

# **Evaluation of Acetophenone for Use as a Cigarette Ingredient**

**October 2005**

## **INTRODUCTION**

Acetophenone (CAS # 98-86-2) is currently used worldwide at levels up to **38 ppm** by Philip Morris International in selected roll your own or conventional cigarette brands manufactured and/or distributed by Philip Morris International. This document is a review of the published toxicology information on acetophenone 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 27<sup>th</sup> 2005, unless otherwise indicated.

### ***Overview***

Acetophenone is an aromatic ketone commonly found as a natural component of berries, seafood, beef, and nuts. It has been shown to be absorbed rapidly from the gut, metabolized efficiently by the liver, and excreted primarily in the urine and to a small extent in the faeces<sup>1</sup>.

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 acetophenone as presenting no safety concerns at current levels of intake when used as a flavouring agent. The daily intake is estimated at 3 µg/kg bw/day in the USA and 0.3 µg/kg bw/day in Europe<sup>1</sup>. 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 10 mg/kg in foods.

Acetophenone 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.

An LD50 of 3000 mg/kg bw was determined after administration by gavage to rats and of 900 mg/kg bw after oral administration also to rats<sup>1</sup>.

A NOEL of 1000 mg/kg bw per day was determined after a 17 week short-term study on rats of food-administered acetophenone<sup>1</sup>.

*In vitro* genotoxicity testing of acetophenone showed no reverse mutation in the standard Ames assay with *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 at 360 mg/plate with and without metabolic activation. Chromosomal aberrations were not induced in Chinese hamster ovary cells incubated with 800-1200 mg/ml of acetophenone without metabolic activation. Positive results were reported in similar studies in which Chinese hamster ovary cells

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<sup>1</sup> Safety evaluations of certain food additives and contaminants, WHO Food Additive Series 48: Aromatic substituted secondary alcohols, ketones, and related esters  
<http://www.inchem.org/documents/jecfa/jecmono/v48je13.htm>

were incubated with 600-1000 mg/ml of acetophenone with metabolic activation. Mutation assays with *Escherichia coli* and *S. typhimurium* were negative when tested with acetophenone between 1-1000 mg/ml with and without metabolic activation<sup>1</sup>.

The following information was generated from the HSDB – Hazardous Substances Data Bank, a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on October 27<sup>th</sup> 2005.

### ***Non-Human Toxicity Excerpts***

1. /Laboratory animals: Acute Exposure/ Acetophenone had a moderate to low acute oral toxicity in laboratory animals and a low dermal toxicity in guinea-pigs. Central nervous system depression occurred in laboratory animals exposed orally and by injection. [\*\*PEER REVIEWED\*\*] [BIBRA working group; TA:Toxicity profile. BIBRA Toxicology International: 4 (1991) ]
2. / Laboratory animals: Acute Exposure/ Acetophenone was a skin irritant in rabbits and guinea-pigs ... . It was a severe eye irritant in rabbits. No skin- sensitizing potential was demonstrated. when solutions of acetophenone were tested on guinea-pigs. [\*\*PEER REVIEWED\*\*] [BIBRA working group; TA:Toxicity profile. BIBRA Toxicology International: 4 (1991) ]
3. / Laboratory animals: Acute Exposure/ ... The irritancy potential of acetophenone in a mouse bioassay that quantified the sudden reflexive drop in respiration caused by a short-duration vapor exposure /is reported/. The concn-related decline in the respiration rate allowed for the calculation of an RD50 value, which corresponded to the irritant concn needed to produce a 50% decr in the initial respiration rate. The RD50 value for acetophenone in male Swiss OF1 mice exposed for 5 min was 500 mg/cu m. [\*\*PEER REVIEWED\*\*] [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 296]
4. / Laboratory animals: Acute Exposure/ Subcutaneous or intravenous injection of acetophenone /into mice/ produced hypnotic effects. Mice survived 0.7 g/kg of acetophenone injected intraperitoneally, but clear-cut hypnotic effects occurred rapidly at dosage levels of 0.4 to 0.5 g/kg. [\*\*PEER REVIEWED\*\*] [American Conference of Governmental Industrial Hygienists. Documentation of Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices for 2001. Cincinnati, OH. 2001., p. 1]
5. / Laboratory animals: Acute Exposure/ Application of acetophenone to the eyes of rabbits as two drops of saturated aqueous solution caused discomfort; however, the effects were limited to a transient optical irregularity of the corneal epithelium, with no opacity, and the eyes returned to normal by the next day. In another study, 0.005 ml of a 15% solution (750 ug) produced severe corneal necrosis in the rabbit eye. [\*\*PEER REVIEWED\*\*] [American Conference of Governmental Industrial Hygienists. Documentation of Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices for 2001. Cincinnati, OH. 2001., p. 1]
6. / Laboratory animals: Acute Exposure/ ... Acetophenone produced grade 8 (severe on a scale of 1-10) ocular damage in albino rabbits based on the total point score 24 hr after treatment. Points were accumulated according to the degree of corneal opacity, necrosis, and iritis observed in the treated eye, with the max total score being 20 points. A grade 8

