Menthone and isomenthone

Toxicity monograph

September 2016

Prepared by:

TABLE OF CONTENTS

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INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of menthone and isomenthone, focussing on the inhalation route of exposure. Menthone occurs as a number of optical and stereoisomers. Menthone is considered to be the *trans*-form and isomenthone the *cis*-form (b) (4) 2000). Data on the inhalation of tobacco smoke containing the ingredient (if available) have not been included in this monograph.

EXPERTISE

(b) (4) was founded[1] 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 of potential relevance. This monograph was based on EFSA, 2015, with additional details from JECFA, 1999. A subsequent search of the primary literature was restricted to (b) (4) and Toxline (the toxicity subset of Medline, via TOXNET) in an attempt to identify more recent data since the 2015 review. In addition, very limited additional searches were conducted in an attempt to identify critical data not included in the Expert-group reviews. The remainder of the TOXNET system (which includes HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB) was also consulted. Since the key review focussed on the use of menthone and isomenthone 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 in PubMed tailored to identify such information (and also cardiopulmonary data).

All searches were conducted in September 2016 using the CAS RNs[2] and (in PubMed only) names identified below, as appropriate.

The data summarised in this report refer to the unheated form unless otherwise stated.

([redacted]

[2] Chemical Abstracts Service Registry Numbers.

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier / status	Menthones		
Name	Menthone	L-Menthone	D-Menthone
Synonym(s)	*trans*-Menthone 5-Methyl-2-(1-methylethyl) cyclohexanone 2-Isopropyl-5-methyl-cyclohexanone *para*-Menthane-3-one	*trans*-L-Menthone L-5-Methyl-2-(1-methylethyl) cyclohexanone L-2-Isopropyl-5-methyl-cyclohexanone L-Menthan-3-one (*2S,5R*-)-5-Methyl-2-(1-methylethyl) cyclohexanone	*trans-D*-Menthone D-5-Methyl-2-(1-methylethyl) cyclohexanone D-2-Isopropyl-5-methyl-cyclohexanone D-Menthan-3-one (*2R,5S*-)-5-Methyl-2-(1-methylethyl) cyclohexanone
CAS RN	89-80-5[3]; 17627-49-5; 7786-64-3	14073-97-3; 21060-23-1	3391-87-5
REACH registration number[4]	Not REACH registered	01-2119983789-09-xxxx	Not REACH registered
Classification, according to EU CLP (EC 1272/2008)	**Harmonised classification:**		
	None available	None available	None available

[3] CAS RN relates to *trans*-menthone according to EFSA (2015).
[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. The REACH dossier has not been consulted for toxicity data.

Identifier / status	Isomenthones		
Name	Isomenthone	L-Isomenthone	D-Isomenthone
Synonym(s)	*cis*-Menthone 5-Methyl-2-(1-methylethyl) cyclohexanone 2-Isopropyl-5-methyl-cyclohexanone	*cis*-L-menthone (-)-Isomenthone (*2S,5S*-)-5-Methyl-2-(1-methylethyl) cyclohexanone	*cis*-D-menthone (+)-Isomenthone (*2R,5R*-)-5-Methyl-2-(1-methylethyl) cyclohexanone
CAS RN	491-07-6[5]; 36977-92-1	None identified	1196-31-2
REACH registration number[6]	Not REACH registered	Not REACH registered	Not REACH registered
Classification, according to EU CLP (EC 1272/2008)	Harmonised classification:		
	None available	None available	None available

In addition, the CAS RNs 10458-14-7[7] and 39037-52-3 appear to relate to mixtures of stereoisomers (i.e. mixtures of L- and D-menthone and L- and D-isomenthone) and were therefore considered relevant in this assessment.

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

Skin irritation

Human

An 8% solution of racemic menthone[8] was not irritating to a group of 25 subjects when applied to the skin under a closed patch for 48 hours (Kligman, 1973). [See also Skin sensitisation section.]

[5] CAS RN appears to relate to a mixture of D- and L-isomenthone, the racemic mixture (b) (4)

[6] 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. The REACH dossier has not been consulted for toxicity data.

