Benzoyl chloride: Human health tier II assessment

27 November 2014

CAS Number: 98-88-4

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.

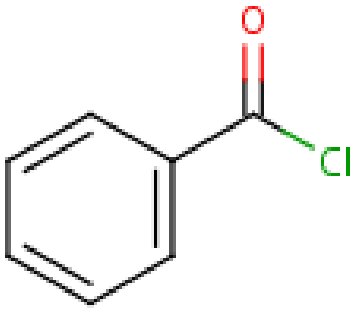
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	benzenecarbonyl chloride benzoic acid, chloride
Structural Formula	
Molecular Formula	C7H5ClO
Molecular Weight (g/mol)	140.57
SMILES	C(=O)(Cl)c1ccccc1

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 European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and eChemPortal: OECD High Production Volume chemical program—OECD HPV, the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource—ACToR, and the US National Library of Medicine's Hazardous Substances Data Bank—HSDB.

The chemical has reported cosmetic use for skin conditioning.

The chemical has reported domestic uses including as:

- adhesives, binding agents; and
- fillers.

The chemical has reported commercial use as a process regulator.

The chemical has reported site-limited use including as a chemical reagent.

Restrictions

Australian

No known restrictions have been identified.

International

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

- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist"); and
- US FDA List of Indirect Additives Used in Food Contact Substances.

Existing Work Health and Safety Controls

Hazard Classification

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

Australia):

- Xn; R20/21/22 (acute toxicity)

- C; R34 (corrosivity)
- Xi; R43 (sensitisation)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

- An exposure limit of 2.8–5.0 mg/m^3 (0.5 ppm) time weighted average (TWA) in different countries such as Austria, Bulgaria, Hungary, Latvia, Norway, Switzerland, the USA (Alaska, Hawaii) and Venezuela; and
- An exposure limit of 2.8 mg/m^3 (0.5 ppm) short-term exposure limit (STEL) in Belgium.

Health Hazard Information

The chemical undergoes rapid hydrolysis to benzoic acid and hydrochloric acid (US EPA, 2012). The hydrolysis of the chemical suggests that local effects such as irritation or corrosion are most likely, and that any systemic effects will result from the hydrolysis products, benzoic acid and hydrochloric acid, which have previously been assessed by NICNAS (US EPA, 2005; NICNASa; NICNASb).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the Hazardous Substances Information System (HSIS) (Safe Work Australia).

The available data (median lethal dose—LD50—2500 mg/kg bw males, 3619 and 1900 mg/kg bw, respectively for male and female Spartan rats and 2528 mg/kg bw for male Wistar rats) (US EPA 2005; US EPA, 2012; REACH) do not support this classification. All animals showed symptoms including sedation, extension spasm and reduced general condition of the animal (US EPA, 2005). No additional signs of toxicity were reported (REACH).

Given the corrosive nature of the chemical, it is not recommended that the classification be removed.

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in HSIS (Safe Work Australia).

The available data (LD50 >2000 mg/kg for New Zealand White rabbits) do not support this classification. Clinical signs reported included all (two female and two male) test subjects exhibiting fissuring at the site of application (US EPA, 2005; US EPA, 2012). Additional data were reported that indicated the LD50 for rabbits (number, sex, strain and additional clinical details not indicated) was 790 mg/kg (US EPA, 2012).

Given the rabbit data and the corrosive nature of the chemical, it is not recommended that the classification be removed.

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 (four-hour median lethal concentration—LC50—1.45–1.98 mg/L for male/female Wistar rats via nose-only inhalation) support this classification (US EPA, 2005; US EPA, 2012; REACH). Clinical signs of toxicity were not reported.

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrase ‘Corrosive’ (C; R34) in HSIS (Safe Work Australia). While available animal data do not clearly support this classification, there are human reports (unverifiable), which suggest that the expected corrosive nature of acyl halides applies to this chemical.

