Methane, trichloro-: Human health tier II assessment

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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.

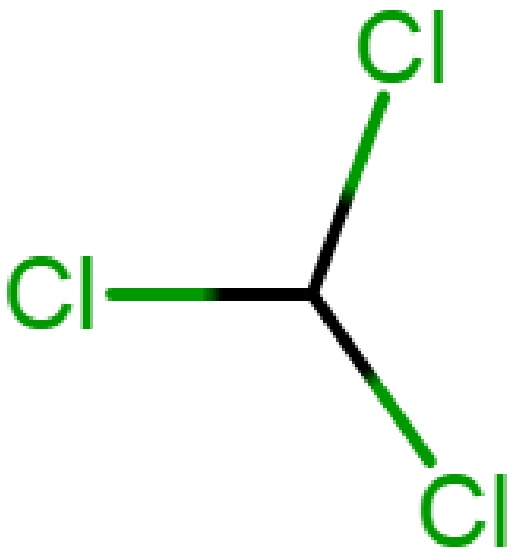
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Chloroform Trichloromethane
Structural Formula	
Molecular Formula	CHCl3
Molecular Weight (g/mol)	119.38
Appearance and Odour (where available)	Colourless liquid with a pleasant odour
SMILES	C(Cl)(Cl)Cl

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 commercial uses, including:

- in photography;
- as a dry cleaning agent; and
- in fire extinguishers.

The chemical has reported site-limited uses, including:

- as an extraction and purification solvent;
- in refrigerant, dye and plastic production; and
- in chemical manufacturing.

The chemical has reported non-industrial use including in drug and pesticide production.

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was between 1 and 100 tonnes.

The National Pollutant Inventory (NPI) holds data for all sources of the chemical in Australia.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; 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; and eChemPortal: Organisation for Economic and Co-operation and Development (OECD) High Production Volume chemical program (HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use as a solvent.

The chemical has reported domestic uses including:

- as a cleaning agent; and
- in adhesives (binding) agents.

The chemical has reported commercial uses, including in:

- lubricant additives and plasticisers;
- fire extinguishers to lower the freezing temperature of carbon tetrachloride; and
- antifoam agents.

The chemical has reported site-limited uses, including:

- as a solvent for fats, oils, rubber, alkaloids, waxes and resins;

- in flotation agents;
- in refrigerant and fluoropolymer production (hydrochlorofluorocarbon-22) (>90 %);
- in organic chemical synthesis; and
- for dye preparation.

The chemical has reported non-industrial uses, including:

- in drug (penicillin) and pesticide production; and
- as an anaesthetic.

Restrictions

Australian

The chemical is listed in Schedule 6 of the *Poisons Standard* (the Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP, 2014) as follows:

'CHLOROFORM except:

(a) when included in Schedule 2 or 4; or

(b) in preparations containing 10 per cent or less of chloroform'.

'Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label.'

The chemical is also listed in schedules 2 and 4 of the SUSMP for the use in preparations for therapeutics and in anaesthesia, respectively.

International

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

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

The chemical is also listed in Annex XVII to REACH Regulations with specific conditions for use 'as substances', or 'as constituents of other substances, or in mixtures in concentrations equal to or greater than 0,1 % by weight, where the substance or mixture is intended for supply to the general public and/or is intended for diffusive applications such as in surface cleaning and cleaning of fabrics'.

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; R22 (acute toxicity)
- Xn; R48/20/22 (repeated dose toxicity)
- Xi; R38 (irritation)
- Carc. Cat. 3; R40 (carcinogenicity)

Exposure Standards

Australian

The chemical has an exposure standard of 10 mg/m^3 (2 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica).

TWA of:

- 9.78-14.7 mg/m^3 (2–3 ppm) in Denmark, Europe, Ireland, Japan, South Africa, United Kingdom and USA;
- 20–24.4 mg/m^3 (5 ppm) in China and Canada (Quebec);
- 40–50 mg/m^3 (8–10 ppm) in Chile, Greece, Malaysia and Canada (Alberta); and
- 2.5 mg/m^3 (0.5 ppm) in Germany.

