Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

1,4-Dioxane

Evaluation statement

30 June 2022

Table of contents

Contents

AICIS evaluation statement 4

Subject of the evaluation 4

Chemical in this evaluation 4

Reason for the evaluation 4

Parameters of the evaluation 4

Summary of evaluation 4

Summary of introduction, use and end use 4

Human health 5

Proposed means for managing risk 7

Public health 7

Workers 7

Conclusions 8

Supporting information 9

Chemical identity 9

Relevant physical and chemical properties 9

Introduction and use 9

Australia 9

International 10

Existing Australian regulatory controls 11

AICIS 11

Public 11

Workers 11

International regulatory status 12

Exposure standards 12

European Union 12
New Zealand 13
United States of America 13
Health hazard information 13
Toxicokinetics 13
Genotoxicity 14
Carcinogenicity 16
Human health risk characterisation 21
Public risk 21
References 23

AICIS evaluation statement

Subject of the evaluation

1,4-Dioxane

Chemical in this evaluation

Name	CAS registry number
1,4-Dioxane	123-91-1

Reason for the evaluation

New information has become available about risks to human health.

Parameters of the evaluation

The chemical 1,4-dioxane (CAS No. 123-91-1) is listed on the Australian Inventory of Industrial Chemicals (the Inventory). It was assessed as a Priority Existing Chemical (PEC No. 7) in 1998 under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS 1998). AICIS replaced NICNAS on 1 July 2020.

Based on the NICNAS assessment and recommendation, the chemical has been classified as a carcinogen – Category 2 (H351 Suspected of causing cancer) on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Recently, the chemical has been reassessed by several overseas regulatory programs, particularly with respect to its potential carcinogenic risk to the public and workers, based on findings from more recent long term carcinogenicity studies in rodents. Following these reviews there have been changes to permitted levels of the chemical as a contaminant in cosmetic and domestic products. This evaluation reviews the new information that has become available, identifies any risk and the proposed means of managing those risks.

Summary of evaluation

Summary of introduction, use and end use

The chemical has a number of site-limited and commercial uses. The main source of public exposure; however, is from its formation as an impurity during ethoxylation processes used to make many chemicals including ethoxylate surfactants. The chemical is reported to be present at residual concentrations in cosmetic and domestic products that contain ethoxylated chemicals. Levels in cosmetics have declined over the years with the majority of products containing <10 ppm. However, levels of up to 75 ppm (cosmetic) and 200 ppm (domestic) have been reported.

Human health

Summary of health hazards

The focus of this evaluation is on genotoxicity and carcinogenicity. The previous assessment concluded that the chemical causes irritation of the eyes, nose, throat and respiratory tract at high levels of exposure. Adverse liver and kidney effects were also observed in experimental animals after both short- and long-term exposure (NICNAS 1998).

There is sufficient evidence in animal studies to demonstrate the carcinogenic effects of 1,4-dioxane. Benign and malignant tumours were found at multiple sites (liver, nasal cavity and peritoneum), in both sexes of 2 different species (rat and mouse) after oral and inhalation exposure to the chemical

Although there are insufficient data to determine the mode of action (MOA) for dioxane carcinogenesis, the relevance to humans of either postulated threshold or non-threshold MOAs must be considered. Therefore, the classification of dioxane as Category 1B carcinogen is warranted. The conclusion of this evaluation is consistent with assessment findings by the EU RAC (2019), US EPA (2020) and UK HSE (2021).

The chemical may have genotoxic potential at high doses based on some evidence from supporting studies; however, the chemical did not induce genotoxicity in vitro, suggesting that it has no direct mutagenic potential. Overall, the available data for 1,4-dioxane are not sufficient to warrant classification for germ cell mutagenicity.

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. This evaluation does not consider classification of physical hazards and environmental hazards. The classifications for serious eye damage/eye irritation and specific target organ toxicity – single exposure, are current classifications under the HCIS and should remain unchanged. The classification for carcinogenicity is different from the current classifications in the HCIS (SWA).

Health hazards	Hazard category	Hazard statement
Serious eye damage/eye irritation	Eye Irrit. 2	H319: Causes serious eye irritation
Carcinogenicity	Carc. 1B	H350: May cause cancer
Specific target organ toxicity – single exposure	STOT SE 3	H335: May cause respiratory irritation

Summary of health risk

Public

Based on the available use information, the public may be exposed to the chemical in trace amounts (as a contaminant) by:

- skin contact during use of cosmetic, personal care and domestic products
- inhalation during use of fragrances, air fresheners and household detergents

- incidental eye contact, ingestion and/or inhalation from spray, aerosolised or loose powder products.

The lifetime cancer risk from the presence of 1,4-dioxane in cosmetic products was estimated by the European Scientific Committee on Consumer Safety (SCCS 2015). The Committee concluded that a trace level of 1,4-dioxane in cosmetic products of ≤10 ppm is considered safe. This was based on a lifetime cancer risk of 10^{-5} and determined to be equivalent to exposure of 55 µg/day. The estimated total exposure if all cosmetic products contain 10 ppm 1,4-dioxane was 87 µg/day. Given that a significant proportion of the products studied contained ≤10 ppm, the SCCS noted the total daily exposure of 1,4-dioxane will probably be considerably less than 87 µg/day.

Currently in Australia, the chemical can be present in cosmetic products at concentrations up to 100 ppm. Use of the chemical at these levels would lead to exposures significantly greater than those determined equivalent to a lifetime cancer risk of 10^{-5}.

The United States Environmental Protection Agency (US EPA 2020) estimated the cancer risk to consumers and bystanders from consumer use of cleaning and furniture care products, and laundry and dishwashing products. The EPA did not identify any risk relative to benchmarks for consumers, bystanders or the general population for any of the uses evaluated. The levels in consumer products to which public are frequently exposed were generally around 10 ppm but higher concentrations were noted in certain products.

Overall, there is a risk to the public that requires management (see **Proposed means for managing risks** section). The risk could be managed by amending the entry in the *Poisons Standard* (SUSMP).

Given that the contaminant levels of 1,4-dioxane have declined substantially over time based on recent measurements the recommended impurity limit of ≤10 ppm for cosmetic and domestic products in dilute preparations in Australia seems achievable.

Workers

During product formulation and repacking, dermal, ocular and inhalation exposure of workers to the chemical might occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, cleaning, and maintenance of equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical long term carcinogenic effects, the chemical could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risk** section).

