

Evaluation of
Ethyl Butyrate
For Use as an Ingredient in
Tobacco Products

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INTRODUCTION

Ethyl butyrate (CAS # 105-54-4) is currently used worldwide at levels up to **28 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 ethyl butyrate abstracted from online toxicity databases.

Overview^a

The following information was generated from the MICROMEDEX database system <http://csi.micromedex.com> on February 24th 2009, unless otherwise indicated.

Ethyl butyrate is a colourless liquid with a fruity odour with a pineapple undertone. Ethyl butyrate is obtained by esterification of n-butyric acid with ethyl alcohol in the presence of sulfuric acid. Ethyl butyrate is used principally as a flavour for foods, beverages, & chewing gums and is also a common 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 ethyl butyrate as presenting no safety concerns at current levels of intake when used as a flavouring agent. The acceptable daily intake (ADI) is estimated at 15 mg/kg bw/day^[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.

The use of ethyl butyrate 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 October 2002), a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on February 24th 2009.

Non-Human Toxicity Excerpts

1. Oral admin to dogs of 3 g in 60 ml of water caused no toxic effects ... in rabbits admin of 2.14 ml/kg caused ... increase in respiratory vol ... intravenous injection, for dogs, 177-222 mg/kg ... had no ... effect [Peer reviewed] [Browning, E. Toxicity and Metabolism of Industrial Solvents. New York: American Elsevier, 1965., p. 580]
2. In vitro it has been shown to have a hemolytic effect slightly greater than that of methyl butyrate. [Peer reviewed] [Browning, E. Toxicity and Metabolism of Industrial Solvents. New York: American Elsevier, 1965., p. 580]
3. Organophosphate-resistant & sensitive houseflies responded in similar manner to treatment with ethyl butyrate indicating that ali-esterases in both strains must be equally active, but perhaps act differently. [peer reviewed] [shatoury hh; experientia 26 (12): 1295 (1970)]

Human Toxicity Excerpts

1. /It is/ irritating to mucous membranes and ... /srp: cns depressant/ in high concentrations. [Peer reviewed] [Sax, N.I. Dangerous Properties of Industrial Materials. 4th ed. New York: Van Nostrand Reinhold, 1975., p. 730]
2. Many ... are highly volatile and ... can act as asphyxiants or ... /srp: cns depressant/; skin absorption as well as inhalation, may be important route of absorption for ... esters which are volatile & have high solvent action. /esters/ [Peer reviewed] [Sax, N.I. Dangerous Properties of Industrial Materials. 6th ed. New York, NY: Van Nostrand Reinhold, 1984., p. 730]
3. Tested at 5% in petrolatum, ethyl butyrate produced no irritation after a 48 hr closed-patch test in 25 human subjects. A maximization test ... on 25 volunteers at a concentration of 5% in petrolatum ... produced no sensitization reactions. /Butyrate/ [Peer reviewed] [Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 353]

Health Hazard Data

The following information was generated from the RTECS – Registry of Toxic Effects of Chemical Substances (last revision December 1997), a database of MICROMEDEX Systems (<http://csi.micromedex.com>) on February 24th 2009.

Acute toxicity

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

Rat

LD50 - ROUTE: Oral; DOSE: 13 gm/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

Rabbit

LD50 - ROUTE: Oral; DOSE: 5228 mg/kg [Industrial Medicine and Surgery. (Northbrook, IL) V.18-42, 1949-73. For publisher information, see IOHSA5. (41,31,1972)]

LD50 - ROUTE: Skin; DOSE: >2 gm/kg [Food and Cosmetics Toxicology. (London, UK) V.1-19, 1963-81. For publisher information, see FCTOD7. (12,719,1974)]

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. (12,719,1974)]

TOXICITY DATA ON BURNT MATERIAL

Data on the toxicity of ethyl butyrate as a cigarette ingredient has been evaluated in a series of studies. The results of these studies may be found in the following references:

Baker R.R. *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 E. *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 C.L. *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**

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

References

1. JECFA. *FAO Nutrition Meetings Report Series N° 44a: Toxicological Evaluation of Some Flavouring Substances and Non-Nutritive Sweetening Agents*. **1967**.