2-Butanone: Human health tier II assessment

22 March 2013

CAS Number: 78-93-3

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.

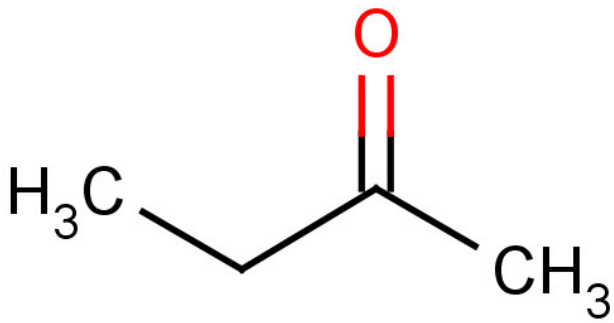
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	MEK Methylethyl ketone Ethyl Methyl Ketone 3-Butanone Methyl Acetone
Structural Formula	
Molecular Formula	C4H8O
Molecular Weight (g/mol)	72.12
Appearance and Odour (where available)	Colourless liquid with a mint or acetone like odour.
SMILES	C(C)(=O)CC

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information:

The chemical has reported domestic use including:

- paints and lacquers;
- detergents;
- printing inks and textile dyeing; and
- paint and adhesive thinners.

The chemical has reported commercial use including:

- industrial and automotive paint;
- solvents and degreasing/dewaxing agents; and
- leather cleaning, stripping and dyeing.

The chemical has reported site-limited use including:

- in polyurethane processing; and
- as a laboratory reagent.

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume between 1,000 and 9,999 tonnes.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR), Galleria Chemica, Substances and Preparations in the Nordic countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory and other data sources via eChemPortal including the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB) and International Programme on Chemical Safety (IPCS) INCHEM- Environmental Health Criteria (EHC) monographs.

The chemical has reported cosmetic use as:

- a fragrance ingredient;
- a solvent applications in nail polish; and
- an ingredient in enamel removers.

The chemical was reported to have domestic use including:

- paints, lacquers and varnishes;
- insulating materials and corrosion inhibitors;
- adhesives and binding agents;
- cleaning/washing agents;
- colouring and odour agents; and

- aerosol propellants.

The chemical was reported to have commercial use including:

- solvent used in lacquers, thinners, rubber cements, adhesives, colourless synthetic resins and polymer processing;
- in paint removers and de-waxing agents;
- process regulators and fuel additives;
- synthetic lubricants and additives;
- construction materials;
- anti-freezing/de-icing agents; and
- water treatment/softeners.

The chemical has reported site - limited use including:

- as a chemical intermediate;
- magnetic tape manufacturing;
- laboratory chemical;
- heat transferring and vulcanising agents; and
- manufacture of explosives and smokeless gunpowder.

Restrictions

Australian

This chemical is listed in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Posions (SUSMP)) in Schedule 5, except in preparations containing 25% or less.

Schedule 5 chemicals are labelled with "CAUTION". These are substances considered to have low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

The chemical is also listed in the Australian Customs (Prohibited Exports) Regulations 1958 - Schedule 9 as a precursor substance requiring pre-export notification process for either the chemical neat, or in mixtures at a concentration of at least 90%.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

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

Xi; R36 (Irritating to eyes)

R66 (Repeated exposure may cause skin dryness or cracking)

R67 (Vapours may cause drowsiness and dizziness)

Exposure Standards

Australian

The chemical has an exposure standard of 445 mg/m³ (150 ppm) Time Weighted Average (TWA).

International

The following exposure standards were identified (Galleria Chemica):

445- 472 mg/m³ (150-160 ppm): Chile and Poland.

590- 600 mg/m³ (200 ppm): USA (California, Tennessee,Vermont, Washington), Canada (Alberta, Saskatchewan,Yukon), European Commission (Scientific Committee for Occupational Exposure Limits to Chemical Agents), United Kingdom.

145- 220 mg/m³ (50-75 ppm): Canada (Quebec), Denmark, Iceland, Norway and Sweden.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed and excreted either unchanged in exhaled air, or as glucuronic acid conjugates in urine. Absorption of the chemical can occur via dermal, inhalation and oral routes. Through inhalation, humans absorb approximately 75 per cent of the chemical. A rapid rate of absorption is also noted via the dermal route (OECD 1997, HSDB 2012).

According to OECD (1997) the chemical has been reported to have a metabolic similarity to 2-butanol. 2-Butanol is intially metabolised to the chemical. Additionally, the chemical can then in turn be metabolised into 3-hydroxy-2-butanone and then reduced to 2,3-butanediol. Nearly all of 2-butanol can be rapidly converted into the chemical with a minimal amount being eliminated as a glucuronide conjugate; it is reported that 96% of orally administered 2-butanol was readily converted to the chemical.