Proposed means for managing risk

Public health

Recommendation to Department of Health

It is recommended that the delegate of the Secretary for Poisons Scheduling amend the entry in the *Poisons Standard* (SUSMP). It is recommended that the potential risks associated with the use of the chemical be managed by:

- reducing the Appendix G entry for dilute preparations from 100 ppm to 10 ppm.

Consideration should be given to the following:

- The chemical is likely to be present in a wide range of cosmetic and domestic products as a contaminant.
- The chemical is carcinogenic in both sexes of multiple species following different routes of exposure (Category 1B carcinogen).
- The chemical is prohibited for cosmetic use overseas.
- Restrictions on the impurity limit of ≤10 ppm 1,4-dioxane in cosmetic, personal care and household products in other countries (see **Restrictions – International** section).
- A level of ≤10 ppm 1,4-dioxane in cosmetic and consumer products seems achievable.

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 should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate control under the relevant jurisdictions and Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from 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 to manage risk arising from storing, handling, and using potential hazardous chemicals depend on the physical form and the manner in which chemicals are used.

These control measures may need to be supplemented with:

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

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

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 safety data sheets (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

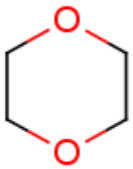
The conclusions of this evaluation are based on the information described in this statement.

Considering the 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, and the proposed means of managing the risks identified during this evaluation are implemented.

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

Supporting information

Chemical identity

Chemical name	1,4-Dioxane
CAS No.	123-91-1
Synonyms	1,4-diethylene dioxide dioxane diethylene ether glycol ethylene ether
Structural formula	
Molecular formula	C4H8O2
Molecular weight (g/mol)	88.11
SMILES	O1CCOCC1
Chemical description	mono-constituent

Relevant physical and chemical properties

The chemical is colourless and transparent liquid with characteristic odour at 20°C and 101.3 kPa. It is miscible with water, has a low partition coefficient (log Pow = −0.42 to −0.27 at 20–25°C) and high vapour pressure (5.3 kPa at 25°C) (US EPA 2020). It is classified as Flammable liquid – Category 2 (Flam. Liq. 2; H225: Highly flammable liquid and vapour) (HCIS SWA).

Introduction and use

Australia

The chemical had previous reported uses as a solvent in chemical synthesis, research and analysis and as an adhesive in celluloid film processing and as a surface coating in optical lens manufacturing industries in Australia. The chemical may be found in trace amounts (residue or byproduct) in the manufacture of other chemicals, e.g., ethoxylated chemicals or surfactants, as well as in certain imported raw materials and end use products. Such impurities may also be present in cosmetics and domestic detergents (NICNAS 1998).

International

The following international uses have been identified through the:

- European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier
- Consumer Product Information Database (DeLima Associates)
- International reviews (EU RAC 2019; Government of Canada 2021; US EPA 2020)
- technical fact sheet (US EPA 2017).

The chemical has no reported cosmetic uses in EU and USA. However, it may be present as a trace contaminant in some cosmetics during the manufacturing process of certain cosmetic ingredients (SCCS 2015; US FDA 2022). Concentrations up to 75 ppm have been reported in a range of cosmetic products, including shampoo, conditioner, shower gel and skin moisturiser (Government of Canada 2010). Surveys conducted in the USA from 1981 to 2018 showed the number of products containing levels of 1,4-dioxane greater than 10 parts per million (ppm) had declined (US FDA 2022). A consolidation of data from 170 products showed that 96% of products had levels below 25 ppm and 90% at 10 ppm or less (ICCR 2017).

The chemical is reported to be present at residual concentrations in domestic products that contain ethoxylated chemicals. Examples of domestic products potentially containing 1,4-dioxane as a residual contaminant are:

- air fresheners
- detergents, cleaning and laundry products
- automotive and marine products (e.g., ethylene glycol-based antifreeze coolants)
- paints, lacquers, varnishes
- inks
- spray polyurethane foam
- textile dyes
- adhesives.

The chemical has reported commercial uses including in:

- baseboard strippers
- degreasers
- polishers
- water treatment products
- cooling liquids
- oil based electric heaters
- adhesive and sealants (professional film cement)
- printing and printing compositions
- dry film lubricant
- inks used in additive manufacturing.

The main use of dioxane as a stabiliser for 1,1,1-trichloroethane (TCA) was discontinued by 1996.The chemical has reported site limited uses:

- as a specialty solvent in manufacture of chemicals, intermediates, paints, lacquers, wood pulp, lubricants, greases, and articles
- in formulation

- in polymers as crosslinking agent
- in pH regulators.

The chemical has reported non-industrial uses as a purifying agent in pharmaceuticals and in insecticides.

Existing Australian regulatory controls

AICIS

Specific information requirements apply for the following circumstances:

a. the function or use of 1,4-dioxane has increased, or is likely to change, significantly
b. the amount of 1,4-dioxane introduced into Australia has increased, or is likely to increase, significantly
c. manufacture of 1,4-dioxane has begun in Australia
d. additional information has become available to the applicant/notifier as to the adverse health and/or environmental effects of 1,4-dioxane
e. levels of 1,4-dioxane in consumer products exceed 100 ppm.

Under *section 101 of the IC Act,* the AICIS Executive Director must be notified within 28 days of the applicant/notifier becoming aware of any of the above circumstances.

Public

The chemical 1,4-dioxane is listed in the *Poisons Standard* (SUSMP 2022) in:

- Schedule 6 (Poison – Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label).
- Appendix E, Part 2 (First Aid instructions).
- Appendix F, Part 3 with Safety Directions:
  - Avoid contact with eyes.
  - Avoid contact with skin.
  - Avoid breathing dust (or) vapour (or) spray mist.
- Appendix G
  - The requirements of this Standard do not apply to 1,4-dioxane at ≤100 mg in dilute preparations.

Workers

The chemical is currently listed on the Hazardous Chemical Information System (HCIS SWA) with the following hazard category and statements:

Health hazards	Hazard category	Hazard statement
Flammable liquid	Flam. Liq. 2	H225: Highly flammable liquid and vapour
Serious eye damage/eye irritation	Eye Irrit. 2	H319: Causes serious eye irritation
Carcinogenicity	Carc. 2	H351: Suspected of causing cancer

Health hazards	Hazard category	Hazard statement
Specific target organ toxicity – single exposure	STOT SE 3	H335: May cause respiratory irritation

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

- 8 hour time weighted average (TWA) = 10 ppm (36 mg/m^3) with notes for skin notation (Sk) and carcinogenicity.

