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

12 September 2013

CAS Number: 108-10-1

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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.

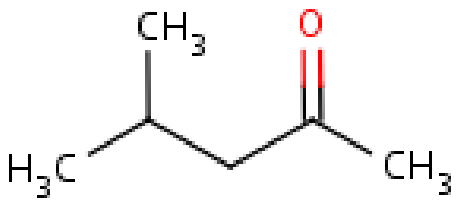
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	methyl isobutyl ketone MIBK 4-methyl-2-pentanone isopropyl acetone isobutyl methyl ketone
Structural Formula	
Molecular Formula	C6H12O
Molecular Weight (g/mol)	100.16
Appearance and Odour (where available)	Colourless liquid with a faint ketonic and camphor odour
SMILES	C(C)(=O)CC(C)C

Import, Manufacture and Use

Australian

The chemical was reported during the 2006 High Volume Industrial Chemicals call for information. The aggregated volume was less than 1000 tonnes per annum.

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

The chemical has reported commercial use including in:

- solvents; and
- viscosity adjusters.

International

The following international uses have been identified through the Consumer Product Information Database (CPID); 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 Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; US Household Products Database; and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use including:

- as a denaturant and solvent in cosmetic products.

The chemical has reported domestic use including in:

- paints, lacquers and varnishes with a concentration of up to 8 % (aerosol) for use in arts and crafts, home maintenance and other uses inside the home; a concentration of up to 12 % (aerosol) for use in auto products at home; and a concentration of up to 35 % (liquid) for home maintenance uses;
- insulating materials & corrosion inhibitors;
- adhesives and binding agents;
- cleaning/washing agents;
- colouring agents;
- fillers;
- anti-condensation agents; and
- surface treatment.

The chemical has reported domestic use in the SPIN database. However, it should be noted that SPIN does not distinguish between direct use of the chemical or use of the materials that are produced from chemical reactions using the chemical.

The chemical has reported commercial use including:

- as a coating solvent in cellulose-based and resin-based coating systems formulations (major use), including automotive, architectural and industrial maintenance coatings;

- in lubricants and additives;
- in hydraulic fluids and additives;
- in construction materials;
- in anti-freezing agents;
- in process regulators and fixing agents;
- in viscosity adjustors;
- in fuels & fuel additives;
- in impregnation materials; and
- in reprographic agents.

The chemical has reported site-limited use including;

- as a chemical intermediate and as a process solvent;
- in laboratory chemicals, e.g., manufacture of methyl amyl alcohol;
- in heat transferring agents;
- in denaturant for alcohol; and
- as a separating agent for metals from solutions of their salts and in the mining industries to extract plutonium from uranium.

The chemical has reported non-industrial use including:

- in non-agricultural pesticides and preservatives; and
- as an extraction solvent in the synthesis and purification of drugs.

Restrictions

Australian

This chemical is listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons) in Schedule 5. The Schedule 5 entry states as follows:

'METHYL ISOBUTYL KETONE, **except** in preparations containing 25 per cent or less of designated solvents'.

Schedule 5 chemicals are labelled with 'Caution'. These are substances with a 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 (SUSMP, 2012).

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):

Xn; R20 (acute toxicity)

Xi; R36/37 (irritation)

R66 (skin dryness or cracking)

Exposure Standards

Australian

The chemical has an exposure standard of 205 mg/m³ (50 ppm) time weighted average (TWA) and 307 mg/m³ (75 ppm) short-term exposure limit (STEL).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (TWA) of 83–208 mg/m³ in different countries such as Canada, Denmark, Europe, Ireland, Japan, Singapore, UK, and the USA.

An exposure limit (STEL) of 164–416 mg/m³ in different countries such as Canada, Europe, Ireland, Spain, Sweden, Switzerland, UK, and the USA.