Short-term exposure limits (STEL) of:

- 225–250 mg/m^3 (50 ppm) in Egypt, France and Mexico;
- 25 mg/m^3 in Netherlands and Sweden;
- 5 mg/m^3 (1 ppm) in Switzerland; and
- 4 ppm in USA (Washington).

Health Hazard Information

Toxicokinetics

The chemical is absorbed rapidly: when inhaled (~80 %); through intact skin (~10 %); and through the gastrointestinal tract when ingested. The rate of absorption increases with physical activity and percentage of body fat. After absorption, the chemical is distributed throughout the body and concentrates (preferentially) in the brain and fatty tissues due to its liposolubility. Most of the chemical is excreted by the lungs unchanged, or as carbon dioxide (CO_2). Small amounts are detected in the urine and faeces (ATDSR, 1997; WHO, 2004; EU RAR, 2007).

The chemical is mainly metabolised in the liver, kidney cortex and nasal mucosa, through two metabolic pathways (oxidative and reductive) mediated by cytochrome P450-2E1 (CYP2E1). The primary metabolites generated by the oxidative pathway are CO_2 and the reactive phosgene. The reductive pathway generates the free radical dichloromethylcarbene. Studies have shown that phosgene binds irreversibly to liver and kidney proteins and could be responsible for the chemical's toxicity. The chemical's metabolism rate was reported to be slower in humans compared with rodents (ATDSR, 1997; US EPA, 2001; WHO, 2004; EU RAR, 2007).

Following oral exposure, the chemical is absorbed almost completely (80–96 %) in animals and partially (50–52 %) in humans. Blood levels peaked after one hour in mice and after 1.5 hours in humans with half-lives of 13 and 90 minutes, for initial and second phase metabolism, respectively in humans (ATDSR, 1997; EU RAR, 2007).

In a dermal absorption study, the chemical was applied (in water or ethanol) to the forearm of male volunteers (aged 23–26 years) for eight hours, and the exhaled air and urine were analysed. Absorption was found to be ~7.8 % in water and ~1.6 % in ethanol. The absorbed dose was eliminated via the lungs (~94 %, CO_2 >88 %) between 15 minutes and two hours post-dosage. Tape-stripping data indicated that the dose remaining in the skin after three days was 0.01 % in water and non-detectable in ethanol (ATDSR, 1997; IARC, 1999; EU RAR, 2007).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The available animal data support this classification.

The reported oral median lethal doses (LD50) range from 450–2000 mg/kg bw in rats and 36–1366 mg/kg bw in mice. Sublethal signs of toxicity include neurological effects (anaesthesia, ataxia and loss of coordination), renal tubular necrosis (mainly in male mice) and cellular proliferation and lesions in the liver, kidneys and nasal tract (WHO, 2004; EU RAR, 2007; REACH).

Dermal

The chemical has low acute toxicity in rabbits following dermal exposure.

In an acute dermal/irritation study (non-guideline), the chemical was applied (occlusively) at doses of 1.0, 2.0, or 3.98 g/kg to the bellies of rabbits for 24 hours. Kidney tubule degeneration and dermal necrosis were observed at all doses. A dermal LD50 of >3980 mg/kg bw was established, based on no deaths at the highest dose tested (EU RAR, 2007; REACH).

Inhalation

The available information indicates that the chemical has moderate acute inhalation toxicity in animals. Therefore, a hazard classification is warranted.

The median lethal concentration (LC50) was 9.2 mg/L in rats and 6.2 mg/L in female mice, with six hours of exposure to the chemical vapour. Male mice were reported to be more sensitive than females following three hours of exposure to 1024 ppm (~5 mg/L), with 15/18 exposed animals dying within 11 days, whereas females survived for several months. The cause of death in male mice was kidney and liver necrosis. The chemical also induced cellular proliferation and lesions in the nasal tract (ATDSR, 1997; WHO, 2004; EU RAR, 2007; HSDB).