In 2019, Safe Work Australia reviewed and recommended to amend this TWA. A TWA of 5 ppm (18 mg/m^3) is recommended to protect for irritation of the eye, effects in the upper respiratory tract and cancer in exposed workers. The notations of Carc. 2 and Sk. were recommended, with the skin notation based on evidence in humans (SWA 2019).

At the time of publication of this evaluation statement, these values were yet to be finalised.

International regulatory status

Exposure standards

The chemical has the following workplace exposure standards (ECHA 2021a; OSHA 2020):

- 8 hour time weighted average (TWA):
  - EU OEL (occupational exposure limit) = 20 ppm or 73 mg/m^3 (current)
  - EU OEL = 6 ppm or 22 mg/m^3; skin notation (recommended as of 27/09/2021)
  - ACGIH TLV (threshold limit value) = 20 ppm; skin notation
  - OSHA PEL (permissible exposure limit) = 100 ppm or 360 mg/m^3; skin notation.

- short term exposure limit (STEL):
  - EU STEL (15 min) = 20 ppm or 73 mg/m^3 (recommended as of 27/09/2021)
  - NIOSH Ceiling (30 min): 1 ppm or 3.6 mg/m^3.

European Union

The chemical is listed in:

- Cosmetics Regulation No 1223/2009, Annex II – List of substances prohibited in cosmetic products (CosIng II/343; EC 2009). The Cosmetics Regulation (EC) No 1223/2009 states that ‘in order to ensure product safety, prohibited substances should be acceptable at trace levels only if they are technologically inevitable with correct manufacturing processes and provided that the product is safe’.

- The chemical is listed on the Candidate List of substances of very high concern (SVHC) for Authorisation for eventual inclusion in Annex XIV (ECHA 2021b). The reason for inclusion in the list is the chemical is considered ‘carcinogenic (Article 57a) and equivalent level of concern having probable serious effects to human health and environment (Article 57f)’. In the European Union (EU), the inclusion in the Candidate List brings immediate obligations for suppliers of the substance, such as:
  - supplying a safety data sheet

- communicating on safe use
- responding to consumer requests within 45 days
- notifying ECHA if the article they produce contains an SVHC in quantities above one tonne per producer/importer per year and if the substance is present in in those articles above a concentration of 0.1% (w/w).

New Zealand

The chemical is listed on the New Zealand Environmental Protection Authority (NZ EPA)'s Chemical Classification and Information Database (CCID):

- Acute toxicity – Category 4
- Eye irritation – Category 2
- Carcinogenicity – Category 1
- Specific Target Organ Toxicity Repeated Exposure – Category 2.

United States of America

According to the National Law Review (2020):

New York has imposed the following limits on the permissible amount of 1,4-dioxane in:

- Cosmetic products:
  - 10 ppm by 31 December 2022

- Personal care and household cleaning products:
  - 2 ppm by 31 December 2022
  - 1 ppm by 31 December 2023

California has adopted warning or disclosure requirements for 1,4-dioxane (as a carcinogen) in products. Manufacturers of cosmetics sold in the state must provide a list of their cosmetic products that contain a chemical identified as a carcinogen. For personal care and cleaning products, the threshold of 1,4-dioxane is 10 ppm for manufactures to disclose on the product label and on the product's internet website information related to chemicals contained in the designated product.

Health hazard information

Toxicokinetics

The chemical is readily absorbed following oral and inhalation, and to a limited extent, through the skin (IARC 1999; NICNAS 1998; SCCS 2015; US FDA 2022). Its low partition coefficient (log Pow = −0.42 to −0.27 at 20–25 °C) and high volatility are not favourable for the chemical to cross the stratum corneum or have sufficient contact time for absorption. However, a fatal case of intoxication was reported when the worker was extensively exposed to high concentrations of 1,4-dioxane, both dermally from a cleaning agent and via inhalation for one week (Johnstone 1959).

The chemical is rapidly distributed to the liver, kidney, spleen, lung, colon and skeletal muscle tissue. Humans, rats and mice metabolise and eliminate dioxane extensively in urine as β-hydroxyethoxyacetic acid (HEAA). In rat and human studies, metabolism is dose dependent and can become saturated at high doses, as evidenced by changes from linear to

non-linear pulmonary and urinary elimination kinetics with increasing doses (Young et al. 1977; 1978). Considering the toxicity of target organs at high daily doses of 1,4-dioxane, saturation is presumed to be associated with the detoxification rather than elimination (EU RAC 2019; NICNAS 1998; SCCS 2015).

Genotoxicity

Data on human or animal germ cell mutagenicity are limited. In vivo genotoxicity results for 1,4-dioxane in somatic cells were inconsistent. An increase in micronucleus formation was reported in several studies in bone marrow cells and hepatocytes, but not in peripheral blood cells. For majority of the studies, the doses causing micronucleus induction in bone marrow cells and in hepatocytes were at or above the limit dose of 2000 mg/kg bw. These study protocols were not compliant with the OECD Test Guideline (TG) 474 (Mammalian Erythrocyte Micronucleus Test). In addition, data on cytotoxicity were not available for most of the in vivo studies so the interpretation of the results was limited, including positive results at doses below 2000 mg/kg bw. The chemical may have genotoxic potential at high doses based on some evidence from supporting studies. However, the chemical did not induce genotoxicity in vitro, suggesting that it has no direct mutagenic potential. Overall, the available data for 1,4-dioxane are not sufficient to warrant classification for germ cell mutagenicity.

The genotoxicity of 1,4-dioxane has been extensively evaluated, and is summarised as follows (EU RAC 2019; NICNAS 1998; UK HSE 2021; US EPA 2020):

In vitro studies

Negative test results for 1,4-dioxane were reported in:

- 6 reverse mutation assays in bacterial cells
- 2 gene mutation assays in mouse lymphoma cells
- a micronucleus assay in Chinese hamster ovary (CHO) cells
- 2 chromosome aberration assays in CHO cells
- a sister chromatid exchange (SCE) assay in CHO cells
- an unscheduled DNA synthesis (UDS) assay in rat hepatocytes.

