



Australian Government
Department of Health
Therapeutic Goods Administration

Regulatory options for appropriate access and safety controls for alkyl nitrites – seeking public feedback

Version 1.0, November 2018

TGA Health Safety
Regulation

Historical consultation document

Copyright

© Commonwealth of Australia 2018

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>

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.

Historical consultation document

Contents

Executive summary	4
Background	4
The Scheduling Policy Framework	6
Purpose	6
The Scheduling Factors	6
Current scheduling status	6
Major themes from public submissions received during 2018	7
People want a safe product to use	8
People want regulation that is proportional to risk	8
People want education on how to use alkyl nitrites safely	8
Summary of the evidence to be considered	9
The Principles of Scheduling	13
The cascading principle	13
Invitation to comment	13
Analysis against factors for prohibited substances (Schedule 9)	14
Analysis against factors for controlled drugs (Schedule 8)	14
Analysis against factors for prescription only medicines (Schedule 4)	14
Analysis against factors for pharmacist only medicines (Schedule 3)	16
Analysis against factors for pharmacy only medicines (Schedule 2)	17
What if alkyl nitrites were available for general sale?	18
International regulations	19
The European Union	19
The United Kingdom	19
The United States of America	19
Canada	19
New Zealand	19

Executive summary

Prior to making a final decision on possible amendments to the Poisons Standard schedule for alkyl nitrites, the TGA decision-maker (delegate) has requested that further public consultation be undertaken.

The reasons for considering amendments to the Poisons Standard for alkyl nitrites, the main components of “poppers”, arose from the need to balance several factors:

- The products have significant use among a number of groups in the Australian community.
- Many products contain prescription-only substances and thus in most cases are not being legally supplied or accessed at present.
- While many people who use alkyl nitrite products do not experience adverse effects, some serious health impacts have been reported in certain users from both inhalation and ingestion these products. Adverse effects include loss of vision (maculopathies or retinal damage) and presentation in hospital emergency departments that can subsequently lead to hospitalisation due to methaemoglobinaemia. Methaemoglobinaemia is a very serious condition which results in less oxygen delivery to bodily organs resulting in chest pain, shortness of breath, altered mental state and possible permanent organ damage.
- More commonly, the alkyl nitrites can cause low blood pressure, tachycardia, dizziness, nausea and fainting, especially if the user is taking certain prescription medicines.

There is some, incomplete evidence that particular members of the family of alkyl nitrite substances may be more toxic than others.

This discussion paper has been prepared to support public comment on the impact of different potential approaches to access and safety controls, and on the risks associated with alkyl nitrites. It analyses the available evidence against the scheduling factors, as stipulated by the [Scheduling Policy Framework](#) established by the Commonwealth and States and Territory governments, and includes discussion on a range of possible options for access controls to alkyl nitrite containing products. These options range from general (unrestricted) sale, through to access in pharmacies, pharmacist only access, prescription only access or prohibited substance status. Consideration is also given as to whether it is appropriate to apply different access controls to different members of the alkyl nitrite family of substances.

Alkyl nitrites may play an important role in the lives of some members of the LGBTIQ community in particular. This consultation will involve expert assessment and community engagement; it will enable the consideration of risks and benefits, purposes for and patterns of use and the public health implications of various options for access and safety controls via the Poisons Standard for alkyl nitrites.

Background

In Australia, medicines and poisons (chemicals classified as “use with caution”, “poison” or “dangerous poison”) are classified into Schedules according to the level of regulatory control required over the access to (availability of) the substance to protect public health and safety. The Schedules are published in the [Poisons Standard](#) and are given legal effect through state and territory legislation. The Poisons Standard is formally referred to as the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Decisions on scheduling of medicines are made by a senior medical officer with the Therapeutic Goods Administration (TGA) acting as a delegate of the Secretary of the Commonwealth Health Department.

On 12 April 2018 a [scheduling amendment was proposed](#) by the delegate of the Secretary of the Department of Health to create a new Schedule 4 (Prescription Only Medicine) group entry for alkyl nitrites, some of which have a street name of 'poppers', and amend the Appendix A listing for lubricants. Alkyl nitrite containing products for sale in adult shops and online include those labelled as 'personal lubricants'. Some suppliers are claiming that the substances in these products are not captured by scheduling because they fall under the exemption for lubricants in Appendix A of the Poisons Standard. The original intention of the Appendix A exemption was to cover lubrication of machinery parts (but not personal lubricants) so the Appendix A entry requires clarification.

The matter was referred to the June 2018 meeting of the Advisory Committee on Medicines Scheduling (ACMS), which comprises medical doctors, pharmacists and senior state and territory government health department officials, with a pharmacy or medicine background. Following receipt of advice from this committee, the delegate's [interim decision on alkyl nitrites](#) was published on 10 September 2018. It proposed to move currently scheduled alkyl nitrites from Schedule 4 (Prescription only substances) to create a new Schedule 9 (Prohibited Substance) group entry for (all) alkyl nitrites and amend the Appendix A listing for lubricants.

A number of public submissions were made on the interim decision.

