Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

# Notice of interim decisions to amend (or not amend) the current Poisons Standard

19 September 2024

**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

# Notice of interim decisions made under Regulation 42ZCZN of the *Therapeutic Goods Regulations 1990*

This publication constitutes a notice for the purposes of regulation 42ZCZP of the *Therapeutic Goods Regulations 1990* (the **Regulations**). In accordance with regulation 42ZCZP, this notice sets out:

- the interim decisions made by a delegate of the Secretary under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee[1] under subdivision 3D.2 of the Regulations in June 2024.
- the proposed date of effect of the proposed amendments (in circumstances where the interim decision proposes an amendment to the current Poisons Standard).

In accordance with regulation 42ZCZP, interested persons (including the applicant requesting the amendment) are invited to make submissions to the Secretary in relation to these interim decisions on or before 18 October 2024.

Submissions should be provided through our consultation hub. Submissions will be considered by the Delegate in making the final decision.

Please note that in accordance with subregulation 42ZCZQ(4) of the Regulations, the Secretary must publish all relevant submissions received, unless the Secretary considers the information to be confidential information.

**Defined terms**

In this notice the following defined terms are used in addition to those above:

- the *Therapeutic Goods Act 1989* (Cth) (the Act)
- the Scheduling Policy Framework 2018 (the SPF)
- the Scheduling handbook: Guidance for amending the Poisons Standard (the Handbook), and
- the Therapeutic Goods Administration (the TGA).

Note: additional terms are also be defined for individual decisions.

[1] Established under sections 52B and 52C of the *Therapeutic Goods Act 1989* (Cth).

# Interim decision on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #45, June 2024)

## Interim decision in relation to sildenafil

### Proposal

The applicant proposed to create a new Pharmacist only (Schedule 3) entry for sildenafil. The proposed amendment would include divided preparations containing 50 mg of sildenafil for oral use, in packs of 4 or fewer dosage units, in Schedule 3 and a new entry for sildenafil in Appendix H to permit advertising of Schedule 3 preparations. Sildenafil is currently included in Prescription Only medicines (Schedule 4).

### Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to not amend the current Poisons Standard in relation to sildenafil.

### Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to sildenafil (the Application)
- The 4 public submissions, with 4 including a written component, received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the Submissions)
- The advice received from the 45th meeting of the Advisory Committee on Medicines Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health
- The Therapeutic Guidelines
- The Australian Medicines Handbook
- The SPF, and
- The Handbook.

### Summary of Committee advice to the Delegate

The Committee recommended that the current Poisons Standard entry for sildenafil remains appropriate.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

## *a) the risks and benefits of the use of a substance*

### Risks:

- Potential risk of use in someone with high risk, particularly in undiagnosed cardiovascular disease (CVD)
- Adverse events – the most serious of which are non-arteritic ischaemic optic neuropathy (NAION), priapism and interactions with nitrates and other drugs.
- Risks of a lack of ongoing medical monitoring under the Schedule 3 model.

### Benefits:

- Effective in treatment of erectile dysfunction (ED)

## *b) the purposes for which a substance is to be used and the extent of use of a substance*

- Used to increase ability to gain and maintain an acceptable erection for sexual activity, in men over 18 years of age.
- Extent of use is likely to be common, especially in younger and older populations due to higher desire/need for ED treatment.
- Likely frequent use, as ED affects up to 50% of men aged 40 to 70 years.

## *c) the toxicity of a substance*

- Well established. Sildenafil has a wide therapeutic index.
- Minimal risk of toxicity at therapeutic doses.

## *d) the dosage, formulation, labelling, packaging and presentation of a substance*

- Proposal suggested a supply of 4 x 50 mg over-the-counter tablets. Product Information will contain information addressing risks. For example, priapism and advice to those who are not fit for sex.
- Dosage proposed is minimal recommended and at minimum quantity in commercially available packages.
- Labelling and packaging alone not likely to address primary risks of mis/underdiagnosed disease.

## *e) the potential for abuse of a substance*

- Evidence of misuse including high risk of concurrent misuse with recreational drugs[2]
- Moderate risk for excessive use
- Evidence of off label or inappropriate use
- Limited potential for dependency

[2] Chan, W. L., Wood, D. M., & Dargan, P. I. (2015). Significant Misuse of Sildenafil in London Nightclubs. *Substance Use & Misuse*, *50*(11), 1390–1394.

### *f) any other matters that the Secretary considers necessary to protect public health*

- Unregulated importation is a concern.
- High rates of seizures of imports
- Limited information on adequacy of current access pathways in respect to recent changes to telehealth models of care and expanded pharmacist scope to deal with Schedule 4 medicines in some States and Territories.
- ED may be a symptom of more serious underlying conditions, which require ongoing medical monitoring (in addition to medical diagnosis).
- Sildenafil meets Schedule 4 factors, requiring medical intervention for monitoring of the condition.
- Insufficient evidence has not been presented to support down-scheduling.
- Risks from non-prescribed access relate to diagnosis and management of CVD and or diabetes mellitus (DM).
- Medication is not always the most effective ED treatment. Other options may be more effective for certain individuals, which are more appropriately determined by a medical practitioner.

