Australian Government
Department of Health and Ageing
NICNAS

INVENTORY MULTI-TIERED ASSESSMENT AND PRIORITISATION (IMAP)

HUMAN HEALTH TIER II ASSESSMENT FOR

Ethane, 1,2-dichloro-

CAS Registry Number: 107-06-2

PREFACE

As part of the reform regarding assessment of Existing Chemicals, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is implementing a new framework to address the human health and environmental impacts of industrial chemicals, not yet assessed, on the Australian Inventory of Chemical Substances (AICS).

The framework provides a more rapid, flexible and transparent approach for the assessment of existing chemicals.

The Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework was developed, with significant input from stakeholders, and will be applied in stages.

Stage One of this program, which will take three years, started 1 July 2012 and is examining 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This includes chemicals for which NICNAS already holds exposure information, chemicals identified as a concern or for which regulatory action has been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

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.

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

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

ACRONYMS & ABBREVIATIONS

ACToR	Aggregated Computational Toxicology Resource (US)
AICS	Australian Inventory of Chemical Substances
ASTDR	Agency for Toxic Substances and Disease Registry (US)
bw	bodyweight
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations (US)
CHO	Chinese hamster ovary
CosIng	Cosmetic Ingredients and Substances database (EU)
d	day
DNA	Deoxyribonucleic acid
EC	European Commission
EC3	Estimated concentration three
ECHA	European Chemicals Agency
ESIS	European Chemical Substances Information System
EU	European Union
EU RAR	European Union Risk Assessment Report
FDA	Food and Drug Administration (US)
FSANZ	Food Standards Australia and New Zealand
g	gram
g/mol	grams per mole
GHS	Globally Harmonized System of Classification and Labelling of Chemicals*
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPMT	Guinea Pig Maximisation Test
h	hour
HGPRT	hypoxanthine guanine phosphoribosyltransferase
HPV	high production volume
HSDB	Hazardous Substances Data Bank
HSIS	Hazardous Substances Information System
HVICL	High Volume Industrial Chemicals List
IARC	International Agency for Research on Cancer
INCHEM	International Programme on Chemical Safety (also known as IPCS)
INCI	International Nomenclature of Cosmetic Ingredients
ip	intraperitoneal
IRIS	Integrated Risk Information System (US)
IUCLID	International Uniform Chemical Information Database
iv	intravenous
kg	kilogram
L	litre
LC50	median lethal concentration
LD50	median lethal dose
LCLo	lowest published lethal concentration
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
m^3	cubic metre
mg	milligram
mg/cm^3	milligrams per cubic centimetre
mg/kg bw/d	milligrams per kilogram bodyweight per day
min	minute
mL	millilitre
µg	microgram
µL	microlitre
(m)SDS	(material) Safety Data Sheet

NIOSH	National Institute for Occupational Safety and Health (US)
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOHSC	National Occupational Health and Safety Commission
NTP	National Toxicology Program (US)
OECD	Organisation for Economic Cooperation and Development
OEL	occupational exposure limit
PCBU	person conducting a business or undertaking
PEL	permissible exposure limit
PND	postnatal day
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
REACH	Registration Evaluation Authorisation of Chemicals (ECHA)
SD	Sprague Dawley
SIAP	SIDS Initial Assessment Profile (OECD)
SIAR	SIDS Initial Assessment Report (OECD)
SIDS	Screening Information Data Set (OECD)
SMILES	simplified molecular-input line-entry system
SPIN	Substances in Preparations In the Nordic countries
STEL	short-term exposure limits
STV	short-term value
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons (The Poisons Standard**)
TCLo	lowest published toxic concentration
TEEL	temporary emergency exposure limits
TSCA	Toxic Substances Control Act (US EPA)
TG	test guideline
TGA	Therapeutic Goods Administration
TLV	threshold limit values
TWA	time weighted average
UN	United Nations
US	United States of America
US EPA	United States Environmental Protection Agency
WHS	Work, Health and Safety
wt	weight
w/w	weight per weight

Glossary

NICNAS uses the IPCS Risk Assessment Terminology (IPCS, 2004) glossary, which includes:
Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment; and
Part 2: IPCS Glossary of Key Exposure Assessment Terminology.
The IPCS Risk Assessment Terminology can be accessed at:
http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

*****Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Can be accessed at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

******The Poisons Standard (the SUSMP) can be accessed at: http://www.tga.gov.au/industry/scheduling-poisons-standard.htm

Ethane, 1,2-dichloro-

CAS No: 107-06-2

Chemical Identity

Synonyms	1,2-Dichloroethane Ethylene dichloride Ethane, 1,2-dichloro- Dichloroethane Ethylene chloride
Structural Formula	
Molecular Formula	C2H4Cl2
Molecular Weight (g/mol)	98.96 g/moles
Appearance and Odour (where available)	A colourless liquid
SMILES	C(Cl)CCl

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under the National Pollutant Inventory.