On 8 November 2018, at a joint meeting of the ACMS and the Advisory Committee on Chemicals Scheduling (ACCS), further consideration was given to the scheduling of alkyl nitrites, with several presentations from external parties given at that meeting.

Following this meeting the delegate considered the advice from ACMS and ACCS, the presentations made at the joint meeting and the public submissions received, and decided that further public consultation was warranted before making a final decision.

The Scheduling Policy Framework

Purpose

[The Scheduling Policy Framework](#) sets out the national policy for applying access restrictions on all “poisons”. As defined in the Poisons Standard, poisons include medicines for human therapeutic use, veterinary medicines, agricultural, domestic and industrial chemicals where there is a potential risk to public health and safety.

Poisons are scheduled according to the risk of harm and the level of access control required to protect consumers. State and territory governments are responsible for imposing legislative controls on the supply of poisons. Generally, these controls flow from the schedule in which the poison has been included.

Provisions for the scheduling of medicines and chemicals are set out in the *Therapeutic Goods Act, 1989* (the Therapeutic Goods Act) and associated Regulations. They have been developed to ensure operational effectiveness while supporting the existing high level of scheduling uniformity across states and territories.

The Scheduling Factors

When making a final decision, the delegate must consider the matters to be taken into account under section 52E of the Therapeutic Goods Act, the *Scheduling Policy Framework*, information obtained through public consultations and meetings, public submissions received, the advice of the advisory committees plus any additional evidence that is considered relevant.

The matters to be taken into account under section 52E of the Therapeutic Goods Act are:

- a) the 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;
- f) any other matters that the Secretary considers necessary to protect public health.

In order to determine the relevant schedule for a substance, factors specific to each schedule need to be considered. These factors are intended to ensure consistency in the application of public health risk consideration when making a scheduling decision.

Current scheduling status

Five (5) alkyl nitrites are currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4 (Prescription only medicines)

AMYL NITRITE

BUTYL NITRITE

ISOAMYL NITRITE

ISOBUTYL NITRITE

OCTYL NITRITE

This makes the use or supply of these substances only by or on the order of persons permitted by State and Territory legislation to prescribe (typically medical practitioners), and should only be available from a pharmacist on prescription from a medical practitioner.

Therefore, the circumstances in which the proposed amendment to the Poisons Standard are being considered are quite serious, given that most access is currently not legal (and there are uncommon but very serious adverse events in some people from use alkyl nitrites). Presently those supplying, possessing and using alkyl nitrites without a prescription are contravening both the laws of their State or Territory as well as Federal laws (i.e. the Therapeutic Goods Act).

It is important that these circumstances are not left unchecked. This paper is concerned to present options to regularise the situation in law, while recognising the significant use of these products but the serious (in several cases life threatening) adverse events in some people who have used them.

Major themes from public submissions received during 2018

From the [public submissions](#) it is clear that people that currently use alkyl nitrites want three main outcomes: a safe product to use; regulation that is proportional to the risks involved with their use and education on how to use alkyl nitrites safely.

These outcomes broadly align with what considerations, including those prescribed by the *Scheduling Policy Framework*, must be taken into account to amend the Poisons Standard.

Turning to the first of the three outcomes sought by the public submissions, some of the considerations that must be made by the decision maker under section 52E(1) of the Therapeutic Goods Act like 'the risks and benefits' of use, 'the purposes' of use, 'the extent' of use, 'toxicity' and the potential for 'abuse', all go to an assessment of whether alkyl nitrites may be a **safe product to use**. For example, both evidence of, on the one hand, the potential for abuse, and on the other hand, the wide and largely safe use by a section of the community for sexual health purposes will be given considerable weight in the deliberations required by the decision-maker under section 52E(1) of the Therapeutic Goods Act.

However, singular consideration cannot be given to whether the alkyl nitrites have a therapeutic use or a therapeutic benefit as defined in law. Consideration must also be given to other factors like the risks of use of alkyl nitrites or of their toxicity or their potential for abuse. Therefore, the fact that alkyl nitrites have a 'therapeutic use', as that term is defined by the Therapeutic Goods Act, such as influencing or modifying a physiological process, is not the end of the matter. In addition, for example, to the benefit for sexual health of the muscle relaxant effect, the associated risks of use along with their toxicity and the potential for abuse are also relevant.

These considerations are consistent with the *Scheduling Policy Framework's* requirement in a number of its schedules to consider whether the alkyl nitrites have an established 'therapeutic value'. This is not the same as 'therapeutic use'. So whilst the muscle relaxant use for alkyl nitrites is its therapeutic use, its therapeutic value is the worth, merit or importance of that use measured having regard to the factors earlier mentioned in the discussion about section 52E(1).

Regulation that is proportional to the risks involved with the use of alkyl nitrites aligns with section 52E(1) factors like 'the risks and benefits' of their use and the 'dosage, formulation, labelling, packaging and presentation of a substance'. For example changes to the current

dosage, formulation, labelling, packaging and presentation of a substance could be considered to encourage safe use and reduce risk or harm, risks of abuse or likelihood of a toxic reaction.