Health Hazard Information

Toxicokinetics

Following oral exposure in rats, the chemical was rapidly absorbed with a Cmax of 0.644 mmol/L (maximum concentration) observed at about 15 minutes post-dosing. The chemical was detected at very low levels (0.006 mmol/L) after nine hours and was not detectable after 12-hours of dosing. The chemical was rapidly metabolised to the major metabolite, 4-hydroxy-4-methyl-2-pentanone (HMP; CAS No. 123-42-2), with a Cmax of 2.03 mmol/L after nine hours, and which remained detectable 12 hours after dosing. The plasma elimination half-life of the chemical was approximately 2.5 hours and that of HMP was 4.45 hours. No compounds other than HMP and the chemical were detected in the blood; the metabolism of the chemical to methyl isobutyl carbinol was also negligible. As dosing with the chemical would result in similar internal exposure to HMP with limited exposure to the chemical due to its rapid metabolism, the toxicity database on HMP can be used appropriately to support the evaluation of the subject chemical (OECD, 2005; REACH).

HMP was also identified as the major metabolite in guinea pigs following a single intraperitoneal (i.p.) administration of the chemical at 450 mg/kg bw. Serum half-life and clearance times of 66 minutes and six hours, respectively, were estimated for the chemical in this study. HMP was cleared from the blood within 16 hours. The percutaneous uptake rate in guinea pigs exposed epicutaneously to the chemical peaked at 10 to 45 minutes after the onset of a 150-minute exposure (US EPA, 2003; REACH).

In human volunteers exposed to the chemical at 10–200 mg/m³ for two hours during light exercise, relative uptake of the inhaled chemical ranged from 56.3 % to 61.7 %. The elimination of chemical from blood following cessation of a two-hour inhalation exposure was biphasic, with a half-life of 11–13 minutes during the first 30 minutes post-exposure in subjects exposed to 100 or 200 mg/m³. The half-life in blood during the second elimination phase (60 and 180 minutes post-exposure) was 59 and 74 minutes in subjects exposed to 100 and 200 mg/m³, respectively (US EPA, 2003).

Acute Toxicity

Oral

The chemical was of low acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats is > 2000 mg/kg bw (OECD, 1996).

Dermal

The chemical was of low acute toxicity in animal tests following dermal exposure. The median lethal dose (LD50) in rats is > 2000 mg/kg bw (REACH).

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in the HSIS (Safe Work Australia). While the available data do not support this classification, a transient anaesthetic effect was observed in humans following inhalation exposure to high vapour concentrations of the chemical (OECD, 1996). Therefore, in the absence of more comprehensive information, there are insufficient data to recommend removal of the current HSIS classification.

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in the HSIS (Safe Work Australia). Although no animal data are available, observations in humans (see **Neurotoxicity**) support this classification (US EPA, 2003).

Skin Irritation

Although the chemical produced no skin irritation in a study performed in accordance with OECD Test Guideline (TG) 404, daily applications of 10 mL on 10 cm² of skin for seven days caused flaking and drying of the skin (OECD, 1999).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in the HSIS (Safe Work Australia). While the available data do not clearly support this classification (OECD 1996; REACH; RTECS), in the absence of more comprehensive information, there are insufficient data to recommend removal of the current HSIS classification.

Sensitisation

Skin Sensitisation

No data are available. The chemical does not include any functional groups generally associated with skin sensitisation.

Repeated Dose Toxicity

Oral

The chemical is not considered to cause serious damage to human health from repeated oral exposure. The major effects noted following repeated exposures to high concentrations of the chemical were in the liver and kidneys (OECD, 2005; US EPA, 2003; REACH).

