Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Benzene, 1-chloro-4-(trifluoromethyl)-

Evaluation statement

26 June 2023

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AICIS evaluation statement

Subject of the evaluation

Benzene, 1-chloro-4-(trifluoromethyl)-

Chemical in this evaluation

Name	CAS registry number
Benzene, 1-chloro-4-(trifluoromethyl)-	98-56-6

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

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

Summary of evaluation

Summary of introduction, use and end use

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

The chemical is solvent used in several applications. Internationally, the chemical has reported domestic use in solvent based fabric stain removal products (for removing cosmetic stains) shoe care products and in aerosol rust inhibitors. The chemical also has commercial uses in, coating products, inks and toners, floor wax finishes and sealers, auto care products, concrete sealers and stain strippers.

Human health

Summary of health hazards

The critical health effects for risk characterisation include:

- carcinogenicity
- local effects of skin sensitisation.

The chemical may cause narcotic effects following acute exposures to high concentrations. No adverse effects were reported from neurobehavioural evaluations, motor activity tests or functional behavioural assessments in a 13 week inhalation study.

The chemical is readily absorbed via the gastrointestinal tract and is distributed predominantly to the lungs and adipose tissue. Most of the absorbed dose is excreted via exhalation.

The chemical has low acute oral, dermal, and inhalation toxicities with median lethal doses (LD50) >5000 mg/kg body weight (bw), and median lethal concentrations (LC50) greater than 32 mg/L. Sub-lethal effects included ataxia, loss of righting reflex and loss of balance and coordination. Following inhalation exposure in humans, sublethal signs and symptoms include laboured breathing, drowsiness, dizziness, shortness of breath, coughing, oedema and chest pain.

Based on the available data, the chemical does not cause skin or eye irritation.

The chemical is a weak skin sensitiser based on results seen in local lymph node assays (LLNAs) in mice (EC3 values >30%).

The chemical is not expected to produce severe adverse systemic effects following repeated oral or inhalation exposure. The observed liver and kidney effects occurred mainly at high doses and were not severe enough to warrant hazard classification.

Based on the available in vitro and limited in vivo data, the chemical is unlikely to be genotoxic although positive results were observed in a limited number of studies.

There is sufficient evidence that the chemical has carcinogenic effects in animals based on the observation of benign and malignant neoplastic lesions in multiple organs in both sexes of mice and rats. In rats, neoplastic lesions were found in the adrenal gland, thyroid gland, and uterus. In mice, neoplastic lesions were found in the liver and harderian gland. B6C3F1/N mice have a high background incidence of liver tumours; however, both the hepatocellular carcinoma and hepatocellular blastoma where significantly increased above the historical control range for B6C3F1/N mice. The mode of action for carcinogenicity of the chemical is uncertain and the availability of mechanistic data is limited. The available data supports a likely threshold mode of action. As there is no established mechanism to determine the carcinogenicity of the chemical, the relevance to humans cannot be ruled out.

Based on the available data, the chemical may cause adverse effects on the reproductive system following inhalation exposure to very high doses of the chemical. Effects on sperm motility, sperm count, and epididymis weight were reported in a 90 day repeat dose toxicity inhalation study at the highest exposures (7.4 mg/L and 14.8 mg/L). No effect on fertility was reported in the 1 generation oral reproductive toxicity study at doses up to 45 mg/kg bw/day. However, the male rats were not exposed to the chemical for a full spermatogenic cycle. Therefore, potential effects on fertility due to sperm effects cannot be fully evaluated in this study.

Hazard classifications relevant for worker health and safety

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

Health hazards	Hazard category	Hazard statement
STOT SE	STOT Single Exp. 3	H336: May cause drowsiness or dizziness

Health hazards	Hazard category	Hazard statement
Skin sensitisation	Skin Sens. 1B	H317: May cause an allergic skin reaction
Carcinogenicity	Carc. 1B	H350: May cause cancer

Summary of health risk

Public

Based on the available use information, the chemical may be present in some domestic products such as solvent based fabric stain removal products (for removing cosmetic stains), shoe care products and in aerosol rust inhibitors. Therefore, the public may be exposed to the chemical:

- at concentrations up to 100%
- via incidental skin and eye contact with the chemical during use of domestic products
- by inhaling aerosols/vapours.

However, the frequency and duration of use of such products is considered to be sufficiently low that exposure to the chemical would be intermittent.

The chemical is carcinogenic with evidence indicating a threshold mode of action. There is uncertainty regarding the extrapolation from continuous exposure studies in animals to repeated, intermittent human exposures. Although we cannot rule out that consumers at the high-end frequency of use could possibly be at risk for chronic health effects, it is expected to be unlikely.

The chemical is a weak sensitiser. Given incidental and intermittent exposure patterns the chemical is unlikely to pose a significant risk of skin sensitisation under the current use patterns.

Therefore, there are no identified risks to the public that require management.

Should additional information become available on potentially frequent public exposure to the chemical, further evaluation of the chemical may be required.

Workers

During product formulation and packaging, 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.

Given the critical systemic long term, systemic acute and local health effects, the chemical could pose a risk to workers. Control measures to minimise dermal and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risks**). Control measures implemented due to the proposed classifications are expected to be sufficient to protect workers from any potential reproductive health effects.

Proposed means for managing risk

Inventory listing

To manage the risks to public health from the introduction and use of the chemical, the Inventory listing should be varied under *Section 86* of the *Industrial Chemicals (IC) Act 2019*.

Term of listing	Details
Specific requirements to provide information to the Executive Director under *Section 101* of the *IC Act*	Obligations to provide information apply. You must tell the Executive Director the volume of introduction, use and end use of the chemical within 20 working days if: • the chemical is being introduced for consumer uses other than in shoe polishes, rust inhibitors and solvent based fabric stain remover products for cosmetic stains.

