Benzene, chloro-: Human health tier II assessment

01 July 2016

CAS Number: 108-90-7

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.

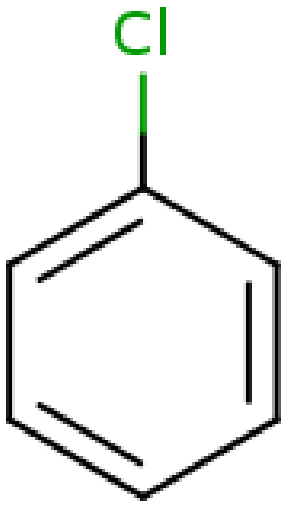
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	chlorobenzene monochlorobenzene phenyl chloride
Structural Formula	
Molecular Formula	C6H5Cl
Molecular Weight (g/mol)	112.55
Appearance and Odour (where available)	Colourless liquid with an almond-like odour
SMILES	c1(Cl)ccccc1

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: the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Household Product database; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments, including from Health Canada.

The chemical has reported domestic uses, including:

- in adhesives for art and craft products; and
- in paints and varnishes for decorative and/or protective purposes.

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

The chemical has reported commercial uses, including:

- in adhesives;
- as a plastic hardener;
- as a solvent;
- as a corrosion inhibitor;
- in paints and varnishes for decorative and/or protective purposes (for roads, furniture, boats, in art); and
- in water treatment products.

The chemical has reported site-limited uses, including:

- as an intermediate in the manufacture of various chemicals, including chloronitrobenzenes and silicones;
- as a fibre-swelling agent in textile processing; and
- in heat transfer fluids.

The following non-industrial use has been identified internationally: as a carrier solvent in pesticides.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

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

- Xn; R20 (acute toxicity)

Exposure Standards

Australian

The chemical has an exposure standard of of 46 mg/m^3 (10 ppm) time weighted average (TWA) (Safe Work Australia).

International

The following exposure standards (TWA) are identified (Galleria Chemica):

- 4.7 mg/m^3 (1 ppm) in United Kingdom;
- 23 mg/m^3 (5 ppm) in Estonia, France, Iceland, Latvia, Norway, Sweden, Spain;

- 46 mg/m^3 (10 ppm) in Canada (Alberta and British Columbia), Denmark, Germany, Indonesia, Japan, Malaysia, Singapore, South Africa, Switzerland;
- 230 mg/m^3 (50 ppm) in Canada (Quebec); and
- 350 mg/m^3 (75 ppm) in Canada (Yukon), Egypt, Greece, India, Mexico, Philippines and most of the USA.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 10 ppm (46 mg/m^3) (Galleria Chemica).

Acute exposure guideline levels (AEGL), defined as 'threshold exposure limits for the general public', were determined for exposure periods ranging from ten minutes to eight hours (AEGL, 2012):

- AEGL-1 (non-disabling) of 10 ppm for all exposure periods;
- AEGL-2 (disabling) of 430 ppm (10 min) to 150 ppm (8 h); and
- AEGL-3 (lethal) of 1100 ppm (10 min) to 400 ppm (8 h).

Health Hazard Information

Toxicokinetics

The chemical is reported to be readily absorbed by the oral and inhalation routes, both in humans and animals. In a human volunteer, 31 % of the administered oral dose was reported to be absorbed. Two workers exposed to 0.5 or 0.84 ppm of the chemical (presumably by inhalation) showed absorption of 45 and 38 %, respectively. Rat studies showed absorption of 18–22 % of the administered oral dose (ATSDR, 1990).

The chemical is lipophilic and accumulates mainly in fatty tissues in humans and animals. It is mainly excreted in the urine as metabolites and little is excreted in the faeces or retained in the body (WHO, 2004). Inhalation studies in rats showed that the amount of unchanged chemical excreted in the urine increased at exposure concentrations above 400 ppm, suggesting that the metabolism was saturated above this concentration (CERI, 2007).

Regardless of the administration route or animal species, the chemical is converted into epoxides (chlorobenzene-3,4-epoxide and chlorobenzene-2,3-epoxide) that have the potential to bind covalently to nucleic acids. These epoxides are formed in the liver, lungs, kidneys and adrenal cortex, then converted into mercapturic acid derivatives or chlorocatechols. At least ten metabolites of the chemical (particularly 4-chlorophenyl-mercapturic acid, 4-chlorocatechol and 4-chlorophenol) can be detected within 24 hours in the urine of humans, monkeys, rats, mice, rabbits and dogs (CERI, 2007).

