(b) (4)

Menthol

Toxicity monograph (with existing HCVs)

August 2016

Prepared by:

(b) (4)

(b) (4)

(b) (4)

TABLE OF CONTENTS

(b) (4)

Menthol

Toxicity monograph (with existing HCVs)

INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of menthol (CAS RNs[1] 89-78-1, 2216-51-5, 15356-60-2 and 1490-04-6), focusing on the inhalation route of exposure. Data on the inhalation of tobacco smoke containing the ingredient have not been included in the monograph.

EXPERTISE

(b)) was founded[2] in 1961 to provide independent, high-quality research, information and advice on chemical toxicology to industry and governmental departments. Its risk assessors have been working together for many years (more than 40 years in some instances) and have a record of objectivity and scientific excellence. All the senior and principal scientists in the current team are accredited and listed in the European (Eurotox) and UK Royal Society of Biology/British Toxicology Society Registers of Toxicologists and are thus bound by their specific codes of conduct.

TOXICITY DATA SEARCH CRITERIA

Searches of the (b) (4) database (see Appendix for details) identified several recent and relevant expert group reports that formed the basis for this assessment. The most recent are EFSA, 2016a and b. A subsequent search of the primary literature was conducted in (b) (4) PubMed (including Medline) and Toxline (via TOXNET, with PubMed hits removed), restricted to data published from 2015 onwards, in an attempt to identify more recent data since the EFSA (2016) reviews. The RTECS databank records for racemic menthol, L-menthol, D-menthol and menthol (unspecified isomer) were also consulted. Since the key reviews focussed on the use of menthol in food and, as such, could not necessarily be relied upon to identify all critical local and systemic inhalation data, no date restriction was placed on searches tailored to identify such information (and also cardiopulmonary data). Finally, the REACH dossiers were consulted for inhalation data and for endpoints for which there were otherwise data gaps or limited data.

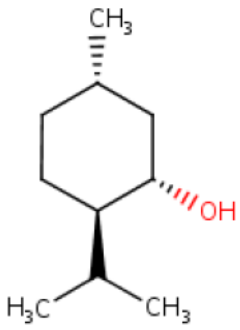
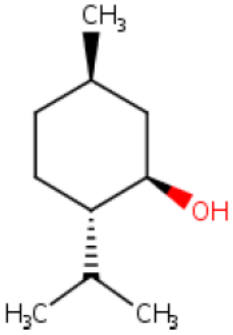
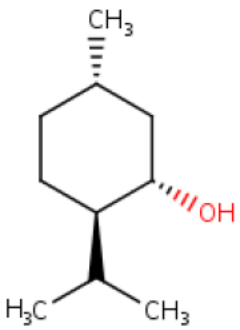
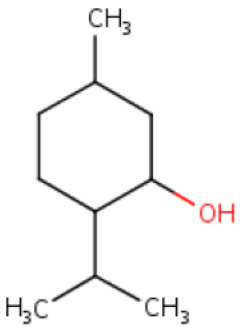
All searches were conducted in February-April 2016 using the CAS RN(s), name(s) and/or synonym(s) identified in the table below, as appropriate. The current report uses the most specific term of tested menthol used in the cited source. The data summarised in this report refers to the unheated form unless otherwise stated.

[1] Chemical Abstracts Service Registry Numbers

[2] (b) (4)

(b) (4)

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier / status				
Name	Menthol			
Synonym(s)	DL-Menthol (racemic mixture) (1R,2S,5R)-Rel-5-methyl-2-(1-methylethyl)-cyclohexanol (+-)-Menthol	L-Menthol (1R,3R,4S)-5-Methyl-2-(1-methylethyl)-cyclohexanol (-)-Menthol	D-Menthol (1S,2R,5S)-5-Methyl-2-(1-methylethyl)-cyclohexanol (+)-Menthol	Menthol (unspecified isomer) 5-Methyl-2-(1-methylethyl)-cyclohexanol
CAS RN	89-78-1[3]	2216-51-5	15356-60-2	1490-04-6
FEMA	2665	Not specified	Not specified	Not specified
REACH registration number[4]	01-2119456815-30-xxxx	01-2119458866-21-xxxx	01-2119511175-50-xxxx	01-2119456818-24-xxxx
Molecular formula	$C_{10}H_{20}O$			
Molecular weight	156.3			
Structure				

[3] CAS RN 15356-70-4 was used by NCI (1979).
[4] REACH registration numbers are substance and company specific. Therefore, the substance-specific part of the registration number is included here, from data disseminated on the ECHA 'registered substance' website.

(b) (4)

Classification, according to EU CLP (EU 1272/2008)	**Harmonised classification:**			
	None available	None available	None available	None available
	REACH joint registrants:			
	(757 of 1203 notifiers)	**(98 of 1158 notifiers)**	**(161 of 230 notifiers)**	**(1 of 1028 notifiers)**
	Skin Irrit. 2. Causes skin irritation (H315)[5] Eye Irrit. 2. Causes serious eye irritation (H319)[6]	Skin Irrit. 2. Causes skin irritation (H315)[7] Eye Irrit. 2. Causes serious eye irritation (H319)[8]	Skin Irrit. 2. Causes skin irritation (H315)[9]	Skin Irrit. 2. Causes skin irritation (H315)[10] Eye Irrit. 2. Causes serious eye irritation (H319)[11]

ADME

Following oral administration, "menthol is readily absorbed" and "is known to be largely eliminated as glucoronides". "Oral doses of menthol are metabolized mainly in the liver" and "mammals can efficiently handle [orally administered] menthol by processes that do not create hazardous products" (JECFA, 1999). Urine collected after daily oral gavage of male rats with 800 mg L-menthol/kg bw/day for 20 days contained the following metabolites: p-menthane-3,8-diol, p-menthane-3,9-diol, 3,8-oxy-p-menthane-7-carboxylic acid and 3,8-dihydroxy-p-menthane-7-carboxylic acid. The main urinary metabolites were p-menthane-3,9-diol and 3,8-dihydroxy-pmenthane-7-carboxylic acid. Menthone was not detected (Madyastha and Srivatsan, 1988).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

Human

During the manufacture in the US of lozenges containing menthol, 49 workers were exposed in the production area to menthol vapour at 4.9-39.4 mg/m^3, with a mean duration of employment of 7.7 years. Upper respiratory tract irritation and a runny nose were experienced, effects said to be due to menthol exposure, although no unexposed controls were evaluated (NIOSH, 1979).

Intranasal spraying with 0.5% menthol solution for 3 hours was said to have produced local irritation, as measured by an increased resistance to airflow (Fox, 1927).

[5] Specific concentration limits: Skin Irrit. 2: C > 25%
[6] Specific concentration limits: Eye Irrit. 2: C > 25%
[7] Specific concentration limits: Skin Irrit. 2: C > 25%
[8] Specific concentration limits: Eye Irrit. 2: C > 25%
[9] No concentrations limits specified.
[10] Specific concentration limits: Skin Irrit. 2: C > 25%
[11] Specific concentration limits: Eye Irrit. 2: C > 25%

(b) (4)

Non-human

Exposure of groups of 4-6 female mice to racemic menthol was associated with mild irritation at 16 ppm [102 mg/m³] but not at 4 ppm [26 mg/m³]. The endpoint measured was the duration of braking, representing a pause in the stimulation of the trigeminal nerve, at the onset of each expiration (Willis *et al.*, 2011).