The chemical has reported commercial use including:
- as a component of solvents to remove grease, resins, glue and dirt; and
- as an anti-knock component of leaded petrol (previous use only).

The chemical has reported site-limited use including:
- as a solvent in the manufacture of polystyrene and styrene butadiene rubber (SBR) latex.

International

The following international uses have been identified via 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, the Substances and Preparations In the Nordic countries (SPIN), Environmental Health Criteria (EHC), eChemPortal (OECD High Production Volume (HPV) chemicals, the Aggregated Computer Toxicology Resources (ACTor), and Hazardous Substances Data Bank (HSDB)).

The chemical has reported commercial use including:
- in solvents;
- in varnish and finish removers, paints, coatings and adhesives for professional use (European product registers contain entries of products with the chemical as an ingredient. The product types are paints and lacquers (concentrations between 1 and 100%), adhesives (concentrations between 10 and 50%) and fertilisers (concentrations below 1%) (OECD, 2002)); and
- as a component in leaded gasoline.

The chemical has reported site-limited use including:
- as a chemical intermediate in the production of vinyl choride monomer which in turn is used in the manufacture of polymers; and

- as a chemical intermediate in the manufacture of other chlorinated solvents.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed in the following:
ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the composition of cosmetic products.

Canada List of Prohibited and Restricted Cosmetic Ingredients (The Cosmetic Ingredient "Hotlist").

New Zealand Cosmetic Products Group Standard - Schedule 4: Components Cosmetic Products Must Not Contain - Table 1.

Existing Worker Health And Safety Controls

Hazard classification

The chemical is currently classified on the Hazardous Substances Information System (HSIS) with the following (Safe Work Australia):
T; R45 Carc. Cat. 2
Xn; R22 (acute toxicity)
Xi; R36/37/38 (irritation)

Exposure standards

Australian

The chemical has an exposure standard of 40 mg/m³ (10 ppm) TWA.

International

The following are identified (Galleria Chemica):
An exposure limit (OEL, TWA, STEL, PEL or STV) of 4 - 325 mg/m³ (1 - 50 ppm) in different countries such as USA (Alaska, Hawaii), Canada (Yukon), Norway and Switzerland.

Health Hazard Information

Toxicokinetics

The substance is well absorbed by all routes of exposure and rapidly distributed throughout the body with preferential affinity to adipose tissues, and is readily released from all compartments without signs of accumulation. The chemical undergoes extensive metabolism (approx. 90 % within 48 h), followed by rapid excretion of metabolites into the urine. Only a minor portion of the substance, i.e. 4–18 % is metabolically converted to carbon dioxide. Urinary metabolites consist mainly of thiodiacetic acid, the corresponding sulfoxide and S-carboxymethylcysteine. Small amounts of chloroacetic acid and very low concentrations of S,S´-ethylene-bis-cysteine and chloroethanol were also found in urine (OECD, 2002).

Acute Toxicity

Oral

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

The chemical is considered moderately toxic via the oral route in rats (LD50 = 770-967 mg/kg bw), mice (LD50 = 413 – 911 mg/kg bw) and rabbits (LD50 = 910 mg/kg bw), but not in dogs (LD50 >2500 mg/kg bw). Signs of toxicity were characterised by lung congestion, pale kidneys and livers as well as congestion of the blood vessels in the intestines. A single maximum tolerated dose (MTD) of 625 mg/kg

bw (oral gavage) in Sprague Dawley (SD) rats was reported to produce liver effects (slight decrease in hepatic porphyrin and cytochrome-P450 content and a more pronounced change in the activity of hepatic aminolevulinic acid dehydratase and the level of glutathione) (OECD, 2002).

Dermal

The chemical is reported to be of low acute toxicity via the dermal route (LD50 = 4270 –5600 mg/kg bw, in rabbits) (OECD, 2002).

