Chlorine: Human health tier II assessment

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CAS Number: 7782-50-5

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	molecular chlorine bertholite warfare gas chloor
Structural Formula	
Molecular Formula	Cl2
Molecular Weight (g/mol)	70.9
Appearance and Odour (where available)	greenish-yellow gas with a pungent, irritating odour
SMILES	ClCl

Import, Manufacture and Use

Australian

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of 10,000-99,999 tonnes.

The following Australian uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported domestic uses, including:

- as a bleaching agent;
- in cleaning and washing agents; and
- as an odour agent.

However, these uses appear to relate to chlorine produced in situ from bleaching agents; direct supply of gaseous chlorine for domestic uses is not permittted under the Poisons Standard (SUSMP, 2016).

The chemical has reported commercial uses, including:

- as a disinfectant; and
- in chlorine bleach cleaners.

The chemical has reported site-limited uses including:

- in manufacture of other chemicals;
- in mining and metal extraction; and
- in production of PVC plastic, synthetic rubber and other chlorinated chemicals.

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

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development (OECD) Screening information data set International Assessment Report (SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Department of Health and Human Services Household Products Database (HHPD); the OECD High Production Volume chemical program (OECD HPV); the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the Agency for Toxic Substances and Disease Registry (ATSDR, 2010); the European Union Risk Assessment Report for chlorine (EU RAR, 2007a); the International Programme on Chemical Safety (IPCS, 1997); the World Health Organisation Food Additives Series 20 Report (WHO, 2015); and WHO Guidelines for Drinking-water Quality (WHO, 1996).

The chemical has reported domestic uses, including:

- as a bleaching agent;
- as a cleaning and washing agent; and
- as an odour agent.

The chemical has reported commercial uses, including:

- in cleaning agents;
- in metal fluxing;
- as a process regulator; and
- as a biocide in cooling water application.

The chemical has reported site-limited uses, including:

- as an intermediate in production of chlorinated and non-chlorinated compounds;
- in production of chlorinated solvents, pesticides, polymers, synthetic rubbers; refrigerants; flame-retardant compounds; batteries;
- as a bleaching agent in the manufacture of paper and cloth;
- in drinking water disinfection;
- in waste water disinfection; and
- in pulp and paper bleaching.

The chemical has reported non-industrial uses, including:

- in processing of some foods;
- in swimming pool disinfection;
- as a post-harvest disinfectant for fruits and vegetables; and
- as an agricultural pesticide.

Restrictions

Australian

This chemical is listed under a group entry 'Chlorinating compounds' in the *Poisons Standard—The Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 5, 6 and 7 (SUSMP, 2015).

Schedule 5:

'Chlorinating compounds containing 20 per cent or less of available chlorine, except:

(a) when separately specified in these Schedules;

(b) sodium hypochlorite preparations with a pH of less than 11.5;

(c) in liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements: WARNING - Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(d) in liquid preparations containing less than 2 per cent of available chlorine; or

(e) in other preparations containing 4 per cent or less of available chlorine'.

Schedule 6:

'Chlorinating compounds except:

(a) when included in Schedule 5;

(b) when separately specified in these Schedules;

(c) sodium hypochlorite preparations with a pH of less than 11.5;

(d) in liquid preparations containing not less than 2 per cent but not more than 4 per cent of available chlorine when labelled with the statements: WARNING - Ensure adequate ventilation when using. Vapour may be harmful. May give off dangerous gas if mixed with other products;

(e) in liquid preparations containing less than 2 per cent of available chlorine; or

(f) in other preparations containing 4 per cent or less of available chlorine'.

Schedule 7 as 'Chlorine'(excluding its salts and derivatives).

Schedule 5 chemicals are labelled with 'Caution'. These are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warning and safety directions on the label' (SUSMP, 2015).

Schedule 6 chemicals are labelled with 'Poison'. These 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' (SUSMP, 2015).

Schedule 7 chemicals are labelled with 'Dangerous Poison'. These are substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply (SUSMP, 2015).

