2-Hexanone: Human health tier II assessment

03 July 2015

CAS Number: 591-78-6

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.

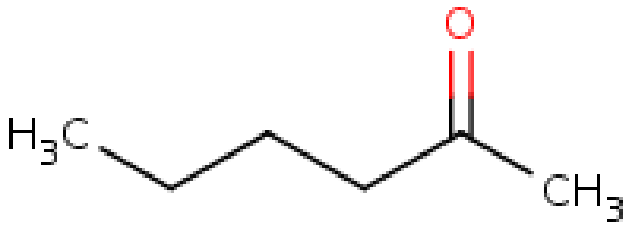
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-oxohexane methyl n-butyl ketone (MBK) propylacetone
Structural Formula	
Molecular Formula	C6H12O
Molecular Weight (g/mol)	100.16
Appearance and Odour (where available)	Colourless liquid with a pungent acetone-like odour
SMILES	C(C)(=O)CCCC

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through Galleria Chemica, the United States (US) Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported domestic uses including in paints and lacquers.

The chemical has reported commercial use in the printing of plasticised fabrics.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- the Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II—Part 1: List of substances which must not form part of the composition of cosmetic products;
- the European Union (EU) Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and
- the New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

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):

- T; R48/23 (repeated dose toxicity)
- Repr. Cat. 3; R62 (reproductive toxicity)
- R67 (vapours may cause drowsiness and dizziness)

Exposure Standards

Australian

The chemical has an exposure standard of 20 mg/m^3 (5 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica).

Exposure limits of 4–410 mg/m^3 (1–100 ppm) TWA and 8–168 mg/m^3 (2–40 ppm) short-term exposure limit (STEL)/MAK/occupational exposure limit (OEL) in different countries such as Canada, Denmark, Estonia, France, Japan, Spain, Sweden, Switzerland and the US.

Health Hazard Information

Toxicokinetics

Based on the available toxicokinetic data, the chemical is well absorbed, rapidly metabolised and eliminated in the breath, urine and faeces.

Human volunteers were exposed to the chemical as vapour at concentrations of 10 or 50 ppm for 7.5 hours or 100 ppm for four hours by inhalation. Approximately 75–92 % of the inhaled chemical was absorbed by the lungs and respiratory tract. Similarly, beagle dogs that inhaled the chemical at concentrations of 50 or 100 ppm for six hours had an absorption rate of approximately 65–68 %. In another human study, at least 66 % of the chemical was absorbed when administered orally at a concentration of 0.1 mg/kg. Approximately 40 and 26 % of the chemical was excreted in the breath and urine, respectively, in the eight days following administration. In a separate study with two human volunteers who were given occlusive application of the chemical to their shaved forearms, the calculated skin absorption rates were 4.8 and 8.0 pg/min/cm^2 (ATSDR, 1992; US EPA IRIS, 2009).

In rats administered the chemical at concentrations of 20 or 200 mg/kg bw by gavage, at least 98 % of the administered chemical was absorbed. Approximately 1.2, 44 and 38 % of the chemical was excreted in the faeces, breath and urine, respectively, with 16 % remaining in the carcass after 48 hours. In another rat study, tissue distribution was reported to be widespread, especially to the liver and blood, after oral administration of the chemical at a concentration of 200 mg/kg bw. The chemical was eliminated from the serum within six hours (ATSDR, 1992; US EPA IRIS, 2009).

The chemical is hydroxylated to 5-hydroxy-2-hexanone, which is then either oxidized to 2,5-hexanedione or reduced to 2,5-hexanediol and, to a small extent, may be converted to 2,5-dimethyl-2,3-dihydrofuran. The predominant metabolite found in blood is 2,5-hexanedione, which is believed to cause neurotoxicity. The metabolites 2,5-hexanediol and 2,5-hexanedione were cleared rapidly in rats in 8 and 16 hours, respectively (ATSDR, 1992; US EPA IRIS, 2009).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) values in rats and mice are 2590 and 2430 mg/kg bw, respectively. No details on observed sub-lethal effects were provided (US EPA IRIS, 2009; HSDB; RTECS).