Acute Toxicity

Oral

The chemical is reported to be of low acute toxicity via the oral route of exposure. The lowest acute oral median lethal dose (LD50) in rats was reported to be 2600 mg/kg bw (OECD 1997).

Dermal

The chemical is reported to be of low acute toxicity via the dermal route of exposure. The lowest LD50 in rats was reported to be 6400 mg/kg bw (OECD 1997).

Inhalation

The chemical is reported to be of low acute toxicity via the inhalation route of exposure. The median lethal concentration (LC50) in rats was reported to be greater than 5000 ppm (OECD 1997).

Corrosion / Irritation

Respiratory Irritation

At high concentrations, the chemical was reported to cause severe upper respiratory tract irritation in rats after a few days (time period not specified) following exposure at 10,000 ppm for 8 hours per day. Guinea pigs exposed to 33,000 ppm of the chemical showed gasping respiration after 180 minutes of exposure and died after 200 to 260 minutes of exposure (ATSDR 1992).

There is sufficient evidence from animal studies and observations in humans to classify the chemical as irritating to the respiratory system.

Skin Irritation

The chemical is classified in Australia as hazardous with the risk phrase ‘Repeated exposure may cause skin dryness or cracking.’ (Xi; R66) in HSIS (Safe Work Australia). The available data support this classification.

Slight desquamation (skin peeling) was reported in guinea pigs after 31 weeks of dermal exposure to increasing amounts of the chemical (ATSDR 1992). Additionally, in a non-guideline study, the chemical was reported to be a mild to moderate skin irritant in rabbits after a 24 hour application period (occluded and un-occluded) (OECD 1997).

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.

The chemical was reported to be a severe eye irritant in rabbits, with Draize test scores (out of a possible 110) of: 21 at one to four hours; 39 at one to two days; 21 at seven to 10 days; and 12 at 14 days (OECD 1997).

In another study, the chemical caused irritation, corneal opacity and conjunctivitis when introduced to the conjunctival sac of rabbits. Effects were reversible in seven to 14 days. However, one of the six rabbits was reported to have corneal damage after day 14, which resulted in Draize scores that classified the chemical as moderately irritating (ATSDR 1992).

Observation in humans

An increased prevalence of upper respiratory tract irritation, ocular symptoms and skin irritation was reported in a group of 41 workers at a cable factory, compared to a control group of 63 workers, when exposed to the chemical at an exposure level range of 149 to 342 mg/m³ (51 to 117 ppm) throughout an 8 hour shift (ATSDR 2010).

Sensitisation

Skin Sensitisation

The chemical was not found to induce dermal sensitisation when tested according to OECD Test Guideline (TG) 406 using female guinea pigs. One test animal displayed a slight red rash, for which the result was deemed inconclusive (REACH 2012). The chemical was also reported not to induce dermal sensitisation in a non-guideline study using albino guinea pigs (OECD 1997).

Repeated Dose Toxicity

Oral

A no observed effect level (NOEL) of 1500 mg/kg bw/day in rats was reported based on results from a reproductive toxicity study using 2-butanol (OECD 1997).

Rats were administed 2-butanol via their drinking water at 0.3, 1.0 or 3.0 % for eight weeks prior to mating. Toxicity (specific details not provided) was reported to be observed only at the 3.0% dose level. The NOEL of 1.0% was reported to be equivalent to 1500 mg/kg bw/day.

Dermal

No data are available.

Inhalation

The chemical is classified in Australia as hazardous with the risk phrase 'Vapours may cause drowsiness and dizziness.' (Xi; R67) in HSIS (Safe Work Australia). The available data from observations in humans support this classification.

In a 90 day repeat dose toxicity study conducted according to OECD guidelines, male and female rats (Fischer 344) were exposed to 0, 1250 or 5000 ppm of the chemical vapour for 6 hours/day, 5 days/week (OECD 1997). The no observed adverse effect concentration (NOAEC) was reported to be 5000 ppm. Decreased body weight in the 5000 ppm exposure group together with changes in liver weight, liver weight/body weight ratio, and liver weight/brain weight ratio at necropsy were noted. These however, were reported as adaptive changes.

Observation in humans

There have been several cases of workers chronically exposed to the chemical reporting in dizziness and drowsiness (ASTDR 2010).

In one case, a worker was chronically exposed to the chemical daily from fumes generated from burning fibreglass material. Exposure concentrations were not reported. The worker self-reported severe chronic headache, dizziness, loss of balance, memory loss, fatigue, tremors, muscle twitches, visual disturbances, throat irritation, and tachycardia. It must be noted that concurrent exposure to other chemicals may have impacted on the effects reported.

In another case report, a worker with inhalation and dermal exposure to solvents containing 100% of the chemical for approximately two years reported dizziness, asthenia, anorexia, and weight loss. Exposure levels were not reported.

Genotoxicity

The chemical is not expected to be genotoxic.