Chlorine is included in the Australian Dangerous Goods Code 7.3 edition (ADG Code, 2014), with an entry for chlorine (UN Number 1017) listed as Toxic, in Class 2.3. The ADG Code contains detailed provisions for packaging, transport and marking containers in Class 2.

International

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

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

Existing Work Health and Safety Controls

Hazard Classification

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

- T; R23 (acute toxicity); and

- Xi; R36/37/38 (irritation).

Exposure Standards

Australian

The chemical has an exposure standard of 3 mg/m^3 (1 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 1.5-3 mg/m^3 (0.5-1 ppm) TWA and 1–9 mg/m^3 (1-3 ppm) short-term exposure limit (STEL)/MAK/occupational exposure limit (OEL) in different countries such as the USA (Alaska, Hawaii), Argentina, Canada (Alberta, British Columbia), Egypt, Hungary, Germany, Norway and Switzerland.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 1 ppm (0.5 mg/m^3) TWA.

Health Hazard Information

Chlorine is a gas with pungent irritating odour. Exposure is expected to be only through inhalation. It is slightly soluble in water and forms hypochlorous acid (HClO) and hydrochloric acid (HCl) on contact with moisture. The chemical HClO is highly unstable and readily decomposes to form oxygen free radicals. Therefore, water enhances the oxidising and corrosive effects of chlorine. Chlorine is a strong oxidising agent that can react explosively or form explosive compounds with many common substances.

Chlorine gas (Cl_2) is formed from bleaches under acidic conditions (OECD, 2003; ATSDR, 2010). It is highly corrosive when comes into contact with moist tissues i.e. eyes, skin and upper respiratory tract (ATSDR, 2010; EU RAR, 2007a; EU RAR, 2007b; IPCS, 1997; OECD, 2003).

In biological systems where the pH is in the range 6-8, chlorine exists in the most active species form of HClO in equilibrium with hypochlorous ion (ClO^-). Therefore, all toxicokinetics studies for chlorine are performed with hypochlorite and its salts which are predominant at physiological pH (IPCS, 1997; OECD, 2003). In aqueous solutions, chlorine levels are expressed as available chlorine, which is the sum of Cl_2, HClO, and ClO^- (OECD, 2003).

Data are generally only available for inhalation toxicity of chlorine. Data for sodium hypochlorite (CAS No. 7681-52-9) (NICNAS) are not considered relevant due to the alkaline nature of this chemical. Relevant systemic toxicity data are included in the assessment of sodium hypochlorite.

Toxicokinetics

Chlorine is readily absorbed by inhalation route. Absorbed chlorine is distributed into plasma, bone marrow, testes, skin, kidney and lung. Chlorine reacts at the site of contact with moist tissues and forms HClO and HCl. The chemical HClO is not enzymatically metabolised and transforms through direct reactions with organic compounds or other chemicals in the cellular environment to form chlorinated organic compounds with their own inherent toxicity. More than 95 % of the inspired chlorine is absorbed in the upper airways and less than 5 % is delivered to the lower airways. Around 50 % of the absorbed chlorine is excreted, mainly in the urine, followed by excretion in faeces (ATSDR, 2010; EU RAR, 2007a; EU RAR, 2007b; IPCS, 1997; OECD, 2003; WHO, 1996; REACH).

Upon oral administration of a single dose of radiolabelled (^{36}Cl) hypochlorous acid in rats, rapid uptake and distribution of the hypochlorite ion in the blood occurred. Peak concentration was reached between 2 to 4 hours and the half-life was between 2 to 4 days (ATSDR, 2010; EU RAR, 2007a; EU RAR, 2007b; NICNAS; REACH).

In humans, groups of five men and five women were exposed to chlorine at concentration of 3 ppm (equivalent to 9 mg/m^3) at respiratory flows of 150, 250 or 1000 mL/sec. Effects of chlorine were mainly limited to the upper respiratory tract with more than 95 % of the inhaled chlorine absorbed in the upper airways and less than 5 % inhaled chlorine penetrating beyond the upper airways (EU RAR, 2007a).