## Reasons for the interim decision (including findings on material questions of fact)

I agree with the Committee's findings on the relevant provisions of section 52E of the Act.

I have made an interim decision not to amend the Poisons Standard with regards to sildenafil. In making this decision I have balanced the potential benefits of increasing access to sildenafil for the treatment of erectile dysfunction (ED) against the potential risks, notably those associated with underlying disease of which ED is a symptom.

I have considered the 4 public submissions received during the pre-meeting consultation period. The Pharmacy Guild of Australia (PGA) supported, the Pharmaceutical Society of Australia (PSA) partially supported, and the Australian Medical Association (AMA) and a private submission opposed the proposal. All public submissions provided a written component. The PSA and the PGA regarded sildenafil to be generally safe and well tolerated with pharmacist intervention. However, the PSA did not support the aspect of the proposal that would permit the advertising of sildenafil. The AMA expressed concern in relation to down-scheduling of sildenafil due to the need to diagnose and manage underlying health conditions associated with ED and because of the potential for adverse events, including drug interactions.

In relation to s 52E(b) of the Act, sildenafil is an approved treatment of erectile dysfunction in adult males, which is highly prevalent in Australia.[3,4] There are various causes of ED including organic, psychogenic, and mixed factors, but is mainly associated with neurovascular disease, diabetes, or as an adverse effect from certain medications.[5] As coexisting conditions are highly likely to exist in the presence of ED, the Therapeutic Guidelines specify a need for medical evaluation.[5] This is consistent with scheduling factor 1 of Schedule 4, where ailments or symptoms that the substance is used for require medical intervention. I concur with the Committee's findings that there is an established

[3] Chew KK, Stuckey B, Bremner A, Earle C, Jamrozik K. Male erectile dysfunction: its prevalence in Western australia and associated sociodemographic factors. J Sex Med. 2008 Jan;5(1):60-9..

[4] Weber, M.F., Smith, D.P., O'Connell, D.L., Patel, M.I., de Souza, P.L., Sitas, F. and Banks, E. (2013), Risk factors for erectile dysfunction in a cohort of 108 477 Australian men. Medical Journal of Australia, 199: 107-111.

[5] Therapeutic Guidelines (eTG)

diagnostic process to identify underlying causes of erectile dysfunction in medical practice and there is a regular need for ongoing monitoring or management.

In relation to s 52E(a)(b) and (c) of the Act, sildenafil is generally well tolerated, safe and effective but has contraindications and can cause severe adverse effects.[6] While the safety concerns of sildenafil are well established and common side effects are mild and transient, there are rare but serious adverse events including non-arteritic ischaemic optic neuropathy (NAION) and priapism.[7] I note sildenafil also has several contraindications, one of which is men for whom sexual intercourse is inadvisable due to certain cardiovascular risk factors.

Additionally, I have considered the potential for drug interactions with sildenafil. Several medicines that interact with sildenafil are used in groups of people that have higher rates of ED. These include medicines like nitrates commonly used for angina, which can cause profound hypotension when used concomitantly with sildenafil. Sildenafil also has the potential to interact with some recreational drugs and combined use has been shown to be highly prevalent in certain population groups.[8]

The applicant provided new post market studies[9, 10] from the United Kingdom where sildenafil has been made available without a prescription. I note both studies were funded by Pfizer, which is a pharmaceutical sponsor of sildenafil products. The first, a prospective real-world observational study showed a modest increase in seeing a medical practitioner among patients who used sildenafil that was made available as a pharmacy medicine. In the second, a web-based survey, I found a small cohort of community pharmacist's perceptions were used to determine the effectiveness of additional risk minimisation measures (aRMM) when providing sildenafil without a prescription.[9] While the studies showed some positive results, I am not satisfied that this body of evidence demonstrates an overall benefit to men's health (compared to the risks) or satisfactorily addresses concerns I have set out in this decision or have been made in previous scheduling decisions seeking to make sildenafil available as a Pharmacist Only medicine (Schedule 3).

In relation to s 52E(f) of the Act, I have considered the ongoing barriers for males accessing the health system for erectile dysfunction in Australia.[11] However, having reviewed the current literature it is not evident that the overall impact of increasing accessibility by making sildenafil available as a Pharmacist Only medicine (Schedule 3), would provide a positive net health benefit.

Finally, I have considered the proposal for entry be limited to supply of 50 mg x 4 tablets, and the safety information that is to be included in the product information leaflet in accordance with s 52E(d) and (f) of the Act. While I acknowledge making available a lower dosage tablet, smaller pack size and relevant warnings may offer a level of risk reduction, I remain concerned about the risks associated with the use of sildenafil as a Pharmacist Only medicine (Schedule 3) despite these measures. Specifically, the risk that making sildenafil available over the counter could lead to inadequate medical assessments, incorrect diagnosis, and the missed opportunity to treat any underlying causational health conditions.