Education on how to use alkyl nitrites safely also feeds into the decision-making delegate's required consideration of the 'the risks and benefits' of their use, 'the purposes' for which they are to be used, 'the extent' of their use, their 'toxicity' and the potential for their 'abuse'. The extent to which education on the safe use of alkyl nitrites is likely to reduce the opportunity for their abuse or the likelihood of a toxic reaction is also considered.

People want a safe product to use

Phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil are available for individuals who have trouble with insertive sexual intercourse.

Inhaled nitrites induce the relaxation of smooth muscle and cause the dilation of blood vessels in the brain and periphery. As a result of muscle relaxation, they prevent and alleviate spasm and have been claimed to prevent potential tearing of the inner sphincter during receptive anal intercourse.

While there are over-the-counter medicines containing glyceryl trinitrate that could cause vasodilation and smooth muscle relaxation, they are not approved for use by individuals who have trouble with receptive sexual intercourse. These medicines can be accessed without a prescription but have not seen significant use for this purpose.

Glyceryl trinitrate, is generally provided as an oil based ointment for the treatment and relief of symptoms of anal fissure or the relief of pain and discomfort after haemorrhoidectomy. The ointment may damage the latex of the condom which could potentially lead to increased transmission of sexually transmitted diseases.

Regulatory guidelines and sale of a safe product with consumer health warnings regarding risks is desirable. For instance, there is a very real risk of hypotension when used with sildenafil citrate which, given similar sexual utility, is often used in combination.

People want regulation that is proportional to risk

Prohibiting the use of alkyl nitrite substances through a Schedule 9 entry (as proposed by the interim decision) in order to protect public health will have legal consequences that vary between jurisdictions. It would criminalise the use of nitrite inhalants by gay and bisexual men, as well as an undetermined number of queer women, non-binary people, and heterosexual men and women who currently use nitrite inhalants. Some submissions emphasised that health risks are significantly greater when alkyl nitrites are ingested compared to their use via inhalation.

Some submissions suggested that including alkyl nitrites in Schedule 9 may not reduce their availability but rather drive the market underground and remove the opportunity to potentially regulate the formulation and packaging of alkyl nitrites as therapeutic products.

People want education on how to use alkyl nitrites safely

More support could be provided to enable consumers to access education on how to use alkyl nitrites safely.

Regulatory responses might include changes in labelling of products to describe safe use, emphasise the risks, and provide advice about child-safe storage; mandating child-proof caps on

packaging and other caps to prevent ingestion but not inhibit inhalation; educational messages about risk reduction; and point of sale restrictions such as minimum age limits for purchase or perhaps making them available via pharmacies where people could access quality advice and safety measures. Not all of these regulatory responses are within the powers of the TGA.

Summary of the evidence to be considered

'Poppers' is the street term for various alkyl nitrites taken for recreational purposes through direct inhalation. These include amyl nitrite, butyl nitrite, isoamyl nitrite, isobutyl nitrite and octyl nitrite, with more recent variations including isopropyl, N-propyl and cyclohexyl nitrite.

They have been used for the reported sensations of head rush, euphoria, uncontrollable laughter or giggling, and other sensations that result from the hypotensive effect and to increase sexual arousal and desire. In addition, the smooth muscles of the anus and vagina are relaxed.

Alkyl nitrite containing products are sold under the guise of room deodorisers, lubricants and cleaning solvents, and are readily available in adult shops and online. While the use of poppers was historically associated more with the LGBTIQ community, it is possible its use has expanded more broadly in the community.

Amyl nitrite (a specific alkyl nitrite) was supplied as a medicine in Australia until 1991 for the treatment of 'angina of effort and the relief of renal and gall bladder colic. It was also employed in the immediate treatment of cyanide poisoning'. There is limited and superseded therapeutic use for amyl nitrite as an antidote for cyanide poisoning. Current alternative treatment recommendations for cyanide poisoning include sodium thiosulfate plus hydroxocobalamin, or sodium nitrite plus sodium thiosulfate.¹

There is currently no medicine containing alkyl nitrites registered on the Australian Register of Therapeutic Goods (ARTG), and thus at this time there are not medicines available in pharmacies. However there are some alkyl nitrite (amyl nitrite) products available as pharmacy or prescription medicines internationally (<https://www.james-alexander.com/ja-pharmaceuticals/>). Further details on the regulation of alkyl nitrites overseas can be found in the section on International Regulation later in this paper.

Regular use of amyl nitrite does not result in dependence. People who use it regularly will not experience significant withdrawal symptoms, however it may take a few days for their body to get used to not having the drug in their system.²

Further facts have been grouped under the matters to be taken into account by the decision-maker under section 52E of the Therapeutic Goods Act:

a) the risks and benefits of the use of a substance;

- Alkyl nitrites are used to induce euphoric (perceived due to dilation of blood vessels in brain and periphery), analgesic and muscle relaxant effects³. Recreationally, it is used

¹ Therapeutic Guidelines, Toxicology and Wilderness, Therapeutic Guidelines Ltd (eTG March 2018 edition)

² Upfal, J. (2016). *Australian Drug Guide* (8th Edition ed.). Melbourne: Black Inc (<https://adf.org.au/drug-facts/amyl-nitrite/>)

³ Docherty et al (2017) 'Poppers Maculopathy': a case report and literature review, *Canadian Journal of Ophthalmology*, In press. DOI: <https://doi.org/10.1016/j.jcjo.2017.10.036>

to enhance sexual experience or to experience a general sense of pleasure. The effects are felt within 30 seconds of taking the drug, and last for around 2-3 minutes⁴.

