Menthone and isomenthone: Human health tier II assessment

29 June 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R,5S)-rel-	89-80-5
Cyclohexanone, 5-methyl-2-(1-methylethyl)-, cis-	491-07-6
Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2S-trans)-	14073-97-3

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using

Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are menthane monoterpenoids with a structure consisting of the cyclohexanone ring with a methyl group and a 2-methyl-propyl group at the 1 and 4 ring position, respectively. The chemicals have two asymmetric carbon centres and, exist in two diastereomeric forms, each with two enantiomers. The isomers with the methyl and isopropyl groups on opposite sides (trans-configuration) are generally termed menthones. The isomers with the methyl and isopropyl groups on the same side (cis-configuration) are termed isomenthones. The most common isomer in nature is menthone (2S,5R) (CAS No. 14073-97-3).

The isomers assessed in this report are:

- CAS No. 89-80-5 refers to menthone enantiomers (2R,5S or 2S, 5R)
- CAS No. 14073-97-3 refers to menthone (2S,5R)
- CAS No. 491-07-6 refers to isomenthone enantiomers (2R,5R or 2S,5S)

The chemicals are structurally similar, with likely similar metabolic and toxicity profiles. The chemical also have common uses including flavouring, perfumes and fragrances.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses were identified through Galleria Chemica; the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier; Substances and Preparations in the Nordic countries (SPIN) database; US Environmental Protection Agency (EPA) Chemical and Product Categories (CPCat); the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary and Cosmetic Ingredients); and Cosmetic Ingredients and Substances (CosIng) database.

The chemicals may have cosmetic uses in perfumes and personal care products.

The chemicals (CAS No. 491-07-6 and 89-80-5) have reported functions as skin protectants (Personal Care Products Council).

The chemicals are listed on the IFRA transparency list of fragrance ingredients (IFRA, 2017).

The chemicals were not reported as being used in cosmetic products in the US (CIUCUS, 2011).

The chemicals may have:

- domestic uses in air care and cleaning products;
- commercial uses in polishes and wax blends as well as in paints, lacquers and varnishes; and
- site-limited uses in formulation of products.

The chemicals may also be used as flavourings in tobacco products and e-cigarettes.

The chemicals may have non-industrial uses in pharmaceuticals and as flavouring in food and beverages.

Restrictions

Australian

No restrictions for industrial use have been identified for the chemicals in Australia.

The chemicals have restrictions for their non-industrial uses in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018 as excipients in medicines (TGA, 2018) at certain concentrations depending on their use as a flavour or a fragrance:

Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.

- If used in a flavour, the total flavour concentration in a medicine must be no more than 5 %.
- If used in a fragrance, the total fragrance concentration in a medicine must be no more than 1 %.

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

The nomenclature for menthones is inconsistent and in many publications the CAS No. is not reported. When no CAS No. is available the nomenclature from the publication in question will be used.

Based on the available information (Scifinder), it is assumed that:

- l- and (–)-menthone refers to menthone (2S,5R, CAS No. 14073-97-3);
- d- and (+)-menthone refers to menthone (2R,5S; CAS No. 3391-87-5);
- l- and (–)-isomenthone refers to isomenthone (2S,5S; CAS No.18309-28-9); and
- d- and (+)-isomenthone refers to (2R,5R; CAS No. 1196-31-2).

Unspecified enantiomers or mixes of enantiomers are generally referred to by combining the symbols dl and ±. As an example, the mixture of menthone isomers (2R,5S and 2S,5R; CAS No. 89-80-5) and are often referred to as dl or (±)-menthone (Scifinder).

Where limited or no data are available for the chemicals, hazard information for the structurally related menthol (CAS No. 89-78-1 or 2216-51-5) or menthone glycerin acetal (CAS No. 63187-91-7) will be used to support the assessment conclusions. Menthol is an alcohol analogue of the chemicals and a metabolite of menthone (refer to ***Toxicokinetics*** section). Menthone glycerine acetal is a synthetic derivative of menthone.

