# Propane, 1,2-dichloro-: Human health tier II assessment

**30 June 2017**

## CAS Number: 78-87-5


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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.

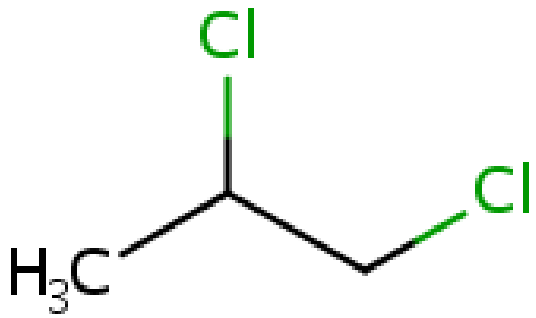
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | 1,2-dichloropropane (DCP)<br>alpha,beta-dichloropropane<br>alpha,beta-propylene dichloride<br>dichloro-1,2 propane<br>propylene dichloride |
| Structural Formula |  |
| Molecular Formula | C3H6Cl2 |
| Molecular Weight (g/mol) | 112.986 |
| Appearance and Odour (where available) | Liquid with chlorform-like odour |
| SMILES | C(C)(Cl)CCl |

# Import, Manufacture and Use

## Australian

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

## International

The following international uses have been identified through Galleria Chemica, European Union Registration, Evaluation, Authorisation and Restriction of Chemicals dossier (REACH), Substances and Preparations in the Nordic countries (SPIN) database, United States (US) Department of Health National Toxicology Program (NTP), US Environmental Protection Agency Chemical and Product Categories (CPCat), Hazardous Substances Data Bank (HSDB), Organisation for Economic Co-operation and Development (OECD, 2003), International Agency for Research on Cancer (IARC) Agency for Toxic Substances and Disease Registry (ATSDR, 1989) and the National Institute of standards and Technology (NIST).

The chemical may have domestic uses including:

- as a solvent for glues, adhesives, degreasers, cleaning and painting products;
- as a stain remover for fabrics;
- in car care products; and
- as a paint remover.

Based on the international assessments, the chemical is not expected to be commonly used in domestic products (ATSDR; OECD, 2003; IARC, 2016). Today, almost all (99.5 %) of the DCP in the United States of America (USA) and in Europe is used as a chemical intermediate. No consumer uses were registered in Danish and French Product Registers (OECD, 2003) and the chemical does not have consumer uses in listed in the US Department of Health and Human Services, Household Products Database (HPD).

The chemical has reported commercial uses, including:

- as a solvent for glues, adhesives, degreasers, cleaning and painting products;
- as a stain remover for fabrics;
- in dry cleaning fluids;
- as a component of spray urethane foam;
- as furniture finishes; and
- in coating agents for paper.

The chemical has reported site-limited uses including:

- as a chemical intermediate;
- as a cleaner in printing industry;
- as a fuel additive;
- as a solvent for oils and fats;
- in ion exchange manufacture;

- in polystyrene production;
- in rubber and wax processing; and
- in photographic film manufacture.

The chemical may also have non-industrial use as an active substance in plant protection products.

# Restrictions

## Australian

The chemical is listed in the *Poisons standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2017) in Schedule 6.

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2017).

## International

The following non-industrial restrictions were identified (Galleria Chemica):

US Food and Drug Administration (FDA) requirements for specific standardised beverages; allowable levels for volatile organic chemicals (VOC's) in bottled water is 0.005 mg/L.

Japan Index of the Positive List System for Agricultural Chemical Residues in Foods (Final Draft) - Provisional Maximum Residue Limit (MRL) for Mineral Waters is 0.04 mg/L.

# Existing Work Health and Safety Controls

## Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute toxicity – category 4; H332 (Harmful if inhaled)
- Acute toxicity – category 4; H302 (Harmful if swallowed)

## Exposure Standards

### Australian

The chemical has an exposure standard of 347 mg/m³ (75 ppm) time weighted average (TWA) and 508 mg/m$^3$ (110 ppm) short-term exposure limit (STEL) (Safe Work Australia).

### International

The following exposure standards are identified through Galleria Chemica:

- TWA range from 4.6-360 mg/m$^3$ (1-75 ppm) (TWA) in different countries such as the Canada, China, France, Iceland, Japan, New Zealand, Spain and US; and
- STEL range from 508-525 mg/m$^3$ (110-115 ppm) (STEL) in countries such as Canada, China, New Zealand, Spain and US.

# Health Hazard Information

## Toxicokinetics

The chemical DCP, is rapidly absorbed, distributed, metabolised and excreted following both oral and inhalation exposure (OECD, 2003; IARC, 2016).

