Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Consultation: Proposed amendments to the Poisons Standard – ACMS, ACCS and joint ACMS-ACCS meetings, March 2023

5 January 2023

TGA Health Safety Regulation

Confidentiality
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission form. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission form.

Contents

1 About this consultation

Subdivision 3D.2 of the *Therapeutic Goods Regulations 1990* (the **Regulations**) sets out the procedure to be followed where the Secretary of the Department of Health and Aged Care receives an application under section 52EAA of the *Therapeutic Goods Act 1989* (the **Act**) to amend the current Poisons Standard or decides to amend the Poisons Standard on his or her own initiative and decides to refer the proposed amendment to an expert advisory committee. These include, under regulation 42ZCZK, that the Secretary publish (in a manner the Secretary considers appropriate) the proposed amendment to be referred to an expert advisory committee, the committee to which the proposed amendment will be referred, and the date of the committee meeting. The Secretary must also invite public submissions to be made to the expert advisory committee by a date mentioned in the notice as the closing date, allowing at least 20 business days after publication of the notice.

In accordance with regulation 42ZCZK of the Regulations, the Secretary invites public submissions on scheduling proposals referred to the March 2023 meetings of the Advisory Committees on Medicines and Chemicals Scheduling. Submissions must be received by close of business **3 February 2023**.

Submissions should be provided through our consultation hub. Any submission about any of the proposals to amend the Poisons Standard will be considered at the next meeting of the Advisory Committee on Medicines Scheduling (ACMS), meeting of the Advisory Committee on Chemicals Scheduling (ACCS), or a joint meeting of these two committees (Joint ACMS-ACCS).

This consultation closes on 3 February 2023.

We aim to provide documents in an accessible format. If you're having problems using this document, please contact medicines.scheduling@health.gov.au.

2 Proposed amendments referred for scheduling advice to ACMS meeting #41

2.1 Celecoxib

Proposal

The applicant has proposed creation of a new Schedule 3 entry for celecoxib for oral use in capsules containing 200 mg or less per capsule when in packs containing not more than 10 dosage units. The new Schedule 3 entry would pertain to celecoxib for short-term treatment of period pain in adults and for the short-term treatment of acute pain in adults with muscle and joint injuries. The proposal also includes a new Appendix H entry for celecoxib to permit advertising of Schedule 3 preparations. Celecoxib is an anti-inflammatory medication currently captured in Schedule 4 of the Poisons Standard.

CAS number

169590-42-5

Alternative names

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide

Applicant

Private applicant

Proposed scheduling

The applicant's proposed amendments to the Poisons Standard are:[1]

Schedule 4

CELECOXIB **except** when included in Schedule 3.

Schedule 3

CELECOXIB for oral use in capsules containing 200 mg or less per capsule and when in pack containing not more than 10 dosage units for the short-term treatment of period pain in adults and for the short-term treatment of acute pain in adults with muscle and joint injuries.

Appendix H

CELECOXIB

[1] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

Index

CELECOXIB

Schedule 4
Schedule 3
Appendix H

Background

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) from the selective cyclooxygenase-2 (COX-2) inhibitor class. Indications for use of celecoxib include rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and pain due to dysmenorrhoea or injury (post-operative musculoskeletal or soft tissue). Celecoxib is presently available on prescription in immediate release capsules in 100 mg or 200 mg dosages.

Summary of applicant's reasons for the proposal

- Down-scheduling celecoxib to Schedule 3 (Pharmacist Only Medicine) would provide an alternative therapeutic agent to be supplied by pharmacists after patient counselling to treat acute pain symptoms.
- Down-scheduling of celecoxib will facilitate better patient access to an effective medicine, support appropriate self-care, minimise the pill burden on the patient and aid compliance.
- A comparative overview of celecoxib with other anti-inflammatory substances concluded that celecoxib presents a safety profile similar to ibuprofen, naproxen and diclofenac (non-selective COX-2 inhibitors) currently available in the Australian market.
- Established associated risks with celecoxib use include cardiovascular events, gastrointestinal ulceration-related events, renal toxicity, fluid retention and edema, hypertension, hypersensitivity, skin reactions and hepatic reactions. These risks are expected to be adequately addressed through:
  - Limitation on pack size to ensure short-term use of Schedule 3 preparations
  - Consultation with a trained pharmacist before purchase
  - Product labeling

