CARVONE

This datasheet holds information on l-carvone (041), d-carvone and the racemic carvone mixture (952).

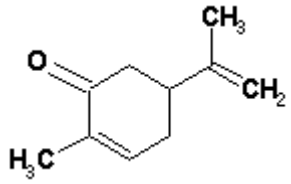
Following a Joint FAO/WHO Expert Committee on Food Additives (JECFA) meeting, the committee concluded in 1991 that (+)-carvone and (-)-carvone should be evaluated separately, as optical enantiomers should not be regarded as compounds which are toxicologically similar [JECFA, 1991].

L-CARVONE (041)

SYNONYMS

(-)-Carvone
(R)-2-Methyl-5-(1-methylethenyl)-2-cyclohexen-1-one
(R)-Carvone
AI3-36200
L(-)-Carvone
l-1-Methyl-4-isopropenyl-6-cyclohexen-2-one
l-6,8(9)-p-Menthadien-2-one
L-Carvone
L-Carvone (natural)
p-Mentha-6,8-dien-2-one, (-)-

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_{10}H_{14}O$

IDENTIFIER DETAILS

CAS Number	:	6485-40-1
CoE Number	:	146
FEMA	:	2249
EINECS Number	:	229-352-5
E Number	:	-

CLP CLASSIFICATION

Ingredient CLP Classification: Yes

Endpoint	Classification	Category
Acute Oral Toxicity	conclusive but not sufficient for classification	-
Acute Dermal Toxicity	conclusive but not sufficient for classification	-
Acute Inhalation Toxicity	data lacking	-
Skin Corrosive/irritant	conclusive but not sufficient for classification	-
Eye Damage/Irritation	conclusive but not sufficient for classification	-
Respiratory Sensitisation	data lacking	-
Skin Sensitisation	H317: May cause an allergic skin reaction	1B
Mutagenicity/Genotoxicity	conclusive but not sufficient for classification	-
Carcinogenicity	data lacking	-
Reproductive Toxicity	conclusive but not sufficient for classification	-
Specific Target Organ Toxicity	conclusive but not sufficient for classification	-
Aspiration Toxicity	data lacking	-

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/.

SPECIFICATIONS

Melting Point: -

Boiling point: 227 - 230 °C

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

ACCEPTABLE	JECFA	1998	No safety concern at current levels of intake when used as a flavouring agent

FDA Status: [CFR21]

Section Number	Comments
182.60 & 582.60	GRAS as a synthetic flavouring substance and adjuvant.

HUMAN EXPOSURE

Natural Occurrence: *L*-carvone can be isolated from spearmint oil. It is also commercially synthesised from *d*-limonene [Fenaroli, 2005]. The *levo* (L) form is present in *Metha vifidis* var. *crispa*, *Mentha longifolia* from South Africa, *Eucalyptus globules* and several mint species [Fenaroli, 2010].

Reported Uses: Present in baked goods at a concentration of 115.4 ppm, cheese 0.2 ppm, frozen dairy 197.4 ppm, meat products 0.1 ppm, relish 60 ppm, soft candy 225.6 ppm, gelatins and puddings 90 ppm, non-alcoholic beverages 41 ppm, alcoholic beverages 144.6 ppm, hard candy 369.4 ppm and chewing gum 349.5 ppm (isomer not specified) [Fenaroli, 2005].

Sources other than foods: Used in perfumes, cosmetics and toiletries.

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 Carvone, L at levels up to 31 ppm, “did not increase the overall toxicity of cigarette smoke” [Carmines, 2002].