Dermal

The chemical has low acute toxicity based on results from an animal test following dermal exposure. The LD50 in rabbits is 4800 mg/kg bw. No details on observed sub-lethal effects were provided (HSDB; RTECS).

Inhalation

Limited data are available. Exposure to 8000 ppm (approximately 32 mg/L) of the chemical for four hours resulted in mortalities in all exposed animals, while exposure to 4000 ppm (approximately 16 mg/L) for four hours did not result in mortalities. In the absence of more comprehensive information, there is insufficient evidence to recommend hazard classification for the chemical (ATSDR, 1992; US EPA IRIS, 2009; HSDB; RTECS).

Corrosion / Irritation

Skin Irritation

Limited data are available. The available data suggest that the chemical is not a skin irritant.

The chemical was applied undiluted to the skin of rabbits for 24 hours. Grade 1 irritation was observed in the animals. The chemical was concluded to be minimally irritating. No further details were provided (ATSDR, 1992).

In a standard Draize test, the chemical was applied onto the skin of rabbits at a dose of 500 mg for 24 hours. Mild skin irritation was observed. No further details were provided (RTECS).

Eye Irritation

Limited data are available. Based on the available data, mild to moderate eye irritation was observed after instillation of the chemical. However, in the absence of more comprehensive information, there is insufficient evidence to recommend hazard classification.

The chemical was instilled undiluted into the eyes of rabbits. Moderate corneal necrosis (Grade 3) was observed in the animals after instillation. No further details were provided (ATSDR, 1992).

In a standard Draize test, the chemical was instilled into the eyes of rabbits at a dose of 500 mg for 24 hours. Mild eye irritation was observed. No further details were provided (RTECS).

Observation in humans

In humans, acute exposure to high vapour concentrations of the chemical caused eye and respiratory irritation. Men exposed to the chemical at concentrations of 9.4, 26.6 or 81.9 mg/L for one minute or less showed strong eye and nasal irritation. Moderate eye and nasal irritation was observed after a brief exposure to 4.1 mg/L or the chemical (US EPA IRIS, 2009; HSDB; RTECS).

Sensitisation

Skin Sensitisation

No data are available.

The chemical and its metabolites have no functional groups that present alerts for skin sensitisation based on their molecular structures as profiled by the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure–Activity Relationship (QSAR) Toolbox v3.2.

Repeated Dose Toxicity

Oral

Based on the available data, signs of neurotoxicity were observed in the animals after repeated oral exposure to the chemical. The effects observed were not sufficient to warrant hazard classification.

In a drinking water study, male CD/COBS(SD) rats (10 animals/group) were administered the chemical (96 % purity) in drinking water at concentrations of 0, 0.25, 0.5 or 1.0 % (approximately 0, 143, 266 or 560 mg/kg bw/day, respectively) for 13 months. Dose-dependent reductions in body weights were observed in all treated animals. Dose-dependent increases in relative liver and kidney weights were observed in the animals in the 0.5 and 1.0 % groups. Significant increases in relative testes weights were also observed in the animals in the 1.0 % group. Clinical signs of neurotoxicity were observed in the animals in the 0.5 and 1.0 % groups, including decreased extension of the hind limbs, hind limb weakness and muscular atrophy of the hind limbs. Axonal swellings and myelin infoldings were observed in all treatment groups. A lowest observed adverse effect level (LOAEL) of 143 mg/kg bw/day was established in this study (US EPA IRIS, 2009; HSDB).

In another drinking water study, female Wistar rats (five animals/group) were administered the chemical (purity unspecified) in drinking water at concentrations of 0, 0.65 or 1.3 % (approximately 0, 480 or 1,010 mg/kg bw/day, respectively) for 120 days. Dose-dependent decreases in food and water consumption, body weight gain and absolute liver weights were observed in the treated animals. Increases in absolute kidney weights and dose-dependent increases in relative kidney weights were also observed in the treated animals. Mild atrophy, affecting the skeletal muscles of the hind limbs, was observed in 2/5 animals in the 0.65 % group and slight to severe atrophy was observed in 4/5 animals in the 1.3 % group. A LOAEL of 480 mg/kg bw/day was established in this study (US EPA IRIS, 2009).