Key uses / expected use

Medicines

Australian regulations

- According to the TGA Ingredient Database,[2] celecoxib is:
  - Available for use as an Active Ingredient in Biologicals, Export Only, Over the Counter, and Prescription Medicines;
  - Available for use as an Excipient Ingredient in Biologicals, Devices and Prescription Medicines;

[2] TGA Ingredient Database https://www.ebs.tga.gov.au/

  - Not available as an Equivalent Ingredient in any application.

- As of December 2022, there were 56 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[3] that contain celecoxib as an active ingredient. These include 50 prescription medicines and 6 medicines for export only.
- Celecoxib is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[4] No.5 of 2022.
- The TGA prescribing medicines in pregnancy database[5] classifies celecoxib as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Celecoxib	B3	Musculoskeletal System	Non-steroidal anti-inflammatory drugs (NSAIDS)	
Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.				

- There are no warning statements pertaining to celecoxib in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.[6]
- Since January 2013, there have been 261 reports of adverse events for products containing celecoxib as an active ingredient on the Database of Adverse Event Notifications (DAEN),[7] with 142 reports where celecoxib was the single suspected medicine.
  - Reported adverse events related mostly to allergic reactions, with symptoms including anaphylaxis, rash, urticaria and pruritus.
  - Death was the reported outcome in 17 cases due to cerebral infarction, cardiomegaly, hypopnoea, hepatic steatosis, hepatomegaly, intracranial haemorrhage, kidney fibrosis, and respiratory depression. Cerebral infarction (one case) was the only report where celecoxib was the single suspected medicine.

[3] ARTG database https://www.tga.gov.au/artg
[4] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[5] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[6] Therapeutic Goods (Medicines Advisory Statements) Specification 2021 https://www.legislation.gov.au/Details/F2021L01888
[7] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx

- As of December 2022, there were no products containing celecoxib as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).[8]

International regulations

- The United States Food and Drug Administration Database[9] includes 23 active products containing celecoxib. All are prescription-only medicines.
- The New Zealand Medicines and Medical Devices Safety Authority (MedSafe)[10] lists celecoxib as prescription only medicine.
- The Health Product Regulatory Authority of Ireland[11] regulates 9 products containing celecoxib in 100 mg and 200 mg capsules. All are listed as prescription-only medicines.
- The United Kingdom electronic medicines compendium[12] (emc) regulates 8 products containing celecoxib in 100 mg and 200 mg capsules. All are listed as prescription-only medicines.
- The Health Canada Drug Product Database[13] includes 32 currently marketed products that contain celecoxib. All are prescription-only medicines.

[9] FDA Approved Drugs Database https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

[10] Medsafe Medicines Classification Database https://www.medsafe.govt.nz/profs/class/classintro.asp

[11] HPRA https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Celecoxib&field=ACTIVESUBSTANCES

[12] Emc https://www.medicines.org.uk/emc/search?q=celecoxib

[13] Health Canada health-products.canada.ca/dpd-bdpp/index-eng.jsp

3 Proposed amendments referred for scheduling advice to the Joint ACMS-ACCS meeting #33

3.1 Azelaic acid

Proposal

The delegates of the Secretary of the Department of Health and Aged Care responsible for medicines and chemicals scheduling have proposed amendments to the Poisons Standard with regards to azelaic acid. The amendments are intended to address non-therapeutic use of the substance, as well as clarify the existing entries in Schedules 2 and 4.

CAS Number:

123-99-9

Alternative names

Nonanedioic acid

Applicant

Delegate-initiated

Proposed scheduling

Azelaic acid is currently listed in Schedules 2 and 4 of the Poisons Standard.

The applicant's proposed amendments to the Poisons Standard are:[14]

Schedule 5

AZELAIC ACID (excluding its derivatives) **except** when included in Schedules 2 or 4.