In a toxicokinetic study performed according to the US Environmental Protection Agency (EPA) test-rule requirements, toxicokinetics and metabolism of $^{14}$C-labelled 1,2-dichloropropane ($^{14}$C-DCP) was assessed in Fischer 344 (F344) rats following inhalation or oral exposure. In the inhalation study, rats (4/sex/dose) were exposed to 0, 5, 50 or 100 ppm (23, 231 and 462 mg/m$^3$ ) of $^{14}$C-DCP in air. In the oral studies, rats were orally treated (gavaged) with either a single dose of 1 or 100 mg/kg bw or multiple doses of 1 mg/kg bw/day of $^{14}$C-DCP for eight consecutive days. Peak plasma radioactivity was generally attained 4 hours post-treatment, irrespective of route, indicating systemic delivery of DCP. The chemical was rapidly eliminated via excretion in urine (40-65 % of recovered radioactivity) and by expired air (20-40 % of recovered radioactivity). Only trace amounts remained in tissues 48 hours after treatment. The main metalbolites in urine and carbon dioxide ($CO_2$) in exhaled air were N-acetylcysteine conjugates (OECD, 2003; IARC, 2016).

In another study, the distribution of DCP was assessed in blood, liver, kidney, lung, and abdominal fat of F344/DuCrlCrlj rats. The rats (36/male/dose) were orally exposed (gavaged) to a single dose of 62 or 125 mg/kg bw of DCP. Blood collection and necropsy were performed at 0, 60, 180, 360, 540, and 1440 min after oral administration of DCP. Maximum concentration in blood was reached after 60 min and DCP was present in the blood at the last time-point (1440 min) in both dose groups. The concentration of DCP in all tissues peaked at 60 min after exposure. In the 125-mg/kg group, DCP was still detectable in the liver, kidney, lung, and abdominal fat 1440 min after administration. The DCP concentration in the abdominal fat was much greater than in the other tissues at each collection time point and for both doses (Take et al., 2017).

The PXB mouse model was utilised to perform a liver metabolism study. These mice are chimeric, with more than 70 % of their liver replaced with normal human hepatocytes; hence, they are a relevant system for studying human liver metabolism. The PXB mice (3/male/dose) were orally treated (gavaged) with the chemical dissolved in olive oil at 500 mg/kg bw. Glutathione-conjugated DCP metabolites were detected in the bile of DCP treated mice at 8, 16 and 24 h after dosing, suggesting that these metabolites have the potential to be excreted into bile of humans exposed to the chemical (Toyoda et al., 2016).

In workers exposed to DCP in air (10, 150 or > 400 mg/m$^3$), the chemical was detected in urine. There was a linear correlation between concentration in the breathing zone and concentration in the urine, indicating systemic absorption through the respiratory tract. The concentration of DCP in urine was not reported (IARC, 2016).

## Acute Toxicity

### Oral

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 4’ and hazard statement ‘Harmful if swallowed’ (H302) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). The reported median lethal doses (LD50) of 1942-2200 mg/kg bw in rats and 860-960 mg/kg bw in mice supports this classification (DFG; German Research Foundation; OECD, 2003; REACH).

Clinical signs of toxicity include salivation, lacrimation, dyspnoea, lethargy, reduced motility, haemorrhage in the gastrointestinal tract, haemolytic anaemia and liver and kidney damage (DFG; German Research Foundation).

In a pre-guideline study, Wistar rats (5/sex/dose) were orally treated (gavage) with undiluted DCP at doses arranged in a logarithmic series that differed by a factor of two. The reported LD50 was 2200 mg/kg bw. No other data are available (OECD, 2003).

In a repeat dose toxicity study in Sprague Dawley (SD) rats, acute clinical effects of DCP were assessed 24 h after single oral exposure (gavage). The male rats (6/dose) were exposed to 0, 100, 250, and 1000 mg/kg bw. There were no mortalities at any of the doses; however, the animals exhibited central nervous system (CNS) depression for at least 1 h following a single dose of the chemical. At the high doses (500 and 1000 mg/kg) the animals remained sedated for longer than 1 h (Bruckner, 1989).

Additionally, the following oral LD50 values have been reported for the chemical:

- 860 mg/kg bw in mice (Latky, 1986) cited in (OECD, 2003). No other data are available.
- 960 mg/kg/ bw in mice (Matsumoto, 1982) cited in (OECD, 2003). No other data are available.

### Dermal

The chemical has low acute toxicity via dermal route. The reported LD50 in rabbits is 10100 mg/kg bw (OECD, 2003).

In a non-guideline study, acute dermal toxicity was assessed in New Zealand White (NZW) rabbits (4/male/dose). The chemical DCP was applied to clipped skin of rabbits under occlusion for 24 h with observation for 14 days after exposure. Under the conditions of the study, the dermal LD50 for DCP in male rabbits was 8.75 ml/kg bw (10100 mg/kg bw) (OECD, 2003).