Acute Toxicity

Oral

Based on the results of the study conducted in Fischer 344/N (F344/N) rats, the chemical is considered to have low acute oral toxicity.

In a study conducted according to the OECD Test Guideline (TG) 401, F344/N rats (n = 5/sex/dose) were administered a single oral dose of the chemical at 250, 500, 1000, 2000 or 4000 mg/kg bw. Three males and four females at 4000 mg/kg bw died within two days. The median lethal dose (LD50) was greater than 2000 mg/kg bw. Symptoms of toxicity included: transient ataxia, laboured breathing, hyperpnoea (increased depth of breathing) and prostration in a dose-related manner at the two highest doses (NTP, 1985; REACH).

Other LD50 values were reported:

- 1110 and 1760 mg/kg bw (vehicle: olive oil) in male and female rats, respectively (HSDB);
- 2250 mg/kg bw in rabbits and guinea pigs (NTP, 1985; RTECS); and
- 1440 mg/kg bw in mice (HSDB).

Dermal

The chemical has low acute dermal toxicity.

The following dermal LD50 values are reported for the chemical:

- >2200 mg/kg bw in rabbits (ChemIDPlus; RTECS)
- >11000 mg/kg bw in guinea pigs (ChemIDPlus; RTECS)

Rats exposed on the tail or 5 % of the body surface to the chemical at doses ≥3600 mg/kg bw were reported to show (unspecified) signs of toxicity (HSDB).

Inhalation

The chemical is classified as hazardous with the risk phrase 'Harmful by inhalation' (Xn; R20) in the HSIS (Safe Work Australia). The available data support this classification.

In a study comparable to OECD TG 403, a median lethal concentration (LC50) of 2965 ppm/6h (equivalent to 13.6 mg/L/6h or 15.5 mg/L/4h) was reported in male Sprague Dawley (SD) rats when exposed to the chemical vapour (CLH, 2013).

Other LC50 values, of 1886 ppm/6h (8.8 mg/L) and 15 mg/m^3, were reported in mice (HSDB; RTECS). Mice (number not specified) exposed to the chemical at 20 mg/L (4000 ppm) for two hours showed 100 % mortality (ATSDR, 1990).

Rabbits exposed to the chemical at 5 mg/L (1090 ppm) for two hours showed neurological effects including muscle spasms and central nervous system (CNS) depression (HSDB).

Following six-hour exposure to the chemical as an aerosol/vapour mixture at 4 mg/L (850 ppm), weight loss and eye and mucous membrane irritation in rats, guinea pigs and rabbits occurred. Exposure to the chemical at 2 mg/L caused blinking, lacrimation and salivation within ten minutes of exposure and increased liver, kidney and testes weights (HSDB).

Observation in humans

Effects from acute exposure to the chemical have been reported.

A 56-year old woman who ingested 400 mL of a dry-cleaning fluid consisting mostly of the chemical became unconscious and showed cyanosis, shallow breathing, low blood pressure, reduced temperature and weak reflexes. Sugar, acetone, urobilinogen and urobilin were found in the urine, and the blood leukocyte count was increased. The patient regained consciousness after a few hours and the clinical parameters were back to normal within two days (MAK, 1999).

In a study in volunteers, inhalation exposure to 60 ppm of the chemical for seven hours caused slight depression of the central nervous system (CNS), including drowsiness, heavy head and headaches, along with irritation to the eyes and respiratory tract. Those effects were not observed in subjects exposed to a lower concentration (10 ppm) eight hours/day, for five days (AEGL, 2012).

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is a skin irritant warranting hazard classification.

In a study compliant with OECD TG 404, three rabbits were exposed (on shaved skin) to the undiluted chemical (0.5 mL) for four hours and observed for 14 days. Mean erythema score over 24, 48 and 72 hours for all animals was 2.7 (out of 4), and two rabbits had erythema scores of 3 over 24, 48 and 72 hours. Mean oedema score over 24, 48 and 72 hours for all animals was 1.0. All observed effects were reversible within six days (MAK, 1999; REACH).

Eye Irritation

The chemical is not irritating to the eyes.

