



Australian Government

Department of Health, Disability and Ageing

Acetic acid, 2,2-dichloro-

Evaluation Statement (EVA00192)

30 September 2026

Draft

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AICIS evaluation statement (EVA00192)

Subject of the evaluation

Acetic acid, 2,2-dichloro-

Chemical in this evaluation

CAS name	CAS number
Acetic acid, 2,2-dichloro-	79-43-6

Reason for the evaluation

New information is available about human health risks

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).

The chemical was assessed in 2016 under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework, under the former National Industrial Chemicals Introduction and Assessment Scheme (NICNAS). The assessment identified chemicals that were not registered under the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation which indicated that the chemical may not have been in use for industrial purposes in Australia, or only used in very small quantities.

The chemical is now registered with the European Chemicals Agency (ECHA), which enables it to be manufactured or imported into Europe. In addition, new information identified the presence of the chemical in cosmetics. This evaluation statement includes a human health risk assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

Based on information provided to AICIS, the chemical has reported use in Australia in personal care products (cosmetics) at concentrations up to 0.1%. Internationally, the chemical has limited reported presence in personal care products (cosmetics) at concentrations up to 0.1%. Typically, these are rinse-off products that include skin applied products and liquid hand soaps. The chemical is primarily present as an impurity due the presence of certain surfactants but potential functional use as an exfoliant and abrasive has been reported. The surfactants in which the chemical is a known impurity have reported uses in a wide range of rinse-off cosmetic products, a limited number of leave-on products such as hair dyes and disposable wipes and some baby products. The concentrations of the chemical as an impurity in personal care products is expected to be significantly below 0.01%.

Based on international information, the chemical has domestic uses in automotive care products and dishwashing products.

The chemical has commercial uses in the manufacture of fabric, textile and leather products and functions as a bleaching agent in the manufacture of arts, crafts and hobby materials (paper). It also functions as a pH regulating agent in various processes.

The chemical has site-limited functional use as an intermediate in the synthesis and manufacture of chemicals.

The chemical has non-industrial uses in agricultural chemical products and therapeutic goods.

Human health

Summary of health hazards

The identified health hazards are based on available data for the chemical. Based on its physicochemical properties, the chemical is expected to be readily absorbed following oral, dermal and inhalation exposures.

Based on the available data the chemical:

- has low acute toxicity by the oral route
- is not considered to be a skin sensitiser.

The chemical is expected to have moderate acute toxicity by the dermal route. The median lethal dose (LD50) was 797 mg/kg bw in a single non-guideline study in rabbits.

The chemical is likely to be corrosive to skin and cause severe eye damage based on the available animal, *in vitro* and physicochemical data. There is insufficient evidence to evaluate the current Category 1A sub-classification.

The chemical is expected to cause serious effects following repeated oral exposure. The chemical caused neurotoxic effects in adult and weanling rats after subchronic oral exposures of duration between 8–13 weeks. Neurotoxicity was most frequently characterised by abnormal gait at doses as low as 16 mg/kg bw/day. At higher doses, the rats exhibited more severe signs of neurotoxicity including decreases in grip strength, righting reflexes and motor activity. In other 90 day studies in rats and dogs, the chemical caused lesions in the cerebellum, which is the part of the brain that is responsible for motor control with effects in dogs occurring at doses less than 100 mg/kg bw/day.

There is no strong evidence that the chemical has genotoxic potential. Mixed genotoxicity results were observed in both *in vitro* and *in vivo* experiments. The available evidence suggests that the positive genotoxicity results may be a result of oxidative stress, rather than direct genotoxicity.

There is sufficient evidence that the chemical has carcinogenic effects in animals. Significantly increased incidences of liver tumours were observed in both sexes of mice and male rats after chronic exposure to high doses of the chemical in drinking water. Whilst B6C3F₁ mice have a high background incidence of liver tumours, the typical incidences of malignant liver tumours (between 60–100%) in the high dose groups were above historical controls. The available data supports a likely threshold mode of action *via* a combination of non-genotoxic mechanisms. While these proposed mechanisms were based on animal studies, the relevance of these mechanisms to humans cannot be ruled out. There are no human studies that demonstrate the chemical is carcinogenic. The United States Environmental Protection Agency (US EPA) determined a benchmark dose limit (BMDL) of 2.1 mg/kg bw/day for carcinogenicity.

The chemical causes adverse effects on both male fertility and development. Adverse effects on male fertility (effects on the testes and sperm) were noted in rats and dogs at doses of 62.5 and 12.5 mg/kg bw/day, respectively. In developmental studies, there was a significantly

increased incidence of cardiovascular malformations in pups born from dams who were exposed to the chemical during gestation. While these malformations occurred at higher doses with some maternal toxicity, these types of malformations are considered severe.

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 work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 3	H311: Toxic in contact with skin
Skin corrosion/irritation	Skin Corr. 1A	H314: Causes severe skin burns and eye damage
Serious eye damage/irritation	Eye Damage 1	H318: Causes serious eye damage
Carcinogenicity	Carc. 1B	H350: May cause cancer
Reproductive toxicity	Repr. 1B	H360FD: May damage fertility and the unborn child
Specific target organ toxicity (repeated exposure)	STOT Rep. Exp. 2	H372: Causes damage to organs through prolonged or repeated exposure (central nervous system)

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemical:

- at concentrations up to 0.1%
- by direct application of the chemical to the skin from cosmetic products
- indirectly through dermal exposure from infrequent use in automotive cleaning products.

The frequency and duration of use of automotive care products is considered to be sufficiently low that exposure to the chemical would be intermittent. Therefore, the dermal exposure to the chemical from these infrequent uses is unlikely to pose a risk to public health.

The critical health effect for risk characterisation is carcinogenicity. While the chemical may be present in personal care products, the available evidence suggests that the chemical is likely an impurity in products that contain surfactants. Estimates of the worst-case daily systemic exposures (assuming simultaneous use of all products containing the chemical at the highest concentration identified) were conducted for the chemical as used in rinse-off products, as an impurity in cosmetic products and baby products. The margins of exposure (MOE) for all exposures were greater than 100, indicating that the presence of the chemical in cosmetics at low concentrations is unlikely to pose a risk to public health.

The chemical also causes systemic toxicity including reproductive toxicity and neurotoxicity. The MOE calculations for carcinogenicity are protective of these hazards. Although the

chemical is corrosive, adverse effects are not expected at concentrations present in consumer products.

Given that the predominant exposure to the chemical is as an impurity, it is unlikely that the public has significant exposure to this chemical. Therefore, there are no identified risks to the public that require management.

Workers

During product formulation and packaging, dermal, inhalation and ocular 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 these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. 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 systemic long-term and local health effects, the chemical could pose a risk to workers.

Control measures to minimise dermal, inhalation and ocular exposure are needed to manage the risk to workers (refer to **Proposed means for managing risk**).

Proposed means for managing risk

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 (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Recommended control measures that could be implemented to manage the risk arising from oral, 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.

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.

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.

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 Executive Director proposes to be satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

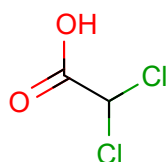
1. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

CAS number	79-43-6
CAS name	Acetic acid, 2,2-dichloro-
Molecular formula	C ₂ H ₂ Cl ₂ O ₂
Associated names	Dichloroacetic acid
Molecular weight (g/mol)	128.94
SMILES (canonical)	O=C(O)C(Cl)Cl

Structural formula



Relevant physical and chemical properties

Physical form	Liquid
Melting point	13.5°C
Boiling point	193–194°C
Vapour pressure	19 Pa at 20°C
Water solubility	Soluble
pK_a	1.48 at 25 °C

Sources: ECHA CHEM n.d.; US EPA 2003

Introduction and use

Australia

Information submitted to AICIS indicates that the chemical has been introduced into Australia in personal care products at concentrations <0.1%. No further information about the function of the chemical or product types was reported.

The chemical has reported non-industrial use as an active ingredient in products regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA n.d.).

International

The chemical has reported domestic uses in automotive care products in the United States of America (USA). These products are typically for cleaning interior and exterior surfaces of cars, with reported concentrations up to 0.006%. The chemical was also reported in a single dishwashing liquid product for professional use with no concentration information available (DeLima Associates n.d.).

The chemical has commercial uses, which include (ECHA 2022; Government of Canada 2021; NICNAS 2016; US CDR 2016):

- fibre and textile manufacturing
- pulp bleaching
- oil recovery
- as pH regulating agent.

The chemical has site-limited functional use as an intermediate in chemical synthesis including the production of polymers and the preparation of iron chelates for fertilisers (ECHA 2022; Government of Canada 2021; NICNAS 2016).

In a 2008 Canadian survey, the volume of manufacture of the chemical in Canada was between 200–2,000 kg. There were no reports of imports of the chemical into Canada at volumes above 100 kg (Government of Canada 2021).

