Pulegone and related substances: Human health tier II assessment

27 October 2017

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, acetate	89-49-6
Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, [1R-(1.alpha.,2.beta.,5.alpha.)]-	89-79-2
Cyclohexanone, 5-methyl-2-(1-methylethylidene)-, (R)-	89-82-7
Benzofuran, 4,5,6,7-tetrahydro-3,6-dimethyl-	494-90-6
Cyclohexanol, 5-methyl-2-(1-methylethenyl)-	7786-67-6
Oils, pennyroyal, Hedeoma pulegioides	8007-44-1
Oils, pennyroyal, Mentha pulegium	8013-99-8
Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, formate, [1R-(1.alpha.,2.beta.,5.alpha.)]-	10588-15-5
Cyclohexanone, 5-methyl-2-(1-methylethylidene)-	15932-80-6

Chemical Name in the Inventory	CAS Number
Cyclohexanone, 5-methyl-2-(1-methylethenyl)-, trans-	29606-79-9
Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, propanoate	39850-64-1
Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, (1.alpha.,2.beta.,5.alpha.)-(.+-.)-	50373-36-9
Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, acetate, [1R-(1.alpha.,2.beta.,5.alpha.)]-	57576-09-7
Terpenes and terpenoids, pennyroyal oil	68917-60-2
Pennyroyal, extracts (Spain-Morocco)	90064-00-9

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 chemical, cyclohexanone, (R)-5-methyl-2-(1-methylethylidene) (CAS No. 89-82-7) along with its isomers and derivatives are assessed together in this report because of their similarities in chemical structure and metabolic profile (see **Toxicokinetics** section).

Pennyroyal oils extracted from the leaves of *Mentha pulegium* (CAS No 8013-99-8; containing 60–90 % of d-pulegone) and *Hedeoma pulegoides* (CAS No. 8007-44-1; containing 30 % d-pulegone) were also included in this report (Anderson et al., 1996; IARC, 2016; HSDB). The toxicity of these oils is expected to be largely due to pulegone. Due to the natural source of pulegone, unspecified pulegone is expected to be predominantly the d-isomer.

The following synonyms and their corresponding CAS numbers will be used in this assessment:

- d-pulegone: CAS No. 89-82-7
- pulegone: CAS No. 15932-80-6
- menthofuran: CAS No. 494-90-6
- isopulegyl acetate: CAS No. 57576-09-7 and CAS No. 89-49-6
- isopulegol: CAS No. 50373-36-9, CAS No. 89-79-2, and CAS No. 7786-67-6
- isopulegyl formate: CAS No. 10588-15-5
- isopulegone: CAS No. 29606-79-9
- isopulegyl propenoate: CAS No. 39850-64-1
- mentha pulegium extracts: (CAS No. 90064-00-9)
- mentha pulegium terpenes: (CAS No. 68917-60-2)

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the chemicals in this group.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the Good Scents Company; Bhatia et al., 2008; Devesa et al., 2004; various international assessments including the World Health Organisation (WHO), 2001; National Toxicology Program (NTP), 2011; the International Agency for Research on Cancer (IARC), 2016; and International Fragrance Agency (IFRA).

The following chemicals have cosmetic use in fragrances and perfumes:

- isopulegol acetate (CAS No. 57576-09-7)
- isopulegyl formate (CAS No. 10588-15-5)
- d-pulegone (CAS No. 89-82-7)
- menthofuran (CAS No. 494-90-6)
- isopulegol (CAS No. 7786-67-6 and 89-79-2)
- mentha pulegium extracts (CAS No. 90064-00-9)
- mentha pulegium terpenes (CAS No. 68917-60-2)

The following chemicals have domestic uses including:

- d-pulegone (CAS No. 89-82-7) and menthofuran (CAS No. 494-90-6)—in washing detergents and oral hygiene products; and
- isopulegol (CAS No. 7786-67-6 and 89-79-2)—in washing and cleaning products, air care products, polishes and waxes, and disinfectants.

The following chemicals have non-industrial uses including:

- d-pulegone (CAS No. 89-82-7) and menthofuran (CAS No. 494-90-6)—in dental products, as flavouring agents, as a component in herbal medicines, and in the manufacture of food products; and
- mentha pulegium extracts (CAS No. 90064-00-9) in herbal medicines at up to 4.4 %.

Restrictions

Australian

The chemicals, d-pulegone (CAS No. 89-82-7) and pennyroyal oil (CAS No. 8007-44-1 and CAS No. 8013-99-8), are listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 6 'except in preparations containing 4 per cent or less of d-pulegone' (SUSMP, 2017).

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2017).

The chemical, pulegone, is listed in the *Australia New Zealand Food Standards (FSANZ) Code* (FSANZ, 2014) in:

- *Schedule 19 — Maximum levels of contaminants and natural toxicants*.

The maximum level of pulegone in confectionary is 350 mg/kg as a natural toxicant.

- *Schedule 24 — Restricted plants and fungi*.

Pulegone – Specie: *Hedeoma pulegioides;* Common names: American pennyroyal and white snakeroot oil; and

Pulegone – Specie: *Mentha pulegium* oil; Common name: European pennyroyal oil.

International

Pulegone (CAS No. 89-82-7) is listed in Annex III of the REACH regulation based on suspected carcinogenicity (Annex III).

The Cosmetic Ingredient Review (CIR) Expert Panel has identified that the concentration of pulegone in cosmetic formulations should not exceed 1 % (Nair, 2001).

Pulegone is listed in Annex III (Presence of certain substances) of the EC Regulation No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods:

- Part A: Substances which shall not be added as such to food.
- Part B: Maximum levels of certain substances, naturally present in flavourings and food ingredients with flavouring properties, in certain compound food as consumed to which flavourings and/or food ingredients with flavouring properties have been added:
  - mint/peppermint—containing confectionery, except micro breath freshening confectionery—maximum level of 250 mg/kg
  - micro breath freshening confectionery—maximum level of 2,000 mg/kg
  - chewing gum - maximum level of 350 mg/kg
  - mint/peppermint—containing non-alcoholic beverages—maximum level of 20 mg/kg
  - mint/peppermint—containing alcoholic beverages—maximum level of 100 mg/kg.

Pulegone is not permitted as a synthetic flavouring agent in the United States (IARC, 2016).

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 chemicals in this group are interrelated by a complex set of metabolic transformations (see **Toxicokinetics** section). This results in the production of the ultimate toxic products, including pulegone and menthofuran, regardless of the original chemical

identity.

Toxicokinetics

There are various metabolic pathways identified for pulegone in rodents. Pulegone is reduced to its corresponding alcohol, and excreted or undergoes allylic oxidation to its 9-hydroxy derivative, which cyclises to menthofuran (EFSA, 2005; IARC, 2016; da Rocha, 2012). In humans, ingestion of pulegone yielded a trace amount of menthofuran (da Rocha, 2012).