A 30-minute exposure to menthol at a concentration of at least 141 mg/m³ induced signs of local irritation in mice (Burleigh-Flayer, 1988). The RD_{50} value[12] was 288 mg/m³ (Burleigh-Flayer, 1988; Cometto-Munez and Cain, 1994; Schaper, 1993).

Exposure of groups of ten mice to 50 or 100 mg menthol/m³ for 5 hours/day for 84 days did not affect the lungs, whereas 1000 mg/m³ for 6 hours/day for 6 days induced erythraemia [increase in the number of red blood cells] (Kowalski *et al.*, 1962).

Inhalation of L-menthol by groups of eight rats for 6.75 hours/day for 5 days/week for up to 10-11 weeks was associated with congestion and inflammation of the lung, indicating local irritation, at 1.66 mg/m³ but not at 0.95 or 0.56 mg/m³ (Rakieten *et al.*, 1954).

Intranasal exposure of rabbits to a 1% menthol aerosol, once per day for 9 months caused local damage to the nasal passages and sinuses (Fox, 1930).

Guinea pigs showed no overt signs of irritation to the respiratory tissues following a 5-minute exposure to 30 mg menthol/m³ (Laude *et al.*, 1994).

Inhalation of an aerosol for 8 hours/day for 14 days, providing about 40 mg menthol/kg bw/day, gave no overt signs of irritation in four monkeys (Alarie, undated).

An increased resistance to airflow was seen in dogs exposed intranasally to a 1 or 5% menthol aerosol (Fox, 1927).

Skin irritation

Human

Mild irritation was reported following "vigorous" application of 20% menthol in oil to the skin [no further details provided] (Bliss and Glass, 1940). A 24- to 48-hour exposure of the back or forearm of 133 healthy volunteers to DL-menthol in a base cream at 0.05 to 0.5% or in ethanol at 99% was associated with very slight erythema in two of the subjects [1.5%] (Takenaka *et al.*, 1970). In patch tests on 1147 dermatitis patients, skin irritation was seen in ten subjects [0.9%] given a 24- or 48-hour exposure to 1% menthol [unspecified isomer] (Uter *et al.*, 2010).

An 8% concentration of L- or DL-menthol in petrolatum did not induce skin irritation in volunteers [number not specified] after 48-hour covered contact (Epstein, 1974; Kligman, 1973). Products containing (probably L-) menthol at 2.8% were applied to the covered skin of ten subjects 3 times/day for 1 week and did not elicit any irritation response (Kligman, 1976).

[12] The RD_{50} is the concentration required to reduce the respiratory rate by 50%; reduced respiratory rate is considered to be a response to the inhalation of respiratory tract irritants.

(b) (4)

Sensory reactions, including stinging and cooling, were reported in >20% of 58 volunteers after 0.5% menthol in water was rubbed briskly over the nasolabial fold ["smile lines"] (Marriott *et al.*, 2005). A covered application of 2.5 ml of 30% menthol in ethanol lasting several minutes was reported to have caused sensory irritation, including burning, coldness and stinging, in nine volunteers (Green and Shaffer, 1992).

Non-human

Undiluted menthol (L-, D- or DL-isomers) induced moderate skin irritation in rabbits. A 5% concentration of L- or DL-menthol induced very mild irritation and 5% D-menthol was not irritating (Haarmann and Reimer, 1989). A maximum non-irritating concentration of 10% was reported for guinea pigs, exposed topically to L-menthol for 24 hours. The higher concentrations tested were not specified (Sharp, 1978).

Eye irritation

Human

Red and watery eyes were associated with exposure to menthol vapour by 49 workers involved in the production of mentholated lozenges in the US. In the production area, menthol vapour concentration was 4.9-39.4 mg/m³ (NIOSH, 1979).

Rubbing the eyes with hands contaminated with menthol caused a burning sensation that lasted for 30 minutes. No tissue damage was observed (Lewin and Guillery, 1913).

Non-human

Continuous whole-body exposure of rats to menthol at 1.4-1.6 g/m³ for 6 months induced eye irritation which persisted for the first few days of treatment. A concentration of 0.7-0.8 g/m³ was without such an effect (Haggard and Greenberg, 1941).

According to an OECD report, "all studied isomers of menthol are... slightly irritating to the eye" (OECD, 2003). The US EPA also considered menthol to be a mild eye irritant (US EPA, 2010).

Guideline studies with L-, D- and DL-menthol at 29-64% in diethyl phthalate and at 100% showed these to be slightly irritating in rabbit eyes (Haarmann and Reimer, 1989). Mild eye irritation was seen in rabbit eyes in response to four-times daily instillation of 0.1 mL of 0.2% menthol (in phosphate buffer with 0.4% Tween-80) for 7 days. No tests were conducted with higher concentrations (Xu *et al.*, 2011).

Severe eye injury was reported following instillation of 0.005 mL of undiluted menthol [purity not specified] or "an excess volume of" 5% menthol [probably in propylene glycol] into rabbits' eyes [limited report] (Carpenter and Smyth, 1946).

Other local effects

Human

In an oral irritation test in 22 healthy adult volunteers, a filter paper disc with 40 µl 0.3% L-menthol[13] was applied to one side of the tongue for 30 seconds, 10 times, 1 minute apart.

[13] Also containing 4% ethanol and 1% Tween.

(b) (4)

The perceived intensity of irritation of menthol decreased with sequential applications ("self-desensitization") in 19/22 of the volunteers and most experienced a cooling sensation (21/22) (Dessirier *et al.*, 2001).

The application of a 5% solution of menthol in ethanol to the mucous membranes of the mouth caused intense irritation and damage (Tainter *et al.*, 1937). A concentration of 0.5% was irritating, but 0.2% was without effect (Bliss and Glass, 1940).

A mentholated lozenge containing 9.62 mg menthol was irritating to the mouths of 35 healthy volunteers who dissolved one every 4-8 hours on two consecutive days (Glassman and Packman, undated.

Non-human

No substance-specific data were identified.

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation

Human

A number of case reports have been identified involving apparent inhalation exposure to menthol following the oral use of a product containing it. For example "a case of asthma due to menthol is reported in a 40-year-old woman with no history of asthma or any other allergy. During the last two years, the patient had presented dyspnoea [shortness of breath], wheezing and nasal symptoms when exposed to mentholated products such as toothpaste and candies. The aetiology was suggested by the history of exposure and diagnosis was established by skin tests and bronchial challenge with menthol. The patient achieved control of symptoms by avoiding menthol and its derivatives" (dos Santos *et al.*, 2001). A woman's daily use of a menthol-containing toothpaste was associated with moderate dyspnoea. She experienced an immediate bronchial response to a double-blind oral challenge with 11 mg/menthol in ethanol (Subiza *et al.*, 1992). Kawane (1996) described a similar case study and Anderson and Hindsén (2007) reported a link between allergic rhinitis and menthol from toothpaste and other consumer products.