1,4-Dioxane induced DNA damage in a comet assay in rat hepatocytes at cytotoxic concentrations of equal to or greater than 0.3 mM.

In vivo studies (somatic cells)

Genotoxicity studies for 1,4-dioxane in somatic cells in mice indicated conflicting results.

No induction of micronuclei was observed in:

- bone marrow cells of Fischer 344 (F344) rats at doses up to 3000 mg/kg bw (oral gavage) (Itoh and Hattori 2019)

- bone marrow cells of B6C3F1 mice at doses up to 4000 mg/kg bw (intraperitoneal injection (ip)):
  - in 1/2 ip studies, a ratio of polychromatic erythrocytes / normochromatic erythrocytes (PCE/NCE) was decreased, indicating the bioavailability and cytotoxicity in the bone marrow.

    - in follow up studies, a decreased PCE/NCE ratio was observed in 1/3 studies in CBA or C57BL6 mice at 1800–3600 mg/kg bw (oral gavage).

- peripheral blood cells (2 studies) of CD-1 mice at doses up to 3000 mg/kg bw (oral gavage) and 3200 mg/kg bw (ip).

Induction of micronuclei was observed in:

- bone marrow cells after oral gavage exposure in
    - C57BL6 mice at 900–3600 mg/kg bw (dose dependent response).
    - CD-1 mice at 1500–3500 mg/kg bw (dose dependent response), associated with 16–37% decrease in PCE/NCE ratio, and 80–90% micronuclei caused by chromosome breakage.

- hepatocytes of F344 rats at 1000–3000 mg/kg (Itoh and Hattori 2019).

- hepatocytes (2 studies) of CD-1 mice at 2000–3000 mg/kg bw with induction of cell proliferation, and at 2500–3500 mg/kg bw with 80–90% micronuclei caused by chromosome breakage.

Supporting in vivo studies that reported negative results include:

- no alkylation of hepatic DNA or DNA repair (2 studies) in F344 and Sprague Dawley (SD) rats at a cytotoxic dose of 1000 mg/kg bw (treatment for 1 and 10 weeks via drinking water, respectively).

- UDS studies in rat hepatocytes (6 studies) and nasal epithelial cells (1 study).

Supporting in vivo studies that reported positive results include:

- a dose related increase in hepatic DNA single strand breaks in a comet assay (1 study) in female SD rats at 2550–4200 mg/kg bw (oral gavage), with no significant cytotoxicity.

- replicative DNA synthesis (RDS) assays (2 studies) in rat hepatocytes:
    - an increase in RDS or cell proliferation at 2000 mg/kg bw, cytotoxicity at 1000–2000 mg/kg bw (a non-validated test method).
    - a dose related increase in RDS at 1000, 1500, and 2000 mg/kg bw, but no significant increase at 4000 mg/kg bw after 24h; no RDS increase at any test concentration after 48h; no data on hepatocytotoxicity available. In a time-course experiment, results were equivocal: an increase in RDS at 2000 mg/kg bw after 24h was reported in one experiment, but only after 48h in another experiment.

These 2 RDS studies with positive results were reported at doses equal to or below the limit dose of 2000 mg/kg bw, indicating that 1,4-dioxane might stimulate cell proliferation (EU RAC 2019).

In vivo studies (germ cells)

No acceptable animal studies are available for evaluation of germ cell mutagenicity for 1,4-dioxane although negative results were reported in:

- a sex linked recessive lethal mutagenicity test in fruit flies (*Drosophila melanogaster*)

- a dominant lethal study in male NMRI mice at 2550 mg/kg bw. The study had methodological deficiencies such as no positive control or reporting of toxicity.

Human studies

No induction of chromosomal aberrations was reported in peripheral lymphocytes in 6 German workers exposed to unspecified airborne levels of 1,4-dioxane over 6–15 years, compared with 6 controls. The study is of limited statistical power.

Carcinogenicity

Based on the available data and weight of evidence analysis, the chemical is presumed to have carcinogenic potential for humans, warranting classification as a Category 1B carcinogen. There is sufficient evidence from well performed animal studies to demonstrate the relevance of tumour formation by 1,4-dioxane in rodents to humans. In addition, there are well conducted mechanistic studies to confirm the liver carcinogenesis of 1,4-dioxane at the molecular level in both rats and mice.

Animal studies consistently show carcinogenic effects of 1,4-dioxane. Effects include tumour formation (both benign and malignant) at multiple sites, in 2 different species (both sexes), via relevant exposure routes (oral and inhalational) and at reasonable exposure levels.

Previous data indicated that 1,4-dioxane was carcinogenic to both sexes of rats, producing nasal carcinomas and hepatocellular adenomas and/or carcinomas; and to both sexes of mice, producing hepatocellular adenomas and/or carcinomas following long term exposure via drinking water (Kociba et al. 1974; NCI 1978). Hepatocellular and renal tubular degeneration and necrosis, as well as hepatocellular regenerative hyperplasia preceding tumour were observed following exposure to toxic levels of ≥1015 mg/kg bw/day 1,4-dioxane (Kociba et al. 1974).

Post 1998, 2 year OECD TG compliant studies by Kano et al. (2009) via drinking water and Kasai et al. (2009) by inhalation have confirmed the carcinogenic properties of 1,4-dioxane. Both studies similarly reported hepatocellular adenoma/carcinoma in both sexes of rats and mice, nasal squamous cell carcinoma in rats, and rare olfactory neuroblastoma and adenocarcinoma in mice. Histopathological findings (e.g., centrilobular swelling and/or necrosis of hepatocytes, and nuclear enlargement and/or squamous cell hyperplasia in the nasal cavity) from the 13 week repeated dose toxicity studies (Kano et al. 2008; Kasai et al. 2008) were consistent with the observed adenomas/carcinomas or preneoplastic lesions progressing to carcinomas in the 2 year studies (Dourson et al. 2014; 2017; EU RAC 2019; UK HSE 2021).

No data on non-neoplastic histopathology were available for peritoneal mesotheliomas in the male F344 strain rats although the tumours were noted following both oral and inhalation exposures. In the absence of information to indicate otherwise, this type of tumour is considered relevant to humans.

Potential carcinogenic effects of 1,4-dioxane from long term exposure in humans or from dermal exposure in animals are not well characterised. 2 animal studies on dermal exposure and 2 studies on intraperitoneal injection were of low quality and; therefore, not discussed in this evaluation.