Male CD/COBS(SD) rats were administered the chemical (96 % purity) at concentrations of 0 or 660 mg/kg bw/day by gavage for 90 days. Significantly reduced body weights were observed in the treated animals after 10 weeks of treatment. Signs of neurotoxicity including severe hind limb dragging, paralysis, multifocal axonal swellings, myelin infolding and paranodal retraction were observed in the treated animals. The treated males also developed atrophy of the germinal epithelium of the testes. However, the statistical significance of this observation was not provided (ATSDR, 1992; US EPA IRIS, 2009; HSDB).

Male SPF-Wistar rats were administered the chemical (98 % purity) at concentrations of 0 or 400 mg/kg bw/day by gavage for 40 weeks. Decreased weight gain was observed in the treated animals. Temporary weakness of the hind limbs was observed in the treated animals from 17–28 weeks of exposure. Recovery was observed after 28 weeks (ATSDR, 1992; US EPA IRIS, 2009; HSDB).

Guinea pigs (five animals/group) were administered the chemical (purity unspecified) in drinking water at concentrations of 0, 0.1 or 0.25 % (approximately 0, 97 or 243 mg/kg bw/day, respectively) for 24 weeks. Increased body weights were observed in the treated animals. The study authors indicated that this effect could be due to decreased locomotor activities observed in the treated animals. Abnormal pupillary responses to light were observed at 0.25 % for the first five weeks of treatment. By the end of the study, significantly impaired pupillary responses were observed in all treatment groups (ATSDR, 1992; US EPA IRIS, 2009; HSDB; RTECS).

Adult leghorn laying hens (three animals/group) were administered the chemical (70 % purity) at concentrations of 0 or 100 mg/kg bw for 90 consecutive days. Decreased body weight was observed in the treated animals. The treated animals developed severe ataxia or near paralysis after 50 days of exposure. Swelling or degeneration of the thoracic and lumbar regions of the spinal cord was also observed in the treated animals (ATSDR, 1992; US EPA IRIS, 2009).

Dermal

Limited data are available. Based on the available data, signs of neurotoxicity were observed in hens after repeated dermal exposure to the chemical. However, in the absence of more comprehensive information, there is insufficient evidence to recommend hazard classification.

The chemical (99 % purity) was applied with a micropipette to the backs of five leghorn laying hens' necks at a concentration of 100 mg/kg bw/day for 90 consecutive days. Ataxia and axonal swellings were observed in the animals. However, it is noted that

no measures to prevent licking the application sites were detailed in the study. Therefore, it was not possible to conclude that the effects observed were only due to dermal absorption of the chemical (ATSDR, 1992; US EPA IRIS, 2009).

Inhalation

The chemical is classified as hazardous with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure through inhalation' (T; R48/23) in the HSIS (Safe Work Australia). Although the animal data are not fully consistent with this classification, the observation of neuropathy in humans exposed to comparatively low concentrations of the chemical indicates that this classification is appropriate.

Male Sprague Dawley (SD) rats (18 animals/group) were exposed to the chemical (purity unspecified) at concentrations of 0, 100 or 330 ppm (approximately 0, 0.41 or 1.35 mg/L, respectively), six hours/day, five days/week for 72 weeks. Reductions in body weight gain were observed in the treated animals. Progressive hind limb weakness was observed in one animal exposed at 330 ppm, while non-progressive slight weakness was observed in three animals exposed at 100 ppm. Severe paralysis of the nerve roots in spinal, sciatic and tibial nerves was observed in one animal exposed to 330 ppm (US EPA IRIS, 2009).

Groups of six young adult rats (strain not specified) were exposed to the chemical (purity unspecified) at a concentration of 1300 ppm (approximately 5.33 mg/L), six hours/day, five days/week for 40 weeks. Slow progressive weight loss was observed after 10 weeks of exposure. Hind limb footdrop, hind- and fore limb weakness, and nerve fibre swelling and degeneration were also observed in the exposed animals (ATSDR, 1992; US EPA IRIS; 2009).

