

14 January 2019

Public Consultation on Alkyl Nitrites  
Therapeutic Goods Administration  
PO Box 100 Woden  
Canberra ACT 2600

**RE: Public Consultation on regulatory options for appropriate access and safety controls for alkyl nitrites**

Thank you for the opportunity to submit feedback regarding amendments to the Poisons Standard schedule for alkyl nitrites before the final decision. This issue is of great importance to the LGBTIQ community in particular, but additionally has broad health implications for the general public.

This submission will consider the matters to be taken into account under 52E of the *Therapeutic Goods Act 1989*. In the process, it will respond to discussion paper as well as making some relevant comments, before concluding with a position summary.

**a. The risks and benefits of the use of a substance**

The primary therapeutic benefit of alkyl nitrites is to enable comfortable and enjoyable receptive intercourse. In this way, alkyl nitrites promote safe and healthy sexual health for people who might otherwise experience difficulties, particularly gay men engaging in receptive anal sex.

Further discussion on the therapeutic benefit appears below in Section B. The discussion paper proposes a general trend of increasing use, exposure and harm as a result of amyl nitrite use. The rest of this section will explore this background information.

The discussion paper notes deaths in several jurisdictions including Australia and the UK attributed to alkyl nitrite. Of the two cases within Australia, one is possibly 22 year old Jacob Langford who died at music festival Rainbow Serpent in 2017 after ingesting a bottle of amyl nitrite.

A coroners report found 16 substances including alcohol, prescription and recreational drugs in Langford's body, and found that the cause of death was 'multi-drug toxicity'. It is important to note that mortality occurred from misuse of alkyl nitrites and that this is unrepresentative of typical use.

Interestingly, the discussion paper cites a 2011 resource from Stratfordshire based charity Re-solv claiming 14 deaths in the UK since 1971, 3 in 2006 alone. It is not clear that this evidence is entirely reliable. According to the UK Office for National Statistics there were no recorded deaths involving alkyl nitrites in 2006.<sup>1</sup>

Additionally, the resource makes several dubious claims for which it offers no evidence. It claims that alkyl nitrite use increases the likelihood of HIV transmission and reduces cognitive inhibitions. A claim linking alkyl nitrites to glaucoma appears alongside the claim that users become dependant on nitrites to achieve sexual climax.

There is limited to no evidence for several of these claims, but they indicate the extent of misinformation regarding the relative risks and harms of alkyl nitrite use. Interestingly, the document does not appear to be peer-reviewed.

The discussion paper also notes an increase in calls to Australian Poison Information Centres [APICs] regarding alkyl nitrite use. APICs received 273 calls about alkyl nitrite exposure in the decade between 2004-2014 nationwide.

In fact, many over-the-counter medicines result in orders of magnitude more calls each year. The Victorian Poisons Information Centre [VPIC] received 2626 calls about paracetamol exposure and 1295 calls about ibuprofen exposure in 2017 alone.<sup>2</sup>

For further context, in that same year, the VPIC received 6 calls relating to alkyl nitrites compared to 187 calls for pen ink exposure and 383 calls for toilet bowl cleaner exposure. The low number of calls regarding alkyl nitrites, as compared to common medicines and household items, suggests that they are relatively safe.

The discussion paper goes on to assert that alkyl nitrites pose a 'risk to child safety' through cases of accidental indigestion, of which there were 10 cases during the 2004-2014 period. This is a relatively low concern given that, for example, twice as many children are admitted to hospital every week after ingesting button batteries.<sup>3</sup>

The paper also contends that alkyl nitrites are a 'sweet-smelling liquid'. This is perhaps the reasoning behind the notion that the substance poses a threat to children: they smell sweet and therefore edible, like children's soap or shampoo.

This characterisation of alkyl nitrites is generous at best and misinformed at worst. Most alkyl nitrites have a sharp, pungent aroma that is vaguely reminiscent of acetone or similar substances. They do not generally smell like something a child might consider palatable.

This discussion points to the fact that there is no overwhelming body of scientific literature confirming significant or widespread harms from typical alkyl nitrite use, which is controlled and occasional, and relatively limited harms from their misapplication.

