

**Evaluation Summary of
Cinnamaldehyde
for Use as a Cigarette Ingredient**

October 2005

INTRODUCTION

Cinnamaldehyde (CAS # 104-55-2) is currently used at levels below **100 ppm** in selected cigarette brands manufactured and/or distributed by Philip Morris International. Cinnamaldehyde is used as a tobacco flavoring materials and may be applied directly to the tobacco during cigarette manufacturing. As such, cinnamaldehyde may be subject to pyrolysis-type reactions when smoked. Cinnamaldehyde may also be applied to the filter as a flavoring material where it would not be subjected to pyrolysis temperatures. This document summarises our internal studies and current published toxicology information on cinnamaldehyde abstracted from online toxicity databases.

TOXICITY DATA ON UN-BURNED MATERIAL

Overview

Cinnamaldehyde is extensively used in the food industry as a flavor ingredient and has been generally recognized as safe (GRAS) for use in food by the Food and Drug Administration (21 CFR § 182.60) and the Flavor and Extract Manufacturers Association (FEMA No. 2286).¹ The Council of Europe (CoE No. 102) also approved it for food uses.² Cinnamaldehyde is rapidly absorbed from the gut, metabolized to polar metabolites and excreted primarily in the urine and to a lesser extent, in the feces. Animal and human studies show a majority of the cinnamaldehyde (>90%) is excreted from the body within 24 hours.³⁻¹¹ Cinnamaldehyde has a low acute oral and dermal toxicity in laboratory animals.¹²⁻¹⁹ In a subchronic study, gavage administration of cinnamaldehyde to rats caused a slight hyperkeratosis of the squamous portion of stomach and slight hepatic cell swelling at 500 mg/kg/day, but no effects were noted at the 125 mg/kg/day. The no observed effect level (NOEL) for this study was considered to be 125 mg/kg per day.²⁰

Health hazard data

Based on the *in vitro* mutagenicity assays in bacteria, cinnamaldehyde lacks direct mutagenic or genotoxic potentials. However, in isolated mammalian cells, cinnamaldehyde produced chromosome aberrations and/or mutations, indicating genotoxic activity.²¹⁻²⁹ The reported *in vitro* genotoxic activity in mammalian cells did not translate into mutagenic, clastogenic, or genotoxic activity *in vivo*.^{23,24,30-40} Cinnamaldehyde was shown to have some anti-mutagenic potential.^{21,41-54} In one *in vivo* gavage study, increases in the frequency of micronucleated cells in rat and mouse hepatocytes and in rat fore stomach cells was noted at high doses of cinnamaldehyde.⁵⁵ As micronuclei formation was dose-dependent, it appears that induction of micronuclei is a threshold phenomenon, which occurs at extremely high levels of cinnamaldehyde intake. Furthermore, as compared to dietary or dermal exposure, the gavage doses are likely to produce much greater exposures to both the fore stomach and liver. The micronuclei induction in this study cannot be considered relevant to the safety of cinnamaldehyde at normal exposure levels because of the apparent threshold and the lack of activity in other *in vivo* studies.⁵⁶

In a primary lung-tumor assay and in a hepatocarcinogenesis study, cinnamaldehyde was not carcinogenic.^{45,57-65} Cinnamaldehyde did not show any reproductive or developmental effects in the absence of high dose maternal toxicity.⁶⁶

Dermal application of cinnamaldehyde has been reported to cause irritation and sensitization in animals and humans.⁶⁷⁻⁷⁶ A certain degree of cross-reactivity between cinnamyl alcohol and cinnamic acid in guinea pigs sensitized to cinnamaldehyde was noted. Interestingly, with regard to the sensitizing potentials of cinnamaldehyde, considerable difference between the results from testing with 1% and 2%

cinnamaldehyde has been reported. It is interesting to note that in the same group of patients, 18.7% reacted to 2% cinnamaldehyde and only 3.3% to 1% cinnamaldehyde.⁷⁷

TOXICITY DATA ON BURNT MATERIAL

Combustion studies

As suggested by purge and trap analysis conducted by PM USA, a small portion of cinnamaldehyde would be expected to distill at 100°C.⁷⁸ However, pyrolysis studies conducted by PM USA offered evidence that cinnamaldehyde would volatilize at higher temperatures, with the production of minor pyrolysis products such as styrene. The formation of small amounts of these materials is expected, since pyrolysis of organic materials may lead to formation of these compounds.⁷⁹

Philip Morris ingredient testing program

Cinnamaldehyde was part of a PM USA testing program that was designed to evaluate the potential effects of 333 ingredients added to typical commercial blended test cigarettes on selected biological and chemical endpoints.⁸⁰⁻⁸³ Three pairs of test cigarettes were produced, each containing different groups of ingredients. Cinnamaldehyde was added to two pairs at target levels of 1, 10 or 31 ppm. No significant effects were noted in cytotoxicity, mutagenic studies or in respiratory tract endpoints in 90-day rat inhalation studies. In addition, smoke chemistry studies from cigarettes containing a mixture of flavors including cinnamaldehyde did not significantly alter the smoke chemistry profile compared to control cigarettes. Based on the results of these studies, the authors concluded that these ingredients (including cinnamaldehyde) added to tobacco do not add significantly to the overall toxicity of cigarettes.

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.

Currently, information is only available for tests utilizing cinnamaldehyde in a mixture of ingredients applied to cigarette tobacco. Studies are ongoing to address the use of cinnamaldehyde as a single ingredient and at higher tobacco application levels. Published studies show there is no meaningful difference in the composition or toxicity of smoke from cigarettes with added ingredients (including cinnamaldehyde) compared to the smoke from cigarettes without added ingredients.⁸⁰⁻⁸⁵ It is our scientific judgement, based on the best available data, that cinnamaldehyde used in our cigarettes does not increase the overall toxicity of cigarette smoke.

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