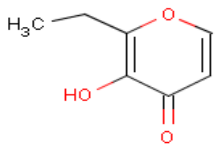
ETHYL MALTOL

SYNONYMS

2-Ethyl-3-hydroxy-4-pyrone
2-Ethyl-3-hydroxy-4h-pyran-4-one
2-Ethylpyromeconic acid
3-Hydroxy-2-ethyl-4-pyrone
Veltol Plus

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_7H_8O_3$

IDENTIFIER DETAILS

CAS Number	:	4940-11-8
CoE Number	:	692
FEMA	:	3487
EINECS Number	:	225-582-5
E Number	:	-

CLP CLASSIFICATION

Ingredient CLP Classification: No

Endpoint	Classification	Category
Acute Oral Toxicity	-	-
Acute Dermal Toxicity	-	-
Acute Inhalation Toxicity	-	-
Skin Corrosive/irritant	-	-
Eye Damage/Irritation	-	-
Respiratory Sensitisation	-	-
Skin Sensitisation	-	-
Mutagenicity/Genotoxicity	-	-
Carcinogenicity	-	-
Reproductive Toxicity	-	-
Specific Target Organ Toxicity	-	-
Aspiration Toxicity	-	-

SPECIFICATIONS

Melting Point: 88 - 92.00 °C (760.00 mmHg)

Boiling point: 289 - 290 °C. (760.00 mm Hg)

PURPOSE

Flavouring substance.

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
-	-	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
0-2	JECFA	1974	Maintained in 2005.

FDA Status:[CFR21]

Section Number	Comments
172.515, 182.10 182.20	Synthetic flavouring substances and adjuvants

HUMAN EXPOSURE

Natural Occurrence: Ethyl maltol is not reported to be found in nature [Fenaroli, 1995].

Reported Uses: Ethyl maltol is reportedly used in non-alcoholic beverages at 12.4 ppm, frozen desserts at 144 ppm, confectionery at 139 ppm, baked goods at 100 ppm, gelatin pudding 220 ppm, and jam at 100 ppm, chewing gum at 20 ppm, meat, meat sauces and soups at 1 ppm, hard candy at 27.9 ppm, and alcoholic beverages at 18.6 ppm [Fenaroli, 2005].

Ethyl maltol has been in use since the 1950's. It has been used in soap at 0.06%, detergent at 0.006%, creams/lotions at 0.01%, and perfume at 0.4% [BIBRA, 1996].

TOXICITY DATA

The Scientific Committee for Food re-examined the existing data for ethyl maltol in 1991 and subsequently reduced the ADI from 2 to 1 mg [BIBRA, 1996]. The per capita intake was estimated to be 0.08333 mg/kg [Fenaroli, 2005].

Carmines (2002), Rustemeier *et al.,* (2002), Roemer *et al.,* (2002) and Vanscheeuwijck *et al.,* (2002) reported on a testing program designed to evaluate the potential effects of 333 ingredients added to typical commercial blended test cigarettes on selected biological and chemical endpoints. The

studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], determination of smoke chemical constituents and a 90-day rat inhalation study. Based on the findings of these studies, the authors concluded that the 288 addition of the combined ingredients, including ethyl maltol at levels up to 288 ppm, "did not increase the overall toxicity of cigarette smoke" [Carmines, 2002].

Baker *et al.,* [2004]; examined the effects of the addition of 482 tobacco ingredients upon the biological activity and chemistry of mainstream smoke. The ingredients, essentially different groups of flavourings and casings, were added in different combinations to reference cigarettes. The addition of ethyl maltol at 117 ppm was determined not to have affected the mutagenicity of the total particulate matter (TPM) of the smoke in either the Ames, *in vitro* micronucleus assay or the neutral red assay when compared with that of the control cigarettes [Baker *et al.,* 2004].

Renne *et al.,* (2006) evaluated the effects of tobacco flavouring and casing ingredients on both mutagenicity, and a number of physiological parameters in Sprague-Dawley (SD) rats. Test cigarettes containing a mixture of either 165 low-uses or eight high-use flavouring ingredients which included ethyl maltol at 9.1 ppm, were compared to a typical commercial tobacco blend without flavouring ingredients. The Ames assay (TA 98, 100,102, 1535 and 1537 ±S9) did not show any increase in Mutagenicity from "low" or "high" cigarette smoke condensate compared to the control. SD rats were exposed by nose-only inhalation for 1h/day, 5 days/wk for 13 weeks to smoke at concentrations of 0.06, 0.2 or 0.8mg/L from the test or reference cigarettes, or to air only. Plasma nicotine, COHb and respiratory parameters were measured periodically. Rats were necropsied after 13wk of exposure or following 13 wk of recovery from smoke exposure. Biological endpoints assessed included; clinical appearance, body weight, organ weights, and lesions (both gross and microscopic). The results of these studies did not indicate any consistent differences in toxicological effects between smoke from cigarettes containing the flavouring or casing ingredients and reference cigarettes [Renne *et al.,* 2006].