- injury corresponded to a point score of 5 or less when 5 ul of a 5% soln of acetophenone was applied, and a point score >5 with a 15% soln. **[\*\*PEER REVIEWED\*\*]** [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 296]
7. / Laboratory animals: Acute Exposure/ ... With ip injection of 0.4-0.5 g/kg to rats, staggering occurred after 5 min, paraparesis in 13 and quadriplegia in about 20 min. ... Expt on guinea pigs, profound torpor, with gradual loss of reflexes, rapid, somewhat irregular resp, weak cardiac action, lowering of temp and some convulsive movements. In dog, with iv injection, deep sleep was followed rapidly by analgesia and anesthesia, dilatation of pupils with diminished light reflex, resp and cardiac modification, with lowering of blood pressure, feeble pulse and resp arrhythmia. **[\*\*PEER REVIEWED\*\*]** [Browning, E. Toxicity and Metabolism of Industrial Solvents. New York: American Elsevier, 1965., p. 453]
  8. / Laboratory animals: Acute Exposure/ Undiluted acetophenone (771 mg) applied to the eyes of rabbits produced moderate irritation and transient corneal injury. ... When held in contact with rabbit skin for 24 hr, acetophenone produced irritation described as a mild burn. When the tails of mice were immersed in acetophenone for 4 hr all the animals died, indicating that acetophenone is readily absorbed percutaneously. **[\*\*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. 4785]
  9. / Laboratory animals: Acute Exposure/ It is ... /cns depressant/ to animals and in high doses can cause death due to resp failure. ... It has also the property of sensitizing and reinforcing the action of acetylcholine on striated muscle of vertebrate animals without any anticholinesterase effect ... and without relation directly to its anesthetic potency. **[\*\*PEER REVIEWED\*\*]** [Browning, E. Toxicity and Metabolism of Industrial Solvents. New York: American Elsevier, 1965., p. 452]
  10. / Laboratory animals: Subchronic or Prechronic Exposure/ ... Acetophenone levels ranging from 1-102 mg/kg/day failed to cause any reduction in body weight or any histopathologic abnormalities in the liver, kidney, spleen, or testis when incorporated in the diet of Sherman rats for 30 days. ... Acetophenone in the diet of male and female Osborne-Mendel rats at levels 1,000, 2,500, or 10,000 ppm (0.1, 0.25, 1.0%) for 17 wk ... found no toxic effects on body weight, hematological indices (red and white blood cell counts, hemoglobin, and hematocrit), nor histopathological abnormalities of the liver, kidney, spleen, heart, testis, muscle, or bone marrow. ... Application of 480 mg/kg of acetophenone to the skin of pregnant rats on days 10-15 of pregnancy did not cause any change in the gestation period, size of litter, weight of the offspring, time for appearance of teeth or hair, opening of the eyes, or appearance of reflexes. **[\*\*PEER REVIEWED\*\*]** [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 298]
  11. / Laboratory animals: Subchronic or Prechronic Exposure/ ... Application of 480 mg/kg of acetophenone to the skin of pregnant rats on days 10-15 of pregnancy did not cause any change in the gestation period, size of litter, weight of the offspring, time for appearance of teeth or hair, opening of the eyes, or appearance of reflexes./ Laboratory animals: Subchronic or Prechronic Toxicity/ **[\*\*PEER REVIEWED\*\*]** [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 297]

