

**Evaluation of  
alpha-Ionone  
for Use as a Cigarette Ingredient**

**October 2005**

## **INTRODUCTION**

Alpha-ionone (CAS # 127-41-3) 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 alpha-ionone 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***

Alpha-ionone, a cyclohexane with a ketone on its side-chain is thought to be metabolized to innocuous products. Quantitative data indicates that it is consumed predominantly in traditional foods<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 alpha-ionone as presenting no safety concerns at current levels of intake when used as a flavouring agent. The daily intake is estimated at 2 µg/kg bw/day in the USA and 5 µg/kg bw/day in Europe<sup>1</sup>

Alpha-ionone 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 4590 mg/kg bw was reported after oral administration of a mixture of  $\alpha$  and  $\beta$ -ionone to rats<sup>1</sup>.

A NOEL of >11 mg/kg bw per day was reported after a 90-day short-term study on rats fed  $\alpha$ -ionone orally. No adverse effects were observed at the highest dose in the study, therefore no exact NOEL could be determined<sup>1</sup>.

Chromosomal aberrations were induced in Chinese hamster ovary cells incubated with 25 nmol/L of  $\alpha$ -ionone with and without metabolic activation. An in vitro gene mutation study was negative using *Salmonella typhimurium* strains incubated with 0.01-50 mg/plate with and without

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<sup>1</sup> Safety evaluation of certain food additives, WHO Food Additives Series: 42, Fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA): Ionones and structurally related substances, Geneva 1999. <http://www.inchem.org/documents/jecfa/jecmono/v042je19.htm>

metabolic activation. The rec assay using *Bacillus subtilis* incubated with 19 mg/disc was also negative. The metabolic activation status was unknown.

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*

LD50/LC50 - LETHAL DOSE/CONC 50% KILL

#### **Mouse**

LD50 - ROUTE: Intraperitoneal; DOSE: 2277 mg/kg [FAO Nutrition Meetings Report Series. (Rome, Italy) No.?-57, 1948-77. Discontinued. (44A,46,1967)].

### **TOXICITY DATA ON BURNT MATERIAL**

Data on the toxicity of alpha-ionone 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. Vanscheuwijck 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\*\*

These studies indicate that the ingredients used in the production of cigarettes do not increase the overall toxicity of cigarette smoke.

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