A randomised placebo-controlled clinical trial was undertaken in which 10 mg nebulized menthol was administered twice a day by inhalation for 4 weeks to eleven asthma patients and a placebo administered to a control group of ten patients. An improvement was noted in the treated group, comprising a reduction in the diurnal variations in peak expiratory flow rate, but without affecting forced expiratory volume in 1 second (FEV_1), and the consumption of bronchodilators was less than in the control group as was the number of wheezing episodes. The menthol group had originally contained 13 patients, but two withdrew from the trial when an inhalation of menthol induced an uncomfortable sensation of the upper airway (Tamaoki *et al.*, 1995; 1996).

Non-human

No substance-specific data were identified.

(b) (4)

Skin sensitisation

Human

A small proportion of dermatology patients exhibited positive responses to patch tests with menthol [enantiomer not specified] in three studies: 10/512 [2.0%] and 1/63 [1.6%] reacted to 5% in petrolatum and 1/1147 [0.1%] to 1% (cited in SCCS, 2012).

Nasal application of menthol drops in young children has been linked to effects as severe as collapse and death. Muscular spasms of the larynx are considered to have been the cause of the observed clinical signs, which included spasms of the glottis, instant collapse, dyspnoea, apnoea [cessation of breathing], unconsciousness, cyanosis [blue colouration] and hyperextensive extremities (cited in (b) (4), 1990). However, in a survey of 124,000 infants, no such effects were seen (cited in Federal Register, 1982). These reports are unclear as to the frequency of exposure (possibly only once in some instances) and the route (in addition to inhalation, local absorption and swallowing cannot always be excluded). It may be that the observed effects are not due to toxicity, but because the trigeminal nerve reflex reaction is known to be especially strong in <2-year-olds when a substance with an intense odour contacts the nasal mucosa. Its autonomic reflexogen action can affect distant organs such as the heart, lungs and circulation and could lead to sudden apnoea and glottal constriction (EMEA, 2008; OECD, 2003).

A total of 20 human sensitisation studies are included in the REACH dossier on DL-menthol. These include, often early reports, of studies involving dermatitis patients (inducing a low incidence of positive reactions with patch tests with menthol; typically about 1% of test subjects), volunteer studies and individual case reports (BASF SE *et al.*, 2015).

Non-human

In a local lymph node assay (LLNA), concentrations of "menthol L H&R" of 1, 10 or 30% were tested on the skin of groups of 4 male mice with no effect on lymphocyte proliferation, indicating a lack of skin sensitisation. The unpublished study was described in the OECD report (OECD, 2003) as being of reliability 1, valid without restriction (Haarmann and Reimer GmbH, 1995). A similar assay in rats involving a 50-µL subcutaneous injection of 5 mg L-menthol (i.e. 10%) also found no sensitisation reaction (Friedrich *et al.*, 2007).

Other regulatory guideline tests in guinea pigs did not produce skin sensitisation: a Beuhler test with 0.5 ml of 0.25% L-menthol and maximization tests with D- and L-menthol (Anon, 1974; Ishihara *et al.*, 1986). An equivocal result was reported for a modified Draize test (Sharp, 1978).

Oral allergy/intolerance

Human

A double-blind, placebo-controlled food challenge was given to 73 subjects who had reported food allergy or intolerance in dietary questionnaire (given to 1483 Dutch individuals). One had a reaction to menthol described as "'aggravation of aphthae' (whitish spots in the mouth that characterize apthous stomatitis)" (Niestijl Janson *et al.*, 1994).

Non-human

No substance-specific data were identified.

(b) (4)

INHALATION TOXICITY STUDIES

Single dose toxicity

Human

Dizziness, confusion, muscle weakness, nausea and double vision may result from the inhalation of a "large" amount of methanol (Natural Medicines, undated). Evidence in support of this statement might have been obtained from a case report in which a 13-year-old boy (with bronchial asthma) who inhaled olbas oil containing menthol at 4.1% and providing an approximate dose of 200 mg menthol, developed ataxia, euphoria, double vision and weakness of the left arm and leg. However, menthol was one of a number of constituents of the oil and it is not clear which was the cause of the adverse effects (O´Mullane *et al.*, 1982).

Workers involved in the manufacture of mentholated lozenges in the US were exposed to menthol vapour at 4.9-39.4 mg/m³ (in the production area). Reduced forced vital capacity and 1-second forced expiratory volume at the end of a work shift were detected in non-smokers and former smokers, but not in current smokers, in a group of 49 who underwent pulmonary function testing (NIOSH, 1979).

Non-human

No overt toxicity was seen in guinea pigs following a 5-minute inhalation of menthol at up to 30 mg/m³ (Laude *et al.*, 1994).

The so-called "lowest published toxic concentration" (TCLo) was 16 mg/m³ in rats for a 4-hour exposure. Toxic effects were described as "behavioral - alteration of classical conditioning; cardiac - arrhythmias (including changes in conduction); kidney/ureter/bladder - renal function tests depressed" (Anon, 2002).

The 4-hour LC_{50}[14] for rats exposed nose-only to an aerosol of DL-menthol was about 5289 mg/m³ (guideline study) (Anon., 2012).

Repeated dose toxicity

Human

No substance-specific data were identified.

Non-human

Rats exposed to L-menthol at 0.56 or 0.95 mg/m³ for 6.75 hours/day on 5 days/week for about 10-11 weeks (6/sex/group) exhibited no signs of overt toxicity. A control group (4 males, 8 females) was unexposed. Microscopic examination of the turbinates, nasopharynx, trachea, lungs and skin (8-11/group) and the liver, spleen, kidney, heart, testis, ovary, intestine and skeletal muscle ("from some of the animals") did not reveal any adverse effects and there was no clear evidence of treatment-related toxicity to the respiratory tract (similar to control incidence) (see Cardiopulmonary effects section for details). In a group exposed to a higher concentration, 1.66 mg/m³, severe lung congestion and inflammation were seen (9/11). No abnormalities were seen in the haematology parameters measured (Rakieten *et al.*, 1954).

[14] Lethal Concentration 50, i.e. the concentration that is lethal to 50% of the exposed group.

(b) (4)

According to a very limited report of an early study there were "no indications of inflammation or injury in the respiratory tract" in rats continuously exposed to menthol at 0, 0.7-0.8 or 1.4-1.6 g/m³ for 6 months (10/group), although the extent of the examination is unclear. Growth was unaffected and eye irritation at the top concentration for the first few days of exposure was the only overt toxicity reported (Haggard and Greenberg, 1941).

There was no effect on the lungs of mice exposed to menthol at 50 or 100 mg/m³ for 5 hours/day for 84 days (10/group) but liver and kidney toxicity (including fatty degeneration and necrotic foci) were reported. A 6-day exposure to 1000 mg/m³ (6 hours/day) had a similar effect on the liver and kidney and was also associated with erythraemia [increase in the number of red blood cells] and small haematoma [solid swelling of clotted blood] in the brain, heart, lung and kidney (Kowalski *et al.*, 1962).

Rabbits "sprayed daily" for 9 months with a 1% menthol aerosol had damaged nasal passages and sinuses. The administration route may have been intranasal, but this is not clear in the limited report (Fox, 1930).

Exposure to an aerosol providing about 40 mg menthol/kg bw/day for 8 hours/day for 14 days did not induce overt toxicity in four monkeys (Alarie, undated).