Toxicokinetics

There are limited toxicokinetic data available for menthone.

Absorption

The chemicals are small lipophilic substances with log Kow values below 5. Therefore the chemicals are expected to be orally bioavailable (Lipinski et al., 2001).

The chemicals are expected to be absorbed through the skin. In an in vitro skin permeation study in heat separated human epidermis (HSHE), the apparent permeability coefficient (P_{app}) was determined for the chemical isomenthone. Isomenthone had a higher P_{app} compared to other terpenes included in the study (limonene and linalool) which are known to be absorbed through skin (NICNASa; NICNASb).

In a rat study, the dermal absorption of menthol was 3 % under occlusion and 1 % without occlusion (OARS, 2014). No further study details are available.

Distribution

No distribution data are available for the menthones. The chemicals are expected to be systemically available following absorption due to their lipophilicity.

Metabolism

The menthones in this group are expected to be reduced to their corresponding secondary alcohol (menthol) and conjugated with glucuronic acid.

In rabbits (8/sex/chemical) treated with 3 g of the chemicals l-menthone or d-isomenthone orally in water, about 30-40 % of the chemical l-menthone was metabolised to glucuronidated hydroxy-derivatives in 48 hours. Approximately 10-15 % of the l-menthone was reduced to d-neomenthol. No quantitative data was obtained for the metabolism of d-isomenthone. However, it was concluded that at least part of the chemical was reduced to d-isomenthol (Williams et al., 1940).

Menthone (referred to as (–)-menthone) was metabolised in human liver microsomes to (+)-neomenthol and 7-hydroxymenthone (Miyazawa et al, 2006).

Simulation of skin metabolism in the OECD Toolbox suggest that menthol is metabolised to menthone in the skin (OECD Toolbox).

Excretion

The glucuronidated metabolites are expected to be mainly excreted via urine (Williams et al., 1940).

Acute Toxicity

Oral

The chemicals are expected to have low acute toxicity based on a guideline acute oral toxicity study using isomenthone with median lethal dose (LD50) level >2000 mg/kg bw in male and females rats. Hazard classification is not warranted.

In an oral acute toxicity study according to Organisation of Economic Co-operation and Development (OECD) test guideline (TG) 401, Wistar rats (5/sex/dose) were orally treated (gavage) with 1000, 1414, or 2000 mg/kg bw of isomenthone (CAS No. 491-07-6) and observed for 14 days. Observed sub-lethal effects included hunched posture, lethargy, ataxia, increased lacrimation, piloerection, splayed or tiptoe and ptosis. No mortality was observed in the low and mid-dose groups. Two females and one male from the high-dose group died within one or two days after dosing. An oral median lethal dose (LD50) of 2119 mg/kg bw was extrapolated for females (REACHa; REACHb).

The following LD50 values were reported for menthone (CAS No. 89-80-5) in rats (no further details are available for these studies):

- 1953 mg/kg bw based on a reported value of 2.18 mL/kg bw and a density of 0.89 g/cm^3 (Opdyke, 1976); and
- 500 mg/kg bw (ChemIDPlus).

Dermal

The chemicals are expected to have low acute dermal toxicity based on the dermal LD50 values of >5000 mg/kg bw in rabbits.

In an acute dermal toxicity study, 4 rabbits received a single dermal application of isomenthone (CAS No. 491-07-6) at 5000 mg/kg bw. No mortalities occurred within 14 days after application. All animals displayed erythema at the application area (Opdyke, 1976a). Similar results were obtained for menthone (CAS No. 89-80-5) (Opdyke, 1976b). No further study details are available.

Inhalation

No data are available for the chemicals.

Corrosion / Irritation

Skin Irritation

Based on the available in vitro guideline study, the chemicals may be skin irritants, warranting hazard classification (refer to ***Recommendation*** section).

In an in vitro study performed according to OECD TG 439, 10 µL of a mix of 76 % menthone and 23.5 % isomenthone was applied to reconstructed human epidermis for 15 min. The mean tissue viability was 10.4 %. Substances that reduce viability to less than 50 % are classified as irritants. Therefore, the chemicals are considered skin irritants (REACHa; REACHc).

