



EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C2 - Management of scientific committees II; scientific co-operation and networks

Scientific Committee on Food

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23 April 2002

Opinion
of the Scientific Committee on Food
on eucalyptol

(expressed on 17 April 2002)

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Terms of reference

The Committee is asked to advise the Commission on substances used as flavouring substances or present in flavourings or present in other food ingredients with flavouring properties for which existing toxicological data indicate that restrictions of use or presence might be necessary to ensure safety for human health.

In particular the Committee is asked to advise the Commission on the implications for human health of eucalyptol in the diet.

Introduction

Previous evaluations

Eucalyptol was evaluated as component of natural sources of flavourings by the Committee of Experts on Flavouring Substances of the Council of Europe (CEFS), resulting in the allocation of a provisional TDI of 0.2 mg/kg bw. This TDI was derived from a minimum lethal dose of 60 mg/kg bw for children applying a safety factor of 300 (Council of Europe, 2000).

When evaluated as chemically defined flavouring substance, eucalyptol was classified in category B, the category of flavouring substances which can be used provisionally in foodstuffs, but for which further information was required before a firm opinion on their safety-in-use could be given. CEFS proposed upper levels of 0.1 mg/kg in beverages and 5 mg/kg in food with the exception of 15 mg/kg in candy and confectionery and 50 mg/kg in alcoholic beverages (Council of Europe, 1992).

Current regulatory status

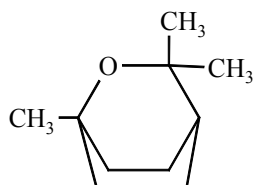
Eucalyptol has been regarded as GRAS (generally recognised as safe) by FEMA (1965) and is approved by the US Food and Drug Administration (FDA) for food use. The FDA advisory review panels on over-the-counter drugs have concluded that eucalyptol is safe for a variety of products, such as lozenges taken every 0.5 - 1 hr at 0.2 – 15 mg or taken every 2 hrs at 1 – 30 mg of eucalyptol (FDA, 1976 – 1990).

Eucalyptol is listed in the register of chemically defined flavouring substances of Commission Decision 1999/217/EC (EC, 1999), as last amended by Commission Decision 2002/113/EC (EC, 2002).

Chemical characterisation

Eucalyptol is a monocyclic terpene with an ether bridge between carbon 1 and 8.

Name:	Eucalyptol (1,8-cineole, 1,8-epoxy-p-menthane)
Synonyms:	1,8-oxido-p-menthane; 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane
FL No:	03.001
CAS No:	470-82-6
FEMA No:	2465
CoE No:	182
EINECS:	207-431-5
Structure:	



Exposure assessment

Eucalyptol is widely distributed in plants. The main food sources are eucalyptus oil (up to 80% eucalyptol), the herbs and spices mugwort, sweet basil, rosemary, sage and cardamom and their essential oils.

Highest exposure from food is likely to arise from hard (cough) candy in which up to about 130 mg eucalyptol/kg or about 2000 mg eucalyptus oil/kg have been reported to be used (Fenaroli, 1995). Consumption of 10 g of hard candy containing 2000 mg eucalyptus oil/kg would result in an intake of up to 16 mg of eucalyptol, equivalent to 0.27 mg/kg bw for an adult of 60 kg.

A mean daily intake of eucalyptol from flavoured foodstuffs in France has been estimated to be 4.5 mg/person, equivalent to 0.075 mg/kg bw (Council of Europe, 2001). This exercise was based on use levels of eucalyptol provided by industry and took into account the market share of all food categories possibly flavoured by plants, extracts of plants or eucalyptus oil. The food intake data were from the French survey on individual consumptions (AFSSA, 2000).

Oral therapeutic doses of eucalyptus oil for adults are 0.05 to 0.2 ml, equivalent to 46 to 184 mg eucalyptol (Pharmaceutical Codex, 1979), and 0.3 – 0.6 g eucalyptus oil/day (Bundesgesundheitsamt, 1990). Maximum concentrations of eucalyptol in cosmetic products have been reported to be 0.4% in soap, 0.04% in detergents, 0.1% in creams and lotions and 1.6% in perfume (Opdyke, 1975).