The carcinogenicity of 1,4-dioxane has been extensively evaluated for oral and inhalation exposures, and they are summarised as follows (EU RAC 2019; NICNAS 1998; UK HSE 2021; US EPA 2020):

Oral (drinking water)

One new study post NICNAS PEC 1998

In a 2 year study (OECD TG 451; Kano et al. 2009):

- F344/DuCrj rats (50/sex/dose) at 0, 200, 1000, 5000 ppm (w/w) in drinking water (M-F: 0, 11–18, 55–83, 274–429 mg/kg bw/day), effects at the highest dose were:
  - hepatocellular adenomas (M 32/50; F 48/50) and carcinomas (M 14/50; F 10/50)
  - peritoneal mesotheliomas (M 28/50)
  - nasal squamous cell carcinomas (M 3/50; F 7/50)
  - mammary gland adenomas or fibroadenomas combined (M 6/50; F 18/50), and mammary gland adenomas (F 16/50)
  - preneoplastic or altered hepatocellular foci (M at ≥1000 ppm; F at 5000 ppm)
  - decreased survival rates, growth rates and terminal body weights (M 22/50; F 24/50 alive for examination at 2 years)
  - increased relative liver weights (M at ≥1000 ppm; F at 5000 ppm).

- Crj:BDF1 mice (50/sex/dose) at 0, 500, 2000, 8000 ppm (w/w) in drinking water (M-F: 0, 49–66, 191–278, 677–964 mg/kg bw/day):
  - hepatocellular adenomas or carcinomas combined (M 37/50 and 40/50 at ≥2000 ppm; F 35/50, 41/50, and 46/50 at ≥500 ppm, respectively)
  - nasal tumours at the highest dose (M 1/50 esthesioneuroepithelioma or olfactory neuroblastoma; F 1/50 adenocarcinoma)
  - decreased survival rates (F at ≥2000 ppm), decreased growth rates and terminal body weights (M-F at ≥2000 ppm), and decreased food and water consumption (M-F at 8000 ppm)
  - increased relative liver weight (M at ≥2000 ppm; F at 8000 ppm).

Five studies pre 1998

In a long term carcinogenicity study (NCI 1978):

- Osborne Mendel rats (35/sex/dose) at 0, 0.5, 1% in drinking water (M-F: 0, 240–350, 530–640 mg/kg bw/day for 110 weeks)
  - hepatocellular adenomas at 0.5% and 1% (F 10/33 and 11/32)
  - nasal squamous cell carcinomas at 0.5% and 1% (M 12/33 and 16/34; F 10/35 and 8/35)
  - decreased survival rates in both sexes at ≥0.5%
  - pneumonia (M 15/31 and 14/33 at 0.5% and 1%; F 25/32 at 1%).

- B6C3F1 mice (50/sex/dose) at 0, 0.5, 1% in drinking water (M-F: 0, 720–380, 830–860 mg/kg bw/day for 90 weeks)
  - hepatocellular carcinomas at 0.5% and 1% (M 18/50 and 24/47; F 12/48 and 29/37), and hepatocellular adenomas or carcinomas combined at 0.5% and 1% (M 19/50 and 28/47; F21/48 and 35/37)
  - decreased survival rates (F at ≥0.5%)
  - hepatic cytomegaly, pneumonia and rhinitis (M-F at ≥0.5%).

In a 716 day study (Kociba et al. 1974):

- Sherman rats (60/sex/dose) at 0, 0.01, 0.1, 1% in drinking water
  (M-F: 0, 9.6–19, 94–148, 1015–1599 mg/kg bw/day), effects at the highest dose were:
  - hepatocellular carcinomas (M-F 10/66), or hepatic tumours, all types (12/66)
  - nasal squamous cell carcinomas (M-F 3/66)
  - decreased survival rates, body weight gain, and water consumption
    (M-F 66/120 alive for examination at 12 months)
  - increased absolute and relative liver weight (M-F)
  - hepatocellular and renal tubular epithelial degeneration and necrosis at ≥0.1%
    (accompanied by regenerative activity), and hepatocellular regenerative hyperplastic
    nodule formation at 1%.

In a 13 month study (Hoch-Ligeti et al. 1970):

- SD rats (30 males/dose) at 0, 0.75, 1, 1.4, 1.8% in drinking water
  (0, 430, 574, 803, 1032 mg/kg bw/day):
  - hepatocellular carcinomas at ≥1.4% (2/30 and 2/30, respectively)
  - nasal squamous cell carcinomas at ≥0.75% (1/30, 1/30, 2/30, 2/30, respectively).

In a 63 week study (Argus et al. 1965):

- Wistar rats (9 males/control vs 26 males at 1%) in drinking water
  (0, 640 mg/kg bw/day):
  - liver tumours (6/26)
  - severe kidney damage.

In a 42 week study (King et al. 1973):

- Osborne Mendel rats (35/sex/dose) at 0, 0.5, 1% in drinking water for 42 weeks:
  - non-neoplastic liver lesions at both doses (M 1/6 and 1/11; F 1/3 and 2/5)
  - non-neoplastic lung lesions at both doses (M 6/6 and 8/11; F 3/3 and 3/5)
  - decreased survival rates at both doses (M 26/35 and 24/35; F 32/35 and 20/35 alive
    at 42 weeks).

- B6C3F1 mice (50/sex/dose) at 0, 0.5, 1% in drinking water for 40–43 weeks:
  - no significant pathological changes
  - minimal effects on survival rates observed.

Inhalation (2 studies)

One new study post NICNAS PEC 1998.

In a 2 year inhalation study (OECD TG 453; Kasai et al. 2009):

- F344/DuCrj rats (50 males/dose) at 0, 50, 250, 1250 ppm (v/v)
  (0, 0.18, 0.9, 4.5 mg/L dioxane vapour) for 6 hours/day, 5 days/week
  - hepatocellular adenomas (21/50) at 1250 ppm
  - nasal squamous cell carcinomas (6/50) at 1250 ppm
  - peritoneal mesotheliomas (14/50, 41/50) at 250 and 1250 ppm
  - preneoplastic lesions such as nasal squamous cell metaplasia (≥250 ppm),
    hyperplasia (1250 ppm) and altered hepatocellular foci and necrosis (1250 ppm)
  - non-neoplastic lesions such as atrophy, respiratory metaplasia, and nuclear
    enlargement in the nasal cavity from low dose (≥50 ppm), as well as nuclear

enlargement in renal proximal tubules from mid dose, and in centrilobular hepatocytes at high dose
    - decreased survival rates at mid and high dose (M 29/50 and 25/50, respectively), and terminal body weight (<10%) at high dose
    - increased relative liver weight and enzymes (liver injury) at high dose.