The chemical is reported to cause central nervous system (CNS) depression in animals following acute inhalation exposure. Significant narcotic effects were observed in rats at 2.1 g/m^3 following four hours of exposure.

Observation in humans

Data are available regarding the clinical use of the chemical as an anaesthetic. The chemical induced anaesthetic effects at vapour concentrations of 24–73 mg/L. Chloroform anaesthesia was eventually abandoned due to chemically-induced effects such as respiratory and cardiac arrhythmias and failure, acute hepatotoxicity (jaundice, liver enlargement, coma), gastrointestinal effects (nausea, vomiting) and neurological effects (dizziness, vertigo). The chemical has been reported to cause discomfort <249 mg/m^3 (50 ppm), illness at 2490 mg/m^3 (500 ppm), and severe effects from a 60 minute exposure at or above 9960 mg/m^3 (2000 ppm) (ATDSR, 1997; WHO, 2004; EU RAR, 2007; REACH).

Following ingestion, the chemical effects were caused from inhalation exposure. Sensitivity to the chemical depends on the individual, with some falling seriously ill after an oral dose of 7.5 g, whereas others survived a dose of 270 g. The mean lethal oral dose for an adult is estimated to be 45 g (WHO, 2004; EU RAR, 2007).

Corrosion / Irritation

Respiratory Irritation

Repeated inhalation/respiratory irritation studies in rodents have shown irreversible local toxicity effects in the form of lesions and cell proliferation in the olfactory epithelium and nasal tract (WHO, 2004; EU RAR, 2007; REACH).

In a subchronic inhalation/respiratory irritation study (OECD Test Guideline (TG) 404 and 413), Fischer 344 rats (F344/N) (n = 5–9/sex/dose) were exposed to the chemical vapour at concentrations of 0, 2, 10, 30, 90 or 300 ppm, six hours/day, seven days/week or five days/week up to 13 weeks. Mild to moderate respiratory irritation (histopathological changes in the ethmoid region of the nasal passage) was observed at doses >2 ppm and increased in severity in rats exposed seven days/week. The nasal lesions were confined to the ethmoid portion of the nasal passages and severity of effects were dose and duration dependent (REACH).

Skin Irritation

The chemical is classified as hazardous with the risk phrase ‘Irritating to skin’ (Xi; R38) in HSIS (Safe Work Australia). The available data support this classification.

In a poorly-documented skin irritation study, the undiluted chemical was applied on the shaven belly of female New Zealand White rabbits for 24 hours. The method of application was adapted from the Draize procedure. Moderate to severe erythema and oedema with some superficial peripheral necrosis were observed. The primary dermal irritation index was 5.6, indicating the chemical to be a severe skin irritant (EU RAR, 2007; REACH).

In another study, skin necrosis and scab formation were observed in rabbits exposed to 1.0 g/kg of the chemical for 24 hours (see **Acute dermal toxicity**). The mean erythema score was 2.3 and the effects were not fully reversible within 14 days (REACH).

Eye Irritation

Based on the available data, the chemical is considered to be an eye irritant and warrants a hazard classification. Although no scores are available, one animal study reported irreversible corneal injury. However, reversible corneal effects in human data led to the classification of 'Irritating to eyes' (R36) rather than 'Risk of serious damage to eyes' (R41) (ECHA, 2011).

In an eye irritation study (Draize’s test), the undiluted chemical (dose not reported) was instilled into one eye of each of six New Zealand White rabbits and observed up to three weeks. Severe irritation and lesions of the conjunctivae, purulent corneal discharge and corneal inflammation were observed in the treated eyes. The effects were not fully reversible within the 21-day observation period, and one rabbit had corneal opacity after three weeks (REACH).