Acute Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in the HSIS (Safe Work Australia). The available data (median lethal concentration (LC50) values of 1200 mg/m^3 in rats and 900 mg/m^3 in mice) support this classification (OECD, 2003; REACH).

In an acute toxicity inhalation study, male Sprague Dawley (SD) rats were exposed to 1500 ppm chlorine for 5 mins. Significant increase in lung resistance was observed up to 3 days after exposure. Histological examination showed epithelial flattening and necrosis, increase in smooth muscle mass and evidence of epithelial regeneration (REACH).

Wistar rats and Swiss Webster mice (five animals/sex/group) were exposed to chlorine at concentrations ranging from 935-1725 mg/m^3 (rats) and 1328-1870 mg/m^3 (mice) for 5, 10, 30 or 60 min. Most of the deaths in rats and mice occurred within the first week of observation. Pathology findings included increased relative lung weights, with no dose-related effects on kidneys and liver. Histopathological findings showed focal aggregates of polymorpho- or mononuclear inflammatory cells, increased septal cellularity and squamous metaplasia of the bronchial epithelium. The LC50 values were in the range of 1248-1423 mg/m^3 (rats) and 1198-1671 mg/m^3 (mice) (REACH).

The NMRI female mice (10 animals/dose) were exposed to different concentration ranges of chlorine for 30 min, 3 hours and 6 hours respectively. Eight of ten animals died within four days after three hours' exposure to 370 mg/m^3 chlorine. Pathological examination revealed pulmonary oedema, necrosis and inflammation of the respiratory epithelium. A LC50 of 370 mg/m^3 for 30 min exposure was reported (REACH).

Male Swiss Webster mice exposed to chlorine at concentrations from 2 to 111 mg/m^3 for 10 min exhibited a 50% decrease in respiratory rate at 27 mg/m^3 air (EU RAR, 2007a; REACH).

Observation in humans

In humans, acute exposure to the chemical led to respiratory changes as a primary response.

In observations made 4.5 years after an incidental exposure to chlorine gas, 13 women reported clinical signs including excessive frequencies of phlegm production, painful breathing, wheezing and shortness of breath. Impaired neurobehavioural functions and elevated profile of mood states (POMS) scores with increased frequencies of symptoms were associated with the chlorine bleach exposure (HSDB; REACH).

A firefighter accidentally exposed to a chlorine gas cloud reported a variety of effects ranging from mucous membrane irritation to acute respiratory distress syndrome and progressive vocal cord dysfunction (REACH).

Nine male patients were admitted to an intensive care unit in a United States Army Combat Hospital (CSH) following chlorine gas exposure after a vehicle-borne improvised explosive devices (VBIED) attack. One patient suffered significant thoracic trauma and all patients developed acute respiratory distress syndrome (ARDS). Eight of the nine patients had refractory hypoxaemia and were placed on airway pressure release ventilation. Three patients were treated with intravenous corticosteroids. One patient died after being on mechanical ventilation for 21 days (REACH).

Various incidents of accidental exposure to chlorine have been reported (EU RAR, 2007a):

- No deaths in 19 people exposed to more than 1000 ppm (3000 mg/m^3) in a railroad car accident;
- In a chemical plant near Bombay, India, the following effects were observed following exposure at the indicated time points:- dyspnoea, coughing, throat and eye irritation, headache, giddiness, chest pain and abdominal discomfort were reported in 88 people exposed to 66 ppm (198 mg/m^3) chlorine for almost one hour;

-signs of respiratory incapacity were reported in 62 individuals 48 hours after exposure; -tracheobronchial congestion was reported in 56 individuals five days after exposure; -scattered haemorrhagic spots under the bronchial mucosa were reported in 28 individuals and bronchial erosion with peristent cough and respiratory distress in seven people up to 25 days after exposure;

- Light-headedness and sore throats were reported in two employees from a chemical plant in Pittsburgh, US after exposure to 34 kgs of chlorine (vapour registered at 2 ppm); and
- Death of a man exposed to chlorine gas cloud for 30 mins due to pulmonary oedema three hour post-exposure.

