

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

**October 2005**

## **INTRODUCTION**

Benzaldehyde (CAS # 100-52-7) is currently used worldwide at levels below **100 ppm** in selected cigarette brands manufactured and/or distributed by Philip Morris International. This document is a review of current published toxicology information on benzaldehyde 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 October 31<sup>st</sup> 2005, unless otherwise indicated.

### ***Overview***

Benzaldehyde occurs naturally as a volatile plant product; for example, benzaldehyde is a major constituent of cranberry aroma. Benzaldehyde is formed in the atmosphere as a product of the photochemical degradation of toluene; as much as 15% of the products resulting from the reaction of toluene with OH radicals will be benzaldehyde. Photochemical reactions of aromatic precursors other than toluene (such as styrene and methylstyrene) can also form benzaldehyde in the atmosphere. Benzaldehyde has been found to occur naturally in various fruits such as peaches, black currants, strawberries, grapes, and raspberries<sup>1</sup>.

Benzaldehyde is a common food flavouring agent that has an almond odour. It is readily metabolized to benzoic acid which is endogenous in humans.

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 benzaldehyde as presenting no safety concerns at current levels of intake when used as a flavouring agent. The total benzaldehyde daily intake is estimated at 600 µg/kg bw/day in the USA and 160 µg/kg bw/day in Europe<sup>2</sup>.

Benzaldehyde 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 HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on October 31<sup>st</sup> 2005.

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<sup>1</sup> HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) viewed on October 31<sup>st</sup> 2005.

<sup>2</sup> Safety evaluation of certain food additives and contaminants, WHO Food Additives series 48: Benzyl derivatives. <http://www.inchem.org/documents/jecfa/jecmono/v48je14.htm>

### *Non-Human Toxicity Excerpts*

1. Epileptiform convulsions observed in rabbits. [\*\*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-167]
2. Benzaldehyde (1%) fed to rats for 14 days decreased body and liver weight gains.... oral administration of 435 mg/kg (approximately one third of the LD50) to rats daily for 4 days caused the death of one out of six rats. ...applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating. [\*\*PEER REVIEWED\*\*] [Opdyke, D.L.J. (ed.). *Monographs on Fragrance Raw Materials*. New York: Pergamon Press, 1979., p. 115]
3. Injected into rabbits it produced a marked relaxation of the intestines and urinary bladder and marked vasodilation of the splanchnic vessel. Injection of 4 ml of a 5% solution iv into a cat caused a fall in blood pressure and slowing of respiration. [\*\*PEER REVIEWED\*\*] [Opdyke, D.L.J. (ed.). *Monographs on Fragrance Raw Materials*. New York: Pergamon Press, 1979., p. 116]
4. Rats & mice were treated daily (5 days/wk) by gavage either in 12 doses of 0 (vehicle control), 100 (rats only), 200, 400, 800, 1600 or (for mice only) 3200 mg/kg/day (followed by 2 days' observation without treatment), or for 90 days in doses of 0, 50, 100, 200, 400 or 800 mg/kg/day (rats) or 0, 75, 150, 300, 600 or 1200 mg/kg/day (mice). In acute studies, benzaldehyde induced deaths & decr body wt gain in both sexes of rats given 800 or 1600 mg/kg/day & caused deaths in both sexes of mice given 1600 or 3200 mg/kg/day. In 90 day studies, deaths occurred in both sexes of rats on 800 mg/kg/day & in male mice on 1200 mg/kg/day. Body-wt gain was depressed in male rats on 800 mg/kg/day, in male mice on 600 mg/kg/day, & in female mice on 1200 mg/kg/day. Necrotic & degenerative lesions were seen in cerebellar & hippocampal regions of brain in both sexes of rats given 800 mg/kg/day, but not in mice. Renal tubular necrosis occurred in male & female rats on 800 mg/kg/day & in male mice on 1200 mg/kg/day. Mild epithelial hyperplasia or hyperkeratosis of forestomach was seen in male & female rats on 800 mg/kg/day. The no-observed toxic effect doses admin by gavage were 400 mg/kg/day in male & female rats, 300 mg/kg/day in male mice & 600-1200 mg/kg/day in female mice. [\*\*PEER REVIEWED\*\*] [Kluwe WM et al; *Food Chem Toxicol* 21 (3): 245-50 (1983)]
5. The sensory irritating potential of a series of saturated & unsaturated aliphatic & cyclic aldehydes was investigated in B6C3F1 & Swiss Webster mice. Cyclic aldehydes produced RD50 values (concn which elicits a 50% decr in respiratory rate) between 60 & 400 ppm. Tentative threshold limit values (TLVs), based upon prevention of sensory irritation, were extrapolated from the RD50 values of Swiss Webster mice. Good agreement was found with currently published TLVs. [\*\*PEER REVIEWED\*\*] [Steinhagen WH, Barrow CS; *Toxicol Appl Pharmacol* 72 (3): 495-503 (1984)]
6. In dilutions of 1:100 in cottonseed oil was germicidal to *Bacillus coli*. Inhibited in vitro growth of *Saprolegnia parasitica* at 2000 ppm but not at 200 ppm. [\*\*PEER REVIEWED\*\*] [Opdyke, D.L.J. (ed.). *Monographs on Fragrance Raw Materials*. New York: Pergamon Press, 1979., p. 117]
7. Benzaldehyde had an inhibitory effect on the proliferation of chemically transformed rat liver epithelial cells, Culb TC/R/TC. Such cells treated with benzaldehyde (2X10<sup>-3</sup> M)