[7] CAS RN relates to a mixture of diastereomers, approximately 25% of each (cited in EFSA, 2015).

[8] CAS RN not specified

Non-human

Mild irritation was reported after undiluted racemic menthone[9] was applied to the intact or abraded skin of rabbits under occlusion for 24 hours (Levenstein, 1973a).

Eye irritation

No substance-specific data were identified.

Other local effects

No substance-specific data were identified.

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation

No substance-specific data were identified.

Skin sensitisation

Human

A maximisation test was carried out on 25 subjects using an 8% solution of racemic menthone[10]. No sensitisation reactions were reported [no further details in citing source; the test procedure typically involves an initial induction phase of five 48-hour covered patch tests, followed 10-14 days later by a 48-hour covered challenge patch] (Kligman, 1973). [See also Skin irritation section.]

No sensitisation reactions occurred when three patients who had developed allergic dermatitis from contact with peppermint oil were patch tested with menthone[11] (Saito and Oka, 1990).

Non-human

No substance-specific data were identified.

Oral allergy/intolerance

No substance-specific data were identified.

INHALATION TOXICITY STUDIES

No substance-specific data were identified.

TOXICITY STUDIES – OTHER EXPOSURE ROUTES

Single dose toxicity

Human

No substance-specific data were identified.

[9] CAS RN not specified
[10] CAS RN not specified
[11] CAS RN not specified

Non-human

LD_{50} values[12] of 1600-1950 mg/kg bw have been reported for oral exposures of rats to menthone (CAS RN 89-80-5) (Igimi and Ide, 1974; Levenstein, 1973b).

A lower oral LD_{50} value of 500 mg/kg bw has been reported for menthone (CAS RN 89-80-5) in rats (Anon., undated), as well as an LDLo[13] of 600 mg/kg bw for intravenous injection of dogs, with effects in the latter species described as "cardiac: change in rate, and vascular: BP lowering not characterized in autonomic section" (Anon., 1953). [See also Cardiopulmonary effects section.]

A dermal LD_{50} value of 5000 mg/kg bw has been reported for racemic menthone[14] in rats (Levenstein, 1973a).

Subcutaneous administration of menthone [CAS RN not specified] to 10 male albino mice resulted in an LD_{50} value of 2180 mg/kg bw [no further details]. In the same study, groups of 10 male albino mice per dose were administered sodium hexobarbital intraperitoneally followed by subcutaneous application of 0 or 500 mg menthone/kg bw 5 minutes later. Menthone increased the sleep time by 46% (Wenzel and Ross, 1957).

Repeated dose toxicity

Human

No substance-specific data were identified.

Non-human

In a high-quality study, groups of 10 rats/sex received oral gavage doses of 0, 200, 400 or 800 mg/kg bw/day for 28 days[15] and the NOAEL[16] was reported as 400 mg menthone (CAS RN 89-80-5)/kg bw/day, based on increased kidney, spleen, liver and brain weights at the highest dose (Madsen *et al.*, 1986).

A NOAEL was not determined after groups of 30 female A/He mice received intraperitoneal injections of 100 or 250 mg menthone (CAS RN 89-80-5)/kg bw/injection approximately 3 times/week for 8 weeks[17] (19 injections providing total doses of 1900 or 4750 mg/kg bw; averaged daily doses of 34 or 85 mg/kg bw/day). There were no increases in the incidences of non-neoplastic lesions in the lung, liver, kidney, spleen, thymus, intestine, or salivary or endocrine glands (Stoner *et al.*, 1973). [See also Carcinogenicity and Cardiopulmonary effects sections.]

[12] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.
[13] Lethal Dose Low, i.e. "the lowest dose (lower than LD50) of a substance introduced by any route, other than inhalation, over any given period of time, in one or more divided portions and reported to have caused death in humans or animals".
[14] [CAS RN not specified but presumably 89-80-5]
[15] Incorrectly reported as a 28-week exposure in JECFA, 1999.
[16] No-observed-adverse-effect level.
[17] Incorrectly reported as a 24-week exposure in EFSA, 2015. Although the full study lasted 24 weeks, the animals were dosed for 8 weeks and observed for 16 weeks.