### Inhalation

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 4’ and hazard statement ‘Harmful if inhaled’ (H332) in the HCIS (Safe Work Australia). The reported median lethal concentration (LC50) of 2000 ppm (9.4 mg/L/4h) supports this classification (OECD, 2003).

In a non-guideline study, acute toxicity of DCP was assessed in male Sherman rats (6/dose) following inhalation exposure. The rats were exposed to the chemical for 4 or 8 h and then observed for 14 days. Vapour of the chemical was mixed with fresh air to produce a series (log base 2) of exposure concentrations (nominal). The reported LC50 for inhalation was 2000 ppm (9.4 mg/L/4h) (OECD, 2003).

In another non-guideline study, acute toxicity (LC50) of DCP was assessed in SD rats (3-5/group) (sex not reported), following inhalation exposure. The rats were exposed to a single dose of 2200 ppm (nominal) of vapour for 7 h. Groups of rats were sacrificed for necropsy on days 0, 1, 2, 4, 7, 9 and 14 days after exposure. Two rats died shortly after exposure whereas the remainder survived until necropsy. The main macroscopic changes observed were fatty liver and slight visceral congestion. The reported LC50 for the study was >2200 ppm (10.7 mg/L/7h) (OECD, 2003).

### Observation in humans

Cases of accidental ingestion of cleaning products containing DCP have been reported (DFG; German Research Foundation; OECD, 2003).

Ingestion of large amounts of DCP (50-180 mL; i.e. drinking cleaning solutions) was reported to be fatal (OECD, 2003). In several cases damage to liver, kidney and red blood cells, as well as dizziness, headache, nausea, metabolic acidosis, heart muscle weakness and shock, were reported following oral ingestion of the chemical (OECD, 2003, ATSDR, 1989). Similar effects were observed following deliberate inhalation of vapours of the chemical (ATSDR, 1989).

One human case with adverse effects from dermal exposure has been reported. However, this patient had also been exposed to toluene and the severity of the reaction was suspected to be worse due to a genetically-based susceptibility (Fiaccadori et al.,

2003).

## Corrosion / Irritation

## Corrosivity

An in vitro study (human skin model) performed in accordance with OECD (TG) 431 suggests that DCP may be corrosive. However, this result is contradicted by only slight skin and eye irritation observed in OECD (TG) studies 404 and 438 (refer to ***Irritation*** section). Therefore, based on the available information, hazard classification is not warranted.

In the OECD (TG) 431 study, the test material was applied uniformly and topically to a three-dimensional human skin model, a reconstructed epidermis with a functional stratum corneum. Corrosiveness of DCP was identified by the ability of the chemical to produce a reduction in viability of the tissue of more than 35 % below negative control. The results indicated that the chemical was corrosive after 4 hours exposure and not corrosive after 1 hour exposure (REACH).

### Skin Irritation

The chemical is reported to be slightly irritating to skin. The effects are not sufficient to warrant hazard classification.

In a study performed in accordance with OECD Test Guideline (TG) 404,White Vienna rabbits (2 male, 1 female) received 0.5 ml of DCP applied to a 2.5 cm x 2.5 cm piece of gauze which was held in contact with clipped rabbit skin (upper back or flank) under semi-occlusive conditions for 4 h. After 24 h, the skin displayed mild erythema (grade 2; maximum score 4) and oedema (grade 1; maxium score 4). After 8 days post-exposure, the skin was almost free of irritation (mild erythema, score, 1 of 4,in one rabbit) and only slight flaking was observed at the application site (REACH; OECD, 2003).

### Eye Irritation

The chemical is reported to slightly irritate eyes in ex vivo and animal studies. However, the data are not sufficient to warrant hazard classification.

The chemical was reported to be slightly irritating when tested ex vivo in isolated chicken eyes according to OECD TG 438. The eye was held in horizontal position and 30 µL of undiluted DCP was applied onto the centre of the cornea such that the entire surface of the cornea was covered. After 10 seconds, the surface was rinsed with saline. The positive control eyes were treated in a similar way with 30 µL of 30 (w/v) % trichloroacetic acid. The negative control eye was treated with 30 µL of isotonic saline. The control eye and test eyes were evaluated pre-treatment and at approximately 30, 60, 75, 120, 180 and 240 minutes after the post-treatment rinse. The cornea thickness and cornea opacity were measured at all time-points. The mean cornea opacity score for chicken eyes was grade 0.5 (maximum score 4) at 75, 120 and 240 min (REACH).

In a non-guideline study in rabbits (strain not reported), undiluted DCP (0.5 ml) was applied to the eyes. Slight redness and oedema with slight opacity were present 1 h post-treatment, with marked redness and oedema and slight opacity at 24 h. The irritation index was 2 out of 10. All signs of irritation had resolved 8 days post-treatment (OECD, 2003).