TOXICITY STUDIES – OTHER EXPOSURE ROUTES

Single dose toxicity

Human

Abdominal pain, convulsions, nausea, vomiting, vertigo, ataxia, drowsiness and coma can occur after a single oral intake of a high dose of menthol (cited in OECD, 2003). A child who drank about 200-250 mg menthol/kg bw became drowsy and somnolent, felt pain in the stomach and vomited, but was symptom free 4 days later (Leiber, 1967).

Fatigue was experienced by three volunteers who ingested 8-9 g menthol [about 120 mg/kg bw[15]]. They also reported a cold burning sensation in the mouth, throat and oesophagus and a cold sensation on nasal mucous membranes and on the skin of the hands and feet (Schwenkenbecher, 1908).

According to a standard text, "the fatal [oral] dose in man has been estimated to be about 2 g" [no further details provided] (Martindale, 1989).

Lozenges containing 1.36 mg menthol each (and other volatile oils) did not induce overt toxicity in 40 healthy volunteers who dissolved 2 lozenges/20 minutes for 2 hours (Mendoza, undated; Seltzer, undated).

Non-human

Reported oral LD_{50} values[16] in mice were 2652-4384 mg/kg bw and in rats 940-3180 mg/kg bw (cited in EFSA, 2015).

[15] Assuming a body weight of 70 kg.

[16] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.

(b) (4)

A single oral dose of L-menthol given to groups of 7-10 male rats was without overt signs of toxicity or effects on body weight, liver and kidney weight or macroscopic appearance or on serum chemistry at 500 mg/kg bw. The stomachs of animals given 50 mg/kg bw were evaluated and a reduction in the acidity of gastric juice accompanied by an increased adhesion of gastric mucus to the stomach wall and inhibition of gastric motility were reported (Rozza *et al.*, 2013).

Rats administered an acute oral dose of menthol at 39.33 mg/kg bw had increased bile secretion and decreased total cholesterol in bile at up to 4 hours after administration, a choleretic effect (Hu *et al.*, 2015).

Repeated dose toxicity

Human

Thirty-five healthy volunteers who dissolved a lozenge containing menthol at 9.62 mg in the mouth every 4-8 hours on 2 consecutive days were said to have no "systemic" symptoms (Glassman and Packman, undated).

Non-human

In good quality studies, rats were administered diets containing DL-menthol at 3750 or 7500 ppm [providing about 188 or 375 mg/kg bw/day[17]] and mice 2000 or 4000 ppm [providing about 300 or 600 mg/kg bw/day] for 2 years. Survival was slightly decreased in female mice, but the top doses tested, 375 and 600 mg/kg bw/day, were described as NOAELs[18] by EFSA (EFSA, 2015; NCI, 1979). (See also Carcinogenicity section.)

Oral gavage administration of menthol at 200, 400 or 800 mg/kg bw/day to rats for 28 days was associated with an increase in liver weight (absolute and relative to body weight) and hepatocyte vacuolisation. The lowest dose tested, 200 mg/kg bw/day, was therefore the LOAEL[19] in this study (Thorup *et al.*, 1983). JECFA considered that the effect "may have reflected adaption" (JECFA, 1999). In contrast, no adverse effects were reported in a 5.5-week dietary study in rats in which menthol was provided at 100 or 200 mg/kg bw/day [no further details available] (Herken, 1961).

Rats fed doses of up to 1500 mg menthol/kg bw/day for 13 weeks (NCI, 1979) also had no treatment-related adverse effects, according to JECFA[20] (1999). In mice, 13 weeks' dietary exposure to menthol at levels of 1100 or 2300 mg/kg bw/day was associated with perivascular lymphoid hyperplasia and interstitial nephritis in females and the high-dose females also had reduced body weight. The NOAEL was 560 mg/kg bw/day (NCI, 1979)

Daily administration of L-menthol by oral gavage at 500 mg/kg bw/day for 3 days was associated with reduced liver and kidney function [no further details in citing source] (Macht, 1939).

[17] Conversions according to EFSA, 2015.
[18] No-observed-adverse-effect levels.
[19] Lowest-observed-adverse-effect level.
[20] Kidney inflammation was seen in the top-dose group, but JECFA did not consider this to be treatment related "since the effect is commonly observed in aged male [F]344 rats"

(b) (4)

Expert-group opinions

"Menthol" was considered by two expert groups to show no genotoxic potential (EFSA, 2016b; JECFA, 1999) and a range of regulatory-approved tests carried out under the US National Toxicology Program provided no evidence of genotoxicity for DL-menthol (NTP, various dates).

Micro-organisms

Bacterial reverse mutation (Ames) tests with DL-menthol (three reports), L-menthol (three reports) or an unspecified enantiomer of menthol (one report) all gave no evidence of mutagenic potential. Test were conducted in several strains of *Salmonella typhimurium* or in *Escherichia coli* WP2 uvrA, with and/or without S9[21] and at test concentrations up to 5 mg/plate. In a rec assay, described by EFSA as having "poor predictive value [for genotoxicity]", one group reported a positive result and one a negative result with L-menthol. In a host-mediated assay, an unspecified enantiomer of menthol was given orally to mice and mutagenicity was assessed in inoculated *Salmonella typhimurium*, with negative results except at lethal doses (EFSA, 2015; 2016a,b).

Mammalian cells (*in vitro*)

Four chromosome aberration tests were cited by EFSA, one on DL-menthol, the others with unspecified enantiomers of menthol, and none reported genotoxicity. Chinese hamster and human cells were used in the tests, with and/or without S9, and cytotoxic concentrations were included. No mutations were detected in a mouse lymphoma assay in L5178Y cells exposed to DL-menthol at up to 0.2 mg/ml ("selected by a preliminary test"), with and without S9, and two sister chromatid exchange (SCE) assays were also negative. At non-cytotoxic concentrations, D-menthol did not increase DNA strand breaks in rat hepatocytes, as measured in an alkaline elution assay (cited in EFSA, 2015; 2016a,b).

Mammals (*in vivo*)

In an alkaline comet assay in which rats were orally administered DL-menthol at 500, 1000 or 2000 mg/kg bw[22] in corn oil for 3 days, no DNA damage was detected in the liver or the stomach (Wada *et al.*, 2015).

Male rats were administered menthol[23] by oral gavage once at 1.45-3000 mg/kg bw or repeated [duration not specified] at 1150 mg/kg bw/day and no cytogenetic effects were seen in bone marrow cells. No toxicity to the bone marrow was observed, but the top dose was limited by lethality. The same doses[24] were tested for dominant lethal mutations, an endpoint that was also negative (FDRL, 1975).

A 3-day intraperitoneal exposure of male mice to DL-menthol at 250-1000 mg/kg bw/day was without effect on the incidence of micronuclei in the bone marrow. The top dose caused 50% mortality but no bone marrow toxicity was seen (Shelby *et al.*, 1993).

[21] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.
[22] The highest dose was toxic.
[23] The study report title gave the test material as: compound FDA 71-57, menthol.
[24] Possibly the same animals.

(b) (4)

CARCINOGENICITY

Human

No substance-specific data were identified.

Non-human

Two high quality chronic dietary studies were performed with DL-menthol. Rats 3750 or 7500 ppm [about 188 or 375 mg/kg bw/day[25]] and mice 2000 or 4000 ppm [about 300 or 600 mg/kg bw/day] for 2 years. No treatment-related increase in the frequency of tumours was seen in either sex of either species (NCI, 1979). (See also Repeated dose toxicity section.)