- ceased proliferation by 4th or 6th day of cultivation, whereas control cells continued to proliferate through the period (14 days). Benzaldehyde also inhibited the accum of cells with no marked morphological change. These effects were temporary & reversible. Data suggested the restoration of cell-cell contact inhibition to Culb TC/T/TC cells by benzaldehyde treatment. [\*\*PEER REVIEWED\*\*] [Nambata T et al; Agric Biol Chem 45 (12): 2815-21 (1981)]
8. Benzaldehyde inhibited the growth of SV40 transformed rat embryo fibroblasts only in the presence of glucose or mannose containing medium. It did not affect the growth of normal rat embryo fibroblasts. [\*\*PEER REVIEWED\*\*] [Watanuki M, Sakaguchi K; Agric Biol Chem 45 (1): 319-21 (1981)]
  9. The effect of the carcinostatic drug benzaldehyde on hyperthermia induced cytotoxicity was studied in various types of cultured mammalian cell lines by colony formation assay. Enhancement of hyperthermic cell killing was much greater in SV40-transformed rat fibroblasts than in the untransformed cell line. The enhancement of cell killing incr as the time & concn of BA treatment were increased at elevated temp. [\*\*PEER REVIEWED\*\*] [Ishida A et al; Cancer Res 43 (9): 4216-20 (1983)]
  10. In in vitro tests benzaldehyde (1:1000 in a 0.9% saline solution) was lethal to male pork ascarids within 4 hr. [\*\*PEER REVIEWED\*\*] [Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 117]
  11. Benzaldehyde was evaluated for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster* by the National Toxicology Program. Canton S wild type males were treated with concentrations of BA that result in approximately 30% mortality. Following treatment, males were mated individually to 3 harems of Basc virgin females to produce 3 broods for analysis. The concentrations of benzaldehyde tested by injection (2500 ppm) and feeding (1150 ppm) were negative in this assay. [\*\*PEER REVIEWED\*\*] [Woodruff RC et al; Environ Mutagen 7:677-702 (1985)]
  12. Benzaldehyde was not mutagenic in six strains of *Salmonella typhimurium* and did not induce chromosomal aberrations in CHO cells, with or without exogenous metabolic activation. Benzaldehyde induced increases in trifluorothymidine resistant mouse lymphoma cells in the absence of exogenous metabolic activation and increased sister chromatid exchanges in CHO cells in both the presence and absence of metabolic activation. Sex linked recessive lethal mutations were not induced in the germ cells of adult male *D. melanogaster* administered benzaldehyde by feeding or by injection. [\*\*PEER REVIEWED\*\*] [DHHS/NTP; Toxicology and Carcinogenesis Studies of Benzaldehyde in F344/N Rats and B6C3F1 Mice (Gavage Studies) p.4 (1988) Technical Rpt Series No. 332 NIH Pub No. 88-2588]