In another eye irritation study (non-guideline), the undiluted chemical (dose not reported) was instilled into one eye of each rabbit (n = 3) and observed for at least one week post-exposure. The chemical was slightly irritating to the conjunctiva, and reversible after one week. Slight but irreversible corneal injury was reported (EC, 2007; REACH).

Observation in humans

Following dermal exposure to the chemical, contact dermatitis (irritation, reddening, blistering and burns) was reported. Accidental splashing of the liquid into the eye caused irritation (lacrimation and inflammation of conjunctivae). Exposure to the concentrated vapour of the chemical evoked a stinging sensation in the eye. The corneal effects were observed to be reversible within three weeks (WHO, 2004; EU RAR, 2007; ECHA, 2011).

Sensitisation

Skin Sensitisation

The available data indicate that the chemical is not likely to be a skin sensitiser.

A skin sensitisation study (conducted according to EU regulations) compared two testing methods for the chemical: the guinea pig maximisation test (GPMT) and local lymph node assay (LLNA). In the GPMT test, the guinea pigs (n = 5) were administered the chemical (doses/concentrations not available) and Freund's complete adjuvant intradermally on day one, and topically (occluded for 48 hours) on day nine. The skin was later challenged with a topical application (occluded for 24 hours) on day 22 and evaluated according to the Draize criteria (48 and 72 hours after the challenge started). An erythema score of 1 or 2 (slight to mild) was observed in all animals and became stronger over time, confirming the chemical as a strong irritant. The sensitisation effects could not be determined due to the strong irritation reaction. Furthermore, the skin reactions were comparable with the controls. The chemical was reported to be negative in this test (EU RAR, 2007; REACH).

In the LLNA test, the chemical at a 10 % concentration in acetone/olive oil was applied to the auricles of female CBA mice (n = 20) at 25 μL for three consecutive days. The stimulation index (SI) obtained was 2.48, and therefore an EC3 (effective concentration inducing an SI of 3) value cannot be determined. The lymphoproliferative activity was used as a sensitisation index. However, primary irritation also activated proliferation through inflammatory cytokine effects and the reactions were hard to differentiate. It was postulated that the reactions observed were due to primary irritation rather than sensitisation (EU RAR, 2007; REACH).

Repeated Dose Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Harmful: danger of serious damage to health by prolonged exposure if swallowed' (Xn; R48/22) in HSIS (Safe Work Australia). The available data support this classification.

The nasal epithelium, liver and kidneys appear to be the main target organs affected following repeated exposure. Cytotoxicity and cell proliferation have been observed in a large number of studies (see **Carcinogenicity** section).

In several 90-day repeated dose toxicity studies, mice administered (by gavage) the chemical in corn oil at 60–270 mg/kg bw/day showed histological changes in the liver (increased weights, vacuolation and lipid accumulation). When the chemical was administered in 2 % Emulphor, increased liver weights were observed at the lowest dose level of 60 mg/kg bw/day in females. In another 90-day study, increased hepatic microsomal activity was observed at 50 mg/kg bw/day in female mice, and liver tissue changes and inflamed kidneys were seen in both sexes. Based on these studies, lowest observed adverse effect levels (LOAEL) of 50–60 mg/kg bw/day were determined (WHO, 2004; EU RAR, 2007; REACH).

When the chemical was administered in drinking water for 104 weeks, the effects observed were significant fatty changes in the liver at ≥65 mg/kg bw/day in female mice and increased liver cholesterol at 81 mg/kg bw/day in male Osborne-Mendel rats (WHO, 2004; EU RAR, 2007; REACH). The LOAELs in this study were reported as 81 mg/kg bw/day for rats and 65–130 mg/kg bw/day in mice (US EPA, 2001).

In a repeated dose toxicity study (EU guideline), beagle dogs (n = 8/sex/dose, except for controls) were administered the chemical in a toothpaste base in gelatine capsules at doses of 0, 15 or 30 mg/kg bw/day, six days a week, for 7.5 years.

