Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

2,5-Cyclohexadiene-1,4-dione (p-benzoquinone)

Evaluation statement

14 January 2022

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

2, 5-Cyclohexadiene-1,4-dione (p-benzoquinone)

Chemical in this evaluation

Name	CAS registry number
2, 5-Cyclohexadiene-1,4-dione	106-51-4

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk evaluation assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of the chemical in Australia.

Based on international information, the chemical is used in a wide range of applications, including in domestic products (home maintenance products such as paint and fillers and photographic chemicals), as an intermediate in the synthesis of chemicals and in the manufacture of other products (refer to the supporting information).

Human health

Summary of health hazards

The critical health effects for risk characterisation include:

- systemic acute effects from oral and inhalation exposure
- local effects including skin, eye and respiratory tract irritation and skin sensitisation
- genotoxicity

The chemical can be expected to be absorbed across biological membranes due to its relatively low molecular weight. The chemical is excreted via the urine after metabolic transformation.

It has moderate acute oral and inhalation toxicity, and is irritating to the eyes, skin and respiratory tract. A guinea pig maximisation test (GPMT) and LLNA test produced positive results indicating that the chemical is a skin sensitiser. Based on positive results in some in vitro and in vivo genotoxicity tests, such as: DNA strand breakage and HRPT locus; and micronuclei in cultured mammalian cells and mice bone-marrow cells; and its metabolic relationship to the known mutagens; the chemical warrants classification as a Category 2 mutagen. No information is available on the reproductive, developmental, or carcinogenic effects of the chemical in animals or humans. Based on the limited information available the chemical is not classifiable as a carcinogen.

Health hazard classification

The chemical satisfies the criteria for the classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE, 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute toxicity - oral	Acute Tox 3	H301 (Toxic if swallowed)
Acute toxicity - inhalation	Acute Tox 3	H331 (Toxic if inhaled)
Skin corrosion/irritation	Skin Irrit. 2	H315 (Causes skin irritation)
Serious eye damage/eye irritation	Eye Irrit. 2A	H319 (Causes serious eye irritation)
Skin sensitisation	Skin Sens. 1B	H317: May cause an allergic skin reaction
Specific target organ toxicity – single (STOT SE)	STOT Single Exp. 3	H335 (May cause respiratory irritation)
Genotoxicity	Muta. 2	H341 (Suspected of causing genetic defects)

Summary of health risk

Public

Based on available use information, the chemical could have specific domestic uses such as for photographic processing by photo hobbyists and as a component in home maintenance products such as paints and fillers, with potential risks associated through dermal exposure. The concentration of the chemical in these products is unknown. However, these are uses of the chemical where dermal exposure would be restricted to only occasional splashes and spills. Therefore, there are no identified risks to the public that require management.

Workers

During product formulation, dermal, ocular and inhalation exposure might 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. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical local, systemic acute and long term effects, the chemical could pose a risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented (see Recommendation section).

Conclusions

The conclusions of this evaluation are based on the information described in this statement. Obligations to report additional information about hazards under section 100 of the Industrial Chemicals Act 2019 apply.

The Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks provided all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

The proposed means of managing the risks identified during this evaluation are set out in the Recommendations section.

Recommendations

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information on managing identified risks

The information in this report including recommended hazard classifications should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the Model Work Health and Safety Regulations.

Control measures that could be implemented to manage the risk arising from dermal, ocular and inhalation exposure to the chemical 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
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used.

These control measures may need to be supplemented with:

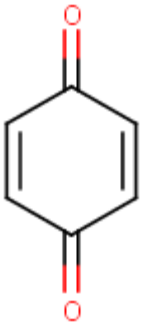
- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.
- conducting air monitoring to ensure control measures in place are working effectively and continue to do so;

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Supporting information

Chemical identity

Chemical name	2,5-Cyclohexadiene-1,4-dione (p-benzoquinone)
CAS No.	106-51-4
Synonyms	Quinone
	1,4-quinone
	p-benzoquinone
	1,4-benzoquine
	1,4-cyclohexadiene dioxide
	cyclohexa-2,5-diene-1,4-dione
Structural formula	
Molecular formula	$C_6H_4O_2$
Molecular weight (g/mol)	108.09
SMILES	O=C1C=CC(=O)C=C1

Relevant physical and chemical properties

Physical form	Yellow brownish crystalline solid
Melting point	115.7°C
Boiling point	180°C

Vapour pressure	0.1 mm Hg at 25°C
Water solubility	14 g/L at 25 °C
log K_{ow}	0.20

Introduction and use

Australia

There is currently no specific information about the introduction, use and end use of the chemical in Australia.