In a 13-week repeated oral (gavage) toxicity study in rats, no treatment-related effects were observed at 50 mg/kg bw/day. Dosing rats of both sexes with 1000 mg/kg bw/day resulted in lethargy for a few hours following dosing, which reportedly decreased in incidence and severity during the study. Doses of 250 mg/kg bw/day resulted in slightly increased terminal absolute or relative kidney weights in males and females. Doses of 1000 mg/kg bw/day resulted in increased terminal absolute and relative kidney weights (25–34 % in males, 20–22 % in females) compared with controls; increased terminal absolute (34 % in males, 39 % in females) and relative (42 % in males, 38 % in females) liver weights; statistically significant differences in other organ weights (adrenal glands, testis); and altered clinical chemistry parameters indicative of adverse liver and kidney effects. Histological examination of kidney tissues at this dose revealed an increased incidence of male rats with mild nephropathy, but no increase in such lesions in females. Aside from the kidney, histopathological lesions were not observed in the liver or adrenal glands or in any other tissue that was examined in the study. As histopathological examination of kidneys or livers from animals administered doses of 250 mg/kg bw/day revealed no adverse effects, a no observed adverse effect level (NOAEL) of 250 mg/kg bw/day was selected. Effects at higher doses included kidney changes, hepatomegaly and alterations in clinical chemistry and urinalysis parameters (OECD, 1996; US EPA, 2003; REACH).

In another repeated dose toxicity study, female Wistar rats were provided drinking water ad libitum (freely available) containing either no chemical or chemical at a saturated aqueous concentration of 1.3 % (estimated to be 1040 mg/kg bw/day) for 120 days. The rats were evaluated for treatment-related changes in food and water consumption, body weight, general appearance and behaviour, gross pathological examination, organ weights (liver, kidney), histopathology (sciatic nerve, brachial plexi, lumbo-sacral spinal ganglia, anterior and posterior thigh muscles, larynx, nasal cavity, brain, spinal cord, heart, lymph nodes, lungs, spleen, liver, and kidney), and performance in neurologic and neuromuscular function tests (balance, coordination, strength and behaviour). Statistically significant increases in mean absolute and relative kidney weights in treated rats were the only findings observed. The kidneys appeared normal at gross examination; histopathology examination revealed only renal tubular cell hyperplasia in 1/5 of the treated rats. Histological changes were not noted in any other organs in the treated rats (US EPA, 2003).

In a repeated dose oral toxicity study (OECD TG 422), Sprague Dawley (SD) rats were dosed (gavage) with 0, 30, 100, 300, or 1000 mg/kg bw/day of HMP (the main metabolite of the chemical) in distilled water for approximately 45 days. Males dosed at 100 mg/kg bw/day and greater had an increased incidence and/or severity of hyaline droplets in the tubular epithelium in the kidneys. Males dosed at 1000 mg/kg bw/day also had altered blood parameters, dilatation of the distal tubules of the kidneys, hepatocellular hypertrophy, and vacuolisation of the zona fasciculata of the adrenal glands. Decreased locomotor activity and stimulation responses were observed in both sexes at 300 and 1000 mg/kg/day. In females, dilatation of the distal tubules and fatty degeneration of the proximal tubular epithelium in the kidneys were observed at 300 mg/kg bw/day. At 1000 mg/kg bw/day, females showed reduced body weight gain, increased liver weight, and hepatocellular hypertrophy and kidney lesions similar to those noted at 300 mg/kg bw/day. The NOAEL was 30 mg/kg bw/day for males, based on a male-rat specific lesion which is not relevant to human hazard assessment (hyaline droplet nephropathy). The NOAEL for females was 100 mg/kg bw/day. The lowest observed adverse effect level (LOAEL) was 100 mg/kg bw/day for males and 300 mg/kg bw/day for females (OECD, 2005; REACH).

Dermal

No data are available.

Inhalation

No adverse systemic effects were reported in subchronic inhalation toxicity studies in rats, indicating that the chemical is likely to be of minimal toxicity from inhalation exposure.

In a repeated-dose inhalation toxicity study (OECD TG 413), B6C3F1 mice and Fischer 344 (F344) rats were exposed to atmospheres containing the chemical vapours at 0, 50, 250 or 1000 ppm (0, 0.20, 1.02 or 4.09 mg/mL), six hours/day for five days each week for 14 weeks. Male rats in the 250 and 1000 ppm groups showed an increase in hyaline droplets within the proximal tubule cells of the kidney, which are lesions specific to male rats. The no observed adverse effect concentration (NOAEC) was 50 ppm (0.20 mg/L) in male rats, based on a male-rat specific lesion not relevant to humans (hyaline droplet nephropathy). The NOAEC was 1000 ppm (4.09 mg/L) for female rats, and for male/female mice, based on a lack of adverse effects on clinical health or growth of the rats or mice at the highest dose (OECD, 2005; US EPA, 2003; REACH).