## Sensitisation

### Skin Sensitisation

The chemical is not considered to be a skin sensitiser.

In a local lymph node assay (LLNA) performed in accordance with OECD TG 429, female BALB/c mice (6/dose) received topical applications of 0, 5, 20 or 80 % DCP in acetone:olive oil on three consecutive days. The chemical did not promote lymph node cell proliferation response. The reported stimulation indices (SI) were 1, 1, 1.2 and 0.8 for concentrations of 0, 5, 20 or 80 %

respectively. Because all SI values were below 3, the estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) value could not be determined (OECD, 2003).

The lack of skin sensitisation potential is supported by the lack of skin sensitisation reactivity alerts from Toxtree v 2.6.6 modelling (Patlewicz et al., 2008) and lack of structural alerts for skin sensitisation using the knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus: 5.0.1 (Lhasa Limited).

In the Danish (Q)SAR database, the chemical was predicted negative for allergic contact dermatitis in guinea pigs and humans, using a battery approach combining results from CASE Ultra, Leadscope and SciQSAR. The applicability domain of the model was satisfied, indicating that the performance statistics of the data in the model were applicable to the chemical (Technical University of Denmark).

### Observation in humans

Two case studies provide weak evidence that DCP may cause allergic skin reactions in humans.

In a study with ten workers exposed to industrial preparations containing 10-40% DCP, the workers exhibited an allergic response after patch testing with DCP with a threshold level at 2 % of DCP. However, all subjects had pre-existing dermatitis due to hand washing using a mixture of solvents (10-40% DCP) and the dermatitis was quickly resolved after cessation of exposure (Baruffini et al., 1989).

In another study, two female workers (no history of allergy) were tested with 1 % DCP or other substances present in the workplace. Both women reacted positively to DCP but one of the women also reacted to several other substances (Grzywa et al., 1981).

## Repeated Dose Toxicity

### Oral

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

Studies in animals indicate that the liver is the primary target organ of DCP (NTP, 1986).

In a 13 week oral gavage study (standard NTP methodology), male and female F344 rats (10/sex/dose) were exposed to daily doses of DCP in corn oil at 60, 125, 250, 500 or 1000 mg/kg bw/day, 5 days a week for 13 weeks. Rats given 1000 mg/kg bw/day and 5 out of 10 males from the 500 mg/kg bw/day group died before necropsy. Final mean body weight was decreased by 16 % in male and 8 % in female rats. The liver was the only organ affected with fatty changes and centrilobular congestion observed in female rats at the highest dose. No DCP-related liver lesions were reported in the male rats. The no observed adverse effect level (NOAEL) of 250 mg/kg bw/day was based upon mortality and lower body weight in male rats and lower body weight in female rats at 500 mg/kg bw/day (NTP, 1986).

In a 13 week oral gavage study in male SD rats (15-16/dose), were exposed to daily doses of DCP in corn oil at 100, 250, 500 or 750 mg/kg bw/day, 5 days a week for 13 weeks. Sedation and reduced food and water consumption were observed at the two highest doses. Doses from 100 mg/kg bw/day caused a reduction in body weight gain, and haemolytic anaemia. All animals in the 750 mg/kg bw/day group died or were euthanised in a moribund state during the first two weeks of the study. The dose of 500 mg/kg bw/day was lethal to approximately 60 % of rats and caused body weight loss and histopathological changes to liver, spleen, adrenals, testes and epididymis. Blood haemoglobin levels were reduced, bilirubin levels increased and the ornithine carbamyl transferase (OCT) and alanine aminotransferase (ALT) significantly increased in the 250 and 500 mg/kg bw/day dose groups.

In a 13 week oral gavage study (standard NTP methodology), B6C3F1 mice (10/sex/dose) were exposed to 30, 60, 125, 250 or 500 mg/kg bw/day, 5 days a week for 13 weeks. One male dosed with 60 mg/kg bw/day died during the first week of the study, and one female from the 500 mg/kg bw/day group died during week 12. Body weights for all treated males were decreased 4-5 % without a dose-relationship. Body weights for females from the 250 and 500 mg/kg bw/day groups were also decreased

slightly by 3-4 %. Since there were no histopathological changes noted, these minor effects on body weight were considered incidental and not related to treatment. An NOAEL of 250 mg/kg bw/day was therefore reported (OECD, 2003).