12. / Laboratory animals: Subchronic or Prechronic Exposure/ No effects on growth, hematological values or macroscopic tissue changes were observed in groups of 10 male and 10 female Osborne-mendel rats exposed to 0, 1000, 2500, 10,000 ppm acetophenone in the diet for 17 weeks. Microscopic exam of the 10,000 ppm group revealed no effects. Thus the 10,000 ppm level was the highest concn at which no effects were observed. Some loss of the compound from the feed due to volatization was reported. [\*\*PEER REVIEWED\*\*] [Hagan E, et al; Food Cosmet Toxicol 5: 141-157 (1967) ]
13. / Laboratory animals: Subchronic or Prechronic Exposure/ Rats (2 wk old) exposed to acetophenone for periods of 1-12 wk showed specific patterns of mitral cell degeneration in olfactory bulb. [\*\*PEER REVIEWED\*\*] [PINCHING AJ, DOEVING KB; BRAIN RES 82 (2): 195-204 (1974) ]
14. /Genotoxicity/ There was no evidence of mutagenicity in Ames bacterial tests. Chromosome damage has been reported in hamster cells in culture. [\*\*PEER REVIEWED\*\*] [BIBRA working group; TA:Toxicity profile. BIBRA Toxicology International: 4 (1991)]
15. /Genotoxicity/ A ... two event model for UV mutagenesis producing class 2 suppressor mutations at glutamine tRNA genes in Escherichia coli /has been examined/ In the model used, the induction/indexing lesion is any type of pyrimidine dimer and the premutational photoproduct at the target site is a cytosine containing dimer. Specific mutation frequency responses were analyzed under conditions in which the ratio of thymine-thymine dimers to cytosine containing dimers was modified by using 313 nm light and 0.0%, 0.1%, or 0.2% acetophenone. Changes observed in the production of class 2 suppressor mutations were consistent with the model and suggested that the G X C mutations are targeted by cytosine containing pyrimidine dimers at the mutational sites. [\*\*PEER REVIEWED\*\*] [Fix D, Bockrath R; Proc Natl Acad Sci USA 80 (40): 4446-9 (1983)]

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 October 27<sup>th</sup> 2005.

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

#### *Acute toxicity*

LDLO/LCLO - LOWEST PUBLISHED LETHAL DOSE/CONC

#### ***Mouse***

LDLo - ROUTE: Subcutaneous; DOSE: 330 mg/kg ['Pharmakologische Prufung von Analgetika, Dissertation,' Herrlen, G., Pharmakologischen Institut der Universitat Tubingen, Fed. Rep. Ger., 1933 (-, -, 1933)]

TOXIC EFFECTS:

*Behavioral* - Somnolence (general depressed activity)

LDLo - ROUTE: Skin; DOSE: 100 pph/4H ['Vrednie chemicheskije veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., Chimia, 1994. (-, -, 1994)]

LDLo - ROUTE: Unreported; DOSE: 510 mg/kg ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

**TOXIC EFFECTS:**

*Lung, Thorax, or Respiration* - Emphysema

*Liver* - Other changes

*Kidney, Ureter, and Bladder* - Other changes

**LD50/LC50 - LETHAL DOSE/CONC 50% KILL**

***Rat***

LD50 - ROUTE: Oral; DOSE: 815 mg/kg [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 (26(8),53,1982)]

LD50 - ROUTE: Oral; DOSE: 2650 mg/kg ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

**TOXIC EFFECTS:**

*Lung, Thorax, or Respiration* - Emphysema

*Liver* - Other changes

*Kidney, Ureter, and Bladder* - Other changes

***Mouse***

LC50 - ROUTE: Inhalation; DOSE: 1200 mg/m<sup>3</sup>/4H ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

**TOXIC EFFECTS:**

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

*Behavioral* - Tetany

*Lung, Thorax, or Respiration* - Respiratory depression

LD50 - ROUTE: Intraperitoneal; **DOSE:** 200 mg/kg [National Technical Information Service. (Springfield, VA 22161) Formerly U.S. Clearinghouse for Scientific & Technical Information. (AD277-689)]

LD50 - ROUTE: Oral; DOSE: 1250 mg/kg ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

**TOXIC EFFECTS:**

*Lung, Thorax, or Respiration* - Emphysema

*Liver* - Other changes

*Kidney, Ureter, and Bladder* - Other changes

LD50 - ROUTE: Oral; DOSE: 740 mg/kg [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 (26(8),53,1982)]

LD50 - ROUTE: Unreported; DOSE: 533 mg/kg ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

**TOXIC EFFECTS:**

*Lung, Thorax, or Respiration* - Emphysema

*Liver* - Other changes

*Kidney, Ureter, and Bladder* - Other changes

***Rabbit***

LD50 - ROUTE: Skin; DOSE: 15900 uL/kg [Union Carbide Data Sheet. (Union Carbide Corp., 39 Old Ridgebury Rd., Danbury, CT 06817) (12/27/1971)]

LD50 - ROUTE: Unreported; DOSE: 1760 mg/kg ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