- They induce the relaxation of smooth muscle and are used to relax and prevent potential tearing of the inner sphincter during receptive anal intercourse.
 - There appears to be an increasing trend with time in the use of volatile alkyl nitrites, with a 56% increase in exposures from 2009 to 2014 according to statistics collected from Australian Poisons Information Centres.
 - The Australian Poisons Information Centres report that exposures have increased six-fold in past decade.
 - There are two deaths attributed to alkyl nitrite use recorded in the National Coronial Information System
 - The Australian Poisons Information Centre's 2018 data for alkyl nitrites is summarised below. Currently more calls are received about alkyl nitrites than about synthetic cannabinoid exposures:
 - § there were 69 cases in total (72% males and 28% females)
 - § an increase in contact with the NSW Poisons Information Centre has been observed (43 calls from 1 January 2018 to 10 October 2018 as compared with 20 in 2017)
 - § the risk of hospitalisation is high after accidental exposure (3 in 4)
 - § 78% of the cases were symptomatic at the time of contact, with Poisoning Severity Scores of minor (34), moderate (5) or severe (1).
 - § 'unintentional misuse' (accidental snorting/ingestion) tends to occur with intoxication or unfamiliarity. A total of 38 of 69 cases involved ingestion of the substance and just 18 of the 69 cases involved inhalation.
 - Over an eleven year period (2004-2014), Australian Poisons Information Centres received 273 calls about alkyl nitrite exposures:
 - § 3.7% of calls (10 cases) which involved accidental paediatric exposures.
 - § hospitalisation was required in 72.5% of all cases with almost all of these requiring a clinical toxicology consultant, indicating high perceived risk or severity.
 - § 15% (41 cases) of the hospital admitted patients presented with methaemoglobinaemia, with 14 requiring treatment with the antidote, methylene blue.
- According to St George's Hospital, University of London, there have been 14 deaths in the UK related to inhaling alkyl nitrites since 1971, three of which were in 2006⁵.
- Alkyl nitrites are sweet-smelling liquids and pose a risk to child safety through cases of accidental ingestion.

⁴ Williams, J. F., Storck, M (2007). Committee on Substance Abuse, & Committee on Native American Child Health. Inhalant Abuse. *American Academy of Paediatrics*, 119(5), 1009-1017.

⁵ <http://www.re-solv.org/wp-content/uploads/2011/12/Poppers.pdf>

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

- There are no products on the ARTG that contain alkyl nitrites.
- While products have been put on the market with claimed uses other than as inhalants, it is unlikely that they are actually used for these purposes.
- Alkyl nitrites are largely used recreationally as 'party drugs'. There has been an increase in the use of alkyl nitrites in Australia over recent years. According to recent reports of the Ecstasy and Related Drugs Reporting System (EDRS)⁶ the use of amyl nitrite has varied over the course of monitoring, ranging from 14% in 2006 to 29% in 2010. In 2017, recent use of alkyl nitrites was reported in 25% of study participants. In 2018, one fifth (22%) reported recent use of amyl nitrite. Frequency of amyl nitrite use was generally low, with participants reporting a median of four days of use in the last six months.

c) The toxicity of a substance:

- Alkyl nitrites are toxic via inhalation. Toxicity includes tachycardia, hypotension, headache, flushing, dizziness, nausea, and syncope.⁷
- Co-use with phosphodiesterase type 5 (PDE-5) inhibitors, such as sildenafil (Viagra®) can lead to severe hypotension (low blood pressure). There is also a risk of cardiovascular harm when used in conjunction with other vasodilators⁸.
- Alkyl nitrites can cause chemical burns to the skin and eyes on direct contact. Inhalation of volatile nitrites has led to severe and extensive contact dermatitis around the face with secondary spread elsewhere on the body⁹.
- Adverse events associated with the use of alkyl nitrites include methaemoglobinaemia and maculopathy.^{10,11} Haemolytic anaemia has also been reported¹² and may be more likely in those with glucose-6-phosphate deficiency¹³.
- Inhalation of alkyl nitrites can lead to methaemoglobinaemia and even death, with significantly increased risk if ingested. Methaemoglobinaemia is potentially life threatening if not treated appropriately¹⁴. Alkyl nitrites reduce the ability of red blood cells to transport oxygen to the tissues, leading to severe, potentially life-threatening clinical features and/or death with chest pain, shortness of breath, altered mental state and possible permanent organ damage.