Increased levels of serum alanine aminotransferase (ALAT) were observed in the high dose group after six weeks, and in the low dose group after 34 weeks. 'Fatty cysts' in the liver, evident of chronic low-grade disruption of hepatocyte function, were also observed at the later phase of the study. There was no treatment-related increase in tumours, cardiovascular changes and mortalities. A LOAEL of 15 mg/kg bw/day was established (ATDSR, 1997; WHO, 2004; REACH).

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the risk phrase 'Harmful: danger of serious damage to health by prolonged exposure through inhalation' (Xn; R48/20) in HSIS (Safe Work Australia). The available data support this classification.

Repeated inhalation exposure to the chemical caused histopathological lesions in the respiratory epithelium, liver and kidneys of rodents. The lowest observed adverse effect concentrations (LOAEC) for mice were reported to be around 49–59 mg/m^3 in 13-week studies. Symptoms observed at higher concentrations included nasal lesions (thickening of bone, respiratory epithelia), and kidney and liver effects (increased weights, necrosis, hyperplasia). At 90 ppm (441 mg/m^3), regenerative cell proliferation was observed in female B6C3F1 mice and in both sexes of BDF1 mice. A long-term exposure study (104 weeks) established a no observed adverse effect concentration (NOAEC) of 25 mg/m^3 in mice based on renal effects and atypical tubule hyperplasia (Health Canada, 2001; US EPA, 2001; WHO, 2004; EU RAR, 2007).

A large number of inhalation studies have been conducted in F344 rats with either five or seven days of exposure per week, up to 13 weeks. The LOAEC was 9.8 mg/m^3 (2 ppm) based on cellular degeneration and enhanced bone growth in the nasal passage tissues. Renal and hepatic lesions were observed at higher concentrations (LOAEC = 123 mg/m^3) (Health Canada, 2001; WHO, 2004; EC, 2007).

Observation in humans

Several occupational studies have reported incidences of gastrointestinal symptoms (nausea, dry mouth, fullness of stomach), hepatic effects (toxic hepatitis) and neurological effects (exhaustion, irritability, depression, insomnia) upon long-term inhalation exposure to the chemical at 100–1000 mg/m^3 (20–200 ppm) in the workplace. Transient jaundice was reported at 80–160 mg/m^3 with less than four months exposure. A high incidence of hepatitis was observed in workers exposed to 10–1000 mg/m^3 for 1–4 years. Although no dose-response curve has been established, the available data suggest a maximum allowable concentration of 20 mg/m^3 in the workplace. Studies still suffer from limitations due to co-exposure to a variety of other chemicals (ATDSR, 1997; US EPA, 2001; WHO, 2004; EU RAR, 2007).

Repeated oral exposure to the chemical in drinking water caused CNS, cardiac and possible reproductive (intrauterine growth, spontaneous abortion) toxicity. However, data are still inadequate to establish a causal link between reproductive effects and ingestion of the chemical (US EPA, 2001).

Genotoxicity

The available data indicate that the chemical has no direct mutagenic or genotoxic potential.

The chemical gave negative results in most of the in vitro bacterial reverse mutation assays with *Salmonella typhimurium/Escherichia coli* and did not induce chromosomal aberrations in human lymphocytes. The chemical was not mutagenic in unscheduled DNA synthesis (UDS) assays using mouse and rat hepatocytes, but produced mixed results in several sister chromatid exchange (SCE) assays in human lymphocytes. Increased SCE was reported at about 1200 mg/L

(without metabolic activation) and at 12 mg/L (with metabolic activation). Therefore, it is concluded that the chemical is not genotoxic in vitro (WHO, 2004; EU RAR, 2007).

The chemical was negative in three of four in vivo bone marrow micronuclei studies in mice, UDS in rodent hepatocytes, and DNA binding studies (methylation, strand breaks and repair) in mice and rats. It induced micronucleus formation and chromosomal aberrations in rodents, and to a lesser extent in hamsters, suggesting clastogenicity. A positive SCE result has been obtained in mouse bone marrow. However, most of the positive results were obtained in studies using doses high enough to cause cytotoxicity, thus, the results are inconclusive (US EPA, 2001; WHO, 2004; EU RAR, 2007).

