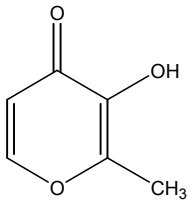
MALTOL

SYNONYMS

3-Hydroxy-2-methyl-4-pyrone
3-Hydroxy-2-methyl-4H-pyran-4-one
Palatone
Veltol
Larixinic acid
2-Methyl pyromeconic acid
Methyl-3-hydroxypyrone

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_6H_6O_3$

IDENTIFIER DETAILS

CAS Number	:	118-71-8
CoE Number	:	148
FEMA	:	2656
EINECS Number	:	204-271-8
E Number	:	E636

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: 160 - 164°C

Boiling point: -

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 – 1mg/kg	JECFA	2005	Established in 1981

DA Status: [CFR21]

Section Number	Comments
172.515	Synthetic flavouring substances and adjuvants permitted for the general addition to food for human consumption.

HUMAN EXPOSURE

Natural Occurrence: Maltol is reportedly found in the bark of young larch trees [*Pinus larix*], pine needles [*Abies alba*], chicory, wood tars and oils, and

roasted malt. Also found in wheat, rye bread, milk, butter, cocoa, coffee, licorice, beans and tamarind [Fenaroli, 2005].

Reported Uses: Maltol is reportedly used in baked goods at 319.9ppm, fats and oils at 18.0ppm, frozen dairy at 286.7ppm, meat products at 0.10ppm, soft candy at 267.2ppm, sweet sauce at 0.40ppm, gelatins and pudding at 243.9 ppm, non-alcoholic beverages at 181.6ppm, alcoholic beverages at 71.25ppm, hard candy at 8.02ppm, and chewing gum at 191.9ppm [Fenaroli, 2005].

The major natural occurrence in food is reported to be 20-45 mg/kg in coffee [CoE, 1992]

TOXICITY DATA

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 addition of the combined ingredients, including maltol at levels up to 100 ppm, "did not increase the overall toxicity of cigarette smoke" [Carmines (2002), Rustemeier *et al*. (2002), Roemer *et al*. (2002) and Vanscheeuwijck *et al.* (2002)].

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 maltol at 13ppm, 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.

In Vivo Toxicity Status

Test Type	Species	Route	Reported Dosage

LD_{50}	rat	oral	1410 mg/kg
LD_{50}	mouse	oral	848 mg/kg
LD_{50}	mouse	i.p.	1400 mg/kg
LD_{50}	mouse	subcutaneous	820 mg/kg
LD_{50}	rabbit	oral	1620 mg/kg
LD_{50}	guinea pig	oral	1410 mg/kg
LD_{50}	chicken	oral	3720 mg/kg

(All LD_{50} values taken from Lewis, 2000 & JECFA, 2006).

When administered to rats by oral administration at 1000 mg/kg/day some kidney effects, reduced growth rates and some death occurred following administration for 90 days [BIBRA, 1990]. When groups of 15 male and 15 female rats consumed up to 500 mg/kg in the diet for 6 months, there was reported to be no adverse treatment related effects, or microscopic findings reported for any major organs examined [Dow, 1967]. In groups of 50 male and 50 female rats, two year dietary administration of 400 mg/kg/day was reported to be associated with reduced growth in males and biochemical changes were noted at both 200 and 400 mg/kg/day. There were no macroscopic or microscopic changes reported in any of the tissues examined [Pfizer, 1978a].

When groups of 50 male and 50 female mice were exposed to dietary concentrations of maltol between 100 and 400 mg/kg/day, reduced growth rates were noted for males treated at 400 mg/kg/day, with a non dosage related decrease in growth rates of female mice. There was reported an increase in the activity of both urea and alkaline phosphatase activity were seen at all doses above 100 mg/kg/day. A reduced kidney weight and degeneration of the testes was reported for males that received 400 mg/kg/day [Pfizer, 1978b].

In the dog, oral administration of maltol at 500 mg/kg/day by oral capsule for 90 days there was reported to be severe clinical signs including, weight loss, vomiting, a lack of co ordination and several deaths. Microscopic investigation revealed changes to the lungs heart, liver, kidneys and testes. There were no treatment related clinical signs reported in four dogs administered maltol at 250 mg/kg/day by oral capsule [Gralla *et al.,* 1969]. Groups of four male and female dogs received up to 300 mg/kg/day for up to three months. Reduced growth rates were reported for all treated female groups [100 mg/kg was the lowest dosage tested], however, there were no clinical signs or microscopic findings reported [Pfizer, 1980].

Carcinogenicity and mutagencitiy

There was no reported treatment related changes in the tumour incidence of groups of 50 male and 50 female rats administered maltol at up to 400 mg/kg/day for 2 years, from parents that had been treated with the same regime [Pfizer, 1978a].