The chemical tested negative in a number of tests for genotoxicity. These included several in vitro tests (OECD Guideline 471: bacterial reverse mutation assay on *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100; OECD Guideline 476: mammalian cell gene mutation assay on mouse lymphoma L5178Y cells; OECD Guideline 473: mammalian chromosome aberration on mammalian cell line and rat liver RL4 cell line) and in vivo tests (OECD Guideline 474: mammalian erythrocyte micronucleus in mouse) (OECD 1997, REACH 2012).

Carcinogenicity

The chemical was not carcinogenic in a one-year, non-guideline dermal caricnogenicity study in male mice (C3H). Application of 50 mg of a 17% solution of the chemical twice weekly did not result in skin tumours. No further study details are available (OECD 1997).

Reproductive and Developmental Toxicity

Reproductive Toxicity

Due to the metabolic similarity between 2-butanol and the chemical, 2-butanol is considered a suitable analogue. It was used in a non-guideline, two-generation reproductive toxicity study using Wistar rats with a teratologic phase incorporated (OECD 1997). The first generation animals were administered 2-butanol in drinking water at three dose levels of 0.3, 1.0 or 3.0 %, prior to mating. The second generation animals were administered 0.3, 1.0 or 2.0 % of 2-Butanol in drinking water, where a 2.0 % dosage level was chosen as the highest dose after first generation animals exhibited toxicity at a level of 3.0 %.

No reproductive toxicity was observed in the parental animals. The lowest observed effect level (LOEL) of 2.0 % was reported based on a significant depression in growth of weanling rats of the offspring of the second generation and mild changes to rat kidney. The author concluded that these effects were not suggestive of overt toxicity and appeared to represent responses to stress. The no observed effect level (NOEL) was at 1.0 % (reported to be equivalent to 1500 mg/kg bw/day).

Developmental Toxicity

Several studies have investigated the effects of the chemical or 2-butanol on foetal development (OECD 1997). The overall conclusion from these studies is that the chemical produced low level developmental delay only at levels that cause maternal toxicity. The chemical was reported to be slightly foetotoxic in rats and mice following inhalation exposure of pregnant rats and mice to 3000 ppm. However, this dose level was also demonstrated to be maternally toxic.

Other Health Effects

Neurotoxicity

The neurotoxic potential of the chemical was assessed over five studies where the chemical was administered via inhalation to rats and via injection to cats (OECD 1997). It was concluded that there was no evidence to indicate that the chemical on its own directly produced nervous system damage. The NOAEL is reported at 5,000 ppm.

Additional studies have indicated the potential increase in neurotoxic potency of methyl n-butyl ketone (MnBK) and n-hexane by the chemical with reported evidence of neurological damage including: muscular weakness; histopathological axonal hypertrophy (enlargement of nerve fibres due to increased cell size); and degeneration in the sciatic nerve. This is reportedly due to its effects on metabolic pathways as a metabolic inhibitor or activator, dependent upon the chemical with which it is constituted.

Risk Characterisation

Critical Health Effects

The chemical possesses hazardous properties such as skin, eye and respiratory tract irritation. The chemical vapours may also cause drowsiness and dizziness.

Public Risk Characterisation

Although the use of this chemical in cosmetic products in Australia is not known, the chemical is reported to be used in a number of cosmetic products overseas.

This chemical is currently listed on Schedule 5 of the SUSMP for products containing greater than 25% of the chemical. There are also adequate first aid and safety instructions provided in the SUSMP document for this chemical.

Provided that normal precautions are taken to avoid prolonged, or repeated, skin contact and inhalation of chemical vapours, the public health risk posed by cosmetic or domestic products containing the chemical is expected to be minimal at expected concentrations.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered low if adequate control measures to minimise occupational exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or an employee at a workplace has adequate information to determine appropriate controls.

NICNAS Recommendation

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

Regulatory Control

Public Health

Considering the available information, sufficient scheduling and labelling is currently in place to mitigate any risks associated with the use of this chemical in domestic products.

Work Health and Safety

The chemical is recommended for classification and labelling under the current Approved Criteria and adopted GHS as below. This 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)* Repeated exposure may cause skin dryness or cracking (R66)* Irritating to respiratory system (Xi; R37)	Causes serious eye irritation - Cat. 2A (H319) Repeated exposure may cause skin dryness and cracking (AUH066) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Other Health Effects	Vapours may cause drowsiness and dizziness (R67)*	May cause drowsiness or dizziness - Specific target organ tox, single exp Cat. 3 (H336)

[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 label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from ocular and inhalation 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 storage, handling and use of a hazardous chemical are dependent 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:

- use of local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimisation of manual processes and work tasks through automation of processes;
- work procedures that minimise splashes and spills;
- regular cleaning of equipment and work areas; and
- use of 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 be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of 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 and physicochemical (physical) hazards) of chemicals are prepared; and
- management of risks arising from storage, handling and use of 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 physical hazards of the chemical has not been undertaken as part of this assessment.

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