Schedule 4

AZELAIC ACID (excluding its derivatives) for therapeutic use **except**:

a) when included in Schedule 2; or

b) in preparations containing 1% ~~per cent~~ or less of azelaic acid for non-human use.

Schedule 2

AZELAIC ACID (excluding its derivatives) in dermal preparations for therapeutic use **except** in preparations containing 1% ~~per cent~~ or less of azelaic acid for non-human use.

[14] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

Index

AZELAIC ACID

Schedule 5
Schedule 4
Schedule 2

Background

Azelaic acid, also known as nonanedioic acid, is a naturally occurring dicarboxylic acid produced by the yeast *Malassezia furfur* and found in whole grain cereals, rye, barley and animal products. Azelaic acid is claimed to possess anti-inflammatory, antibacterial, keratolytic, comedolytic, and antioxidant activity.

Current regulatory controls in Australia only allow the sale and supply of Schedule 2 (Pharmacy Medicine) or Schedule 4 (Prescription Only Medicine) products containing azelaic acid, with an exemption for non-human use at <1% concentration. Although no information is available on the non-therapeutic use of azelaic acid in Australia, the chemical is reported internationally to be present in consumer products for domestic use. Incidental dermal and ocular exposure may occur from using these products. However, based on the available hazard information (skin and eye irritation), there are no identified risks to the public that require management where use of the chemical as a dermal or topical application is not intentional.

The AICIS evaluation statement on azelaic acid,[15] completed in September 2021, recommends that the Poisons Standard entry for azelaic acid be amended to recognise the range of identified industrial uses of the chemical which are not captured by the existing entries. The list of factors included for consideration in the statement include the existence of several derivatives of the substance which are utilised in various applications, the limited identified health hazards associated with exposure, and the limitations of the current scheduling.

Summary of the reasons for the proposal

- The chemical is currently listed in Schedules 2 and 4 of the Poisons Standard. There is a range of legitimate industrial uses for the chemical and its derivatives which are not allowed under the current listings, although it is probable that industrial users of this chemical are not aware of the restrictions associated with the current scheduling.
- The existing Schedule 2 and 4 listings should be amended so that they are limited to therapeutic use of azelaic acid, to allow industrial use of the substance. Due to its simple chemical structure, the entries for azelaic acid should also exclude derivatives to avoid inadvertently capturing unrelated substances.

Key uses / expected use

Medicines, cosmetics, industrial uses.

Australian regulations

- According to the TGA Ingredient Database,[16] azelaic acid is:

[15] AICIS evaluation statement https://www.industrialchemicals.gov.au/sites/default/files/2021-09/EVA00010%20-%20Evaluation%20Statement%20-%2014%20September%202021%20%5B702%20KB%5D.pdf
[16] TGA Ingredient Database https://www.ebs.tga.gov.au/

  - Available for use as an Active Ingredient in Biologicals, Export Only, Over the Counter and Prescription Medicines;
  - Available for use as an Excipient Ingredient in Biologicals, Devices and Prescription Medicines;
  - Not available as an Equivalent Ingredient in any application.

- As of December 2022, there were 4 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[17] that contain azelaic acid as an active ingredient. These include 2 export-only products and 2 non-prescription medicines (one lotion containing 20% azelaic acid, and one gel containing 15% azelaic acid).
- Azelaic acid is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[18] No.5 of 2022.
- The TGA prescribing medicines in pregnancy database[19] classifies azelaic acid as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Azelaic acid	B1	Drugs used in dermatology	Topical	
Category B1 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.				