International

The following international uses have been identified through the:

- European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers
- Chemwatch
- US Environmental Protection Agency (EPA)
- Substances in preparations in Nordic countries (SPIN) database
- US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported potential domestic uses, including in:

- surface coatings, paints, lacquers and varnishes
- fillers; putties, plasters and modelling clay
- photographic chemical.

The chemical has reported commercial uses, including:

- as a stabiliser
- in photochemicals
- as oxidising agents
- in leather tanning
- in construction materials additives
- as tanning agents
- in pulp and paper
- as a solvent and carrier.

The chemical has reported site limited uses, including:

- in the production of polymers
- in textile manufacture
- as an intermediate in the production of hydroquinone and dyes.

The chemical has reported non-industrial uses, including:

- in pharmaceuticals
- in the production of fungicides, petrochemicals and agrochemicals.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

The chemical is listed on the Hazardous Chemical Information System (HCIS) with the following classifications (SWA).

- Acute Toxicity – Category 3; H301 (Toxic if swallowed)
- Acute toxicity – Category 3; H331 (Toxic if inhaled)
- Skin irritation – category 2; H315 (Causes skin irritation)
- Eye irritation – Category 2; H319 (Causes serious eye irritation)
- Specific target organ toxicity (single exposure) – category 3; H335 (May cause respiratory irritation).

The chemical is listed on the HCIS with the following exposure standard:

- Time Weighted Average (TWA): 0.1 ppm (0.44 mg/m^3).

In 2020, Safe Work Australia reviewed and recommended to retain this TWA. The TWA was recommended to minimise eye irritation and disturbance in vision in exposed workers (SWA 2020).

International regulatory status

Exposure standards

The following exposure standards are identified (Chemwatch):

TWA: 0.44 mg/m^3 (0.1 ppm)—New Zealand, USA, Canada, South Korea, Singapore, Vietnam, Belgium)

STEL (Short-term Exposure Limit): 1.2 mg/m^3 (0.3 ppm)—USA, Canada, Vietnam

Health hazard information

Toxicokinetics

Absorption, Metabolism and Excretion

The chemical is reported to be readily absorbed from the gastrointestinal tract and subcutaneous tissue (REACH). The chemical, or quinones in general, have been shown to undergo oxidation reduction cycles involving quinone, hydroquinone, and molecular oxygen, resulting in the formation of oxygen radicals and semiquinone radicals. The chemical can be conjugated with glutathione resulting in mono-, di-, and tri-glutathione conjugates, which are detectable in the bile. The glutathione conjugates can be further metabolised to cysteine conjugates and mercapturic acids.

The primary route of elimination is via the urine (>85 %), in the form of water soluble metabolites. The major urinary metabolites are glucuronide conjugates (45−56 %) and sulfate conjugates (19-43 %). Only a small fraction (about 1−3 %) is excreted unchanged in the urine. It is also excreted as conjugates of its own metabolite, hydroquinone (IARC, 1977).

No information is available on the toxicokinetic effects following inhalation (REACH).

Acute toxicity

Oral

The acute oral median lethal dose (LD50) of the chemical derived from reliable data, but with restrictions, ranged between 130 and 165 mg/kg bw (REACH). Exposure to high levels of the chemical (not specified) resulted in severe effects on the central nervous system including paralysis, loss of reflexes and depressed respiration. The LD50 of the chemical derived from valid quantitative structure–activity relationship (QSAR) model equivalent or similar to OECD Test Guideline (TG) 423, with adequate and reliable documentation and justification, was calculated to be 197 mg/kg bw (REACH). These results are consistent with the current classification for acute oral toxicity in the HCIS (Safe Work Australia).

Dermal

No data are available for the chemical.