Metabolic pathways for the other chemicals in this group include: hydrolysis of isopulegyl acetate (CAS No. 57576-09-7 and 89-49-6) to isopulegol and acetic acid; conjugation and excretion of isopulegol (CAS No. 50373-36-9, 89-79-2 and 7786-67-6) as a glucuronide; reversible oxidation of isopulegol to isopulegone, and reversible isomerisation of isopulegone to pulegone (WHO, 2001).

The chemicals in this group have a range of similar metabolic products and the levels excreted in the urine are proportional to the administered dose. Therefore, the isomers and derivatives of d-pulegone are expected to have similar ultimate toxic metabolites (WHO, 2001; EFSA, 2005; IARC, 2016; da Rocha, 2012).

Male and female Fischer (F344) rats (n=4–8/group) were administered single or multiple doses of radiolabelled d-pulegone by gavage at doses of 8 or 80 mg/kg bw in corn oil and via intravenous injection at doses of 0.8 mg/kg in a mixture of water, Emulphor and ethanol. Urine was collected up to 72 hours and incubated with glucuronidase or sulfatase at 37 °C for 17 hours. Approximately, 44–71 % of the administered dose was detected in the urine after 24 hours. Three pathways of metabolism of d-pulegone were identified:

1. reduction to menthone and hydroxylation which is the major pathway at low doses;
2. conjugation with glutathione which could result in glutathione depletion; and
3. hydroxylation in ring/side chain to yield menthofuran which is observed at higher doses (Chen et al., 2001; EFSA, 2005).

A single oral dose of radiolabelled pulegone was administered to F344/N rats and B6C3F1 mice at 0.8 or 80 mg/kg. Pulegone was rapidly absorbed from the gastrointestinal tract of both animals. In rats, 45 % and up to 61 % of the administered dose were excreted in the urine at the respective doses, within 24 hours, with a significant amount present in the faeces and breath. Radioactivity was also observed in the liver, kidneys, blood and lungs of all animals 24 hours after administration (NTP, 2011). The levels of pulegone and its metabolites were found to be highest in the liver for both species and sexes; however high levels of pulegone and its metabolites were also seen in the kidneys of male rats. The study concluded that the chemical could be binding to alpha-μ2-globulin. Bile analysis revealed that there was a dose-dependent increase in the concentration of menthofuran-glutathione conjugate at a higher dose. At a lower dose, phase II conjugates of hydroxylated menthofuran predominated the metabolites in the urine (EFSA, 2005).

Male rats were intraperitoneally (ip) injected with phenobarbital in aqueous solution at a dose of 80 mg/kg bw/day, for 3–4 days. After the rats were euthanised, the microsomes were extracted and incubated with d-pulegone, isopulegone or menthofuran in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) and oxygen (O_2). The chemical d-pulegone was metabolised to 9-hydroxypulegone which was rapidly converted to menthofuran. Isopulegone formed menthofuran via 9-hydroxypulegone but at a slower rate. Menthofuran was converted to pulegone-8-aldehyde (Madyastha & Raj, 1990).

Female BALB/c mice (n=2–4 animals/dose) were ip injected with cimetidine (CYP1A2 inhibitor) in saline at 150 mg/kg, disulfiram (CYP2E1 inhibitor) in dimethyl sulfoxide (DMSO) at 100 mg/kg, or both. One hour after injection, the animals were ip injected with pulegone in corn oil at 300 mg/kg. Animals were euthanised after 24 hours. Blood and serum samples were collected and analysed to determine serum glutamate pyruvate transaminase (SGPT) levels. Significantly lower SGPT levels were reported in animals that were pre-treated with cimetidine alone or in combination with disulfiram. This indicates that d-pulegone metabolism via CYP1A2 enzymes is responsible for hepatotoxicity (Sztajnkrycer et al., 2003).

Female Fischer rats (n=28) were administered d-pulegone (CAS No. 89-82-7) in the diet at doses of 0, 75 or 150 mg/kg bw/day, 5 days/week for 4–6 weeks (see **Repeated dose toxicity: Oral** section). Urine analyses showed the presence of pulegone, piperitone, piperitenone and menthofuran (IARC, 2016).

An in vitro assay was conducted as part of a carcinogenicity study in F344/N rats (see **Carcinogenicity** section). Rats were dosed with d-pulegone at 75 or 150 mg/kg bw/day, 5 days/week for up to 104 weeks. The urine was analysed and found to contain the following chemicals at various respective concentrations: d-pulegone (0.36 and 0.46 mM); piperitenone (0.93 and

1.15 mM); piperitone (0.50 and 0.41 mM); menthofuran (0.11 and 0.18 mM); and menthone (concentration not determined; da Rocha et al., 2012).

Six volunteers were orally administered pulegone at a dose of 0.5 mg/kg bw. Urine analysis identified six metabolites including the major metabolite, 10-hydroxypulegone, which was converted to menthofuran via ring cyclisation (IARC, 2016). Other studies have demonstrated that 9-hydroxypulegone cyclises to menthofuran (IARC, 2016; WHO, 2001). The identification of 10-hydroxypulegone as the metabolite in this case may be incorrect.

A case study of a 22-month old female infant ingesting an unknown amount of pennyroyal oil was reported. The infant was initially treated with 190 mg/kg bw N-acetylcysteine, followed by doses of 70 mg/kg every 4 hours thereafter (Anderson et al., 1996). The chemical N-acetylcysteine is a drug given to patients to restore hepatic glutathione concentrations to prevent hepatic injury (Heard, 2008). Serum samples were collected 10 hours after ingestion of pennyroyal oil. Three of the samples collected were positive for menthofuran, with a concentration of 40 ng/mL in the earliest sample collected (Andersen et al., 1996).

Acute Toxicity

Oral

Studies conducted in animals and case studies in humans (see **Observation in humans** section) indicate that d-pulegone (CAS No. 89-82-7) is highly toxic following acute exposure. Isopulegol (CAS No. 89-79-2), isopulegone (CAS No. 29606-79-9) and isopulegyl acetate (CAS No. 57576-09-7) are less toxic than d-pulegone (CAS No. 89-82-7). Menthofuran (CAS No. 494-09-8) has the highest toxicity amongst all the chemicals in this group (WHO, 2001). Taken together, the median lethal doses (LD50) for the chemicals in this group range from 300 to >5000 mg/kg bw, warranting hazard classification for pulegone, isopulegone, menthofuran and the pennyroyal oils.

A group of SD rats (n=5/sex/dose) were administered isopulegol (CAS No. 89-79-2 and 7786-67-6) via gavage at a single dose of 285, 570, 1140, 2275 or 4550 mg/kg bw. The animals were observed after 0.5, 1, 2, 4 and 24 hours and then daily for 14 days. Mortality was reported at 570 (1/10), 1140 (6/10), 2275 (10/10) and 4550 (10/10) mg/kg bw. The following sub-lethal effects were observed: unconsciousness prior to death (occurred within two hours of administration), salivation, respiratory congestion, ataxia and lacrimation. The median lethal dose (LD50) for isopulegol was determined to be 936 mg/kg bw (WHO, 2001; Bhatia et al., 2008; REACH).