In Vivo Toxicity status

Species	Test Type	Route	Reported Dosage
Rat	NOEL	Oral	125 mg/kg [Hagan *et al*., 1967]
Rat	LD_{50}	Oral	1640 mg/kg
Rat	LD_{50}	Oral	3710 mg/kg
Guinea Pig	LD_{50}	Oral	766 mg/kg
Mouse	NOEL	Gavage	328 mg/kg [JECFA, 1999]

Mouse	LD_{50}	Intravenous	56 mg/kg [RTECS, 1997]
Mouse	LD_{50}	Intraperitoneal	426.6 mg/kg (de Sousa *et al*., 2007)

Chronic and sub-chronic effects of carvone (unspecified stereochemistry, although it is predicted to be (-) isomer) were investigated by orally administering 50 mg/kg/bw per day for 27-28 weeks, 125 mg/kg/bw per day for 1 year or 750 mg/kg/bw per day for 16 weeks to 5 male and 5 female Osbourne-Mendel weanling rats. There were no changes in body weight, food intake or haematology apart from rats in the 750mg/kg/bw per day which displayed decreased body weight gain and testicular atrophy [Hagan *et al*., 1967].

Dermal Toxicity

Perioral contact dermatitis has been observed after toothpaste use containing *L*-carvone (used in toothpastes due to its association with spearmint/ peppermint oil) and may be the cause of some allergies to toothpaste [Worm *et al.,* 1998].

An opinion on fragrance allergens which included Carvone, L-, was published by the EC Scientific Committee on Consumer Safety (SCCA). Clinical, epidemiological and experimental studies were evaluated, as well as modelling studies performed, to establish lists of (i) established fragrance allergens, (ii) likely fragrance allergens and (iii) possible fragrance allergens [SCCS, 2012].

Inhalation Toxicity

The addition of *L*-carvone at 12 ppm to reference cigarettes, used in a 90 day-sub-chronic inhalation exposure study 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 *L*-carvone 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].

A recent study investigated the effect of various additives of cigarettes in three combinations, in a 90 day nose-only smoke inhalation study in rats. These ingredients included *L*-carvone at 31 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].

Other relevant studies

The antinociceptive effects of L-carvone were investigated in adult 3 month old male albino Swiss mice. Mice were administered 50, 100 or 200 mg/kg

-(-)carvone (along with 6 mg/kg morphine) by intraperitoneal injection, followed by intraperitoneal injection of 0.8 % acetic acid (10 ml/kg) 30 min later. Test mice injected with -(-)carvone, before the administration of acetic acid, exhibited a significant decrease in the number of writhes when 100 and 200 mg/kg was administered, compared to control mice not injected when -(-)carvone prior to administration of acetic acid. In a second experiment mice were initially administered 50, 100 and 200 mg/kg -(-)carvone (along with 100 mg/mg acetyl salicylic acid) After 30 min 20 µl of 2.5 % formalin was injected into the paw. Test mice receiving the initial injection of -(-)carvone exhibited reduced licking of the paw, when compared to control. Naloxone, an opioid agonist, had no influence on the antinociceptive action of -(-)carvone and performance on the rota-rod was not affected in -(-)carvone treated mice. It was also observed that 10 µM -(-)carvone was able to inhibit the excitability of an isolated sciatic nerve. It was concluded that (-)carvone has antinociceptive activity associated with decreased peripheral nerve excitability [Gonçalves *et al*., 2008].

(R)-(-)carvone, and its enantiomer (S)-(+)-carvone, have been reported to have a depressant effect on the central nervous system (CNS). Male Swiss mice were administered 50, 100 or 200 mg/kg (R)-(-) carvone by intraperitoneal injection. Mice exhibited decrease in response to touch and ambulation and an increase in sedation, palpebral ptosis (drooping of upper eyelid) and antinociceptive effects when observed over a period of two hours [de Sousa *et al*., 200].

The spasmolytic activity of (-)-carvone was investigated in the isolated ileum of guinea-pigs. The animals were sacrificed and a distal proportion of the ileum was removed and suspended in an organ bath containing Tyrode solution. (-)-Carvone was added to the ileum to determine the potency of its spasmolytic properties and it was reported that (-)-carvone produced ileum relaxation in guinea pigs and was more potent than its enantiomer (+)-carvone [de Sousa el al., 2008].