***Guinea Pig***

LD50 - ROUTE: Skin; DOSE: >20 mL/kg [Journal of Industrial Hygiene and Toxicology. (Cambridge, MA) V.18-31, 1936-49. For publisher information, see AEHLAU. (26,269,1944)]

LD50 - ROUTE: Unreported; DOSE: 2000 mg/kg ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

***Mammal - Unspecified Species***

LC50 - ROUTE: Inhalation; DOSE: 1200 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 (32(10),25,1988)]

LD50 - ROUTE: Oral; DOSE: 2700 mg/kg [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 (32(10),25,1988)]

**OTHER LD/LC - OTHER LETHAL DOSE/CONC**

***Rat***

LC - ROUTE: Inhalation; DOSE: >210 ppm/8H [Union Carbide Data Sheet. (Union Carbide Corp., 39 Old Ridgebury Rd., Danbury, CT 06817) (12/27/1971)]

***Irritation***

**SKIN - OPEN DRAIZE TEST**

***Rabbit***

ROUTE: Skin; DOSE: 10 mg/24H ; REACTION: Not Reported [Journal of Industrial Hygiene and Toxicology. (Cambridge, MA) V.18-31, 1936-49. For publisher information, see AEHLAU. (26,269,1944)]

ROUTE: Skin; DOSE: 515 mg ; REACTION: Mild [Union Carbide Data Sheet. (Union Carbide Corp., 39 Old Ridgebury Rd., Danbury, CT 06817) (12/27/1971)]

#### EYE - STANDARD DRAIZE TEST

##### **Rabbit**

ROUTE: Eyes; DOSE: 750 ug; REACTION: Severe [American Journal of Ophthalmology. (Ophthalmic Pub. Co., 435 N. Michigan Ave., Suite 1415, Chicago, IL 60611) Series 3: V.1-1918- (29,1363,1946)]

#### *Reproductive effects*

##### **Rat**

TDLo - ROUTE: Oral; DOSE: 32 gm/kg; DURATION: male 4W and 10D of pregnancy-3D after birth prior to mating [Toxicologist. (Soc. of Toxicology, Inc., 475 Wolf Ledge Parkway, Akron, OH 44311) V.1- 1981- (72,76,2003)]

##### TOXIC EFFECTS:

*Effects on Newborn* - Live birth index (similar to T26, except measured after birth)

*Effects on Newborn* - Viability index (e.g., # alive at day 4 per # born alive)

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

#### *Genetic effects*

#### CYTOGENETIC ANALYSIS

##### **Hamster**

CELL TYPE: lung; DOSE: 600 mg/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)]

#### *Other multiple dose toxicity data*

##### **Rat**

TCLo - ROUTE: Inhalation; DOSE: 77 mg/m<sup>3</sup>/106D intermittent ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., Chimia, 1994. (-,461,1994)]

##### TOXIC EFFECTS:

*Brain and Coverings* - Other degenerative changes

*Liver* - Other changes

*Biochemical* - True cholinesterase

TCLo - ROUTE: Inhalation; DOSE: 15 mg/m<sup>3</sup>/167D intermittent ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., Chimia, 1994. (-,461,1994)]

##### TOXIC EFFECTS:

*Behavioral* - Alteration of classical conditioning

*Kidney, Ureter, and Bladder* - Other changes in urine composition

*Biochemical* - Porphyrin including bile pigments

TDLo - ROUTE: Oral; DOSE: 21 gm/kg/28D intermittent [Toxicologist. (Soc. of Toxicology, Inc., 475 Wolf Ledge Parkway, Akron, OH 44311) V.1- 1981- (72,76,2003)]

##### TOXIC EFFECTS:

*Behavioral* - Change in motor activity (specific assay)

*Behavioral* - Changes in psychophysiological tests

TDL<sub>o</sub> - ROUTE: Oral; DOSE: 21 gm/kg/28D intermittent [Toxicologist. (Soc. of Toxicology, Inc., 475 Wolf Ledge Parkway, Akron, OH 44311) V.1- 1981- (72,76,2003)]

TOXIC EFFECTS:

*Behavioral* - Food intake (animal)

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

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

TDL<sub>o</sub> - ROUTE: Oral; DOSE: 6.3 gm/kg/28D intermittent [Toxicologist. (Soc. of Toxicology, Inc., 475 Wolf Ledge Parkway, Akron, OH 44311) V.1- 1981- (72,76,2003)]

TOXIC EFFECTS:

*Gastrointestinal* - Changes in structure or function of salivary glands

TDL<sub>o</sub> - ROUTE: Oral; DOSE: 18000 mg/kg/60D intermittent ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

