PARA-DIMETHOXYBENZENE

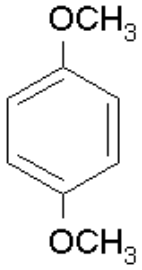
SYNONYMS

1,4-Dimethoxybenzene
Dimethyl hydroquinone
Hydroquinone, dimethyl ether
DMB
Benzene, p dimethoxy
Dimethyl ether hydroquinone
p-Methoxy anisole
Quinol dimethyl ether
USAF AN-9
1,4-Dimethoxybenzol
Anisole, p-methoxy-
Benzene, 1,4-dimethoxy-
Dimethylhydroquinone ether
Methyl p-methoxyphenyl ether
Quinol dimethyl ether
p-Dimethoxybenzene
p-Methoxyanisole

CHEMICAL FORMULA

$C_8H_{10}O_2$

CHEMICAL STRUCTURE



IDENTIFIER DETAILS

CAS Number	:	150-78-7
CoE Number	:	2059
FEMA	:	2386
EINECS Number	:	205-771-9
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: 60°C

Boiling point: 213°C

PURPOSE

Flavouring substance.

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
-	5	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
Acceptable	JECFA	2003	No safety concern at current levels of intake when used as a flavouring agent

FDA Status:[CFR21]

Section Number	Comments
172.515	Synthetic flavoring substances and adjuvants

HUMAN EXPOSURE

Natural Occurrence: para-dimethoxybenzene is reportedly found in hyacinth [*Hyacinthus orientalis*] essential oil, in *Rhodophyllus icterius*, in papaya, mint

tea [green], peppermint oil, green tea, cooked shrimp and cherimoya [Fenaroli, 1995 and 2005; CoE 2000].

Reported Uses: para-dimethoxybenzene is reportedly used in baked good at 66.53 ppm; fats and oils at 0.10 ppm; frozen dairy at 48.77 ppm; soft candy at 48.25 ppm; confectionary icing at 15.00 pm; gelatin pudding at 53.68 ppm; non-alcoholic beverages at 14.12 ppm; hard candy at 0.33 ppm and chewing gum at 21.94 ppm [Fenaroli, 1995].

Sources other than foods: It is reported to be found in hyacinth (*Hyacinthus orientalis* Lin) essential oil and in *Rhodophyllus icterius* [Fenaroli, 1995]

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 para dimethoxybenzene at levels up to 1 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)].

In Vivo Toxicity Status

Test Type	Species	Route	Reported Dosage
LD_{50}	Rat	Oral	3600 mg/kg
LD_{50}	Rat	I.P	1100 mg/kg
Irritation (Mod)	Rabbit	Skin	500 mg/kg 24 hr
Irritation (Mod)	Rabbit	Skin	40% 24 hr
			[Lewis, 2000]
LD_{50}	Mouse	Oral	4000 mg/kg
LD_{50}	Mouse	I.P	100 mg/kg
			[RTECS 16/01/02]

Carcinogenicity and mutagenicity

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 dimethoxybenzene at 1.3 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.

Groups of Wistar rats fed 2% dimethylhydroquinone in the diet for 4 weeks induced no macroscopically visible lesions in the oesophagus or fore-stomach [Altman *et al.,* 1985].

Dermal toxicity

When rabbit skin was treated with 5 ml of suntan oil containing either 1 or 10% dimethylhydroquinone for 5 days/week for 30 days, there was reported to be no effect of treatment upon bodyweight gain or haematology, however, at necropsy there was reported to be gross pitting of the kidneys of some of rabbits from each dosage group. The skin was also reported to show marked irritation with sloughing and with atrophy of the epidermis [Hodge *et al.,* 1949].

In 24 humans a maximisation test was carried out with exposure to 4% dimethylhydroquinone in petroleum. It was reported to be non-sensitising; a similar finding was also reported for guinea pigs [Opdyke, 1978]. The same negative finding was also reported for guinea pigs by Sharp (1978), that they did not become sensitised to both subcutaneous and topical application of dimethyl hydroquinone.

Similarly, a recent mouse skin painting study investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including para-dimethoxybenzene at 1 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 1 ppm in cigarettes, in a 13-week inhalation study, the presence of para-dimethoxybenzoate "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] [Gaworski *et al.,* 1998].

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 para-dimethoxybenzene at 1 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 para-dimethoxybenzene at 29 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 para-dimethoxybenzene 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]

Other relevant studies

Dimethyl hydroquinone was reported to reduce the sleeping time of hexobarbital induced rats and prevent apomorphine hypothermia of both mice and rats [Opdyke, 1978].

In rabbits the administration of 1,4 dimethoxy benzene gives rise to the formation of p-methoxyphenol [HSDB, 2002].

For rats fed a diet containing either 0, 0.5%, 2% and 10% dimethyl hydroquinone for 5 weeks, there was reported to be a slight retardation of growth of those rats fed at 2% in the diet and a complete lack of growth in those rats fed at 10% in the diet. The haematology was reported to be normal, and no histological changes reported related to treatment [Hodge *et al.,* 1949]. In rabbits fed either 1% dimethyl hydroquinone or 5% rising to 10% in the diet for 1-2 months, there was found to be no pathological changes related to treatment, all animals gained weight and had a normal haematology profile [Hodge *et al.,* 1949].

Behavioural data

No data identified

***In Vitro* Toxicity Status**

Carcinogenicity and mutagenicity

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”.

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 para dimethoxybenzene at levels up to 1 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 para-dimethoxybenzene at 29 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].

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/was not increased by the addition of the ingredients, which included para dimethoxybenzene at levels up to 583 ppm.

Para dimethoxy benzene has been demonstrated to be negative in the Ames *Salmonella* mutagenicity assay with the following strains TA98, TA100, TA1535, TA1537 at 10-666 μg/plate both with and without metabolic activation [Haworth *et al.,* 1983].

Rat liver microsomes are reportedly able to metabolise dimethyl hydroquinone *in vitro* by performing o-demethylation of the ring [Foster *et al.,* 1974].

PYROLYSIS AND TRANSFER STUDIES

Information relating to the pyrolysis and/or transfer of dimethoxybenzene, para 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 para dimethoxybenzene was found to transfer 99.8% intact, the other breakdown product included dimethoxytoluene (0.2%).

REACH Statement

This ingredient has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manufacture or import. This information includes data on hazardous properties (covering various toxicological endpoints), guidance on safe use and classification and labelling. The European Chemicals Agency (ECHA) makes this information publicly available on its website: http://echa.europa.eu/.

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