The chemical is not listed in cosmetic or personal care products lists including the European Commission's Cosmetic ingredient database (CosIng), the International Nomenclature of Cosmetic Ingredients (INCI) database, or the International Fragrance Association (IFRA) transparency list (EC n.d.; IFRA n.d.; Personal Care Products Council n.d.). However, based on information available in the USA, the chemical may be present in personal care products at concentrations up to 0.1% (US EPA n.d.). Only a small number of products containing the chemical were reported to the California Safe Cosmetics Program (CSCP). A total of 13 products were reported between 2009 and 2025 with 5 of those products having either been discontinued or had the chemical removed from the products since the initial reports. The types of products in which this chemical included bath products, hair care products, rinse-off skin care product and hand washes (CSCP 2023, CSCP n.d.). Online product searches indicate that the chemical is present in a small number of facial cleanser products (EWG n.d.).

The chemical has a reported function as a contaminant or impurity on the CSCP database (CSCP n.d.). In addition, the Cosmetic Ingredient Review (CIR) expert panel identified that the chemical was present in concentrations of less than 0.1% in 4 surfactants that are widely used in cosmetics: coco-betaine, disodium cocoamphodiacetate, disodium lauroamphodiacetate and sodium cocoamphoacetate (CIR 2014; CIR 2023; CIR 2026). These surfactants are diluted for cosmetic end use, with the maximum reported concentrations of the surfactant being 20% in rinse-off cosmetic products and 5.4% in leave-on cosmetic products. As the chemical is only an impurity in these surfactants at less than 0.1% concentration, the concentrations of the chemical as an impurity are expected to be significantly lower than the concentration of the surfactant. These surfactants were also reported in rinse-off baby products such as baby shampoos at a maximum reported end use concentration of 5.4%. These surfactants were also reported in disposable wipes for both adults and babies. The chemical also had reported function as an abrasive/exfoliant in 2 products (CSCP n.d.).

The chemical has non-industrial uses as a therapeutic and as a component of pesticides. The chemical may be present in drinking water as a by-product of disinfection process (ECHA 2022; Government of Canada 2021; IARC 2014).

Existing Australian regulatory controls

Public

No current regulatory controls are available for the industrial use of the chemical.

The chemical is listed in the Australian Drinking Water Guidelines as a by product of chlorination with a health guideline value of 0.1 mg/L (NHMRC 2025).

Workers

The chemical is listed on the HCIS with the following classification for hazard classes relevant for work health and safety (SWA n.d.):

Health hazards	Hazard category	Hazard statement
Skin corrosion	Skin Corr. 1A	H314: Causes severe skin burns and eye damage

No workplace exposure standard is currently available for the chemical (SWA n.d.). Safe Work Australia has published the [Workplace Exposure Limits for airborne contaminants \(WEL list\)](#). From 1 December 2026 and following implementation into the work health and safety laws of the Commonwealth, states and territories, new Workplace Exposure Limits (WEL) for airborne contaminants (WEL list) will be adopted throughout Australia. The WEL for the chemical is an 8 hour time weighted average (TWA) of 0.5 ppm (reported as 2.5 mg/m³). An advisory notation accompanies the listing and states that: "Absorption through the skin may be a significant source of exposure. Extra control measures should be used to minimise the risk of skin contact. These control measures could include gloves, protective clothing, safety eyewear and closed systems to transfer liquids or gases." (SWA 2025).

International regulatory status

Exposure standards

The following exposure standards were identified (Chemwatch n.d.; IARC 2014):

- TWA: 2.5–2.7 mg/m³ (0.5 ppm) – Belgium, Canada, Colombia, Nicaragua, Portugal, South Korea, United Arab Emirates, Uruguay
- STEL (Short-term Exposure Limit): 4 mg/m³ – Belarus
- MAK values (Maximum Concentrations at the Workplace): 2.2 mg/m² (0.4 ppm) – Switzerland
- MAK values: 1.1 mg/m² (0.2 ppm) – Germany
- Protective action criteria (PAC) 1, 2 and 3 of 1.5, 8.9 and 140 ppm respectively, in the United States of America.

The American College of Governmental Industrial Hygienists (ACGIH) have recommended a TWA of 0.5 ppm (reported as 2.6 mg/m³) for the chemical (ACGIH 2005).

Human exposure

Public

The public exposure to the chemical was estimated for scenarios relating to its use in personal care (cosmetic) products. In this exposure assessment, the reasonable worst

case scenario is used, in which estimates are based on worst case, but use a plausible exposure scenario. For the exposure assessment, use amounts were based on values established by the EU Scientific Committee on Consumer Safety (SCCS) or the Danish National Institute for Public Health and the Environment (RIVM) (RIVM 2025; SCCS 2023; SCCS 2024). A default dermal absorption value of 100% was assumed for these estimates as no experimental data on dermal absorption was available. Oral and inhalation exposures were not considered in the following estimates based on the types of products identified. A default adult body weight of 60 kg was assumed for all scenarios.

Each of the below estimates of exposure assumes simultaneous use of all products with conservative assumptions that the chemical is used at the maximum reported concentration. As the products are not widely reported, it is expected that actual systemic exposures would be significantly lower.

Exposures from rinse-off personal care products

Personal care products (cosmetics) containing the chemical are expected to be used daily. Depending on the type of product, dermal contact with personal care products can be limited to specific areas of the body such as the eye region, face, hands, nails, or feet, or it can be more extensive, covering large areas of the trunk as well as the face. The duration of exposure for various products may differ substantially; for rinse-off products such as soaps or shampoos, exposure might only be for a few minutes, although some residual product can remain, whereas for leave-on products, exposure could last for several hours. For these products, the dermal route is the most significant route of exposure.

Based on Australian and international information, the chemical is reported to be used in a limited number of rinse-off personal care products with a maximum concentration of 0.1% (see **Introduction and use**). The daily systemic dermal exposure to representative products was estimated and the values are presented in **Table 1**. The combined worst case daily systemic exposure to the chemical in representative rinse-off cosmetic products was 0.0088 mg/kg bw/day.

Table 1 – Daily dermal systemic exposure to the chemical from rinse-off cosmetic products*

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Shampoo	10,460	0.10	0.01	0.0017
Conditioner	3,920	0.10	0.01	0.0007
Shower gel	18,670	0.10	0.01	0.0031
Hand wash soap	20,000	0.10	0.01	0.0033
Total	-	-	-	0.0088

*Daily systemic exposure = (amount × C × RF × DA)/BW with DA = 100% and BW = 60 kg. C = chemical concentration; RF = retention factor; DA = dermal absorption; BW = body weight.

Exposures from impurities in personal care products

The chemical has also been reported as in impurity in some surfactants that have reported uses in personal care products for both adults and children (see **Introduction and use**). A conservative daily systemic exposure estimate was calculated for the chemical based on the available use data of these surfactants in cosmetics.

Adults

As the direct exposure estimate in **Table 1** accounts for exposures to all identified rinse-off products, exposures to the chemical as an impurity in leave-on products only were estimated. For these estimates, a worse-case concentration of the chemical of 0.0054% (leave-on products) and 0.0005% (disposable wipes) was assumed as:

- the chemical as an impurity in surfactants with concentration of less than 0.1%.
- the surfactants are used in leave-on personal care products with end use concentrations up to 5.4% (CIR 2014; CIR 2023; CIR 2026) and 0.5% in disposable wipes (Rodriguez et al. 2020).

The most common leave-on products identified for surfactants that may contain the chemical as an impurity include body lotions, face creams, hand creams, hair dyes and disposable wipes (CIR 2014; CIR 2023; CIR 2026). For disposable wipes the amount of product used per day (approximately 3,500 mg/day) was calculated using default values from the Facial Cleansing Wipes scenario of the RIVM Cosmetics Fact Sheet (RIVM 2025). The combined daily systemic exposure from these representative products containing the chemical as an impurity was 0.011 mg/kg bw/day (see **Table 2**).

Table 2 – Daily dermal systemic exposure to the chemical as an impurity in leave-on cosmetic products*

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.0054	1	0.0070
Face cream	1,540	0.0054	1	0.0014
Hand cream	2,160	0.0054	1	0.0019
Hair dye	4,000	0.0054	0.1	0.0004
Disposable wipes	3,500	0.0005	1	0.0003
Total	-	-	-	0.011

*Daily systemic exposure = (amount × C × RF × DA)/BW with DA = 100% and BW = 60 kg. C = chemical concentration; RF = retention factor; DA = dermal absorption; BW = body weight.

Children (0-3 years)

The surfactants which may contain the chemical as an impurity also had reported use in baby products (see **Introduction and use**). The available information indicates that the surfactants are used in rinse-off products only such as baby shampoos and other cleansers and in baby wipes. Except for baby wipes for which a concentration of 0.0005% of the chemical was used, the highest reported end use concentration of the impurity in baby products (0.0016%) was used for these estimates as the concentrations of the surfactants reported for baby products were generally lower than those for adult products (CIR 2023, CIR 2026). For rinse-off products, values for daily product exposure for children in mg/kg bw/day were based on values previously used by the SCCS (SCCS 2024). For baby wipes the amount of product used per day was calculated using default values from the RIVM Cosmetics Fact Sheet (RIVM 2025). The daily product exposure was scaled using conservative body weights of 4.8 kg and 11.9 kg for children aged 0–1 and 1–3 years old, respectively (SCCS 2024).

The combined daily systemic exposure from these products containing the chemical was 0.013 and 0.0056 mg/kg bw/day for children aged 0–1 and 1–3 years old, respectively (see **Table 3**).