### 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 13 week inhalation study, F344 rats (10/sex/dose) were exposed (whole body) to 0, 15, 50 or 150 ppm/day DCP vapour (69, 231 or 693 mg/$m^3$) for 6 h/day, 5 days a week for 13 weeks. One male from the 15 ppm group died on day 81 from non-treatment related haemorrhagic cystitis. No other clinical or obvious signs of toxicity were reported in any of the treated animals. Body weights were significantly decreased throughout the study (females 7 %, males 10 % at termination) in the 150 ppm dose group. Histopathological effects were confined to the upper respiratory tract with a slight degeneration of the olfactory mucosa noted for all groups exposed to 50 or 150 ppm of DCP (no effect at 15 ppm). The reported no observed adverse effect concentration (NOAEC) was 15 ppm (69 mg/$m^3$) (OECD, 2003).

In a 13 week inhalation study, F344/DuCrj (SPF) rats (10/sex/dose) rats were exposed (whole body) to 0, 125, 250, 500, 1000, or 2000 ppm (578, 1155, 2310 or 4621 mg/$m^3$) DCP vapour 6 h/day, 5 days a week for 13 weeks. One female from the highest dose group died during the 12th week of the study. Growth rates were supressed in both male and female rats at the two highest doses. Haemolytic anaemia was reported at concentrations 500 ppm and above. Spleen weights were significantly increased in rats exposed to 2000 ppm. Liver weights were significantly increased in females exposed to 500 ppm and above. Damage to the olfactory epithelium was detected in rats exposed to 125 ppm and above. Histopathological changes in the liver were seen in rats exposed to 2000 ppm. Significant fatty changes in the adrenal gland were seen in females at 2000 ppm. An NOAEC was not reported from this study as the lowest dose damaged the olfactory epithelium (Umeda et al. 2010).

In a 13 week inhalation study, B6C3F1 mice (10/sex/dose) were exposed (whole body) to 0, 15, 50 or 150 ppm/day DCP vapour (69, 231 or 693 mg/$m^3$) 6 h/day, 5 days a week for 13 weeks. No clinical signs of toxicity were recorded and body weights were unaffected. Dose independent effects were reported in haematological parameters. No treatment related histopathological changes were present. Due to a lack of dose-response and an absence of histopathological changes in bone marrow and spleen the slight haematological changes were considered low toxicological relevance. The reported NOAEC was 150 ppm (693 mg/$m^3$) (OECD, 2003).

In a 13 week inhalation study, B6D2F1/Crlj (SPF) mice (10/sex/dose) were exposed to (whole body) 50, 100, 200, 300 or 400 ppm (231, 462, 924, 1386 or 1848 mg/$m^3$) DCP vapour 6 h/day, 5 days a week for 13 weeks. Six male mortalities in the 400 ppm dose group and two in the 300 ppm dose group occurred during the first two weeks of the exposure period. One female mortality occurred in the 400 ppm dose group at the end of the exposure period. Growth rates were dose-dependently reduced and significantly suppressed in males exposed to 200 ppm and above. No effect on female growth rate was reported. The liver and spleen weights were significantly increased in mice exposed to 300 or 400 ppm and above, respectively. Haematological changes were reported in males exposed to 50 ppm and above and in females exposed to 300 ppm and above. Pathological changes were detected in the nasal cavity, stomach, liver, hematopoietic system and heart. Respiratory tract metaplasia, atrophy, and necrosis occurred in both male and female mice exposed to 300 ppm and above. Swelling of centrilobular hepatocytes was significantly increased in both male and females exposed 300 ppm and above. Necrosis of hepatocytes was noted in males exposed to 300 ppm DCP. In the bone marrow, congestion was observed in all six dead male mice and increased erythropoiesis in the female mice exposed to 300 ppm and above. Atrophy of the spleen was observed in most of the dead males. As haematological effects were present at the lowest dose of DCP, an NOAEC was not obtained from this study. An LOAEC of 50 ppm (231 mg/$m^3$) was reported based on haematological effects (Matsumoto et al., 2013).

### Observation in humans

In a study of printing company workers with bile duct cancer (10 males), health examination records during employment and after retirement were obtained to analyse their blood parameters. The patients or their relatives were also interviewed about lifestyle and occupational history. The workers had been exposed to DCP at concentrations ranging from 100 to 670 ppm for 6-17 years (estimated concentrations). Liver enzymes including γ-GTP, ALT and AST were increased either during or after exposure indicating effects on the liver. However, the majority of the workers had also been exposed to other solvents including dichloromethane and kerosene, and several workers were heavy smokers or drinkers. Therefore, the liver effects may not have been solely due to DCP exposure (Kumagai et al., 2014).

## Genotoxicity

In general the weight of evidence from the available well-conducted in vitro and in vivo genotoxicity studies suggests that the chemical is not clastogenic. However, positive results for point mutations were seen in an Ames test and in an in vivo comet assay following inhalation exposure. In vivo studies in germ cells did not indicate potential for heritable mutations (Suzuki, 2014).