The major in vivo metabolites of R-(-)-carvone in a metabolism of ingestion in humans correlated amounts (MICA) experiment were newly identified as alpha,4-dimethyl-5-oxo-3-cyclohexene-1-acetic acid (dihydrocarvonic acid), alpha-methylene-4-methyl-5-oxo-3-cyclohexene-1-acetic acid (carvonic acid), and 5-(1,2-dihydroxy-1-methylethyl)-2-methyl-2-cyclohexen-1-one (uroterpenolone) on the basis of mass spectral analysis in combination with syntheses and NMR experiments. Minor metabolites were identified as reduction products of carvone, namely, the alcohols carveol and dihydrocarveol. The previously identified major in vivo metabolite in rabbits, 10-hydroxycarvone, could not be detected, indicating either concentration effects or interspecies differences. Metabolic pathways for carvone in humans including oxidation of the double bond in the side chain and, to a minor extent 1,2- and 1,4 + 1,2-reduction of carvone, are discussed [Engel, W. 2001].

Behavioural Data

The potential Anxiolytic activity of (R)-(-)-carvone was tested on male Wistar rats (weighing 250 g at the beginning of the experiments) submitted to the elevated T-maze (ETM). The ETM allows the measurement of two defensive responses: inhibitory avoidance and one-way escape. In terms of psychopathology, these responses have been related to generalized anxiety and panic disorder, respectively. Treatment with the (R)-(-)-Carvone impaired ETM avoidance latencies, without altering escape, in a way similar to the reference drug diazepam ($P < 0.05$) ($P < 0.05$; avoidance 1: control = 91.9 ± 31.5; carvone = 11.6 ± 1.8; diazepam = 8.1 ± 3.3). These results were not due to motor changes since no significant effects were detected in an open field. These observations suggest that (R)-(-)-carvone exerts anxiolytic-like effects on a specific subset of defensive behaviors that have been implicated in generalized anxiety disorder [Hatano *et al*, 2012].

In Vitro Toxicity Status

Carcinogenicity and Mutagenicity

(-)-Carvone (preincubation)	Gene mutation	*S. typhimurium* - 333 µg/plate - Negative (TA98, TA100, TA1535 & TA1537).
(-)-Carvone	Gene mutation	*S. typhimurium* - 333 µg/plate Negative (TA98, TA100, TA1535 &TA1537).
(-)-Carvone	Sister chromatid	Chinese hamster ovary cells - 502µg/ml Equivocal exchange
(-)-Carvone	Chromosomal	Chinese hamster ovary cells - 400 µg/ml Equivocal aberration

[JECFA, 1999].

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 including L-carvone at levels up to 31 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 ingredient essentially different groups of flavourings and casings were added in different combinations to reference cigarettes. The addition of L-carvone at 12 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 L-carvone at levels up to 11 ppm.

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”.

Other Relevant Studies

No data identified.

PYROLYSIS AND TRANSFER STUDIES

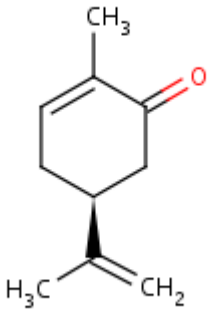
Information relating to the pyrolysis and/or transfer of L-carvone is detailed in the Report on Thermochemical Properties of Ingredients document. In the aforementioned document, the term ‘pyrolysis’ means the heating of an ingredient in isolation under controlled conditions in an analytical device to 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 Carvone, L was found to transfer 99.3% intact, other breakdown product included Dimethylcyclohexadiene (0.3%), Dimethylethylcyclohexadiene (0.2%) and Methoxypropenylbenzene (0.2%) [Baker and Baker, 2004].