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Human

No substance-specific data were identified.

Non-human

Brief summaries of unpublished reports indicated that no teratogenicity had been induced by menthol[26] given by oral gavage to mice, rats and hamsters on days 6-15 of gestation and to rabbits on days 6-18. The highest doses tested were 185, 218, 405 and 425 mg/kg bw/day, respectively, which were the NOAELs for teratogenicity (FDRL, 1973).

Histopathological examination of the reproductive organs in 13-week dietary studies with DL-menthol revealed no treatment related changes in male or female rats or mice. The highest doses tested were about 1500 mg/kg bw/day in rats and 2300 mg/kg bw/day in mice. A similar lack of effect was seen in 2-year studies at up to 380 or 600mg/kg bw/day, respectively (NCI, 1979). (See also Repeated dose toxicity section.)

CARDIOPULMONARY EFFECTS

In the dietary studies cited in the Repeated dose toxicity section, evaluation included gross and microscopic examination of the heart, trachea, lungs and mainstem bronchi. No treatment-related abnormalities were reported in rats that received up to 375 mg/kg bw/day or mice up to 600 mg/kg bw/day for 2 years (NCI, 1979).

In a repeated inhalation toxicity study, rats were exposed to L-menthol at 0.56, 0.95 or 1.66 mg/m³ for 6.75 hours/day on 5 days/week for about 10-11 weeks (6/sex/group) and a control group (4 males, 8 females) was unexposed. Various tissues were examined microscopically and at the low and mid-exposure concentrations there were no adverse effects noted in the turbinates, nasopharynx, trachea or lungs of 8-11 animals/group, nor in the heart of an unspecified range of animals. There was no clear evidence of treatment-related toxicity to the respiratory tract in these two groups, in that it was similar to the control incidence. Six of nine control rats showed no respiratory tract abnormality, one had mild tracheitis [inflammation of the trachea] and two had pneumonitis [inflammation of lung tissue]. One of eight rats exposed to 0.56 mg/m³ had mild tracheitis and at 0.95 mg/m³, two

[25] Conversions according to EFSA, 2015.

[26] The study report title gave the test material as: FDA 71-57 (menthol natural, Brazilian).

(b) (4)

had mild pulmonary congestion, one had chronic pneumonia with bronchial hyperplasia and one had mild tracheitis. However, at the high exposure concentration of 1.66 mg/m³, severe lung congestion and inflammation were seen in nine of the eleven rats (Rakieten *et al.*, 1954). (See also Repeated dose toxicity section.)

As noted in the Repeated dose toxicity section, the lungs were unaffected when groups of ten mice were exposed to 50 or 100 mg menthol/m³ for 5 hours/day for 84 days. Exposure to 1000 mg/m³ for 6 hours/day for 6 days was associated with erythraemia [increase in the number of red blood cells] and small haematoma [solid swelling of clotted blood] in the heart and lungs (Kowalski *et al.*, 1962).

Two people with "excessive intakes" of sweets containing peppermint oil [providing about 5 mg menthol/kg bw/day] had heartbeat irregularities (Thomas, 1962).

In a double-blind placebo-controlled, randomised, cross-over trial, 22 healthy, non-smoking individuals chewed gum containing 4 mg nicotine and/or 30 mg menthol. The increased heart rate seen with nicotine was attenuated by menthol (Arendt Nielsen *et al.*, 2015).

"Irritation of the nasal membranes, tachycardia [abnormal heart rate], dyspneia [dyspnoea, shortness of breath], loss of consciousness [and] metabolic acidosis" were noted in thirteen children (aged 1 month to 3 years) exposed accidentally to menthol by nasal instillation. Few details were provided regarding the exposure, but the subjects had also been exposed to eucalyptol and it is not clear whether this was separately or concurrently, nor which of the effects were specifically attributable to menthol (Melis *et al.*, 1989).

Menthol prolonged the duration of expiration when applied nasally to anaesthetized dogs, breathing through traceostomy, an effect mediated through the posterior nasal nerve (Kanamuaru *et al.*, 1999).

Nasal application of menthol drops in young children has been linked to effects as severe as collapse and death. Its autonomic reflexogen action can affect distant organs such as the heart, lungs and circulation and could lead to sudden apnoea and glottal constriction (EMEA, 2008; OECD, 2003). (See Skin sensitisation section for further details.)

(b) (4)

EXISTING HEALTH CRITERIA VALUES (HCVs)

Agency/ organisation/ company	HCV (including route)	Value and unit	Critical effect(s) and effect level (e.g. NOAEC), relevant population	Reference
DL-Menthol (89-78-1)				
REACH registrants	DNEL[27] (inhalation)	16.3 mg/m³	No information on critical effect level. General population, inhalation route, lon term or acute/short-term exposure, systemic effects.	BASF SE *et al.*, 2015
REACH registrants	DNEL (inhalation)	0.5 mg/m³	No information on critical effect level. General population, inhalation route, long-term or acute/short-term exposure, local effects.	BASF SE *et al.*, 2015
REACH registrants	DNEL (inhalation)	66.28 mg/m³	No information on critical effect level. Workers, inhalation route, long-term or acute/short-term exposure, systemic effects	BASF SE *et al.*, 2015
REACH registrants	DNEL (inhalation)	1 mg/m³	No information on critical effect level. Workers, inhalation route, long-term or acute/short-term exposure, local effects	BASF SE *et al.*, 2015
JECFA	ADI (oral)	4 mg/kg bw	NOEL 380 mg/kg bw/day (the highest dose tested), 2-year rat dietary study (NCI, 1979).	JECFA, 2000

[27] A DNEL is the level of exposure to the substance above which humans should not be exposed. Health risks are considered to be adequately controlled if exposures are kept below the DNELs. These values represent the views of the submitting consortium. In general, the amount of information disseminated on the ECHA website is insufficient for easy or independent verification of these DNELs.

(b) (4)

Agency/ organisation/ company	HCV (including route)	Value and unit	Critical effect(s) and effect level (e.g. NOAEC), relevant population	Reference
"No safety concern" from the use of DL-menthol as a food flavouring agent based on current estimated levels of intake of up to approximately 18 mg/day in Europe and 10 mg/day in the USA) (JECFA, 2000).				
L-Menthol (2216-51-5)				
REACH registrants	DNEL (inhalation)	33 mg/m³	Dose descriptor starting point after route-to-route extrapolation NOAEC[28], 326 mg/m³ (highest dose tested). General population, inhalation route, long-term exposure, systemic effects.	BASF SE *et al.*, 2016
REACH registrants	DNEL (inhalation)	132 mg/m³	Dose descriptor starting point after route-to-route extrapolation NOAEC[29], 661 mg/m³ (highest dose tested). Workers, inhalation route, long-term exposure, systemic effects.	BASF SE *et al.*, 2016
REACH registrants	DNEL (inhalation)	10 mg/m³	No information on critical effect level.[30] Workers, inhalation route, long-term and acute/short-term exposure, local effects.	BASF SE *et al.*, 2016

[28] Derived from chronic repeated-dose oral toxicity data with an overall assessment factor of 10.
[29] Derived from chronic repeated-dose oral toxicity data with an overall assessment factor of 5.
[30] Derived from skin irritation data [no further information provided]