Table 3 – Daily dermal systemic exposure to the chemical as an impurity in rinse-off baby products. Estimates were calculated for 2 age groups: 0–1 year old and 1–3 years old.*

Product type	Daily product exposure at 0–1 year old (mg/kg bw/day)	Daily systemic exposure at 0–1 year old (mg/kg bw/day)	Daily product exposure at 1–3 years old (mg/kg bw/day)	Daily systemic exposure at 1–3 years old (mg/kg bw/day)
Shower gel	7.4	0.00012	9.37	0.00015
Hand soap	7.4	0.00012	9.37	0.00015
Shampoo	4.79	0.00008	4.52	0.00007
Conditioner	-	-	4.52	0.00007
Baby wipes	2,550	0.01275	1,030	0.00515
Total	-	0.013	-	0.0056

*Daily systemic exposure = daily product exposure × C × DA) with C = 0.0016% and DA = 100%. C = chemical concentration; DA = dermal absorption.

Additional exposures from non-industrial uses

Additional non-industrial sources of exposure to the chemical include drinking water and water from swimming pools as the chemical is a disinfectant byproduct (Government of Canada 2021; IARC 2014).

The NHMRC reports that the typical concentration of the chemical in drinking water in Australia is between 0.01 and 0.1 mg/L. In a 1998 study of 7 Australian cities, the chemical was detected in drinking water at concentrations between 1 and 46 µg/L (IARC 2014; NHMRC 2025).

Health hazard information

Where relevant, toxicological studies that used the sodium salt of the chemical, sodium dichloroacetate (CAS No. 2156-56-1), were used as read across to support the hazard conclusions.

Toxicokinetics

The chemical is readily absorbed from the gastrointestinal tract in humans and rodents. When administered orally in humans, the plasma concentration of the chemical peaked 15–30 minutes after exposure (IARC 2014; US EPA 2003). No information on the dermal absorption of the chemical is available.

The chemical is expected to be widely distributed in both humans and rodents (IARC 2014; US EPA 2003). In one rat study, most of the radiolabelled chemical was detected in the liver, muscle, skin, blood and intestine, 48 hours after oral exposure. At 24 hours, 10–15% of the radiolabel was also identified in the kidney, stomach, adipose, testes, lung, spleen, heart,

brain and bladder. However, at 48 hours, only 1–2% of the dose was identified in these tissues (US EPA 2003).

The chemical is primarily metabolised to glyoxylate *via* oxidative dechlorination by enzymes. Glyoxylate can be transaminated in the peroxisomes to form glycine, which can be incorporated into protein or oxidised to form oxalic acid or glycolic acid metabolites that are excreted in the urine. Similar metabolic pathways have been observed in rodents and humans. Other metabolic pathways have been identified including reductive dechlorination of the chemical to form monochloroacetic acid. In humans and rats, the chemical also inhibits the enzyme that also causes this metabolic transformation. As the dose of the chemical increases, it is expected that greater amounts of the unmetabolised chemical will be detected in the organism or excreted in the urine (IARC 2014; US EPA 2003). In animal studies, the average concentrations of the unmetabolised chemical found in the urine after oral exposure was less than those detected in human studies. However, the amount excreted increased with an increasing dose. A small fraction of the chemical (1-2%) was found in the faeces in animal studies.

Acute toxicity

Oral

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

In a non-guideline acute oral toxicity studies not compliant with good laboratory practice (GLP), the chemical had an LD50 of (ECHA CHEM n.d.):

- 2,820 and 4,480 mg/kg bw in rats
- 3,997–4,280 mg/kg bw in ICR mice
- 5,520 mg/kg bw in albino mice.

Dermal

Based on the available data, the chemical has moderate acute dermal toxicity, warranting hazard classification (see **Hazard classifications relevant for worker health and safety**).

In a non-GLP compliant non-guideline acute dermal toxicity study, rabbits received a single dose of the chemical. The dermal LD50 was 0.51 mL/kg bw, which is equivalent to 797 mg/kg bw using a density of 1.563 g/mL (ECHA CHEM n.d.). No information on clinical signs or local effects were reported.

Inhalation

No data are available.

Corrosion/Irritation

The chemical is classified as hazardous in the HCIS with hazard category “Skin Corrosion – Category 1A” and hazard statement “H314: Causes severe skin burns and eye damage” (SWA n.d.). The limited available animal and *in vitro* data indicates that the chemical is likely to be corrosive to skin and cause severe damage to rabbit eyes, warranting hazard classification (see **Hazard classifications relevant to worker health and safety**). The chemical is a strong acid ($pK_a = 1.48$ at 25°C) (US EPA 2003). Therefore, it is expected to be corrosive to the skin and eyes. As there is insufficient evidence to evaluate the Category 1A sub-classification, no amendments to the existing hazard classification for skin corrosion are proposed.

Skin irritation

In non-GLP compliant skin irritation study, the chemical was reported to have a primary skin irritation score of 7/10 (ECHA CHEM n.d.). No further details on the study protocol or effects were available. However, it has been reported that other studies performed by the same authors indicate that a score of 7/10 corresponds to necrosis of the skin (BG RCL 2006).

In an *in vitro* skin corrosion assay, the chemical at 36.1% concentration was applied to the three-dimensional human skin model Skin² ZK 1350 for 10 seconds. After 24 hours, the cell viability was reported to be $21.8 \pm 14.3\%$. In this assay, a cell viability less than 80% was considered corrosive (Liebsch et al. 1995).

The chemical was also reported to be corrosive in an *in vitro* study using the Corrositex test for determining chemical packaging groups. No further study details are available (BG RCL 2006).

The chemical is predicted to cause skin irritation or corrosion in mammals using the expert rule-based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus version 2.6. The prediction is based on the alerts "Short chain alkyl carboxylic acid" and "Alkyl halide". The prediction was considered plausible (Lhasa Limited n.d.).

The chemical is predicted to be corrosive to skin using OASIS-TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator) version 2.31 (OASIS LMC n.d.). However, the chemical is included as a positive result in the training set of the 'Skin irritation corrosion v.06' model.

Eye irritation

In a non-GLP compliant eye irritation study, the chemical was reported to be highly corrosive to rabbit eyes with a grade of eye irritation score of 10/10 (ECHA CHEM n.d.).

The chemical is predicted to be irritating or corrosive to eyes using OASIS-TIMES version 2.31 (OASIS LMC n.d.). However, the prediction was outside the applicability domain of the 'Eye irritation v.06' model.

Sensitisation

Skin sensitisation

No data are available. The chemical is not likely to be a skin sensitizer based on *in silico* results.

The chemical has a structural alert for protein binding based on the general mechanistic profiling functionality of the OECD QSAR Toolbox version 4.5 (OECD 2021). The alert is based on nucleophilic substitution of proteins at sp³ carbon atoms on alpha-Activated haloalkanes.

The chemical is predicted to be a non-sensitizer using the expert rule-based system, DEREK Nexus version 2.6 (Lhasa Limited n.d.).

The chemical is predicted to be non-sensitising using OASIS-TIMES version 2.31 GHS model (OASIS LMC n.d.). The prediction was 88.33% inside the structural domain.

Repeat dose toxicity

Oral

Based on the available 90 day studies in rats and dogs, the chemical is expected to cause serious systemic health effects following repeated oral exposure warranting hazard

classification (see **Hazard classifications relevant for worker health and safety**). The target organs for toxicity are the testes and the central nervous system with some effects in the peripheral nervous system reported in humans (see **Reproductive and development toxicity** and **Neurotoxicity** for more details).

Generally, dogs were more sensitive to the adverse effects induced by the chemical than rats. Repeated exposures to the chemical also caused significant changes in liver histopathology and relative liver weights in both rats and dogs. However, the effects occurred mainly at high doses or were not severe enough to warrant GHS hazard classification. In chronic studies, the chemical induced liver tumours in mice and rats (see **Carcinogenicity** for more details).

Other adverse effects reported in 90 day studies in rats and dogs or chronic studies in mice such as those of the kidney were reversible or only occurred at high doses that do not warrant hazard classification.

90 day studies in rats

In a 90 day study conducted in accordance with OECD TG 408, SD rats (10–15/sex/dose) were administered the sodium salt of the chemical by gavage daily at 0, 125, 500 and 2,000 mg/kg bw/day. An additional 5 animals were added to the control and highest dose groups for further observation during a 4 week recovery period. Clinical signs of toxicity included hind limb paralysis and frequent urination. There was a significant dose-dependent decrease in body weight gain in all dose groups which was associated with decreased food consumption. There were significant and dose-dependent increases in the mean relative weights of the liver, kidneys and adrenal glands. Animals in the dosed groups had decreases in blood glucose and lactate levels and increases in creatinine levels compared to controls. Minor effects on haematology were observed in the 2 highest dose groups. All effects on absolute and relative organ weights, clinical chemistry and haematology reversed during the recovery period. Brain lesions were observed in 60% of the animals in the 125 mg/kg bw/day dose groups and 100% of the animals in the higher dose groups. These lesions typically occurred in the cerebrum (and to a lesser extent, the cerebellum) and were characterised by vacuolation of the myelinated white tracts. In 3/8 rats the lesions persisted throughout the recovery period. Male animals that were exposed to the chemical exhibited significant decreases in total serum proteins, triglycerides, iron and calcium levels and increases in bilirubin, sodium and potassium levels when compared to controls. The lowest observed adverse effect level (LOAEL) was reported to be 125 mg/kg bw/day for the chemical, based on adverse effects on body and organ weights, clinical chemistry, histopathology and adverse effects on the brain in all dose groups (ECHA CHEM n.d.; US EPA 2003).