**In vitro studies**

Several in vitro assays were conducted using the chemical (IARC, 2016). These included:

- Positive in vitro point mutation results were observed in *Salmonella typhimurium* strains TA100, 1535, at concentrations up to 5000 µg/mL, with or without metabolic activation.
- Negative in vitro point mutation results were observed in *S. typhimurium* TA1537, TA1538 and TA98, at concentrations up to 5800 µg/mL and in strain TA1978 at concentrations up to 25000 µg/mL, with or without metabolic activation.
- Negative in vitro forward mutation results were observed in *Streptomyces coelicolor* (metabolic activation not tested).
- Negative in vitro genetic crossing-over and forward mutations results were observed in *Aspergillus nidulans* at concentrations of 17400 and 58000 µg/mL respectively.
- Positive results were seen for in vitro sister chromatid exchange in Chinese hamster ovary and lung fibroblast V79 cells at concentrations of 113 and 370 µg/mL respectively with and without metabolism.

**In vivo studies**

The chemical gave mostly negative results for in vivo genotoxicity assays:

- Negative results were observed in a micronucleus test (OECD TG 474) in male CD1 mice orally exposed to the chemical at 0, 150, 300 or 600 mg/kg bw. No significant increases in micronucleated polychromatic erythrocytes or inhibition of bone marrow cell proliferation were seen (OECD, 2003).
- Negative results were observed in a transgenic rodent mutation assay (OECD TG 488) in male F344 gpt delta rats orally exposed to DCP at 100 or 200 mg/kg bw/day for four weeks (Hirata et al., 2016).
- Negative results were observed in a Pig-a gene mutation assay and in a micronucleus assay in blood from B6CR1F mice exposed to 150, 300 or 600 ppm/day (693, 1386 or 2773 mg/m$^3$/day) DCP vapour for 6 weeks (Suzuki, 2014).
- Positive results were observed in *Drosophila melanogaster larvae*, in a wing spot test in larvae exposed 7.7 µg/L (7.2 mg/m$^3$) DCP by inhalation in air (IARC, 2016).
- Positive results (dose-dependent) were observed in the DNA damage alkaline comet assay in liver from B6CR1F mice exposed to 150, 300 and 600 ppm DCP vapour for 6 weeks (Suzuki, 2014).
- Positive results were observed for the DNA damage marker gamma-H2AX in the liver of C57BL/6J mice exposed to 100, 200 and 400 ppm vapour for two days, 6 h on the first day, followed by 3 h on the second day (Toyooka et al., 2017).
- Negative results were obtained *Drosophila melanogaster* with no increase in, sex-linked recessive lethal mutations in flies exposed to 7200 ppm (33270 mg/m$^3$) DCP by inhalation (IARC, 2016).
- Negative results were observed in a dominant lethal study (US EPA guideline study 40 CFR 789.4700) in male SD rats fed with the chemical at doses up to 162 mg/kg bw/day for 14 weeks (OECD, 2003).

**Obervations in humans**

Whole-exome analysis was performed on four cholangiocarcinoma patients that had been exposed DCP for 6-11 years while working for a printing company. One of the patients had also been exposed to dichloromethane. All workers had approximately 30-fold higher level of mutations in their tumour tissue compared to common control cholangiocarcinoma tissues. The mutational signature of the printing workers was partially recapitulated in whole-genome analysis of *Salmonella typhimurium* TA100 strain treated with DCP. However, the most prominent trinucleotide mutational signature, GpCpY to GpTpY was not repopulated in the TA100 strain. No significant increase in the mutation rate was observed using a human cholangiocarcinoma cell line NCC-CC1 and HEK293 cells either treated with a single, or repeated cytotoxic doses of DCP (Mimaki et al., 2016).

## Carcinogenicity

The chemical is carcinogenic in experimental OECD TG studies and may induce bile duct cancers in humans, warranting hazard classification (refer to ***Recommendation*** section).

The chemical is also classified as 'Carcinogenic to humans' (Group 1) by the International Agency for Research on Cancer (IARC) and Carcinogenic 1B by the European Union Committee for Risk Assessment (ECHA RAC).

**Experimental data**

In a carcinogenicity study (OECD TG 451), F344/N rats (50/sex/dose) were orally treated (gavaged) with 0, 125, or 250 mg/kg bw/day (females) and 0, 62, and 125 mg/kg bw/day of DCP (males), 5 days a week for 103 weeks. The survival in male rats was 78, 84 and 82 % and in female rats 74, 86 and 32 % in the controls, low dose or high dose groups, respectively. In female rats, mammary gland hyperplasia was significantly increased in the low dose group (controls, 10/50; low dose, 20/50) and the incidence of mammary adenocarcinoma was increased in the high dose group (NTP, 1986).