## ***National Toxicology Program Reports***

1. 2-Year studies were conducted by administering 0, 200, or 400 mg/kg benzaldehyde in corn oil by gavage, 5 days per week for 103 weeks to groups of 50 male B6C3F1 mice. Groups of 50 female B6C3F1 mice were administered 0, 300, or 600 mg/kg benzaldehyde for 103 weeks. Mean body weights of dosed ... mice were similar to their respective vehicle controls throughout the studies. No ... significant differences /in survival/ were observed between any groups ... of mice (survival--vehicle control male mice: 32/50; low dose 33/50; high dose 31/50; female mice: 30/50; 27/50; 35/50). The only effects of benzaldehyde were those seen in the fore-stomach of mice. The incidences of uncommonly occurring squamous cell papillomas of the fore-stomach in both exposure groups were significantly greater than those in vehicle controls (male: vehicle control, 1/50; low dose, 2/50; high dose, 5/50; female: 0/50; 5/50; 6/50). the increased incidences of papillomas were accompanied by dose related increases in the incidences in fore-stomach hyperplasia (male: 7/50; 8/50; 16/50; female 12/50; 23/50; 39/50). ... Under the conditions of these 2 year gavage studies, ... there was some evidence of carcinogenic activity of benzaldehyde for male or female B6C3F1 mice, as indicated by increased incidences of squamous cell papillomas and hyperplasia of the fore-stomach. Male and female mice might have been able to tolerate higher doses. [\*\*PEER REVIEWED\*\*] [DHHS/NTP; Toxicology and Carcinogenesis Studies of Benzaldehyde in F344/N Rats and B6C3F1 Mice (Gavage Studies) p.3 (1988) Technical Rpt Series No. 378 NIH Pub No. 88-2588]
2. 2 Year studies were conducted by administering 0, 200, or 400 mg/kg benzaldehyde in corn oil by gavage, 5 days per week for 103 weeks to groups of 50 male and 50 female /F344/N/ rats. ... Mean body weights of dosed rats were similar to their respective vehicle controls throughout the studies. The survival of the high dose group of male rats was lower than that of the vehicle controls after 1 year, no other significant differences were observed between any groups of rats (survival--male rats: vehicle control, 37/50; low dose, 29/50; high dose, 21/50; female rats: 33/50; 33/50; 29/50). ... Under the conditions of these 2 year gavage studies, there was no evidence of carcinogenic activity of benzaldehyde for male or female F344/N rats receiving 200 or 400 mg/kg per day. Female rats might have been able to tolerate higher doses. [\*\*PEER REVIEWED\*\*] [DHHS/NTP; Toxicology and Carcinogenesis Studies of Benzaldehyde in F344/N Rats and B6C3F1 Mice (Gavage Studies) p.3 (1988) Technical Rpt Series No. 378 NIH Pub No. 88-2588]

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) October 31<sup>st</sup> 2005.

### ***Health hazard data***

#### *Acute toxicity*

LDLO/LCLO - LOWEST PUBLISHED LETHAL DOSE/CONC

#### ***Rat***

LDLo - ROUTE: Subcutaneous; DOSE: 5 gm/kg [Archives Internationales de Pharmacodynamie et de Therapie. (Heymans Institute of Pharmacology, De Pintelaan 185, B-9000 Ghent, Belgium) V.4- 1898- (27,163,1922)]

TOXIC EFFECTS:

*Lung, Thorax, or Respiration* - Respiratory depression  
*Lung, Thorax, or Respiration* - Other changes