- There are no warning statements pertaining to azelaic acid in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.[20]
- From January 1971 to December 2022, there have been 6 reports of adverse events for products containing azelaic acid as an active ingredient on the Database of Adverse Event Notifications (DAEN).[21] In all cases azelaic acid was the single suspected medicine. The events were diverse in nature and affected a range of organ classes.
- As of December 2022, there was no products containing azelaic acid as an active constituent listed on the Public Chemical Registration Information System Search (PubCRIS).[22]

[17] ARTG database https://www.tga.gov.au/artg
[18] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[19] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[20] Therapeutic Goods (Medicines Advisory Statements) Specification 2021 https://www.legislation.gov.au/Details/F2021L01888
[21] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[22] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris

International regulations

- The United States Food and Drug Administration[23] lists 7 preparations of azelaic acid, all of which are Prescription Only topical gels or foams containing 15% or more of azelaic acid.
- Ireland's Health Products Regulation Authority[24] lists one product containing azelaic acid, a topical gel containing 15% azelaic acid which is a prescription-only medicine.
- New Zealand MedSafe's Classification Database[25] lists azelaic acid as a prescription-only medicine except in preparations for dermal use, which are pharmacy only medicines.
- The European Commission[26] database of cosmetics and ingredients lists the functions of azelaic acid as a buffer and in fragrances.

[23] Food and Drug Administration (FDA) https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

[24] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Azelaic+acid&field=ACTIVESUBSTANCES

[25] New Zealand Medicines and Medical Devices Safety Authority https://www.medsafe.govt.nz/regulatory/dbsearch.asp

[26] European Commission database for cosmetic substances and ingredients https://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.details_v2&id=74538

4 Proposed amendments referred for scheduling advice to ACCS #37

4.1 Bromoxynil

CONTENT WARNING

The information below contains information regarding self-poisoning that some people may find distressing.

The Department of Health and Aged Care acknowledges the devastating effects associated with acts of self-harm on individuals, their families, friends and communities.

If you or someone you know needs additional support, please contact any of the below crisis support helplines:

Support services and information sources

Adult

- Lifeline: 13 11 14
- Suicide Call Back Service: 1300 659 467
- Beyond Blue: 1800 512 348
- MensLine Australia: 1300 789 978

Youth

- Kids Helpline (5-25 years): 1800 551 800
- Headspace: 1800 650 890
- ReachOut

Proposal

The applicant is requesting a new entry in Schedule 7 of the Poisons Standard for bromoxynil. Preparations containing greater than 1% of bromoxynil will be captured by the new entry, while all other preparations will continue to be captured by the existing Schedule 6 entry.

CAS Number

1689-84-5 (bromoxynil)

1689-99-2 (bromoxynil octanoate)

56634-95-8 (bromoxynil heptanoate)

Alternative names

3,5-Dibromo-4-hydroxybenzonitrile

3,5-dibromo-4-hydroxyphenyl cyanide

2,6-dibromo-4-cyanophenol broxynil

Applicant

Private

Proposed scheduling

Bromoxynil is currently listed in Schedule 6 of the Poisons Standard.

The proposed amendments to the Poisons Standard are:[27]

Schedule 7

BROMOXYNIL in preparations containing more than 1% of bromoxynil.

Schedule 6

BROMOXYNIL **except** when in Schedule 7.

Index

BROMOXYNIL

Schedule 7
Schedule 6

Key uses / expected use

Herbicide

Background

Bromoxynil is a nitrile and organic cyanide compound used as a selective herbicide. It is used by spraying broadleaf plants and most effective when used post-emergently on broad leaf annual weeds. Bromoxynil is used in both domestic and commercial settings, with preparations intended for domestic use typically containing significantly lower concentrations of the substance. Concerns regarding increasing incidence of deliberate self-poisoning involving bromoxynil have prompted this proposed change in scheduling.

Summary of applicant's reasons for the proposal

- Combination herbicides containing bromoxynil and MCPA have become more popular domestically with the development of soft leaf buffalo grasses which cannot tolerate other combination herbicides. The increase in the use of this combination herbicide has been accompanied by an increase in deliberate self-poisonings.
- The proposal aims to reduce the rate of self-harm by limiting public access. Evidence suggests that means restriction is effective in preventing deaths by self-harm without an equivalent shift to the use of other methods.
- Bromoxynil poses a significant health risk, with a high mortality rate despite appropriate and timely expert medical care. There is no specific antidote for this poisoning.
- Products containing a lower concentration of bromoxynil for domestic use will be available for general purchase, thus maintaining access to this effective weedkiller in a safer formulation. The concentrated formulation will be available in Schedule 7 for use by

[27] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

registered commercial users, who will benefit most from the convenience and cost saving of transporting a concentrated product for dilution on use.