In a 90 day study conducted in accordance with OECD TG 408, male SD rats (10/dose) were administered the chemical in drinking water at 0, 0.05, 0.5 or 5 g/L (approximately equivalent to 0, 3.9, 35.5 or 345 mg/kg bw/day). Compared to the control group, animals in the 345 mg/kg bw/day dose group exhibited:

- significantly decreased water consumption, 2 months after the first dose (also observed in 35.5 mg/kg bw/day dose group)
- significant increases in liver and kidney organ-to-body weight ratios (also observed in 35.5 mg/kg bw/day dose group)
- significant decreases in terminal body weights (also observed in 35.5 mg/kg bw/day dose group)
- histopathological changes in the liver, characterised by focal hepatocellular enlargement, intracellular swelling and glycogen accumulation
- histopathological changes in the kidney, characterised by degeneration of the tubular epithelium and glomeruli
- increased spleen-to-body weight ratio, but no changes to spleen histopathology
- significantly decreased total serum proteins

- significantly increased alkaline phosphatase and alanine aminotransferase levels.

The no observed adverse effect level (NOAEL) was reported to be 3.9 mg/kg bw/day for the chemical, based on significant changes in liver and kidney effects observed at 35.5 mg/kg bw/day group (ECHA CHEM n.d.; US EPA 2003).

In a 12 week limit test similar to OECD TG 408, Wistar rats (6/males/dose) were administered the chemical in diet initially at 516 mg/kg bw/day and later reduced to 323 mg/kg bw/day. Compared to the control group, the dosed group exhibited:

- lower food consumption and lower body weight gain
- significantly decreased absolute organ weights: brain, spleen, lung, heart and epididymis
- significantly increased organ-to-body weight ratios: adrenal glands, brain and kidney
- enlarged livers
- hind limb weakness and abnormal gait
- decreased nerve conduction velocities and sizes of sural, tibial and motor nerves.

A NOAEL could not be derived as adverse effects were observed at the only dose tested (ECHA CHEM n.d.; US EPA 2003).

In a 90 day limit test similar to OECD TG 408, SD rats (5/males/dose) were administered the chemical (purity >99%) in drinking water at 0 or 1,100 mg/kg bw/day. Compared to the control group, the dosed group exhibited:

- decreased body weights (66% of controls). (The authors noted that body weight reductions may be due to decreases in food and water consumption).
- significantly increased liver weights (111% of the controls) and liver-to-body weight ratios (5.5% compared to 3.3%)
- increased liver collagen deposits
- perivascular inflammation in the lung
- focal vacuolation and gliosis in the forebrain and brain stem.

A NOAEL could not be derived as adverse effects were observed at the only dose tested (ECHA CHEM n.d.; US EPA 2003).

90 day studies in dogs

In a 90 day study conducted in accordance with OECD TG 409, beagle dogs (5/sex/dose) were administered the chemical by oral capsule at 0, 12.5, 39.5 or 72 mg/kg bw/day once daily. Clinical signs of toxicity included difficulty breathing, general depression, reduced activity, hind-limb weakness and/or paralysis and diarrhoea. There were 3 treatment-related mortalities from the high dose group (one female and 2 male). Dry or inflamed eyes and clear ocular discharges were observed in animals from all dose groups. Reductions in weight gain (9–16%) were noted in the 39.5 and 72 mg/kg bw/day groups, when compared to the controls. This may be associated with a general reduction in food and water consumption. In all dose groups, the relative liver weights were significantly increased when compared to the control. Relative kidney weights were significantly increased compared to the controls in the 39.5 and 72 mg/kg bw/day groups only. In the 72 mg/kg bw/day group, the relative brain and lung weights were also increased compared to the control. Between days 30 and 90, there were statistically significant decreases in total erythrocyte counts and haemoglobin levels in the high dose group. There were also significant increases in alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase levels in the blood. At necropsy, there were distinct changes in the gross pathology of the lungs, kidney, liver, trachea, pancreas and gall bladder in the high dose group. With respect to histopathology, the treated animals had haemosiderosis in the liver and chronic inflammation and degeneration of the pancreas. Mild vacuolisation of the liver was noted prevelantly in the low dose group. In the

brains of dosed animals, there was a mild vacuolisation of white myelinated tracts that presented in the cerebrum and/or cerebellum. The LOAEL was reported to be 12.5 mg/kg bw/day for the chemical, based on increased liver weights and the vacuolisation of liver and brain cells in the low dose group (ECHA CHEM n.d.; US EPA 2003).

In a 13 week study conducted in accordance with OECD TG 409, beagle dogs (3/sex/dose) were administered the sodium salt of the chemical by oral capsule at 0, 50, 75 or 100 mg/kg bw/day once daily. One additional animal of each sex was included in the control and 100 mg/kg bw/day groups for further observations during a 5 week recovery period. Clinical signs of toxicity in the 75 and 100 mg/kg bw/day groups included anorexia, general weakness, ataxia, hind limb weakness, vomiting, bloody stools and paralysis. There were 2 treatment-related mortalities in a female from the 75 mg/kg bw/day group and in a male from the 100 mg/kg bw/day group. There were significant ocular anomalies reported at all doses levels that were characterised by dry and/or inflamed eyes, corneal vascularisation and an opacity of the lens. Food consumption was significantly decreased in females but not males, and both sexes exhibited dose dependent weight loss that was reversible during the recovery period. In all dosed groups, there were dose-related decreases in erythrocyte counts, haematocrits, and haemoglobin levels when compared to control groups. Mean blood glucose, lactate, and pyruvate levels were also significantly decreased in all treated animals. These decreases were negligible after the 5 week recovery period. At necropsy, there was increased lung consolidation in the dosed groups. In all dosed groups, there were observations of brain lesions that were characterised by slight to moderate vacuolation of the white myelinated tracts in the cerebrum and cerebellum. In the treated animals, there were increased rates of haemosiderin-laden Kupffer cells in the liver (up to 83% at 100 mg/kg bw/day) and cystic mucosal hyperplasia in the gall bladder (up to 100% at 100 mg/kg bw/day). All histopathological findings persisted throughout the recovery period. The LOAEL for the study was reported to be 50 mg/kg bw/day for the chemical, based on adverse effects on organ weights, clinical chemistry and the histopathological findings (ECHA CHEM n.d.; US EPA 2003)

Chronic studies in mice

In a 26 week chronic oral toxicity study, Tg.AC hemizygous mice (15/sex/dose) were administered the chemical in drinking water at 500, 1,000 or 2,000 mg/L. An additional group of mice (10/sex/dose) were administered the same doses for an additional 15 weeks. Slightly lower mean body weights were noted in the 41 week study which may be related to decreased water consumption. The incidences of liver cell vacuolisation were increased in both males and females at both 26 and 41 weeks (NTP 2007).

In a 26 week chronic oral toxicity study, p53 haploinsufficient mice (15/sex/dose) were administered the chemical in drinking water at 500, 1,000 or 2,000 mg/L. An additional group of mice (10/sex/dose) were administered the same doses for an additional 15 weeks. Lower mean body weights were observed in the 1,000 and 2,000 mg/L groups, which may be related to decreased water consumption. The incidences of liver cell vacuolisation were increased in dosed males at 26 weeks and in dosed females at both 26 and 41 weeks. No other chronic adverse effects were reported (NTP 2007).

Dermal

In a 26 week chronic dermal toxicity study, Tg.AC hemizygous mice (15/sex/dose) were administered the chemical dermally at 31.25, 125 or 500 mg/kg bw/day for 5 days per week. An additional group of mice (10/sex/dose) were administered the same doses for an additional 13 weeks. In the 39 week group, females administered 500 mg/kg bw/day had increased mean body weights. A 50% increase in absolute liver weights was observed in both males and females in the 500 mg/kg bw/day group at 39 weeks. The incidences of epidermal hyperplasia and hyperkeratosis at the site of application were significantly increased in the 125 and 500 mg/kg bw/day groups at 26 weeks. There was a dose-related

increase in the mean severity of liver vacuolisation. The incidence of kidney lesions in males from the 500 mg/kg bw/day group was increased at 26 weeks (NTP 2007).

Inhalation

No data are available.

Observation in humans

Most of the available evidence of human exposures to repeated doses of the chemical are from clinical studies and involve reports relating to neurotoxic effects (see **Neurotoxicity**).

In one of these studies, it was reported that subjects receiving 43–57 mg/kg bw/day of the chemical over 6–7 days had significantly altered clinical chemistry at the end of the treatment period. These included decreases in fasting blood glucose, plasma lactate, alanine, cholesterol and triglyceride levels. These effects reversed during a subsequent 7 or 15 day recovery period (US EPA 2003).

