2-Pentanone, 4-hydroxy-4-methyl-: Human health tier II assessment

12 September 2013

CAS Number: 123-42-2

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.

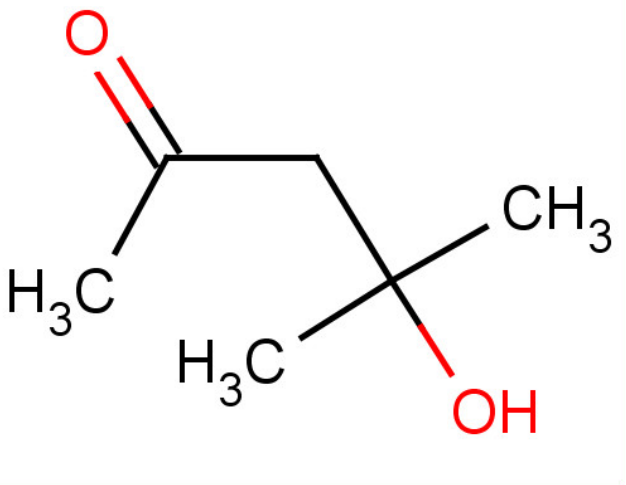
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Diacetone alcohol 4-hydroxy-4-methylpentan-2-one 4-Hydroxy-4-methyl-2-pentanone Pentan-2-one, 4-hydroxy-4-methyl- 2-Hydroxy-2-methyl-4-pentanone
Structural Formula	
Molecular Formula	C6H12O2
Molecular Weight (g/mol)	116.16
Appearance and Odour (where available)	Colourless to yellowish liquid with a mild odour.
SMILES	C(C)(=O)CC(C)(C)O

Import, Manufacture and Use

Australian

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of between 1000 and 9999 tonnes.

The following Australian industrial uses were reported:

- Commercial use as a viscosity adjuster in surface coatings; and
- Site-limited use as a solvent in the manufacturing of other chemicals.

International

The following international uses have been identified via the Organisation for Economic Cooperation and Development (OECD) SIDS Initial Assessment Report (SIAR), Galleria Chemica, the European Commission Cosmetic Ingredients and Substances (CosIng) database, the US National Library of Medicine's Household Products Database and via eChemPortal sources including the US National Library

of Medicine's Hazardous Substances Data Bank (HSDB):

The chemical has reported cosmetic use:

- as a masking agent; and
- as a fragrance ingredient.

The chemical has reported domestic use including:

- in paints, lacquers and varnishes; and
- in cleaning/washing agents.

The chemical has reported commercial use including:

- as a solvent for cellulose acetate, nitrocellulose, celluloid, fats, oils, waxes, and resins;
- as an additive for tobacco products;
- in antifreeze and lubricant products;
- in coating applications;
- in the manufacturing of photographic film;
- in wood preservatives; and
- as an electroplating agent.

The chemical has reported site-limited use including:

- as an intermediate in the synthesis of mesityl oxide, hexalene glycol and other organic chemicals; and
- in making artificial silk and leather.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified. However, the chemical is listed on the Canada Ingredient Disclosure List [regulation (SOR 88-64) under the *Hazardous Products Act*] with a disclosure limit of 1% w/w; if the chemical is found in a controlled product above this concentration cut-off, its identity and concentration must be disclosed on a Material Safety Data Sheet (MSDS).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrase for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xi; R36 (irritation)

Exposure Standards

Australian

The chemical has an exposure standard of 238 mg/m^3 (50 ppm) time weighted average (TWA).

International

The following exposure standards (TWA) are identified (Galleria Chemica):

- 240 mg/m^3 (50 ppm) in countries such as Canada (Yukon), Denmark, France, Greece, Ireland, South Africa, and USA;
- 120 mg/m^3 (25 ppm) in Norway and Sweden; and
- 96 mg/m^3 (20 ppm) in Germany and Switzerland.

Health Hazard Information

Toxicokinetics

In a study in mice (Charles River), the chemical was detected at 430, 300, 160 and 50 mg/mL in blood and 430, 300, 150 and 60 mg/g in brain at 15, 30, 60 and 90 minutes after administration via intraperitoneal injection of 2.5 mmol/kg of the chemical (REACH).

The chemical is also identified as the major metabolite of methyl isobutyl ketone (MIBK) in blood serum (REACH). Several oral and inhalation toxicokinetic studies in rats and mice confirmed the rapid transformation of MIBK to the chemical.