In a carcinogenicity study (OECD TG 451), male and female B6C3F1 mice (50/sex/dose) were orally treated (gavaged) with 0, 125, or 250 mg/kg bw/day of DCP, 5 days a week for 103 weeks. Survival in male mice was 70, 66 and 70 % and in female mice 70, 58 and 52 % for control, low dose and for the high dose groups, respectively. The liver tumour incidence (adenoma and carcinoma combined) was increased in high dose male and low and high dose female mice. Two high dose female mice developed follicular cell carcinomas in the thyroid. In the high dose females, the combined incidence of follicular cell adenomas and carcinomas was significantly higher than that in the controls (NTP, 1986).

In a 2 year inhalation study, F344/DuCrj (SPF) rats (10/sex/dose) were exposed to DCP vapour (whole body) at 80, 200, or 500 ppm (370, 924, or 2310 mg/m$^3$) 6 h/day, 5 days a week for 104 weeks. Survival was not affected by the treatments. Incidences of nasal cavity papillomas increased in both male and female rats in a concentration-dependent manner and this increase was statistically significant at the highest concentration. Three cases of nasal esthesioneuroepitheliomas were observed in males exposed to 80 (two cases) and 200 (one case) ppm DCP. Since there were no previous historical cases (48 two-year carcinogenicity studies) of this tumour type in male F344 rats, the tumours were considered to be induced by the chemical. Hyperplasia of the nasal transitional epithelium was significantly increased in all DCP-exposed groups of both sexes and squamous cell hyperplasia was significantly increased in males rat the two highest concentrations. Total pre-neoplastic lesions were significantly increased at all concentrations in both male and female rats (Umeda et al. 2010).

In a carcinogenicity study (OECD TG 451), male and female B6D2F1 mice (50/sex/dose) were exposed to DCP vapour at 32, 80 or 200 ppm (148, 370 or 924 mg/m$^3$), 6h/day, 5 days a week for 2 years. At the end of the 2 year study, the survival rates of the 0, 32, 80 and 200 ppm exposed groups were 64, 66, 66 and 82 % for male mice and 58, 56, 52 and 60 % for female mice, respectively. A dose-dependent increase in incidence of bronchiolo-alveolar carcinomas (lung) was seen in the females and the combined incidence of bronchiolo-alveolar adenomas and carcinomas was significantly increased in females at 200 ppm. A dose-independent increase in the incidence of bronchiolo-alveolar adenomas was reported in males. The incidence of liver histiocytic sarcoma was significantly increased in males exposed to 80 ppm. Nasal cavity atrophy and respiratory metaplasia was observed in males exposed to 80 and 200 ppm DCP, respectively. In females respiratory metaplasia was observed at 32 and 200 ppm and nasal cavity atrophy at 80 ppm (Matsumoto et al., 2013).

**Human data**

Cases of cholangiocarcinoma (bile duct cancer) were reported among 17 relatively young employees of printing firms in Japan (Kumagai 2013, Kubo, 2014). The workers were diagnosed at 25–45 years of age and had been exposed to chlorinated solvents such as DCP, dichloromethane or trichloroethane over 6-16 years. Of the 17 cases, six were exposed to DCP only. Other chemicals used in the printing industry were ruled out as causative agents due to their lower consumption or shorter

period of exposure (Ministry of Health in Japan, Labour and Welfare; MHLW). The pathological changes found in the bile duct of the patients included duct sclerosis, biliary epithelial injuries/proliferation, and focal bile duct losses, consistent with chronic bile duct damage similar to cholangiocarcinoma patients with predisposing bile duct or liver pathologies. This suggests that the cancerous lesions may have developed from chronic bile duct injury. Additional cases have since been described at other plants (Yamada 2014) and the total number of legal claims for printing plant work-related cholangicarcinomas was 37 in November 2015 (JISHA, 2017).

In a follow-up study, cumulative exposures to DCP were estimated in an offset proof-printing company in Osaka. The exposure levels in the printing rooms were estimated to range between 148-15864 $mg/m^3$ and the cholangiocarcinoma incidence risk increased with increasing cumulative exposure among 95 printing plant workers (Kumagai et al., 2016). An increased incidence of cholangiocarcinoma in printing workers has also been demonstrated outside Japan; however, estimates of exposures to DCP was not included in the studies (Vlandeeren et al., 2013, Ahrens et al., 2014).

Several national authorities including ECHA, IARC and MHLW agree that DCP is likely to be the cause of cholangiocarcinoma in the printing plant workers in Japan; however, human data are limited and a large epidemiological study analysing confounding factors is not available (ECHA, IARC, 2016, MHLW).

## Reproductive and Developmental Toxicity

Based on the information available, the chemical does not show specific reproductive or developmental toxicity.