Genotoxicity

Overall there is no strong evidence that the chemical has genotoxic potential. The chemical had some mutagenic and clastogenic activity in bacterial and mammalian cells *in vitro*. There was equivocal evidence for genotoxicity in available *in vivo* micronucleus tests and the chemical was negative in an *in vivo* chromosome aberration test. The evidence was mixed for DNA damage *in vivo*. Positive genotoxicity results were identified *in silico*. However, these were largely associated with the positive experimental results *in vitro*. The chemical is a soft electrophile that preferentially reacts with thiol groups on proteins rather than directly with DNA. Therefore, the observed toxic effects may result from decreased glutathione (a thiol containing protein). The available data suggest that the positive mutagenic and genotoxic results may be a result of oxidative stress, rather than direct genotoxicity (NTP 2017).

In vitro

Positive

Positive results were reported in the following *in vitro* genotoxicity studies using the chemical in (ECHA CHEM n.d.; IARC 2014; US EPA 2003):

- a bacterial reverse mutation assay (similar to OECD TG 471) in *Salmonella typhimurium* TA100 with and without metabolic activation at concentrations above 50 ppm
- a bacterial reverse mutation assay in *S. typhimurium* TA98, TA100 and RSJ100 without metabolic activation at concentrations up to 5,160 µg/mL. However, negative results were reported for strains TA98 and RSJ100 with metabolic activation
- a bacterial reverse mutation assay in liquid medium in *S. typhimurium* TA100 with and without metabolic activation at concentrations up to 1,500 µg/mL
- a non-guideline microscreen phage-induction assay in *Escherichia coli* with metabolic activation at concentrations above approximately 2 mg/mL
- a non-guideline DNA repair assay in *S. typhimurium* TA1535 (umu operon) with S9 metabolic activation at a concentration of 58.5 µg/mL
- a non-guideline DNA repair assay (SOS chromotest) in *E. Coli* PQ37 without S9 metabolic activation at a concentration of 500 µg/mL
- a mammalian gene mutation assay (OECD TG 476) in the thymidine kinase (*Tk*) locus in mouse lymphoma L5178Y cells at concentrations up to 1,200 µg/mL
- a mammalian gene mutation assay in the *Hprt* locus in Chinese hamster ovary K1 cells without metabolic activation at concentrations up to 1,290 µg/mL

- a mammalian chromosomal aberration test in mouse lymphoma L5178Y cells without metabolic activation at concentrations up to 800 µg/mL.

Negative

Negative results were reported in the following *in vitro* genotoxicity studies using the chemical in (ECHA CHEM n.d.; IARC 2014; US EPA 2003):

- a bacterial reverse mutation assay (similar to OECD TG 471) in *S. typhimurium* TA100, TA1535, TA1537 and TA1538 with and without metabolic activation. However, a weakly positive result was reported in *S. typhimurium* strain TA98 without metabolic activation at concentrations up to 10 µg/plate.
- a bacterial reverse mutation assay (similar to OECD TG 471) in *S. typhimurium* TA102 and TA2638 and *Escherichia coli* WP2/pKM101 and WP2uvrA/pKM101 with metabolic activation at doses up to 5,000 µg/plate
- a bacterial reverse mutation assay in microsuspension in *S. typhimurium* TA104 with and without metabolic activation at concentrations of 150 µg/plate
- a bacterial reverse mutation assay (similar to OECD TG 471) in *Klebsiella pneumoniae* at concentrations up to 0.01% (v/v)
- a DNA damage and repair assay in *S. typhimurium* DNA-repair deficient TS24, TA2322, TA1950 with and without metabolic activation at concentrations up to 31,000 µg/plate
- a mammalian gene mutation assay (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (*Hprt*) locus in Chinese hamster lung cells (V79) with and without metabolic activation at concentrations up to 1,000 µg/mL
- an *in vitro* mammalian cell micronucleus test in mouse lymphoma L5178Y cells without metabolic activation at doses up to 800 µg/mL
- a series of non-guideline assays for DNA strand breaks in B6C3F₁ mouse hepatocytes, F344 rat hepatocytes or human CCRF-CEM lymphoblastoid cells without metabolic activation at concentrations of 2,580, 1,290 and 1,290 µg/mL, respectively. A small increase in DNA strand breakage was noted in the mouse hepatocytes after 4 hour exposure but was not considered significant
- a non-guideline assay for DNA strand breaks and alkali labile damage in Chinese hamster ovary cells without metabolic activation at concentrations up to 3,225 µg/mL.

Negative results were reported in the following *in vitro* genotoxicity studies using the sodium salt of the chemical in (ECHA CHEM n.d.; IARC 2014):

- a bacterial reverse mutation assay (OECD TG 471) in *S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation at doses up to 5,000 µg/plate
- a bacterial reverse mutation assay (similar to OECD TG 471) in *E. Coli* WP2uvrA with and without metabolic activation at doses up to 5,000 µg/plate
- a mammalian gene mutation assay (OECD TG 476) in the *Tk* locus in mouse lymphoma L5178Y cells with and without metabolic activation at concentrations up to 5,000 µg/mL
- an *in vitro* mammalian chromosome aberration assay (OECD TG 473) in Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations up to 5,000 µg/plate.

In vivo

In a series of mammalian erythrocyte micronucleus tests conducted in accordance with OECD TG 474, male B6C3F₁ mice (n=10/dose) were treated with the chemical in drinking water at doses of 95, 190, 380 or 665 mg/kg bw/day for 9 or 28 days. In the mice from the highest dose group that were treated for 9 days, there was a slight and statistically significant

increase in the incidence of micronuclei in bone marrow polychromatic erythrocytes compared to the controls. These increases were not observed in the mice exposed to the chemical for 28 days. In parallel experiments, mice receiving the highest dose of the chemical for 10, 26 or 31 weeks had slight, but not statistically significant, increases in the incidence of micronuclei in bone marrow polychromatic erythrocytes compared to the controls. These results indicate that the chemical may be weakly clastogenic (ECHA CHEM n.d.; IARC 2014; US EPA 2003).

In a mammalian erythrocyte micronucleus test, B6C3F₁ mice (n=10/dose) were treated with the chemical in drinking water at doses of 67, 125, 250, 500 or 1,000 for 3 months. In female mice, there was a small dose-dependent increase in the number of micronucleated erythrocytes. However, none of the individual numbers were statistically significantly different from the control group. There were no increases in micronucleated erythrocytes in male mice. The percentages of polychromatic erythrocytes were not significantly affected by exposure to the chemical. Overall, the study provided equivocal evidence of micronucleus formation *in vivo* (NTP 2007).

No significant increases in the induction of micronuclei were reported in chronic studies in Tg.AC hemizygous mice that received the chemical in drinking water or dermally (see **Repeat dose toxicity**). In these studies, the percentages of polychromatic erythrocytes were not statistically significantly affected by exposure to the chemical (NTP 2007).

In a GLP compliant mammalian bone marrow chromosomal aberration test conducted in accordance with OECD TG 475, SD rats (n=5/sex/dose) were administered the sodium salt of the chemical by intravenous injection at doses of 275, 550 or 1,100 mg/kg bw/day. The incidence of chromosome aberrations in bone marrow did not increase in any of the treated groups, indicating lack of clastogenicity (ECHA CHEM n.d.; IARC 2014)

In a non-guideline *in vivo* mammalian DNA damage study, male transgenic B6C3F₁ mice harbouring the bacterial *lacI* gene were treated with the chemical in drinking water at concentrations of 1.0 g/L or 3.5 g/L (approximately equivalent to 190 or 665 mg/kg bw/day) for 4, 10 or 60 weeks. In the 4 and 10 week groups, there were no statistically significant changes in mutation frequency at the *lacI* loci. In the 60 week groups, there were statistically significant increases in mutation frequencies at the *lacI* loci that were attributed to the chemical. However, as the mutation frequency only increased after 60 weeks, it cannot be ruled out that the mutations may be secondary to other toxicological changes in the liver (ECHA CHEM n.d.; IARC 2014; US EPA 2003).

In a series of non-guideline *in vivo* DNA damage studies, male B6C3F₁ mice were exposed to a single dose of the chemical orally at 1,290 mg/kg bw. No DNA damage was reported in the liver cells, splenocytes or epithelial cells from the stomach and duodenum of these animals. In related studies, no DNA damage was detected in liver cells of F344 rats that were exposed to the chemical orally at up to 645 mg/kg bw. Additionally, no DNA damage was observed in mice received the chemical at 5,000 mg/kg bw/day in drinking water for 7-14 days or in rats received the chemical at 2,000 mg/kg bw/day in drinking water for 30 weeks (IARC 2014).

Positive results were reported in the following non-guideline *in vivo* studies with limited details (ECHA CHEM n.d.; IARC 2014):

- assays for DNA strand breaks in the liver cells of B6CF₁ mice that were exposed to a single dose of the chemical by oral gavage at 10 and 13 mg/kg bw
- assays for DNA strand breaks in the liver cells of SD rats that were exposed to a single dose of the chemical by oral gavage at 30 mg/kg bw
- an assay for unscheduled DNA synthesis in liver cells of male B6CF₁ mice that were exposed to the chemical in drinking water for 5 days at concentrations up to 2,000 mg/L.