Studies performed in accordance with OECD Test Guideline (TG) 404 with deviations, do not support the classification. New Zealand White rabbits (three/sex) were exposed under a semi occlusive bandage to 0.5 mL of the chemical for four hours and observed for 72 hours. All rabbits exhibited signs of low to moderate skin irritation. The overall primary irritation score was reported to be 3.8. Reversibility of the observed effects was not checked (REACH).

In other non-guideline studies the classificationof this chemical is supported. New Zealand White rabbits (two animals, sex not reported) were exposed under an occlusive bandage to 0.5 mL of the chemical for 24 hours and then observed for seven days. Severe erythema and oedema were observed up to seven days and, in the last days, necrosis was observed. Scores were not available (REACH).

In humans

While it has not been possible to find specific case reports, multiple sources imply that benzoyl chloride is a corrosive chemical in humans (Vincoli, 1996; Bruze et al, 2000; IPCS, 2014; HSDB).

Eye Irritation

It was concluded in a study that the chemical is a strong irritant for eyes and corrosive for the cornea. When 100 µL of the chemical was applied to the eye of New Zealand White rabbits, severe redness and moderate to severe chemosis of the conjunctivae were reported. In addition, slight to moderate swollen and hyperaemic iris, and slight diffuse opacity of the cornea were observed. The reversibility of the findings was not reported (REACH).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). The chemical was found to induce dermal sensitisation when tested according to OECD TG 406 in a guinea pig maximisation test (GPMT) using Hartley guinea pigs (REACH).

The skin sensitising potential of the chemical was tested at 2 % and 5 % after determining the maximum non irritant concentration to the skin on three Freund's complete adjuvant (FCA) pre-treated animals. For the challenge exposure, benzoyl chloride diluted to 5 % and 2 % with mineral oil were retained from the range-finding study. In the control group, a slight cutaneous reaction was noted 24 hours after the patch was removed, which was then noted to reverse in less than 24 hours. In

the tested group, the application of the chemical induced a slight to well-defined erythema in 90 % of the animals. The reaction was noted to persist 48 hours after patch removal (REACH).

Repeated Dose Toxicity

Oral

No data are available.

The chemical undergoes rapid hydrolysis to benzoic acid and hydrochloric acid. Repeated oral exposure to benzoic acid is not considered to cause serious damage to health (NICNASa) and repeated oral exposure to hydrochloric acid is associated with short-term local effects (NICNASb). Based on the weight of evidence, only local effects are expected from repeated oral exposure to the chemical.

Dermal

The no observed effect leval (NOEL) and no observed adverse effect level (NOAEL) were not derived from the reported data (REACH).

Female ICP mice were exposed to the chemical for three days/week for four weeks, and two days/week for 37 weeks (5 and 10 µL/animal (538 and 1077 mg)), and two days/week for 50 weeks (2.3 µL/animal (285 mg)). Marked irritation of the eyes, skin and respiratory system were noted a few minutes after exposure. Jumping, running and scratching of the painted area was also observed. At the painted area, erythema and swelling were initially recorded and alopecia, induration, marked keratinisation were noted after a period. In some mice, ulcers and/or necrosis of the epidermis were reported. No mortality was observed in the test group exposed to 5 µL/animal. In the 2.3 µL/animal exposure group, mortality at termination was 20 % for the control and 5 % in the treated group (REACH).

Inhalation

Only limited data are available. Male ICR mice were exposed to the chemical for 30 minutes/day, two days/week for five months, then observed for a further nine months, during a non-guideline repeated dose inhalation toxicity study. Hair-loss and inflammation were observed in the mice. At necropsy, inflammation of the lymph nodes, liver and spleen were noted; mild keratosis and hyperplasia of the gastric mucosa were also reported. Pathological changes in the respiratory system and skin were observed.

Due to the rapid hydrolysis of the chemical to benzoic acid and hydrochloric acid, the repeated dose inhalation toxicity of the products have also been considered. Benzoic acid is not considered likely to cause serious damage to health and the available data indicate that local irritation effects would likely be from repeated inhalation exposure to hydrochloric acid.