[6] Australian Medicines Handbook

[7] www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2010-PI-04881-3&d=20240710172310101

[8] Chan, W. L., Wood, D. M., & Dargan, P. I. (2015). Significant Misuse of Sildenafil in London Nightclubs. *Substance Use & Misuse*, *50*(11), 1390–1394.

Lem J, Collins J, Maguire T, Sobel RE. A web-based survey of UK pharmacists to assess the effectiveness of Viagra Connect® additional risk minimisation measures. Int J Clin Pharm. 2022 Jun;44(3):608-618.

[10]Lee LJ, Maguire TA, Maculaitis MC, Emir B, Li VW, Jeffress M, Li JZ, Zou KH, Donde SS, Taylor D. Increasing access to erectile dysfunction treatment via pharmacies to improve healthcare provider visits and quality of life: Results from a prospective real-world observational study in the United Kingdom. Int J Clin Pract. 2021 Apr;75(4):e13849.

[11] www.health.gov.au/sites/default/files/2023-07/men-s-and-boys-barriers-to-health-system-access-a-literature-review.pdf

I am not satisfied the risks are adequately reduced following the modest findings of the observational study provided by the applicant, which includes the availability of 50 mg tablets of sildenafil as pharmacy medicine in the UK.

Sildenafil has been considered for down scheduling on 3 previous occasions, in 2017, 2018 and 2020. I remain concerned of other risks raised in previous decisions, including the misuse of sildenafil. I agree with the conclusions of previous decisions that it was most appropriate for sildenafil to be retained exclusively in Schedule 4.

In my view there is an insufficient body of new evidence to support the down-scheduling of sildenafil since it was last considered in 2020.

# Interim decisions on proposed amendments referred to the Advisory Committee on Chemicals Scheduling (ACCS #39, June 2024)

## Interim decision in relation to allyl esters

### Proposal

The Delegate proposed an amendment to the Schedule 6 entry for allyl esters to include allyl phenoxyacetate; allyl amyl glycolate; allyl (2-methylbutoxy)acetate; and allyl (cyclohexyloxy)acetate. The proposal was initiated following a recommendation by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS; now known as the Australian Industrial Chemicals Introduction Scheme, AICIS) in their evaluation of allyl esters of acetic acid ethers published in June 2019. These substances are currently captured in the Poisons Standard under the Schedule 7 and Appendix J entries for allyl alcohol.

### Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision not to amend the current Poisons Standard in relation to allyl amyl glycolate or allyl (2-methylbutoxy)acetate, which will continue to be captured under the Schedule 7 and Appendix J entries for allyl alcohol. The delegate has also made a decision to amend the current Poisons Standard in relation to allyl phenoxyacetate and allyl (cyclohexyloxy)acetate, as follows:[12]

**Schedule 6 – Amend Entry**

ALLYL ESTERS (excluding derivatives) being:

(a) ALLYL CYCLOHEXANEACETATE (CAS No. 4728-82-9); or

(b) ALLYL CYCLOHEXANEPROPIONATE (CAS No. 2705-87-5); or

(c) ALLYL HEPTANOATE/ALLYL HEPTYLATE (CAS No. 142-19-8); or

(d) ALLYL HEXANOATE (CAS No. 123-68-2); or

(e) ALLYL ISOVALERATE (CAS No. 2835-39-4); or

(f) ALLYL NONANOATE (CAS No. 7493-72-3); or

(g) ALLYL OCTANOATE (CAS No. 4230-97-1); or

(h) ALLYL PHENYLACETATE (CAS No. 1797-74-6); or

(i) ALLYL TRIMETHYLHEXANOATE (CAS No. 68132-80-9); or

(j) ALLYL PHENOXYACETATE (CAS No. 7493-74-5); or

(k) ALLYL (CYCLOHEXYLOXY)ACETATE (CAS No. 68901-15-5);

in preparations containing 0.1% or less of free allyl alcohol by weight of allyl ester except in preparations containing 5% or less of allyl esters with 0.1% or less of free allyl alcohol by weight of allyl esters.

[12] 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.

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**ALLYL ESTERS** (excluding derivatives)

Schedule 6

## Materials considered

In making this interim decision, the Delegate considered the following material:

- The proposal to amend the current Poisons Standard with respect to allyl phenoxyacetate, allyl amyl glycolate, allyl (2-methylbutoxy) acetate, and allyl (cyclohexyloxy) acetate (the Proposal)
- That there were no public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the Submissions)
- The advice received from the 39th meeting of the Advisory Committee on Chemicals Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health
- The SPF, and
- The Handbook.

## Summary of Committee advice to the Delegate

The Committee recommended that the current Poisons Standard entry for allyl amyl glycolate and allyl (2-methylbutoxy)acetate remains appropriate, whilst the Poisons Standard should be amended in relation to allyl phenoxyacetate and allyl (cyclohexyloxy)acetate.