Isomenthone or racemic menthone (neat; CAS Nos not specified) were mildly irritating when applied to intact or abraded rabbit skin under occlusion for 24 h (Opdyke, 1976a; Opdyke 1976b). No further study details are available.

Eye Irritation

The chemicals may be slightly irritating to eyes. The effects are not sufficient to warrant hazard classification.

In an OECD TG 405 eye irritation study, 0.1 mL of isomenthone was applied to one eye of 4 rabbits (strain and sex not specified) while the other eye served as the control. The irritation scores at the 3 different time-points (24, 48 and 72 h) were combined and averaged. The average irritation scores for the 4 individual rabbits were 0, 0, 0.2, 0 for the cornea; 0, 0, 0, 0 for the iris; 1.33, 1, 0.67, 1 for conjunctivae redness and 0, 0.33, 0.33, 0.33 for chemosis. After 7 days the irritation had completely resolved (REACHc).

In an in vitro study conducted according to OECD TG 437, 3 bovine corneas isolated from donor cattle were treated with an undiluted mix of menthone and isomenthone (proportions not specified) for 10 min followed by washing with saline. The mixture caused a slight increase in corneal opacity but permeability effects were not observed. The calculated mean irritation score was 1.76 (the threshold for corrosivity or severe irritancy is > 55.1). Therefore, the chemicals were not considered irritating to the eyes (REACHc).

Observation in humans

Isomenthone and racemic menthone produced no irritation in 48 h closed patch-test in humans at 8 % of the chemicals in petrolatum (Opdyke, 1976a; Opdyke 1976b). No further study details are available.

Sensitisation

Skin Sensitisation

Ambiguous sensitisation potential was reported in local lymph node assays (LLNAs) for the chemicals. The chemicals are not expected to be potent skin sensitisers based on the weight of evidence including:

- available experimental data on skin sensitisation and skin irritation
- information from a human repeat insult patch test (HRIPT) (refer to ***Observation in humans*** section)
- structural analogue information
- predictions from four (quantitative) structure activity relationship (Q)SAR) models.

In a LLNA performed in accordance with OECD TG 429, female CBA/J mice (4/dose) received topical applications of 25, 50 or 100 % (v/v) of a mix of menthone and isomenthone (proportions not specified) in acetone/olive oil on three consecutive days. The reported stimulation indices (SI) were 0.9, 4.3 and 3.2 for concentrations of 25, 50 and 100 % respectively. The reported concentration producing a three-fold increase in lymphocyte proliferation (EC3) was 40.6 % indicating weak sensitisation potential (REACHb). No clear dose response relationship was reported.

In an LLNA performed in accordance with OECD TG 429, female CBA/J mice (4/dose) received topical applications of 25, 50 or 100 % (v/v) of menthone (CAS No. 14073-97-3) in acetone/olive oil on three consecutive days. The reported SI were 1.3, 2.5 and 9 for concentrations of 25, 50 and 100 % respectively. The reported EC3 was 54.2 % indicating weak sensitisation potential (REACHc).

False positives in the LLNA may be due to non-specific skin irritation, rather than chemical sensitisation (Basketter et al., 1998). The chemicals are irritating to the skin (see ***Corrosion/Irritation*** section).

Structural analogue information

A structural analogue of the chemicals, menthone glycerine acetal (CAS No. 63187-91-7) was negative in a guinea pig maximisation test conducted according to OECD TG 406. The female Himalayan albino guinea pigs (30), were intradermally induced using 2 % (w/w) of menthone glycerine acetal in polyethylene glycol followed by topical induction at 100 %. Two weeks later, the test animals were challenged by applying at 0, 5, 10, 24 % of the chemical in polyethylene glycol. No positive reactions were observed during the epidermal challenge phase (REACHf).

The structural analogue of menthone, menthol, is predicted to be metabolised to menthone by enzymes in the skin (OECD Toolbox). Menthol was negative in two animal sensitisation tests.