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 relating to safe introduction and use

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

Control measures that could be implemented to manage the risk arising from dermal 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
- minimising manual processes and work tasks through automating processes
- 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 this hazardous chemical depend on the physical form and how 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.

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.

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.

Conclusions

The conclusions of this evaluation are based on the information described in this statement.

Considering the identified uses and proposed means of managing risks, the Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that:

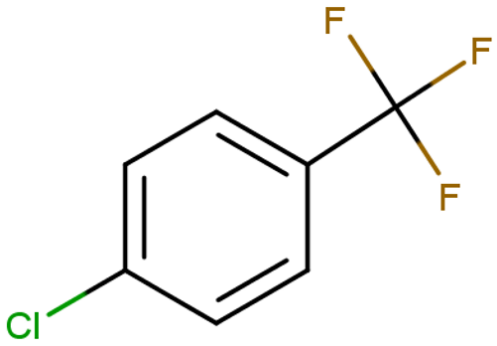
- all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory
- the proposed means of managing the risks identified during this evaluation are implemented.

However, the risk conclusions for the public were driven by the fact that the currently identified consumer products resulted only in intermittent exposure. Given that the chemical is a widely used solvent with many applications and a suspected carcinogen, it is important that the introduction and use of the chemical in Australia are known so that the risks can be appropriately managed. Therefore, a variation to the term of the listing for these chemicals, to add a specific requirement to provide information, is necessary to manage the risks from introduction of the chemicals (see **Proposed means of managing risk**).

Note: Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.

Supporting information

Chemical identity

Chemical name	Benzene, 1-chloro-4-(trifluoromethyl)-
CAS No.	98-56-6
Synonyms	Parachlorobenzotrifluoride (PCBTF) (*p*-chlorophenyl)trifluoromethane *p*-chlorobenzotrifluoride
Molecular formula	C7H4ClF3
Molecular weight (g/mol)	180.56
SMILES	FC(F)(F)C1=CC=C(Cl)C=C1
Chemical description	Volatile clear colourless liquid with an aromatic odour
Structural formula	

Relevant physical and chemical properties

The chemical consists of a benzene ring substituted with the electron-withdrawing groups, chlorine and trifluoromethyl. Both these substituents deactivate the aryl ring with respect to electrophilic attack (and oxidation). In addition, the carbon-fluorine bond of the trifluoromethyl group is less prone to chemical or enzymatic attack than the carbon-hydrogen bond of a methyl group (OEHHA 2020).

Physical form	liquid
Melting point	-33ºC
Boiling point	139.3ºC
Vapour pressure	7.63 mmHg [1017 Pa] at 25ºC
Water solubility	84.5 mg/L at 25ºC
log K_{ow}	3.60 at 25ºC (estimated)

Introduction and use

Australia

There is currently no specific information about the introduction, use and end use of the chemical in Australia. Australian SDS indicate the chemical is being introduced in several products aligning with uses identified internationally.

International

The following international uses have been identified (DeLima Associates n.d.; IARC 2020; NTP 2018; OEHHA 2020; REACH n.d.; US EPA 2016 and 2012; Wolf and Morris 2006):

Based on international use information, the chemical has reported domestic uses in:

- solvent based fabric stain removal products for removing cosmetic stains (at >99%),
- aerosol rust inhibitors (up to 3%)
- shoe care products (at 5–30%), which includes a reported use in an aerosolised product at 30% (DeLima Associates n.d.).

The chemical has reported commercial uses in:

- coating products
- inks and toners
- floor wax finishes and sealers
- auto care products
- concrete sealers
- stain strippers.

The chemical is extensively used in the automotive sector. The chemical has reported commercial use in products at concentrations at 10–90% (DeLima Associates n.d.; IARC 2020; US EPA 2016 and 2012).

The chemical has reported site limited uses:

- as a chemical intermediate.

The chemical has reported non-industrial uses in pesticides and pharmaceuticals (OEHHA 2020).

The United States Environmental Protection Agency's (US EPA) Chemical Data Report database, developed under the *Toxic Substances Control Act* (TSCA), indicates that total production and import of the chemical in the US was in the range of 5000 to 25000 tons per year from 2012 through 2015 (OEHHA 2020; US EPA 2016 and 2012).

Volatile organic compounds (VOCs) are organic compounds that have high vapour pressure at atmospheric conditions. VOCs participate in atmospheric photochemical reactions, for example, reacting with nitrogen oxides to form ozone. Certain VOCs which have been determined by approved test methods to have low phytochemical reactivity may be excluded from the US EPA's definition of VOC for regulatory purposes. These are commonly referred to as VOC exemptions (US EPA n.d.). The chemical, benzene, 1-chloro-4-(trifluoromethyl)-, is excluded from the definition of VOC based on the chemical's negligible contribution to tropospheric ozone formation (US EPA 1994).

Existing Australian regulatory controls

AICIS

No specific controls are available for this chemical. However, the chemical is listed on the AICIS website 'list of chemicals with high hazards for categorisation'.

Public

No specific controls are available for this chemical.

Workers

The chemical is not listed on the Hazardous Chemical Information System (HCIS) and has no specific workplace exposure standards in Australia (SWA n.d.).

International regulatory status

Exposure standards

No specific exposure standards for the chemical have been identified.

Human exposure

Workers

Occupational hygiene data from the US indicates that workers may be exposed to the chemical during manual cleaning work when it is used as a solvent, or during spray gun application. The PCBTF exposure measurements (personal and area combined) were 0.1–12.2 ppm (geometric mean 2.0 ppm, ± 2.9 ppm) for the vehicle manufacturing plants and 0.1–7.7 ppm (geometric mean 0.8 ppm, ± 3.1 ppm) for the paint manufacturing plants (Lee et al. 2015).

