(b) (4)

alpha-Terpineol

Toxicity monograph

October 2016

Prepared by:

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alpha-Terpineol

Toxicity monograph

INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of *alpha*-terpineol (CAS RN[1] 98-55-5; also covering CAS RNs 7785-53-7, 10482-56-1 and 8006-39-1), focussing on the inhalation route of exposure. Data on the inhalation of tobacco smoke containing the ingredient (if available) have not been included in this monograph.

EXPERTISE

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TOXICITY DATA SEARCH CRITERIA

Searches for toxicity data were restricted to the (b) (4) (see the Appendix for details) and the TOXNET system of databases and databanks (which includes Toxline (the toxicity subset of Medline), HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB). Since these searches could not necessarily be relied upon specifically to identify cardiopulmonary data, and to ensure all critical local and systemic inhalation data were identified, additional searches were conducted in PubMed tailored to identify such information. In relation to *alpha*-terpineol (CAS RN 98-55-5) and (L)-*alpha*-terpineol (CAS RN 10482-56-1) specifically, the EFSA (2015) and Bhatia *et al.* (2008a) reviews were used as the basis for the monograph. Limited additional searches were conducted in an attempt to identify critical data not included in these reviews. (b) (4) and Toxline were searched for more recent data since the 2008 and 2015 reviews and no date restriction was placed on searches in PubMed.

All searches were conducted in October 2016 using the CAS RN(s) and (in PubMed only) name identified below, as appropriate.

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

[1] Chemical Abstracts Service Registry Number.

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IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier / status				
Name	*alpha*-Terpineol (isomer unspecified)	(D)-*alpha*-Terpineol	(L)-*alpha*-Terpineol	Terpineol
Synonym(s)	*alpha*-Terpinenol *p*-Menth-1-en-8-ol *alpha*,*alpha*,4-Trimethyl-3-cyclohexene-1-methanol	(R)-(+)-*alpha*-Terpinenol (R)-(+)-*p*-Menth-1-en-8-ol (1R)-*alpha*,*alpha*,4-Trimethyl-3-cyclohexene-1-methanol	(S)-(-)-*alpha*-Terpinenol (S)-(-)-*p*-Menth-1-en-8-ol (S)-*alpha*,*alpha*,4-Trimethyl-3-cyclohexene-1-methanol	Terpinenol Mixture of *p*-menthenols
CAS RN	98-55-5	7785-53-7	10482-56-1	8006-39-1[3]
REACH registration number[4]	01-2119980717-23-0000	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	None available

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

Skin irritation

Human

No skin irritation was observed when undiluted *alpha*-terpineol (CAS RN 98-55-5) was applied, under occlusion, to the skin of 30 volunteers for periods of 15 minutes up to 4 hours (Basketter *et al.*, 2004).

[3] CAS RN 8000-41-7 is for a mixture of *alpha*-, *beta*-, *gamma*- and *delta*-terpineol. Its inclusion as a search term might identify data of relevance to this monograph.

[4] REACH registration numbers are substance and company specific. As the dossier lists only one registrant, there is only one registration number to included here, from data disseminated on the ECHA 'registered substance' website. The REACH dossier has not been consulted for toxicity data.

Non-human

alpha-Terpineol (CAS RN 98-55-5) was applied to the clipped skin of female rabbits (3-4/ group) for 4 hours under semi-occlusion. No irritation was observed when tested at 50% in diethyl phthalate, however slight to moderate irritation was seen when applied undiluted (cited in Bhatia *et al.*, 2008b).

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

In a 48-hour closed-patch test, positive skin sensitisation reactions were produced in two out of 1200 Italian dermatitis patients (0.17%) treated with *alpha*-terpineol (CAS RN not specified) at 5% in petrolatum (Santucci *et al.*, 1987)

Non-human

alpha-Terpineol (CAS RN not specified) produced no sensitisation reactions in a closed epicutaneous test in which guinea pigs were tested at a concentration of 10%. The test procedure involved an initial induction phase of six alternate day 48-hour patch tests. Following a 14-day rest period, a 48-hour challenge patch was applied (Ishihara *et al.*, 1986).

In a popliteal lymph node assay 10 female rats were subcutaneously injected with *alpha*-terpineol (CAS RN 98-55-5) at 10% in dimethylsulphoxide (5 mg/paw). Although individual positive responses were produced in two animals, the investigators classified *alpha*-terpineol as negative for skin sensitisation since the weight and cellularity indices were below 2 and 5, respectively (Friedrich *et al.*, 2007).

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.

Non-human

An oral LD_{50} value[5] for *alpha*-terpineol (CAS RN 98-55-5) of 2830 mg/kg bw was reported for mice following gavage administration (Yamahara *et al.*, 1985).

Following intraperitoneal injection LD_{50} values for *alpha*-terpineol (CAS RN 98-55-5) of 895 and 800 mg/kg bw were reported for male and female rats respectively and following intramuscular injection an LD_{50} value of 200 mg/kg bw was reported for mice (cited in Bhatia *et al.*, 2008b).

Repeated dose toxicity

Human

No substance-specific data were identified.

Non-human

A/He mice received 24 intraperitoneal injections of *alpha*-terpineol (CAS RN 98-55-5) in tricaprylin over a 20 week period and the maximum tolerated dose was determined to be 400 mg/kg bw/injection (Stoner *et al.*, 1973).

GENOTOXICITY

Mammals (*in vivo*)

No substance-specific data were identified.

Mammalian cells (*in vitro*)

In three mouse lymphoma assays, in L5178Y cells, no mutagenicity was observed following treatment with *alpha*-terpineol (CAS RN 98-55-5) at up to 0.5 mg/mL without S9[6] and up to 0.7 mg/mL with S9 (cited in EFSA, 2015).

Micro-organisms

No mutagenicity was detected in four bacterial reverse mutation (Ames) assays with *alpha*-terpineol (CAS RN 98-55-5), including one spot test, at various concentration ranges up to 10 mg/plate in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538. Tests were conducted with and without S9 (cited in EFSA, 2015). In another study, a dose-related weak mutagenic response was detected with *alpha*-terpineol (CAS RN 98-55-5) in *S. typhimurium* strain TA102, but not in strains TA97a, TA98 and TA100, when tested with and without S9 at up to 2.5 mg/plate (Gomes-Carneiro *et al.*, 1998).

A rec assay for DNA damage[7] in *Saccharomyces cerevisiae* conducted with *alpha*-terpineol (CAS RN 98-55-5) [metabolic activation not specified] did not show any genotoxic effects (Oda *et al.*, 1979).

[5] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.
[6] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.
[7] An indicative test, based on DNA repair.

CARCINOGENICITY

No substance-specific data were identified.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No substance-specific data were identified.

CARDIOPULMONARY EFFECTS[8]

No substance-specific data were identified.

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[8] Potential effects on the heart, blood vessels and/or respiratory tract.

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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
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