In a study compliant with OECD TG 405, the chemical (0.1 mL) was instilled into the conjunctival sac of one eye of each of the three New Zealand White rabbits. Mean scores over 24, 48 and 72 hours were 0.1 for corneal opacity, 0.9 for conjunctival redness, 0.4 for chemosis and 0 for iris effects. Effects were fully reversible within seven days (MAK, 1999; REACH).

The contact of the chemical with eyes of rabbits was reported to cause transient conjunctival irritation, reversible within 48 hours (HSDB).

Observation in humans

Dermal exposure to the chemical caused local skin effects in humans.

Five volunteers dermally exposed to the chemical for one hour reported burning pain and showed hyperaemia (increased blood flow in the vessels), wheals (raised and pruritic areas of the skin) and erythema formation at the application site. Minimal local vesiculation was observed 12 hours post-exposure (RAC, 2014).

Occasional contact with the chemical was reported to cause slight skin irritation in humans. Repeated exposure to the chemical over a period of seven days can cause moderate erythema and mild superficial necrosis. In another case, it was reported that contact with the chemical at 5 % in olive oil could lead to the formation of acneiform skin eruptions (MAK, 1999).

Sensitisation

Skin Sensitisation

Only limited information is available, suggesting the chemical is not a skin sensitiser.

The chemical was reported to be non-sensitising in tests including a guinea pig maximisation test (AEGL, 2012; CERI, 2007) and a mouse local lymph node assay (LLNA) (HSDB). Study details are not available.

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not considered to cause severe health effects from repeated oral exposure at doses up to 125 mg/kg bw/day.

In a subchronic gavage study, F344/N rats (n = 10/sex/dose) were administered the chemical (in corn oil) at doses of 0, 60, 125, 250, 500 or 750 mg/kg bw/day, five days per week for 13 weeks. There were decreased survival rates at 500 and 750 mg/kg bw/day (6/10 males and 7/10 females, and 1/10 male and 2/10 females survived, respectively). There were marginal to moderate decreases in body weight gain in females and males receiving doses $\geq$ 500 mg/kg bw/day and $\geq$ 250 mg/kg bw/day respectively (final body weights were 10 % lower compared with controls). Several histological changes were reported, mostly in the 500 and 750 mg/kg bw/day dose groups. Liver lesions included dose-dependent centrilobular hepatocellular necrosis, of moderate severity at 750 mg/kg bw/day and minimal severity at 250 mg/kg bw/day. Kidney lesions (proximal tubular degeneration and necrosis) were seen at 500 (in males only) and 750 mg/kg bw/day (in both sexes). Lymphoid depletion of the thymus and spleen was seen at 750 mg/kg bw/day in both sexes. Myeloid depletion of the bone marrow was observed at 750 and 500 mg/kg bw/day. Haematological effects including decreased white blood cell count and increased reticulocyte percentage were seen at the highest dose in the surviving animals (two females and one male). Urinary coproporphyrin and uroporphyrin excretion were increased in male rats at 500 and 750 mg/kg bw/day and in female rats at 500 mg/kg bw/day (NTP, 1985). Based on the results of this study, a no observed adverse effect level (NOAEL) of 125 mg/kg bw/day can be determined.

In another subchronic gavage study, B6C3F1 mice (n = 10/sex/dose) were administered the chemical (in corn oil) at doses of 0, 60, 125, 250, 500 or 750 mg/kg bw/day, five days per week for 13 weeks. Mice exhibited effects similar to rats at doses $\geq$ 250 mg/kg bw/day, including decreased survival, dose-dependent hepatocellular necrosis, and lymphoid or myeloid depletion of the thymus, spleen and bone marrow (NTP, 1985).

In a carcinogenicity study, F344/N rats (n = 50/sex/dose) were administered the chemical by gavage at 0, 60 or 120 mg/kg bw/day, five days per week for 103 weeks (see **Carcinogenicity** section). No clinical signs of toxicity were observed during the study. Survival of male rats at 120 mg/kg bw/day decreased significantly (26/50 survived), compared with the vehicle control group (39/50 survived). The incidences of cytoplasmic changes and inflammation in the liver were found to be lower in treated animals compared with untreated and vehicle controls. The incidence of hepatocellular necrosis (mild or minimal severity) appeared to have slightly increased in treated animals but was not significantly different from controls. Inflammation of the lung and foreign body aspiration were observed in treated animals and possibly caused by the gavage method rather than the chemical (NTP, 1985).