In silico

The chemical has structural alerts for DNA binding, *in vitro* mutagenicity (Ames test) and *in vivo* mutagenicity (Micronucleus) based on the general mechanistic and endpoint specific profiling functionality of the OECD QSAR Toolbox version 4.5. The DNA alerts are based on a radical mechanism where geminal polyhaloalkane derivatives cause reactive oxygen species to form after glutathione depletion. The mutagenicity alerts are based on the presence of aliphatic halogens. Some of the metabolites predicted by the Hydrolysis simulator (neutral), *in vivo* Rat metabolism simulator and Rat liver S9 metabolism simulator also had similar structure alerts for DNA binding, *in vitro* mutagenicity and *in vivo* mutagenicity (OECD 2021).

The chemical is predicted to be mutagenic to bacteria *in vitro* using the expert rule-based system, DEREK Nexus version 2.6. The prediction is based on the structural alert “gem-Dihalide”. The prediction was considered plausible (Lhasa Limited n.d.).

The chemical is predicted to be positive in the Ames test (*in vitro*), Chromosomal Aberrations test with S9 (*in vitro*) and in the micronucleus test (*in vivo*) using OASIS-TIMES version 2.31 (OASIS LMC n.d.). However, the chemical is included in the training sets as a positive result for *in vitro* mutagenicity and chromosomal aberrations and as a negative result for *in vivo* micronucleus.

Carcinogenicity

Based on the available data from animal studies, the chemical is expected to be carcinogenic, warranting hazard classification (see **Hazard classifications relevant to worker health and safety**). The chemical induced liver tumours in male rats and in both sexes in mice. While many of the available studies were not conducted according to OECD test guidelines or have limited information, the weight of evidence shows that the chemical induces malignant liver tumours in both rats and mice at incidences above historical controls. Although the chemical may have some genotoxic potential at high concentrations or specific experimental circumstances (see **Genotoxicity**), the available data supports a likely threshold mode of action. Both IARC and NTP concluded that the chemical most likely induces liver tumours *via* a combination of non-genotoxic mechanisms (see **Mode of action**). While these proposed mechanisms were based on animal studies, the relevance of these mechanisms to humans cannot be ruled out.

Overall, the strength of evidence is considered sufficient to place the substance in Category 1, based on the incidence of liver tumours with an incidence above historical controls in 2 species (rats and mice) and 2 sexes (mice). There are no available human data that provide sufficient evidence of carcinogenicity (US EPA 2003). Therefore, the chemical satisfies the criteria for Category 1B according to GHS criteria.

Studies in mice

Carcinogenicity studies in mice indicate that the chemical induces hepatocellular adenomas and carcinomas when administered at high doses in drinking water (see **Table 4**). Several of the mice studies had limitations which included:

- Reporting was focused on the liver, and other histopathological observations were omitted from study reports.
- Most studies were not conducted with sufficient numbers of animals (<50/dose) or a sufficient exposure duration (2 years) compared to standard test guidelines.

Despite these limitations, these carcinogenicity studies consistently showed that the chemical:

- Induces hepatocellular adenomas and carcinomas in B6C3F₁ mice.
- Causes statistically significant increases in liver tumours in studies of 52–82 weeks at doses of ≥ 2 g/L (approximately 300 mg/kg bw/day) with reported incidences typically above 80%
- Causes statistically significant increases in the incidence of liver tumours at doses from 0.5 g/L (approximately 80–88 mg/kg bw/day) in studies ≥ 87 weeks in duration.
- Induces multiple liver tumours per animal.

Most of the studies used the male B6C3F₁ mice, which are considered susceptible to the induction of liver tumours by chemical agents in carcinogenicity experiments. The National Toxicology Program (NTP) historical control data indicates that hepatocellular carcinomas occur with a mean frequency of 23.86% in these mice (NTP 2024). The frequency these carcinomas in the higher dose groups from the below studies exceeded the historical control values.

In chronic oral repeated dose studies in Tg.AC hemizygous mice (see **Repeat dose toxicity**), there were reported incidences of alveolar or bronchiolar adenomas and carcinomas in the higher dose groups. However, there was no evidence of carcinogenicity in p53 haploinsufficient mice under similar conditions. In related chronic dermal studies in Tg.AC hemizygous mice, there were significantly increased incidences of squamous cell papillomas at the site of application in the highest dose group as well as increased incidences of pulmonary adenomas (NTP 2007).

Table 4 – Summary of carcinogenicity studies in B6C3F1 mice. In all experiments mice were exposed to the chemical in drinking water. Male mice were used unless otherwise indicated. * indicates a statistically significant increase in incidence compared to control groups (ACGIH 2005; IARC 2014; US EPA 2003).

Study duration (weeks)	Doses (g/L)	Incidence of hepatocellular adenomas (benign)	Incidence of hepatocellular carcinomas (malignant)	Notes and observations
104	0.5 (approx. 88 mg/kg bw/day)	Control: 1/20 Dosed: 10/24*	Control: 2/20 Dosed: 15/24*	Incidence of hyperplastic nodules (2/24) in dosed group was not statistically significant.
104	0.5, 3.5	-	Control: 1/39 Dosed: 1/25, 23/25*	-
104	0.5, 3.5 (approx. 80, 400 mg/kg bw/day)	-	-	Reported as total hepatocellular tumour incidence as a percentage of female mice with tumours Control: 7.7% Dosed: 20%, 100%
100	0.05, 0.5, 1, 2, 3.5 (approx. 8, 84, 168, 315, 429 mg/kg bw/day)	Control: 10% (n=10) Dosed: n.r.; 20% (n=24), 51.4% (n=32), 42.9% (n=14), 45% (n=8)	Control: 26% (n=50) Dosed: n.r.; 48% (n=24), 71%* (n=32), 95%* (n=14), 100%* (n=8)	Data presented as percentage of mice with tumours. Mice (10/dose) that were analysed at week 78 had a lower reported incidence of tumours in all dose groups.
87	0.5, 2	-	-	Reported as total liver hyperplastic nodules, hepatocellular adenomas or carcinomas. Control: 4/7 Dosed: 17/19*, 5/5
82	0.259, 0.86, 2.59 (approx. 40, 115, 330 mg/kg bw/day)	Control: 2/90 Dosed: 3/50, 7/28, 16/19*	Control: 2/90 Dosed: 0/50, 1/28, 7/19*	Study used female mice.
76	5 (approx. 900 mg/kg bw/day)	Control: 2/24 Dosed: 83/89*	Control: 2/24 Dosed: 66/89*	Mice dosed 5 days/week.

Study duration (weeks)	Doses (g/L)	Incidence of hepatocellular adenomas (benign)	Incidence of hepatocellular carcinomas (malignant)	Notes and observations
60–75	0.05, 0.5, 3.5, 5 (approx. 7.6, 77, 410, 486 mg/kg bw/day)	Control: 0/28 Dosed: 2/29, 1/27, 12/12*, 24/30*	Control: 2/28 Dosed: 5/29, 2/27, 8/12*, 25/30*	NOAEL reported as 7.6 mg/kg bw/day. Incidences were combined for all dose groups from 3 smaller experiments.
61	5 (approx. 1,000 mg/kg bw/day)	Control: 2/22 Dosed: 25/26*	Control: 0/22 Dosed: 21/26*	-
52	1, 2 (approx. 140, 300 mg/kg bw/day)	Control: 0/35 Dosed: 0/11, 2/24	Control: 0/35 Dosed: 0/11, 6/24	Other liver lesions and hyperplastic nodules reported in all dose groups. No liver tumours were reported in a satellite group of females (10/dose) in same study conditions.
52	0.1, 0.5, 2	-	-	Reported as total liver hyperplastic nodules, hepatocellular adenomas or carcinomas Control: 1/20 Dosed: 2/20/ 5/20, 12/19*

Studies in rats

In a carcinogenicity study, male F344 rats (60/dose, except for controls which had 50) received the chemical at doses of 0, 0.05, 0.5 or 2.4 g/L in drinking water for up to 104 weeks. The mean daily doses of the chemical in the animals were 3.6 and 40.2 mg/kg bw/day in the 0.05 and 0.5 g/L dose groups, respectively. The actual dose received by the 2.4 g/L group was not reported.

At 45 and 60 weeks, there were no significant incidences of liver tumours in the 0.05 and 0.5 g/L dose groups. Animals from the 2.4 g/L dose group; however, exhibited a statistically significant increase in the number of hyperplastic nodules in the liver (19/27 animals). Additionally, there were hepatocellular adenomas in 7/27 animals and hepatocellular carcinomas in 1/7 animals. The animals from the 2.4 g/L group were terminated at week 60. At 104 weeks, hepatocellular adenoma was reported in 1/23 rats in the control group. No liver tumours were reported in the 0.05 g/L dose group. In the 0.5 g/L dose group at 104 weeks, there were reports of hyperplastic nodules (3/29 animals), hepatocellular adenomas (6/29 animals) and hepatocellular carcinomas (3/29 animals). The combined incidence of liver neoplasia (nodules, adenomas and carcinomas) and various liver lesions were statistically significantly increased compared to the controls. The prevalence of mononucleated leukaemia was 24%, 20% and 43% in the 0, 0.05 and 0.5 g/L dose groups,

respectively, after 104 weeks of exposure to the chemical. None of these incidences at 104 weeks were considered statistically significant. Based on the incidences of liver tumours in the 40.2 mg/kg bw/day (0.5 g/L) group at 104 weeks, the NOAEL for carcinogenicity in F344 rats is 3.6 mg/kg bw/day (0.05 g/L) (ACGIH 2005; ECHA CHEM n.d.; IARC 2014).