Weak DNA binding, primarily in the kidneys, lungs and liver, has been reported in several rodent tests. It was concluded that the metabolites of the chemical (phosgene, dichloromethyl radical) were more likely to bind and react with DNA, producing unreliable results (US EPA, 2001). Positive results observed in the kidneys and bone marrow cells of rodents were assumed to be 'consistent with a mechanism of oxidative damage due to glutathione depletion' (EU RAR, 2007). Although it was proposed that the chemical be classified as a Category 3 mutagen (EU RAR, 2007), the EU Committee for Risk Assessment (RAC) did not adopt this proposal due to lack of evidence to meet the classification criteria (ECHA, 2011).

Carcinogenicity

The chemical is classified as hazardous, Category 3 carcinogenic substance, with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40) in HSIS (Safe Work Australia). The available data support this classification.

The International Agency for Research on Cancer (IARC) concluded that there is ‘sufficient evidence’ in laboratory animals for the carcinogenicity of chloroform and 'inadequate evidence' for the carcinogenicity of chloroform in humans. Based on the evidence, IARC classified the chemical as ‘possibly carcinogenic to humans (Group 2B)’ (IARC, 1999). The US Environmental Protection Agency (US EPA) has also classified the chemical as a ‘probable human carcinogen (B2)' (US EPA, 2001).

In several carcinogenicity studies, the chemical produced renal tubular tumours in rodents, and hepatocellular tumours in mice following oral (gavage) exposure. The chemical has been reported to cause increased incidences of liver and kidney tumours in mice, and kidney tumours in rats, following exposure through different routes. Carcinogenicity was observed only at high dose concentrations and secondary to cytotoxicity (sustained or repeated) and regenerative hyperplasia. Cytotoxic effects were attributed to the metabolites of the chemical (mainly phosgene) formed during oxidative metabolism (see **Toxicokinetics**). The most susceptible organs to chemically-induced cytotoxicity and proliferative lesions in a range of species were observed to correlate well with the distribution of the CYP2E1 (predominant enzyme in metabolism) within the animals (IARC, 1999; US EPA, 2001; WHO, 2004).

In a chronic/carcinogenicity study, F344 rats (n = 50/sex/dose) and BDF1 mice were exposed (whole body inhalation) to the chemical vapour (at 10, 30, or 90 ppm for rats and 5, 30, or 90 ppm for mice), six hours/day, five days/week for 104 weeks. At doses above 30 ppm, male mice displayed a statistically significant increase in renal cell adenomas and carcinomas, and histopathological changes in the kidneys (cytoplasmic basophilia, atypical tubule hyperplasia). Female mice in the 90 ppm group displayed significant increases of hepatocellular tumours. No significant changes in tumour incidence or increased incidence of liver lesions were observed in rats. Nasal lesions (bone thickening, respiratory metaplasia) were observed in all rats at doses >10 ppm. An NOAEC for kidney tumours was established as 5 ppm and 10 ppm for mice and rats, respectively (EU RAR, 2007; REACH).

As stated above, human data were limited to epidemiological studies, where exposure to the chemical via drinking water (as a disinfection by-product) was evaluated. These studies were largely based on assumptions (exposure levels, limited sampling, other water contaminants) and data were inconsistent. Therefore, the epidemiological evidence was not considered to be sufficient to determine any association between oral exposure to the chemical and cancer (ATDSR, 1997; IARC, 1999; EU RAR, 2007).

Reproductive and Developmental Toxicity

Based on the available information, the chemical is not considered to have specific reproductive toxicity. Evaluating the available developmental toxicity data for the chemical, the European Union risk assessment recommended a hazard classification for developmental toxicity (Category 3; R63) (EU RAR, 2007). The EU RAC adopted this proposal (ECHA, 2011). However, the

weight of evidence in animal studies implies that developmental effects were only observed secondary to maternal toxicity. Therefore, no change to the current Australian classification is warranted based on this IMAP Tier II assessment.