The Committee recommended an implementation date of 1 February 2025, due to the lack of foreseeable burden on industry resulting from this decision.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

### *a) the risks and benefits of the use of a substance*

#### Risks:

– Allyl esters form toxic metabolites (allyl alcohol and acrolein).

– In some cases, specific safety data for the substances under consideration is not available.

#### Benefits:

– Allyl esters are used as excipients in medicines and biologicals, and in fragrances, cosmetics, domestic products, and act as intermediates in chemical synthesis.

– They are widely used at low concentrations without significant adverse effects reported.

### *b) the purposes for which a substance is to be used and the extent of use of a substance*

- Cosmetic and Household Products: All 4 allyl esters are widely used in cosmetic formulations, particularly perfumes, due to their fragrance properties. They are also found in household products like air fresheners and cleaning agents. Use in these settings is typically at low concentrations (< 5%).
- Therapeutic Goods: In Australia, some of these allyl esters are included in the Australian Register of Therapeutic Goods (ARTG) as excipients in non-prescription medicines. They are permitted in listed medicines under specific concentration limits, particularly when used as flavours or fragrances.

### *c) the toxicity of a substance*

- Systemic toxicity of the esters is driven by their metabolism into the known toxin allyl alcohol, while local toxicity can vary dependent on the substance.
- Allyl phenoxyacetate is a moderate skin sensitiser.
- Allyl amyl glycolate is an acute inhalational toxin.

### *d) the dosage, formulation, labelling, packaging and presentation of a substance*

- Products generally contain less than 5% total allyl esters.
- Labelling and presentation vary significantly across a wide range of products.

### *e) the potential for abuse of a substance*

- Nil.

### *f) any other matters that the Secretary considers necessary to protect public health*

- The revised Schedule 6 entry should maintain the existing limit of total allyl esters (which will include any additional substances resulting from consideration of the proposal) of 5%.
- The amount of free allyl alcohol in any preparation containing one or more of the substances in the Schedule 6 entry remains limited to 0.1%.

## Reasons for the interim decision (including findings on material questions of fact)

I agree with the Committee's findings on the relevant provisions of section 52E of the Act. I note that no public submissions were received during the pre-meeting consultation period.

Esters of allyl alcohol are used as fragrance and flavouring excipients or active ingredients in a variety of medicines and biologicals, fragrances, cosmetics, and domestic products. Esters of allyl alcohol act as intermediates in chemical synthesis. There are currently two non-prescription medicines listed on the Australian Register of Therapeutic Goods (ARTG) containing either allyl (cyclohexyloxy)acetate or allyl amyl glycolate. While allyl phenoxyacetate, allyl amyl glycolate, allyl (2-methylbutoxy)acetate and allyl (cyclohexyloxy)acetate are not explicitly listed in the Poisons Standard, they are captured under the Schedule 7 group entry for allyl alcohol and Appendix J, clause 1 (Conditions for availability and use of certain poisons included in Schedule 7). Preparations containing 5% or less of allyl esters with 0.1% or less of free allyl alcohol by weight of allyl ester are exempt under the Schedule 7 entry. The proposal to amend the Schedule 6 entry for allyl esters to include the above allyl esters follows the recommendation by NICNAS in their assessment of allyl esters of acetic acid ethers published in June 2019.

With regards to s 52E(1)(a) of the Act, the above allyl esters are widely used at low concentrations in a variety of products for their flavouring and fragrant properties without reports of significant adverse effects. However, allyl esters can form toxic metabolites, including hydrolysis to allyl alcohol and subsequent metabolism of allyl alcohol to acrolein in the liver. I also note that allyl amyl glycolate poses a risk of acute inhalation toxicity that is consistent with the SPF factors of Schedule 7. While there is limited toxicity data for allyl (2-methylbutoxy)acetate, the NICNAS assessment of allyl esters of acetic acid ethers posits that its toxicity will be similar to that of its 3-methyl isomer. The available data for allyl (3-methylbutoxy)acetate (allyl amyl glycolate) supports that the substance poses an acute risk of inhalation toxicity.

The above-mentioned allyl esters are currently used in a variety of cosmetic and household products as well as therapeutic goods. In considering s 52E(1)(b) and (d) of the Act, I note that all four allyl esters are widely used at low concentrations (5% or less) in cosmetic formulations, particularly perfumes, due to their fragrance properties. They are similarly used in household products like air fresheners and cleaning agents. Allyl (cyclohexyloxy)acetate and allyl amyl glycolate are also included in the Australian Register of Therapeutic Goods (ARTG) as excipients in non-prescription medicines. Allyl esters are permitted in listed medicines under specific concentration limits of 5% when used as a flavouring and less than 1% as a fragrance. Specifically with regards to s 52E(1)(d) of the Act, I note that labelling and presentation of products containing allyl esters varies by usage.