(b) (4)

Agency/ organisation/ company	HCV (including route)	Value and unit	Critical effect(s) and effect level (e.g. NOAEC), relevant population	Reference
D-Menthol (15356-60-2)				
REACH registrant	DNEL (inhalation)	13 mg/m³	No information on critical effect level[31]. General population, inhalation route, long-term or acute/short-term exposure, systemic effects, and long-term exposure, local effects.	Symrise AG, 2015
REACH registrant	DNEL (inhalation)	13 mg/m³	Dose descriptor starting point after route-to-route extrapolation NOAEC[32] General population, inhalation route, acute/ short-term exposure, local effects	Symrise AG, 2015
REACH registrant	DNEL (inhalation)	52.5 mg/m³	Dose descriptor starting point after route to route extrapolation NOAEC[33] Workers, inhalation route, long-term, systemic and local effects.	Symrise AG, 2015
REACH registrant	DNEL (inhalation)	280 mg/m³	Dose descriptor starting point after route-to-route extrapolation NOAEC[34] Workers, inhalation route, acute/short-term exposure, systemic and local effects	Symrise AG, 2015
Menthol (1490-04-6)				
No HCVs identified.				

[31] Derived from repeated-dose toxicity data with an overall assessment factor of 25
[32] Derived from acute toxicity data with an overall assessment factor of 50.
[33] Derived from repeated-dose toxicity data with an overall assessment factor of 12.5
[34] Derived from acute toxicity data with an overall assessment factor of 12.5.

(b) (4)

REFERENCES

Alarie Y [undated]. Unpublished data [cited in Federal Register, 1976].

Andersson M and Hindsén M (2007). Rhinitis because of toothpaste and other menthol-containing products. Allergy 62, 336-337.

Anon (1974). Study report [cited in ECHA REACH dossier for D-menthol (Symrise AG, 2015)].

Anon (2002). Toksikologicheskii Vestnik (5), 52 [no further bibliographic details provided] [cited in RTECS, 2010].

Anon (2012). Study report [cited with filename "Acute Toxicity: inhalation" in the ECHA REACH dossier for DL-menthol (BASF SE *et al.* 2015)].

Arendt Nielsen T, Nielsen BP, Wang K, Arendt-Nielsen L and Boudreau SA (2015). Psychophysical and vasomotor responses of the oral tissues: a nicotine dose-response and menthol interaction study. Nicotine and Tobacco Research Aug 4. pii: ntv163. [Epub ahead of print] [cited from PubMed abstract].

BASF SE *et al.* (2015). European Chemicals Agency. REACH registration dossier for DL-Menthol, CAS RN 89-78-1. First published 03-Mar-2011, last modified 29-Dec-2015. Registrants/ Suppliers BASF SE *et al.* http://echa.europa.eu/registration-dossier/-/registered-dossier/13758/1

BASF SE *et al.* (2016). European Chemicals Agency. REACH registration dossier for L-Menthol, CAS RN 2216-51-5. First published 16-Mar-2011, last modified 08-Jan-2016. Registrants/ Suppliers BASF SE *et al.* http://echa.europa.eu/registration-dossier/-/registered-dossier/15383/1

Belsito D, Bickers D, Bruze M, Calow P, Greim H, Hanifin JM, Rogers AE, Saurat JH, Sipes IG and Tagami H (2008). A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients. Food and Chemical Toxicology 46 (Suppl. 11), S1-S71.

Bhatia SP, Mcginty D, Letizia CS and Api AM (2008). Fragrance material review on L-menthol. Food and Chemical Toxicology 46 (Suppl. 11), S218-S223.

(b) (1990). Toxicity Profile: Menthol. (b) , Wallington, Surrey, UK.

Bliss AR and Glass HB (1940). A chemical and pharmacological comparison of the menthols. Journal of the American Pharmacists Association 29, 171-175 [cited in (b) (4) 1990].

Burleigh-Flayer HD (1988). Evaluation of the sensory irritation potential and assessment of the respiratory response during exposure to menthol vapor. Report 51-552. Bushy Run Research Center [cited in Heck, 2010].

Carpenter CP and Smyth HF Jr (1946). Chemical burns of the rabbit cornea. American Journal of Ophthalmology 29, 1363-1372 [cited ((b) (4) 1990].

(b) (4)

nez JE and Cain WS (1994). Sensory reactions of nasal pungency and odor to volatile organic compounds: the alkylbenzenes. American Industrial Hygiene Association Journal 55, 811-817.

Dessirier JM, O'Mahony M, Carstens E (2001). Oral irritant properties of menthol sensitizing and desensitizing effects of repeated application and cross-desensitization to nicotine. Physiology and Behaviour 73, 25-36.

dos Santos MA, Santos Galvao CE and Morato Castro F (2001). Menthol-induced asthma: a case report. Journal of Investigational Allergology and Clinical Immunology 11, 56-58 [cited in SCCS, 2012].

EFSA (2015). European Food Safety Authority. Scientific opinion on flavouring group evaluation 9, revision 6 (FGE.09Rev6): Secondary alicyclic saturated and unsaturated alcohols, ketones and esters containing secondary alicyclic alcohols from chemical group 8 and 30, and an ester of a phenol derivative from chemical group 25. EFSA Journal 13(9), 4243, 81pp. http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4243.pdf

EFSA (2016a). European Food Safety Authority. Scientific opinion on flavouring group evaluation 90, revision 1 (FGE.90Rev1): Consideration of six substances evaluated by JECFA (68th meeting) structurally related to aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols, aromatic tertiary alcohols and their esters evaluated by EFSA in FGE.18Rev1 and FGE.75Rev1. EFSA Journal 14(1), 4336, 37pp. http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4336.pdf

EFSA (2016b). European Food Safety Authority. Scientific opinion on flavouring group evaluation 51, revision 2 (FGE.51Rev2): Consideration of alicyclic ketones and secondary alcohols and related esters evaluated by JECFA (59th meeting) structurally related to alicyclic ketones secondary alcohols and related esters in FGE.09Rev6 (2015). EFSA Journal 14(1), 4338, 57pp. http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4338.pdf

EMEA (2008). European Medicines Agency. Evaluation of Medicines for Human Use. Assessment report on Mentha x piperita L., aetheroleum. 4 September 2008. EMEA/HMPC/349465/2006. http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2010/01/WC500059311.pdf

Epstein WL (1974). Unpublished report to RIFM, 9 July [cited (b) (4) 1990].

FDRL (1973). Food and Drug Research Laboratories, Inc., 1973. Teratologic evaluation of FDA 71-57 (menthol natural, Brazilian). Food and Drug Research Laboratories, Inc. Morgareidge K Lab. no. 1573k, study no. FDABF-GRAS-134, June 1, 1973. Unpublished report submitted by EFFA to FLAVIS Secretariat [cited in EFSA, 2015].

(b) (4)

FDRL (1975). Food and Drug Research Laboratories Inc. Mutagenic evaluation of compound FDA 71-57, menthol. Litton Bionetics, Inc. Weir, R.J. January 14, 1975. Unpublished report submitted by EFFA to FLAVIS Secretariat [cited in EFSA, 2016a,b].

Federal Register (1976). Over-the-Counter Drugs. Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. 41, 38312.