D-CARVONE (952)

SYNONYMS

(S)-(+)-p-Mentha-6,8-dien-2-one
(S)-Carvone
(S)-d-p-Mentha-6,8,(9)-dien-2-one
Carvone, (+)-
CCRIS 2385
D(+)-Carvone
d-1-Methyl-4-isopropenyl-6-cyclohexen-2-one
d-Carvone
d-Carvone (natural)
d-p-Mentha-6,8,(9)-dien-2-one

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_{10}H_{14}O$

IDENTIFIER DETAILS

CAS Number	:	218-827-2
CoE Number	:	146
FEMA	:	2249
EINECS Number	:	229-352-5
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: -

Boiling point: 230°C

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 – 1 mg/kg bw	JECFA	1990	No safety concern at current levels of intake when used as a flavouring agent. The 1990 ADI of 0-1 mg/kg bw was maintained at the fifty-first meeting (1998).

FDA Status: [CFR21]

Section Number	Comments
182.60 & 582.60	GRAS as a synthetic flavouring substance and adjuvant.

HUMAN EXPOSURE

Natural Occurrence: Usually prepared by fractional distillation of caraway, dillseed and dillweed oils. The first one differs in odour and flavour from the latter.

Reported Uses: Present in baked goods at a concentration of 115.4 ppm, cheese 0.2 ppm, frozen dairy 197.4 ppm, meat products 0.1 ppm, relish 60 ppm, soft candy 225.6 ppm, gelatins and puddings 90 ppm, non-alcoholic beverages 41 ppm, alcoholic beverages 144.6 ppm, hard candy 369.4 ppm and chewing gum 349.5 ppm (isomer not specified) [Fenaroli, 2005].

Sources other than foods*:* Used as a precursor for l-carvone, as a carminative and in perfumes and soaps.

TOXICITY DATA

In Vivo Toxicity Status

Carcinogenicity / Mutagenicity

D-carvone in corn oil was administered by gavage in doses of 375 or 750 mg/kg to groups of 50 male and 50 female B6C3F_1 mice, for 5 days/week, for 103 weeks (2 years). At the end of the study, male mice survival was similar to that of the control group, while female mice survival was greater in the treated group than in the control group. No increase in tumour incidence was seen in the treated groups, and the number of male mice with primary neoplasms, as well as the total number of primary neoplasms was lower in dosed groups than in the control groups. The NTP concluded that, given the conditions of this study, no evidence of d-carvone related carcinogenicity was seen [NTP, 1990].

D-carvone was tested in an *in vivo* UDS assay in the liver of male rats, in accordance with the OECD guideline 468. The doses administered by oral gavage were 0 (corn oil), 500, 1000, 5000 mg/kg. No unscheduled DNA synthesis was observed [CLH REPORT FOR [CARVONE], 2012].

Dermal Toxicity

D-carvone caused a 24-h lasting erythema when applied at full strength to either intact or abraded rabbit skin for 24 hours. When tested in humans at a concentration of 4% in petrolatum, d-carvone was reported to be non-irritating under an occluded patch for 48 hours. A maximisation test was performed on 25 human volunteers using d-carvone at a concentration of 2% in petrolatum, and no sensitisation reactions were reported [Opdyke 1976].

Reproductive / Developmental Toxicity

A 2-generation study (in accordance with the OECD guideline 416) was performed using d-carvone, administered 10 days prior to mating via gavage

to rats (F0 generation) at doses of 0, 3, 10 and 30 mg/kg day. A group of animals in the F1 generation started being treated with 90 mg/kg carvone when they reached the age of 3-5 weeks. α2u-globulin accumulation was seen in male rats, but this was not considered to be toxicologically relevant to humans. A reduction in body weight and bodyweight gain was noticed in females of the F0 generation (treated with 30 mg/kg carvone), but this was not observed in the females of the F1 generation, so the findings were not considered to be relevant to humans. A 15% liver size increase was observed in F1 generation males treated with carvone at 90 mg/kg day, while only a 5% increase was seen in F1 generation males treated with 30 mg/kg day. Histopathology was not performed on the liver. The NOAEL for systemic toxicity was considered to be 30 mg/kg bw/day, and the NOAEL for reproductive effects (two generations of rats) was considered to be 90 mg/kg bw/day (based on the lack effects of carvone on reproductive parameters) [CLH REPORT FOR [CARVONE], 2012].