One study pre-1998.

In a 2 year inhalation study (Torkelson et al. 1974):

- Wistar rats (192/sex/control vs 288/sex at 111 ppm) (0, 0.4 mg/L dioxane vapour) for 7 hours/day, 5 days/week
    - no systemic effects, hepatocellular or nasal carcinomas observed.

Given the very low levels of exposure, together with no examination of the nasal cavity for any non-neoplastic or preneoplastic lesion, this study was excluded from the evaluation of carcinogenic potential of 1,4-dioxane (EU RAC 2019).

Supporting (dose range finding) studies:

In two 13 week studies, 1,4-dioxane was administered to F344/DuCrj rats and Crj:BDF1 mice at a dose range of 0–25000 ppm in drinking water (OECD TG 408; Kano et al. 2008), and to the same strain of rats at 0–6400 ppm by inhalation, 6h/day and 5 days/week (OECD TG 413; Kasai et al. 2008). Histopathological findings were similar in both studies, revealing lesions in the liver and nasal cavity (respiratory, olfactory, tracheal, and bronchial epithelia). The effects were reported in a dose related manner in both sexes of rats and mice, and through both routes of exposure, although locations of enlarged nuclei varied between the 2 species and routes of exposure. Nuclear enlargement (hypertrophy) of nasal respiratory epithelial cells was the most sensitive in rats in both studies (by 6h inhalation exposure at ≥100 ppm or 73 mg/kg bw/day, or via drinking water at ≥1600 ppm or 126 mg/kg bw/day). Preneoplastic lesions such as altered hepatocellular foci were also reported in rats at higher doses. Dioxane-induced liver lesions were characterised by single cell necrosis and centrilobular swelling of hepatocytes in both sexes of rats and mice (at ≥4000 ppm or 585 mg/kg bw/day). These early histopathological changes were considered supportive evidence for the 2 year carcinogenicity studies (Dourson et al. 2014; 2017; EU RAC 2019; UK HSE 2021).

Human studies

Limited human data are available. Three epidemiological studies for occupational settings all were of small cohort sizes, limited latency periods and low statistical power, as well as exposures were at low levels and/or for relatively short duration. They were considered inconclusive for evaluation of 1,4-dioxane carcinogenic potential in humans (EU RAC 2019; NTP 2021)

- In a cross-sectional study of 74 German workers (24 workers exposed to dioxane at up to 13 ppm for 5–51 years, 23 others previously exposed for 3–38 years, and 27 pensioners for 12–41 years), no increases in liver or kidney cancer or cancer related mortality were reported, compared to the general population. Two fatalities among the retired workers were diagnosed with squamous epithelial carcinoma and myelofibrosis leukemia, with no confirmation of a causal relationship due to other confounding factors (Thiess et al. 1976; US EPA 2020).

- In a prospective study of 165 US workers exposed to dioxane (<25 ppm or 0.09 mg/L for <5 years) since 1954, no significant differences between observed deaths from overall cancer and expected number of deaths (based on Texas 1960–1969 mortality rates). There were 7 and 5 deaths with 2/7 and 1/5 from cancer, reported from a dioxane manufacturing and a processing department, respectively (Buffler et al. 1978; US EPA 2020).

- In a retrospective study of 80 'dioxane workers' where airborne dioxane concentrations were up to 36.7 ppm or 0.132 mg/L, 4 cancer deaths (colonic cancer, pulmonary carcinoma, lymphosarcoma, and glioblastoma) were reported. The observed cancer deaths were not significantly different from expected deaths (NTP 2021).

Mode of action

There are insufficient data to determine the exact mode of action (MOA) for dioxane-induced carcinogenesis. However, the postulated threshold or non-threshold MOAs for dioxane are still relevant to humans. Exposure to the chemical can produce tumours at multiple sites, in both sexes of rats and mice at reasonable levels of exposure and cannot be discounted (EU RAC 2019; NICNAS 1998; UK HSE 2021; US EPA 2020).

Limited data are available for the MOA of nasal squamous cell carcinomas and peritoneal mesotheliomas caused by dioxane. For liver tumours, a number of possible mechanisms have been proposed, including tumour promotion, mutagenic or genotoxic MOA, or metabolic saturation, then cytotoxicity followed by regenerative hyperplasia MOA in rats and mice (Bull et al. 1986; Chappell et al. 2021; Chen et al. 2022; Dourson et al. 2014; 2017; Gi et al. 2018; Kano et al. 2008; Kasai et al. 2008; King et al. 1973; Lafranconi et al. 2021).

Although the mechanistic studies have certain limitations and inconsistent results, they collectively have confirmed the carcinogenicity of 1,4-dioxane with key events at the molecular level in both rats and mice. Considering the toxicokinetic similarities between rodents and humans (including the possible metabolic saturation at high daily doses, as well as the toxicity of the metabolite HEAA), a threshold response to 1,4-dioxane in liver carcinogenesis may be plausible. However, the current data do not allow its identification. Therefore, it is proposed that the calculation of lifetime cancer risk (LCR) is made on the basis of linear extrapolation (i.e., non-threshold response) (SCCS 2015).

The chemical causes multisite and multispecies tumour responses. In addition, evidence exists for the early histopathological changes (e.g., single cell necrosis and centrilobular swelling of hepatocytes in both sexes of rats and mice) in the 90 day studies that are consistent with liver adenomas or preneoplastic lesions progressing to carcinomas seen in the 2 year studies. Preneoplastic lesions such as altered hepatocellular foci were reported in rats at high doses in the 90 day studies (Kano et al. 2008; Kasai et al. 2008). The chemical may also have genotoxic potential in vivo at high doses, possibly as a result of various metabolic processes, although it has no direct mutagenic potential (see Genotoxicity section).

In conclusion, the available data are not sufficient to determine the MOA for dioxane carcinogenesis. This concurs with recent overseas assessments and conclusions (EU RAC 2019; UK HSE 2021; US EPA 2020).