In another carcinogenicity study, B6C3F1 mice (n = 50/sex/dose) were administered the chemical by gavage at 0, 60 or 120 mg/kg bw/day in females and 0, 30 or 60 mg/kg bw/day in males, for 103 weeks (see **Carcinogenicity** section). Survival was 'marginally less' in treated male rats (28/50 and 29/50 survived in the low- and high-dose groups, respectively) than in the vehicle control group (39/50) and in the untreated control group (35/50). Overall, no signs of toxicity related to the treatment were observed during the study (NTP, 1985).

The NTP (1985) stated that 'non-neoplastic lesions clearly attributable to chlorobenzene were not observed in the two-year studies' in rats and mice and that there is only 'little potential for chlorobenzene to produce progressive non-neoplatic toxicity more severe than that observed in the 13-week studies' (NTP, 1985).

Dermal

No data are available.

Inhalation

Based on the available data, the chemical is not expected to cause severe health effects following repeated inhalation exposure.

In a chronic toxicity study, male SD rats and male rabbits (numbers not specified) were exposed to the chemical vapour at 0, 75 or 250 ppm (approximately 0, 350 and 1170 mg/m^3), seven hours per day, five days per week, for up to 24 weeks. Haematological changes in rats were considered

to be statistically treatment-related (details not available). In rats, effects at the low concentration included increased liver weight, vacuolated adrenal reticular cells, degeneration of renal tubules, increased haematocrit and platelet count and decreased reticulocyte (immature red blood cell) count. In the high-dose group of rats, the effects included increased liver and kidney weights, decreased serum aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) activities, decreased monocyte (type of white blood cell) and reticulocyte count and increased neutrophil (type of white blood cell) count. In rabbits, effects at the low concentration included variations in LDH activity and decreased level of serum uric acid. At the high dose, effects included liver and kidney congestion, increased leukocyte count, decreased serum uric acid and AST activity, increased lung and liver weights (CERI, 2007; Dilley et al., 1977). Values of no observed adverse effect concentrations (NOAECs) could not be determined.

In a two-generation reproduction study (see **Reproductive & Developmental Toxicity** section), groups of SD rats (n = 30/sex/dose) were exposed to vapours of the chemical at concentrations of 0, 50, 150 or 450 ppm (0, 234, 702 and 2106 mg/m^3) ten weeks prior to mating and during mating and also for females during gestation and lactation. No mortalities occurred during the study. Body weights and food consumption for all treated groups were comparable to controls. Increased liver weight in males and females, hepatocellular hypertrophy and renal changes (tubular dilation with eosinophilic material, interstitial nephritis, and foci of regenerative epithelium) among F0 (parent generation) and F1 (progeny of the F0 generation) male rats were observed at 150 and 450 ppm. A NOAEC of 50 ppm (234 mg/m^3) was determined in this study (CERI, 2007; Nair et al., 1987).

In a teratology study (see **Reproductive & Developmental Toxicity** section), F344/N rats were exposed to the chemical at concentrations of 0, 75, 210 or 590 ppm via inhalation for six hours per day during the period of major organogenesis. Exposure to 590 ppm caused elevated liver weights and decreased body weight gain (CERI, 2007; John et al., 1984).

Drowsiness, suppression of body weight gain and decreased food consumption were observed in male and female mice exposed to 535 ppm (2500 mg/m^3) of the chemical seven hours per day, for three weeks (CERI, 2007).

Observation in humans

A man and a woman who used a glue containing the chemical at 70 % for a period of six years (frequency and route of exposure not stated) experienced headaches and irritation of the upper airways and eyes. At the age of 70, the woman developed aplastic anaemia (MAK, 1999).

Genotoxicity

The overall information is inconclusive. Although two in vivo assays for gene mutation and clastogenicity in somatic cells produced positive results (micronuclei and chromosome aberrations in rats and mice following intraperitoneal injection), only negative results were reported in other in vivo assays, including three germ cell mutagenicity assays.

In 2012, the National Advisory Committee for AEGLs stated that 'chlorobenzene has some potential to induce DNA damage, which is further underpinned by the formation of epoxide metabolites' but that 'because of conflicting results from mutagenic tests in vitro and in vivo, it is unclear whether the genotoxic activity could represent a risk to human health' (AEGL, 2012).