The following LD50 values have been reported, with no additional study details (WHO, 2001):

- isopulegyl acetate (CAS No. 57576-09-7): >5000 mg/kg bw;
- d-pulegone (CAS No. 89-82-7): 470 mg/kg bw.

The information below has been provided for the following chemicals based on studies in rats (WHO, 2001):

- isopulegol (CAS No. 89-79-2) was not toxic at 600 mg/kg bw;
- d-pulegone (CAS No. 89-82-7) caused 9/16 deaths at 400 mg/kg bw;
- isopulegone (CAS No. 29606-79-9) caused 3/13 deaths at 500 mg/kg bw and 3/5 at 600 mg/kg bw; and
- menthofuran (CAS No. 494-90-6) caused 5/15 deaths at 200 mg/kg bw and 10/16 at 300 mg/kg bw.

Dermal

Limited data are available. Based on the dermal LD50 value of isopulegol, this chemical has low toxicity via the dermal route. In the absence of more comprehensive information, classification for this particular endpoint is not warranted for the chemicals in this group.

Isopulegol (CAS No. 89-79-2 and 7786-67-6) was applied to intact or abraded skin of New Zealand White (NZW) rabbits (n=2/sex/dose) under occlusive patches for 24 hours at doses of 0, 1.25, 2.5, 5 or 10 mL/kg bw (equivalent to approximately 0,

1125, 2250, 4500 or 9000 mg/kg bw). The animals were observed for 14 days. Mortality was reported at 4500 (1/4) and 9000 mg/kg bw (4/4). Clinical signs of toxicity included ataxia and lacrimation. The LD50 was determined to be approximately 2700–4500 mg/kg bw (Bhatia et al., 2008; REACH).

Inhalation

No data are available for the chemicals.

Observation in humans

Pennyroyal oil causes death in humans at doses ≥250 mg/kg bw. In several case studies, consumption of pennyroyal oil induced moderate to severe toxicity. Patients developed gastrointestinal and central nervous system effects including gastritis, seizures and cramping 1–2 hours after ingestion of ≤10 mL pennyroyal oil (Andersen et al., 1996). Other physiological effects include centrilobular hepatic necrosis, pulmonary oedema and internal bleeding. Ingestion of pennyroyal oil at ≥15 mL (equivalent to 250 mg/kg bw) resulted in death (WHO, 2001; IARC, 2016).

In another case, two women drank pennyroyal tea to induce menstruation. The women were reported to have suffered dizziness, weakness, abdominal pain and nausea (Anderson et al., 1996; IARC, 2016).

Corrosion / Irritation

Skin Irritation

Considering the available data in guinea pigs and humans (see **Observation in humans** section), isopulegol is not considered to be irritating to the skin.

In a study conducted in albino Hartley guinea pigs (number and sex not specified), 10, 30 or 50 % isopulegol (CAS No. 89-79-2 and 7786-67-6) in acetone was applied to shaved backs (one side of the back was irradiated and the other remained non-irradiated) for 4 hours. No irritation effects were reported (Bhatia et al., 2008).

Eye Irritation

No data are available for the chemicals.

Observation in humans

No irritations were observed in two studies where isopulegol (CAS No. 89-79-2 and 7786-67-6) was applied on the skin of human volunteers under occlusion for up to 48 hours (Bhatia et al., 2008).

Sensitisation

Skin Sensitisation

Information was only available for isopulegol. The chemical is not considered to be a skin sensitiser in animals and humans based on guinea pig maximisation test (GPMT) and human maximisation test (see **Observation in humans** section). In the absence of more comprehensive information, hazard classification for this particular endpoint is not warranted for the chemicals in this group.

In a GPMT, Hartley guinea pigs (n=5 female/dose) were treated with 10 % isopulegol (CAS No. 89-79-2; 7786-67-6) in propylene glycol: acetone (1:1) for intradermal induction; 10 % isopulegol in propylene glycol: acetone (1:1) for epicutaneous induction; and 5, 10, 20 or 40 % isopulegol in propylene glycol: acetone (1:1) for epicutaneous challenge. No positive reactions were reported (Bhatia et al., 2008; REACH).

In an open epicutaneous test, guinea pigs (n=6–8/sex/dose; strain not specified) were applied (as a pre-test) with 1, 3, 10, 30 or 100 % isopulegol (CAS No. 89-79-2; 7786-67-6) (vehicle not specified) on clipped flanks for 24 hours. The animals were then induced with isopulegol at concentrations of 0.3, 1, 3, 10, 30 or 100 % and challenged with isopulegol at a concentration that produced minimal irritation. No positive reactions were reported (Bhatia et al., 2008; REACH).

Observation in humans

In a human maximisation test, 25 male volunteers were pretreated with 5 % sodium lauryl sulfate (SLS) under occlusion for 24 hours. Following a 10-day rest period, isopulegol (CAS No. 89-79-2 and 7786-67-6) at 8 % concentration was applied to the same pretreated sites under occlusion on five alternate days. Each application of the chemical was preceded with a one hour pretreatment with 10 % SLS. Patches were removed and sites were observed after 24 hours. No positive reactions were observed (Bhatia et al., 2008).

Repeated Dose Toxicity

Oral

The main toxic effects for this group of chemicals result from the formation of reactive metabolites which bind to liver proteins (see **Toxicokinetics** section). Consequently, large doses could potentially lead to glutathione depletion resulting in hepatoxicity (Anderson et al., 1996; WHO, 2001). Kidney damage (nephropathy) was also reported in rodents (NTP, 2011; IARC, 2016). Based on the treatment-related effects reported in various repeated dose toxicity studies, repeated oral exposure to the chemicals is considered to cause serious damage to health.

Male Wistar rats (numbers not specified) were administered with isopulegol (CAS No. 89-79-2 and 7786-67-6) in the diet at 1 % (equivalent to approximately 500 mg/kg bw/day) for 14 days. Increases in liver weight, and levels of cholesterol, triacylglycerol and Apo A1 (protein responsible for lipid metabolism) were observed (Bhatia et al., 2008).

In a screening test conducted in rats (number and species not specified), menthofuran (CAS No. 494-90-6) was administered in the diet at 23 mg/kg bw/day for 14 days. No effects were observed (IARC, 2016).

A group of F344/N rats (n=10/sex/dose) were administered d-pulegone (CAS No. 89-82-7) by gavage at doses of 0, 9.375, 18.75, 37.5, 75 or 150 mg/kg bw/day for 14 weeks. One death was reported in the highest dose prior to study termination. Decreased body weights were reported at doses ≥75 mg/kg bw/day. Statistically significant increases in relative liver, thymus and kidney weights were observed at ≥18.75 mg/kg bw/day. There were increases in alkaline phosphatase and bile acids/salts in both sexes at doses ≥37.5 mg/kg bw/day. At the highest dose, gamma glutamyltranspeptidase and alanine aminotransferase were increased. Haematology examinations revealed increases in reticulocytes, and decrease levels of red blood cells, haematocrit and haemoglobin in females at 37.5 mg/kg bw/day with higher incidences observed in the two highest doses for both sexes. Histological examination showed hepatocyte hypertrophy and bile duct hyperplasia in males at 75 mg/kg bw/day. Significant increase in bone marrow hyperplasia was observed in both sexes at ≥75 mg/kg bw/day groups. The NOAEL was determined to be 9.375 mg/kg bw/day based on increased organ weights at 18.75 mg/kg bw/day (EFSA, 2005).