Human health risk characterisation

Public risk

Several international reviews of the risk to the public due to the presence of the chemical as an impurity in consumer products are available. Two reviews estimated the lifetime cancer risk. These are summarised below.

The US EPA (2020) has evaluated 8 consumer uses of surface cleaners, laundry/dishwashing detergents, paint/floor lacquer, etc. where 1,4-dioxane is present as a byproduct and found no unreasonable risks. The chronic cancer risk was determined for surface cleaners, laundry and dishwashing products. Maximum concentrations of 1,4-dioxane used in the estimates were:

- 9 ppm for surface cleaner
- 204 ppm for dish soap
- 9.7ppm for dishwashing detergent
- 14 ppm for laundry detergent.

The EPA estimated potential cancer risk to 1,4-dioxane by multiplying inhalation unit risk or dermal cancer slope factors by the chronic exposure levels. Risk estimates for each use scenario were compared to benchmark margin of exposures (MOEs) or cancer risk benchmarks. The EPA used 10^{-6} as the benchmark for the cancer risk to consumers and bystanders from consumer use of cleaning and furniture care products and laundry and dishwashing products. The EPA did not identify risks relative to benchmarks for consumers, bystanders or the general population for any of the uses evaluated (US EPA 2020).

Surveys conducted in the USA reported that cosmetic products contained an average of 19 ppm 1,4-dioxane, with a range of 6–34 ppm in 1997. These trace levels had declined significantly, particularly 80% of the surveyed products in 2018 contained <1 ppm, 12% between 1–10 ppm, and 8% between 10–12 ppm 1,4-dioxane (US FDA 2022).

The European Commission's independent scientific advisory committee (Scientific Committee on Consumer Safety (SCCS)) evaluated the carcinogenic risk of traces of 1,4-dioxane in cosmetics. The SCCS did not support the NOAEL approach for 1,4-dioxane and; therefore, calculated the lifetime cancer risk (LCR) based on T25 (the chronic dose rate that will give 25% of the animal tumours at a specific tissue site) and linear extrapolation. It is recognised that linear extrapolation may in some cases result in overestimation of risks at low exposures. The SCCS considers a LCR of 10^{-5} as a tolerable risk level but notes that the decision of an acceptable/tolerable or less than serious risk is in the end a risk management decision. A LCR of 10^{-5} was calculated as representing an exposure of 55 µg/day (SCCS 2015).

Total exposure if all cosmetic products contained 10 ppm 1,4-dioxane (92% of the products studied contained ≤10 ppm) was estimated to be 87 µg/day (assuming 17.4 g/day aggregate exposure and 50% dermal absorption). The SCCS noted that 'since about 2/3 (65%) of all cosmetic products analysed contained ≤1 ppm, the total daily exposure of 1,4-dioxane will probably be considerably less than 87 µg and the LCR from 1,4-dioxane in cosmetics will probably be $<10^{-5}$ and should be considered tolerable.'

In a consolidation of data from 170 cosmetic and household products, although 96% of products had levels of 1,4-dioxane <25 ppm and 90% at ≤10 ppm, 2 shower gels and one

‘bubble bath’ products contained 1,4-dioxane between 10–25 ppm (ICCR 2017; SCCS 2015).

References

Argus MF, Arcos JC, Hochligeti C (1965) Studies on the carcinogenic activity of protein-denaturing agents: hepatocarcinogenicity of dioxane, *Journal of National Cancer Institute*, 35(6):949–958.

Buffler PA, Wood SM, Suarez L, Kilian DJ (1978) Mortality follow-up of workers exposed to 1,4-dioxane. *Journal of Occupational Medicine* 20(4):255–59.

Bull RJ, Robinson M, Laurie RD (1986) Association of carcinoma yield with early papilloma development in SENCAR mice, *Environmental Health Perspectives*, 68:11–17.

Chappell GA, Heintz MM, Haws LC (2021) Transcriptomic analyses of livers from mice exposed to 1,4-dioxane for up to 90 days to assess potential mode(s) of action underlying liver tumor development, *Current Research in Toxicology*, 12(2):30–41.

Chen Y, Wang Y, Charkoftaki G, Orlicky DJ, Davidson E, Wan F, Ginsberg G, Thompson DC, Vasiliou V (2022) Oxidative stress and genotoxicity in 1,4-dioxane liver toxicity as evidenced in a mouse model of glutathione deficiency, *The Science of the Total Environment*, 806(Pt 2):150703.

DeLima Associates (n.d.) Consumer Product Information Database (CPID) 1,4-Dioxane, Delima Associates website, accessed March 2022.

Dourson M, Reichard J, Nance P, Burleigh-Flayer H, Parker A, Vincent M, McConnell EE (2014) Mode of action analysis for liver tumors from oral 1,4-dioxane exposures and evidence-based dose response assessment, *Regulatory Toxicology and Pharmacology*, 68(3):387–401.

Dourson ML, Higginbotham J, Crum J, Burleigh-Flayer H, Nance P, Forsberg ND, Lafranconi M, Reichard J (2017) Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1,4-dioxane, *Regulatory Toxicology and Pharmacology*, 88:45–55.

EC (European Commission) (2009) Cosmetic Ingredients & Substances database (CosIng), EC website, accessed February 2022.

ECHA (European Chemicals Agency) (2021a) Draft scientific report for evaluation of limit values for 1,4-dioxane at the workplace, ECHA website, accessed March 2022.

ECHA (European Chemicals Agency) (2021b) Decision – Inclusion of substances of very high concern in the Candidate List for eventual inclusion in Annex XIV, ECHA website, accessed February 2022.

EU RAC (European Union Committee for Risk Assessment) (2019) Opinion proposing harmonised classification and labelling at EU level of 1,4-dioxane, ECHA website, accessed April 2022.

Gi M, Fujioka M, Kakehashi A, Okuno T, Masumura K, Nohmi T, Matsumoto M, Omori M, Wanibuchi H, Fukushima S (2018) In vivo positive mutagenicity of 1,4-dioxane and quantitative analysis of its mutagenicity and carcinogenicity in rats. *Archives of Toxicology*, 92(10):3207–3221.

Government of Canada (2010) Screening assessment for the challenge 1,4-dioxane, canada.ca, accessed April 2022.

