BENZOIN RESINOID

SYNONYMS

Benzoe resinoid
Benzoin tincture
Gum benjamin Sumatra
Gum benzoin
Sumatra benzoin
Siam benzoin
Styrax benzoin dryander
Styrax paralleloneurus
Styrax tonkinensis

CHEMICAL STRUCTURE

Ill defined (mixture of components).

CHEMICAL FORMULA

Varying composition consisting chiefly of resins, gums, essential and volatile oils, various esters of benzoic and cinnamic acids together with the free acids. It is chiefly composed of cinnamic and benzoic acids together with free acids. Sumatra benzoin contains 70 – 80 % coniferyl cinnamate, cinnamyl cinnamate, and coniferyl benzoate. Small amounts of benzoic acid, and trace amounts benzaldehyde, vanillin, and styrene are also present [Leung *et al*., 1996].

It is reported to be extracted by extracting normal benzoin with benzene and then distilling off the solvent [Opdyke 1973].

IDENTIFIER DETAILS

CAS Number	:	9000-05-9 (9000-72-0 Benzoin Resin Siam)
CoE Number	:	439
FEMA	:	2133
EINECS Number	:	232-523-7
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: undefined (mixture of components)

Boiling point: undefined (mixture of components)

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
Not allocated	JEFCA	1977	-

FDA Status: [CFR21]

Section Number	Comments
172.510	Natural flavouring substances and natural substances used in conjunction with flavours.

HUMAN EXPOSURE

Natural Occurrence: Benzoin resin or styrax resin is a balsamic resin obtained from the bark of several species of trees in the genus *Styrax*. It principally contains benzoic acid. Commonly called "benzoin", it is called "benzoin resin" here to distinguish it from the crystalline compound benzoin. Benzoin resin does *not* contain this crystalline compound [Fenaroli, 2005].

Reported Uses: Used as a flavouring ingredient in baked goods 14.5 ppm, frozen dairy 2.97 ppm, soft candy 5.99 ppm beverages 8.82 ppm and chewing gum 9.6 ppm [Fenaroli 2005].

Sources other than foods: Benzoin resinoid is widely used within the perfumery and cosmetics industry. It is also used as for preserving ointments. In addition, it has been used topically as an antiseptic and to promote healing; as an inhalant for bronchitis; orally as an expectorant. It is also used as an oral protective agent for respiratory inflammations [NLM, 2002].

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 benzoin resinoid at levels up to 460 ppm, “did not increase the overall toxicity of cigarette smoke” [Carmines, 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 benzoin resinoid at 26 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 1 h/day, 5 days/wk for 13 weeks to smoke at concentrations of 0.06, 0.2 or 0.8 mg/L from the test or reference cigarettes, or to air only. Plasma nicotine, COHb and respiratory parameters were measured periodically. Rats were necropsied after 13 wk 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

Species	Test Type	Route	Reported Dosage
Rat	LD_{50}	Oral	10 g/kg
Rabbit	LD_{50}	Dermal	8.87 g/kg

Carcinogenicity and Mutagenicity

Similarly, a recent mouse skin painting study [Gaworski *et al.*, 1999], investigated the carcinogenicity of condensate prepared from cigarettes containing a number of additives in combination, including benzoin resin at 2 ppm. The authors concluded that the study "did not indicate any substantive effect of these ingredients on the tumorigenicity of cigarette smoke condensate". 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].

Dermal Toxicity

10 % gum benzoin in ethanol is not thought to be irritating to the skin of most individuals [no further details given] [BIBRA, 1989].

Twenty-five volunteers were tested for sensitisation by applying five 48 hour closed patch tests, of 8 % gum benzoin in petrolatum, to the skin over a 10 day period. They were then challenged 10 - 14 days later with a final 48 hour closed patch test using the same 8 % solution. None of the individuals exhibited any signs of sensitisation. However, positive results have been achieved in separate studies using concentrations of 1 % or 10 % gum benzoin in ethanol or petrolatum, in individuals reacting to products containing gum benzoin. In two similar studies, 35 out of 1835 patients [probably suffering from contact dermatitis] developed sensitisation reactions to 10% gum benzoin in ethanol [closed patch test, for 24 or 48 hours] [TNO BIBRA, 1989].

Numerous studies have been reported on the sensitisation reactions to tincture of benzoin have been reported in the literature with eczema as one of the major dermatological manifestations [Opdyke 1973]. It has also been suggested that those individuals sensitive to gum benzoin may also react to balsam of Peru, storax, eugenol, vanillin, pinene, benzyl alcohol and benzyl cinnamate [TNO BIBRA, 1989].

When applied at 10 % in petrolatum to the skin of guinea-pigs for 24 hours, no irritation was seen, and in addition a solution of 0.25 % applied intradermally produced only slight irritation [TNO BIBRA, 1989].

A report of a skin rash on the face and trunk was reported for the inhalation of an unspecified quantity of gum benzoin form a vapouriser [Fox, 1874].

A rare occurrence of necrotising dermatitis was reported after a single

application of topical benzoin tincture and a pressure bandage to the eye of a patient following enucleation of the eye [Tripathi *et al.,* 1990]. Severe gastro-intestinal haemorrhage has been reported following the accidental oral ingestion of a non specified amount of tincture of benzoin [Arys *et al.,* 1987].

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. These ingredients included benzoin resinoid at 460 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 benzoin resinoid at 53 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 benzoin resinoid 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].

When tested at 2 ppm in cigarettes, in a 13-week inhalation study, the presence of benzoin resin "…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].

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 Benzoin resinoid at levels up to 96 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

Other relevant studies

A sensitisation study on a group of guinea pigs showed that when injected intradermally with 0.625 % gum benzoin at four sites, and challenged 14 days

later with either a further intradermal injection of 0.25 % gum benzoin, or dermal application with 10 % gum benzoin [solvent/carrier not stated], no reaction occurred. However, the experiment was then repeated [presumably with the same animals] and evidence of sensitisation was seen. No details are given concerning the incidence of sensitisation [BIBRA, 1989].

Benzoin resinoid has been reported to be used for decades to improve the stickiness of the skin for improved adherence of surgical bandages and dressings [Carrington, 2000].

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, 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 benzoin resinoid at levels up to 460 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 benzoin resinoid at 53 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 not increased by the addition of the ingredients, which included benzoin resinoid at levels up to 72 ppm [In

vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-44)].

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 benzoin resinoid 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".

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 Benzoin resinoid at levels up to 96 ppm, did not change the overall in vivo/vitro toxicity profile of the mainstream smoke.

PYROLYSIS AND TRANSFER STUDIES

No data identified

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