Inhalation

Based on the estimated LC50 (vapour) for rats (about 8000 mg/m³), the chemical is classifiable as hazardous according to the Approved Criteria and the adopted GHS.

Rat LC50 (vapour) = 4100 mg/m³/7.2 h and 49400 mg/m³/0.5 h. Rat LC50 (4 h) of about 8000 mg/m³ (= 1900 ppm) was derived from the concentration response graph in this study. Another study reported a 6 h LC50 of 1650 ppm (= 6670 mg/m³) in rats (OECD, 2002).

In mice, the LC50 after a 6 h exposure was determined to be 272 ppm (= 1080 mg/m³), and in guinea pigs an LC50 of 6400 mg/m³/7 h was reported (OECD, 2002).

After inhalation, a steep concentration response relationship associated with sudden, often unexpected mortality was characteristic of the chemical. For example, among dose groups of SD rats receiving 1300 to 1700 ppm, mortality increased steeply from about 17 to 75%. The mortalities observed in male albino rats were 0/10 animals at 500 mg/kg bw, 3/10 at 630 mg/kg bw after 1 to 5 days, 5/10 at 795 mg/kg bw after 1 day and 8/10 at 1000 mg/kg bw after 2 to 3 days. Similar results were seen with rabbits and mice (OECD, 2002).

Corrosion / Irritation

Skin irritation

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

The animal data available are equivocal. The chemical is reported not to be irritating in rabbits in one study when applied with an occlusive dressing (4 h) to intact skin. A second test revealed moderate irritation on the intact and scarified skin of rabbits, based on the primary irritation index score of 4.7 (out of 8). A third non-standard test on skin of guinea pigs treated with 1 mL of the neat material for up to 16 h under occluded conditions, produced mild signs of irritation after 4 and 16 hours' exposure, but none after 15 or 60 minutes. Effects were microscopically characterised as slight degenerative changes in the epidermis. No macroscopic indicators for irritation were reported (OECD, 2002). In addition to animal data, skin irritation has been observed in humans (see Observations in Humans).

Eye irritation

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

The eye irritating properties of the chemical were investigated in rabbits, dogs and guinea pigs. Moderate lacrimation, abrasion of the corneal epithelium and mild to moderate catarrhal conjunctivae were observed in rabbits instilled with 0.1mL of pure chemical. In addition, regenerating keratitis was evident on day 7 which disappeared after another seven days. In this study the substance was reported to be slightly irritating, based on an overall Draize score ranking with 7 of the maximum 110. In another rabbit study, 0.1 mL of the neat material was applied into the conjunctival sac. Slight reddening in 2/6 animals as well as annular conjunctival swelling in one animal were observed. All symptoms were reported to have disappeared completely within three days (OECD, 2002).

After single inhalation exposure to 1000 and 1500 ppm (4110 and 6165 mg/m³) of the chemical for 7 h, dogs experienced corneal turbidity and oedema, an effect not found in other species tested apart from a fox (among the tested were cats, monkeys, rabbits, chickens and various rodents). At a concentration of

1000 ppm, symmetric turbidity of the corneas was observed in 8/10 dogs, while at the toxic concentration of 1500 ppm, 1/6 dogs showed corneal damage, one developed faint turbidity and 4/6 showed intense clouding of both corneas which cleared within one week in one animal. Resistance to the cornea effects of the chemical developed and remained unchanged even after cessation of exposure for two to four weeks. Prolonged exposure to 400 ppm (about 1600 mg/m³) for 25 weeks gave no evidence of eye damage, whereas during exposure to the toxic concentration of 1000 ppm (about 4000 mg/m³) corneal opacity was prominent. Guinea pigs were exposed to concentrations of 600 to about 70000 ppm (2500 to about 29,000 mg/m³) of the chemical. Signs of eye and nose irritation (including squinting and lacrimation) occurred after exposure to toxic concentrations of 2000 to 4000 ppm within less than 10 minutes, but no signs of irritation and intoxication were reported at 1200 ppm (approx. 5000 mg/m³) after exposure for several hours (OECD, 2002).

Respiratory irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). No data were identified to amend this existing hazard classification.

Observation in humans

In a study of workers exposed to the chemical through fumigation of freight containers between 2007 and 2010 (length of exposure not reported), 14 of 26 patients reported: headaches; concentration and memory problems; dizziness and nausea; irritation of the skin and mucous membranes; a reduced ability to do exercise and reactive airways dysfunction syndrome (RADS) (Preisser et al., 2011).