In a 13-week repeated dose inhalation toxicity study, SD rats were exposed to the chemical at 0, 250, 750, or 1500 ppm (0, 1024, 3073, and 6146 mg/m³) for six hours/day, five days/week, to evaluate effects on clinical signs, body weight, organ weights (liver and kidney), and gross pathology. One half of the rats at each exposure level were maintained on a restricted diet and the other half were fed ad libitum. The treatment groups on restricted diets also underwent daily schedule-controlled operant behavioural (SCOB) testing before exposure, throughout the 13-week exposure period, and for two weeks after exposure ceased. Although no treatment related clinical signs were noted, reduced activity was observed in the animals of 6146 mg/m³ group for the first 10 weeks and to a lesser degree in 3073 mg/m³ group during the first eight weeks of the study. Among the restricted-diet rats, no significant differences between treatment groups and the control group were observed in any of the SCOB test measurements. Mean relative and liver and kidney weights were significantly higher in the 3073 and 6146 mg/m³ groups fed ad libitum. The treatment had no effect on gross pathology of various organs. A NOAEL was not stated for this study (US EPA, 2003).

Additional repeated dose inhalation studies in rats and mice (nine days to five months) have either resulted in no effects or increased liver and kidney weights and hyaline droplet formation. Some evidence of slight narcosis and reduced activity has also been reported. While exposure to dogs at 410 mg/m³ for 90 days had no effect, one of the two monkeys exposed for the same time period to the same concentration, had focal chronic renal inflammation (OECD, 1996).

Genotoxicity

The chemical and its main metabolite (HMP) are not considered to have mutagenic or genotoxic potential as reported below.

The chemical tested negative (with and without metabolic activation) in several bacterial reverse mutation assays and in a gene mutation assay with *Saccharomyces cerevisiae*. The chemical also tested negative in a cell transformation assay using BALB/3T3 mouse embryo cells, in the unscheduled DNA synthesis assay in rat primary hepatocytes, and in the micronucleus cytogenetic assay in mice administered the chemical intraperitoneally. Although the chemical tested negative in a mouse lymphoma cell forward mutation assay (conducted using mouse lymphoma cell L5178Y tk+/tk- —with metabolic activation), results were equivocal when conducted without metabolic activation (OECD, 1996; US EPA, 2003; REACH). The main metabolite of the chemical (HMP) also tested negative in a bacterial reverse mutation assay and in a chromosomal aberration assay using a Chinese hamster lung cell line (CHL/IU) (OECD, 2005; REACH).

Carcinogenicity

The available data indicate that the chemical should be classified with the risk phrase ‘Limited evidence of a carcinogenic effect’ (Xn; R40) (REACH; IARC, 2012).

In a recent chronic inhalation toxicity study (OECD TG 451), F344 rats and B6C3F1 mice were exposed (whole body) to the chemical at concentrations of 0, 450, 900 or 1800 ppm for six hours a day, five days a week for two years. Although mortality was observed in all groups of rats, the survival was significantly decreased in males at 1800 ppm compared with controls (32/50 vs. 19/50). The treatment has no effect on the survival of female rats across all groups. Although chronic progressive nephropathy (CPN) was observed in all rats (including controls), there were significant treatment-related increases in both the incidence (1800 ppm) and severity in all exposed groups. In male rats, there were also increases in renal tubule hyperplasia at all exposure concentrations, and in renal tubule adenoma and adenoma or carcinoma (combined) at 1800 ppm; these lesions

are thought to represent a continuum in the progression of proliferative lesions in renal tubule epithelium resulting in increased severity of CPN, either through a2µ-globulin-dependent or independent mechanisms. Adrenal medullary hyperplasia was increased at 1800 ppm, and there was a positive trend for increases in benign or malignant phaeochromocytomas (combined). A a2µ-globulin-induced nephropathy suggests a mechanism leading to xenobiotic-induced renal carcinogenesis that is specific to the male rat and not relevant to humans (REACH).