The chemical is considered an exempt VOC with non-ozone depleting status, which may result in higher end-user applications than other solvents (NTP 2018).

Health hazard information

Toxicokinetics

In rat studies, oral administration of the chemical in corn oil and alpha cyclodextrin resulted in rapid absorption via the gastrointestinal tract, with reported average absorption of half-lives at 17 and 98 minutes, respectively. The concentration of the chemical in the blood was reported to be proportional to the oral dose administered, with peak blood concentrations occurring within one hour of administration of the chemical in corn oil (Yuan et al. 1991; Quistad and Mulholland 1983; REACH n.d.).

In a study in Sprague Dawley (SD rats), six hours following inhalation exposure, the highest concentration of the chemical was reported in adipose tissue, followed by the lungs, then in the liver, brain, kidneys, and blood. Except for fat, the chemical was largely eliminated from blood and tissues 24 hours post administration. The lowest concentration of the chemical was reported in muscle tissue (Newton et al. 1998)

In a study in SD rats following oral exposure most of the administered dose (62–82%) was rapidly transported to the lung and exhaled un-metabolised, and 16–18% was excreted via the urine and faeces. In the urine the chemical was present as glucuronides of dihydroxybenzotrifluoride and 4-chloro-3-hydroxybenzotrifluoride, and to a mercapturic acid conjugate of the chemical in lesser amounts (IARC 2020; Quistad and Mulholland 1983; REACH n.d.).

Following intravenous administration of the chemical in corn oil to rats, its biological half-life in the blood was 19 hours, with an elimination rate of 0.034 L/hour (Yuan et al. 1991; REACH n.d.).

Acute toxicity

Oral

Based on the available data the chemical has low acute oral toxicity.

In an acute oral toxicity study (limited details available), SD rats (n=8/sex) were administered the chemical by oral gavage at a dose of 5 mL/kg bw (equivalent to ~6800 mg/kg bw). Sublethal signs of toxicity were observed, including ataxia, hypoactivity, tremors, loss of righting reflex, loss of limb tone, hypothermia, lacrimation, piloerection, and ‘hostility’. A median lethal dose (LD50) of 6800 mg/kg bw was determined. The observation period after exposure was not reported (NTP 2009).

In an acute oral toxicity study, male Wistar rats (n=10/dose) were administered the chemical in sesame oil via oral gavage at doses of 4000, 6300 or 10000 mg/kg bw. At doses above 4000 mg/kg bw, less than 50% of the animals survived. Reported sublethal observations included convulsions and loss of balance. An LD50 of 5546 mg/kg bw was determined (REACH n.d.).

Dermal

Based on the available data, the chemical has low acute dermal toxicity.

In a non-GLP compliant acute dermal toxicity study, New Zealand White (NZW) rabbits (n=5/sex) were administered 2 mL/kg bw (~2700 mg/kg bw) of the chemical for 24 hours under occlusive conditions. Test animals were observed for 14 days. Most of the animals survived the study (9/10). Therefore, the LD50 was determined to be >2700 mg/kg bw. Local effects included erythema and oedema. No systemic sublethal signs of toxicity were observed (NTP 2009; REACH n.d.).

In a non-GLP compliant acute dermal toxicity study in Himalayan Rabbits (n=6, sex not specified), 5000 mgs of the chemical was applied to shaved skin of the neck for 5 hours, and test animals were observed for 7 days post administration. No adverse effects or mortality were reported. An LD50 value of >3300 mg/kg bw was reported (REACH n.d.).

Inhalation

Based on the available data the chemical has low acute inhalation toxicity.

In an acute inhalation toxicity study conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guidelines (TG) 403, Wistar rats (n=5/sex) were administered the chemical as an aerosol (nose only) for 4 hours at 32.03 mg/L. The test animals were observed for 14 days post administration. All animals survived the study. Sublethal signs of toxicity included ataxia, irregular and increased respiration, stupor, stilted and un-coordinated gait, tremors, prone position, increased salivation, and “palpebral fissure narrow”. A median lethal concentration (LC50) of >32.03 mg/L was reported (REACH n.d.).

In an acute inhalation toxicity study, SD rats (n=5/sex/dose) were exposed to the chemical (the form of the chemical was not reported) via inhalation at concentrations of 6.03, 20.8, 28.4, 39.1, or 66.7 mg/L for 4 hours and observed for 14 days. Four, 6, and 8 mortalities were reported at doses of 28.4, 39.1, and 66.7 mg/L, respectively. Necropsy of the test animals revealed discolouration of the kidneys and lungs with red foci observed in the lungs. Clinical signs of toxicity included laboured breathing, muscle spasms, lacrimation, excessive salivation, nasal discharge, hair loss, limb ataxia, hypersensitivity to noise, and increased activity. The LC50 was determined to be between 28.4 mg/L and 39.1 mg/L (NTP 2009).

Observation in humans

Based on narcotic effects in humans and sublethal effects in animals (see **Acute toxicity oral** and **Acute toxicity inhalation**), the chemical may cause transient narcotic effects warranting hazard classification.

The chemical may cause laboured breathing, drowsiness, dizziness, shortness of breath, coughing, oedema, and chest pain after inhalation exposure in humans (NTP 2018).

Corrosion/Irritation

Skin irritation

Based on the available data, the chemicals in this group may be slightly irritating to skin. Hazard classification is not warranted.

In a non-GLP compliant skin irritation study, Himalayan rabbits (n=6, sex not specified) were treated with the chemical for 24 hours under occlusive conditions. Observations were recorded at 24, 48 and 72 hours after patch removal. The following mean scores for individual animals can be calculated (from reported scores at each timepoint): 0.3, 1.0, 0.3, 0, 0.3, and 0 for erythema 1.0, 2.3, 2.3, 2.0, 1.3 and 0.7 for oedema. Treatment with the chemical at 10% in sesame oil using the same protocol induced almost no irritation (REACH n.d.).

