

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

October 2005

INTRODUCTION

Acetanisole (CAS # 100-06-1) is currently used worldwide at levels below **5 ppm** in selected cigarette brands manufactured and/or distributed by Philip Morris International. This document is a review of current published toxicology information on acetanisole 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 27th 2005, unless otherwise indicated.

Overview

Acetanisole is an aromatic ketone that is predicted to be metabolized to innocuous products. It is also reported to occur naturally in foods¹

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 acetanisole as presenting no safety concerns at current levels of intake when used as a flavouring agent. The daily intake is estimated at 1 µg/kg bw/day in the USA and 3 µg/kg bw/day in Europe¹. 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 20 mg/kg in foods.

Acetanisole 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 27th 2005.

Health hazard data

Acute toxicity

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

Rat

LD50 - ROUTE: Oral; DOSE: 1720 mg/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (12,927,1974)]

¹ 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>

LD50 - ROUTE: Oral; DOSE: 4300 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. (-,465,1994)]

TOXIC EFFECTS:

Brain and Coverings - Other degenerative changes

Nutritional and Gross Metabolic - Weight loss or decreased weight gain

Mouse

LD50 - ROUTE: Oral; DOSE: 820 mg/kg [Gigiena i Sanitariya. For English translation, see HYSAAV. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1- 1936- (50(4),86,1985)]

TOXIC EFFECTS:

Behavioral - Somnolence (general depressed activity)

Behavioral - Muscle weakness

Behavioral - Irritability

LD50 - ROUTE: Oral; DOSE: 820 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. (-,465,1994)]

TOXIC EFFECTS:

Brain and Coverings - Other degenerative changes

Nutritional and Gross Metabolic - Weight loss or decreased weight gain

Rabbit

LD50 - ROUTE: Skin; DOSE: >5 gm/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (12,927,1974)]

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. (12,927,1974)]

Other multiple dose toxicity data

Rat

TCLo - ROUTE: Inhalation; DOSE: 152 mg/m³/4H/13W intermittent [Gigiena i Sanitariya. For English translation, see HYSAAV. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1- 1936- (50(4),86,1985)]

TOXIC EFFECTS:

Brain and Coverings - Recordings from specific arc-as of CNS

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

Biochemical - Other transferases

TCLo - ROUTE: Inhalation; DOSE: 152 mg/m³/4H/90D intermittent ['Vrednie chemichescie veshstva, galogen I kislorod sodergashie organicheskie soedinenia'. (Hazardous substances. Galogen and oxygen containing substances), Bandman A.L. et al., *Chimia*, 1994. (-,465,1994)]

TOXIC EFFECTS:

Biochemical - Other transferases

Biochemical - Plasma proteins not involving coagulation

TOXICITY DATA ON BURNT MATERIAL

Data on the toxicity of acetanisole 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 27th 2005.

Health hazard data

Acute toxicity

TDLO/TCLO - LOWEST PUBLISHED TOXIC DOSE/CONC

Human

TCLO - ROUTE: Inhalation; DOSE: 1700 ug/m³/39W intermittent [Gigiena i Sanitariya. For English translation, see HYSAAV. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1- 1936- (50(4),86,1985)]

TOXIC EFFECTS:

Cardiac - Pulse rate increased without fall in BP

Vascular - BP elevation not characterized in autonomic section

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 acetanisole used in our cigarettes does not increase the overall toxicity of cigarette smoke.