⁶ [The Ecstasy and Related Drugs Reporting System \(EDRS\)](#)

⁷ Romanelli, F. et al., (2004) 'Poppers: Epidemiology and Clinical Management of Inhaled Nitrite Abuse', *Pharmacotherapy*, 24(1), pp.69-78

⁸ <https://www.drugs.com/drug-interactions/amyl-nitrite-with-viagra-200-0-2061-1352.html>

⁹ Bos JD, et al. (1985) Allergic contact dermatitis to amyl nitrite ('poppers'). *Contact Dermatitis*; 12: 109

¹⁰ Tiew S, Choudhary A. (2015) 'Poppers maculopathy or retinopathy?' *Eye*. 29, 147-8

¹¹ Hunter, L. et al., (2011) 'Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: A review', *British Journal of Clinical Pharmacology*, 72(1), pp.18-26

¹² Romeril KR, Concannon AJ (1981). Heinz body haemolytic anaemia after sniffing volatile nitrites. I; 1: 302-3

¹³ Neuberger A, et al. (2002) Hemolytic anemia in a G6PD-deficient man after inhalation of amyl nitrite ('poppers'). *Isr Med Assoc J*; 4: 1085-6

¹⁴ Hunter, L. et al., (2011) 'Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: A review', *British Journal of Clinical Pharmacology*, 72(1), pp.18-26

- Bilateral vision loss has been reported due to damage to the foveal photoreceptors; in some patients symptoms improved over several weeks¹⁵. Complete recovery of visual function in chronic users, even after drug use is ceased is rare.¹⁶ According to a 2016 UK government report (Advisory Council on the Misuse of Drugs) there are around 30 published cases of ophthalmological damage associated with use of alkyl nitrites.
- Ophthalmologists in Australia are also seeing an increase in cases of temporary and permanent macula damage caused by recreational drug use of alkyl nitrite compounds^{17,18}. Ophthalmologists believe that chronic use could lead to irreversible damage. Alkyl nitrite ‘popper’ maculopathy causes gradual vision loss and clinically is the equivalent of having a hole burned in the macula from gazing at the sun.
 - § Macula damage is a rare but serious complication of alkyl nitrite inhalation.
 - § Acute toxicity in occasional users appears to have a reasonable prognosis for full recovery¹⁹.
 - § Chronic toxicity in long term frequent users is associated with long term irreversible bilateral structural macula damage.
 - § Reported cases seem to be associated with isopropyl nitrite isoform.
- In the EU in 2007 and in Canada in 2013, regulatory action was taken to ban the sale of the formulations commonly included in poppers products, such as amyl and isopropyl nitrite. This led to some manufacturers deciding to include different alkyl nitrite formulations in poppers. Since that time there have been several reports of a new form of visual loss termed ‘poppers maculopathy’. It is thought that a change in compound from isobutyl nitrite to isopropyl nitrite might be responsible for the increase in the number of cases of macula damage. Some users have reported the reformulated products often cause an intense headache, ‘blue lips’ and a characteristic chesty cough in the days after use. *The Lancet*²⁰ attributes ‘poppers maculopathy’ to the reformulated product.

d) the dosage, formulation, labeling, packaging and presentation of a substance

- Currently, products containing alkyl nitrites are not approved for human use so they are not subject to appropriate quality controls or labelling to include directions for use or safety warnings. Public submissions noted the deficiency in the labelling of these products.
- Accidental swallowing by children and adults, and potentially deliberate swallowing by adults due to lack of information on how the drug should be taken would need to be minimised, given their association with emergency department visits and hospitalisation.

¹⁵ Vignal-Clermont C, et al. (2010) Poppers-associated retinal toxicity. *N Engl J Med*; 363: 1583–5

¹⁶ Audo, I. et al., (2011). Foveal damage in habitual poppers users. *Archives of Ophthalmology*, 129(6), p.703–708.

¹⁷ Davies AC et al (2012) Adverse ophthalmic reaction in poppers users: case series of ‘poppers maculopathy’. *Eye* p. 1479-85

¹⁸ Van Bol LB et al (2017) Clinical Phenotypes of Poppers Maculopathy and Their Links to Visual and Anatomic Recovery. *Ophthalmology*, p.1425-26

¹⁹ Audo I et al, (2011) Foveal Damage in Habitual Poppers Users *Archives Ophthal*, p. 703-8

²⁰ Gruener, A.M., et al.(2014) Poppers maculopathy. *Lancet*, **384**(vol 9954): p. 1606.

e) the potential for abuse of a substance:

- Products are being used for euphoric and muscle relaxant effects. Use of these products has resulted in harm to the user due to adverse events.

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

- Amendments to the Appendix A lubricant entry will clarify its intent, restricting the Appendix A exemption under the Poisons Standard to machinery use, not personal care use.

The Principles of Scheduling

The Poisons Standard lists poisons in ten Schedules according to the degree of control recommended to be exercised over their availability to the public.

Poisons for therapeutic use (medicines) are mostly included in Schedules 2, 3, 4 and 8 with progression through these Schedules signifying increasingly restrictive regulatory controls.

For some medicines and agricultural, domestic and industrial poisons, Schedules 5, 6 and 7 represent increasingly stricter container and labelling requirements with special regulatory controls over the availability of the poisons listed in Schedule 7.

Schedule 9 contains substances that should be available only for teaching, training, medical or scientific research including clinical trials

Schedule 10 contains a list of substances which should be prohibited because of their known dangerous properties.

The cascading principle

The model for making scheduling decisions embodies a 'cascading principle'²¹.