Male SD rats (10 animals/group) were exposed to the chemical (purity unspecified) at concentrations of 0, 100 or 1000 ppm (approximately 0, 0.41 or 4.1 mg/L, respectively), six hours/day, five days/week for 25–29 weeks. Significant reductions in body weight were observed at 1000 ppm at weeks 2–10 and 20–24. In all treated animals, significant decreases in the maximum motor conduction velocity of the sciatic-tibial nerves and the ulnar nerves were observed at weeks 29 and 17, respectively. Behavioural changes including reduced response rate in bar-pressing studies were also observed. These effects manifested earlier at 1000 ppm. A lowest observed adverse effect concentration (LOAEC) of 0.41 mg/L was established in this study (ATSDR, 1992; US EPA IRIS, 2009; HSDB).

SD rats (six animals/group) were exposed to the chemical (96.7 % purity) at concentrations of 0 or 100 ppm (approximately 0 or 0.41 mg/L, respectively), 22 hours/day, seven days/week for six months. After four months of exposure, giant axonal swellings and demyelination were observed in the fibres of the tibial nerves, medulla oblongata and cerebellum. However, no clinical signs of neuropathy were observed (ATSDR, 1992; US EPA IRIS, 2009).

Male Crl:COBS/CD[SD]BR rats (five animals/group) were intermittently exposed to the chemical (96.1 % purity) at concentrations of 0 or 700 ppm (approximately 0 or 2.87 mg/L, respectively) for 11 weeks. Significant reductions in weight gain were observed in the exposed animals within three days of exposure. After eight weeks, marked reductions in total leukocyte counts were observed in the exposed animals. However, no damage to the bone marrow was observed. Marked and significant reductions in absolute and relative testes weight and atrophy of testicular germinal epithelium were observed in the exposed animals. Clinical signs of neurotoxicity including reduced body muscle tone and weakened hind- and fore limb grasping of a wire mesh were observed after two weeks of exposure (ATSDR, 1992; US EPA IRIS, 2009; HSDB).

Severe neurotoxicity was observed in rats (strain not specified) continuously exposed to the chemical at a concentration of 225 ppm (approximately 0.9 mg/L) for seven days. In another study, signs of neurotoxicity including paralysis and axonal swelling were observed in rats (strain not specified) exposed to the chemical at a concentration of 225 ppm for 9.5 weeks or 400 ppm (approximately 1.6 mg/L) for six weeks. In another study, histopathological effects including demyelination of the sciatic nerve and axonal hypertrophy were observed in Wistar rats (20 animals/group) exposed eight hours/day, five days/week to the chemical at concentrations of 40 ppm (approximately 0.16 mg/L) for 22–88 days or 50 ppm (approximately 0.2 mg/L) for six months (ATSDR, 1992; US EPA IRIS, 2009; HSDB).

Male monkeys were exposed to the chemical (purity unspecified) at concentrations of 0, 100 or 1000 ppm (approximately 0, 0.41 or 4.1 mg/L, respectively), six hours/day, five days/week for up to 10 months. Significant decreases in the motor conduction velocity of the sciatic-tibial nerves and the ulnar nerves were observed at 1000 ppm. Decreased amplitude of evoked muscle action potential was also observed at 1000 ppm. Similar effects were observed at 100 ppm. The recovery to pre-exposure motor conduction velocity values took two and six months for the 100 and 1000 ppm groups, respectively (ATSDR, 1992; US EPA IRIS, 2009; HSDB).

Cats were exposed to the chemical (purity unspecified) at concentrations of 0 or 400 ppm (approximately 1.6 mg/L), 24 hours/day for five weeks or more. The initial exposure to 600 ppm of the chemical was decreased to 400 ppm to prevent weakness and weight loss. Hind limb dragging, followed by fore limb weakness and eventual paralysis were observed in the exposed animals. Axonal swelling and demyelination of the nerve fibres, and a significant decrease in the ulnar nerve conduction velocity were observed in the exposed animals. In a follow-up study on one of the exposed animals, the animal showed signs of recovery during a 4.5-month treatment-free period (ATSDR, 1992; RTECS).