Increased incidences of CPN were also observed in female rats at all exposure concentrations and in severity at 1800 ppm, indicating that CPN was increased by mechanisms in addition to those related to a2µ-globulin. There were also renal mesenchymal tumours in two female rats exposed at 1800 ppm, that had not been observed in historical control animals. In mice, the incidences of hepatocellular adenomas, and hepatocellular adenoma or carcinoma (combined) were increased in both sexes exposed to 1800 ppm of the chemical. Based on these findings, the chemical was considered to be a hepatocarcinogen in both sexes of mice. The study also indicated the primary target of toxicity and carcinogenicity for the chemical were the kidneys in rats and the liver in mice (REACH).

Based on the above study, the International Agency for Research on Cancer (IARC) has evaluated the chemical as possibly carcinogenic to humans (Group 2B) (IARC, 2012). It was also suggested that the chemical-induced tumours in rodents probably arose through a non-genotoxic mechanism. This is supported by the findings that the chemical is generally not genotoxic in a variety of systems (see **Genotoxicity**), although its two metabolites (4-hydroxymethyl isobutyl ketone and 4-methyl-2-pentanol) have not been completely evaluated for genotoxicity (IARC, 2012).

Reproductive and Developmental Toxicity

Results of reproductive and developmental toxicity studies conducted in animals indicate that the chemical or its metabolites are not expected to be specific reproductive or developmental toxins (OECD, 1996; OECD, 2005; REACH).

In a two-generation inhalation reproduction toxicity study (US EPA OPPTS Guideline 870-3800; OECD TG 416), rats were exposed (whole body) to the chemical at 0, 500, 1000 and 2000 ppm (0, 2.04, 4.09 and 8.18 mg/L or 0, 2012, 4093 and 8178 mg/m^3) for six hours a day, seven days a week. There were no effects on reproductive parameters, offspring growth, or developmental landmarks at any exposure level. The NOAEC for parental systemic toxicity (apart from male nephropathy) was considered to be 1000 ppm (4.09 mg/L), based on transient reduced body weight gain and food consumption. The NOAEC for reproductive toxicity was considered to be 2000 ppm (8.18 mg/L), the highest concentration tested (OECD, 1996; REACH).

In another reproductive toxicity study (OECD TG 422), rats were treated orally (gavage) with the metabolite (HMP) for 45 days, with doses of 30, 100, 300, and 1000 mg/kg bw/d in distilled water, beginning 14 days before mating. Some effects in reproductive parameters (decreased fertility and implantations) and pup viability at the highest dose (1000 mg/kg bw/d) were seen in the presence of maternal toxicity (reduced weight gain, statistically significant changes in haematology, clinical biochemistry and relative organ weights; renal and hepatic histopathological lesions). Developmental and reproductive NOAELs of 300 mg/kg bw/d, based on reduced live pup births and other pup viability parameters, and lower reproductive indices (fertility and implants) at 1000 mg/kg bw/d, were determined (OECD, 2005; REACH).

In a developmental toxicity study (OECD TG 414), female rats and mice were exposed (whole body) to vapours of the chemical at 0, 300, 1000, or 3000 ppm (0, 1.23, 4.09, or 12.3 mg/L) (1229, 4106, 12292 mg/m^3) on gestational days 6–15, for six hours a day. Foetal toxicity was observed only in the presence of maternal toxicity. The NOAEC for maternal toxicity was 1000 ppm (4.09 mg/L) in both species, based on clinical signs of toxicity, increased kidney weights and decreased food consumption (rat only) and increased liver weights (mice only) at 3000 ppm. The NOAEC for foetotoxicity was 1000 ppm (4.09 mg/L) in both species, based on reduced foetal body weights, increased occurrence of retarded ossification, and an increased incidence of dead foetuses (mice only) at 3000 ppm. There were no developmental effects associated with the exposure to the metabolite at any concentration in either species; the NOAEL for developmental toxicity was 3000 ppm (12.3 mg/L) (OECD, 1996; REACH).