In an LLNA performed in accordance with OECD TG 429, female CBA/Ca mice (4/dose) received topical applications of 1, 10 or 30 % (v/v) of menthol (CAS No. 2216-51-5) in acetone on three consecutive days. The reported SI were 1.3, 1.8 and 0.9 for concentrations of 1, 10 and 30 % respectively. Because all SI values were below 3, an EC3 value could not be determined (REACHg).

In a Buehler test performed in accordance with OECD TG 406, 20 Hartley guinea pigs were exposed to the menthol at 25 % w/v in ethanol : diethylphtalate (1:1) once weekly for three weeks. Challenge with 25 % (w/v) of the chemical produced no dermal responses (REACHg).

Quantitative Structure-Activity Relationship (QSAR) information

The QSAR modelling for skin sensitisation using the OECD QSAR Toolbox (version 3.4) indicated that there were no alerts for skin sensitisation for either the parent chemical or its metabolites (skin metabolism and autoxidation).

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.0 was utilised to estimate the skin sensitisation potential of the chemicals. The chemicals did not match any structural alerts or examples for skin sensitisation or contained any unclassified or misclassified features. Therefore, the chemicals were predicted non-sensitisers.

Negative in domain predictions were obtained for the chemicals for allergic contact dermatitis in guinea pigs and humans using the battery approach in the Danish QSAR database.

Skin sensitisation was predicted using OASIS–TIMES (tissue metabolism simulator) software (version 2.27.13). The chemicals and their metabolites were predicted non-sensitisers (91 % in domain).

Observation in humans

Isomenthone and racemic menthone produced no sensitisation reactions in a Kligman maximisation test in 25 volunteers at 8 % of the chemical in petrolatum (Opdyke, 1976a; Opdyke 1976b). No further study details are available.

Repeated Dose Toxicity

Oral

Limited data are available for the chemicals. However, based on the available information, the chemicals are not expected to cause serious damage to health from repeated oral exposure.

The menthones are generally regarded as safe (GRAS) for use as flavour ingredients by the US Food and Drug Administration, reflecting the low level of concern regarding their potential for long-term toxicity via the oral route (Adams et al., 1996). Furthermore, the Joint Food and Agriculture Organization of the United Nations (FAO) and World Health Organisation (WHO) Expert Committee on Food Additives (JECFA) indicated that the menthone was not a safety concern at the current daily intake levels of 17 µg/kg bw/day in Europe, and 42 µg/kg bw/day in USA (JECFA, 1999).

In a 4 week oral gavage study, Wistar rats (10/sex/dose) were treated with racemic menthone (97 % purity) in soybean oil at 0, 200, 400 or 800mg/kg bw/day, 5 days a week for 4 weeks. In females receiving 800 mg/kg bw/day the dose was halved after 19 days due to signs of toxic effects, resulting in an average dose of 671 mg/kg bw/day. No treatment-related mortality was observed. Reduced food consumption accompanied by reduced body weight, significantly increased relative organ weights (kidney, spleen, liver and brain) and altered blood parameters such as creatinine, alkaline phosphatase and bilirubin were reported at the highest dose. All the above described effects were dose-dependent. No histological changes were observed in the liver. Histological examination of the brain revealed, dose-related cyst-like spaces in the white matter of the cerebellum in the two highest dose groups. No clinical symptoms were associated with this observation (Madsen et al., 1986). Upon re-examination of the brain histology by the Flavor and Extract Manufacturers Association of the United States (FEMA) expert panel, the lesions were considered artefacts due to inadequate tissue fixation procedures (Adams, 1997). A no observed adverse effect level (NOAEL) of 400 mg/kg bw/day can be deducted from the study based on effects on body weight, organ weights, and blood parameters in both males (800 mg/kg bw/day) and females (average dose of 671 mg/kg bw/day) receiving the highest dose.