Australian regulations

- Bromoxynil is not included in the TGA Ingredient Database,[28] the Australian Register of Therapeutic Goods (ARTG),[29] the Therapeutic Goods (Permissible Ingredients) Determination[30] No.5 of 2022, the TGA prescribing medicines in pregnancy database,[31] or the Therapeutic Goods (Medicines Advisory Statements) Specification 2021..[32]
- As of December 2022, there were no reports of adverse events for products containing bromoxynil on the Database of Adverse Event Notifications (DAEN).[33]
- As of December 2022, there were 146 products containing bromoxynil (or bromoxynil octanoate) listed on the Public Chemical Registration Information System Search (PubCRIS).[34]
- In 2009-2022, 6 reports of incidents, including one associated with crop health and 5 reports associated with human health were recorded for bromoxynil in the APVMA Adverse Experience Reporting Program database (AERP).[35]

International regulations

- The United States Environmental Protection Agency's (US EPA) Office of Pesticides Programs[36] lists a number of bromoxynil compounds, including bromoxynil, bromoxynil octanoate and bromoxynil heptanoate, as under Registration Review.
- The European Chemicals Agency (ECHA)[37] lists bromoxynil (and bromoxynil octanoate) as suspected to be toxic to reproduction and skin sensitising. In addition, according to the harmonised classification and labelling approved by the European Union, the substance is
  - very toxic to aquatic life,
  - very toxic to aquatic life with long lasting effects,
  - is toxic if swallowed,
  - toxic if inhaled,
  - suspected of damaging the unborn child, and
  - may cause an allergic skin reaction.

[28] TGA Ingredient Database https://www.ebs.tga.gov.au/
[29] ARTG database https://www.tga.gov.au/artg
[30] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[31] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[32] Therapeutic Goods (Medicines Advisory Statements) Specification 2021 https://www.legislation.gov.au/Details/F2021L01888
[33] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[34] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[35] APVMA Adverse Experience Reporting Program database (AERP) https://apvma.gov.au/node/10946
[36] The US EPA Pesticide Chemical Search ordspub.epa.gov/ords/pesticides/f?p=CHEMICALSEARCH:1:
[37] ECHA echa.europa.eu/search-for-chemicals

The classification provided by companies to ECHA in the REACH registrations identifies that this substance is toxic if swallowed and is suspected of damaging fertility or the unborn child.

- Approval of bromoxynil as an active substance was not renewed by the European Commission Standing Committee on Plants, Animals, Food and Feed[38] in September 2021, due to identified high risk to children despite mitigation measures, and a high long-term risk from dietary exposure for wild mammals for the representative uses.
- The New Zealand Inventory of Chemicals (NZIoC)[39] lists bromoxynil as approved with controls, while bromoxynil octanoate does not have an individual approval but may be used an appropriate group standard.

4.2 Dioxane

Proposal

The delegate of the Secretary of Department of Health and Aged Care responsible for chemicals scheduling (the Delegate) is proposing an amendment to the current Poisons Standard following a referral from the Australian Industrial Chemicals Introduction Scheme (AICIS). The referral stems from an evaluation statement on dioxane published in June 2022, and the basis for the included advice to reschedule the substance is summarised as follows.

The AICIS referral suggests that the Appendix G entry for dioxane should be removed from the Poisons Standard, due to carcinogenicity and genotoxicity concerns regarding the substance and modern manufacturing practices which are now capable of achieving lower levels of dioxane contamination. The chemical is currently listed in Schedule 6 of the Poisons Standard, with an Appendix G entry which exempts the substance from scheduling when present at or below a concentration of 100 mg/kg. The removal of the Appendix G entry would effectively place the default Poisons Standard limit of 10 mg/kg on dioxane and include preparations containing greater than 10 mg/kg of dioxane in Schedule 6.