The following in vitro assays are available for the chemical, showing both positive and negative results for genotoxicity (CERI, 2007; NTP, 1985):

- there was no evidence of mutagenicity in any of the bacterial gene mutation tests on *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, at doses up to 11243 µg/plate, with and without metabolic activation;
- mixed results were observed in bacterial gene mutation tests on *Saccharomyces cerevisiae* — positive results at doses of 0.05–6 µg/plate, with and without metabolic activation, and negative results at doses of 0.01–5 µg/plate, with and without metabolic activation;
- there was a dose-dependent increase in the number of revertants in cultures of *Actinomycetes antibioticus* 400 exposed to 0.05 or 0.1 mL of the chemical, with metabolic activation only;
- the chemical gave negative results in a gene mutation test in mouse lymphoma L5178Y cells exposed to doses up to 0.1 µg/mL, with or without metabolic activation;
- positive results were observed in another gene mutation test in mouse lymphoma L5178Y cells with doses of 6.25–200 µg/mL, with or without metabolic activation;
- negative results were observed in two unscheduled DNA synthesis (UDS) tests on rat hepatocytes at doses up to 150 µg/mL;
- in a sister chromatid exchange (SCE) assay in Chinese hamster ovary (CHO) cells, positive results were seen without metabolic activation (at 1000 µg/mL) and negative results with metabolic activation (at 300 µg/mL); and
- negative results were observed in a chromosomal aberration test on CHO cells exposed to the chemical at 500 µg/mL.

The following in vivo assays in somatic cells are available for the chemical, showing dose- and time-dependent clastogenic effects:

- there was no evidence of mutagenicity in a micronucleus test on mice given oral doses of the chemical up to 400 mg/kg bw (CERI, 2007);

- a positive result was seen at all doses in another micronucleus test on male NMRI mice given two equal intraperitoneal injections of the chemical (24 hours apart), at doses of 225 (2 x 112.5) to 900 (2 x 450) mg/kg bw (Mohtashamipur et al., 1987);
- the chemical induced micronuclei and chromosomal aberrations in Norway male rats given a single intraperitoneal dose of the chemical at 1250 mg/kg bw — results were positive 24 hours post-exposure, but negative 12 and 48 hours post-exposure (CCRIS; Faisal Siddiqui et al., 2006); and
- negative results were observed in a SCE test on mice given oral doses up to 400 mg/kg bw (CERI, 2007).

The following in vivo assays in germ cells are available for the chemical, showing negative results:

- in two sex-linked recessive lethal tests on *Drosophila melanogaster* exposed to the chemical at doses up to 50000 mg/m^3 (CERI, 2007); and
- in a dominant lethal test on mice given oral doses of the chemical up to 400 mg/kg bw (CERI, 2007).

Genotoxic effects were assessed in workers (n = 240) manufacturing the chemical in Hungary. Blood sample donors included 147 exposed workers, 33 non-exposed workers and 60 historical controls (Major et al., 1992). The mutation frequencies in the hypoxanthine-(guanine)-phosphoribosyl transferase (hgprt) genes located on the X chromosome were slightly but significantly increased among the workers exposed to the chemical compared with the industrial and historical controls.

Carcinogenicity

The overall information is not strongly indicative of carcinogenicity.

The NTP concluded that there was 'some but not clear evidence of carcinogenicity of chlorobenzene in male rats', based on the increased incidence of neoplastic nodules in the liver, but there was no evidence of carcinogenicity in female rats or in male or female mice (NTP, 1985).

In a carcinogenicity study, F344/N rats (n = 50/sex/dose) were administered the chemical by oral gavage doses (in corn oil) of 0, 60 or 120 mg/kg bw/day, five days per week for 103 weeks. Neoplastic nodules in the liver occurred with a significant positive trend in male rats, with a significantly higher incidence in the high dose group (8/49 male rats) compared with the vehicle group (2/50 male rats). These were not observed in female rats. A few relatively rare tumours were observed in treated rats and not in control rats: a transitional cell papilloma of the urinary bladder in the low- (1/46) and high-dose (1/46) male groups, and a renal tubular cell adenocarcinoma in the high-dose female group (1/50). There was a statistically significant decrease in the incidence of pituitary adenomas in female rats (13/43) and pituitary adenomas, adenocarcinomas or carcinomas in male rats (3/47) at the high dose compared with female (23/46) and male (10/50) vehicle controls, respectively. The incidence of endometrial stromal polyps in female rats was significantly lower in the low-dose group (4/49) compared with female vehicle controls (16/50), but not in the high-dose group (10/50) (NTP, 1985).