Hazard identification / characterisation

Absorption, distribution, metabolism and excretion

Eucalyptol undergoes oxidation *in vivo* with the formation of hydroxycineole which is excreted as glucuronide (Williams, 1959). In rats, 2-hydroxycineole, 3-hydroxycineole and 1,8-dihydroxycineol-9-oic acid were identified as main urinary metabolites (Madyastha and Chadha, 1986). After oral administration to brushtail possums (*Trichosurus vulpecula*), p-cresol, 9-hydroxycineole and cineol-9-oic acid were found in urine (Southwell *et al.*, 1980). Rabbits given eucalyptol by gavage excreted 2-exo- and 2-endo-hydroxycineole as well as 3-exo- and 3-endo-hydroxycineole in the urine (Miyazawa *et al.*, 1989).

Acute toxicity

The acute oral LD₅₀ in rats was reported to be 1560 mg/kg bw (Brownlee, 1940) and 2480 mg/kg bw (Jenner *et al.*, 1964).

In rats, a lethal dose caused rapid cyanosis and stupor accompanied by irregular breathing, extreme sensitivity to noise, convulsions, and death from respiratory failure (Brownlee, 1940). Single subcutaneous doses of 250 or 500 mg/kg bw increased the activity of drug-metabolizing enzymes and stimulated bile flow (Jori *et al.*, 1969 and 1972). An increase in liver enzyme activity was also found in mice given 500 mg/kg bw orally (Noble *et al.*, 1982).

Subacute toxicity

Groups of 6 male and 6 female Fischer 344 rats received eucalyptol for 28 days either by stomach tube on 5 days/wk at doses of 150, 300, 600 and 1200 mg/kg bw or in encapsulated form with the diet at concentrations of 3750, 7500, 15000 and 30000 mg/kg, equivalent to 381 – 3342 mg/kg bw/day for the male rats and to 353 – 3516 mg/kg bw/day for the female rats. At dose levels of 600 mg/kg bw and higher, dose-related decrease of body weight gain and absence of a normal degree of hepatic centrilobular cytoplasmic vacuolization was observed in male rats. In addition, other dose-related lesions in the liver, kidneys and parotid salivary glands were found at all dose levels in male rats fed encapsulated eucalyptol (Wolff *et al.*, 1987a).

Groups of 10 male Wistar rats were given 0, 500, or 1000 mg eucalyptol/kg bw/day by gavage for 28 days. Statistically significant decreases in the terminal body weight and

increased relative liver and kidney weights were found in both dose groups, whereas the relative brain weight was increased only in the highest dose group. No macroscopical changes were seen. Only brain, liver and kidneys were examined histopathologically, showing no changes in the brain and minor focal infiltration of mononuclear cells in the liver among all groups. In kidneys, a dose-related accumulation of eosinophilic protein droplets containing $\alpha_2\mu$ -globulin in the cytoplasm of proximal tubular epithelial cells was induced (Kristiansen and Madsen, 1995).

Groups of 6 male and 6 female B6C3F1 mice were fed eucalyptol for 28 days either by stomach tube on 5 days/wk at doses of 150, 300, 600 and 1200 mg/kg bw or in encapsulated form at concentrations of 3750, 7500, 15000 and 30000 mg/kg, equivalent to 600 – 5607 mg/kg bw/day for male and 705-6777 mg/kg bw/day for female mice. The liver weight/body weight ratio in males was increased at all but the lowest dose given in encapsulated form as was the brain weight/body weight ratio in females at the top dose level. Microscopic examination revealed a minimal hypertrophy of centrilobular hepatocytes in animals of both sexes fed the encapsulated compound, especially at the two highest dose levels (Wolff et al, 1987b).