GENOTOXICITY

Expert group opinion

In its evaluation of secondary alicyclic saturated and unsaturated alcohols, ketones and esters containing secondary alicyclic alcohols, the EFSA CEF Panel[18] noted that "trans-Menthone [CAS RN 89-80-5] was genotoxic in an Ames test (Andersen and Jensen, 1984) and in a somatic mutation and recombination test (SMART) with *D. melanogaster* (Franzios *et al.*, 1997). The observed effects were not very pronounced. Further, trans-menthone is easily converted to menthol, which is estimated to be, overall, negative in genotoxicity tests". The conclusion was that "overall, the genotoxic potential of this group of flavouring substances cannot be fully assessed as it is now. However, the data available do not indicate a genotoxic potential and therefore do not preclude their evaluation via the Procedure" (EFSA, 2015).

Mammals (*in vivo*)

In a micronucleus test, groups of 5 mice/sex received an oral dose of L-menthone (CAS RN 14073-97-3) at 0, 500, 1000 or 2000 mg/kg bw. No micronucleus induction was seen in bone marrow cells 24 or 48 hours later (Scognamiglio *et al.*, 2010).

Mammalian cells (*in vitro*)

No substance-specific data were identified.

Micro-organisms

Menthone (CAS RN 89-80-5) was tested at concentrations up to 0.8 mg/plate in a bacterial reverse mutation (Ames) assay using *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537, with and without S9[19]. In the absence of metabolic activation, menthone was mutagenic in TA1537 at 32 mg/mL but not at higher concentrations, and there was a concentration-dependent increase in TA97 revertants (Andersen and Jensen, 1984).

Other

A 2-fold increase in mutation frequency was reported in a Somatic Mutation and Recombination Test using *Drosophila melanogaster* exposed "whole body" to menthone (CAS RN 89-80-5) at 1.3 µL/disk [1.2 mg/disk[20]] (Franzios *et al.*, 1997). According to the citing source (EFSA, 2015), the validity of this study is unclear.

CARCINOGENICITY

Human

No substance-specific data were identified.

Non-human

No high quality substance-specific carcinogenicity studies were identified.

[18] EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids.
[19] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.
[20] Assuming a density of 0.89 g/mL.

In a limited study, no neoplastic lesions were seen in the lung, liver, kidney, spleen, thymus, intestine, or salivary or endocrine glands after groups of 30 female A/He mice received 19 intraperitoneal injections of 100 or 250 mg/kg bw/injection (approximately 3 times/week for 8 weeks[21], providing total doses of 1900 or 4750 mg/kg bw/day) (Stoner *et al*., 1973). [Modern guidelines recommend the administration of several dose levels by a physiological route to groups of 50/sex for lifetime followed by histopathological examination of a comprehensive range of tissues and organs.] [See also Repeated dose toxicity and Cardiopulmonary effects sections.]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No substance-specific data were identified.

CARDIOPULMONARY EFFECTS[22]

An LDLo[23] of 600 mg/kg bw was reported for menthone (CAS RN 89-80-5) for intravenous injection of dogs, with effects described as "cardiac: change in rate and vascular: BP lowering not characterized in autonomic section" (Anon., 1953). [See also Single dose toxicity section.]

There were no increases in the incidences of lesions in the lung in mice injected intraperitoneally with 100 or 250 mg menthone (CAS RN 89-80-5)/kg bw/injection approximately 3 times/week for 8 weeks (Stoner *et al*., 1973). [See Repeated dose toxicity and Carcinogenicity sections for further details.]

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ChemIDplus powered by Toxnet, 2016 available at http://chem.sis.nlm.nih.gov/chemidplus/

[21] Incorrectly reported as a 24 week exposure in EFSA, 2015. Although the full study lasted 24 weeks, the animals were dosed for 8 weeks and observed for 16 weeks.
[22] Potential effects on the heart, blood vessels and/or respiratory tract.
[23] Lethal Dose Low, i.e. "the lowest dose (lower than LD50) of a substance introduced by any route, other than inhalation, over any given period of time, in one or more divided portions and reported to have caused death in humans or animals".

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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