For medicines, a substance is first assessed against the factors for Schedule 10, 9 and 8. If those factors are not applicable, the substance is assessed against the Schedule 4 factors and if not applicable, against the Schedule 3 factors. If the Schedule 3 factors are not applicable, then it is assessed against the Schedule 2 factors.

Invitation to comment

You are invited to comment on possible options for the future scheduling of alkyl nitrites.

Submissions can be provided along with any supporting evidence against all, or any, of these options. You may also wish to comment on whether it would be appropriate for scheduling to vary for individual members of the alkyl nitrite family of substances.

²¹ <https://www.tga.gov.au/sites/default/files/scheduling-handbook-guidance-amending-poisons-standard.pdf>

Analysis against factors for prohibited substances (Schedule 9)

1. The substance is included in either Schedule IV to the United Nations Single Convention on Narcotic Drugs, 1961 or in Schedule I to the United Nations Convention on Psychotropic Substances 1971.

Not relevant as alkyl nitrites are not included in these schedules.

2. The substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use.

Several commonly used alkyl nitrites, like isopropyl nitrite, are currently not scheduled. There is a correlation of the use of poppers with illegal drug use. In addition, some alkyl nitrites that are currently in schedule 4 are obtained without a prescription, which is illegal.

Would a schedule 9, entry for all of these substances be appropriate? Should some remain in schedule 4 (such as amyl nitrite, where there is some clinical experience with the use of the substance), and all of the others be put into schedule 9?

If all alkyl nitrites were put into Schedule 9, then responsibility for enforcement of these regulatory controls would be given to state and territory law enforcement/police departments.

Analysis against factors for controlled drugs (Schedule 8)

1. The substance is included in Schedule I or II of the United Nations Single Convention on Narcotic Drugs 1961 or in Schedule II or III of the United Nations Convention on Psychotropic Substances 1971.

Alkyl nitrites are not included in these documents.

2. The substance has an established therapeutic value but its use, at established therapeutic dosage levels, is recognised to produce dependency and has a high propensity for misuse, abuse or illicit use.

Alkyl nitrites for inhalation to treat problems associated with receptive sexual intercourse do not produce dependency like other substances in schedule 8 such as cocaine, fentanyl, morphine or oxycodone²².

Analysis against factors for prescription only medicines (Schedule 4)

1. The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention²³.

Due to the mode of action of the alkyl nitrites and the resultant cardiovascular effects, medical review and assessment of the user may be beneficial before the substance is used. This would enable medical diagnosis of any underlying medical conditions such as cardiovascular disease, glaucoma

²² <https://adf.org.au/drug-facts/amyl-nitrite/>

²³ For the purposes of the document medical, veterinary or dental intervention is considered to include other authorised prescribers as described in relevant legislation of Australian states and territories.

or an enzyme deficiency (glucose-6-phosphate deficiency) that may be exacerbated by self-administration of alkyl nitrites.

2. The use of the substance requires adjunctive therapy or evaluation or specialised handling for administration.

The use of alkyl nitrites may require specialised handling for administration given that adverse effects are dependent on the amount used, how frequently they are used and how long they are used for, as well as the person's health and the other medications they may be taking. Since it is difficult to control how much is inhaled, people can accidentally overdose. Swallowing these products can lead to serious medical complications and may be fatal.

3. The use of the substance at established therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use.

Alkyl nitrites for inhalation to treat problems associated with receptive sexual intercourse do not produce dependency²⁴. However, products containing alkyl nitrites have been misused. Accidental swallowing by children and adults, and potentially deliberate swallowing by adults due to lack of information on how the drug should be taken could be minimised if made available as a prescription only medicine, and proper advice on use and possible adverse effects was provided.

4. The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical, veterinary or dental practitioner is required to minimise the risk of using the substance.

This factor appears to be particularly relevant due to the seriousness and severity of adverse events experienced by some alkyl nitrite users. Monitoring or intervention by a health care professional such as a medical practitioner may be beneficial in order to protect public health.

People with certain medical conditions and those taking certain medications (particularly drugs used to treat erectile dysfunction, and other drugs such as high blood pressure medications, certain migraine drugs, and high doses of aspirin) or illicit drugs are at particular risk of suffering adverse effects from use.

Amyl nitrite may increase intra-ocular and intracranial pressure and should be used with caution in patients with glaucoma, recent head trauma, or cerebral haemorrhage.

It is possible that medical advice about possible adverse events such as low blood pressure, tachycardia, dizziness, nausea and fainting, especially if the user is taking prescription medicines that lower blood pressure may assist to minimise the risks of using the substance.

Some people may be strongly encouraged by doctors or pharmacist not to try alkyl nitrites based on their medical history. It is unlikely that more serious and possibly permanent effects such as loss of vision (maculopathies or retinal damage) or methaemoglobinaemia could be minimised utilising medical monitoring or advice, since these are consequential following the use of the substance rather than associated with the problem being treated.

5. The margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical, veterinary or dental intervention to minimise the risk of using the substance.