CAS Number

123-91-1

Alternative names

1,4-dioxane;

1,4-diethylene ether;

1,4-diethylene dioxide

Applicant

Delegate initiated.

[38] EC Reg 1107/2009 ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances/details/483

[39] NZIoC http://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/

Proposed scheduling

Dioxane is currently listed in Schedule 6 of the Poisons Standard.

The proposed amendments to the Poisons Standard are:[40]

Schedule 6

DIOXANE

Appendix E, Part 2

POISON	STANDARD STATEMENTS
DIOXANE	A,G3,E1,R1,S1
A - For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once). **G3** - If swallowed, do NOT induce vomiting. **E1** - If in eyes wash out immediately with water. **R1** - If inhaled, remove from contaminated area. Apply artificial respiration if not breathing. **S1** - If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.	

Appendix F, Part 3

Substance	WARNING STATEMENTS	SAFETY DIRECTION
DIOXANE		1,4,8
1 - Avoid contact with eyes. **4** - Avoid contact with skin. **8** - Avoid breathing dust (or) vapour (or) spray mist.		

[40] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

Appendix G

POISON	CONCENTRATION (QUANTITY PER LITRE OR KILOGRAM)
~~DIOXANE~~	~~100 mg~~

Index

DIOXANE

Schedule 6
Appendix E, Part 2
Appendix F, Part 3
~~Appendix G~~

Key uses / expected use

Industrial, commercial, household and cosmetic products.

Background

Dioxane is a heterocyclic organic compound, also known as diethylene ether. Although there are 1,2- and 1,3- variants, the term dioxane is most often used to refer to 1,4-dioxane. Dioxane was first included in Schedule 6 of the Poisons Standard by the Poisons Advisory Panel in April 1963. The substance was previously used mainly as a stabiliser for 1,1,1-trichloroethane in storage and transport, however this use was phased out in the late 1990s due to that substance's status as a potent greenhouse gas. Dioxane is miscible in water and still persists at measurable levels in the current environment.

Dioxane is classified as carcinogenic by all routes of exposure, with animal studies showing increased incidence of tumours in a number of organ systems of exposed subjects. In November 1990, the Drugs and Poisons Schedule Committee (DPSC) noted that while dioxane was classified as a Category 2B carcinogen, there was no concentration cut-off associated with existing Schedule 6 entry, and therefore use of dioxane as a stabilising agent for 1,1,1-trichlorethane was also captured under this entry. After discussing the low probability of sufficient exposure to dioxane to warrant concerns of carcinogenicity based on levels typically found in commercially available products, the DPSC considered that the carcinogenic risk was minimal in this case.

In November 1998, the National Drugs and Poisons Scheduling Committee (NPDSC) considered a report on dioxane from the National Industrial Chemicals Notification and Assessment Scheme (NICNAS, now AICIS). The NDPSC noted that the report concluded that the current scheduling of dioxane was appropriate, however that public exposure and risk estimates were based on an upper limit of 30 ppm of dioxane as a contaminant in consumer products. It was concluded by the NDPSC that 100 ppm of dioxane in consumer products was toxicologically acceptable, and as the presence of dioxane in consumer products was not considered to pose a significant health risk to the general public, a new entry for dioxane was created in Appendix G to exclude preparations containing less than 100 ppm (or 100 mg/kg) of dioxane from the requirements of the Poisons Standard.