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

**Rat**

LD50 - ROUTE: Oral; DOSE: 1300 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

LD50 - ROUTE: Oral; DOSE: 2400 mg/kg ['Vrednie chemichescie veshestva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,396,1984)]

**Mouse**

LD50 - ROUTE: Intraperitoneal; DOSE: 9 mg/kg [European Journal of Toxicology and Environmental Hygiene. (Paris, France) V.7-9, 1974-76. For publisher information, see TOERD9. (9,99,1976)]

TOXIC EFFECTS:

*Behavioral* - Somnolence (general depressed activity)

*Behavioral* - Tremor

*Lung, Thorax, or Respiration* - Other changes

LD50 - ROUTE: Oral; DOSE: 28 mg/kg [European Journal of Toxicology and Environmental Hygiene. (Paris, France) V.7-9, 1974-76. For publisher information, see TOERD9. (9,99,1976)]

TOXIC EFFECTS:

*Behavioral* - Somnolence (general depressed activity)

*Behavioral* - Tremor

*Lung, Thorax, or Respiration* - Other changes

LD50 - ROUTE: Oral; DOSE: 2020 mg/kg ['Vrednie chemichescie veshestva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,396,1984)]

**Rabbit**

LD50 - ROUTE: Subcutaneous; DOSE: 5 gm/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (14,693,1976)]

**Guinea Pig**

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

TOXIC EFFECTS:

*Behavioral* - Tremor

*Gastrointestinal* - Ulceration or bleeding from small intestine

*Kidney, Ureter, and Bladder* - Urine volume increased

***Mammal - Unspecified Species***

LD50 - ROUTE: Oral; DOSE: 2020 mg/kg [Gigiena i Sanitariya. For English translation, see HYSAAV. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1- 1936- (39(4),86,1974)]

OTHER LD/LC - OTHER LETHAL DOSE/CONC

***Rat***

LC - ROUTE: Inhalation; DOSE: >500 mg/m<sup>3</sup> [Gigiena Truda i Professional'nye Zabolevaniya. Labor Hygiene and Occupational Diseases. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1-36, 1957-1992. For publisher information, see MTPEEI (18(11),40,1974)]

TOXIC EFFECTS:

*Sense Organs and Special Senses (Nose, Eye, Ear, and Taste)* - Conjunctive irritation

*Behavioral* - Somnolence (general depressed activity)

*Lung, Thorax, or Respiration* - Other changes

***Mouse***

LC - ROUTE: Inhalation; DOSE: >500 mg/m<sup>3</sup> [Gigiena Truda i Professional'nye Zabolevaniya. Labor Hygiene and Occupational Diseases. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1-36, 1957-1992. For publisher information, see MTPEEI (18(11),40,1974)]

TOXIC EFFECTS:

*Sense Organs and Special Senses (Nose, Eye, Ear, and Taste)* - Conjunctive irritation

*Behavioral* - Somnolence (general depressed activity)

*Lung, Thorax, or Respiration* - Other changes

*Irritation*

SKIN - STANDARD DRAIZE TEST

***Rabbit***

ROUTE: Skin; DOSE: 500 mg/24H; REACTION: Moderate [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (14,693,1976)]

*Genetic effects*

MUTATIONS IN MAMMALIAN SOMATIC CELLS

***Mouse***

CELL TYPE: lymphocyte; DOSE: 400 mg/L [National Toxicology Program Technical Report Series. (Research Triangle Park, NC 27709) No.206- (NTP-TR-378,1990)]

CYTOGENETIC ANALYSIS

***Rat***

ROUTE: oral; DOSE: 0.5 ppb [Environmental and Molecular Mutagenesis. (Alan R. Liss, Inc., 41 E. 11th St., New York, NY 10003) V.10- 1987- (39,69,2002)]

***Mouse***

ROUTE: oral; DOSE: 0.5 ppb [Environmental and Molecular Mutagenesis. (Alan R. Liss, Inc., 41 E. 11th St., New York, NY 10003) V.10- 1987- (39,69,2002)]