Similarly, it seems apparent that there are relatively few mortalities and harmful exposures as compared to other regulated substances. Finally, there is no clear scientific or statistical

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<sup>1</sup> UK Office for National Statistics, *Deaths involving alkyl nitrites in England and Wales, 1993 to 2015, 2017* <<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007149deathsinvolvingalkylnitritesinenglandandwales1993to2015>>

<sup>2</sup> Victorian Poisons Information Centre, *VPIC Annual Report, 2017* <<http://www.austin.org.au/Assets/Files/VPIC%20Annual%20Report%202017.pdf>>

<sup>3</sup> Australian Competition & Consumer Commission & Product Safety Australia, *Button Batteries, 2018* <<https://www.productsafety.gov.au/products/electronics-technology/button-batteries>>

evidence that amyl nitrites represent a significant risk to children and the TGA should reconsider the veracity of this claim.

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

The discussion paper notes that amyl nitrite products are available on the market with described uses other than inhalants. This is often true but bears further exploration in relation to public health in at least two respects.

Firstly, the paper notes that the described use on a bottle of an alkyl nitrite (often sold in a tongue-in-cheek way as leather cleaner) may differ from its intended purpose. Ironically, perhaps, this has served to promote public health.

The accessibility of nitrites has meant that consumers can enjoy easier and healthier sexual intercourse but has also meant that there is no black market for these substances. Commercially available poppers are likely significantly more safe than the possibility of 'home-brewed' alkyl nitrites.

The cat-and-mouse game between producers of alkyl nitrites and international regulators has undercut more dangerous markets and may account for the relatively limited examples of irreversible harms and mortality. Moving alkyl nitrites to Schedule 8 or 9 risks reversing this trend and encouraging a harmful black market.

Secondly, it is important to recognise that although the bottle might claim to be leather or CD cleaner, that virtually all users are aware of this ruse. The branding and cultural context of alkyl nitrites has meant that people, particularly in the LGBTIQ community, are aware of their correct usage and the possible harms.

This is reinforced by the context of alkyl nitrite sales, which usually occurs in adult stores or sex on premises venues, where staff may engage in harm prevention strategies through peer education. The adult nature of the places of sale has also served to prevent minors access to alkyl nitrites.

The discussion paper suggests that the primary use is recreational. It is true that alkyl nitrites are often used in conjunction with recreational substances, however, the same can be said for many regulated or prescription drugs. However, recreational use is likely secondary.

Rather, the primary use of alkyl nitrites is for their analgesic and muscle relaxant effects, as noted in the TGA Interim Decision report. When inhaled, alkyl nitrites relax smooth muscle in the body which facilitates easier and safer sex, particularly receptive anal sex.

Difficulties with penetrative sex, particularly anal sex among men who have sex with men, can cause discomfort, pain and tearing in the anal mucosa. Alkyl nitrites have a crucial therapeutic use in enabling comfortable and enjoyable receptive intercourse and reducing the probability of pain, anal tears or fissures.

As discussed above, alkyl nitrites promote safe and healthy sexual intercourse for people who might otherwise have difficulties, particularly men who have sex with men engaging in receptive anal sex.

In this context, it is crucial to note that alkyl nitrite use is higher than average among gay and bisexual men, with 32-37% of the FLUX study cohort reporting recent use in the last six month period. The majority of consumers use an alkyl nitrite monthly or less.<sup>4</sup>

For these reasons, moving alkyl nitrites to Schedule 8 or 9 would disproportionately risk the health of people in the LGBTIQ community, particularly gay and bisexual men, by leaving them without therapeutic recourse, promoting marginalisation, or by fostering a harmful black market.

### **c. The toxicity of a substance**

The discussion paper notes that alkyl nitrites can be accompanied by some side effects, including tachycardia, hypotension, headaches, flushing, dizziness and nausea. Some of these side effects, such as flushing and dizziness are often mild and last only for a few seconds.

Other side effects such as nausea and headaches are less common, and generally only occur after overuse of alkyl nitrites. It is interesting to note that the cited source regards all alkyl nitrite use as 'abuse' and does not recognise the therapeutic benefit as such.<sup>5</sup>

While acknowledging the possibility of such side effects, it is important to note that other comparable prescription drugs have similar side effects, such as sildenafil or Viagra which is a phosphodiesterase-5-inhibitor often used as a sex aid by heterosexual men.

Side effects of sildenafil, even when correctly used, may include headaches, dizziness, flushing, indigestion, nasal congestion, swelling, rashes, redness, muscle pain, stomach pain, diarrhoea, and irritability.<sup>6</sup>

Some users of viagra may also experience priapism, abnormal vision such as changes in colour vision, blurred vision and sudden loss of vision in one or both eyes. The lattermost can be a sign of non-arteritic anterior ischemic optic neuropathy. Viagra use has also rarely resulted in heart attack, stroke and mortality.<sup>7</sup>

Sildenafil and alkyl nitrites are comparable in their use as sex aids, several of their side effects and their potential to exacerbate pre-existing conditions. Despite these side effects and possible harms, sildenafil is regulated and widely available in Australia.