Summary of reasons for the proposal

- Dioxane has a number of industrial uses but the primary health concern is the substance's formation as a contaminant in industrial synthesis, particularly in the manufacture of ethoxylate surfactants. This is pertinent to cosmetics and domestic products, including shampoos, conditioners, shower gels and skin moisturisers, which have been reported to contain up to 200 mg/kg of dioxane. Other products which may contain dioxane as a residual contaminant include air fresheners, paints and varnishes, inks, polyurethane foams, dyes and adhesives.
- There is sufficient evidence in animal studies to warrant a Category 1B carcinogen classification for dioxane, which is consistent with assessments by regulators in the USA, European Union and United Kingdom. Carcinogenicity studies in humans have been limited in scope and number. The evidence for genotoxicity is less robust, and only supported for high doses.
- In 2015, the European Scientific Committee on Consumer Safety concluded that a trace level of 10 ppm (equivalent to 10 mg/kg) of dioxane in cosmetic products was considered safe.[41] Further, dioxane is listed in Regulation (EC) No 1223/2009, Annex II which prohibits the use of the substance in cosmetic products.[42]
- The state of New York, USA recently instituted a 10 ppm limit on dioxane in cosmetic products, which will come into effect on 31 December 2022.

Australian regulations

- According to the TGA Ingredient Database,[43] dioxane is:
  - Available for use as an Active Ingredient in Biologicals and Prescription Medicines;
  - Available for use as an Excipient Ingredient in Biologicals, Devices, Export Only and Prescription Medicines;
  - Available for use as an Equivalent Ingredient in Export Only and Listed Medicines.
- As of December 2022, there was one product currently active on the Australian Register of Therapeutic Goods (ARTG)[44] that contains dioxane as an excipient in a disinfectant spray.
- Dioxane is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[45] No.5 of 2022.

[41] Considerations on Acceptable Trace Level of 1,4-Dioxane in Cosmetic Products ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_194.pdf
[42] Regulation (EC) No 1223/2009 health.ec.europa.eu/system/files/2016-11/cosmetic_1223_2009_regulation_en_0.pdf
[43] TGA Ingredient Database https://www.ebs.tga.gov.au/
[44] ARTG database https://www.tga.gov.au/artg
[45] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

- Dioxane is not included in the TGA prescribing medicines in pregnancy database.[46]
- There are no warning statements pertaining to dioxane in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.[47]
- As of December 2022, there were no reports of adverse events for products containing dioxane as an active ingredient on the Database of Adverse Event Notifications (DAEN).[48]
- As of December 2022, there were no products containing dioxane as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).[49]

International regulations

- The New Zealand Inventory of Chemicals[50] (NZIoC) lists 1,4-dioxane as "approved with controls".
- EC Regulation 1223/2009[51] prohibits the use of dioxane in cosmetic products in the European Union, based on its status as a Category 2 carcinogen.
- The European Chemicals Agency[52] lists dioxane as carcinogenic and under assessment as persistent, bioaccumulative and toxic.
- The United States Environmental Protection Agency's Final Risk Evaluation on dioxane,[53] completed in December 2020, found no unreasonable risks to the environment, consumers or bystanders, workers or the general population from any conditions of use of dioxane.

[46] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[47] Therapeutic Goods (Medicines Advisory Statements) Specification 2021 https://www.legislation.gov.au/Details/F2021L01888
[48] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[49] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[50] New Zealand Inventory of Chemicals (NZIoC) https://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/DatabaseSearchForm/?SiteDatabaseSearchFilters=36&Keyword=acequinocyl&DatabaseType=NZIOC
[51] Regulation (EC) No 1223/2009 health.ec.europa.eu/system/files/2016-11/cosmetic_1223_2009_regulation_en_0.pdf
[52] ECHA infocard on dioxane echa.europa.eu/substance-information/-/substanceinfo/100.004.239
[53] EPA Final Risk Evaluation on dioxane http://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-14-dioxane

5 How to respond

Submissions must be provided by the closing date of **3 February 2023** through our consultation hub. Any submission about any of the proposals to amend the Poisons Standard will be considered at the next meeting of the Advisory Committee on Medicines Scheduling (ACMS), meeting of the Advisory Committee on Chemicals Scheduling (ACCS), or a joint meeting of these two committees.

6 What will happen

All public submissions will be published on the TGA website at Public submissions on scheduling matters, unless marked confidential or indicated otherwise in the submission coversheet (see Privacy information).

Following consideration of public submissions received before the closing date and advice from the expert advisory committee/s, decisions on the proposed amendments will be published as interim decisions on the TGA website: Scheduling delegate's interim decisions & invitations for further comment in June 2023.