In a study conducted in Wistar SPF rats (n=10/sex/dose), d-pulegone (CAS No. 89-82-7) in soya bean oil was administered via gavage at doses of 0, 20 80 or 160 mg/kg bw/day for 28 days. Dose-dependent atonia (loss of muscle strength) was observed before completion of the study. Animals at the highest dose (160 mg/kg bw/day) had significantly dose-dependent decrease in plasma creatine levels, increased neutrophil granulocytes and distended stomachs. Histopathological changes included vacuolization of hepatocytes at 80 and 160 mg/kg bw/day. Dose-related "cyst-like spaces" were observed in the white matter of the brain. The NOAEL was determined to be 20 mg/kg bw/day (Thorup et al., 1983; WHO, 2001; EFSA, 2005).

In a study using the same protocol as above, 1–3 % d-pulegone (CAS No. 89-82-7) in peppermint oil was administered via gavage at doses of 0, 10, 40 or 100 mg/kg bw/day. Mortality was not reported. The only histopathological change was the white

matter in the brain, which was of the appearance of 'cyst-like spaces' (WHO, 2001).

Female F344/N rats (n=20/dose) were administered d-pulegone in corn oil by gavage at doses of 0, 75 or 150 mg/kg bw, 5 days/week for 4 or 6 weeks. All animals were euthanised and tissue examinations were conducted from animals (n=10) treated for 4 weeks only. No mortality was reported. Clinical findings included decreased body weight gain, bloody nasal mucous and alopecia around the mouth and urogenital area. Scanning electron microscopy (SEM) revealed extensive urothelial superficial cell necrosis and exfoliation in all treated groups, and were more severe at the highest dose. These effects indicate that treatment with pulegone induces cytotoxicity of the bladder surface as similar effects were not in seen in the control group. In addition, bromodeoxyuridine (BrdU) labelling index, an immunohistochemical test parameter to evaluate the urothelial cells in the urinary bladder, was also significantly increased at the highest dose. The results of the study indicated that pulegone induced urothelial cytotoxicity and necrosis with consequent increase in cell proliferation. The cell proliferation leads to urethelial hyperplasia, and on long term exposure, could eventually lead to tumour formation (da Rocha et al., 2012).

Female Fischer rats (n=28) were administered d-pulegone (CAS No. 89-82-7) in the diet at doses of 0, 75 or 150 mg/kg bw/day, 5 days/week for 4–6 weeks. Superficial cell layer necrosis and exfoliation as well as a significant increase in cellular proliferation were observed in the bladders of rats treated with the chemical at 150 mg/kg bw/day. Urine analyses revealed the presence of pulegone, piperitone, piperitenone and menthofuran (IARC, 2016).

In a two year study, F344/N rats (n=50/sex/dose) were administered d-pulegone in corn oil via gavage at doses of 18.75 (males only), 37.5, 75, or 150 mg/kg/bw/day (females only), 5 days per week for up to 104 weeks (see **Carcinogenicity** section). Decreases in mean body weight were reported at ≥75 mg/kg bw/day. Other clinical findings included lethargy and ruffled fur. Incidences of hyaline glomerulopathy and olfactory epithelium degeneration were significantly increased in all dosed females, and at 37.5 and 75 mg/kg bw in males. At 37.5 and 75 mg/kg bw in males, and 75 and 150 mg/kg bw in females, incidences of nephropathy and diffuse hepatocyte cellular alteration were significantly increased. Significant increases in the incidences of liver lesions including fatty changes, and bile duct cyst were also reported (NTP, 2011; IARC, 2016).

A similar study was conducted in B63CF1 mice (n=50/sex/dose). Mice were administered d-pulegone in corn oil via gavage at doses of 0, 37.5, 75, or 150 mg/kg bw/day, 5 days per week for up to 105 weeks (see **Carcinogenicity** section). The incidences of hyaline glomerulopathy were significantly increased in all dosed males and in females at ≥75 mg/kg bw/day. At 150 mg/kg bw/day, the incidences of nephropathy and congestion of the glomerulus were increased in both sexes. At ≥75 mg/kg bw/day, non-neoplastic liver lesions including clear cell, eosinophilic, and mixed cell foci; focal fatty change; centrilobular hepatocyte hypertrophy; intravascular hepatocyte; necrosis; and pigmentation were significantly increased. Olfactory epithelial degeneration of the nose in all dosed female groups and in males at ≥75 mg/kg bw/day was significantly increased (NTP, 2011; IARC, 2016).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

In a case study, a 24-year old woman ingested pennyroyal extract (48–56% in alcohol) for 2 weeks to induce an abortion (see **Reproductive and developmental toxicity** section). The woman experienced cardiopulmonary arrest 7.5 hours after the final ingestion which was reported as leading to her death. Autopsy revealed centrilobular degeneration and necrosis of the hepatic cell. Liver samples revealed protein-bound menthofuran (Anderson et al., 1996).

Genotoxicity

Several in vitro mutagenicity assays have been conducted using d-pulegone (CAS No. 89-82-7), isopulegol (CAS No. 89-79-2, 7786-67-6) and menthofuran (CAS No. 494-90-6). An in vivo mutagenicity assay was also conducted using d-pulegone. Based

on the available data, the chemicals in this group are not considered to be genotoxic (IARC, 2016).

In vitro

The chemical d-pulegone (CAS No. 89-82-7) gave positive results in an Ames mutation assay in *Salmonella typhimurium* strain TA98 and *Escherichia coli* strain WP2, with and without metabolic activation at concentrations up to 1000 µg/plate (NTP, 2011). In another Ames mutation assay, the chemical gave negative results in *S. typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 with and without metabolic activation at concentrations =800 mg/plate (WHO, 2001; NTP, 2011; EFSA, 2005; IARC, 2016).

The chemical was weakly positive in a wing spot mutation assay in *Drosophila melanogaster* larvae at a concentration of 6.15 µM (1.23 µmol; 0.2 µL; WHO, 2001; EFSA, 2002). Negative results were reported at a concentration of 4.6 µM (9 µmol; 2 µL; WHO, 2001).

Isopulegol (CAS No. 89-79-2 and 7786-67-6) was negative in an Ames mutation assay using *E. coli* strain uvrA, with and without metabolic activation at concentrations of up to 5000 µg/plate. A reduction in growth of bacterial colonies at doses of 1250 and 5000 µg/plate were observed (Bhatia et al., 2008; REACH).

Menthofuran (CAS No. 494-90-6) was negative in an Ames mutation assay using *S. typhimurium* strains TA98, TA100 and TA1535 with and without metabolic activation at a concentration of 1000 µg/plate (WHO, 2001; EFSA, 2005).