Federal Register (1982). Over-the-Counter Oral Health Care and Discomfort Drugs. Establishment of a Monograph. 47, 22711.

Federal Register (1989). Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for Over-the-Counter Human Use; Proposed Amendment to Monograph for OTC Antitussive Drug Products. 54, 28442.

Fox N (1927). Effect of camphor, eucalyptol and menthol on the vascular state of the mucous membrane. Archives of Otolaryngology 6, 112-122.

Fox N (1930). The effect of camphor, eucalyptol and menthol on the nasal mucosa. Archives of Otolaryngology-Head and Neck Surgery 11, 48-54.

Friedrich K, Delgado IF, Santos LM and Paumgartten FJ (2007). Assessment of sensitization potential of monoterpenes using the rat popliteal lymph node assay. Food and Chemical Toxicology 45, 1516-1522.

Glassman S and Packman EW [undated]. Draft of unpublished data. Menthol-eucalyptus cough drops: safety: intensive use. CRD 71-25. OTC Volume 040298. Docket no. 76N-0052 [cited in Federal Register, 1989].

Green BG and Shaffer GS (1992). Psychophysical assessment of the chemical irritability of human skin. Journal of Society of Cosmetic Chemists, Japan 43, 131-147 [cited in Belsito *et al.*, 2008].

Haarmann and Reimer GmbH (1989). Assessment of the skin irritant effect of HR 89/620006 in rabbits. Prepared for: 3450 Holzminden, Lab. No. 11876, 1 – 9. Assessment of the skin irritant effect of HR 89/131136 in rabbits. Prepared for: 3450 Holzminden, Lab. No. 11877, 1 – 9. Assessment of the skin irritant effect of HR 89/620001 in rabbits. Prepared for: 3450 Holzminden, Lab. No. 11874, 1 – 9. Assessment of the skin irritant effect of HR 89/920005 in rabbits – Menthol-D. Prepared for: 3450 Holzminden, Lab. No. 11875, 1 – 9 [cited as 1989a in OECD, 2003].

Haarmann and Reimer GmbH (1995). Menthol L H&R Local Lymph Node Assay, Lees D, Leah AM. Zeneca Central Toxicology Laboratory, Report No: CTL/E/160, 20.12.1995 [cited in OECD, 2003].

Haggard HW and Greenberg LA (1941). Concentration of menthol in the smoke from mentholated cigarets [sic]. A study of local and systemic effects. Archives of Otolaryngology 33, 711-716.

Heck JD (2010). A review and assessment of menthol employed as a cigarette flavouring ingredient. Food and Chemical Toxicology 48 (Suppl. 2), S1-38.

Herken H (1961). Pharmakologisches gutachten über die vertraglichkeit von natürlichem (L-) und synthetischem (D,L-) menthol. Unpublished report from the director, Pharmakologischen Institute der Freien Universität, Berlin-Duhlem, submitted to the World Health Organisation by Schering AG . Cited in JECFA, 1976 [cited in EFSA, 2015].

Hu G, Yuan X, Zhang S, Wang R, Yang M, Wu C, Wu Z and Ke X (2015). Research on choleretic effect of menthol, menthone, pluegone, isomenthone, and limonene in DanShu capsule. International Immunopharmacology 24, 191-197 [cited from PubMed abstract].

Ishihara M, Itoh M, Nishimura M Kinoshita M, Kantoh H, Nogami T and Yamada K (1986). Closed epicutaneous test. Skin Research 28 (Suppl. 2), 230-240 [cited in Bhatia *et al.*, 2008].

JECFA (1999). Safety evaluation of certain food additives. Menthol. Prepared by the Fifty-First Meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 42. http://www.inchem.org/documents/jecfa/jecmono/v042je04.htm

JECFA (2000). Evaluation of certain food additives. Fifty-first Meeting of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, 9–18 June 1998. WHO Technical Report Series no. 891. http://apps.who.int/iris/bitstream/10665/42245/1/WHO_TRS_891.pdf

Kanamaru A, Mutoh T, Kojima K, Nishimura R, Sasaki N, Kuwahara M and Tsubone H (1999). The posterior nasal nerve plays an important role on cardiopulmonary reflexes to nasal application of capsaicin, distilled water and L-menthol in anesthetized dogs. Journal of Veterinary Medical Science 61, 85-88 [cited from PubMed abstract].

Kawane H (1996). Menthol and aspirin induced asthma. Respiratory Medicine 90, 247.

Kligman AM (1973). Report to RIFM, 12 January [cited in (b) , 1990].

Kligman AM (1976). Unpublished data [cited in Federal Register, 1976].

Kowalski Z, Dutkiewicz T and Szymczykiewicz K (1962). [Study to set a value for the maximum admissible concentration of natural essential oils in air]. Medycyna Pracy 13, 69-84.

Laude EA, Morice AH and Grattan TJ (1994). The antitussive effects of menthol, camphor and cineole in conscious guinea-pigs. Pulmonary Pharmacology 7, 179-184.

Leiber B (1967). Menthol-eine kritische Bestandsaufnahme. In: Dost F, Leiber B, editors. Menthol and menthol-containing external remedies. Stuttgart: Georg Thieme Verlag p. 7-32 [cited in OECD, 2003].

Lewin L and Guillery H (1913). In Die Wirkungen von Arzneimittein und Giften auf das Auge. 2nd edition. Berlin: August Hirschwald [cited in (b) , 1990].

Macht DI (1939). Comparative pharmacology of menthol and its isomers. Archives Internationales de Pharmacodynamie 63, 43-58 [cited in (b) , 1990].

Madyastha KM and Srivatsan V (1988). Studies on the metabolism of L-menthol in rats. Drug Metabolism and Disposition 16, 765–772 [cited in EFSA, 2015].

Marriott M, Holmes J, Peters L, Cooper K, Rowson M and Basketter DA (2005). The complex problem of sensitive skin. Contact Dermatitis 53, 93-99 [cited in Belsito *et al.*, 2008].

Martindale (1989). The Extra Pharmacopoeia. 29th Edition. The Pharmaceutical Press, London [cited ((b) , 1990].

Melis K, Bochner A and Janssens G (1989). Accidental nasal eucalyptol and menthol instillation. European Journal of Pediatrics 148, 786-787 [cited in Posadzki *et al.*, 2012].

Mendoza JA [undated]. Draft of unpublished data. Clinical Safety tests on Vicks cough drops. OTC Volume 040298. Docket no. 76N-0052 [cited in Federal Register, 1989].

Natural Medicines (undated). A monograph of the Natural Standard Research Collaboration on peppermint oil. https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements.aspx?letter=P [cited in EMEA, 2008].

NCI (1979). National Cancer Institute. Bioassay of DL-menthol for possible carcinogenicity. U.S. Department of Health, Education, and Welfare. April 1978. NCI Technical Report Series, no. 98 https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr098.pdf [cited in EFSA, 2015; JECFA, 1999, with additional details from the study report itself].

Niestijl Janson JJ, Kardinaal AFM, Huijbers G, Vlieg-Boerstra BJ, Martens BPM and Ockhuizen T (1994). Prevalence of food allergy and intolerance in the adult Dutch population. Journal of Allergy and Clinical Immunology 93, 446-456 [cited in JECFA, 1999].