Of course, the dangers of exacerbating conditions and harmful drug interactions represent a legitimate harm minimisation concern. An individual with a heart condition or who is taking Viagra may experience difficulties if also using alkyl nitrites.

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<sup>4</sup> F J Mohamed, M A Hammoud, L Maher, L Degenhardt, A Bourne, T Lea, S Vaccher, J Grierson, B Haire, G P Prestage, 'Age-related prevalence and twelve-month incidence of illicit drug use in a cohort of Australian gay and bisexual men: Results from the Flux Study', *Drug and Alcohol Dependence*, vol. 188, 2018, p. 177; M Hammoud, F Jina, L Degenhardt, T Lea, L Maher, H Grierson, B Mackie, M Pastorelli, C Bartouney, N Bath, J Bradely, G P Prestage, 'Following Lives Undergoing Change (Flux) study: Implementation and baseline prevalence of drug use in an online cohort study of gay and bisexual men in Australia', *International Journal of Drug Policy*, vol. 41, 2017.

<sup>5</sup> F Romanelli, K Smith, A Thornton, C Pomeroy, 'Poppers: Epidemiology and Clinical Management of Inhaled Nitrite Abuse', *Pharmacotherapy*, vol. 24 no. 1, 2004.

<sup>6</sup> Consumer Medicine Information: Viagra <<http://secure.healthlinks.net.au/content/pf/retriever.cfm?product=pfcviagt10513>>

<sup>7</sup> Viagra (sildenafil citrate) tablets: Wondering about possible side effects? <<https://www.viagra.com/learning/what-are-possible-side-effects>>

This being said, mortality from alkyl nitrite use is rare, compared to more than 6000 deaths relating to alcohol in Australia every year.<sup>8</sup> Accurate packaging detailing the correct usage, possible side effects and noted drug interactions (particularly with Viagra) of alkyl nitrites would be a productive harm minimisation strategy.

Moreover, the noted toxicity of alkyl nitrites often arises from misuse or misapplication. For instance, ingestion or contact with skin and eyes is dangerous but does not represent typical use of these substances. In this respect, it is vital to avoid misconstruing or exaggerating the approximate toxicity of alkyl nitrites.

On that point, the discussion paper claims that inhalation of amyl nitrites can lead to death, though there is no confirmed case of mortality solely attributable to the inhalation of an alkyl nitrite in the absence of drug interaction, pre-existing conditions or other relevant circumstances.

As noted above, certain alkyl nitrites may cause maculopathy.<sup>9</sup> Maculopathy has been associated with isopropyl nitrite but not alkyl nitrites more generally.<sup>10</sup> Importantly, there have only been relatively few cases across several decades.

Historically, cases of vision loss or damage from alkyl nitrite use were extremely rare. However, an EU decision to ban isobutyl nitrite led to a new formula including isopropyl nitrite. Isopropyl nitrite is not generally available in Australia.

While more research should be conducted in this area, the TGA might consider a Schedule 9 ban on isopropyl nitrite specifically, while considering more appropriate scheduling for other therapeutically beneficial alkyl nitrites.

#### **d. The dosage, formulation, labelling, packaging and presentation of a substance**

The discussion paper notes that since alkyl nitrites are not approved for human use that they are not subject to quality controls. This represents an appropriate and proportionate opportunity for the sensible regulation of a therapeutically beneficial substance.

Though the harms of alkyl nitrites are limited when correctly used, there is good reason to believe that consumers would welcome the assurance of quality control. Safety warnings and directions for use would minimise or prevent harms, especially for first-time users outside of the LGBTQI community.

Given the pungent smell of alkyl nitrites, their packaging, places of sale and their socio-cultural context, the likelihood of accidental ingesting by adults or children is relatively low. There is limited potential for misapplication by deliberate swallowing which can be adequately addressed with informative packaging.

#### **e. The potential for abuse of a substance**

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<sup>8</sup> Australian Institute of Health and Welfare, *Impact of Alcohol and Illicit Drug Use on the Burden of Disease and Injury in Australia: Australian Burden of Disease Study*, 2018.

<sup>9</sup> G Docherty, M Eslami, H O'Donnel, "'Poppers Maculopathy': A Case Report and Literature Review", *Canadian Journal of Ophthalmology*, 2017.

<sup>10</sup> A Gruener, M Jeffries, Z El Housseini, L Whitefield, 'Poppers maculopathy', *Clinical Picture*, vol. 384, no. 9954, 2014.