Inhalation

The chemical is classified as hazardous in the HCIS as ‘Acute toxicity – Category 3; H331 (Toxic if inhaled). Limited information on acute inhalation toxicity is available for the chemical to review this classification

A median lethal concentration (LC50) (2h) of 250 ppm has been reported (SWA, 2020) The National Institute of Occupational Safety and Health derived an IDLH (Immediately Dangerous to Life or Health) value of 100 mg/m^3 based on oral acute toxicity data in animals (NIOSH, 2014).

Corrosion/Irritation

Skin irritation

Limited information on skin irritation effects of the chemical is available. The International Agency for Research on Cancer (IARC) reported that in human skin, exposure to the chemical resulted in skin discolouration, erythema, swelling and the formation of papules and vesicles. Prolonged contact with the chemical may also lead to necrosis (no further details on chemical concentration or exposure time were reported). In an in vitro skin corrosion assay

conducted in accordance with OECD TG 431 (Reconstructed Human Epidermis (RHE) Test Method), the test chemical was applied to reconstructed human epidermis for 3 and 60 minutes. The mean tissue viability was 37 % and 76.3 % after 3 and 60 minutes, respectively. The test results showed above average viability of affected tissues. According to the evaluation criteria, if the viability after a 3 minute exposure is between <50 % and ≥25 %, the test item should be regarded as a skin irritant, within Sub-category 1B/1C. Local cutaneous changes from exposure to the chemical, such as discolouration, severe irritation, erythema, swelling and the formation of papules and vesicles, were also reported (USEPA, 1999; REACH). These results are consistent with the current classification for skin irritation in the HCIS (Safe Work Australia).

Eye irritation

Limited data are available on the eye irritation effects of p-benzoquinone. In an in vivo eye irritation test, vapours of benzoquinone at 0.5 ppm in air were irritating, and at 3.0 ppm were very irritating to the eyes. Acute exposure to high levels of quinone vapours is highly irritating to the eyes, resulting in discolouration of the conjunctivae and cornea, (USEPA 1999). These results are consistent with the current classification for eye irritation in the HCIS (Safe Work Australia).

Respiratory irritation

The chemical is classified as hazardous in the HCIS as 'Specific target organ toxicity (single exposure) –Category 3; H335 (May cause respiratory irritation). No data are available to review this classification.

Observation in humans

Occupational exposure to the chemical has been reported to produce skin irritation and eye irritation with visual disturbance (SWA, 2020).

Sensitisation

Skin sensitisation

The chemical, p-Benzoquinone is a strong skin sensitiser. In a guinea pig maximisation test (GPMT, OECD TG 406) in albino Dunkin Hartley guinea pigs, following intradermal induction with 0.005% of the substance (6-8 days) and topical induction with 2.5% (occlusive) in acetone-polyethylene glycol 400 (70:30 v/v) (vehicle), strong skin reactions were elicited when challenged with 2.5 % p-benzoquinone (REACH). The Local Lymph Node Assay (LLNA) was also reported the chemical to be positive when tested, indicating extreme sensitisation. However, experimental results did not appear to be presented (REACH). Published studies by Mbiya et al. (2016) and Robert et al. (2009) also confirm the high sensitisation potential of p-benzoquinone. Based on these observations, the chemical warrants classification for skin sensitisation.

Repeat dose toxicity

Oral

Limited data are available for the chemical. Safe Work Australia reported that an oral exposure of 2 mg/kg bw/day of the chemical in mice 6 days/week, for 6 weeks has significantly reduced blood levels of erythrocytes and haemoglobin. Lymphocytes, bone

marrow cells, and thymus were also reduced. Granulocytes, relative organ weights of the spleen, abdominal, thoracic, lymph nodes were significantly increased. A loss of the cytoplasmic details of the hepatocytes in the liver, decrease in the size of the lymph follicles in the spleen and the lobules in the thyroid gland were also reported (SWA 2020).

Dermal

No data are available for the chemical.

Inhalation

Limited data are available for the chemical. Safe Work Australia reported that rats exposed for 4 hours a day for 4 months at 0.6−0.8 ppm showed symptoms including weight loss, fatigue, transient anaemia and thrombopenia (SWA 2020).

Genotoxicity

Based on the available data and the metabolic interconversion of p-benzoquinone with hydroquinone, which is a known mutagen (NICNAS 2014), the chemical warrants classification for genotoxicity.