Adult leghorn laying hens (five animals/group) were exposed to the chemical (70 % purity) at concentrations of 0, 10, 50, 100, 200 or 400 ppm (approximately 0, 0.04, 0.2, 0.4, 0.8 or 1.6 mg/L) for 13 weeks, followed by a 4-week recovery period. Mortalities were observed in 1/5 and 2/5 animals at 200 and 400 ppm, respectively. Reductions in body weights were observed at 100, 200 and 400 ppm. Mild ataxia, which progressed to near-paralysis, was observed after four weeks of exposure to 50 ppm of the chemical. This effect was observed earlier at higher concentrations. Axonal swellings and demyelination were observed in the spinal cord at 50 ppm and in both spinal cord and peripheral nerves at 100, 200 and 400 ppm. It is noted that the test substance used in this study also contained 30 % methyl isobutyl ketone (MIBK; CAS No. 108-10-1). Therefore, it was not possible to ascertain whether or not the effects observed were caused by the chemical (ATSDR, 1992; US EPA IRIS, 2009; RTECS).

Genotoxicity

No data are available.

The chemical and its metabolites have no functional groups that present alerts for mutagenicity based on their molecular structures as profiled by the OECD QSAR Toolbox v3.2.

Carcinogenicity

No data are available.

The chemical and its metabolites have no functional groups that present alerts for carcinogenicity based on their molecular structures as profiled by the OECD QSAR Toolbox v3.2.

Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 3 substance toxic to reproduction—with the risk phrase ‘Possible risk of impaired fertility’ (Xn; R62) in the HSIS (Safe Work Australia). The available data support this classification.

Male Crl:COBS/CD[SD]BR rats (five animals/group) were intermittently exposed to the chemical (96.1 % purity) at concentrations of 0 or 700 ppm (approximately 0 or 2.87 mg/L, respectively) for 11 weeks. Significant reductions in weight gain were observed in the exposed animals within three days of exposure. Marked and significant reductions in absolute and relative testes weight and atrophy of testicular germinal epithelium were observed in the exposed animals (ATSDR, 1992; US EPA IRIS, 2009; HSDB).

In a drinking water study, male CD/COBS(SD) rats (10 animals/group) were administered the chemical (96 % purity) in drinking water at concentrations of 0, 0.25, 0.5 or 1.0 % (approximately 0, 143, 266 or 560 mg/kg bw/day, respectively) for 13 months. Dose-dependent reductions in body weights were observed in all treated animals. Significant increases in relative testes weights were also observed in the animals in the 1.0 % group (US EPA IRIS, 2009; HSDB).

Pregnant Fischer 344 (F344) rats (25 animals/group) were exposed to the chemical (purity unspecified) at concentrations of 0, 1000 or 2000 ppm (approximately 0, 4.10 or 8.19 mg/L, respectively), six hours/day on gestational days (GD) 1-21. Reductions in maternal weight gain were observed at 1000 and 2000 ppm. Hair loss, lack of muscular coordination and weakness were observed in some of the animals after 20 days of exposure to the chemical at 2000 ppm. Significant decreases in the number and weight of live offspring were observed at 2000 ppm. Significant dose-dependent reductions in growth were observed in the male offspring. Behavioural alterations, including reduced activity in the open field, increased activity in the running wheel and deficits in avoidance conditioning, were observed in the offspring of the exposed animals. The results indicated that maternal exposure to the chemical was associated with hyperactivity in young rats and decreased activity in the elderly rats. The authors

suggested that this was due to premature ageing resulting from hyperactivity at an earlier age. A lowest observed adverse effect concentration (LOAEC) of 1000 ppm (approximately 4.10 mg/L) for maternal toxicity was established in this study while the effects on offspring (not of a type to be secondary to maternal toxicity) were seen from 2000 ppm (approximately 8.19 mg/L) (ATSDR, 1992; US EPA IRIS, 2009; HSDB; RTECS).