The low chronic toxicity via oral route is supported by the structurally related menthol (CAS No. 89-78-1) (OECD, 2003). In the study, F344 rats (10/sex/dose) male rats received 59, 114, 231, 472 or 937 mg/kg bw/day and female rats received 67, 142, 285, 521 or 998 mg/kg bw/day of d/l-menthol in the feed for 13 weeks. The only effect noted was a slight increase in the severity of spontaneous interstitial nephritis in males at the highest dose. This finding was considered of questionable significance since it is particularly common in males of this rat strain. Therefore the reported NOAEL was 998 mg/kg bw/day for males and 937 mg/kg bw/day for females (OECD, 2003).

Dermal

No data are available for the chemicals.

Inhalation

No data are available for the chemicals.

Genotoxicity

Based on the weight of evidence analysis of the available information, the chemicals are not likely to be genotoxic. Menthone (CAS No. 14073-97-3) was negative in an in vivo micronucleus test indicating lack of in vivo genotoxicity. Additionally, most mammalian or bacterial in vitro tests and (Q)SAR predictions were negative. However, menthone (CAS No. 89-80-5) was genotoxic in a single study in two bacterial strains and in a Somatic Mutation and Recombination Test (SMART) in *Drosophila*.

In vitro studies

The chemicals were negative in several in vitro assays (REACHa–e):

- point mutation studies in *Salmonella typhimurium* strains TA98, TA100, TA 1535, TA1537 and *Escherichia coli* WP2 at concentrations up to 5000 µg/plate, with and without metabolic activation;

- point mutation studies in Chinese hamster lung fibroblasts (V79) cells at concentrations up to 1280 µg/mL with and without metabolic activation; and
- chromosome aberration assay in human lymphocytes at concentrations up to1543 µg/mL for 4 h with and without metabolic activation or 20 h with metabolic activation.

Menthone (CAS No. 89-80-5) was positive in one in vitro assay in *S. typhimurium* in strains TA1537 at concentration up to 32 µg/plate and in TA97 at doses up to 160 µg/plate, without metabolic activation. With metabolic activation the chemical was negative in both strains (REACHd).

In vivo studies

Menthone (CAS No. 14073-97-3) was negative in an in vivo micronucleus test with no significant increase in polychromatic erythrocytes after oral treatment of Naval Medical Research Institute (NMRI) mice (12/sex/dose) with a single dose of the chemical at 500, 1000 and 2000 mg/kg bw for 24 h or 2000 mg/kg bw for 48 h at (REACHc).

Menthone (CAS No. 89-80-5) was positive in a SMART assay in *Drosophila.* A two-fold increase in mutation frequency as compared to control was observed at a dose equivalent to the LD50. In the same study the chemical was considered not recombinogenic (Franzios et al., 1997).

Quantitative Structure-Activity Relationship (QSAR) information

Genotoxicity was predicted using OASIS–TIMES (tissue metabolism simulator) software (version 2.27.13). The chemicals and their metabolites were predicted to be non-genotoxic (Ames mutagenicity). All predictions were in domain of the model.

The knowledge based expert system DEREK Nexus version 6.0.0 was utilised to estimate the genotoxicity potential of the chemicals. The chemicals did not match any structural alerts or examples for bacterial in vitro mutagenicity, or contain any unclassified (not found in the reference set) or misclassified features (found in non-alerting mutagens) . Therefore, the chemicals were predicted to be inactive in the Ames mutagenicity test.

Carcinogenicity

Based on the limited available data and the long history of exposure to menthone and menthol through food, the chemicals are not expected to be carcinogenic.

In a carcinogenicity study in mice (strain A pulmonary tumour system; Stoner et al., 1973) female mice (20/dose) were given intraperitoneal injections of menthone at doses of 1900 or 4750 mg/kg bw/day three times per week for eight weeks. The animals were observed for an additional 16 weeks. There were no increases in neoplastic or non-neoplastic lesions in the lung, liver, kidney, spleen, thymus, intestine, or salivary or endocrine glands in the treated animals compared to control animals.

Carcinogenicity studies using menthol, also indicate that the chemicals are not carcinogenic.

