Benzene, 1-chloro-4-(trichloromethyl)-: Human health tier II assessment

21 April 2016

CAS Number: 5216-25-1

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.

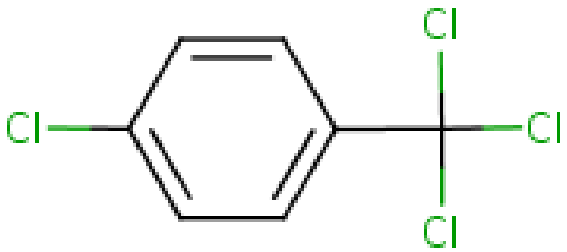
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	4-chloro-benzotrichloride alpha,alpha,alpha,4-tetrachlorotoluene p-chlorobenzotrichloride
Structural Formula	
Molecular Formula	C7H4Cl4
Molecular Weight (g/mol)	229.9
Appearance and Odour (where available)	colourless to yellow liquid
SMILES	C(Cl)(Cl)(Cl)c1ccc(Cl)cc1

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica and the United States of America (USA) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR).

The chemical has reported site-limited use as an intermediate in the manufacture of dyes and pharmaceuticals.

Restrictions

Australian

No known restrictions have been identified.

International

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

- 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
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

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; R21/22 (acute toxicity);
- Xi; R37/38 (irritation);
- T; R48/23 (repeat dose toxicity);
- T; R45 Carc. Cat 2 (carcinogenicity); and
- Xn; R62 Rep. Cat 3 (reproductive toxicity).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available data (median lethal dose—LD50 values ranging between 572 and 687 mg/kg bw) support this classification. Reported signs of toxicity included: changes in breathing, locomotion and behavioural posture, and weight loss. Congestion in the lungs, liver, kidneys and stomach was reported (REACHa; REACHb).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in the HSIS (Safe Work Australia). No data are available to evaluate this classification.

Inhalation

The chemical has moderate acute toxicity based on results from animal tests following inhalation exposure. The median lethal concentration (LC50) in rats is 1.4 mg/L. Based on the available data classification is considered to be warranted (refer **Recommendation** section).

In a non-guideline study, three groups of Sprague Dawley (SD) rats were exposed continously for 4 hours to the chemical in the form of a respirable aerosol at the atmosphere concentrations of 0.99, 1.31 and 2.32 g/m^3. The calculated LC50 was established at 1.48 g/m^3 of air. Observed sublethal effects included rales, sensitivity to touch and aggressive behaviour. Hepatisation (a state of lungs when gorged with effused matter and are no longer pervious to air) and numerous dark sub-pleural foci were observed in the lungs (REACHb).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in the HSIS (Safe Work Australia). No data are available to evaluate this classification.

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 support this classification.

In a skin irritation study conducted similarly to OECD Test Guideline (TG) 404, intact and abraded skin of male New Zealand White (NZW) rabbits (six animals) was treated with 500 µL of the chemical by occlusive dermal application for 24 hours. Development of superficial, whitish corrosive crusts with paleness of the skin was observed at 24 hours after application. Dry and slightly brown discoloured skin was reported eight days after the treatment. Moderate to high irritation was reported for intact skin after 24 and 72 hours with mean oedema scores of 3.67 and 3.33, respectively (REACHa).

The chemical was also reported to be highly irritating in another study in NZW rabbits (three animals) although erythema and oedema scores at 24–72 hours were not provided (REACHb)

Eye Irritation

The chemical was reported to slightly irritate the eyes when tested according to OECD TG 405. The effects were not sufficient to warrant hazard classification.

In a eye irritation test conducted according to OECD TG 405, 100 µL of the chemical was instilled into the eyes of six male NZW rabbits. Mild overall irritation was reported in all treated animals. The average scores for corneal opacity, iritis, conjunctivae (redness) and conjunctivae (chemosis) were given as 1/0/1.9/1.7, respectively. All signs of irritation were fully reversible after 8 days (REACHa).