Acute Toxicity

Oral

The chemical was reported to have low acute toxicity via the oral route.

Acute oral median lethal dose (LD50) values of the chemical are reported to be 2520 - 4000 (rats), 3950 (mice) and 4653 mg/kg bw (rabbits) (OECD, 2000; ChemIDplus).

Dermal

The chemical was reported to have low acute toxicity via the dermal route.

The acute dermal LD50 in rabbits is reported to be 13630 mg/kg bw (OECD, 2000).

The acute dermal LD50 in rats, following OECD Test Guideline (TG) 402, was reported to be greater than 2 mL/kg bw (equivalent to greater than 1875 mg/kg bw). No mortalities were reported (REACH).

Inhalation

Based on the data available the chemical is considered of low inhalation toxicity.

Acute inhalation median lethal concentration (LC50) values in rats were reported to be greater than 7.23 mg/L/8 h or 7.6 mg/L/4 h with no mortalities (OECD, 2000; REACH).

A lowest lethal concentration (LCLo) inhalation of 1000 ppm/4 h (equivalent to 4.1 mg/L) in rats has also been reported (ChemIDplus).

Corrosion / Irritation

Skin Irritation

The chemical is not considered to be irritating to the skin.

In a skin irritation test (OECD TG 404 with deviations: occlusive dressing was used instead of semi-occlusive dressing, and observations at one hour and on day two were not reported), very slight transient erythema was observed in 3/6 rabbits with abraded skin, which was fully reversible by day three. No irritation was observed in animals with intact skin (0.5 mL of neat chemical). The chemical was considered to be non irritant (REACH).

The chemical was reported to be a moderate skin irritant following 500 mg application in rabbits. No further details were reported (OECD, 2000; IUCLID, 2000).

There are insufficient data and evidence to warrant hazard classification for skin irritation.

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available data support this classification.

In an eye irritation test (OECD TG 405), slight iritis, slight to moderate conjunctival irritation and slight to moderate corneal opacity were observed at 24, 48 and 72 hours. All these effects cleared in four, seven and twenty one days, respectively (REACH).

In another eye irritation test (Directive 84/449/EEC, B.5), the chemical was reported to be moderately irritating to rabbit eyes (OECD,2000; IUCLID, 2000).

Observation in humans

In humans, exposure to the chemical at 0.475 mg/L for 15 minutes caused eye, nose and throat irritation and the majority of volunteers complained of an unpleasant odour and taste in addition to headaches, nausea or vomiting (OECD, 2000).

Sensitisation

Skin Sensitisation

The chemical is not considered to be a skin sensitiser.

In a skin sensitisation assay in guinea pigs (OECD TG 406), signs of irritation were observed at the site of application in both control and treated groups following topical induction (on day 10). Following the challenge phase, no erythema or oedema were observed at 24 and 48 hours. No mortality or clinical signs were observed throughout the test. The chemical was considered to be a non-sensitiser (REACH).

Repeated Dose Toxicity

Oral

In an oral gavage study (up to 44 days) in rats, the no observed adverse effect levels (NOAELs) were reported to be 30 mg/kg bw/day in males and 100 mg/kg bw/day in females (OECD, 2000).

In a combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422), Sprague Dawley (SD) rats were exposed to the chemical at 0, 30, 100, 300 or 1000 mg/kg bw/day by gavage for 44 days in males and from 14 days before mating to day three of lactation in females. The NOAELs for repeat dose toxicity were based on the following observed effects:

- decreased locomotor activity and increased basophilic tubules in males and females of the 300 and 1000 mg/kg groups;
- decrease in body weight gain during the premating period in females of the 1000 mg/kg group;
- increased platelet count, total protein, total cholesterol, total bilirubin, blood urea nitrogen, creatinine and calcium, and a decrease of glucose, dilatation of the distal tubules in kidneys, and vacuolisation of the cells of the zona fasciculata in the adrenals at the dose of 1000 mg/kg in male rats;
- increased deposition of hyaline droplets in the proximal tubular epithelium at doses of 100 mg/kg or more in kidneys of male rats;
- slight but not significant increases of dilated distal tubules and fatty degeneration of the proximal tubular epithelium in kidneys of female rats at doses of 300 and 1000 mg/kg.

Hepatocellular hypertrophy was evident in both sexes of the 1000 mg/kg group.

Dermal

No data are available.