Pulmonary oedema in humans is reported to be the main cause of death after chlorine exposure; however, other causes related to exposure to very high chlorine concentrations over short periods of time include bronchoconstriction, shock, immediate respiratory arrest and cardiac complications (ATSDR, 2010; EU RAR, 2007a; IPSC, 1997). Use of chlorine in humans at very high concentrations during World War I led to burning sensation in the throat, cough, feeling of suffocation, dyspnoea and death due to acute pulmonary oedema within 24 hours of exposure. The survivors reportedly suffered from bronchitis, pulmonary emphysema and asthma (ATSDR, 2010).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory tract' (Xi; R37) in the HSIS (Safe Work Australia). The available data support this classification

Exposure to high concentrations of chlorine gas for short periods have led to severe respiratory effects in animals and humans. Histological changes in the upper respiratory tract have been reported at chlorine concentrations as low as 1-3 ppm (ATSDR, 2010; IPSC, 1997).

Skin Irritation

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

The ATSDR (2010) reported that direct contact with liquid chlorine or concentrated vapour causes severe chemical burns, leading to cell death and ulceration.

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia).

Exposure to 12 ppm chlorine six hours/day, five days/week for 10 days in rats caused swelling around eyes (ATSDR, 2010).

In another ocular irritation study in rats for six weeks, signs of irritation were reported at 3 ppm chlorine and 1 ppm chlorine has no effect (ATSDR, 2010).

Severe eye irritation was reported on rats exposed to 5 ppm chlorine for 62 days and conjunctival irritation with exudation were reported in monkeys after exposure to 2.3 ppm chlorine for one year (ATSDR, 2010).

Chlorine is irritating to the eyes as shown by most of the acute inhalation toxicity studies with chlorine gas. Exposure to chlorine in humans at concentrations ranging from 0.6 to 12 mg/m^3 is reported to cause burning of conjunctivae and eye irritation (ATSDR, 2010; EU RAR, 2007a; EU RAR, 2007b; REACH).

Observation in humans

Chlorine gas produces immediate severe effects at the site of contact including the skin, eyes and respiratory tract (OECD, 2003).

In a case study, observations taken two weeks after an accident involving spillage of 200 ppm chlorine gas in a tanker cars derailment, skin rashes and skin burns were reported in 16-25 % of the 682 people exposed. In another derailment incident, people exposed to the vapour were reported to have minor first-degree skin burns (ATSDR, 2010).

Skin irritation complaints were reported by fire fighters who responded to a chlorine gas leak in Henderson, Nevada, with exposure to <0.2 to 17 ppm of chlorine concentrations in the air (ATSDR, 2010).

In a human study conducted according to the principles of good laboratory practice (GLP), eight male volunteers were exposed to chlorine vapour at concentrations of 0, 0.1, 0.3 or 0.5 ppm (0, 0.3, 0.9 or 1.5 mg/m^3) for six hours/day for three consecutive days for each of the four exposure concentrations. No significant effects on lung function parameters and respiratory function for up to 0.5 ppm were observed (REACH).

Sensitisation

Skin Sensitisation

No data are available for the chemical. However, based on the available information for sodium hypochlorite (NICNAS), the chemical is not expected to be a skin sensitiser.

Repeated Dose Toxicity

Oral

Based on the treatment-related effects reported in various repeated dose toxicity studies, repeated oral exposure to chlorine is not considered to cause serious damage to health.

In a 90-day oral repeated dose study, SD rats (10 animals/sex/dose) were given chlorine in drinking water at concentrations of 0, 25, 100, 175 or 250 mg/L (equivalent to 0, 2.1, 7.5, 12.8 or 16.7 mg/kg bw/day for males and 0, 3.5, 12.6, 19.5, 24.9 mg/kg bw/day for females). Significantly increased haemoglobin concentrations were observed in females at 12.6 and 19.5 mg/kg bw/day. Males at 12.8 mg/kg bw/day showed decreased monocyte count. Significant increase in the phosphate levels was

reported in both sexes at 7.5 and 12.8 mg/kg bw/day. These effects were not seen in the highest dose groups. No treatment-related changes in organ weights were seen. No observed adverse effect levels (NOAEL) reported were ≥ 16.7 and ≥ 24.9 mg/kg bw/day for males and females, repsectively (WHO, 1996; HSDB; REACH).