In a 103 week study, Fischer 344 (F344) rats (50/sex) received 3750 or 7500 ppm racemic menthol (CAS No. 89-78-1) in the diet, equivalent to approximately 188 and 375 mg/kg bw/day of the chemical, and B6C3F1 mice received 2000 and 4000 ppm, equivalent to approximately 334 and 667 mg/kg bw/day. In rats, no neoplastic lesions were found in any organs. In male mice, there was a slight increase in hepatocellular carcinoma and an increased incidence of alveolar/bronchial adenoma or carcinoma in females. Neither of these changes was statistically significant when compared to controls (OECD, 2003).

Reproductive and Developmental Toxicity

No specific reproductive studies have been undertaken with menthone or the closely related chemical menthol.

However, the long history of human exposure to the chemicals in food have not indicated any reproductive or developmental toxicity.

Furthermore, in repeated dose toxicity and carcinogenic studies in rats with menthol (refer to ***Repeated dose toxicity*** and ***Carcinogenicity*** sections) no histopathological changes were observed in any of the reproductive organs (OECD, 2003).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is skin irritation.

Public Risk Characterisation

Considering the range of domestic, cosmetic and personal care products that may contain these chemicals, the main route of public exposure is expected to be through the skin and inhalation from products applied as aerosols, and potential oral exposure from lip and oral hygiene products.

Dermal application of products containing the chemical at high concentrations may give rise to irritation. However, concentrations in products are expected to be relatively low.

Although the public could be exposed to the chemicals through potential cosmetic and domestic uses, given the expected low concentrations in products and low hazard of the chemicals, the chemicals are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, dermal exposure of workers to the chemicals may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Given the critical local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in HCIS (refer to ***Recommendation*** section).

NICNAS Recommendation

Assessment of these chemicals are considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Not Applicable	Causes skin irritation - Cat. 2 (H315)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures to minimise the risk from dermal exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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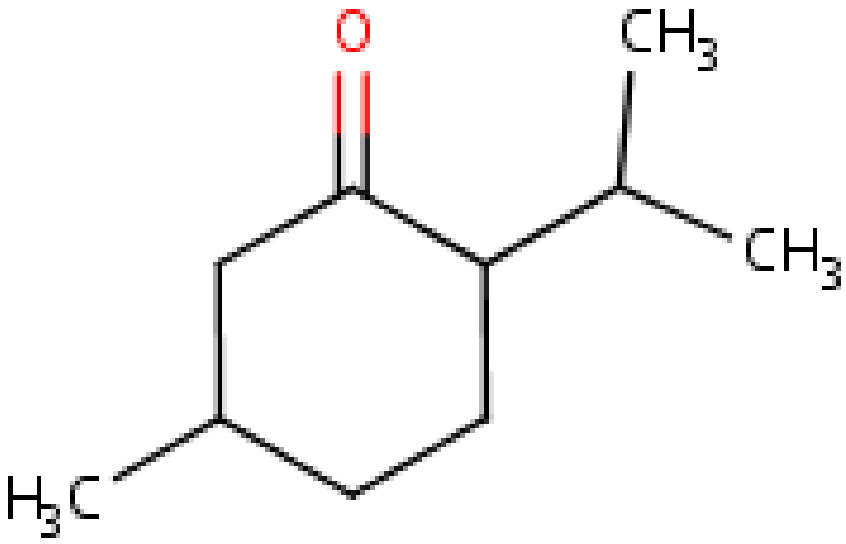
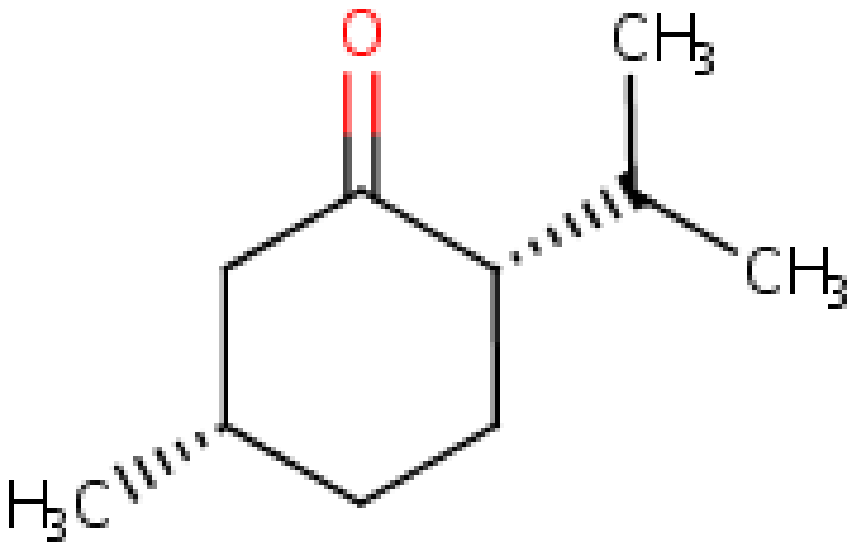
Last Update 29 June 2018