Inhalation

Based on the data available, the chemical is not likely to cause serious damage to health through repeated inhalation exposure.

In a six-week repeated inhalation dose study, a group of rats (Wistar) were exposed to the chemical at doses of 0.232, 1.035 or 4.494 mg/L for 6 hr/day, 5 day/week. The no observed adverse effect concentration (NOAEC) was considered to be 0.232 mg/L based on: a slight lethargy during and after exposure, reduced body weight gains and increased plasma lactate dehydrogenase (LDH) in female rats and increased liver and kidney weights and histologic changes in the proximal tubules of the kidneys in male rats at 4.494 mg/L, and increased liver weight at 1.035 mg/L (OECD, 2000).

Genotoxicity

Based on the data available, the chemical is not likely to be genotoxic.

The chemical was not mutagenic with and without metabolic activation in bacterial point mutation tests (OECD TG 471: *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 uvrA strains) at up to 4000 µg/plate and in mitotic recombination tests (*Saccharomyces cerevisiae* JD1) at up to 5 mg/mL. The chemical also gave negative results in chromosomal aberration tests using cultured Chinese hamster lung (CHL/IU) cells (OECD TG 473) at up to 1.2 mg/mL (10 mM) with and without metabolic activation (OECD, 2000).

No in vivo mutagenicity data are available.

Carcinogenicity

While no specific data are available on this chemical, it is a major metabolite of MIBK, which has been assessed by NICNAS and is recommended for hazard classification as a Category 3 carcinogen with the risk phrase ‘Limited evidence of a carcinogenic effect’ (Xn; R40) (NICNAS).

In a two year inhalation carcinogenicity study (OECD TG 451), groups of rats (F344N) and mice (B6C3F1) were administered (whole body) MIBK vapour, at concentrations of 0, 450, 900 or 1800 ppm for six hours per day, five days per week. A NOAEC of 450 ppm (1.84 mg/L) for both rats and mice was established based on neoplastic and non-neoplastic lesions observed in the kidneys and livers at higher dose levels of 900 and 1800 ppm in both rats and mice respectively (REACH; IARC, 2012).

A REACH dossier reported this as a read-across study for the chemical, although no classification for carcinogenicity was applied.

The International Agency for Research on Cancer (IARC) has also classified MIBK as ‘Probably carcinogenic to humans’ (Group 2A), based on sufficient evidence for carcinogenicity in animal tests, but inadequate evidence for carcinogenicity in humans.

Although the chemical is a major metabolite of MIBK, which is a potential carcinogen, there is insufficient evidence to indicate that the chemical itself causes carcinogenic effects.

Reproductive and Developmental Toxicity

Reproductive and developmental effects were observed secondary to maternal toxicity and at high doses that do not warrant classification. Based on the data available, the chemical is not considered to be a specific reproductive or developmental toxin.

In a combined repeat dose and reproductive/developmental toxicity study (OECD TG 422), groups of SD rats were orally exposed to the chemical at doses of 0, 30, 100, 300 or 1000 mg/kg bw/day. Developmental toxicity was only seen at the maternally toxic dose of 1000 mg/kg dose. Effects included decreased fertility index, decreased number of implantations, implantation index and birth index. Two dams were also observed to be unable to normally carry their litter. While these effects

were not statistically significant, the NOAEL for reproductive/developmental toxicity was considered to be 300 mg/kg bw/day (REACH; OECD, 2000).

Risk Characterisation

Critical Health Effects

Exposure to the chemical vapours or liquid may cause eye irritation.

Public Risk Characterisation

Although uses in products available to the public in Australia have not been reported, the chemical is reported to be used in cosmetic and domestic products overseas that are likely to be available in Australia; these include nail care and colour products, aerosol home office and arts and crafts products, home maintenance and auto products.

Eye exposure may occur when using aerosol domestic products containing the chemical. However, based on limited US information derived from the National Library of Medicine (NLM) Household Products Database, the concentration in these products is not considered to be sufficiently high to cause detrimental effects. Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

Given the critical health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemical are implemented. The chemical 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 appropriate controls.

Based on the available data, the hazard classification in HSIS is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation.

Work Health and Safety

The chemical is recommended for classification and labelling under the current Approved Criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)

[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 chemical should be used according to the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from ocular exposure to the chemical 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 chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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 chemical.

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 assist with meeting 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 chemical 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 the chemical has not been undertaken as part of this assessment.

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