***Hamster***

CELL TYPE: lung; DOSE: 1 gm/L [Eisei Shikenjo Hokoku. Bulletin of the Institute of Hygienic Sciences. (Kokuritsu Eisei Shikenjo Kagaku, 18-1 Bushitsu Johobu, Setagaya-ku, Tokyo 158, Japan) V.1- 1886- ((103),64,1985)]

SISTER CHROMATID EXCHANGE

***Hamster***

CELL TYPE: ovary; DOSE: 50 mg/L [Environmental and Molecular Mutagenesis. (Alan R. Liss, Inc., 41 E. 11th St., New York, NY 10003) V.10- 1987- (10(Suppl 10),1,1987)]

SPECIFIC LOCUS TEST

***Rat***

ROUTE: oral; DOSE: 0.5 ppb [Environmental and Molecular Mutagenesis. (Alan R. Liss, Inc., 41 E. 11th St., New York, NY 10003) V.10- 1987- (39,69,2002)]

***Mouse***

CELL TYPE: lymphocyte; DOSE: 400 mg/L [Environmental and Molecular Mutagenesis. (Alan R. Liss, Inc., 41 E. 11th St., New York, NY 10003) V.10- 1987- (17,196,1991)]

ROUTE: oral; DOSE: 0.5 ppb [Environmental and Molecular Mutagenesis. (Alan R. Liss, Inc., 41 E. 11th St., New York, NY 10003) V.10- 1987- (39,69,2002)]

*Tumorigenic effects*

***Mouse***

TDLo - ROUTE: Oral; DOSE: 206000 mg/kg/103W intermittent [National Technical Information Service. (Springfield, VA 22161) Formerly U.S. Clearinghouse for Scientific & Technical Information. (PB90-253782/AS)]

TOXIC EFFECTS:

*Tumorigenic* - Neoplastic by RTECS criteria

*Gastrointestinal* - Tumors

TDLo - ROUTE: Oral; DOSE: 154500 mg/kg/103W intermittent [National Technical Information Service. (Springfield, VA 22161) Formerly U.S. Clearinghouse for Scientific & Technical Information. (PB90-253782/AS)]

TOXIC EFFECTS:

*Tumorigenic* - Neoplastic by RTECS criteria

*Gastrointestinal* - Tumors

TDLo - ROUTE: Oral; DOSE: 154 gm/kg/2Y continuous [National Toxicology Program Technical Report Series. (Research Triangle Park, NC 27709) No.206- (NTP-TR-378,1990)]

TOXIC EFFECTS:

*Tumorigenic* - Neoplastic by RTECS criteria

*Gastrointestinal* - Tumors

*Other multiple dose toxicity*

**Rat**

TCLo - ROUTE: Inhalation; DOSE: 500 ppm/6H/14D continuous [American Industrial Hygiene Association Journal. (AIHA, 475 Wolf Ledges Pkwy., Akron, OH 44311) V.19-1958- (52,503,1991)]

TOXIC EFFECTS:

*Liver* - Changes in liver weight

*Blood* - Changes in other cell count (unspecified)

*Nutritional and Gross Metabolic* - Weight loss or decreased weight gain

TCLo - ROUTE: Inhalation; DOSE: 26 mg/m<sup>3</sup>/5H/17W intermittent [Gigiena Truda i Professional'nye Zabolevaniya. Labor Hygiene and Occupational Diseases. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1-36, 1957-1992. For publisher information, see MTPPEI (18(11),40,1974)]

TOXIC EFFECTS:

*Blood* - Changes in erythrocyte (RBC) count

*Blood* - Changes in leukocyte (WBC) count

*Nutritional and Gross Metabolic* - Weight loss or decreased weight gain

TDLo - ROUTE: Oral; DOSE: 9600 mg/kg/16D intermittent [National Toxicology Program Technical Report Series. (Research Triangle Park, NC 27709) No.206- (NTP-TR-378,1990)]

TOXIC EFFECTS:

*Others* - Death

TDLo - ROUTE: Oral; DOSE: 52 gm/kg/13W intermittent [National Toxicology Program Technical Report Series. (Research Triangle Park, NC 27709) No.206- (NTP-TR-378,1990)]

TOXIC EFFECTS:

*Brain and Coverings* - Other degenerative changes

*Liver* - Fatty liver degeneration

*Kidney, Ureter, and Bladder* - Changes in tubules (including acute renal failure, acute tubular necrosis)

TDLo - ROUTE: Oral; DOSE: 78 gm/kg/13W intermittent [National Toxicology Program Technical Report Series. (Research Triangle Park, NC 27709) No.206- (NTP-TR-378,1990)]

TOXIC EFFECTS:

*Kidney, Ureter, and Bladder* - Changes in tubules (including acute renal failure, acute tubular necrosis)

*Others* - Death

TDLo - ROUTE: Oral; DOSE: 600 mg/kg/5W intermittent ['Vrednie chemichescie veshstva, galogen I kislород sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., Chimia, 1994. (-,396,1994)]

TOXIC EFFECTS:

*Lung, Thorax, or Respiration* - Other changes

*Liver* - Multiple effects

**Mouse**

TDLo - ROUTE: Oral; DOSE: 9600 mg/kg/16D intermittent [National Toxicology Program Technical Report Series. (Research Triangle Park, NC 27709) No.206- (NTP-TR-378,1990)]  
TOXIC EFFECTS:

*Others* - Death

**TOXICITY DATA ON BURNT MATERIAL**

Data on the toxicity of benzaldehyde 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. 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\*\*

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\*\*

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 October 31<sup>st</sup> 2005.

### ***Human Toxicity Excerpts***

1. May cause contact dermatitis. [\*\*PEER REVIEWED\*\*] [Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 165]
2. Acts as a feeble local anesthetic. Causes CNS depression in small doses and convulsions in larger doses. [\*\*PEER REVIEWED\*\*] [Sax, N.I. Dangerous Properties of Industrial Materials. 6th ed. New York, NY: Van Nostrand Reinhold, 1984., p. 354]
3. Produces ... Respiratory failure. [\*\*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-167]
4. Vapors cause slight irritation of eyes [\*\*PEER REVIEWED\*\*] [Grant, W. M. Toxicology of the Eye. 2nd ed. Springfield, Illinois: Charles C. Thomas, 1974., p. 178]
5. In patch tests using 5% benzaldehyde in vaseline, positive reactions were observed in ten of 100 patients. Positive reactions occurred in patients with sensitivity to benzoic acid or vanillin. [\*\*PEER REVIEWED\*\*] [Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 116]
6. The effect of the carcinostatic drug benzaldehyde on hyperthermia-induced cytotoxicity was studied in various types of cultured mammalian cell lines by colony formation assay. The treatment of HeLa cells with nontoxic concn (1X10<sup>-4</sup> mM) at 42 & 43 deg C for up to 3 hr induced enhancement of cell killing. The enhancement of cell killing incr as the time & concn of BA treatment were increased at elevated temp. [\*\*PEER REVIEWED\*\*] [Ishida A et al; Cancer Res 43 (9): 4216-20 (1983)]
7. Benzaldehyde caused a dose-dependent reduction of proliferation of HeLa cells in vitro. This effect might be caused by a reversible & mild growth modulation, since no serious morphological damage was observed. Delay of the S & G2 periods in the cell cycle upon addition of benzaldehyde was observed by the pulse labeling technique using (3)H thymidine. [\*\*PEER REVIEWED\*\*] [Nambata T et al; Gann 72 (2): 289-92 (1981)]
8. ... Oral fatal dose in man is estimated to be about 2 ounces. [\*\*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-167]
9. All the aldehydes possess anesthetic properties, but this is obscured by their highly irritant action on the eyes & mucous membranes of the respiratory tract. /Aldehydes/ [\*\*PEER REVIEWED\*\*] [Sax, N.I. Dangerous Properties of Industrial Materials. 6th ed. New York, NY: Van Nostrand Reinhold, 1984., p. 354]
10. May be harmful if absorbed through skin or inhaled. /CNS depressant/ in high concentrations. Acts as local anesthetic. Irritating to skin, eyes, & respiratory system. [\*\*QC REVIEWED\*\*] [Fire Protection Guide to Hazardous Materials. 12 ed. Quincy, MA: National Fire Protection Association, 1997., p. 49-25]
11. Effect of benzaldehyde on growth of malignant human cells (HL60 promyelocytic leukemia cells, KG-1 myeloid leukemia cells, chronic lymphocytic leukemia cells & human tumor colony forming cells from 30 patients with solid tumors), & its effects in vivo against 2 human tumor xenografts (T222 epidermoid carcinoma & T380 ovarian carcinoma) established from primary specimens were studied. Benzaldehyde was found