Government of Canada (2021) Guidelines for Canadian drinking water quality: Guideline technical document – 1,4-Dioxane, canada.ca, accessed April 2022.

Hoch-Ligeti C, Argus MF, Arcos JC (1970) Induction of carcinomas in the nasal cavity of rats by dioxane, *British Journal of Cancer*, 24(1):164–167.

IARC (International Agency for Research on Cancer) (1999) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol 71, Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide, 1,4-Dioxane, Lyon, pp 589–602.

ICCR (International Cooperation on Cosmetics Regulation) (2017) Report of the ICCR Working Group: Considerations on acceptable trace level of 1,4-dioxane in cosmetic products, ICCR website, accessed April 2022.

Itoh S and Hattori C (2019) In vivo genotoxicity of 1,4-dioxane evaluated by liver and bone marrow micronucleus tests and Pig-a assay in rats, *Mutation Research Genetic Toxicology Environmental Mutagenesis*, 837:8–14.

Johnstone RT (1959) Death due to dioxane? *AMA Archives of Industrial Health*, 20:445–447.

Kano H, Umeda Y, Kasai T, Sasaki T, Matsumoto M, Yamazaki K, Nagano K, Arito H, Fukushima S (2009) Carcinogenicity studies of 1,4-dioxane administered in drinking-water to rats and mice for 2 years, *Food and Chem Toxicology*, 47(11):2776–2784.

Kano H, Umeda Y, Saito M, Senoh H, Ohbayashi H, Aiso S, Yamazaki K, Nagano K, Fukushima S (2008) Thirteen-week oral toxicity of 1,4-dioxane in rats and mice, Journal of Toxicological Sciences, 33(2):141–153.

Kasai T, Kano H, Umeda Y, Sasaki T, Ikawa N, Nishizawa T, Nagano K, Arito H, Nagashima H, Fukushima S (2009) 2-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats, *Inhalation Toxicology*, 21(11):889–897.

Kasai T, Saito M, Senoh H, Umeda Y, Aiso S, Ohbayashi H, Nishizawa T, Nagano K, Fukushima S (2008) Thirteen-week inhalation toxicity of 1,4-dioxane in rats, *Inhalation Toxicology*, 20(10):961–971.

King ME, Shefner AM, Bates RR (1973) Carcinogenesis bioassay of chlorinated dibenzodioxins and related chemicals, *Environmental Health Perspectives*, 5:163–70.

Kociba RJ, McCollister SB, Park C, Torkelson TR, Gehring PJ (1974) 1,4-Dioxane. I. Results of a 2-year ingestion study in rats, *Toxicology and Applied Pharmacology*, 30:275–286.

Lafranconi M, Budinsky R, Corey L, Klapacz J, Crissman J, LeBaron M, Golden R, Pleus R (2021) A 90-day drinking water study in mice to characterize early events in the cancer mode of action of 1,4-dioxane, *Regulatory Toxicology and Pharmacology*, 119:104819.

National Law Review (2020) New York, California, and EPA tackle 1,4-dioxane, National Law Forum LLC, accessed March 2022.

NCI (National Cancer Institute) (1978) Technical Report TR-80 Bioassay of 1,4-dioxiane for possible carcinogenicity, National Toxicology Program, US Department of Health and Human Services website, accessed March 2022.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (1998) Priority Existing Chemical (PEC) Assessment Report No. 7 1,4-Dioxane, AICIS website, accessed February 2022.

NIOSH (National Institute for Occupational Safety and Health) (2019) Pocket Guide to Chemical Hazards for Dioxane, Centers for Disease Control and Prevention (CDC) website, accessed March 2022.

NTP (National Toxicology Program) (2021) Report on Carcinogens – 1,4-Dioxane, 15th edn, US Department of Health and Human Services website, accessed March 2022.

NZ EPA (New Zealand Environmental Protection Authority) (n.d.) Chemical Classification and Information Database (CCID), NZ EPA website, accessed March 2022.

OSHA (Occupational Safety & Health Administration) (2020) Dioxane (diethylene dioxide), US Department of Labor website, accessed March 2022.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d) Registered dossier for 1,4-dioxane, CAS No 123-91-1, ECHA website, accessed February 2022.

SCCS (Scientific Committee on Consumer Safety) (2015) Scientific Opinion on The Report of the ICCR Working Group: Considerations on acceptable trace level of 1,4-dioxane in cosmetic products, EC website, accessed April 2022.

SWA (Safe Work Australia) (2019) Workplace exposure standards (WES) review, Release 7 Dioxane, SWA website, accessed March 2022.

SWA (Safe Work Australia) (n.d.) *Hazardous Chemical Information System (HCIS)*, SWA website, accessed February 2022.

The Poisons Standard (2022) The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP No. 35), accessed April 2022.

Thiess AM, Tress E, Fleig I (1976) Medical examination of persons exposed to dioxane, *Priivcntiv-med*, 11(2):36–46.

Torkelson TR, Leong BKJ, Kociba RJ, Richter WA, Gehring PJ (1974) 1,4-Dioxane. II. Results of a 2-year inhalation study in rats, *Toxicology and Applied Pharmacology*, 30(2):287–298.

UK HSE (United Kingdom Health and Safety Executive) (2021) Agency technical report on the classification and labelling of 1,4-dioxane, HSE website, accessed April 2022.

UNECE (United Nations Economic Commission for Europe) (2017) *Globally Harmonized System of Classification and Labelling of Chemicals, 7th edn (GHS)*, UNECE Information Service, Geneva.

US EPA (United States Environmental Protection Agency) (2017) Technical fact sheet – 1,4-Dioxane, US EPA website, accessed April 2022.

US EPA (United States Environmental Protection Agency) (2020) Final risk evaluation for 1,4-dioxane, US EPA website, accessed April 2022.

US FDA (United States Food & Drug Administration) (2022) 1,4-Dioxane in cosmetics: A manufacturing by product, US FDA website, accessed March 2022.

Young JD, Braun WH, Gehring PJ (1978) Dose-dependent fate of 1,4-dioxane in rats, *Journal of Toxicology and Environmental Health*, 4(5–6):709–726.

Young JD, Braun WH, Rampy LW, Chenoweth MB, Blau GE (1977) Pharmacokinetics of 1,4-dioxane in humans, *Journal of Toxicology and Environmental Healt*h, 3(3):507–20.