In a carcinogenicity study, male F344 rats (78/dose) received the chemical at 0 or 1.6 g/L in drinking water (approximately 139 mg/kg bw/day) for up to 103 weeks. Similarly to the above rat carcinogenicity study, some animals were terminated at 45 and 60 weeks. However, no histopathological data is available. At 103 weeks, the prevalence of hyperplastic nodules, hepatocellular adenoma and hepatocellular carcinoma in the 33 remaining control group animals were 3%, 0% and 3% respectively. The prevalence of hyperplastic nodules, hepatocellular adenoma and hepatocellular carcinoma in the 28 remaining animals in the treated group were 3.6%, 10.7% and 21.4% respectively, with statistically significant increase in the incidence of hepatocellular carcinoma. A renal tubular adenoma was observed in one animal in the treated group. The incidence of this adenoma in F344 rats in historical controls was 0.7% (NTP 2013). The prevalence of mononucleated leukaemia was 9% and 11% in the control and dose groups, respectively, after 103 weeks of exposure to the chemical. A NOAEL could not be derived as adverse effects were observed at the only dose tested (ECHA CHEM n.d.; IARC 2014).

Mode of action

There is uncertainty about the exact mechanisms by which the chemical induces carcinogenic effects; however, the weight of evidence supports a likely threshold mode of action.

There is no single widely accepted MOA for carcinogenicity of DCA. Several biologically plausible mechanisms were proposed to be responsible for the carcinogenicity of DCA and other haloacetic acids (IARC 2014; NTP 2017): These include:

- tumour promotion via altered cell proliferation/apoptosis
- DNA hypomethylation and altered oncogene expression
- metabolic reprogramming
- oxidative stress
- weak indirect genotoxicity.

Of these, it has been proposed that oxidative stress mechanisms are likely to contribute to the weak genotoxicity (and carcinogenicity) rather than a direct genotoxic mechanism. The chemical is a soft electrophile that will preferentially react with thiol-containing proteins over DNA (NTP 2017). Therefore, while some genotoxic activity has been reported, the overall evidence suggests that genotoxicity is not the principal mode of action for carcinogenicity.

Reproductive and development toxicity

Based on the available data, the chemical is expected to cause adverse effects on fertility, warranting hazard classification (see **Hazard classifications for worker health and safety**). The target organ for the chemical is the testes, with adverse effects on sperm noted in rats and dogs at doses of 62.5 and 12.5 mg/kg bw/day, respectively. The adverse effects on sperm were dose dependent, with near complete impairment of sperm activity observed at doses of 500 mg/kg bw/day or higher in rats, and at doses around 100 mg/kg bw/day in dogs. In the available reproductive toxicity study there was some evidence of effects on fertility at a dose of 125 mg/kg bw/day. However, rodents have a larger sperm reserve than humans and can better tolerate effects on sperm without influencing fertility (Green et al. 2024). Therefore, the relevance of the effects in humans cannot be discounted.

There is limited data on the developmental effects of the chemical. In prenatal developmental studies, the chemical induced cardiovascular defects (typically a septal defect) at doses of

140 mg/kg bw/day. While there was evidence of maternal toxicity (decreased weight gain and increased absolute organ weights) at these doses, these defects are considered to be of high concern (ECETOC 2002). In addition, cardiovascular defects were also observed in non-guideline developmental studies where the animals were exposed to the chemical at doses >900 mg/kg bw/day. Other *in vitro* studies have indicated that the chemical is teratogenic to both mouse and rat embryos (US EPA 2003). Based on the weight of evidence and severity of defects in animal studies, hazard classification for developmental toxicity is warranted.

Reproductive toxicity studies

In a non-guideline one generation reproduction toxicity study, male Long Evans rats (18–19/dose) were administered the sodium salt of the chemical *via* gavage once daily at 0, 31.25, 62.5 or 125 mg/kg bw/day for 10 weeks. After the chemical exposure period, males were mated with a female that had not been exposed to the chemical. After successful mating, the females were allowed to progress to gestation day (GD) 14. Pregnant females were then examined for the number of live and dead implants, resorbed fetuses, and corpora lutea. There were reduced body weights in the males at termination (day 75) in the 62.5 and 125 mg/kg bw/day groups. There were significant decreases in the absolute weight of the epididymis and preputial gland in all dosed males. However, absolute testes weights did not change significantly during the study. The treated males from the 62.5 and 125 mg/kg bw/day groups had significantly reduced sperm motility, sperm motions and epididymis sperm and counts. In the highest dosed group, there were also reduced prostate and seminal vesicle weights and increased relative testes weights. No gross pathological changes in the testes or histopathological changes in the epididymis were reported. There was statistically significant reduction of the number of live implants per dam on GD 14 in the 125 mg/kg bw/day group. A reduced number of pregnant dams and implantation rate was reported at the high dose but this was not statistically significant. Individual animal data were not provided. The LOAEL was reported to be 31.25 mg/kg bw/day based on organ weight changes (ECHA CHEM n.d.; Toth et al. 1992; US EPA 2003).

In a reproductive toxicity study, adult male rats were administered the chemical orally at doses of 0, 18, 54, 160, 480 or 1440 mg/kg bw/day once daily, for up to a maximum of 14 days. At doses of 54 mg/kg bw/day or higher, there were observations of delayed spermiation and formation of atypical bodies. At doses of 160 mg/kg bw/day and higher, there were decreases in epididymal sperm count and increased numbers of fused epididymal sperm compared to control groups. In the 480 and 1440 mg/kg bw/day dose groups there were observations of changed sperm morphology (distorted sperm heads and acrosomes), decreases in the percentage of mobile sperm and significant reductions in epididymal weight. The NOAEL for male reproductive toxicity was 18 mg/kg bw/day for the chemical, based on observations of delayed spermiation at higher doses (ECHA CHEM n.d.; US EPA 2003).

Evidence of the testes as a target organ for the toxicity were observed in several 90 day oral repeat dose toxicity studies (see **Repeat Dose Toxicity** for full study details). Key observations that support classification of the chemical for reproductive toxicity included:

- Significant testicular degeneration, syncytial giant cell formation in the testes and decreased or no sperm production in SD rats dosed with the sodium salt of the chemical at 500–2,000 mg/kg bw/day.
- Observations of damaged sperm cells and decreases in absolute testes and epididymis weights and in Wistar rats dosed with the chemical at 323–516 mg/kg bw/day.
- Significantly decreased absolute testes weights, mild to severe degeneration of the testes, multinucleated giant cell formation in the seminiferous tubules and disrupted sperm formation in SD rats dosed with the chemical at 1,100 mg/kg bw/day.
- Adverse effects on the testes including syncytial giant cell formation and degeneration of the germinal epithelium in Beagle dogs dosed with the chemical at 12.5–72 mg/kg bw/day.

- Dose-dependent degeneration of the prostate gland and degeneration of the germinal epithelium in Beagle dogs dosed with the chemical at 50–100 mg/kg bw/day.

Developmental toxicity studies

In a prenatal developmental toxicity study conducted similarly to OECD TG 414, pregnant Long Evans rats (19–20/dose) were administered the chemical via oral gavage at 0, 14, 140 or 400 mg/kg bw/day on GD 6–15. Dams were sacrificed on GD 20 and the fetuses were examined. Maternal weight gain was significantly decreased to 63% and 77% of the control group in the 140 and 400 mg/kg bw/day groups, respectively. Absolute liver weight was increased between 3–14% in the treated groups. A dose related hypertrophy was also observed in the liver, spleens and kidneys of the 140 and 400 mg/kg bw/day groups. Compared to the control groups, there were significant:

- Decreases in foetal crown-rump length (-5%) and foetal body weights (-7%) in the 400 mg/kg bw/day group.
- Increases in incidences of soft tissue anomalies in the 140 and 400 mg/kg bw day groups.
- Increases in cardiovascular anomalies in the 400 mg/kg bw/day. There were observations of cardiovascular anomalies in the 140 mg/kg bw/day but their incidence was not statistically significant. These anomalies were typically characterised as an intraventricular septal defect between the ascending aorta and right ventricle.

The NOAEL for developmental effects was reported to be 14 mg/kg bw/day for the chemical based on effects on maternal toxicity and foetal anomalies observed at 140 mg/kg bw/day (ECHA CHEM n.d.; US EPA 2003).

In a prenatal developmental toxicity study, pregnant Long Evans rats (19–21/dose) were administered the chemical by oral gavage at 0, 900, 1,400, 1,900 or 2,400 mg/kg bw/day on GD 6–15. There were 8 mortalities in total from the 1,400 mg/kg bw/day or higher dose groups during the study. There was a significant decrease in maternal weight gain (approximately 60% that of controls) in all dosed groups. There were significant increases in absolute liver (13% to 19%), spleen (16% to 28%) and kidney (12% to 18%) in all dosed groups. Compared to the control groups, there were:

- Significant increases in mean percentage of resorbed implants per litter in all dose groups.
- Small dose-dependent decreases in foetal weights (approximately 89% of the control) and foetal crown-rump length (approximately 75–86% of the control) in all dose groups.
- Significant dose-dependent increase in the incidence of soft tissue and cardiovascular anomalies in the fetuses from all dose groups.
- Increased incidences of external malformations in the fetuses from the dams exposed at doses 1,400 mg/kg bw/day.
- Significant decreases (-27%) in the number of live fetuses per litter in the highest dose group.