Sensitisation

Skin sensitisation

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

In a Local Lymph Node Assay performed ex-vivo in mice (CBA strain), three groups of four animals received the chemical at the concentration of 25, 50 or 100% in a mixture of acetone/olive oil (volume ratio 4:1). The chemical did not induce delayed contact hypersensitivity (ECHA, 2012).

Repeat Dose Toxicity

Oral

Considering the LOELs available from 90 day/13 week rat studies (18-75 mg/kg bw/d) and based on the treatment related effects reported in various repeat dose studies, the chemical is not considered to have high repeat dose oral toxicity.

In the 90 day study, male and female Sprague Dawley rats received the chemical by oral gavage at doses of 0, 37.5, 75, and 150 mg/kg bw/d. There were no treatment related effects pertaining to clinical observations. Body weight gain and total food consumption were significantly decreased in high dose males. There were slight, but significant differences in haemoglobin, haematocrit, red blood cell count, platelets, albumin, and alkaline phosphatase values in the 75 and/or 150 mg/kg bw/d groups, in one or both sexes, as compared to concurrent controls. In males, relative brain, kidney, and liver weights were significantly increased at 75 and 150 mg/kg bw/d. There were also differences in spleen, adrenal, and testes weights (absolute and/or body weight relative). In females, absolute and/or relative kidney and liver weights were significantly increased at 150 mg/kg bw/d (liver) and at 75 and 150 mg/kg bw/d (kidney). There were no apparent treatment related effects pertaining to mortality, ophthalmology, gross pathology, or histopathology. Based on these results, a NOAEL of 37.5 and LOEL of 75 mg/kg bw/d were established (ECHA, 2012).

In another 13-week gavage study conducted in F344 rats, equivalent doses of the chemical between 18 and 480 mg/kg bw/d (5 d/week) resulted in pronounced clinical signs of toxicity (tremor, hypersalivation, ruffled fur as well as dyspnoea) and high mortality (90 to 100 % at the higher dose levels). No substance related abnormalities of blood chemical parameters, or histopathological organ changes were detectable, apart from minimal to mild hyperplasia and inflammation of the mucosa of the forestomach in the second highest dose group of males ($p < 0.05$) as well as necrosis of the thymus and cerebellum in the second highest dose group of males and in the highest dose group of females ($p < 0.05$). Increases in the absolute

and relative kidney and liver weights were observable in all dose groups to different extents. The NOAELs were 120 and 150 mg/kg bw/d for male and female F344 rats, respectively, based on treatment related effects in the forestomach and clinical symptoms. The LOEL was determined to be 18 and 30 mg/kg bw/d, the lowest dose tested, based on significant increases in liver and kidney weight in females and males, respectively, which is considered as biologically relevant, but likely to be adaptive (OECD, 2002).

Several drinking water studies were performed over 13-week in rats (Fischer 344, Osborne-Mendel and Sprague Dawley rats), at doses 500 to up to 8000 mg/L (50 and 730 mg/kg bw/d). NOAELs were not established due to large reductions in water consumption. Two drinking water studies were performed in mice (B6C3F1 and CD-1), at doses of up to 8000 mg/L (4200 – 4900 mg/kg bw/d). A NOAEL was not established in male mice because of renal tubular regeneration. For females, the NOAEL was 2500 mg/kg bw/d, based on mortality at higher doses (ECHA, 2012; OECD, 2002).

In a two year non-standard oral study in rats, a NOAEL of 25 mg/kg bw/d was established. There was no impairment of feed consumption or body weight gain. By 14 months, all animals including controls began to suffer from chronic respiratory disease causing high mortality rates. Examination of liver weights, hepatic fat content, various serum parameters did not support any effect on liver and kidney function. In a previous range-finding study, only a slight increases in hepatic total fat and triglycerides ($p < 0.05$) were found after feeding of about 80 mg/kg bw/d for seven weeks. The NOAEL was 30 mg/kg bw/d (OECD, 2002).

Dermal

No data are available.

Inhalation

The data available indicate the chemical to be of low repeat dose inhalation toxicity.