In another carcinogenicity study, B6C3F1 mice (n = 50/sex/dose) were administered the chemical by oral gavage in corn oil doses of 0, 60 or 120 mg/kg bw/day for the females and 0, 30 or 60 mg/kg bw/day for the males, five days per week for 103 weeks. The study reported that no statistically significant site-specific tumors or nonneoplastic pathology occurred in either male or female mice (NTP, 1985).

Based on the NTP studies, the ATSDR stated that the existing information was 'inadequate to characterise the potential for chlorobenzene to cause cancer in humans and animals' (ATSDR, 1990). The US Environmental Protection Agency (EPA) assessed the chemical as a Category D — Not classifiable as to human carcinogenicity (EPA, 1999).

Reproductive and Developmental Toxicity

Based on the available data in rats, the chemical is not considered to cause reproductive toxicity. Developmental effects were observed in rats only at maternally toxic doses and were considered secondary to maternal toxicity. In rabbits, developmental effects did not appear to be dose-related.

In a two-generation reproduction study, groups of SD rats (n = 30/sex/dose) were exposed to vapours of the chemical at concentrations of 0, 50, 150 or 450 ppm (0, 234, 702 and 2106 mg/m^3) ten weeks prior to mating and during mating and also in females during gestation and lactation. Exposure of F1 animals followed the same method, one week postweaning and up to 11 weeks prior to mating and through mating, gestation and lactation. All F2 (progeny of the first generation F1) pups were observed through weaning at which time they were sacrificed. There was an increased incidence of degeneration of the testicular germinal epithelium in F0 males at 450 ppm and in F1 males at 150 and 450 ppm. However, this effect was not clearly related to the chemical, as there was no increase in intensity and/or incidence of testicular lesions among F1 adults that had longer exposure. Overall, mating and fertility indices for males and females for both generations were considered unaffected by the treatment (CERI, 2007; Nair et al., 1987).

In a teratology study, F344/N rats and New Zealand White rabbits were exposed to the chemical at concentrations of 0, 75, 210 or 590 ppm (0, 350, 981 and 2756 mg/m^3 respectively) via inhalation for six hours per day during the period of major organogenesis. In rats, slight delay in skeletal development of the foetuses was observed at the highest concentration, but this effect was considered as secondary to maternal toxicity (enlarged liver and decreased weight gain — see **Repeat Dose Toxicity – Inhalation** section). In rabbits, some visceral malformations were reported in foetuses at the highest concentration and not in the control group but these observations were not reproducible in a second assay. The chemical did not cause embryotoxic or teratogenic effects in this study (CERI, 2007; John et al., 1984).

Other Health Effects

Neurotoxicity

The available data on animals and humans have shown that acute exposure to the chemical could induce slight CNS depression (see **Acute toxicity** section). These effects were not considered severe enough to warrant hazard classification for specific target organ effects from single exposure.

In a study on volunteers, inhalation exposure to the chemical caused changes in electroencephalogram (EEG) readings. Based on the observed changes in electrical brain activity, 0.2 mg/m^3 (0.044 ppm) was determined as a threshold concentration while 0.1 mg/m^3 (0.022 ppm) was determined to be the no-effect concentration (AEGL, 2012).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from inhalation exposure) and skin irritation.

Public Risk Characterisation

No Australian use information is available. However, given the uses identified overseas (in adhesives for art and craft and in paints and varnishes — SPIN), it is likely that the public will be exposed to the chemical. The concentrations of the chemical in consumer products overseas are reported to be less than 0.01 % (US Household Products Database).

Based on the identified hazards, the risk to public health is not considered to be unreasonable if the chemical is used up to 20 % concentration in consumer/domestic products.

Occupational Risk Characterisation

During product formulation, dermal and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. 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 could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation 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.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (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, 2016).

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]
Acute Toxicity	Harmful by inhalation (Xn; R20)*	Harmful if inhaled - Cat. 4 (H332)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Irritating to skin (Xi; R38)	Causes skin irritation - Cat. 2 (H315)

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

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

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

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal 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 that could minimise the risk include, but are not limited to:

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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.

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Last update 01 July 2016

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