Other Health Effects

Neurotoxicity

The chemical is classified as hazardous with the risk phrase 'Vapours may cause drowsiness and dizziness' in the HSIS (Safe Work Australia). Acute inhalation data are not available to indicate whether acute central nervous system depression occurs after exposure to the chemical. However, on repeated dosing, peripheral neurotoxicity has been widely reported.

Signs of neurotoxicity, including muscle weakness, ataxia, paralysis, axonal swellings, myelin infoldings and a decrease in the motor nerve conduction velocity, were observed in the animals after repeated oral, dermal and inhalational exposure to the chemical (refer to **Repeated Dose Toxicity** section).

Four male beagle dogs were administered the chemical (>97 % purity) at a concentration of 300 mg/kg bw/day by daily subcutaneous injection for 11 months. Signs of neurotoxicity including muscle weakness, difficulty in walking and axonal swellings in the distal peripheral nerves were observed in the treated animals (US EPA IRIS, 2009).

Leghorn laying hens (three animals/group) were administered the chemical (70 % purity) at concentrations of 100 or 200 mg/kg bw/day by intraperitoneal (i.p.) injections for 90 days. Progressive ataxia to paralysis was observed in the treated animals. Histopathological changes including axonal degeneration and macrophages were also observed in the treated animals (US EPA IRIS, 2009).

Observation in humans

In 1973, an outbreak of distal polyneuropathy was reported in 86/1157 workers exposed to the chemical for 10 months in a fabric production plant. The approximate atmospheric concentrations of the chemical were calculated to be 9.2 and 36 ppm in front of and behind the printing machines, respectively. Characteristic signs of neuropathy observed included muscle weakness, sensory loss in the hands and feet, and loss of reflexes. Reduced motor conduction velocities and increased distal latencies were observed in the ulnar, peroneal, tibial and sural nerves. Weight loss was observed in eight workers who had moderate to severe neurological impairment. Marked improvement was observed in the affected workers when the use of the chemical was discontinued. However, it was not possible to determine if the effects observed were synergistic effects with other chemicals used at the plant (ATSDR, 1992; US EPA IRIS, 2009; HSDB).

Symmetrical polyneuropathy was observed in a 35-year-old man who was occupationally exposed to lacquer products containing the chemical and other compounds. The onset of polyneuropathy occurred in the patient after approximately six months of repeated exposure to the chemical. Clinical signs of polyneuropathy observed included tingling of the feet and mild clumsiness of gait which progressed rapidly to the upper extremities, finally resulting in a wheelchair-bound condition. At biopsy, diffused fibrosis and loss of nerve fibres at the sural nerves, and enlarged axons with neurofibrillary tangles were observed. After removal of the chemical from lacquer products, recovery was observed. A similar reversible progressive distal extremity weakness was observed in a 19-year-old co-worker of the patient (US EPA IRIS, 2009; HSDB).

In an investigation on 26 painters, one probable and two definite cases of peripheral neuropathy were identified. The paints used contained the chemical at a concentration of 44 %. In these cases, weight loss, numbness and tingling of the feet, and progressive weakness from lower to upper extremities were observed after repeated exposure to the paints. The weakness eventually progressed until the patients could not stand without assistance. None of these patients had a history of alcoholism, neurological disease or took medications that could result in the effects observed (US EPA IRIS, 2009).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (neurotoxicity and reproductive toxicity), particularly by inhalation of the chemical as vapour.

Public Risk Characterisation

The use of the chemical in domestic products in Australia is not known. Internationally, the chemical is reported to be used in domestic products (paints and lacquers). However, the US National Library of Medicine (NLM) Household Products Database did not identify any domestic product containing the chemical. The hazards of the chemical are widely known and alternate chemicals, such as MIBK (CAS No. 108-10-1), are expected to be used in place of the chemical. 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

During product formulation, inhalational exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise inhalational exposure 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 the appropriate controls.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) 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

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 and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)*	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	Suspected of damaging fertility - Cat. 2 (H361f)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Other Health Effects	Vapours may cause drowsiness and dizziness (R67)*	May cause drowsiness or dizziness (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 industry

Control measures

Control measures to minimise the risk from inhalational 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 that could 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 help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the 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.

References

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