In Vivo Toxicity Status

Species	Endpoint	Route	Dose (mg/kg bw)
Rat	LD_{50}	Oral	1150-1220
Mouse	LD_{50}	Oral	780
Mouse	LD_{50}	S.C.	910-1200
Chicken	LD_{50}	Oral	1270

The above table is constructed from data provided by BIBRA (1996).

A 90-day oral study was carried out involving groups of 10 male and 10 female rats. The animals were dosed with 0, 250, 500, or 1000 mg ethyl maltol/kg bw/day in the diet. Survival, growth and organ weights were not significantly affected. The high dose group suffered kidney damage, as found by microscopic examination. The low dose group demonstrated slight changes in blood composition [mild anaemia]. In a similar 2 year study,

groups of 15 male and 15 female rats received 0, 50, 100 or 200 mg ethyl maltol/kg bw/day in the diet. A comprehensive examination of the tissues revealed no clear increase in the incidence of gross or microscopic abnormalities, although the incidence of pyelonephritis may have been elevated at doses of 100 mg/kg bw/day and above. Again, there was no effect on survival, growth, urinalysis or blood composition [BIBRA, 1996].

Similarly, there were no treatment related gross or microscopic effects, and growth, organ weights and urinalysis were normal, when groups of 8 dogs were administered ethyl maltol capsules equating to 0, 50, 100 or 200 mg/kg bw/day. The animals were dosed for 5 days per week, for up to 2 years. Apart from a slight elevation in the level of enzymes in the blood of 4 dogs (indicative of liver damage), the blood composition was considered normal. In a 90-day oral study, 4 dogs received 0, 125, 250 or 500 mg ethyl maltol/kg bw/day via capsules. Again, growth, organ weights and urinalysis was normal. All those receiving the high dose, and 2 animals receiving the low dose had elevated bile pigment levels in the blood [indicative of liver damage]. Microscopic examination of a comprehensive range of tissues revealed mild cellular changes in the liver of animals in the mid- and low- dose groups. There was no evidence of carcinogenicity [BIBRA, 1996].

(BIBRA highlight that the 2 year feeding studies described have a limited ability to detect carcinogenicity due to the small number of animals used, and although 2 years is sufficient for the rat study, a longer duration of 7 years is required for dog studies) [BIBRA, 1996].

Dermal Toxicity

Ethyl Maltol [10% in petrolatum] was non-irritant to 25 volunteers following covered skin contact for 48 hours. No local reactions indicative of sensitisation were found following a maximisation test involving 25 volunteers exposed to five consecutive 48-hr patch tests, followed by a 48 hr challenge test 10-14 days later [10% concentration] [BIBRA, 1996].

When administered neat to intact or abraded rabbit skin, ethyl maltol was found not to be irritant [BIBRA, 1996].

Ethyl maltol applied at 5 g/kg bw to the skin of a rabbit was not found to be fatal [length of exposure not given but BIBRA suggest 24 hours covered contact] [BIBRA, 1996].

A recent mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including ethyl maltol at 4 ppm. The authors concluded that the study “did not indicate any substantive effect of these ingredients on the tumorigenicity of cigarette smoke condensate” [Gaworski *et al.,* 1999].
[It should be noted that the cigarettes contained a typical American blend humectant and sugar component (*i.e.* glycerine ≈ 20,000 ppm, propylene glycol at ≈ 24,000 ppm, and brown invert sugar at ≈ 24,000 ppm), Gaworski *et al.,* 1999].

Inhalation Toxicity

When tested at 4 ppm in cigarettes, in a 13-week inhalation study, the presence of ethyl maltol "…had no discernible effect on the character of extent of the biologic responses normally associated with inhalation of mainstream cigarette smoke in rats."[Gaworski *et al.,* 1998]. [However, it should be noted that the cigarettes had been spiked with a number of flavour ingredients in combination prior to smoking, and they contained a typical American blend humectant and sugar component (*i.e.* glycerine ≈ 20,000 ppm, propylene glycol at ≈ 24,000 ppm, and brown invert sugar at ≈ 24,000 ppm].

A recent study investigated the effect of cigarettes, containing various additives in three combinations, in a 90-day nose-only smoke inhalation study in rats. These ingredients included ethyl maltol at 288 ppm, a level described as a multiple of its typical use in a US cigarette. The data from this study along with that from a number of other biological and chemical studies indicate that the addition of the combined ingredients "did not increase the inhalation toxicity of the smoke, even at the exaggerated levels used" [Vanscheeuwijck *et al.,* 2002].

The addition of ethyl maltol at 117 ppm to reference cigarettes, used in a 90 day-sub-chronic inhalation exposure in rats, led to a series of pathological changes to smoke exposure that were indistinguishable from those changes caused by the control cigarettes. This indicated that addition of ethyl maltol to a reference cigarette had no discernable effect upon the type or severity of the treatment related pathological changes associated with tobacco smoke exposure [Baker *et al.,* 2004]

Mice exposed to ethyl maltol vapour for one hour [concentration not stated] developed a slightly increased physical activity [one group only] [BIBRA, 1996].