In a 90-day study in B6C3F1 mice (groups of 10/sex/dose), chlorine was administered in drinking water at concentrations of 0, 12.5, 25, 50, 100 or 200 mg/L (males: 0, 2.7, 5.1, 10.3, 19.8 or 34.4 mg/kg bw/day and females: 0, 2.8, 5.8, 11.7, 21.2 or 39.2 mg/kg bw/day) for 90 days. Statistically significant reduction in average water consumption in females at 21.2 and 39.2 mg/kg bw/day was observed. All treated mice showed decreased body weight gain and male mice in the 19.8 and 34.4 mg/kg bw/day groups showed significant reduction of >10 %. No other effects were observed. A NOAEL of 10 mg/kg bw/day was reported (HSDB).

Male CR-1:CD-1 mice (30 animals/dose) were administered chlorine at doses of 0.02, 0.2, 2.9 or 5.8 mg/kg bw/day in drinking water for 120 days. No statistically significant treatment-related effects were seen in all treated mice. A NOAEL of 5.8 mg/kg bw/day was reported (WHO, 1996).

Inhalation

Based on the available data, repeated inhalation exposure to chlorine is associated with local effects.

Groups of Fischer 344 (F344/N) rats (10 animals/sex/dose) were exposed to chlorine gas at concentrations of 0, 1, 3 or 9 ppm (0, 3, 9 or 27 mg/m^3) for six hours/day, five days/week for 6 weeks by whole body exposure. Three females in the 9 ppm (27 mg/m^3) group died before the end of the study. All males and females at 9 ppm (27 mg/m^3) showed inflammation of the respiratory tract with hyperplasia and hypertrophy of epithelial cells of the respiratory bronchioles, alveolar ducts and alveoli. Focal inflammation of the nasal turbinates and slight to moderate inflammation around the respiratory bronchioles and alveolar ducts were observed in male rats at 1 or 2 ppm (3 or 9 mg/m^3). A LOAEL of 1 ppm for local effects was reported (ATSDR, 2010; EU RAR, 2007a; HSDB).

Groups of 70 male and female F344/N rats and B6C3F1 mice were exposed to 0, 0.4, 1.0 or 2.5 ppm (0, 1.2, 3 or 7.5 mg/m^3) of chlorine gas for six hours/day and five days/week (all mice and male rats) and three alternate days/week (female rats) for 2 years. All the exposed animals showed exposure-dependent lesions in the nasal cavity. Chlorine-induced lesions observed include respiratory and olfactory epithelial degeneration, septal fenestration, mucosal inflammation, respiratory epithelial hyperplasia, squamous metaplasia, goblet cell hypertrophy and hyperplasia, and secretory metaplasia of the transitional epithelium of the lateral meatus. A LOAEL of 0.4 ppm (1.2 mg/m^3) for rats and mice was reported (ATSDR, 2010; EU RAR, 2007a; US NTP, 1992; OECD, 2003; REACH).

In a one year study, rhesus monkeys (four animals/sex) were exposed to chlorine at 0, 0.1, 0.5 or 2.5 ppm (0, 0.3, 1.5 or 3.9 mg/m^3) for 6 hours/day, five days/week by whole body inhalation exposure. Monkeys in the 2.5 ppm (3.9 mg/m^3) showed signs of ocular irritation, superficial conjunctival irritation and tracheal lesions. Histopathology showed treatment-induced lesions in the respiratory tract including focal, concentration-related epithelial hyperplasia with loss of cilia and decreased numbers of goblet cells. A LOAEL of 0.1 ppm was reported (ATSDR, 2010; EU RAR, 2007a; HSDB).