Chronic toxicity/carcinogenicity

Eucalyptol was tested as constituent of toothpaste in an oral long-term study with specific pathogen-free CFLP mice. Groups of 52 male mice were given 0, 8 and 32 mg eucalyptol/kg bw/day in 1 ml toothpaste base/kg bw/day by gavage 6 days/week for 80 weeks followed by an observation period between 16 and 24 weeks according to the number of survivors. No treatment-related effects on body weight, food consumption, survival, weight of adrenals, kidneys, liver, lungs or spleen, on the microscopic appearance of brain, lungs, liver and kidneys and on the tumour incidence were observed (Roe *et al.*, 1979).

Genotoxicity

Eucalyptol did not show mutagenic effects in the following strains of *Salmonella typhimurium* with or without metabolic activation: TA 98, TA 100, TA 1535 and TA 1537 (Haworth *et al.*, 1983), and TA 97a, TA 98, TA 100 and TA 102 (Gomes-Carneiro *et al.*, 1998).

In CHO cells, eucalyptol did not induce chromosome aberrations with or without metabolic activation. Sister chromatid exchanges were induced in CHO cells only in the absence of metabolic activation at doses that induced cell cycle delay (Galloway *et al.*, 1987). Sister chromatid exchanges induced by mitomycin C in CHO K-1 cells were not increased by posttreatment with eucalyptol (Sasaki *et al.*, 1989).

The rec-assay in *Bacillus subtilis* did not give evidence for DNA damage (Oda *et al.*, 1978, Yoo, 1986).

Reproductive and developmental toxicity

There are no conventional studies on reproductive and developmental toxicity.

The effect of eucalyptol on the liver microsomal enzyme activity of foetal and newborn rats was studied in Sprague-Dawley rats. The dams were treated with eucalyptol (500 mg/kg bw/day subcutaneously for 4 days) (a) between day 10 and 14 of pregnancy, (b) during the last 4 days of pregnancy or (c) between the 2nd and the 6th day after delivery. These treatments greatly enhanced the liver microsomal enzyme activity of the mothers, induced the enzyme activity in the foetus livers, but did not induce the microsomal activity of the suckling newborn rats (Jori and Briatico, 1973).

Human data

Accidental intoxications have been reported following ingestion of eucalyptus oil. The lowest lethal doses reported are 4-5 ml (MacPherson, 1925) in adults and 1.9 g eucalyptus oil in a 10 year old boy (Neale, 1893). In other cases, however, ingestion of higher doses caused less severe effects or was even asymptomatic (Webb and Pitt, 1993).

Summary of hazard identification / characterisation

Subacute oral toxicity studies with eucalyptol revealed dose-related effects in liver, kidneys and salivary glands of male rats. In similar studies with mice, slight changes were only seen in the liver of males and females. These studies were limited with respect to the number of animals and duration.

A limited long-term study with mice did not show treatment related effects including effects on tumour incidence. The study was performed with males only and the histopathological examination was limited to only a few organs. No other carcinogenicity data are available.

No evidence for genotoxicity has been found in bacterial tests. In CHO cells, chromosomal aberrations were not induced; sister chromatid exchanges were only observed at cytotoxic doses.

It is difficult to draw general conclusions from reports on accidental intoxications with eucalyptus oil. In most cases, the amounts ingested could only be estimated roughly and the quality and precise composition of the ingested product was not reported. The contribution of eucalyptol and other constituents to the reported intoxications with eucalyptus oil remains open.

Risk characterisation

The available toxicological studies are limited and inadequate to derive an ADI. However, the available animal data do not indicate a cause of concern associated with the daily intake from food including hard candies estimated from the small amount of information available.

The case reports on acute toxicity in humans refer to the ingestion of eucalyptus oil and not to eucalyptol as such. They do not provide information for adequate estimates of toxic dose levels for eucalyptol. Even if eucalyptol were responsible for the acute toxicity of eucalyptus oil, the estimated daily intake of eucalyptol from food including hard candies would be much lower than the amount tentatively assumed to be present in the lowest lethal doses of eucalyptus oil reported.

For a more precise risk characterisation, further data on exposure and toxicity would be needed.

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