Roemer (2014) and Schramke (2014) reported on a testing program designed to evaluate the potential effects of 350 ingredients added to an experimental kretek cigarette on selected biological and chemical endpoints. The studies performed included a bacterial mutagenicity screen [Ames assay] a mammalian cell cytotoxicity assay [neutral red uptake], Mouse Lymphoma assay, determination of smoke chemical constituents, a 4-day in vivo micronucleus assay and a 90-day rat inhalation study. Based on the results of these studies, the authors concluded that the addition of ingredients commonly used in the manufacture of kretek cigarettes, including ethyl maltol at levels up to 291 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other Relevant Studies

Behavioural data

No data identified

In Vitro Toxicity Status

Carcinogenicity and Mutagenicity

Roemer *et al.,* (2002), reported on a study in which cigarettes containing various additives in three different combinations were produced. Smoke condensates prepared from these cigarettes were then tested in two different *in vitro* assays. The mutagenicity of the smoke condensate was assayed in the *Salmonella* plate incorporation [Ames] assay with tester strains TA98, 100, 102, 1535 and 1537 (+/- S9 metabolic activation). The cytotoxicity of the gas/vapour phase and the particulate phase was determined in the neutral red uptake assay with mouse embryo BALB/c 3T3 cells. The authors concluded that the *in vitro* mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients which included ethyl maltol at levels up to 288 ppm [a multiple of its typical use in a US cigarette] [Roemer *et al.,* 2002].

The mutagenicity of the smoke condensate was assayed in the *Salmonella* plate incorporation [Ames] assay with the tester strain TA98 in the presence of an S9 metabolic activation system. The cytotoxicity of the cigarette condensate was determined in the neutral red uptake assay and the (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium, inner salt assay (MTS assay) with the human hepatocellular liver carcinoma cell line, HEP-G2. It was concluded that the *in vitro* mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients, which included ethyl maltol at levels up to 17 ppm.

A total of 95 ingredients were tested individually through addition at different concentrations to the tobacco of experimental cigarettes. Mainstream cigarette smoke chemistry analysis, bacterial mutagenicity testing, and cytotoxicity testing were conducted. The authors concluded that these ingredients, which included ethyl maltol applied at levels up to 10,000 ppm on cigarettes produced minimal changes in the overall toxicity profile of mainstream cigarette smoke, and in some cases, the addition of high levels of an ingredient caused a small reduction in toxicity findings, probably due to displacement of burning tobacco [Gaworski *et al*., 2011].

Additional information concerning the *in vitro* mutagenicity of this material may be found in “An Interim report on data originating from Imperial Tobacco Limited’s Genotoxicity testing programme September 2003” or “An updated report on data originating from Imperial Tobacco Limited’s external Genotoxicity testing Programme – Round 2, August 2007”.

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assay, determination of smoke chemical constituents, a 4-day in vivo micronucleus assay and a 90-day rat inhalation study. Based on the results of these studies, the authors concluded that the addition of ingredients commonly used in the manufacture of kretek cigarettes, including ethyl maltol at levels up to 291 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other Relevant Studies

Following oral administration, ethyl maltol is rapidly absorbed and eliminated through conjugation reactions, and excretion via the urine [Opdyke, 1975].

Mice receiving 150+ mg ethyl maltol/kg bw suffered central nervous system depression, demonstrated by reduced spontaneous activity, anti-convulsant action, and loss of righting reflex. Additionally, an increased hexabarbital sleeping time was noted, which the authors state is suggestive of an effect on liver enzymes [length of exposure to ethyl maltol, or number of animals used is not given] [BIBRA, 1996].

Intraperitoneal injections of up to 980 mg ethyl maltol/kg/bw to groups of four mice was not lethal within 30 hrs and chromosomal damage was not induced in the bone marrow of the test animals [Wild *et al.,* 1983; BIBRA, 1996].

BIBRA (1996) summarised that ethyl maltol has been found to be "weakly mutagenic" in the Ames test [at concentrations up to 3.6 mg/plate] with *S. typhimurium* [including strains TA1535, 100, 1537,1538 and TA98] with and without a liver metabolic activation system [Wild *et al.,* 1983; BIBRA, 1996].

Ethyl maltol did not produce lethal heritable mutations when fed to *Drosphila melanogaster* [dose not given] [BIBRA, 1996].

PYROLYSIS AND TRANSFER STUDIES

Information relating to the pyrolysis and/or transfer of ethyl maltol is detailed in the Report on Thermochemical Properties of Ingredients document. In the aforementioned document, the term 'pyrolysis' means the heating of an ingredient in isolation under controlled conditions in an analytical device to examine its degradation potential. The expression 'transfer data' on the other hand is used to describe the fate of an ingredient in qualitative and quantitative terms following the smoking of a tobacco product to which it has been applied.

A 2004 study by Baker and Bishop analysed the pyrolytic breakdown of 291 tobacco ingredients using combustion conditions that simulate cigarette combustion. Due to the combustion conditions the results likely predict the natural behaviour of these compounds during combustion on the cigarette, and allow estimation of the degree of intact transfer into the mainstream smoke. Under pyrolysis ethyl maltol was found to transfer 92.8% intact, other

breakdown product included ethylmaltol isomer (6.2%) and 2 unidentified compounds (4.1%).

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