With respect to s 52E(1)(c) of the Act, I agree with the Committee that all four allyl esters exhibit differences in toxicity and warrant individual consideration. Generally, I note that allyl esters are less toxic than allyl alcohols. However, toxic metabolites can be formed though allyl ester hydrolysis to allyl alcohol and further hepatic metabolism to acrolein. I also note that, allyl esters pose a risk of toxicity through oral exposure, although based on available usage data this is an unlikely route of exposure. I agree with the Committee that allyl amyl glycolate poses a risk of acute inhalation toxicity, which is consistent with the SPF factors concerning substances of high health hazard in Schedule 7. Regarding allyl (2-methylbutoxy)acetate, I am of the opinion that there are insufficient safety data to support down-scheduling to Schedule 6. I also agree with the Committee that allyl (2-methylbutoxy)acetate, as the 3-methyl isomer of allyl amyl glycolate, may pose a similar risk of acute inhalation toxicity. Noting the SPF factors, I am of the view that allyl (2-methylbutoxy)acetate does not meet the criteria for Schedule 6 and should continue to be captured under the Schedule 7 group entry for allyl alcohol. Similarly, both allyl amyl glycolate and allyl (2-methylbutoxy)acetate require additional controls over access to substances in Schedule 7 through inclusion in Appendix J, particularly where the potential for severe and possibly irreversible injury may occur without the user being aware of exposure. I agree with the Committee that allyl phenoxyacetate and allyl (cyclohexyloxy) acetate pose a risk of acute oral toxicity, and that the former acts as a moderate skin sensitiser. I agree with the Committee's advice that the toxicity profile of allyl phenoxyacetate and allyl (cyclohexyloxy)acetate is consistent with Schedule 6 SPF factors.

In consideration of s 52E(1)(f) regarding other matters relevant to scheduling, I note that the Schedule 6 entry for allyl esters includes an existing limit of total allyl esters (which will include any additional substances resulting from consideration of the proposal) of 5%. Furthermore, the amount of free allyl alcohol in any preparation containing one or more of the substances in the Schedule 6 entry remains limited to 0.1%. I am of the view that this exemption remains appropriate for both allyl phenoxyacetate and allyl (cyclohexyloxy)acetate based on the toxicity profile of these substances.

I have decided on an implementation date of 1 February 2025 as the decision to down-schedule allyl phenoxyacetate and allyl (cyclohexyloxy)acetate, and maintain the current scheduling of allyl amyl glycolate and allyl (2-methylbutoxy)acetate, should not adversely impact industry.

## Implementation date

1 February 2025

# Interim decision in relation to glyoxylic acid

## Proposal

The Delegate proposed the creation of a Schedule 6 entry for glyoxylic acid. The proposal was initiated following a recommendation by the Australian Industrial Chemicals Introduction Scheme (AICIS) in their evaluation of glyoxylic acid published in December 2022. The recommendation proposed to create a new Schedule 6 entry in the Poisons Standard, similar to the entry for glycolic acid, except for cosmetic preparations containing over 12% glyoxylic acid and when featuring warning labels. This substance is not currently captured in the Poisons Standard.

## Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to glyoxylic acid as follows:[13]

**Schedule 6 – New Entry**

GLYOXYLIC ACID (including its salts and esters) in cosmetic products.

**Appendix E, clause 3 (First aid instructions for poisons) – New Entry**

| Item | Poison | Statement code (and statement) |
|---|---|---|
| 138a | GLYOXYLIC ACID | 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).)<br>G3 (If swallowed, do NOT induce vomiting.)<br>E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.) |

**Appendix F, clause 4 (Poisons that must be labelled with warning statements and safety directions) – New Entry**

| Item | Poison | Warning statement item number (and statement) | Safety direction item number (and statement) |
|---|---|---|---|
| 160a | GLYOXYLIC ACID | 79 (Will irritate eyes) | 1 (Avoid contact with eyes)<br>5 (Wear protective gloves when mixing or using)<br>6 (Wash hands after use)<br>31 (Do not use on broken skin)<br><br>*[Either of:]*<br>9 (Use only in well ventilated area.)<br>10 (Ensure adequate ventilation when using.) |

[13] 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 – New entry**

GLYOXYLIC ACID

Schedule 6
Appendix E, clause 3
Appendix F, clause 4

## Materials considered

In making this interim decision, the Delegate considered the following material:

- The proposal to amend the current Poisons Standard with respect to glyoxylic acid (the Proposal)
- That there were no public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the Submissions)
- The advice received from the 39th meeting of the Advisory Committee on Chemicals Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health
- The case series investigation published in the American Journal of Kidney Diseases[14]
- The SPF, and
- The Handbook.

## Summary of Committee advice to the Delegate

The Committee recommended that a new entry for glyoxylic acid be created in Schedule 6 in the Poisons Standard.