In vivo

The chemical d-pulegone (CAS No. 89-82-7) was administered to B6C3F1 mice (male and female, number unspecified) via gavage at doses up to 150 mg/kg bw/day for 3 months. No significant increases in micro-nucleated erythrocytes were observed (NTP, 2011; IARC, 2016).

Carcinogenicity

The International Agency for Research on Cancer (IARC) has classified pulegone (CAS No. 89-82-7) as ‘Possibly carcinogenic to humans’ (Group 2B), based on limited evidence for carcinogenicity in humans, and less than sufficient evidence for carcinogenicity in experimental animals (IARC, 2016). Based on the metabolic interrelation of the chemicals, the chemicals in this group are considered to have carcinogenic potential, warranting hazard classification.

In a two year study, F344/N rats (n=50/sex/dose) were administered d-pulegone in corn oil via gavage at doses of 18.75 (males only), 37.5, 75 or 150 mg/kg/bw/day (females only), 5 days per week for up to 104 weeks. Due to unscheduled deaths, treatment was terminated after week 60 for dose groups 75 mg/kg bw/day (in males only) and 150 mg/kg bw. These groups were given the vehicle only until the end of the study. At the highest dose (150 mg/kg bw/day), the incidences of urinary bladder papilloma and of papilloma or carcinoma (combined) were significantly increased (NTP, 2011; IARC, 2016). All dosed females also had significantly increased incidences of respiratory metaplasia of the olfactory epithelium. In 37.5 and 75 mg/kg bw males, and in 75 and 150 mg/kg bw females, significant increases in the incidences of liver alterations including oval cell hyperplasia, bile duct hyperplasia, and portal fibrosis were reported. At 75 mg/kg bw/day, increased incidences of epithelial hyperplasia and perforation in the stomach were reported in male rats (NTP, 2011; IARC, 2016).

In a two year study, B63CF1 mice (n=50/sex/dose) were administered d-pulegone in corn oil via gavage at doses of 0, 37.5, 75, or 150 mg/kg bw/day, 5 days per week for up to 105 weeks. The incidences of multiple hepatocellular adenoma were significantly increased in all dosed male groups. The combined incidences of hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma were significantly increased and a significant positive trend at 75 mg/kg bw/day in males and at 150 mg/kg bw/day in females. Squamous hyperplasia in the forestomach were significantly increased in males at ≥75 mg/kg bw/day and in females at 150 mg/kg bw/day. Incidences of nerve atrophy and olfactory epithelium metaplasia in the nose were significantly increased at 150 mg/kg bw/day in both sexes. At 75 mg/kg bw/day, the incidence of osteoma or osteosarcoma (combined) in all organs of females exceeded the historical control data (NTP, 2011; IARC, 2016).

Reproductive and Developmental Toxicity

Pennyroyal oil was commonly used in women as an abortion-inducing agent; however, abortions were only observed at doses that caused severe maternal toxicity (WHO, 2001; IARC, 2016).

Twelve hours after ingesting two bottles of pennyroyal oil, spontaneous abortion was reported in a 24-year-old woman. In another case, spontaneous abortion was reported 4 days after a woman ingested 15 mL of pennyroyal oil. Severe toxicity was observed including coma, respiratory depression, acute renal failure. The 24 year old woman died after 14 days of ingestion (Anderson et al., 1996).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity). The chemicals can also cause harmful effects following repeated oral exposure. The target organs are the liver and the kidneys following repeated exposure.

Pulegone, isopulegone, menthofuran and pennyroyal oil can also cause systemic acute effects from oral exposure.

Public Risk Characterisation

While Australian use information is not available, the chemicals in this group have reported international use in domestic, cosmetics and personal care products. Considering the range of products that may contain the chemicals, the main route of public exposure is expected to be through the skin, inhalation from products applied as aerosols, and potential oral exposure from lip and oral hygiene products.

The available dermal and inhalation studies indicated low toxicity via these routes of exposure. Although these chemicals are harmful following repeated exposure and have carcinogenic potential, the chemicals are expected to be used at very low concentrations. It should also be noted that isopulegol and its esters have low oral toxicity.

In humans, long term exposure to high levels of pulegone is not expected because of its high volatility and the noxious sensation when exposed to such high concentrations used in experimental animals. Therefore, the tumour induction observed in animals was not considered relevant to human (da Rocha et al., 2012).

It appears that restrictions to pulegone (5 % in concentrate), isopulegone (1 % in concentrate) and menthofuran (0.5 % in concentrate) are also available (Good Scents Company). These restrictions are expected to make the concentrations of these chemicals in the end-use products (domestic and cosmetic products) even lower.

Pulegone and pennyroyal oil are currently listed on Schedule 6 of the SUSMP for preparations containing greater than 4 % of d-pulegone. At concentrations greater than 4 % d-pulegone, a number of warning statements, first aid instructions and safety directions relating to pulegone apply (SUSMP, 2017).

The current SUSMP controls and the expected low use concentrations of these chemicals, are considered adequate to minimise the risk to public health posed by domestic and cosmetic products containing the chemicals. Therefore, the chemicals are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

Given the critical systemic long-term and acute health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation 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 a new entry to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of these chemical 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

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2017).

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. The acute toxicity classification does not apply to isopulegol and its esters.

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]
Acute Toxicity	Not Applicable	Toxic if swallowed - Cat. 3 (H301)
Repeat Dose Toxicity	Not Applicable	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Carcinogenicity	Not Applicable	Suspected of causing cancer - Cat. 2 (H351)