TOXIC EFFECTS:

*Behavioral* - Somnolence (general depressed activity)

*Biochemical* - Catalases

### ***Rabbit***

TCL<sub>o</sub> - ROUTE: Inhalation; DOSE: 15 mg/m<sup>3</sup>/167D intermittent ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

TOXIC EFFECTS:

*Behavioral* - Alteration of classical conditioning

*Kidney, Ureter, and Bladder* - Other changes in urine composition

*Biochemical* - Porphyrin including bile pigments

TDL<sub>o</sub> - ROUTE: Oral; DOSE: 45.5 mg/kg/13W intermittent ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

TOXIC EFFECTS:

*Behavioral* - Somnolence (general depressed activity)

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

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

TDL<sub>o</sub> - ROUTE: Oral; DOSE: 4.55 mg/kg/13W intermittent ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

TOXIC EFFECTS:

*Behavioral* - Alteration of classical conditioning

### ***Mammal - Unspecified Species***

TCLo - ROUTE: Inhalation; DOSE: 0.07 mg/m<sup>3</sup>/75D intermittent ['Vrednie chemichescie veshstva, galogen I kislород sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,461,1994)]

TOXIC EFFECTS:

*Behavioral* - Alteration of classical conditioning

*Kidney, Ureter, and Bladder* - Other changes in urine composition

*Biochemical* - Porphyrin including bile pigments

## **TOXICITY DATA ON BURNT MATERIAL**

Data on the toxicity of acetophenone after combustion 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 chemicals 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 27<sup>th</sup> 2005.

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

1. /Human exposure studies/ Only effects on human beings have been examined as result of its use as hypnotic or sedative, and with fairly high dosage there appears to be a slightly depressant action on pulse and slight but continuous decrease of hemoglobin. [\*\*PEER REVIEWED\*\*] [Browning, E. Toxicity and Metabolism of Industrial Solvents. New York: American Elsevier, 1965., p. 453]
2. / Human exposure studies / Skin contact ... may result in marked irritation and transient corneal injury depending upon extent and duration of contact. Its vapors are not expected to present a problem unless acetophenone is heated. [\*\*PEER REVIEWED\*\*] [Patty, F. (ed.). Industrial Hygiene and Toxicology: Volume II: Toxicology. 2nd ed. New York: Interscience Publishers, 1963., p. 1762]
3. / Human exposure studies / Among healthy subjects no effects of any kind were perceptible following ingestion of 0.1-0.3 g, but with 0.45-0.6 g micturition was increased, pulse weakened and slowed after 5-6 hr, and there was slight but continuous decrease of hemoglobin, returning to normal when dosage ceased. [\*\*PEER REVIEWED\*\*] [Patty, F. (ed.). Industrial Hygiene and Toxicology: Volume II: Toxicology. 2nd ed. New York: Interscience Publishers, 1963., p. 454]
4. / Human exposure studies / ... /Due to reports of rash to the face, neck, arms, and legs, eye and throat irritation, headaches, dizziness, and nausea, the Kentucky Dept of Labor analyzed bulk and air samples for formaldehyde and acetophenone in a uniform manufacturing plant./ Medical interviews were conducted with 9 of 13 employees who had reported symptoms. Questionnaires were administered to all 13 employees. Industrial hygiene air monitoring data for formaldehyde obtained by the Kentucky Department of Labor was reviewed. Bulk samples /of fabric/ had residual formaldehyde concentrations of 260 to 450 ppm and 33,500 to 46,500 ppm acetophenone. The Kentucky Department of Labor /air/ monitoring data showed average formaldehyde concentrations of 0.15 to 0.18 ppm. ... It was concluded that formaldehyde exposures at the facility could cause the observed symptoms. Acetophenone exposure also may have contributed to the symptoms, although little is known about its toxicity. Recommendations included providing exhaust ventilation system, cooperating with textile mills to obtain fabrics with minimal concentrations of latent formaldehyde and acetophenone, and airing the fabrics to allow /release/ of formaldehyde. [\*\*PEER REVIEWED\*\*] [DHHS/NIOSH; Hazard Evaluations and Technical Assistance Branch Report No. HETA-83-301-1478, 23 pp. (1984) ]
5. / Human exposure studies / No skin sensitization was noted when 2% acetophenone in petrolatum was tested on humans. [\*\*PEER REVIEWED\*\*] [Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 299]

## **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 acetophenone used in our cigarettes does not increase the overall toxicity of cigarette smoke.