The Committee recommended an extended implementation date due to the variety of consumer and professional products containing glyoxylic acid that are likely available across Australia and given its uses in non-consumer industrial processes. The Committee expected that there would be some impact on industry and recommended an extended implementation date of 1 June 2025.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

### *a) the risks and benefits of the use of a substance*

#### Risks:

- Corrosive / irritant to the eyes (pH dependent)
- Causes skin sensitisation.
- Recent case studies of kidney injury

[14] Bnaya et al. (2023) Acute Kidney Injury and Hair-Straightening Products: A Case Series. *Am J Kidney Dis*., 82(1):43-52.e1. doi: 10.1053/j.ajkd.2022.11.016. https://www.sciencedirect.com/science/article/abs/pii/S0272638623000069?via%3Dihub

- Inhalational toxicity risk

Benefits:

- Various uses reported internationally.
- Used as formaldehyde substitute in hair products.

### *b) the purposes for which a substance is to be used and the extent of use of a substance*

- Used in hair straightening products in hair salons and available for purchase at chemists for home use as an alternative to formaldehyde products. Use in other cosmetic products, skin care etc.
- Reported other uses internationally as a surface treatment, corrosion inhibitor for industrial scale manufacture of cleaning and furnishing products, pH regulator, preservative, manufacturing intermediate and anti-scaling agent.

### *c) the toxicity of a substance*

- The critical health effects for glyoxylic acid include local effects:
  - corrosive/irritant to the eyes (pH dependent)
  - causes skin sensitisation
  - may be a respiratory irritant.
- Emerging data/evidence of kidney injury from case studies
- Warning statement required on packaging of glyoxylic acid containing products to provide adequate ventilation when product is being used.

### *d) the dosage, formulation, labelling, packaging and presentation of a substance*

- Typical commercial product formulations contain 50% w/v
- Cosmetic preparations reported to contain approximately 12%.

### *e) the potential for abuse of a substance*

- Nil

### *f) any other matters that the Secretary considers necessary to protect public health*

- Need for adequate ventilation due to respiratory irritant effect
- Need for safety glasses (for eye protection)
- Heating can generate by-products possibly including formaldehyde.

## Reasons for the interim decision (including findings on material questions of fact)

I agree with the Committee's findings on the relevant provisions of section 52E of the Act. I note that no public submissions were received during the pre-meeting consultation period.

With regards to s 52E(1)(a) and (c) of the Act, I note that glyoxylic acid is reportedly used in hair straightening products as they are purported to be a safe, ‘formaldehyde-free’ alternative. However, I

concur with the Committee that glyoxylic acid in itself poses several risks to consumers and professional users. Notably, glyoxylic acid has corrosive properties, causes skin sensitisation and can cause eye irritation when at low pH, such as in hair straightening products. Glyoxylic acid also poses a risk of acute inhalation toxicity, particularly during use of aerosolised products and subsequent heating during hair straightening.

As noted by the Committee, multiple emerging case studies have reported kidney injury or failure in patients linked to exposure to 'formaldehyde-free' hair straightening products containing glycolic acid derivatives. This was exemplified by the case series published in the American Journal of Kidney Diseases in 2023 and comprised 26 affected patients.[15] I agree with both the Committee and the applicant that whilst not specified in these case studies, glyoxylic acid likely presents with a similar risk of kidney toxicity as glycolic acid derivatives. I am of the view that the risks posed by the use of glyoxylic acid, particularly in hair straightening products, warrant additional controls for both workers and consumers using these products.

The risks from the use of glyoxylic acid aligns with the Schedule 6 SPF factors. The local adverse skin and eye effects of glyoxylic acid pose a reasonable risk of harm to users that can be reduced through strong label warnings and extensive safety directions. Similarly, the acute inhalation toxicity of the substance poses a moderate health hazard commensurate with the Schedule 6 SPF factors. I agree with the Committee that first aid instructions (Appendix E), and warning statements and safety directions (Appendix F) to mitigate the risks posed by glyoxylic acid would be appropriate. I am also of the view that an additional Appendix F safety direction regarding adequate ventilation during usage is necessary to minimise the risks from inhalational exposure.

With respect to s 52E(1)(b) and (d) of the Act, I note that glyoxylic acid is used in professional hair straightening products in hair salons and is also available for consumer purchase and use from pharmacies. Commercial products contain formulations at concentrations of 50% glyoxylic acid, whilst consumer cosmetic preparations reportedly contain approximately 12%. These products often present as 'formaldehyde-free' preparations that imply a greater level of safety that formaldehyde-based products. I also note that glyoxylic acid is used in other cosmetic products, such as skin care preparations, though there were a lack of domestic usage data for consideration. Internationally, glyoxylic acid is also used as a surface treatment, corrosion inhibitor in the manufacturing of cleaning and furnishing products, pH regulator, preservative and an anti-scaling agent.

In considering s 52E(1)(f) of the Act, I agree with the Committee that the risk of inhalation toxicity may be exacerbated during heating of hair straightening products containing glyoxylic acid. Both formaldehyde and oxalic acid byproducts may be produced by high temperatures during high straightening, both of which are acute respiratory irritants. To mitigate this risk, appropriate ventilation is required for both consumer and professional users. I am of the view that these risks can be minimised through extensive label statements, i.e. first aid instructions and labelling requirements implemented through Appendix E and F, respectively.