There was reported to be no changes in the incidence of tumours in groups of 50 male and 50 female mice that had been administered maltol at concentrations up to 400 mg/kg/day, for 1.5 years. A microscopic examination of an extensive range of tissues failed to find any treatment related effects [Pfizer, 1978b].

Dermal toxicity

In 48 hour occluded patch tests in human volunteers with 10% maltol in petrolatum there was reported to be no irritation after 48 hours exposure [Kligman 1974].

There was reported to be no sensitisation of 25 human volunteers exposed to 10% maltol in petrolatum following five 48 hour patch tests during a ten day period [Kligman *et al.,* 1975].

Neat maltol was reported to be moderately irritating to the intact and abraded skin of the rabbit [Moreno, 1974].

Reproductive and developmental toxicity

There was reported to be no effect of reproduction noted in a three-generation study in groups of rats administered up to 400 mg/kg/day. There were no signs of foetal toxicity and none of the offspring demonstrated any treatment related effects [Pfizer, 1978a].

Inhalation toxicity

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 [Vanscheeuwijck *et al.*, 2002]. These ingredients included maltol at 100ppm, 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 maltol at 257ppm 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 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].

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 Maltol at levels up to 9 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other relevant studies

Aluminium injected intravenously with maltol with a 1:4 molar ratio at a dose of 0.25 mmol Al/kg was found to be transported to the liver and was associated with an increase in the plasma activities of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] in mice [Maitani *et al.,* 1996]. Maltol has also been shown to increase the neurotoxicity of aluminium, and has been demonstrated to strongly enhance the accumulation of aluminium in the serum, brain and bone in a dosage dependent manner [Van Ginkel *et al,* 1993].

Maltol has been shown to chelate iron with a high degree of both selectivity and affinity. The resulting neutral metal ligands are then able to pass readily through cell membranes. The authors suggested that this might facilitate the transfer of iron across the intestinal wall [Barrand *et al.,* 1987].

Maltol has been shown to induce nerofilamentous tangles in cultured neurones from rat brain hemispheres, more tangles being induced by the maltol aluminium mixture [Langui *et al.,* 1990]. Maltol is also known to enhance aluminium induced nerofibrally degeneration in neuronal systems. Maltol was found to induce a dosage related toxicity to the viability of two neuroblastoma cell lines, and was also found to be toxic to murine fetal hippocampul neurones in a dosage dependent manner at micromolar concentration levels. On examination of the DNA via electrphoresis from maltol damaged cells, the authors reported that the DNA had a laddering effect which was suggestive of apoptotic death [Hironishi *et al.,* 1996].

Maltol has also been reported to inhibit the rate of oxidation of DL Dopa, dopamine, n-acetyl dopamine and epinephrine by tyrosinase, however only when it was assayed spectrophotometrically and not when assayed polographically. The authors suggest that maltol quickens the disappearance of quinones possibly by conjugating with them. [Kahn *et al.,* 1997]

The administration of maltol at 100 mg/kg to male ICR mice for 5 consecutive days was demonstrated to markedly reduce the symptoms of kainic acid treatment (50 mg/kg s.c.), when mice were challenged half an hour after the last administration of maltol. Treatment of kainic acid to control animals lead to severe seizures that caused approximately 50% mortality and damaged the pyramidal cells of the hippocampus in those that survived. Exposure to kainic acid also caused the formation of thiobarbituric acid reactive substances [TBARS] and lead to the depletion of total glutathione and glutathione peroxidase activity in brain tissues, pretreatment with maltol prevented the effects of kainic acid. Pretreatment with 50 mg/kg of maltol for 5 days prior to

kainic acid exposure, failed to show any remarkable protection [Kim *et al.,* 2004].

Maltol has been reported to have a cytotoxic action to the oral human normal and tumor cells, with activity against both human promyelocytic leukaemia HL60 and human oral squamous cell carcinoma HS2 cell line. Maltol did not activate caspase 3,8,9 in HL60 cells, but activated caspase 3 slightly in the presence of Fe3+ [Yasumoto *et al.,* 2004].

Maltol has been shown to be a principal antioxidant component of ginseng. Sun ginseng (SG) (steamed up to 120°C) resulted in a temperature dependent increase in maltol content. Maltol was also individually assessed for its radical scavenging activity and exhibited both peroxynitrite and strong hydroxyl radical scavenging activity [Kang *et al.,* 2006].

Behavioural data

No data identified.

***In Vitro* Toxicity Status**

Carcinogenicity and mutagenicity

Maltol was shown to be negative in the Ames test with strains with TA97, TA102 with or with out metabolic activation at 0.1-10mg/plate [Fujita *et al.,* 1992] and negative in strains TA104, TA92, TA98, TA100 with out metabolic activation at 1.5-11 mg/plate, [Gava *et al.,* 1989].

Maltol was shown to be positive in the Ames test, with strains TA98, TA100 both with and without a liver metabolic activation system [BIBRA, 1990].