Presently, the risk profile of alkyl nitrites is not well defined. The risk factors for adverse effects, interactions and contraindications are known however the incidence of adverse events with the use of alkyl nitrites for inhalation to treat problems associated with receptive sexual intercourse is not

²⁴ <https://adf.org.au/drug-facts/amyl-nitrite/>

well characterised in comparison with medicines that have been through the TGA's safety, quality and efficacy evaluation to become registered on the Australian Register of Therapeutic Goods.

Again, some people may be strongly encouraged by doctors not to try alkyl nitrites based on their medical history.

6. The seriousness or severity and frequency of the interactions of the substance (medicine-medicine, medicine-food, or medicine-disease) are such that monitoring or intervention is required by a medical, veterinary or dental practitioner.

Alkyl nitrites taken in combination with other vasodilators such as sildenafil are potentially life-threatening. The combination could lead to dangerously low blood pressure and heart rate, causing a person to faint, or even have a heart attack or stroke, therefore medical supervision of treatment could prevent harm and protect the public.

7. The use of the substance has contributed to, or is likely to contribute to, communal harm.

Not applicable

8. The experience of the use of the substance under normal clinical conditions is limited.

There is very little clinical experience with the use of alkyl nitrites. However, doctors can prescribe the following substances currently in Schedule 4: amyl nitrite; butyl nitrite; isoamyl nitrite; isobutyl nitrite and octyl nitrite. Patients may currently be able to access these substances through providing a prescription to a compounding pharmacy, or through access to unapproved medicines pathways.

Analysis against factors for pharmacist only medicines (Schedule 3)

1. The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine. There may be potential for harm if used inappropriately.

If there was an available commercial product, perhaps it could be made available from a pharmacist in a pharmacy if guidance was provided on appropriate use.

Guidance could include counselling about the adverse event profile, including warnings about transient effects such as low blood pressure, tachycardia, dizziness, nausea and fainting, especially if the user is taking prescription medicines that lower blood pressure.

In addition, advice could be given about more serious and possibly permanent effects such as loss of vision (maculopathies or retinal damage). The risk of possible hospitalisation due to methaemoglobinaemia could be emphasised, particularly if the product were ingested or repeatedly inhaled.

It appears that consumers should be counselled about the adverse event profile and risk of more serious and possibly permanent effects such as loss of vision (maculopathies or retinal damage) and hospitalisation due to methaemoglobinaemia.

2. The use of the medicine is not expected to produce dependency at either the established therapeutic dose or at suprathreshold doses. Where risk of misuse, abuse or illicit use is identified, the risk can be minimised through pharmacist-consumer consultation.

Alkyl nitrites for inhalation to treat problems associated with receptive sexual intercourse do not produce dependency²⁵. However, products containing alkyl nitrites have been misused. Accidental swallowing by children and adults, and potentially deliberate swallowing by adults due to lack of information on how the drug should be taken. Perhaps these risks could also be minimised if made available as a pharmacy-only medicine, and proper advice on use and possible adverse effects was provided by a pharmacist.

3. The risk profile of the medicine is well defined and the risk factors for adverse effects, interactions and contraindications are known, identifiable and manageable by a pharmacist.

Presently, the risk profile of alkyl nitrites is not well defined. The risk factors for adverse effects, interactions and contraindications are known however the incidence of adverse events with the use of alkyl nitrites for inhalation to treat problems associated with receptive sexual intercourse is not well characterised in comparison with medicines that have been through the TGA's safety, quality and efficacy evaluation to become registered on the Australian Register of Therapeutic Goods.

4. Where the medicine is intended for recurrent or subsequent treatment of a chronic condition, pharmacist intervention is required to monitor safe use of the medicine following recommendation by a medical practitioner or other authorised prescriber.

Problems associated with receptive sexual intercourse do not require medical diagnosis, however given the poorly characterised risk profile of alkyl nitrites the consumer may find it difficult to self-monitor the safe ongoing use of the medicine.

5. The use of the medicine at established therapeutic dosage levels may mask the symptoms or delay diagnosis of a serious condition.

The use of alkyl nitrites is unlikely to be safe to use in people with undiagnosed cardiovascular disease due to the mode of action being vascular dilatation and smooth muscle relaxation.

Analysis against factors for pharmacy only medicines (Schedule 2)

1. The quality use of the medicine can be achieved by labelling, packaging, and/or provision of other information; however access to advice from a pharmacist should be available to maximise the safe use of the medicine.

There is currently no medicine containing alkyl nitrites for inhalation registered on the Australian Register of Therapeutic Goods. If there was, should it be available on the shelves in a pharmacy for consumers to access without first having to speak to a pharmacist for guidance on appropriate use?

2. The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low.

The potential for harm from inappropriate use does not appear to be low. If available, the use of medicines containing alkyl nitrites could lead to methaemoglobinaemia in users if the product was taken incorrectly and ingested. There could also be added risks for people with glaucoma or anaemia, and those with enzyme deficiencies that make them more prone to methaemoglobinaemia. Alkyl nitrites taken in combination with other vasodilators such as sildenafil could lead to dangerously low blood pressure and heart rate, causing a person to faint, or even have a heart attack or stroke.