Eye irritation

Based on the available data, the chemical is not expected to cause eye irritation following ocular exposure.

In a non-GLP compliant eye irritation study conducted according to the United States Food and Drug Administration (US FDA) guidelines, the chemical was instilled into 1 eye each of Himalayan rabbits (n=6, sex not specified). The eyes were washed out after 24 hours, and animals were observed for 72 hours post-dosing. The scores reported at 24, 48 and 72 hours were 0/2 for corneal opacity, iritis, conjunctival redness and chemosis. The chemical was considered to not be irritating to the eyes under the conditions of the test (REACH n.d.).

Observation in humans

The chemical may cause local irritation upon exposure to skin, eye, respiratory tract, and mucous membranes in humans (NTP 2018).

Sensitisation

Skin sensitisation

Based on the available data the chemical is considered to be a weak skin sensitiser.

In a local lymph node assay (LLNA) conducted according to OECD TG 429, female CBA mice (n=4/dose) received topical applications of 25%, 50%, 75% or 100% of the chemical in dimethylformamide (DMF). The reported stimulation indices (SI) at these concentrations were 1.1, 8.1, 6.9 and 7.3, respectively. The reported concentration producing a 3 fold increase in lymphocyte proliferation (EC3) was 31.8%, indicating that the chemical has a weak sensitisation potential (REACH n.d.).

In an LLNA conducted similarly to OECD TG 429, female BALB/c mice (n=5/dose) were administered topical applications of 0, 50, 75 or 100% of the chemical in acetone. The reported SI values were 2.6, 5.3, and 5.3 for concentrations of 50, 75 and 100% of the chemical, respectively. The reported EC3 value was 53.1%, indicating weak sensitisation potential (Franko et al. 2011).

Repeat dose toxicity

Oral

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated oral exposure. The observed liver and kidney effects occurred mainly at high doses and were not severe enough to warrant hazard classification. Nephrosis in male rats can be attributed to hyaline droplet accumulation, which is not a relevant mechanism for human kidney damage (Swenberg 1993).

In a 3 month oral repeat dose toxicity study conducted similarly to OECD TG 408, Fischer 344 rats (n=15/sex/dose) were treated with the chemical in corn oil by oral gavage at doses of 0,10, 40,150 or 500 mg/kg bw/day for 3 months. Mortality occurred at the lowest dose (1 male) and at the highest dose (2 males). Decreased food consumption was observed in all dose groups except males receiving 500 mg/kg bw/day. Total bilirubin was elevated in rats of the 500 mg/kg bw/day dose groups. Alkaline phosphatase levels were slightly elevated in all treated males. Dose dependent minimal to moderate renal tubule degeneration was observed in all male dose groups. Centrilobular hypertrophy in the liver was reported in both sexes at the highest two doses. Total erythrocytes were reduced in high dose males while a dose related increase in neutrophils and a decrease in lymphocytes were reported. A no observed adverse effect level (NOAEL) of 40 mg/kg was reported based on liver and kidney effects at the two highest doses (REACH n.d.).

In a 28 day subchronic oral toxicity study conducted similarly to OECD TG 407, SD rats (n=6/sex/dose) were administered the chemical by gavage at 0, 10, 100 or 1000 mg/kg bw/day for 28 days. All animals survived the study. The only clinical sign of toxicity was salivation in the high dose group. High dose males had a statistically significant decrease in body weight gain. Food intake was not decreased. Male rats had significant dose dependent increases in blood cholesterol and triglycerides. In females, there was a small dose dependent increase in serum lactate dehydrogenase. Hyaline droplet nephrosis was observed in males receiving 1000 mg/kg bw/day. This was accompanied by a significant increase in relative kidney weight and an increase in lipid vacuoles of the adrenal cortex. Slight nephrosis was also observed in males given 100 mg/kg bw/day. Both male and female rats had a significant increase in relative liver weight at a dose of 1000 mg/kg bw/day. An NOAEL of 10 mg/kg was reported based on kidney effects at the two highest doses (IARC 2019; Macri et al. 1987).

In a 14 day oral repeat dose toxicity study, F344/N rats (n=5/sex/dose) were administered the chemical by oral gavage at doses of 0, 10, 50, 400 or 1000 mg/kg bw in alpha-cyclodextrin or corn oil. Clinical signs of toxicity included “burrowing in bedding and rubbing face with forepaws”. Mortality (1 female) was reported in the 1000 mg/kg bw group. Males in the 1000 mg/kg bw/day (corn oil) group had reduced final body weights. Increased kidney weights were observed in females treated with 1000 mg/kg bw/day of the chemical and in males treated at ≥400 mg/kg bw. Increases in liver weight was reported at doses ≥50 mg/kg bw/day. Minimal to mild hypertrophy of hepatocytes was reported in both sexes. Dose dependent nephropathy was observed in male rats starting from doses of 50 mg/kg bw/day. Changes to various haematological parameters were reported in both male and female rats at 1000 mg/kg bw/day. An NOAEL of 10 mg/kg was reported based on liver kidney effects at 50 mg/kg bw/day (NTP 1992).

In a 14 day oral repeat dose toxicity study, B6C3F1 mice (n=5/sex/dose) were administered the chemical by oral gavage at doses of 0, 10, 50, 400 or 1000 mg/kg bw/day in alpha-cyclodextrin or corn oil. Clinical signs of toxicity included “burrowing in bedding,

rubbing face with forepaws". Hepatocellular hypertrophy was reported in mice at the 2 highest doses. Therefore, the NOAEL can be determined to be 50 mg/kg (NTP 1992).