No skeletal malformations were observed at any dose level. The LOAEL for development was 900 mg/kg bw/day for the chemical, based on the increased resorptions, decreased foetal weights and increased incidence of anomalies (ECHA CHEM n.d.; US EPA 2003).

In a non-guideline prenatal developmental toxicity study, pregnant Long Evans rats were administered the chemical via oral gavage at 1,900 mg/kg bw/day on consecutive days between GD 6–15 or 2,400 mg/kg bw once between GD 10–13; or 3,500 mg/kg bw once between GD 9–13. In the 1,900 mg/kg bw/day group, there were observations of decreased body weights of the fetuses from dams exposed to the chemical between GD 6–8 and increased cardiac malformations in pups from dams exposed to the chemical between either GD 9–11 or 12–15. An increased incidence of cardiac defects was also reported in the

foetuses from dams that were exposed to single doses of 2,400 or 3,500 mg/kg bw of the chemical. The LOAEL was reported to be 1,900 mg/kg bw/day for the chemical, based on changes in foetal body weight and increased malformations at this dose (ECHA CHEM n.d.; US EPA 2003).

In a non-guideline developmental study, pregnant CDR(CD) SD rats were administered the chemical orally at 300 mg/kg bw/day between GD 6–15. There were observations of reduced maternal weights and reduced foetal weights. There were no increases in heart malformations reported in the study (ACGIH 2005).

Neurotoxicity

Based on the available data, the chemical is expected to be neurotoxic, warranting hazard classification. In humans, the chemical was reported to cause sedation, drowsiness, dizziness and/or peripheral neuropathy after repeated exposures. In rat studies, the chemical induces neurotoxicity characterised by altered gait, decreased grip strength, decreased righting reflex and decreased motor activity from doses of 16 mg/kg bw/day after exposure for 12–13 weeks. In 90 day repeat dose studies in rats and dogs, the chemical induced brain lesions on the cerebrum and cerebellum (responsible for motor activity) were observed, and it is plausible that these lesions are related to observed neurotoxicity (see **Repeat Dose Toxicity**).

Studies in rats

In a chronic neurotoxicity study, weanling rats were initially administered the chemical in drinking water at 2.5 or 3.5 g/L for 24 months. The doses were reduced and/or stopped due to excessive toxicity, resulting in an average exposure of 235 mg/kg bw/day over 6 months for the high dose group and 137 mg/kg bw/day over 24 months for the low dose group. During the study, in greater than 50% of the animals from both dose groups, there were severe gait abnormalities, decreased hind limb grip strength, righting deficits and tremors. There were also observations of decreased forelimb grip strength, chest clasp and inhibited pupil response throughout the 2 year period. The neurotoxicity was considered permanent, with no evidence of recovery after 18 months (US EPA 2003).

The potential for neurotoxicity was tested in a related series of experiments in rats exposed to the chemical by oral gavage or drinking water for acute, subchronic and chronic exposures. These studies were not performed according to guideline and did not employ control groups. **Table 5** shows a summary of these studies and indicates the LOAEL for neurotoxicity. At higher doses of the chemical, both strains of rats exhibited adverse effects such as: decreased fore and hind limb grip strengths, altered righting reflex, lower motor activity, tremor, decreased muscle tone and decreased pupil reflexes. In some studies there was partial recovery of some of the reported neurotoxic effects. However, detailed data was not available for all studies (US EPA 2003).

Table 5 – Subchronic neurotoxicity studies of the chemical in rats. The chemical was administered in drinking water unless otherwise stated (US EPA 2003)

Rat Age/Strain	Doses (mg/kg bw/day)	Duration of exposure (weeks)	LOAEL (neurotoxicity) and observations
Adult Long Evans	30, 100, 300, 1,000 (by oral gavage)	10 (plus 1 week recovery)	300 mg/kg bw/day based on altered gait
Adult Long Evans	23, 122, 220	8 (plus 2 weeks recovery)	122 mg/kg bw/day based on altered gait, decreased fore and hind limb grip strength
Adult F344	18, 91, 167	8 (plus 2 weeks recovery)	18 mg/kg bw/day based on altered gait.
Weanling F344	162, 308	12 (plus 5 weeks recovery)	162 mg/kg bw/day based on abnormal gait, decrease fore and hind limb grip strength, altered righting reflex, lower motor activity
Weanling F344	16, 66, 172	12 (plus 15 weeks recovery)	16 mg/kg bw/day based on altered gait
Weanling F344	176 (by oral gavage)	12 (plus 15 weeks recovery)	176 mg/kg bw/day based on altered gait
Weanling Long Evans	17, 88, 192	13	17 mg/kg bw/day based on abnormal gait
Weanling F344	16, 89, 173	13	16 mg/kg bw/day based on abnormal gait

Observation in humans

The available evidence in humans demonstrates that repeated doses of the chemical can induce sedation. However, the available evidence is from clinical reports where the subjects were being treated with the chemical for different underlying conditions (US EPA 2003). These conditions may confound the results and dose levels at which sedative effects are reported.

In a review of approximately 25 years of clinical use of the chemical, over 50% of subjects that received between 25 and 50 mg/kg bw/day of the chemical either orally or intravenously had reported sedative effects (US EPA 2003).

In clinical studies investigating the potential therapeutic uses of the sodium salt of the chemical, the following adverse effects were reported (ACGIH 2005; US EPA 2003):

- Mild sedation in subjects administered approximately 43–57 mg/kg bw/day of the sodium salt of the chemical for 6–7 days.

- Drowsiness, moderate sedation and temporary nausea were reported in subjects receiving 50 mg/kg bw of the chemical, five 30 minute infusions every 2 hours. No adverse effects were reported in subjects dosed in the same way with 10 or 25 mg/kg bw of the chemical.
- Dose-dependent increase in reports of headache, dizziness and somnolence in subjects receiving two 30 minute infusions that were 8 hours apart at doses ranging from 15–100 mg/kg bw.

Three cases of peripheral neuropathy were reported in subjects receiving the chemical at doses 40–80 mg/kg bw/day for 16–20 weeks. The neurotoxic effects were reversed 6 months after stopping treatment with the chemical. In one case, treatment with the chemical at lower doses of 10–25 mg/kg bw/day was tolerated for a further 2 years with no signs of neurotoxicity (ACGIH 2005; US EPA 2003). In another study, nerve conduction velocities were measured in 27 patients receiving 50 mg/kg bw/day for 1 year. Twelve of the subjects who had prior normal baseline physiology exhibited neuropathy (decreased nerve conduction velocities) at the end of treatment (US EPA 2003).

Human health risk characterisation

Critical health effects

The critical health effect for risk characterisation from chronic exposures to the chemical is carcinogenicity. The US EPA previously determined the benchmark dose lower confidence limit (BMDL) of 2.1 mg/kg bw/day for cancer effects derived from the fit of the multistage model to the cancer incidence data from the 100 week study in B6C3F₁ mice (see **Carcinogenicity**). The weight of evidence above (see **Genotoxicity** and **Carcinogenicity**) indicates that the chemical is a threshold carcinogen therefore, use of the BMDL as the point of departure is considered appropriate.

As the BMDL is lower than any of the NOAEL values or LOAEL values (with uncertainty factors of 3 applied) for all systemic effects including reproductive and developmental toxicity and neurotoxicity, this point of departure is suitable for risk assessment and considered sufficiently protective for all endpoints.

Public risk

A quantitative risk assessment using a MOE methodology was used to characterise the risk to human health associated with systemic exposure to the chemical following end use of these chemicals. The MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB 2003).

The MOE risk estimate provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. In general, an MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

The starting points for risk characterisation were the conservative estimated systemic exposure levels (see **Human exposure**). Using the BMDL of 2.1 mg/kg bw/day, MOEs were calculated for chronic exposures to the chemical in rinse-off products used:

- by adults
- as an impurity in other products used by adults

- as an impurity in products used by children between 0 and 3 years of age.

The MOE values are shown in **Table 6**. All of the MOE values exceeded 100. The combined exposure to the chemical as an ingredient in rinse-off and leave-on products (0.020 mg/kg bw/day) would also result in an MOE greater than 100. In addition, this is a conservative estimate since it assumes simultaneous use of all products containing the chemical at the highest concentration identified and 100% dermal absorption. Therefore, it is unlikely that the chemical poses a health risk in cosmetic products either as a component of the product or as an impurity.

Table 6 – Margins of exposure for worst case scenario exposures to the chemical in cosmetic products and as an impurity in cosmetic products

Scenario	Daily systemic exposure (mg/kg bw/day)	Margin of exposure (MOE)
Rinse-off cosmetic products (adult)	0.0088	240
Impurity in leave-on cosmetic products (adult)	0.011	190
Impurity in rinse of baby products (0–1 years old)	0.013	160
Impurity in rinse of baby products (1–3 years old)	0.0056	380

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