In summary, I am of the view that the risks posed by glyoxylic acid present in cosmetic products, align with the SPF factors for Schedule 6. I also agree with the advice of Committee regarding the impact of this decision on industry given the variety of consumer and professional products containing glyoxylic acid and its uses in in non-consumer industrial processes. I have decided on an extended implementation date to allow industry adequate response time to implement the labelling changes and to avoid disruption to the supply of glyoxylic acid containing products.. As such, I have decided on an implementation date of 1 June 2026.

## Implementation date

1 June 2026

[15] Bnaya et al. (2023) Acute Kidney Injury and Hair-Straightening Products: A Case Series. *Am J Kidney Dis*., 82(1):43-52.e1. doi: 10.1053/j.ajkd.2022.11.016. https://www.sciencedirect.com/science/article/abs/pii/S0272638623000069?via%3Dihub

# Interim decisions on proposed amendments referred to the Advisory Committees on Medicines and Chemicals Scheduling in joint session (ACMS-ACCS #37, June 2024)

## Interim decision in relation to sulfonamides

### Proposal

The Delegate has proposed amendments to the current Schedule 4 entry for sulfonamides. The proposal is intended to clarify the status of sulfonamides when used in a variety of settings, including therapeutically and industrially. The proposal follows a referral from the Australian Industrial Chemicals Introduction Scheme (AICIS) evaluation of sulfonamides published in January 2022.

### Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to sulfonamides as follows:[16]

**Schedule 4**

SULFONAMIDE ANTIBIOTICS **except**:

(a) when separately specified in thisese Schedules~~; or~~

(b) ~~when included in Schedule 3, 5 or 6; or~~

(c) ~~when packed and labelled solely for use as a herbicide~~

**Index**

**SULFONAMIDES**
cross reference: SULFACETAMIDE, SULPHANILAMIDE

Schedule 4

### Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to sulfonamides (the Application)
- The 1 public submission, with no written component was received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the Submissions)
- The advice received from the 37th meeting of the Advisory Committee on Medicines and Chemicals Scheduling in joint session (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance;

[16] 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.

(e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health

- The SPF, and
- The Handbook.

## Summary of Committee advice to the Delegate

The Committee recommended that amending the Schedule 4 entry for sulfonamides in the Poisons Standard was appropriate. The Committee suggested that the entry should specify sulfonamide antibiotics and retain the exemption for sulfonamide antibiotics already included in other schedules or appendices but recommended the Delegate reviews these substances individually.

The Committee did not recommend an implementation date. Instead, they advised that the Delegate may wish to seek further advice regarding the possible impacts of the amendment on industry, including preparations for veterinary use that may contain sulfonamide antibiotics, prior to deciding on the implementation date.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

### *a) the risks and benefits of the use of a substance*

#### Risks:

– Primary reason for inclusion of sulfonamides in Schedule 4 is to minimise the risk of further development of antibiotic resistance.

– Some of the sulfonamides have antimicrobial activity and are used, either singly or in combination with other sulfonamides to treat infections in humans as well as animals. The risks associated with sulfonamide containing antibiotics, include allergic reactions and development of antibiotic resistance.

– Industrial use of sulfonamides generally presents with low acute and repeat dose toxicity in the liver and bladder by most routes of administration, and they are not expected to be genotoxic or carcinogenic.

#### Benefits:

– Sulfonamides have a diverse and significant range of benefits in many applications, including pharmaceuticals as topical antibiotics, and industrial uses.

### *b) the purposes for which a substance is to be used and the extent of use of a substance*

– Safe therapeutic use of sulfonamide antibiotics, to treat diseases in humans and food-producing animals requires oversight by a suitable health professional.

### *c) the toxicity of a substance*

– Sulfonamide antibiotics have well documented side-effects.

– Incidental dermal and ocular exposure to toluenesulfonamides may occur from use of paints and coating products containing sulfonamides. Dermal exposure to toluenesulfonamides is expected to be significantly higher through during normal use of cosmetic nail polish products, although intentional topical application is required for such usage.

- Based on the hazard profile, the chemicals are unlikely to pose a risk to workers in industrial applications where catalytic or low concentrations are employed.
- Systemic long-term effects may occur following repeated exposure to high doses of herbicidal sulfonamides, but rigorous use of safe handling protocols and personal protective equipment should mitigate this risk.

### *d) the dosage, formulation, labelling, packaging and presentation of a substance*

- Not applicable.

### *e) the potential for abuse of a substance*

- Use of sulfonamides as growth promotants in agricultural settings can lead to the development of antimicrobial resistance.

### *f) any other matters that the Secretary considers necessary to protect public health*

- The intent of the original scheduling was related to risks associated with sulfonamide antibiotics, particularly when used in humans and food-producing animals.
- The current entry inadvertently captures multiple industrial and agricultural chemicals, many of which may not require scheduling due to low toxicity and/or low likelihood of consumer exposure.
- A more detailed review of the potential longer-term impact of herbicidal applications may be necessary.
- Overuse of sulfonamide herbicides since 1980s has resulted in resistance in non-target plants.
- Case by case consideration of sulfonamides where there is risk of consumer exposure; not already scheduled and have an identified health risk.