Dermal

No data are available.

Inhalation

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated inhalation exposure. The observed liver, kidney, and Harderian gland effects occurred mainly at high exposures and were not severe enough to warrant hazard classification.

In a 3 month inhalation repeat dose toxicity study, SD rats (n=10/sex/dose) were exposed to the chemical by whole body inhalation at vapour concentrations of 0, 125, 250, 500, 1000, or 2000 ppm (equivalent to ~0.9, 1.8, 3.7, 7.4 or 14.8 mg/L) for 6 hours/day, 5 days/week for 14 weeks (NTP 2018).

There was no exposure related effect on survival. Clinical signs of toxicity, predominantly observed at the highest concentration, included tremors, eye and nasal discharge, and lethargy. Final mean body weights and body weight gains of females exposed to ≥500 ppm were increased compared with controls. Effects on organs were generally minimal to mild and occurred mainly at high doses.

Effects related to the liver included increases in:

- weights at ≥250 ppm in males, and ≥500 ppm in females
- centrilobular hepatocyte hypertrophy at 1000 and 2000 ppm in females and in males at ≥250 ppm
- necrosis of the liver in 2 and one males at 1000 and 2000 ppm respectively
- alkaline phosphatase activity at ≥250 ppm
- alanine aminotransferase and sorbitol dehydrogenase activity at 2000 ppm
- cholesterol and triglyceride levels in females at ≥250 ppm and in males at ≥500 ppm
- bile salt concentrations in females at ≥500 ppm.

Effects on the kidney included:

- increased kidney weights at ≥250 ppm
- chronic concentration dependent nephropathy in all males (including controls)
- dose dependent chronic nephropathy, hyaline droplet accumulation and increased kidney weight in males
- chronic nephropathy in females was less frequent and of less severity (minimal to mild) compared to males
- cytoplasmic vacuolisation in the adrenal cortex was increased at ≥1000 ppm in females and at 2000 ppm in males.

Effects on blood parameters included:

- decreased leukocyte count in 2000 ppm females
- decreased lymphocyte count at 2000 ppm
- increased neutrophil counts in males at ≥500 ppm
- increased globulin concentrations in males at ≥1000 ppm.

Other reported adverse effects included:

- degeneration of the Harderian gland at exposures ≥250 ppm
- increases in mammary gland hyperplasia in females (≥1000).

A NOAEL of 125 ppm (0.9 mg/L) can be determined based on kidney and harderian gland effects at 250 ppm (1.8 mg/L).

In a 3 month inhalation repeat dose toxicity study, B6C3F1/N mice (n=10/sex/dose) were exposed to the chemical by whole body inhalation at vapour concentrations of 0, 125, 250, 500, 1000, or 2000 ppm for 6 hours/day, 5 days/week for 14 weeks (NTP 2018). Higher final mean body weights and body weight gains were observed in males and females exposed to 500 and 250 ppm or greater (respectively).

The liver effects were more severe in mice compared to rats particularly at the highest concentration (2000 ppm, 14.8 mg/L). In male mice the most significant effects were in the liver and included:

- increased liver weights at ≥250 ppm
- increased incidences of centrilobular hepatocyte hypertrophy in males at ≥250 ppm and females at ≥500 ppm with dose dependent increases in severity
- increases in the incidences of centrilobular hepatocyte necrosis and multinucleated hepatocytes in males at ≥500 ppm and females dosed at ≥1000 ppm.

Effects on the kidneys included:

- increased kidney weights in males at ≥500 ppm and females at ≥1000 ppm
- increased incidences of zona fasciculata hypertrophy at 2000 ppm in the adrenal cortex.

Effects on other organs included increases in:

- thymus weights at 2000 ppm
- epithelial hyperplasia of the forestomach at ≥500 ppm
- incidences of granulomatous inflammation in the forestomach at 2000 ppm
- incidences of megakaryocyte and erythrocytic hematopoietic cell proliferation in the spleen in females at ≥250 ppm and in males at ≥1000 ppm.

Effects related to blood included decreases in:

- erythrocyte counts, haematocrit values and packed cell volumes in females at ≥1000 ppm and males at 2000 ppm
- haemoglobin concentration at 2000 ppm
- reticulocyte counts at ≥1000 ppm.

A NOAEL of 250 ppm (1.8 mg/L) can be determined based on liver effects at 500 ppm (3.7 mg/L).

In a 2 year carcinogenicity study in rats (see **Carcinogenicity**) significant non-neoplastic histological effects included increased incidence of:

- fibrosis in the lungs in all exposed males and in females at ≥250 ppm

- haemorrhage the lungs in all exposed males and in females at 1000 ppm
- adrenal medulla hyperplasia in 250 and 1000 ppm females
- granular kidneys in all exposed male groups
- centrilobular hepatocyte hypertrophy in all exposed males and in 250 and 1000 ppm females
- atypical hyperplasia of the endometrium (considered pre-neoplastic) at 1000 ppm.

In a 2 year carcinogenicity study in mice (see **Carcinogenicity**) significant non-neoplastic histological effects included increased incidence of:

- alveolar/bronchiolar epithelial hyperplasia and peribronchiolar fibrosis in all treated groups
- larynx squamous epithelium hyperplasia and inflammation in males at 400 ppm
- forestomach epithelial hyperplasia in females at 400 ppm
- hepatocyte hypertrophy in all groups of exposed males, and in females at ≥200 ppm
- hepatocyte necrosis was observed in both sexes at 400 ppm.

Observation in humans

No data are available.

Genotoxicity

Based on the available data, the chemical is unlikely to have genotoxic potential.