to lack significant activity against most human tumors tested in these exptl systems. [\*\*PEER REVIEWED\*\*] [Taetle R, Howell SB; Cancer Treat Rep 67 (6): 561-6 (1982)]

### ***Probable Routes of Human Exposure***

1. Occupational exposure to benzaldehyde can occur through dermal contact and inhalation of vapors. Benzaldehyde's use as a flavoring agent and its natural occurrence in many foods will expose the general population through oral consumption(1,2). The general population is also exposed to benzaldehyde through its occurrence in ambient air(SRC). [\*\*PEER REVIEWED\*\*] [(1) Williams AE; Kirk-Othmer Encycl Chem Technol 3rd ed. NY,NY: John Wiley & Sons 3: 736-43 (1978) (2) National Research Council; Formaldehyde and Other Aldehydes. USEPA-600/6-82-002 (NTIS PB82-180498) (1982)]
2. NIOSH (NOES Survey 1981-1983) has statistically estimated that 30,517 workers are potentially exposed to benzaldehyde in the USA(1). NIOSH (NOHS Survey 1972-1974) has statistically estimated that 15,985 workers are potentially exposed to benzaldehyde in the USA(2). [\*\*PEER REVIEWED\*\*] [(1) NIOSH; National Occupational Exposure Survey (NOES) (1983) (2) NIOSH; National Occupational Hazard Survey (NOHS) (1974)]

### ***Body Burdens***

Benzaldehyde was qualitatively detected in 8 of 12 samples of human milk collected from volunteers in Bayonne, NJ, Jersey City, NJ, Bridgeville, PA, and Baton Rouge, LA(1). [\*\*PEER REVIEWED\*\*] [(1) Pellizzari ED et al; Bull Environ Contam Toxicol 28: 322-8 (1982)]

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) October 31<sup>st</sup> 2005.

### ***Health hazard data***

#### ***Acute toxicity***

**TDLO/TCLO - LOWEST PUBLISHED TOXIC DOSE/CONC**

##### ***Human***

**TCLo - ROUTE:** Inhalation; **DOSE:** 0.15 mg/m<sup>3</sup> ['Vrednie chemichescie veshestva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,396,1984)]

**TOXIC EFFECTS:**

*Sense Organs and Special Senses (Nose, Eye, Ear, and Taste) - Conjunctive irritation*

*Lung, Thorax, or Respiration - Cough*

**LDLO/LCLO - LOWEST PUBLISHED LETHAL DOSE/CONC**

##### ***Human***

**LDLo - ROUTE:** Oral; **DOSE:** 714.3 mg/kg ['Vrednie chemichescie veshestva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,396,1984)]

*Genetic effects*

SISTER CHROMATID EXCHANGE

***Human***

CELL TYPE: lymphocyte; DOSE: 1 mmol/L [Mutation Research. (Elsevier Science Pub. B.V., POB 211, 1000 AE Amsterdam, Netherlands) V.1- 1964- (206,17,1988)]

## **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 judgement, based on the best available data, that benzaldehyde used in our cigarettes does not increase the overall toxicity of cigarette smoke.