²⁵ <https://adf.org.au/drug-facts/amyl-nitrite/>

3. The use of the medicine is very unlikely to produce dependency (at either the established therapeutic dose or suprathreshold doses) and the medicine is very unlikely to be misused, abused or illicitly used.

Alkyl nitrites for inhalation to treat problems associated with receptive sexual intercourse do not produce dependency²⁶. However, products containing alkyl nitrites have been misused. Accidental swallowing by children and adults, and potentially deliberate swallowing by adults due to lack of information on how the drug should be taken. This risk is unlikely to be minimised if it was available on the shelves in a pharmacy for consumers to access without first having to speak to a pharmacist for guidance on appropriate use.

4. The risk profile of the medicine is well defined and the risks can be identified and managed by a consumer through appropriate packaging and labelling, including consultation with a health professional if directed by labelling.

Presently, the incidence of adverse events with the use of alkyl nitrites not well characterised in comparison with medicines that have been through the TGA's safety, quality and efficacy evaluation.

5. The use of the medicine at established therapeutic dosage levels is not likely to mask the symptoms or delay diagnosis of a serious condition.

The use of alkyl nitrites is unlikely to be safe to use in people with undiagnosed cardiovascular disease due to the mode of action being vascular dilatation and smooth muscle relaxation.

What if alkyl nitrites were available for general sale?

There is currently no medicine containing alkyl nitrites for inhalation registered on the Australian Register of Therapeutic Goods. Despite this, people that use alkyl nitrites are buying bottles of isopropyl nitrite (currently an unscheduled substance) from adult shops or online.

There are several risks of allowing these products to remain unregulated. The main risk is that manufacturers are not compelled to ensure that the substance in the bottle matches what is on the label; provide any guidance on safe use; give warnings on possible adverse effects; directions in the case of overdose; present the product in packaging to minimise accidental or deliberate swallowing or even the identity of the manufacturer so that product complaints can be directed appropriately.

There has already been an increase in the number of hospitalisations over time, and use is becoming more widespread and not limited to use in the LGBTIQ community. Making alkyl nitrites available for general sale increases its general acceptance as a safe product, when current evidence of adverse events suggests otherwise.

Making alkyl nitrites available for general sale is unlikely to protect public health in line with the legislative requirements.

²⁶ <https://adf.org.au/drug-facts/amyl-nitrite/>

International regulations

The European Union

In the European Union (EU), isobutyl nitrite was classified as a class 2 carcinogen under the EU Directive 76/769/EEC, making it illegal for shops to sell this variety of poppers. The European Medicines Agency doesn't have any information on products containing alkyl nitrites as active substances, however some of these products may be licensed directly for prescription as medicines by individual countries of the European Union.

The United Kingdom

In January 2016, the United Kingdom (UK) government's proposal to include alkyl nitrites in the Psychoactive Substances Act 2016²⁷ was overturned, following a review conducted by the Advisory Council on the Misuse of Drugs, which includes an assessment of the harms associated with use of these substances.

The UK Advisory Council on the Misuse of Drugs' statement on alkyl nitrites in 2016 concluded that their misuse is "not seen to be capable of having harmful effects sufficient to constitute a societal problem"²⁸. However the mandate of this council was to consider potential for abuse and misuse rather than the broader issue of benefits and harms of particular substances.

The United States of America

Amyl nitrite is a [prescription drug](#) has been used for the treatment of angina pectoris.

No alkyl nitrites are listed in the [FDA's Controlled Substances Act](#).

Canada

In Canada, products containing alkyl nitrites, such as poppers, are considered prescription drugs under the *Food and Drugs Act*.

Currently, no alkyl nitrite products are authorised for sale by Health Canada. When found for sale at retail outlets by Health Canada Inspectors, the products are seized. Health Canada has published several public advisories between [June 2013 to June 2017](#) and in [December 2017](#) on alkyl nitrites to warn Canadians about their potential serious risks.

New Zealand

In New Zealand, there are currently no approved medicines containing alkyl nitrites as active ingredients. Of all the alkyl nitrites, only amyl nitrite is classified in New Zealand. The remainder of the substances described are unscheduled. However, New Zealand usually only schedules active ingredients for medicines, and does not usually schedule substances if they are considered not to have therapeutic benefits.

Amyl nitrite was last considered by the Medicines Classification Committee (MCC) at the 50th meeting held on 13 November 2013. The [minutes have been published](#) on the Medsafe website.

²⁷ <https://services.parliament.uk/bills/2015-16/psychoactivesubstances.html>

²⁸ Home Affairs Committee, Psychoactive Substances (report), London: Stationery Office, 23 Oct 2015, p. 14 <https://publications.parliament.uk/pa/cm201516/cmselect/cmhaff/361/361.pdf>

The recommendation was *that the classification of amyl nitrite should be amended to prescription medicine; except when sold to a person who holds a controlled substances licence (issued under section 95B of the Hazardous Substances and New Organisms Act 1996) authorising the person to possess cyanide; except when sold to an exempt laboratory covered by a Hazardous Substances and New Organisms Act 1996 approved code of practice.*

Historical consultation document

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Scheduling Project Management	30 November 2018

Historical consultation document

Historical consultation document

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
<https://www.tga.gov.au>

Reference/Publication #