The chemical was also reported to be slightly irritating in another sudy in NZW rabbits (three animals), although irritation scores at 24–72 hours were not provided (REACHb)

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser based on the positive results seen in a single local lymph node assay (LLNA). Classificication is considered to be warranted (refer **Recommendation** section).

In a mouse local lymph node assay (LLNA), the chemical was applied to the ears of female CBA mice (15 animals/dose) at concentrations of 1, 5 or 10 % w/v for three consecutive days. All animals were injected with ^{3}H-thymidine, three days after the exposure. Animals in the 10 % w/v group had largest auricular lymph nodes and some animals showed slight body weight reduction. The stimulation index (SI) values reported for different concentrations of the chemical were 7.2, 15.9 and 19.5, respectively (REACHa). These values indicate that the EC3 value for the chemical is < 1 %.

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Toxic: danger of serious damage to health by prolonged exposure through inhalation’ (T; R48/23) in the HSIS (Safe Work Australia). No data are available to evaluate this classification.

Genotoxicity

Sufficient data are not available to draw conclusions regarding the genotoxicity of the chemical. Positive and negative results have been reported in bacterial point mutation assays. No in vitro tests in mammalian cells or in vivo data are available.

In an Ames test, the chemical was tested for genotoxicity in *Salmonella typhimurium strains* TA98, 100, 1535, 1537 and 1538 and *Escherichia coli* strain *WP2uvrA* with or without metabolic activation at concentrations in the range of 0.16 - 500 μg/plate. A dose-dependent increase in number of revertant colonies was observed in *S. typhimurium* strain TA98, both with and without metabolic activation. Slight increase in the number of revertant colonies was also observed in *S.typhimurium* strains TA100 and TA 1537 (REACHa).

In two independent experiments, the chemical was tested up to concentrations of 0.1μg/plate in S. *typhimurium* strains TA1537, TA1535, TA98, TA100 and TA102 both in the absence and presence of metabolic activation. No positive mutagenic effects were observed (REACHb).

Carcinogenicity

The chemical is currently classified as hazardous as a Category 2 carcinogen with the risk phrase ‘May cause cancer’ (T; R45) in the HSIS (Safe Work Australia) (SCCP, 2005). The available data support this classification.

In a 17.5 week study, the chemical was orally administered to female ICR mice (30 animals/dose) at 0.05, 0.13, 0.32, 0.8 or 2 μL (equivalent to 0.05, 0.13, 0.32, 0.8 or 2 mg/kg bw/day) in 1 mL of sesame oil, twice a week. Mice exposed to 2 μL (11/29) and 0.8 μL (3/29) were reported to have malignant lymphoma and thymoma. Adenocarcinomas and adenomas in the lungs were seen in all treated mice; however, the highest incidence was seen in mice at 0.8 μL (25/29). Other tumours reported in mice at 2 μL included squamous cell carcinomas, sarcomas and adenocarcinomas of the skin, mammary cancer and salivary gland cancer. A dose-dependent development of tumours was observed with total number of mice with tumours observed as 6/22, 10/28, 17/22, 27/29 and 25/29 at 0.05, 0.13, 0.32, 0.8 and 2 μL, respectively (REACHa).

Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 3 substance toxic to reproduction)—with the risk phrase ‘Possible risk of impaired fertility’ (Xn; R62) in the HSIS (Safe Work Australia) (SCCP, 2005). No data are available to evaluate this classification.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity and reproductive toxicity), systemic acute effects (through all routes of exposure) and local effects (skin sensitisation). The chemical can also cause skin and respiratory irritation.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, oral, 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 containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term and systemic acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

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	Irritating to skin (Xi; R38)* Irritating to respiratory system (Xi; R37)*	Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)*	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	Suspected of damaging fertility - Cat. 2 (H361f)

[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 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;
- 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.

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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