Chemical Identities

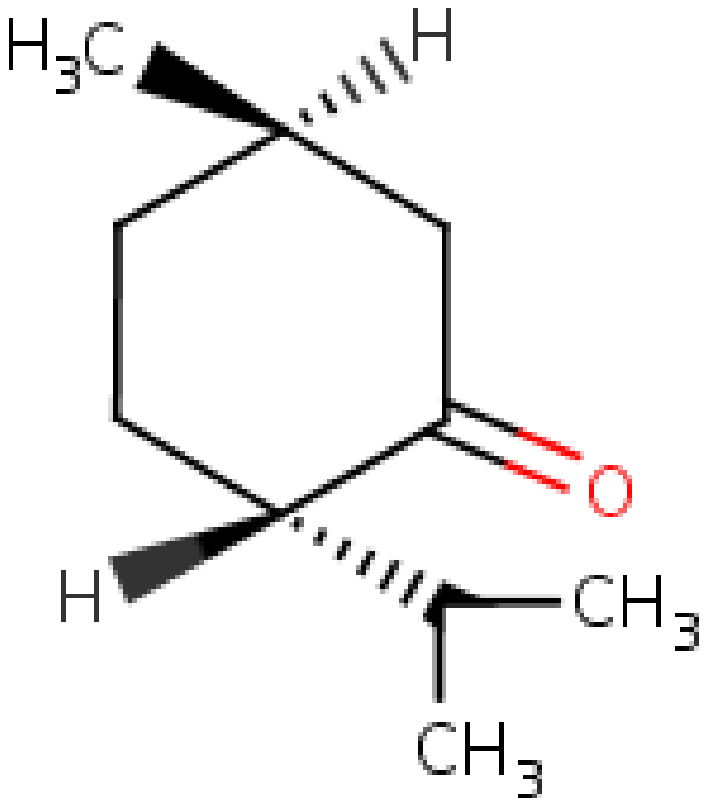
Chemical Name in the Inventory and Synonyms	**Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R,5S)-rel-** cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2R, 5R)-rel- menthone p-menthan-3-one (dl)-menthone trans-menthone
CAS Number	89-80-5
Structural Formula	

	
Molecular Formula	C10H18O
Molecular Weight	154.25

Chemical Name in the Inventory and Synonyms	**Cyclohexanone, 5-methyl-2-(1-methylethyl)-, cis-** cyclohexanone, 5-?methyl-?2-?(1-?methylethyl)?-?, (2R,?5R)?-?rel- isomenthone p-menthan-3-one dl-isomenthone (±)-isomenthone
CAS Number	491-07-6
Structural Formula	

	
Molecular Formula	C10H18O
Molecular Weight	154.25

Chemical Name in the Inventory and Synonyms	**Cyclohexanone, 5-methyl-2-(1-methylethyl)-, (2S-trans)-** (-)-menthone (2S,5R)-(-)-menthone l-menthone
CAS Number	14073-97-3
Structural Formula	

	
Molecular Formula	C10H18O
Molecular Weight	154.25

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