In a two-generation study performed according to EPA guidelines (EPA OTS 798.4700), SD rats were exposed to 0, 0.024, 0.1 or 0.24 % (w/v), equivalent to 20-30, 70-130 or 130-250 mg/kg bw/day, respectively, in water for 10-14 weeks before mating; during mating and gestation; in the rest period between pregnancies; and during lactation. A dose-related decrease in water consumption was apparent in animals from both the founder (F0) and first (F1) generations, most likely due to the palatability of the water. There were no treatment-related differences in male or female reproductive performance or the reproductive organs at termination. Body weight gain during pregnancy was significantly reduced by approximately 20 % in high dose dams and 7-13 % in mid dose females. The number of pups born alive was similar in the control and test groups from both phases of the study. However, in the high dose group, postnatal survival in F1 litters was significantly lower and in second generation (F2) litters 10 % lower (14-21 days after birth) than controls. Body weights in F1 neonates were significantly decreased (15 % lower on day 21 after birth). Body weights of F2 neonates were less severely affected with 4 – 7 % reduction in body weight on day 21. The authors of the study suggested that the slight decrease in bodyweight and postnatal survival was due to maternal dehydration. The reported parental, developmental (offspring) and reproductive NOAELs were 20-30 (0.024 %), 70-130 and 130-250 mg/kg bw/day (OECD, 2009).

In a developmental toxicity study (EPA OTS 798.4900), pregnant SD rats (30/dose) were orally treated (gavaged) with 0, 10, 30 or 125 mg/kg bw/day DCP in corn oil on gestation days (GD) 6-15 and foetuses examined on GD 20. A significant increase in delayed ossification of the skull bones was reported in high dose offspring. These skeletal variations occurred at maternally toxic doses. The reported NOAELs for maternal toxicity and teratogenicity were 30 and 150 mg/kg bw/day, respectively (OECD, 2003).

In another developmental toxicity study (EPA OTS 798.4900), New Zealand White rabbits (4-5/dose) were treated with 15, 50 or 150 mg/kg bw/day DCP on GD 7-19 and foetuses examined on GD 28. Treatment-related skeletal effects in foetuses were detected at maternally toxic doses. Two NOAELs were established, for maternal toxicity and teratogenicity, 50 and 150 mg/kg bw/day respectively (OECD, 2003).

## Other Health Effects

### Neurotoxicity

The chemical can induce transient CNS depression in experimental animals and dizziness, disorientation, and coma in humans at high doses (refer to ***Acute toxicity*** section), warranting hazard classficication (refer to ***Recommendation*** section).

In a 13 week neurotoxicity study according to EPA guidelines (functional observation battery = EPA 798.6050; motoractivity = EPA798.6200; neuropathology = EPA798.6400.), F344 rats (15/sex/dose) were orally treated (gavaged) with 0, 20, 65 or 200 mg/kg bw/day DCP in corn oil. Temporary clinical signs (lacrimation, blinking, and decreased spontaneous motor activity) were reported after 3-4 days of treatment. There were no effects attributable to DCP in, grip strength, or motor activity. No treatment-related lesions were observed in brain or other parts of the nervous system at the end of the study (OECD, 2003).

Central nervous system depression has been reported in humans exposed to DCP at high concentrations (IARC, 2016).

# Risk Characterisation

## Critical Health Effects

The main critical health effect for risk assessment is carcinogenicity.

The chemical can also have acute systemic and local effects from oral and inhalation exposure.

## Public Risk Characterisation

The chemical is currently listed on Schedule 6 of the SUSMP.

Based on information on use of the chemical internationally (refer to ***Import, Manufacture and Use*** section), the chemical is not likely to be widely available for domestic use and exposure similar to that reported for printing workers is not expected. Hence, the public risk from this chemical is not considered to be unreasonable and further risk management is not considered necessary for public safety.

## Occupational Risk Characterisation

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposures 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.

There is some evidence that the chemical DCP causes cholangiocarcinoma in the printing plant workers; however, human data are limited and a large epidemiological study analysing confounding factors is not available. *Guidance on the interpretation of workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia, 2013).

The existing hazard classification for worker health and safety requires amendment to include the classification for carcinogenicity (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, 2017).

### Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Acute Toxicity | Not Applicable | Harmful if swallowed - Cat. 4 (H302)* Harmful if inhaled - Cat. 4 (H332)* |
| Carcinogenicity | Not Applicable | May cause cancer - Cat. 1B (H350) |
| Other Health Effects | Not Applicable | May cause drowsiness or dizziness - Specific target organ tox, single exp Cat. 3 (H336) |

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

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

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

## Advice for consumers

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

## Advice for industry

Control measures to minimise the risk from dermal and inhalation exposures 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 eliminating 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;
- 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.

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