[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 consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal and inhalation 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:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- 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 safety data sheets (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 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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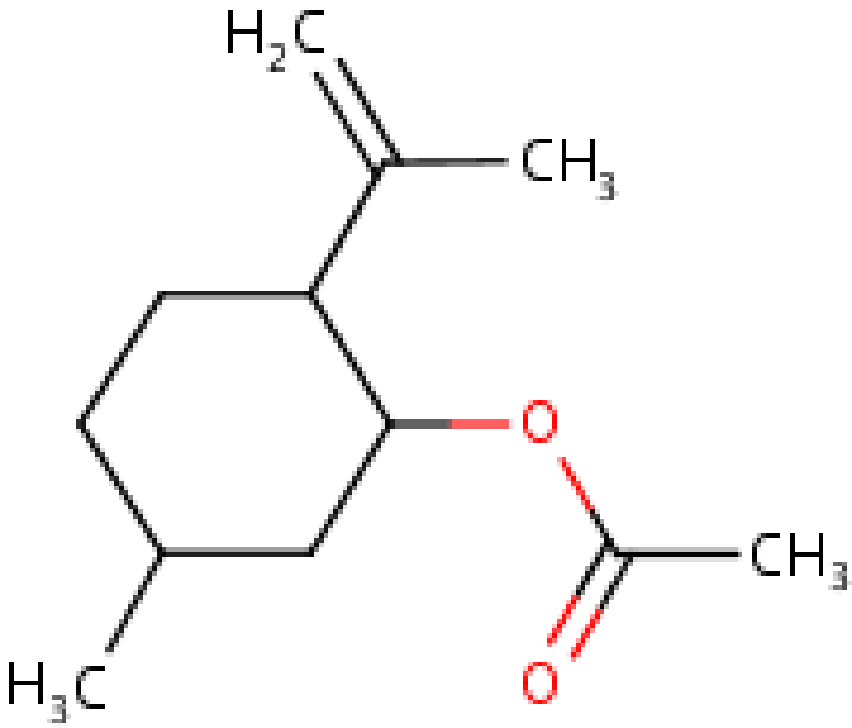
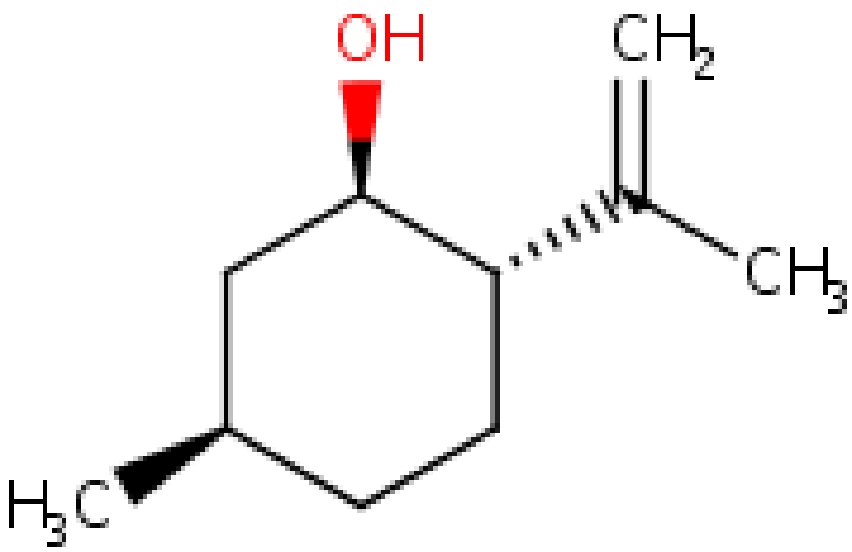
Last Update 27 October 2017

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, acetate** p-menth-8-en-3-ol, acetate isopulegyl acetate
CAS Number	89-49-6
Structural Formula	
Molecular Formula	C12H20O2
Molecular Weight	196.29

Chemical Name in the Inventory and Synonyms	**Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, [1R-(1.alpha.,2.beta.,5.alpha.)]-** isopulegol p-menth-8-en-3-ol, (1R,3R,4S)-(-)- l-isopulegol
CAS Number	89-79-2

Structural Formula	
Molecular Formula	C10H18O
Molecular Weight	154.25

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CAS Number	89-82-7
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	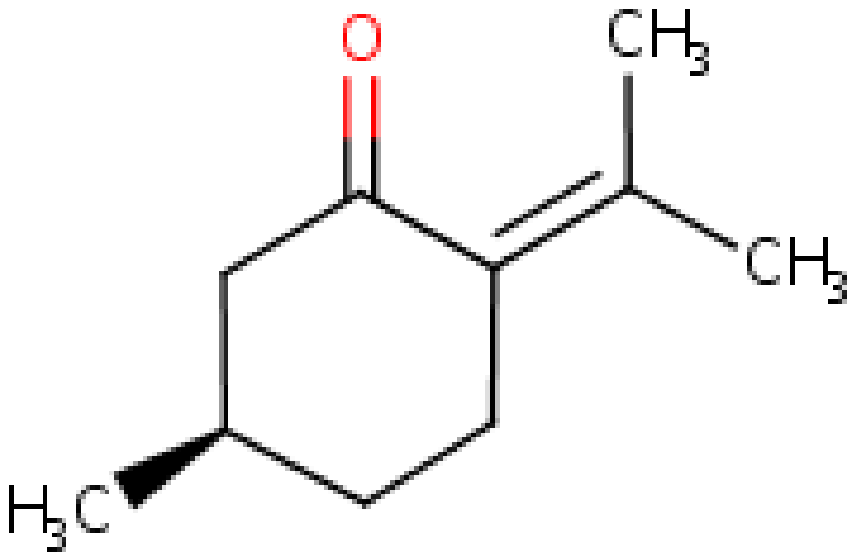
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Molecular Weight	154.25

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	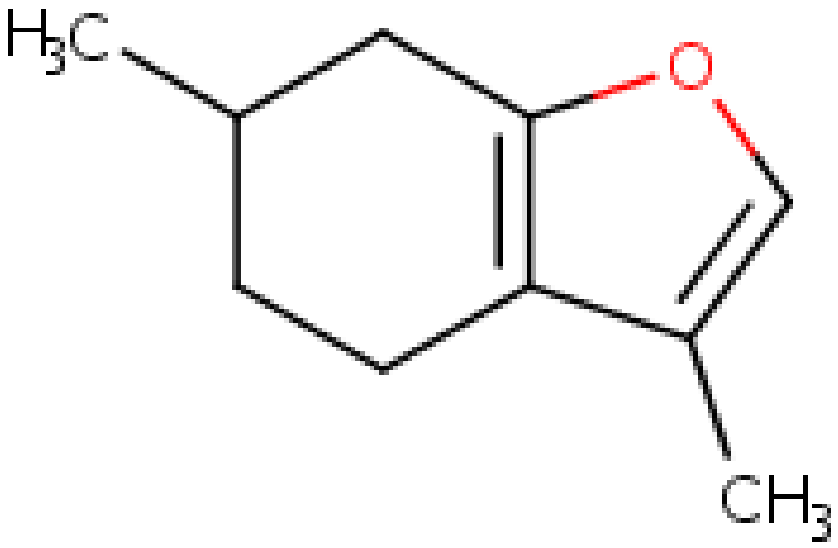
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	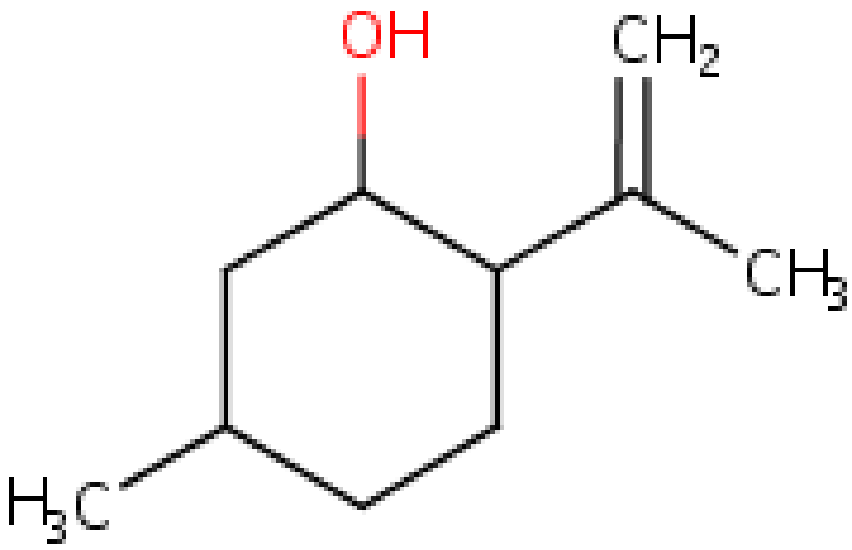
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CAS Number	8007-44-1
Structural Formula	**No Structural Diagram Available**