A teratogenicity study (in accordance with OECD guideline 414) was performed using d-carvone at 0, 20, 70 and 200 mg/kg bw/day (female rats, treated at days 6-20 of gestation). AChE activity was determined in the brains of both dams and foetuses, and in the plasma of dams, collected at day 21. Due to the absence of relevant toxicological effects, as well as the absence of a clear conclusion on the effects of carvone on brain/plasma AChE activity, the NOAEL was considered to be the highest carvone dose administered (200 mg/kg) [CLH REPORT FOR [CARVONE], 2012.

Inhalation Toxicity

No data available.

Other relevant studies

(R)-(-)carvone, and its enantiomer (S)-(+)-carvone, have been reported to have a depressant effect on the central nervous system (CNS). Male Swiss mice were administered 50, 100 or 200 mg/kg (R)-(-) carvone by intraperitoneal injection. Mice exhibited decrease in response to touch and ambulation and an increase in sedation, palpebral ptosis (drooping of upper eyelid) and antinociceptive effects when observed over a period of two hours [de Sousa *et al*., 200].

Behavioural data

No data available.

***In Vitro* Toxicity Status**

Carcinogenicity / Mutagenicity

(+)-Carvone	Gene mutation	*S. typhimurium* – up to 333 µg/plate - Negative - (preincubation) (TA98, TA100, TA1535 & TA1537).

(+)-Carvone	Gene mutation	*S. typhimurium* – up 333 µg/plate Negative (TA98, TA100, TA1535 &TA1537).
(+)-Carvone	Sister chromatid	Chinese hamster ovary cells, - Positive
(+)-Carvone	Chromosomal	Chinese hamster ovary cells – Positive

[NTP, 2013].

Other Relevant Studies

No data available.

PYROLYSIS AND TRANSFER STUDIES

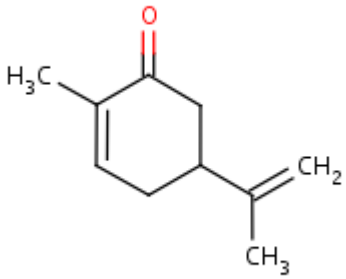
No data available.

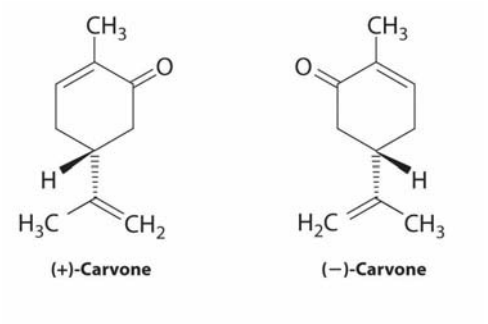
RACEMIC MIX

SYNONYMS

1-Carvone
2-Cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)-
2-Methyl-5-(1-methylethenyl)-2-cyclohexen-1-one
2-Methyl-5-isopropenyl-2-cyclohexenone
6,8(9)-p-Menthadien-2-one
6,8-p-Menthadien-2-on
Carvol
Carvone
Carvone (natural)
delta(sup 6,8)-(9)-terpadienone-2
delta-1-Methyl-4-isopropenyl-6-cyclohexen-2-one

CHEMICAL STRUCTURE





CHEMICAL FORMULA

$C_{10}H_{14}O$

IDENTIFIER DETAILS

CAS Number	:	99-49-0
CoE Number	:	146
FEMA	:	2249
EINECS Number	:	202-759-5
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: -

Boiling point: 231 ºC

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
-	-	-	-

FDA Status: [CFR21]

Section Number	Comments
-	-

HUMAN EXPOSURE

Natural Occurrence: -

Reported Uses: Present in baked goods at a concentration of 115.4 ppm, cheese 0.2 ppm, frozen dairy 197.4 ppm, meat products 0.1 ppm, relish 60 ppm, soft candy 225.6 ppm, gelatins and puddings 90 ppm, non-alcoholic beverages 41 ppm, alcoholic beverages 144.6 ppm, hard candy 369.4 ppm and chewing gum 349.5 ppm (isomer not specified) [Fenaroli, 2005].