In vitro

In vitro genotoxicity non-conclusive or non-guideline studies reported positive results in the following (REACH):

- In the bacterial reverse mutation assay with *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA104 and TA 2637 (tested dose not specified), p-benzoquinone (BQ) was positive only in TA104. Negative results were reported for all other strains. Inclusion of oxygen species scavengers in the TA104 growth medium indicated that the mutagenicity was attributable to oxidative injury after BQ reduction and to DNA adducts that form with BQs that have electrophilic substituents (REACH).

- In an in vitro DNA damage and/or repair study (non-guideline), the chemical and 1,2,4-benzenetriol as the metabolites of benzene induced DNA strand breakage in mouse lymphoma L5178YS cells. Between 65 and 73 % single-stranded DNA was observed following a 30-minute treatment with 4.0-6.0 µM benzoquinone. The chemical was notable as the most potent metabolite in inducing the single-stranded DNA in the test.

- In a number of mammalian cell micronucleus tests (OECD TG 487), the chemical induced micronuclei in mammalian cell lines, (V79, IEC-17, 18 and, HuFoe-15 embryonal human liver cells) and human lymphoblastoid cells (TK6), without metabolic activation. The test substance concentrations were 5.4, 0.01, and 0.275 µg/mL, respectively (justified as the lowest effective dose or highest ineffective dose). Colchicine and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were used as positive controls in some of these tests.

- In an in vitro DNA damage/repair study (non-guideline), the chemical and benzene and five of its known metabolites were examined for DNA damage in human lymphocytes using the alkaline comet assay with and without metabolic activation (S9 mix). The chemical and Benzene and all its metabolites investigated

were reported to have positive responses (at 100 µM of test concentration) with metabolic activation and were significantly different from the corresponding controls (positive control H_2O_2).

- In an in vitro gene mutation study in mammalian cells (non-guideline) the chemical induced gene mutation in Chinese hamster lung V79 cells without metabolic activation at 0.54 µg/mL (justified as the lowest effective dose or highest ineffective dose). The mutagenic effects occurred at low, and virtually non-cytotoxic, concentrations.

- In an in vitro sister chromatid exchange (SCE) assay in mammalian cells (in vitro DNA damage and/or repair study using human lymphoblastoid cells (TK6) (equivalent or similar to OECD TG 479), the chemical induced an increased sister chromatid exchange frequency in the absence of metabolic activation at 0,55 µg/mL, lowest effective dose. The results indicated that the chemical along with others such as benzene, phenol, 1,2,4-benzenetriol, and hydroquinone induce SCEs in human T-lymphocytes from MNL cultures exposed in vitro without any additional activating system. The chemical was more potent than catechol at inducing SCE at 5 and 50 µM.

In vivo

In the only available in vivo test, p-benzoquinone did not give clear evidence of mutagenicity.

In the mammalian somatic cell (cytogenicity / bone marrow chromosome aberration) study, equivalent to EU Method B.12 (Mutagenicity - In Vivo Mammalian Erythrocyte Micronucleus Test), p-benzoquinone produced evident toxic effects in CD-1 mice dosed 20 mg/kg bw/day orally, but did not induce any evident genotoxic effects. However, it produced significant increase of micronuclei when administered by oral route and at 42 h after treatment. Bone marrow depression appeared at 24 h and then it decreased slowly. The same amount (20 mg/kg bw) was extremely toxic after intraperitoneal injection; therefore, animals were treated with 5 mg/kg bw. Under these conditions no significant micronucleus increases were induced, but high levels of toxicity were present at all the times checked (18-48 h).

The IARC also reported that the chemical induced micronuclei in the bone-marrow cells of mice treated in vivo without exogenous metabolic system after oral administration or intraperitoneal injection (IARC 1999).

Carcinogenicity

The chemical has been tested for carcinogenicity in mice by skin application and inhalation and in rats by subcutaneous injection. The IARC has reported that the data are insufficient to evaluate the carcinogenicity of this compound. The chemical induced depressed bone marrow production in mice and can inhibit protease enzymes involved in cellular apoptosis (IARC 1977; IARC 1999).

Reproductive and development toxicity

No data are available for the chemical.

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