Observation in humans

No effects were observed in volunteers exposed to 0.4 mg/kg bw/day chlorine at 1.5 L/day in distilled water for four weeks (ATSDR, 2010).

In a group of ten human volunteers, 5 mg/L chlorine (approximately 0.036 mg/kg bw/day) in drinking water for 12 weeks had no adverse effects (ATSDR, 2010).

Human volunteers exposed to chlorine at 0.5 ppm (1.5 mg/m^3) for three days caused no effects (EU RAR, 2007b).

Groups of 29 male and female volunteers were exposed to chlorine at 0, 0.5, 1 or 2 ppm for four or eight hours. Most subjects reported itching and burning of the throat by the end of a 8-hour exposure to 1 ppm chlorine. Severe irritation and significant

changes in the pulmonary functions were observed in groups exposed to 1 or 2 ppm chlorine for eight hours (ATSDR, 2010).

In an incident in Mjondalen, Norway, 85 people were hospitalised after exposure to fumes at concentrations of approximately 30-60 ppm (90-180 mg/m^3) following release of 7-8 tonnes chlorine. Two individuals died immediately after exposure and another died five days after exposure (EU RAR, 2007b).

Genotoxicity

No data are available for the chemical. Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies in sodium hypochlorite, chlorine is unlikely to be genotoxic. Several in vitro studies indicated equivocal results but all in vivo tests were negative (NICNAS).

Carcinogenicity

Based on the available data, the chemical is not considered to be carcinogenic.

In a drinking water study, groups of 70 F344/N rats and 10 B6C3F1 mice were exposed to chlorine in drinking water at concentrations of 0, 70, 140 or 275 ppm for up to 2 years. Slight reduction in the mean body weights of all treated male rats, high-dose female rats and all treated mice were observed. Female rats in the 140 ppm dose group showed increased incidence of mononuclear leukaemia as compared to controls. No indication of leukaemia and no neoplastic changes were seen in male rats and or either sex in mice (US NTP, 1992; HSDB; NICNAS; REACH).

In a previously described two-year inhalation study in F344/N rats and B6C3F1 mice (see **Repeat dose toxicity: inhalation**), no significant treatment related carcinogenic effects were observed (US NTP, 1992; REACH)

Reproductive and Developmental Toxicity

No reproductive or developmental effects were noted in rabbits and rats exposed to the chemical through oral and inhalation exposure.

In a reproductive toxicity study conducted similarly to OECD TG 415, Long-Evans rats (12 males and 24 females) were administered chlorine solution at doses of 0, 1, 2 or 5 mg/kg bw/day by gavage for 66-76 days. Males were treated 56 days prior to breeding and treatment continued for 10 days of the breeding cycle. Females were treated 14 days prior to breeding through breeding, gestation, lactation and weaning at day 21. No effects on litter survival, litter size, and pup weight were reported (EU RAR, 2007a; EU RAR, 2007b; OECD, 2003; HSDB; NICNAS; REACH).

Female SD rats (6 animals/group) were administered chlorine in drinking water at concentrations of 0, 0.1, 10 or 100 mg/L per day for 2.5 months prior to conception and throughout gestation. No significant reproductive or developmental effects were observed (EU RAR, 2007a; EU RAR, 2007b; NICNAS).

In a multigenerational study in BDII rats (60 rats/sex), drinking water containing 100 mg/L available chlorine was administered throughout the life span of the animals. No reproductive or developmental effects were reported (EU RAR, 2007b).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from inhalation exposure). The gas can also cause irritation of the eye and respiratory system.

Public Risk Characterisation

The general public could be exposed through the skin or inhalation when using domestic products which release the chemical. The chemical in these domestic products is sufficiently controlled by the Poisons Standard entries. Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During direct use of the chemical or in product formulation, dermal, ocular 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. Worker exposure to the chemical at lower concentrations could also occur while using formulated products which release the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular 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.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2015).

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	Toxic by inhalation (T; R23)*	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)

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

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

* Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

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

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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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