Genotoxicity

Overall, the in vitro data indicate that the chemical has no mutagenic or genotoxic potential (REACH).

In vitro data using the reverse mutation assays with various strains of *Salmonella typhimurium, Escherichia coli* and the *Bacillus subtilis* recombination assays (with and without metabolic activation) were negative for genotoxicity (REACH).

Genotoxicity was not observed in the in vivo micronucleus assays where clastogenic effects on the chromosomes of bone marrow erythroblasts were not noted (US EPA 2012).

Carcinogenicity

The International Agency for Research on Cancer (IARC) has indicated that there is 'limited evidence' in humans for the carcinogenicity of the chemical. It has also been indicated that there is 'inadequate evidence' in laboratory animals regarding the carcinogenicity of the chemical (IARC, 1999).

Repeated dose toxicity in dermal studies were conducted on female ICP mice that were exposed to the chemical for three days/week for four weeks and two days/week for 37 weeks (5 and 10 µL/animal (538 and 1077 mg)), and two days/week for 50 weeks (2.3 µL/animal (285 mg)). Signs of irritation were observed (refer to **Repeat dose toxicity: Dermal** section). No mortality was observed in the test group exposed to 5 µL/animal of the chemical; tumorigenic activity for the skin was reported as having developed in 2/10 mice (20 %) (i.e. one developed carcinomas of the skin and the other skin papillomas). In the higher exposure group (10 µL/animal) 3/10 mice (30 %) had lung adenomas; no other tumours were detected. In the 2.3 µL/animal exposure group, mortality at termination was 20 % for the control and 5 % in the treated group. The number of mice with tumours in the treated group was 7/20 (35 %). Two mice developed squamous–cell carcinomas of the skin and five others had lung adenomas. There were two cases of lung adenomas reported in the control group, but no other tumours. The results suggest a weak carcinogenic potential of benzoyl chloride (REACH).

Reproductive and Developmental Toxicity

No data are available. The chemical undergoes rapid hydrolysis to benzoic acid and hydrochloric acid, which have been assessed by NICNAS previously (NICNASa; NICNASb). The reproductive and developmental toxicity of benzoic acid and hydrochloric acid have been considered in this assessment. Based on the properties of these products, it is likely that the chemical is not a reproductive or developmental toxicant.

There was no evidence of reproductive or developmental toxicity from benzoic acid (NICNASa). A four-generation study was conducted using male and female rats where benzoic acid was introduced into the diet of the first and second generations at approximately 250 or 500 mg/kg bw/d. The third and fourth generation were treated for 16 and four weeks respectively. No unfavourable side-effects were noted (NICNASa). Teratologic effects were determined by exposing Wistar rats to a single dose of benzoic acid of 510 mg/kg bw at day nine of gestation. The malformations and resorption rates were comparable with those in the control animals (NICNASa).

Limited data were available regarding the reproductive and developmental toxicity of hydrochloric acid, although only short-term local effects are anticipated (NICNASb). The reproductive and developmental toxicity of hydrochloric acid was determined during a 90-day inhalation study where Sprague Dawley (SD), Fischer 344 rats and B6C3F1 mice were exposed to hydrochloric acid vapour (up to 75 mg/m^3) for six hours/day five days/wk. Exposure-related effects in the reproductive organs were not noted (NICNASb).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (corrosivity and skin sensitisation).

Public Risk Characterisation

Due to the rapid hydrolysis of the chemical, it is assumed that any formulation based on the chemical and available to the public will actually contain the hydrolysis products. Given the uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Given the local 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.

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

Considering the available information indicates low public exposure from this chemical, no regulatory controls are recommended.

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 if swallowed (Xn; R22)* Harmful in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Causes burns (C; R34)*	Causes severe skin burns and eye damage - Cat. 1B (H314)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)

[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 oral/dermal/ocular/inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from 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 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;
- health monitoring for any worker who is at risk of exposure to the chemical[s], if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

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

Obligations under workplace health and safety legislation

Information in this report should be taken into account to 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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