Several subchronic to chronic inhalation studies show largely consistent results after exposure to concentration levels ranging from 100 to 400 ppm (approx. 400 and 1600 mg/m³, respectively) for about 15 weeks (7 h/d, and 5 d/wk), for 17 weeks (6 h/d, and 5 d/wk), and for more than 40 weeks (7 h/d, and 5 d/wk). The findings in rats revealed that no significant to marginal treatment-related effects were seen at 150 ppm, but none at 50 ppm over 18 or 24 months, respectively. The toxicity profile of the chemical in rats is further supplemented by the findings in other species including rabbits and guinea pigs, dogs, monkeys, involving similar concentrations and exposure periods as in rats. Based on the chronic studies in rats, NOAEL of 50 ppm (approx. 400 mg/m³) and LOAEL of 200 ppm (approx. 800 mg/m³) were determined. In rats, 74 exposures (about 15 weeks; 7 h/d, 5 d/wk) at 100 ppm produced no signs of toxicity (strain not specified), whereas in Osborne Mendel and Wistar rats, 200 ppm caused significant toxicity associated with early mortality (<6 and < 27 days, respectively). It was assumed that respiratory arrest and/or cardiovascular failure lead to death. In general, the toxic pattern was similar to that found after oral ingestion, including hepatic fatty degeneration and proliferative changes in the renal tubular epithelia, but, more often than not, involving lung damage too, such as congestion and haemorrhage (OECD, 2002).

Observation in humans

In severe cases of exposure in humans, central nervous system signs appear first within several hours of exposure and are followed by a quiescent period. On the second day, diminished urine production (oliguria) and hepatic effects may develop. Severe ingestions produce widespread organ damage (especially kidney, liver, and adrenal gland) as well as gastrointestinal bleeding (OECD, 2002).

Genotoxicity

Based on the data available (including positive bacterial test systems and limited positive in vivo data on sister chromatid exchanges in Swiss mice at very low doses), the chemical is considered a Category 3 mutagen. In the absence of any positive experimental evidence for the chemical to cause mutations in germ cells, it is not classified as a Category 2 mutagen.

The mutagenicity of the chemical was investigated in several Ames tests under standard and

preincubation conditions using *Salmonella typhimurium* strains TA98, 100, 1530, 1535, 1537 and 1538 both in the presence and absence of a metabolic activation system. Apart from a few exceptions, the test material was demonstrated to be mutagenic in *S. typhimurium* strains TA1530 and 1535, both with and without metabolic activation. Regardless of the concentrations and in the presence of activating factors the mutagenic response was enhanced. In contrast, the compound did not induce point mutations in *S. typhimurium* strains TA98, 100, 1537 and 1538, respectively, both with and without metabolic activation. In a reverse mutation assay conducted in *Escherichia coli* WP2 uvrA, the chemical was only weakly mutagenic in the absence of a metabolic activation system at concentrations < 990 µg/mL (OECD, 2002).

The genotoxicity of the chemical was studied in a series of in vitro assays using mammalian cells (CHO/CHL-cells and human AHH-1/TK6 lymphoblastoid cell lines) and investigating different end points such as unscheduled DNA-synthesis (UDS), chromosomal aberrations (CA), gene mutations (HGPRT / TK ± -test) and cell transformations. In the HGPRT-assay performed in Chinese Hamster Ovary (CHO) cells, dose-related gene mutation was noted both in the absence and presence of metabolic activation at substance concentrations of about 100 – 5000 µg/mL (1 – 50 mM) as derived from a loss of the thymidine-kinase activity. The same result was obtained in the HGPRT assays using the human AHH-1 and TK6 lymphoblastoid cell-lines at concentrations of 100 and 500 µg/mL, respectively, both in dose related manner without metabolic activation. In CHL fibroblasts, the chemical was shown to increase the incidence of chromosomal aberrations (chromatid breaks and exchanges, no chromosome breaks) in the presence of metabolic activation at concentrations of 1000 µg/mL after 6 h exposure with no effect at 0.5 mg/mL, while without metabolic activation no effects were obvious at 200 - 4000 µg/mL after 24- and 48 hours, while an ambiguous result was found at 6000 µg/mL. In primary rat hepatocytes, significant induction of unscheduled DNA-synthesis was reported at concentrations of >13 µg/mL in the absence of metabolic activation. Unscheduled DNA-synthesis reportedly induced in human lymphocytes is based on an unsuitable test method using [3H]-TdR incorporation. In a cell transformation experiment conducted in BALB/C-3T3-cells, no mutagenic effects were observed without metabolic activation at concentrations ranging from 5 to 50 µg/mL (OECD, 2002).