In vitro

Negative genotoxicity results were reported by the World Health Organisation (WHO) International Agency for Research on Cancer (IARC 2020) and California Office of Environmental Health Hazard Assessment (OEHHA 2020), unless otherwise cited below:

- in a bacterial reverse mutation test conducted with deviations from OECD TG 471 in *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without metabolic activation (S9 mix) across 5 doses of the chemical up to 10000 µg/plate (Haworth et al. 1983)
- in two bacterial reverse mutation tests conducted with deviations from OECD TG 471 in *S. typhimurium* strains TA1535, TA1537, TA98, and TA100, and *Escherichia coli* strain WP2 *uvr*A/Pkm101, with or without metabolic activation (S9 mix) at doses up to 1000 µg/plate of the chemical in TA1535, TA 1537, and up to 6000 µg/plate in TA98, TA100, and *E. coli* WP2 *uvr*A/Pkm101 (NTP 2018)
- in a bacterial reverse mutation test conducted according to OECD TG 471 in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 with and without metabolic activation (S9 mix) at doses up to 5000 µg/plate of the chemical (REACH n.d.)
- in an Ames reverse mutation assay in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 at doses of the chemical up to 2500 µg/plate with and without metabolic activation
- in an Ames reverse mutation assay in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, and *S. cerevisiae* (D4) at doses up to 10 µL/plate of the chemical with and without metabolic activation
- in an Ames reverse mutation assay in *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 at doses up to 0.4 µL/plate of the chemical with and without metabolic activation

- in a forward mutation assay in *S. typhimurium* strains TA1535, and TA100 at doses up to 150 µg/plate of the chemical.

Both positive and negative results were reported in mammalian cell in vitro assays (IARC 2020; OEHHA 2020).

Positive results were reported in:

- an unscheduled DNA synthesis assay in human embryonic epithelial cells at concentrations up to 10 µL/mL of the chemical without metabolic activation
- a sister chromatic exchange assay in L5178Y mouse lymphoma cells at doses up to 0.04 µL/mL of the chemical with and without metabolic activation.

Negative results were reported in:

- a forward mutation assay in L5178Y mouse lymphoma cells at doses up to 50 nL/mL of the chemical with and without metabolic activation
- a mitotic recombination assay in *S. cerevisiae* (6117) at doses up to 2000 µg/plate of the chemical with and without metabolic activation
- an in vitro mammalian chromosome aberration assay conducted with deviations from OECD TG 473 in Chinese hamster ovary (CHO) cells with and without metabolic activation (S9) (treated for 2 and 12 hours respectively) at doses up to 130 nL/mL of the chemical in dimethylsulfoxide (DMSO) vehicle (REACH n.d.)
- an in vitro mammalian cell transformation assay in BALB/c-3T3 cells at doses up to 300 µg/mL of the chemical in DMSO solvent with and without metabolic activation (REACH n.d.).

In vivo

Negative results were reported for a mammalian erythrocyte micronucleus test in SD rats (n=10/sex/dose) administered the chemical via inhalation at doses of 0, 125, 250, 500, 1000, or 2000 ppm for 6 hours/day, 5 days/week for 14 weeks in a 3 month repeat dose toxicity study (see **Repeat Dose Toxicity: Inhalation**). No statistically significant increases in micronucleated polychromatic erythrocytes or normochromatic erythrocytes were observed in peripheral blood samples taken at the end of the study (NTP 2018).

Positive results were reported for a mammalian erythrocyte micronucleus test in B6C3F1/N mice (n=10/sex/dose) administered the chemical via inhalation at doses of 0, 125, 250, 500, 1000, or 2000 ppm for 6 hours/day, 5 days/week for 14 weeks in a 3 month repeat dose toxicity study (see **Repeat Dose Toxicity: Inhalation**). Statistically significant increases in normochromatic erythrocytes were observed in peripheral blood taken from mice at the highest dose level (compared with controls); however, this was within the historical control ranges for females. A dose related increase in the proportion of micronucleated polychromatic erythrocytes was reported in female mice indicating that the chemical “may have stimulated erythropoiesis in female mice” (NTP 2018).

Negative results were reported in a study, described with limited details, in SD rats (male and female) that were tested for chromosomal aberrations via harvesting of bone marrow cells 6, 24, and 48 hours after a single dose of the chemical by oral gavage at either 0.5, 1.7, or 5 mL/kg bw (IARC 2020; OEHHA 2020).

Carcinogenicity

Based on the available animal data the chemical is considered to be carcinogenic following inhalation exposure. Benign and malignant tumours were observed in multiple organs and both sexes of mice and rats. In rats, neoplastic lesions were found in the adrenal gland, thyroid gland and uterus, and in mice in the liver and harderian gland. B6C3F1/N mice have a high background incidence of liver tumours; however, both the hepatocellular carcinoma and hepatocellular blastoma where significantly increased above the historical control range for B6C3F1/N mice. As there is no established mechanism to determine the carcinogenicity of the chemical, the relevance humans cannot be ruled out.

The IARC's recent assessment concluded that the chemical is possibly carcinogenic to humans (Group 2B) (IARC 2020) based on sufficient evidence of cancer in experimental animals. The evidence of cancer in humans is inadequate as no data were available. The sufficient evidence of carcinogenicity in experimental animals is based on the induction of malignant neoplasms in two species. The mechanistic evidence was inadequate (IARC 2020).

The United States Environmental Protection Agency (US EPA) concluded that there was some evidence of carcinogenic activity of the chemical in male and female SD rats based on increased incidence of:

- C-cell adenoma in the thyroid gland in males
- benign pheochromocytoma in the adrenal medulla of the gland
- adenocarcinoma of the uterus in females
- stromal polyp of the uterus in females.

The combined occurrences of alveolar/bronchiolar adenoma or carcinoma in the lung of male rats may have been related to treatment. They also concluded that there was clear evidence of carcinogenic activity of the chemical in female B6C3F1/N mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma in the liver. The combined incidences of adenoma or adenocarcinoma in the Harderian gland of female mice were also considered to be related to treatment (NTP 2018).