Molecular Formula	Unspecified
Molecular Weight	Unspecified

Chemical Name in the Inventory and Synonyms	**Oils, pennyroyal, Mentha pulegium** oil of pennyroyal, European
CAS Number	8013-99-8
Structural Formula	**No Structural Diagram Available**
Molecular Formula	Unspecified
Molecular Weight	Unspecified

Chemical Name in the Inventory and Synonyms	**Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, formate, [1R-(1.alpha.,2.beta.,5.alpha.)]-** p-menth-8-en-3-ol, formate (1R, 2S, 5R)-5-methyl-2-(1-methylethenyl)-cyclohexanol formate l-isopulegyl formate
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	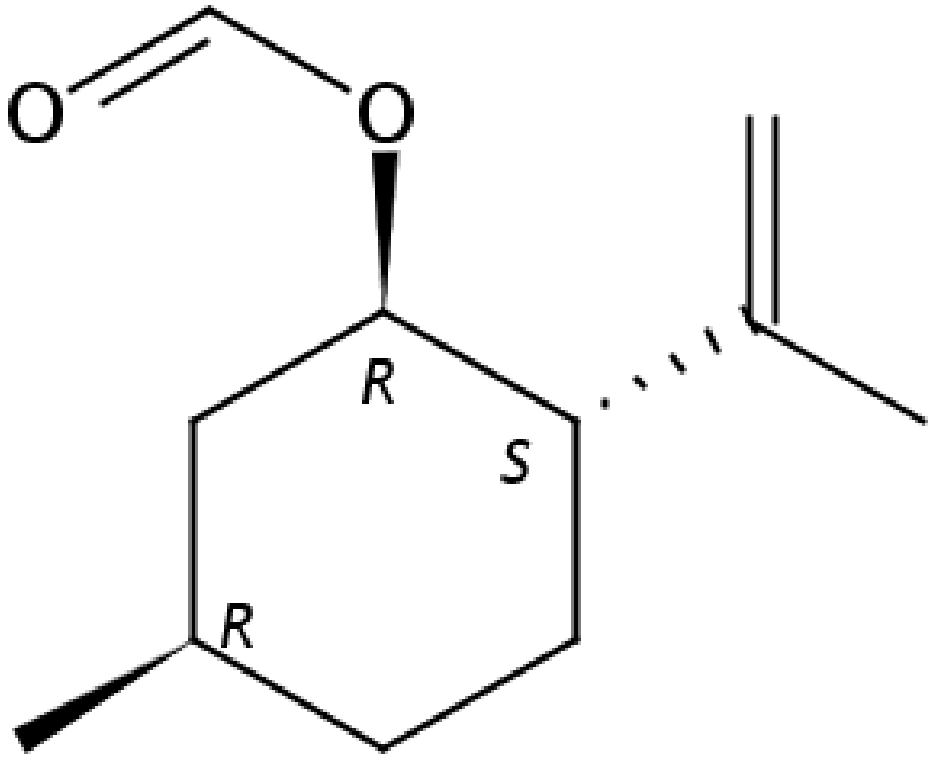
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	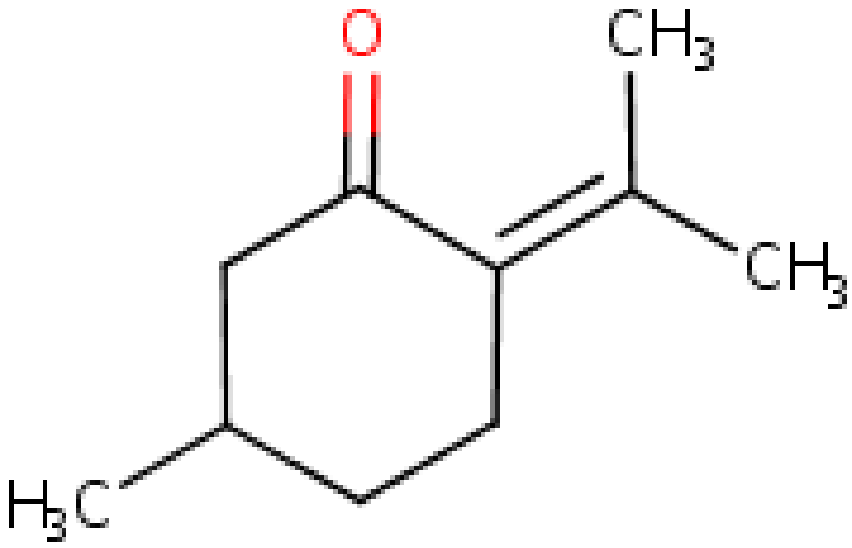
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Molecular Weight	152.24

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	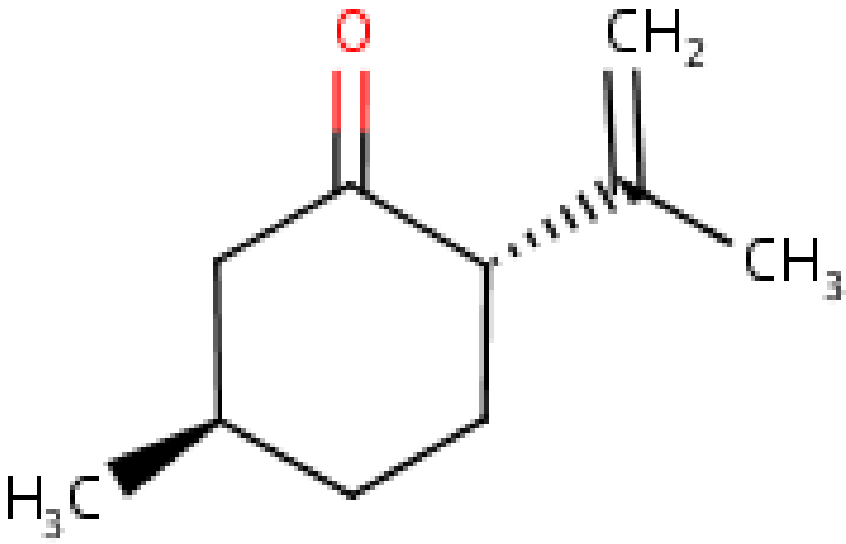
Molecular Formula	C10H16O
Molecular Weight	152.24