The chemical was subject to several in vivo mutagenicity studies. In a micronucleus test in male and female NMRI mice, no increases in the number of micronucleated polychromatic erythrocytes (PCEs) were noted in bone marrow cells (6 h after the last dose when the maximum possible dose of 396 mg/kg bw was given twice in an interval of 24 h by intraperitoneal (i.p.) injection). In a second micronucleus test on lymphoma prone transgenic mice (Eµ-PIM-1), repeated oral gavage dosing (in corn oil) of the chemical at 200 mg/kg in males and 300 mg/kg in females (reduced to 100 and 150 mg/kg bw, respectively due to toxicity) failed to demonstrate any deleterious effect on peripheral polychromatic and normochromatic erythrocytes after 14 and 41 weeks of exposure. A third micronucleus test was negative after single i.p. injection of 100 mg/kg bw into male CBA mice. In a sister chromatid exchange (SCE) study on bone marrow cells of male Swiss mice, the chemical in peanut oil was administered by i.p. injection at doses of 0, 0.5, 1.0, 2.0, 4.0, 8.0 and 16 mg/kg bw. The material led to a dose dependent increase in the number of SCEs at 1.0 mg/kg bw and above ($p<0.01$ at 2 mg/kg bw and higher). At 4 mg/kg bw, the chemical caused doubling of the spontaneous SCE rate. There was no increase in the number of SCEs at 0.5 mg/kg bw, but no positive control was included in the test (OECD, 2002).

The DNA-breaking potential of the chemical (in-vivo/in-vitro DNA unwinding assay) was tested in male B6C3F1 mice. Single doses of the substance were administered orally, by i.p. injection and by inhalation, and the presence of single strand breaks and alkali labile sites in isolated hepatic double-strand DNA was examined by using the in-vitro alkaline DNA-elution technique. After 4 h oral and i.p. application of the chemical, sublethal and subtoxic doses of 100 to 200 mg/kg bw (oral) as well as of 150 to 300 mg/kg bw (i.p.) were able to induce DNA damage, demonstrated by a distinct decrease in the double-strand fractions as compared to the vehicle controls. After 4 h inhalation exposure, no such effect was found at subtoxic concentrations up to 500 ppm (approx.2000 mg/m³), whereas clear DNA damage occurred at (hepato-) toxic and lethal exposures of 1000 and 2000 ppm. The differences may be explained by the completely different invasion and elimination kinetics for the various exposure routes (OECD, 2002).

In a two-generation reproduction study, a dominant lethal test was undertaken twice in male Swiss mice

of the first (F1) and second (F2) descendants which had been delivered from pre-treated parents (F0 and F1). After administration of the chemical in drinking water (0, 0.03, 0.09 or 0.29 mg/mL), the repeatedly treated F1 and F2 males were mated to virgin females. There was no evidence of increases in pre and post implantation losses, no significant effects on the number of foetal implants and viable foetuses. Therefore, the ability of the chemical to produce genotoxic effects on germ cells of male mice is considered unlikely (OECD, 2002).

In conclusion, the chemical was found to be weakly mutagenic in bacterial tests systems, but was shown to produce clear mutagenic effects in mammalian cytogenetic and gene mutation assays. Metabolic activation is primarily required to cause these effects, which accords with the known metabolism of the material involving the cytochrome-P450 and the glutathione-dependent pathways, where both pathways were considered as possible steps in the bioactivation cascade leading to reactive metabolites. The results of available in vivo studies failed to show a mutagenic potential of the chemical, as three MN and one questionable DL assay were negative. However, evidence of DNA damaging in vivo activity/genotoxicity is shown by positive results in SCE assay and single DNA strand-break analysis.

Carcinogenicity

The chemical is classified as hazardous with the risk phrase ‘May cause cancer' (T; R45 Carc. Category 2) in HSIS (Safe Work Australia). The data available support this classification.

Animal data

Following oral administration, the chemical (at dose 97 mg/kg bw/d and above) produced benign and malignant tumours of the lung and malignant lymphomas in B6C3F1 mice of each sex, hepatocellular carcinomas in males and mammary and uterine adenocarcinomas in females. Oral administration in Osborne Mendel rats (47 mg/kg bw/d and above) produced carcinomas of the forestomach in males, benign and malignant mammary tumours in females and haemangiosarcomas in animals of each sex.