Sources other than foods: -

TOXICITY DATA

In Vivo Toxicity status

Carvone (unspecified stereochemistry) was administered orally to male Wistar rats for 14 days at 500 mg/kg of body weight per day. Increases in serum cholesterol and triacylglyceride concentrations were observed in rats fed

carvone, when compared to controls. Food consumption and body weight also decreased in rats treated with carvone [Imaizumi *et al*., 1985].

Carcinogenicity / Mutagenicity

In vivo micronucleus testing: carvone (unspecified isomer ratio) was administered to mice using i.p. injection at a dose of 1000 mg/kg. No mortality occurred, and the PCE/NCE ratio was slightly (but not significantly decreased) in both sexes, nor was there any increase in the frequency of micronucleated cells at any time point. As a result of these findings, carvone was concluded to be non-genotoxic *in vivo* [CLH REPORT FOR [CARVONE], 2012].

Dermal Toxicity

A recent report indicated a woman with positive patch-test reactions to carvone (newly added to the North American Contact Dermatitis Group standard series) and dermatitis on the head. She had used a hair conditioner with a "mint" scent, and the dermatitis resolved when she discontinued using this product. While the manufacturer would not confirm carvone as an ingredient, the clinical course, patch-test results, and ingredient list strongly suggest that this was a relevant allergen in this case of allergic contact dermatitis [Quertermous & Fowler, 2010].

Carvone (unspecified isomer ratio) was used in a single dose of 4000 mg/kg bw (no vehicle used) in an acute dermal exposure study performed in accordance with the OECD guideline 402. No mortality, systemic or skin effects were observed. The dermal LD50 for carvone was set at >4000 mg/kg bw [CLH REPORT FOR [CARVONE], 2012].

Reproductive / Developmental Toxicity

No data available.

Inhalation Toxicity

A single dose of 5.66 g/m^3 carvone (d/l isomer ratio of min. 4:1) was administered in rats. The only pathological abnormalities were observed in a female rat which died one day after exposure: dark and foamy lungs, air-filled stomach/intestines and light coloured liver. Signs observed during exposure to carvone include a decreased breathing frequency (which increased post-exposure), post-inspiratory apnoea (which was also observed post-exposure) and superficial breathing, as well as restlessness, stress, incoordination and tremor. A few rats exhibited alopecia at days 7-13. Although body weight gain was impaired in some rats in the week following the treatment, it returned to normal in the second week, with the exception of two female rats, which showed only marginal body gain. The respiratory LC50 of carvone in rats was set at >5.66 mg/m^3. The study was performed in accordance with the OECD guideline 403 [CLH REPORT FOR [CARVONE], 2012].

Other relevant studies

Monoterpenoids such as carvone (form not specified) administered to Balb/c mice at a concentration of 100 µM/kg bw/dose/animal caused a significant increase in the total number of white blood cells, total antibody production, number of spleen antibody producing cells, bone marrow cellularity and α-esterase positive cells compared to untreated controls [Raphael & Kuttan, 2003].

Carvone is reported to be metabolised to innocuous products [JECFA, 1999].

Behavioural data

No data available.

In Vitro Toxicity Status

Carcinogenicity and Mutagenicity

Carvone	Gene mutation	*S. typhimurium* - 3 µmol/plate - Negative (TA1535, TA1537, TA98 & TA100).
Carvone	Rec assay	*Bacillus subtilis* H17 (rec^+) and M45 (rec^-) 0.6ml/disc - Negative

[JECFA, 1999].

Other Relevant Studies

No data available.

PYROLYSIS AND TRANSFER STUDIES

No data available.

REFERENCES

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