., reduced weight gain)

TDLo - ROUTE: Oral; DOSE: 430 mg/kg; DURATION: female 6-15D of pregnancy [Journal of Toxicology and Environmental Health. (Hemisphere Pub., 1025 Vermont Ave., NW, Washington, DC 20005) V.1- 1975/76- (12,235,1983)]

TOXIC EFFECTS:

Effects on Embryo or Fetus - Fetal death

Specific Developmental Abnormalities - Musculoskeletal system

Specific Developmental Abnormalities - Urogenital system

TDLo - ROUTE: Oral; DOSE: 43 mg/kg; DURATION: female 6-15D of pregnancy ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., Chimia, 1994. (-,135,1994)]

TOXIC EFFECTS:

Effects on Newborn - Growth statistics (e.g., reduced weight gain)

TDLo - ROUTE: Oral; DOSE: 430 mg/kg; DURATION: female 6-15D of pregnancy ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., Chimia, 1994. (-,135,1994)]

TOXIC EFFECTS:

Specific Developmental Abnormalities - Eye, ear

Specific Developmental Abnormalities - Musculoskeletal system

Specific Developmental Abnormalities - Urogenital system

TDLo - ROUTE: Skin; DOSE: 14 gm/kg; DURATION: female 6-15D of pregnancy [United States Environmental Protection Agency, Office of Pesticides and Toxic Substances. (U.S. Environmental Protection Agency, 401 M St., SW, Washington, DC 20460) History unknown. (8EHQ-0186-0587)]

TOXIC EFFECTS:

Effects on Fertility - Post-implantation mortality (e.g., dead and or resorbed implants per total number of implants)

Effects on Embryo or Fetus - Fetotoxicity (except death, e.g., stunted fetus)

Specific Developmental Abnormalities - Other developmental abnormalities

TDL_o - ROUTE: Skin; DOSE: 4300 mg/kg; DURATION: female 6-15D of pregnancy [United States Environmental Protection Agency, Office of Pesticides and Toxic Substances. (U.S. Environmental Protection Agency, 401 M St., SW, Washington, DC 20460) History unknown. (8EHQ-0186-0587)]

TOXIC EFFECTS:

Specific Developmental Abnormalities - Musculoskeletal system

Genetic effects

MUTATIONS IN MICROORGANISMS

Yeast - S Cerevisiae

DOSE: 1000 ppm (-S9) [Genetical Research. (Cambridge Univ. Press, 32 E. 57th St., New York, NY 10022) V.1- 1960- (13,107,1969)]

OTHER MUTATION TEST SYSTEMS

Mouse

CELL TYPE: Ascites tumor; DOSE: 8360 umol/L [Biochemical Pharmacology. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.1- 1958- (22,2511,1973)]

Other multiple dose toxicity data

Rat

TDL_o - ROUTE: Oral; DOSE: 6 gm/kg/30D intermittent [Gigiena i Sanitariya. For English translation, see HYSAAV. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1- 1936- (50(2),70,1985)]

TOXIC EFFECTS:

Blood - Changes in serum composition (e.g., TP, bilirubin, cholesterol)

Blood - Changes in leukocyte (WBC) count

Biochemical - True cholinesterase

TDL_o - ROUTE: Oral; DOSE: 6052 mg/kg/17W intermittent [Voprosy Pitaniya. Problems of Nutrition. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1-10, 1932-41; V.11- 1952- (33(5),48,1974)]

TOXIC EFFECTS:

Blood - Changes in serum composition (e.g., TP, bilirubin, cholesterol)

Biochemical - True cholinesterase

Biochemical - Transaminases

TDL_o - ROUTE: Skin; DOSE: 90 mL/kg/90D intermittent ['Vrednie chemicheskije veshstva, galogen I kislород sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., Chimia, 1994. (-,135,1994)]

TOXIC EFFECTS:

Blood - Normocytic anemia

Blood - Changes in leukocyte (WBC) count

Nutritional and Gross Metabolic - Weight loss or decreased weight gain

TOXICITY DATA ON BURNT MATERIAL

Data on the toxicity of benzylcarbinol 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**

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 *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**

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 benzylcarbinol as an ingredient, at the levels used in our brands, does not increase the overall toxicity of tobacco smoke.