In male ddY-mice maltol, were given single intraperitoneal injections of 125, 250 or 500 mg/kg bw was demonstrated to be positive in the micronucleus test inducing an increased number of micronucleated polychromatic erythrocytes, however, the level of increase was reported to be not statistically significant [Hayashi *et al.,* 1988].

Maltol has been shown to induce sister chromatid exchanges in both the SCL +D and SC1+D assays [Jansson *et al.,* 1989].

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, TA100, TA102, TA1535 and TA1537 in the presence and absence of an S9 metabolic activation system. 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 maltol at levels up to 100 ppm [a multiple of its typical use in a US cigarette] [Roemer *et al.,* 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 maltol at 257 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].

Irradiated maltol (with either UVA or UVC for 3 minutes in sodium phosphate buffer (pH 7.4)) caused mutagenicity in *S.typhimurium* strains TA100, TA104 and TA97. Mutational spectrum analysis revealed induction of predominant base substitutions 1) G:C → T:A transversions and 2) G:C → A:T transitions. The mutagenic photoproduct remained stable for 60 minutes after UVA-irradiation. However, mutagenicity was diminished with the addition of thiol products such as cysteine or glutathione. In contrast photomutagenicity was not observed when maltol was irradiated with UVA in 100mM sodium chloride solution or water [Watanbe-Akanuma *et al.,* 2007]

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 added ingredients, which included Maltol at levels up to 10,000ppm 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].

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 Maltol at levels up to 9 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other relevant studies

The effect of maltol on hydrogen peroxide (H_2O_2) induced apoptosis was assessed in Human Neuroblastoma Cells (SHSY5Y) using flow cytometry analysis of mitochondrial function and phosphatidylserine (PS) inverting percentage to determine apoptosis. In addition the MTT assay was used to

determine cell viability, DNA electrophoresis to detect DNA fragmentation, fluorescence emission to assess the level of intracellular calcium concentration and western blot analysis to assess NF-kappaB. Results demonstrated that pre-treatment with maltol for 2 hours prevented H_2O_2 induced apoptosis in the human SHSY5Y neuroblastoma cells by reducing the inverting percentage of PS, DNA fragmentation and intracellular calcium, enhancing the cellular function of the mitrochondria [Yang *et al.,* 2006].

An *in vitro* nitric oxide (*NO) generating system was used to assess the *NO-scavenging effects of compounds present in heat processed phenolic compounds. Increased maltol levels resulted in an inhibition of *NO production in a concentration dependant manner and enhanced *NO-scavenging activity *in vitro* [Kang *et al.,* 2006].

Apoptosis of HL60 cells by maltol in the presence of iron (FeSO(4)) was assessed using flow cytometry and DNA fragmentation analysis. Maltol in the presence of FeSO(4) resulted in the production of reactive oxygen species via redox cycling and consequently apoptotic cell death. No effects were observed in HL60 cells individually treated with either iron or maltol [Murakami *et al.,* 2006].

The treatment of Hepa 1c1c7 cells (a mouse, liver, heptoma cell line) with maltol significantly induced the Cyp1a1 enzyme (involved in the chemical activation of xenobiotics to carcinogenic derivatives) at both the mRNA and protein level in a concentration dependent manner. Induction was inhibited using an RNA synthesis inhibitor actinomycin D, indicating that de novo RNA synthesis through transcriptional activation is probably required. Maltol also induced aryl hydrocarbon receptor (AhR)-dependent luciferase reported gene expression suggesting that maltol may directly induce Cyp1a1 gene expression in a AhR-dependent manner [Anwar-Mohamed & El-Kadi, 2007].

Kang *et al.,* (2008) examined inhibitors of advanced glycation end products (AGEs), having the potential as preventive agents against diabetic complications. The in-vitro AGE inhibitory effects and free radical scavenging activity of maltol were investigated. In addition, the in-vivo therapeutic potential of maltol against diabetic renal damage was tested using streptozotocin (STZ)-diabetic rats. Maltol showed a stronger AGE inhibitory effect than aminoguanidine, stated to be a well known AGE inhibitor. In addition, the hydroxyl radical scavenging activity of maltol on electron spin resonance (ESR) spectrometry was slightly stronger than that of aminoguanidine. Maltol was found to have stronger in-vitro AGE inhibiting activity whem compared to aminoguanidine. The administration of 50 mg/kg/day of maltol suppressed the elevated serum levels of glycosylated protein, renal fluorescent AGEs, carboxymethyllysine, receptors for AGEs, and nuclear factor-kappaB p65 in diabetic control rats. The beneficial effects of maltol against STZ-diabetic renal damage were thought by the authors to result from its free radical scavenging and AGE inhibitory effects [Kang et al 2008].

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”.

PYROLYSIS AND TRANSFER STUDIES

Information relating to the pyrolysis and/or transfer of 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.

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