No increase in tumour incidence was found after inhalation exposure in two experiments in rats (at 50 ppm for two years) or in one experiment in Swiss mice (up to 250 ppm for 78 weeks), but these studies were considered to be inadequate. In two other inhalation studies, one in BDF1 mice (at doses 10 ppm and above for 104 weeks) and one in rats, increased incidence of tumours at various sites including the liver, lung and mammary gland were reported (doses not reported) (IARC, 1999).

Observations in humans

Five cohort studies and one nested case–control study of brain tumours have examined the risk of cancer among workers with potential exposure to the chemical. Excesses of lymphatic and haematopoietic cancers were observed in three studies and stomach cancer in one study, while an excess of pancreatic cancer was observed in one study. All the cohort studies included workers with potential exposure to multiple agents and were not able to examine the excess risk associated with 1,2-dichloroethane. The IARC concluded that, there is *inadequate evidence* in humans for the carcinogenicity of the chemical, but there is s*ufficient evidence* in experimental animals for the carcinogenicity of 1,2-dichloroethane (IARC, 1999).

Reproductive and developmental toxicity

Based on the data available, there is no evidence that the chemical induces reproductive or developmental effects at repeated doses up to 240 mg/kg bw/d orally or up to 300 ppm via inhalation.

Reproductive performance in rats and mice, including fertility of either sex, and foetal viability was not impaired after repeated oral doses of 50 mg/kg bw/d (via food and drinking water) and after inhalation exposure of up to 150 ppm in several generation studies. Furthermore, no histopathological adverse effects on the gonads were reported in two oral long-term studies in rats and mice (OECD, 2002).

In two well conducted investigations on developmental toxicity, no significant toxicity was noted in the offspring of rats receiving up to maternally toxic oral (gavage) and inhalation doses during pregnancy. The NOAELs for developmental effects were the highest doses employed, 240 mg/kg bw/d and 300 ppm, respectively. Results of previous, more limited studies in rats and rabbits are consistent with these

observations (OECD, 2002).

Other Health Effects

Neurotoxicity

In humans it is reported that the chemical is a central nervous system depressant and effects are manifested by unspecific symptoms such as nausea, vomiting, headache, lightheadedness and weakness, reduced responsiveness (stupor), dysequilibrium, coma, and respiratory arrest (OECD, 2002).

Risk Characterisation

Critical Health Effects

The main critical effects to human health are carcinogenicity and mutagenicity. The chemical will cause irritation to the eyes, skin and respiratory system and may cause harmful effects if swallowed.

Public Risk Characterisation

The European product registers contain entries of products with the chemical as an ingredient. The product types are paints and lacquers (concentrations between 1 and 100 %), adhesives (concentrations between 10 and 50 %) and fertilisers (concentrations below 1 %) (OECD, 2002).

The chemical is not expected to be used in domestic products or cosmetics in Australia. Hence, the public risk from this chemical is low.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered high if adequate control measures to minimise occupational exposure to the chemical are not implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or an employee at a workplace has adequate information to determine appropriate controls. The existing hazard classification for worker health and safety requires amendment to include the classification for mutagenicity.

NICNAS Recommendation

The chemical is sufficiently assessed and risk managed provided the recommendation for classification and labelling is followed. No further assessment is required.

Regulatory Control

Public Health

As the chemical is not expected to be used in consumer products in Australia, no regulatory controls are recommended.

Occupational Health and Safety

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

	Approved Criteria (HSIS)[a]	***GHS Classification***
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)* Irritating to respiratory system (Xi; R37)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

* Existing Hazard Classification. No change recommended to this classification.

Advice for industry

Control measures

Control measures to minimise the risk from dermal/ocular/inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storage, handling and use of a hazardous chemical are dependent on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include but are not limited to:

- use of closed systems or isolation of operations;
- use of 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;
- minimisation of manual processes and work tasks through automation of processes;
- work procedures that minimise splashes and spills;
- regular cleaning of equipment and work areas; and
- use of protective equipment that is designed, constructed, and operated to ensure that, the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

Personal protective equipment should not be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of hazardous chemical are prepared; and
- management of risks arising from storage, handling and use of a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant Codes of Practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These Codes of Practice are available from the Safe Work Australia website.

A review of physical hazards of the chemical has not been undertaken as part of this assessment.

References

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