In a GLP compliant 2 year carcinogenicity study conducted according to National Toxicology Program (NTP) TGs, SD rats (n=50/sex/dose) were exposed to the chemical by whole body inhalation at vapour concentrations of 0, 100 (0.738 mg/L), 300 (2.2 mg/L), or 1000 (7.3 mg/L) ppm for 6 hours/day, 5 days/week for 104 to 105 weeks (NTP 2018). Survival was reduced in the 1000 ppm male dose group (NTP 2018).

Overall, there was a statistically significant negative trend reported in the survival of male rats across groups. Observations of neoplastic lesions included statistically significant increased incidences in:

- thyroid C-cell adenoma in both sexes
- thyroid C-cell adenoma or carcinoma combined in females
- benign pheochromocytoma of the adrenal medulla in females
- uterine stromal polyps or stromal carcinoma.

A positive trend was reported in the incidence of uterine adenocarcinoma in females. Unusual bronchioloalveolar carcinoma was observed in 5 males. Incidence of neoplastic lesions at the different doses compared to historical controls are outlined in (Table 1 and 2) (IARC 2020: NTP 2018; NTP 2020a).

Table 1 Incidences of neoplastic lesions in male rats

Tumour type	0 ppm	100 ppm	300 ppm	1000 ppm	Historical control
Thyroid C-cell adenoma	2/50 (10%)	5/49 (10%)	3/49 (6.1%)	12/50 * (24%)	104/637 (16.3%)
Thyroid C-cell carcinoma	1/50 (2%)	0/49	1/49 (2%)	1/50 (2%)	9/637 (1.4%)
Alveolar/bronchiolar adenoma and alveolar/bronchiolar carcinoma	0/50	2/50 (4%)	0/50	3/50 (6%)	7/638 (1.1%)

*P < 0.001 (Poly-3 test),

Table 2 Incidences of neoplastic lesions in female rats

Tumour type	0 ppm	100 ppm	300 ppm	1000 ppm	Historical control
Thyroid C-cell adenoma	2/50 (4%)	8/50 (16%)	8/50 (16%)	14/50* (28%)	105/638 (16.5%)
thyroid C-cell carcinoma	0/50	2/50 (4%)	0/50	1/50 (2%)	9/638 (1.4%)
Thyroid C-cell adenoma or carcinoma (combined)	2/50 (4%)	10/50** (20%)	8/50 (16%)	15/50*** (30%)	113/638 (17.7%)
Adrenal pheochromocytoma (benign)	0/49	3/50 (6%)	4/50 (8%)	6/50[#] (12%)	13/635 (2.1%)
Uterine adenocarcinoma	1/50 (2%)	1/50 (2%)	0/50	5/50	27/500 (5.4%)
Uterine stromal polyp	7/50 (14%)	9/50 (18%)	16/50[a] (32%)	12/50 (24%)	75/500 (15%)

*P=0.003 (Poly-3 test), **P = 0.017 (Poly-3 test), ***P = 0.002 (Poly-3 test), [#] P = 0.035 (Poly-3 test), [a]P = 0.047 (Poly-3 test)

In a GLP compliant 2 year carcinogenicity study conducted according to NTP TGs, B6C3F1/N mice (n=50/sex/dose) were exposed to the chemical by whole body inhalation at vapour concentrations of 0, 100 (0.74 mg/L), 200 (1.48 mg/L), or 400 ppm (2.95 mg/L) 6 hours/day, 5 days/week for 104 to 105 weeks (NTP 2018).

The survival of both sexes in the highest dose group was decreased. An increase in mortality was caused primarily by hepatocellular tumours. Observations of neoplastic lesions included statistically significant increased incidences in hepatocellular adenoma in females, hepatocellular carcinoma and hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma combined in both sexes, harderian gland adenoma in females and harderian gland adenomas and carcinomas combined in females. Incidence of neoplastic lesions at the different doses compared to historical controls are outlined in Tables 3 and 4 below (IARC 2020: NTP 2018; NTP 2020b).

Table 3 Incidences of neoplastic lesions in male mice

Tumour type	0 ppm	100 ppm	200 ppm	400 ppm	Historical control
Hepatocellular adenoma	25/50 (50%)	24/50 (48%)	31/50 (62%)	29/50 (58%)	398/789 (50.4%)
Hepatocellular carcinoma	8/50 (16%)	19/50* (38%)	16/50* (32%)	35/50** (70%)	201/789 (25.5%)
Hepatocellular blastoma	1/50 (2%)	1/50 (2%)	1/50 (2%)	15/50** (30%)	25/789 (3.2%)
Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined)	31/50 (62%)	37/50 (74%)	40/50*(80%)	48/50**(96%)	520/789 (65.9%)

*P < 0.05 (Poly-3 test), **P < 0.001 (Poly-3 test)

Table 4 Incidences of neoplastic lesions in female mice

Tumour type	0 ppm	100 ppm	200 ppm	400 ppm	Historical control
Hepatocellular adenoma	12/50 (24%)	14/50 (28%)	24/50* (48%)	34/50** (68%)	150/839 (17.9%)
Hepatocellular carcinoma	7/50 (14%)	8/50 (16%)	12/50 (24%)	34/50 (69%)**	71/839 (8.5%)
Hepatocellular blastoma	0/50	0/50	1/50 (2%)	8/50[a] (16%)	4/839 (0.5%)
Harderian gland adenoma	2/50 (4%)	6/50 (12%)	6/50 (12%)	8/50[b] (16%)	45/840 (5.4%)
Harderian gland carcinoma	0/50	0/50	3/50 (6%)	0/50	16/840 (1.9%)
Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined)	18/50 (36%)	18/50 (36%)	29/50[c] (58%)	46/50** (92%)	203/839 (24.2%)

*P = 0.004 (Poly-3 test), **P < 0.001 (Poly-3 test, [a]P = 0.003 (Poly-3 test), [b]P = 0.041 (Poly-3 test), [c]P = 0.008 (Poly-3 test),

Mechanistic studies

The mode of action for carcinogenicity of the chemical is uncertain and the availability of mechanistic data is limited. Toxicokinetic studies in rats demonstrate that the chemical is readily absorbed via inhalation and is distributed to multiple organs (liver, kidney, lungs, muscle and adipose tissue). Accumulation occurs predominantly in adipose tissue (IARC 2020; NTP 2018).