NIOSH (1979). National Institute for Occupational Safety and Health. Health hazard evaluation determination report no. HE 77-66-531, Sucrets Department, Merck, Sharp and Dohme, West Point, Pennsylvania (cited in Heck, 2010 and Philip Morris USA, 2001).

NTP (various dates). US National Toxicology Program. NTP Investigation of DL-Menthol. Available via http://tools.niehs.nih.gov/cebs3/ui/?search=testArticle

OECD (2003). Menthols. SIDS Initial Assessment Report for SIAM 16. OECD SIDS. UNEP Publications. http://www.chem.unep.ch/irptc/sids/oecdsids/MENTHOLS.pdf

O'Mullane NM, Joyce P, Kamath SV, Tham MK and Knass D (1982). Adverse CNS effects of menthol-containing olbas oil. Lancet 319, 1121.

Philip Morris USA (2001). Evaluation of Menthol for use as a Cigarette Ingredient. 2067617005/7095. http://legacy.library.ucsf.edu/tid/nox75a00

Posadzki P *et al.* (2012). Adverse effects of aromatherapy: A systematic review of case reports and case series. International Journal of Risk and Safety in Medicine 24, 147-161.

Rakieten N, Rakieten ML and Boykin M (1954). Effects of menthol vapor on the intact animal with special reference to the upper respiratory tract. Journal of the American Pharmaceutical Association 43, 390-392.

Rozza AL, Hiruma-Lima CA, Takahira RK, Padovani CR, Pellizzon CH (2013). Effect of menthol in experimentally induced ulcers: pathways of gastroprotection. Chemico-biological Interactions 206, 272-278.

RTECS (2010). Registry of Toxic Effects of Chemical Substances. Record for cyclohexanol, 5-methyl-2-(1-methylethyl)-, CAS RN 1490-04-6. Last updated Jan-2010.

SCCS (2012). Scientific Committee on Consumer Safety. Opinion on fragrance allergens in cosmetic products. SCCS/1459/11. Annex I: Clinical evidence regarding sensitisation to individual fragrance chemicals and to natural extracts. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_073_annex1.pdf

Schaper M (1993). Development of a database for sensory irritants and its use in establishing occupational exposure limits. American Industrial Hygiene Association Journal 54, 488-454.

Schwenkenbecher A (1908). Über Mentholvergiftung des Menschen. Münchener medizinische Wochenschrift 55, 1495-1496 [cited in OECD, 2003].

Seltzer S [undated]. Draft of unpublished data. Clinical safety tests on Vicks cough drops. OTC Volume 040298. Docket no. 76N-0052 [cited (b) (4) , 1990].

Sharp DW (1978). The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9, 261-271 [cited in (b) , 1990 and OECD, 2003].

Shelby MD, Erexson GL, Hook GJ and Tice RR (1993). Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. Environmental and Molecular Mutagenesis 21, 160–179 [cited in EFSA, 2016a,b].

Subiza J, Subiza JL, Valdivieso R, Escribano PM, Garcia R, Jerez M and Subiza E (1992). Toothpaste flavor-induced asthma. Journal of Allergy and Clinical Immunology 90, 1004-1006.

Symrise AG (2015). European Chemicals Agency. REACH registration dossier for D-Menthol, CAS RN 15356-60-2. First published 17-Mar-2011, last modified 24-Dec-2015. Registrants/ Suppliers Symrise AG. Available at: http://echa.europa.eu/registration-dossier/-/registered-dossier/12128/1

Tainter ML, Throndson AH and Moose SM (1937). Studies in topical anesthesia: II. Further observations on the efficacy of the more common local anesthetics when used on the gums and oral mucosa. Journal of the American Dental Association 24, 1480-1487 [cited in (b) (4) 1990].

Takenaka T, Hasegawa E, Takenaka U, Saito P and Odaka T (1970). [Fundamental studies of safe compound perfumes for cosmetics. The primary irritation of compound materials to the skin.] Parfum Cosmétique Savons, 13, 699-706.

Tamaoki J, Chiyotani A, Sakai A, Takemura H and Konno K (1995). Effect of menthol vapor on airway hyper responsiveness in patients with mild asthma. Respiratory Medicine 89, 503-504.

Tamaoki J, Chiyotani A, Sakai A, Takemura H and Konno K (1996). Menthol and aspirin induced asthma. Reply to Dr Kawane. Respiratory Medicine 90, 247.

Thomas JG (1962). Peppermint fibrillation. Lancet 279, 222 [cited in (b) , 1990].

Thorup I, Wurtzen G, Carstensen J and Olsen P (1983). Short-term toxicity study in rats dosed with pulegone and menthol. Toxicology Letters 19, 207–210 [cited in EFSA, 2015, with additional details from PubMed abstract].

(b) (4)

US EPA (2010). United States Environmental Protection Agency. Menthol summary document registration review: initial docket. Case # 4063. EPA-HQ-OPP-2009-0900. https://archive.epa.gov/oppsrrd1/registration_review/web/html/index-184.html

Uter W, Geier J, Frosch P and Schnuch A (2010). Contact allergy to fragrances: current patch test results (2005-2008) from the Information Network of Departments of Dermatology. Contact Dermatitis 63, 254-261.

Wada K, Fukuyama T, Nakashima N and Matsumoto K (2015). Assessment of the in vivo genotoxicity of cadmium chloride, chloroform, and D,L-menthol as coded test chemicals using the alkaline comet assay. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 786-788, 114-119.

Willis DN, Liu B, Ha MA, Jordt SE and Morris JB (2011). Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. FASEB Journal 25, 4434-4444.

Xu X, Yu N, Bai Z, Xun Y, Jin D, Li Z and Cui H (2011). Effect of menthol on ocular drug delivery. Graefe's Archive for Clinical and Experimental Ophthalmology 249, 1503-1510.

(b) (4)

APPENDIX: The ((b) (4) database and databank

(b) (4)

(b) (4) includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources and websites. In addition to primary literature on the health effects of chemicals, (b) (4) covers official publications and evaluations issued by authoritative groups including:

- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- OECD SIDS dossiers/SIARS
- IUCLID data sets
- EU Risk Assessment Reports
- EU expert committee opinions (including EU scientific committees, and EFSA scientific panels) and other reports from EU agencies and institutes etc (including ECHA, ECVAM, EMA and CPS&Q)
- ECETOC, HERA, Council of Europe and other pan-European programmes
- UK government agency (including Defra, EA, FSA, DoH, HSE, HPA, PSD and VMD) and advisory committee (e.g. COT, COM, COC, ACNFP, SACN, ACP, ACAF, VPC, VRC and ACRE) reports and evaluations
- Opinions from other UK organisations such as the Royal Society
- US agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS, CDC, OEHHA and ACGIH)
- Health Canada evaluations
- BUA, DFG, BG Chemie and BfR reports and monographs
- Gezondheidsraad opinions, including those from its various committees such as DECOS
- RIVM reports
- Danish EPA reviews
- Reports and other information provided by Swedish governmental organisations, including the National Food Administration and the Swedish Chemicals Agency
- Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
- Australian agency reviews including NICNAS Priority Existing Chemical Assessments, APMVA reports and (jointly with New Zealand) FSANZ assessments
- Japanese Chemical Industry Ecology-Toxicology & Information Center reports
- CIR, RIFM and other specialist industry groups
- (b) Toxicity Profiles