In a two-generation reproductive toxicity study according to the Reproductive Assessment by Continuous Breeding (RACB) protocol, groups of CD-1 mice (20 pairs/dose) were administered (by gavage) the chemical in corn oil at doses of 0, 6.6, 15.9, or 41.2 mg/kg bw/day, for 31 weeks. No mortalities or effects on body weights, reproductive parameters or accessory organs were observed. A systemic no observed adverse effect level (NOAEL) of 15.9 mg/kg bw/day was established based on significantly higher absolute and relative liver weights in the females, and increased right epididymis weights (due to 'vacuolar degeneration of ductal epithelium in the cauda epididymis') in the males at the highest dose (EU RAR, 2007). The epididymal effect was considered to be 'minimal' and there were no effects on sperm mobility, density and percentage of abnormal sperm. The NOAEL for reproductive toxicity was established as >41.2 mg/kg bw/day (EU RAR, 2007; REACH).

Several developmental toxicity studies are available. Upon inhalation exposure to the chemical during gestation, rats and mice displayed significant decreases in maternal weight gain, litter size and pregnancy rate. In several inhalation and oral exposure studies, the offspring displayed symptoms such as decreased foetal weight and crown-rump length, an imperforate anus (rats) and a cleft palate (mice). These effects were observed at concentrations or doses that caused maternal toxicity. Adverse skeletal and visceral effects were reported in rats, but were neither dose-related nor statistically significant compared with controls (ATDSR, 1997; US EPA, 2001; WHO, 2004).

A study in which Wistar rats were exposed to the chemical through inhalation at a concentration of 0, 3, 10 or 30 ppm, for seven hours/day on each of gestation days 7–16, the US EPA (2001) established 10 ppm (50 mg/m^3) as a NOAEC for developmental toxicity (based on significantly reduced foetal weights and crown-rump length at 30 ppm), and a LOAEC for maternal effects (reduced body weights and weight gain at this dose).

Risks of adverse pregnancy outcomes (stillbirths, reduced birth weights) have been reported in epidemiology studies. However, these studies suffered from limitations such as lack of exposure data, low participation rates and the presence of other contaminents (ATDSR, 1997; CalEPA, 2004; EU RAR, 2007).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic acute effects through oral and inhalation exposure; and
- systemic long-term effects (carcinogenicity).

While classified for carcinogenicity, these relate to long-term, high level exposure, which are not likely to be from industrial uses.

The chemical might also cause skin and eye irritation and adverse effects following repeated oral or inhalation exposure. At high vapour concentrations, CNS depression can lead to unconciousness.

Public Risk Characterisation

The chemical is currently listed on Schedule 6 of the SUSMP (2014) for preparations containing more than 10 % of the chemical. A number of warning statements, first aid instructions and safety directions apply. The current controls are considered adequate to minimise the risk to public health posed by the use of any domestic products containing the chemical (identified from international uses). Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Provided that normal precautions are taken to avoid inhalation, and prolonged skin and eye contact, the risk to public health posed by using products containing the chemical at concentrations at less than 10 % is not considered to be unreasonable. At higher concentrations, potential harm is reduced by using strong warnings and safety directions on the label.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. Worker exposure to the chemical at lower concentrations may 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 health effects, 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.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation** section).

NICNAS Recommendation

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

Regulatory Control

Public Health

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

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 if swallowed (Xn; R22)* Harmful by inhalation (Xn; R20)	Harmful if swallowed - Cat. 4 (H302) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Irritating to eyes (Xi; R36) Irritating to skin (Xi; R38)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure through inhalation (Xn; R48/20)* Harmful: Danger of serious damage to health by prolonged exposure if swallowed (Xn; R48/22)*	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
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 instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, 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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