## Reasons for the interim decision (including findings on material questions of fact)

I agree with the Committee's findings on the relevant provisions of section 52E of the Act.

I have made an interim decision to amend the Poisons Standard with regards to the sulfonamides group entry in Schedule 4. This follows an evaluation by AICIS, which was published in January 2022. I have found the existing sulfonamide’s entry in Schedule 4 inadvertently captures a broad range of substances, notably toulensulfonamides, that are inconsistent with Prescription Only (Schedule 4) medicines. I have, therefore, found it appropriate to refine the entry to capture sulfonamide antibiotics, except when listed in another schedule.

I have considered the sole public submission received during the pre-meeting consultation period. The public submission supported the proposal but did not provide a written component.

I note the scheduling decision to create a ‘sulfonamides’ group entry in Schedule 4, which was made by the National Drugs and Poisons Schedule Committee (NDPSC) in June 2004. At that time, the NDPSC considered the scheduling of sulfonamide antibiotics as part of the response to the recommendations of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) and the subsequently convened Expert Advisory Committee on Antimicrobial Resistance (EAGAR). EAGAR recommended that all sulfonamide antibiotics with products registered for use in humans and food animals be included in Schedule 4 due to the potential of antibiotic resistance. However, the ‘sulfonamides’ group entry that was created at the time, now inadvertently captures a broad range of substances with a sulfonamide functional group in their structure.

In relation to s 52E(1)(b) of the Act, sulfonamides are widely used for therapeutic purposes. There are a range of drugs with a sulfonamide functional group in their structure. These include drugs with and without antibiotic activity. Those without antibiotic activity, such as furosemide (diuretic) and celecoxib (anti-inflammatory), are already listed separately in Schedule 4. There are also inactive sulfonamides that are used in medicinal formulations, such as saccharin as a sweetener.

I agree with the Committee's advice, that sulfonamide antibiotics currently captured by Schedule 4 remain appropriate. A primary reason for their inclusion is to minimise the risk of antibiotic resistance from uncontrolled use, which can cause communal harm as per scheduling factor 7 of Schedule 4 in the SPF. Sulfonamide antibiotics also meet scheduling factor 1 of Schedule 4 as they are used to treat a range of bacterial infections that require medical or veterinary intervention.

Besides the broad use of sulfonamides in pharmaceuticals, they have a highly varied range of applications including pesticides, food additives, cosmetics, coating products, and as components of sealants and adhesives. I note for example that there are almost 300 listings on the industrial chemicals inventory described as 'sulfonamide', which cover a wide range of chemistry and uses. While many of these substances have not been individually considered for scheduling, there are several sulfonamides, some with antibiotic activity, listed explicitly in schedules other than Schedule 4. In line with the Committee's advice, the scheduling of sulfonamide antibiotics listed in other Schedules or Appendices is likely to require review.

However, on this occasion I have considered the scheduling of non-antibiotic sulfonamides such as toluensulfonamides, following the evaluation by the Australian Industrial Chemicals Introduction Scheme (AICIS). Toluensulfonamides do not have any therapeutic or antibiotic activity. Therefore, I find it inappropriate for them to be subject to medical or veterinary prescribing requirements as a consequence of the current scheduling. Toluensulfonamides are reported to have industrial uses in cosmetic nail polish products at concentrations of up to 10%. They are also reported to be used in paint and coating products, inks and toners, adhesives, sealants and as a chemical intermediate for fluorescent pigments. Along with a range of industrial uses, toluensulfonamides are used in low concentrations as a preservative in agricultural products.

The use of paints and coating products containing toluensulfonamides present a risk of incidental dermal and ocular exposure. Whereas dermal exposure to toluensulfonamides is expected to be significantly higher during normal use of cosmetic nail polish products. I note there is limited information on the use pattern of toluensulfonamides across its entire range of applications. Based on the AICIS evaluation, toluensulfonamides are expected to have low acute oral, dermal, and inhalation toxicity (s 52E(1)(a) and (c)). They may cause slight skin and eye irritation but are not expected to cause skin sensitisation, genotoxicity, carcinogenicity or specific reproductive or developmental toxicity. The margin of exposure from the use of toluensulfonamides in nail polish products indicate a low risk of adverse health effects. I note products solely packed and sold for industrial use are covered by labelling requirements under jurisdictional Work Health and Safety laws.

It is for these reasons that I have decided to exclude non-antibiotic sulfonamides, such as toluensulfonamides, from scheduling by restricting the entry in the Poisons Standard to sulfonamide antibiotics only, except when listed in another schedule.

I have decided on an implementation date of 1 February 2025 as the amended entry for sulfonamides should not adversely impact industries manufacturing or selling products containing either antibiotic or non-antibiotic sulphonamides.

## Implementation date

1 February 2025

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