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	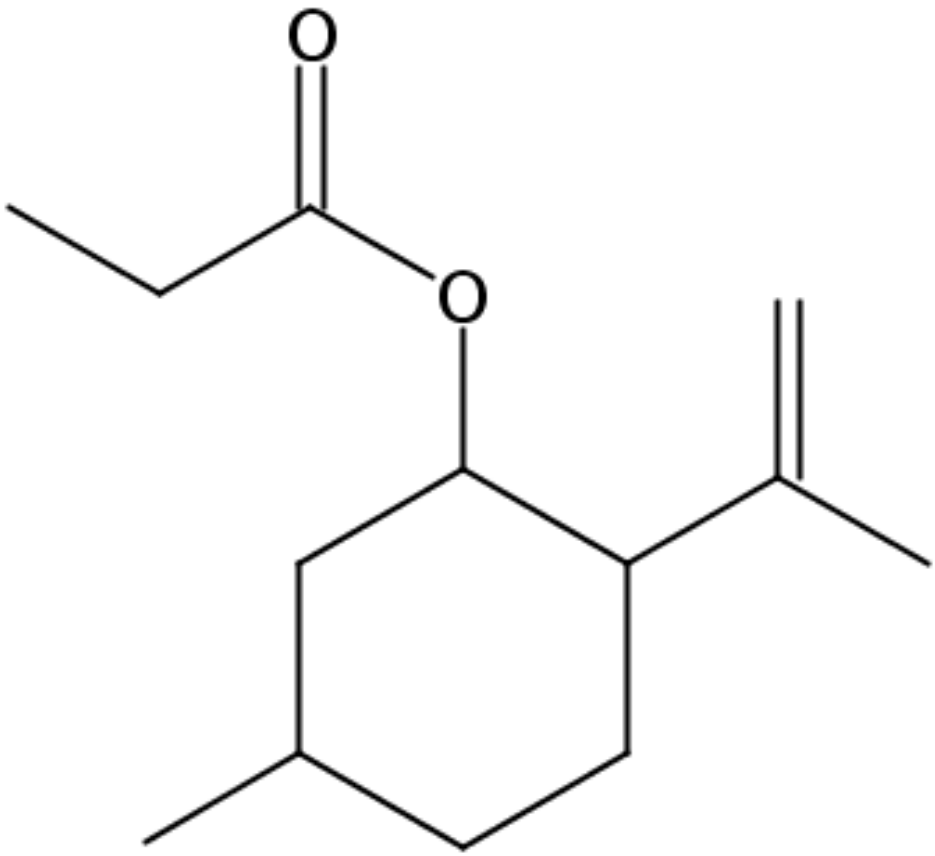
Molecular Formula	C13H22O2
Molecular Weight	210.31

Chemical Name in the Inventory and Synonyms	**Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, (1.alpha.,2.beta.,5.alpha.)-(.+-.)-** l-isopulegol
CAS Number	50373-36-9
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	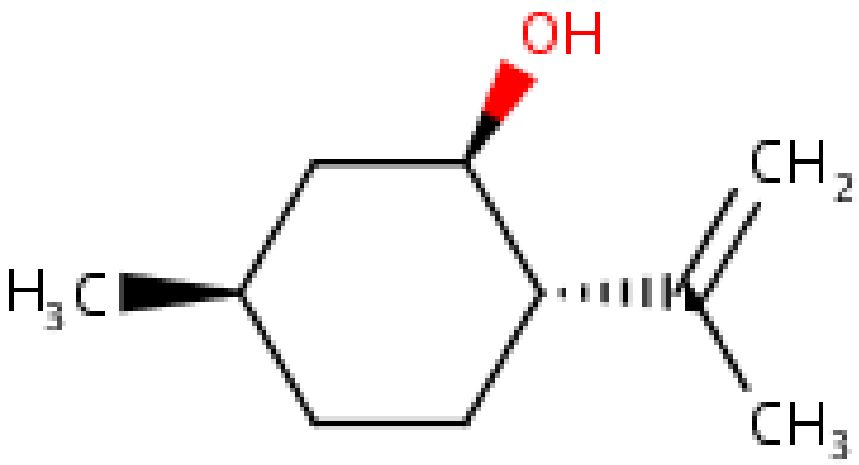
Molecular Formula	C10H18O
Molecular Weight	154.25

Chemical Name in the Inventory and Synonyms	**Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, acetate, [1R-(1.alpha.,2.beta.,5.alpha.)]-** l-isopulegyl acetate 1-methyl-4-isopropenylcyclohexan-3-yl acetate
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	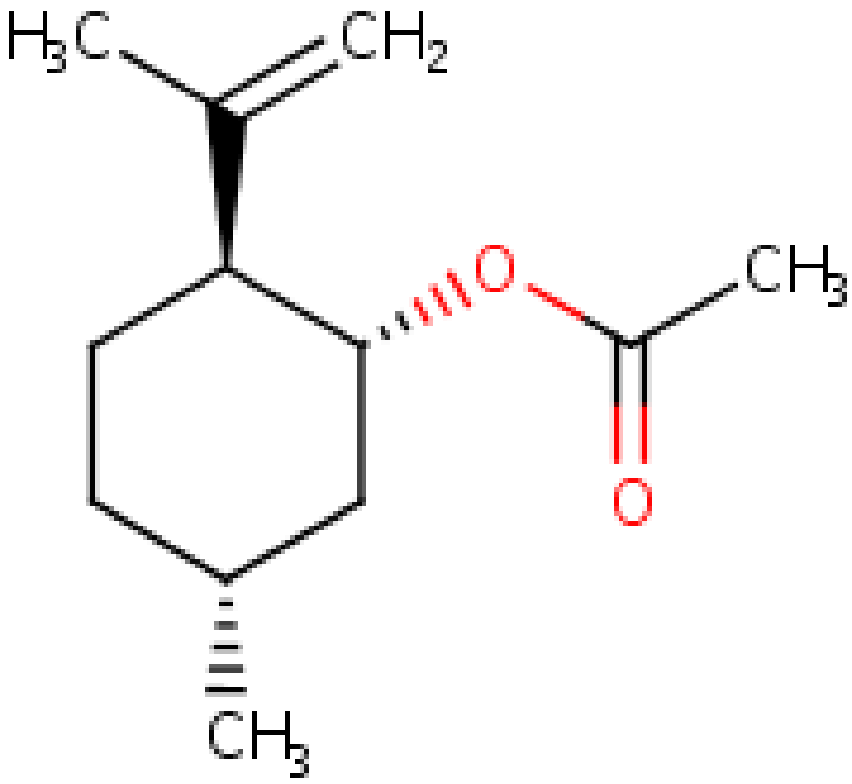
Molecular Formula	C12H20O2
Molecular Weight	196.29

Chemical Name in the Inventory and Synonyms	**Terpenes and terpenoids, pennyroyal oil** Pennyroyal oil, terpene fraction
CAS Number	68917-60-2
Structural Formula	**No Structural Diagram Available**

Molecular Formula	Unspecified
Molecular Weight	Unspecified

Chemical Name in the Inventory and Synonyms	**Pennyroyal, extracts (Spain-Morocco)** Mentha pulegium, extract
CAS Number	90064-00-9
Structural Formula	**No Structural Diagram Available**
Molecular Formula	Unspecified
Molecular Weight	Unspecified

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