Other Health Effects

Neurotoxicity

The available data indicate that the chemical may result in some neurological effects and may enhance the neurotoxicity of other chemicals (OECD, 1996; US EPA, 2003).

Acute inhalation exposure of humans to the chemical has resulted in transient sensory irritation, neurological effects, and strong odour sensation. The incidence of sensory irritation generally increased with the exposure level. The thresholds for odour and irritation were reported to be 402 and 1393 mg/m³, respectively. An index of the prevalence and intensity of neurological symptoms was significantly increased in a group exposed to 200 mg/m³, compared with a 10 mg/m³ group (US EPA, 2003).

In a more detailed study in humans, volunteers were exposed to the chemical in an exposure chamber at 10, 100, or 200 mg/m³ on three separate occasions for two hours under conditions of light exercise. The mean index of neurological effects was marginally significantly different between exposure levels. It was also reported that the mean index of reported neurological symptoms (headache, nausea, and vertigo) generally increased with the exposure level and decreased rapidly after cessation of exposure. The data also indicated that neurological effects (vertigo) occurred in one of the eight volunteers at 10 mg/m³ and two of the eight subjects reported headache and vertigo with exposure to 100 or 200 mg/m³ (US EPA, 2003).

Several studies of occupational exposures to solvent vapour mixtures that contained the chemical have also reported various neurological effects. As exposure levels for individual solvents were not reported, the degree to which the chemical contributed to the observed neurological effects from the solvent vapour mixtures is uncertain (US EPA, 2003).

Several studies in animals have also been conducted to examine the potential of the chemical to induce neurotoxicity. Although some studies have reported evidence of neurobehavioural effects, this was not the case in several other studies designed specifically to measure neurotoxicity (OECD, 1996). The chemical has also been shown to enhance the known peripheral neurotoxicity of hydrocarbons such as n-hexane (OECD, 1996).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity under conditions of high dose repeated exposure), systemic acute effects (acute toxicity from inhalation route of exposure), and local effects (eye and respiratory irritation). Following repeated application of the chemical, flaking and drying of the skin could also occur.

Public Risk Characterisation

Although use in cosmetic and domestic products in Australia is not known, the chemical has reported domestic uses overseas, along with potential cosmetic use, where the general public may be exposed to the chemical through dermal and/or inhalation routes. The main domestic use of the chemical is in paints with stated concentrations of up to 12 % for aerosol form and up to 35 % for liquid form, with other products containing lower levels (see **Import, manufacture and use**). Skin, eye and respiratory irritations are not expected from exposure to low concentrations of the chemical in products other than certain paints.

In Australia, for industrial uses, the chemical is currently listed on Schedule 5 of the SUSMP for preparations containing 25 per cent or less of designated solvents. At concentrations greater than 25 %, a number of warning statements, first aid instructions and safety directions relating to the chemical apply.

Given that the chemical has been recommended for classification as a Category 3 carcinogen (see **Carcinogenicity**), the chemical may pose an unreasonable risk to public health in products where it is present at higher concentrations. The risks could be managed through changes to poisons scheduling, where warning statements, safety directions and first aid instructions will then apply to any cosmetic or domestic products containing the chemical.

Occupational Risk Characterisation

Given the critical health effects (systemic long-term/systemic acute/local), the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise (dermal, ocular and inhalation) 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.

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendments to scheduling and classification are 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

It is recommended that an amendment to the current entry for the chemical in the SUSMP be considered. The safety directions and warning statements should also be reviewed.

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]
Acute Toxicity	Harmful by inhalation (Xn; R20)*	Harmful if inhaled - Cat. 4 (H332)
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)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	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 chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, 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 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:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- 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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