Genotoxicity studies were mainly negative; however, positive results were observed in an in vitro unscheduled DNA synthesis study in human cells and a sister-chromatid exchange study in rodent cells (see **Genotoxicity**). Genetic mutations in Ctnnb1 (beta-catenin) and Hras are common in hepatocellular tumours in mice. In a study investigating these mutations in hepatocellular carcinoma in B6C3F1/N mice, there was no effect on Ctnnb1 mutations. A statistically significant difference in the frequency of Hras mutation (fewer mutation in the benzene, 1-chloro-4-(trifluoromethyl)- group) was observed when comparing spontaneous carcinoma and carcinoma induced by the chemical (IARC 2020; NTP 2018).

The dose related increase in the incidence of atypical hyperplasia in the endometrium in rats (see **Repeat dose toxicity**) suggests that the chemical may increase cell proliferation. Benzene, 1-chloro-4-(trifluoromethyl)- has been shown to increase CYP1A1 and CYP1A2 activity by twofold and CYP2B activity by fivefold. CYP2B activation via constitutive androstane receptor is a well known mechanism of tumour promotion activity in the liver of rodents. Liver weights and nonneoplastic lesions observed in the 3 month and 2 year studies are consistent with a potential CAR-mechanism of action and similar responses have been observed in other studies with CAR/CYP2B inducers. However, when the potential for benzene, 1-chloro-4-(trifluoromethyl)- to activate CAR was evaluated in the Tox21 screening program the results were inconclusive. Results for activation of the estrogen receptor were also inconclusive (IARC 2020; NTP 2018).

Reproductive and Development Toxicity

Based on the available data exposure to very high concentration of the chemical may lead to damage of male reproductive organs. While there is insufficient information for hazard classification, adverse effects on male fertility cannot be excluded.

No effect on fertility was reported in the one generation oral reproduction toxicity study. However, the male rats were not exposed to the chemical for a full spermatogenic cycle. Therefore, potential effects on fertility due to sperm effects cannot be determined. Effects on sperm motility, sperm count, and epididymis weight were reported in a 90 day repeat dose toxicity inhalation studies at the highest exposures (7.4 mg/L and 14.8 mg/L). In females, there were effects on the oestrous cycle at the highest dose. However, female fertility was not affected in females in the one generation oral reproduction toxicity study.

In a one generation reproduction toxicity study conducted with deviations from OECD TG 415, SD rats (n=20/sex/dose) were administered the chemical by oral gavage in corn oil once daily at 0, 5, 15, and 45 mg/kg bw/day for a total of 76 to 83 days. Exposure started 4 weeks prior to mating for male and female rats. This exposure does not cover a full spermatogenic cycle; therefore, potential sperm effects cannot be assessed with certainty. During lactation, pups were exposed to the chemical via the milk. At weaning (PND21), F1 animals were maintained under the same dosing regimen as their parents. In F0 rats, statistically significant increases in body weight gain were reported for all male treatment groups at week 14 of the study. High dose F0 females had decreases in body weight gain. Statistically significant changes in haematology and clinical chemistry were reported from doses of 5 mg/kg in F0 rats. Reproductive performance was not affected in F0 rats. No adverse effects were reported in F1 rats (REACH n.d.).

Adverse effects on the sex organs and reproductive parameters of male and female rats were reported in a 3 month inhalation repeat dose toxicity study in SD rats (see **Repeat Dose Toxicity: Inhalation**). Germ cell degeneration in testes and exfoliated germ cell in the epididymis duct including germ cell apoptosis and vacuolation was significantly increased at the highest dose, 2000 ppm (14.8 mg/L). Decreased cauda and epididymis weights and numbers of sperm per cauda epididymis were observed at the highest dose and decreases

in sperm motility at the two highest doses (2000 ppm, 14.8 mg/L and 1000 ppm, 7.4 mg/L). Parameters of the female reproductive cycle was affected in rats exposed to 2000 ppm (14.8 mg/L) of the chemical (NTP 2018).

In a 3 month inhalation repeat dose toxicity study in B6C3F1/N mice (see **Repeat Dose Toxicity: Inhalation** section), a statistically significant concentration related decline in sperm motility was observed across all groups of males treated with the chemical (125–2000 ppm). All treated females had a statistically significant lengthening of the oestrous cycle (NTP 2018).

Neurotoxicity

In a 13 week chronic inhalation toxicity study, SD rats (n=25/sex/dose) were treated with the chemical at concentrations of 0, 10, 51, and 252 ppm (whole body) for 6 hours/day, 5 days/week for 13 weeks. Groups of rats (10 sex/dose) were subjected to neurotoxicity evaluations prior to exposure and after 4, 8, and 13 weeks of exposure and a further 5 animals/sex/dose were evaluated after 13 weeks of recovery from exposure. No adverse effects were reported from neuro behavioural evaluations, motor activity tests or functional behavioural assessments. Sensory evaluations, group mean landing foot splay and grip strength in exposed groups were comparable to controls or pre-exposure values (Newton et al. 1998).

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