Alkyl nitrite use is common while significant harms such as maculopathy and mortality are extremely rare. The FLUX study demonstrates that most use occurs only occasionally, with most users reporting monthly use, further limiting the chances of abuse. Members of the LGBTQI community have used alkyl nitrites therapeutically without significant incident for approximately 50 years.

Further, dosing alkyl nitrites is particularly easy and overdoses are extremely rare. Significant harms are restricted to misapplication through ingestion or uncharacteristically high levels of inhalation, neither of which represent typical use by the broader community.

Importantly, alkyl nitrites have no risk of dependency and the duration of effects is very short. There is some suggestion that poppers have a 'self-limiting' effect where the side-effects such as headaches discourage over-use in a therapeutic or recreational setting.

Furthermore, alkyl nitrites have no demonstrable psychoactive effects and are not chemically addictive. As discussed above, most people use them occasionally, and their use does not interfere with physical or social wellbeing.

#### **f. Any other matters necessary to protect public health**

It is crucial to recognise that any broad prohibition on alkyl nitrites will instigate product substitution involving increasingly dangerous substances. This was the case in Canada and the EU where a ban on isobutyl nitrite led to its substitution with isopropyl nitrite, causing few but severe cases of maculopathy.

Additionally, a comprehensive ban on alkyl nitrites would foster a black market and increase the likelihood of harmful exposure. Such a ban would create an incentive for domestic 'home-brewed' compounds or products available online which cannot be regulated. This situation would pose a significantly greater threat to public health than the status quo.

An illicit market is highly likely in the event of a ban given the important therapeutic use of alkyl nitrites and the lack of ready alternatives. Pharmaceutical products like Rectogesic cream and glyceryl trinitrate spray are relatively potent and more laborious to dose. Anaesthetic creams do not relax the muscles involved in receptive sex and so do not fulfil the current therapeutic use of alkyl nitrites.

In addition to creating a new illicit market, a general ban would incentivise consumers to substitute alkyl nitrites with more dangerous alternatives on the existing market, such as crystal methamphetamine and GHB which are sometimes used to enable sexual intercourse. These substances are materially stronger and carry a higher risk of dependency and overdose.

Furthermore, the prohibition of alkyl nitrites risks harming the mental health of consumers through exposure to criminalisation, policing and surveillance. This concern is particularly acute for members of the LGBTQI who have a long history of marginalisation and stigmatisation as a result of criminalisation.

#### **Scheduling Recommendations**

##### *Schedule 9 – Prohibited Substance*

A Schedule 9 entry for any alkyl nitrite substances, except isopropyl nitrite, is excessive and not recommended for several reasons.

Alkyl nitrites have established and longstanding therapeutic benefits for people engaging in receptive anal sex, particularly gay and bisexual men and others within the LGBTQI community. There is no risk of dependency and relatively low risk of misuse or abuse as compared to alcohol or prescription medication.

Given the association between isopropyl nitrite and maculopathy, it may be appropriate to move isopropyl nitrite alone to Schedule 9 pending further research in this area while placing other alkyl nitrites in lower Schedules. It should be noted that isopropyl nitrite is not widely available in Australia currently.

The report notes a correlation between the use of poppers and recreational drug use. While this may be superficially true, the same can be said of alcohol or prescription medications which are nevertheless legal or regulated.

Strict prohibition as represented by Schedule 9 risks encouraging policing and prosecution of historically marginalised communities, harming their physical and mental wellbeing. It additionally risks fostering an unregulated black market.

#### *Schedule 8 – Controlled Drug*

A Schedule 8 entry for all alkyl nitrite substances is excessive and not recommended for several reasons. As discussed above, there is no risk of dependency and relatively low risk of misuse or abuse as compared to other regulated substances.

Alkyl nitrites are dissimilar from other substances in this category, such as cocaine, fentanyl or morphine. The TGA might consider moving isopropyl nitrite singularly to Schedule 8 while moving other alkyl nitrites to lower Schedules.

#### *Schedule 4 – Prescription Only*

There are benefits and disadvantages to placing alkyl nitrites in Schedule 4 which should be considered evenly.

Pushing consumers to a GP or clinic could be a beneficial step insofar as it may allow for the diagnosis of underlying medical conditions including cardiovascular diseases or glaucoma. However, such a move is a double-edged sword.

While it allows for the possibility of constructive intervention, it also provides for a significant probability of stigma. People who cannot access specialised LGBTQI health services may face stigma and judgement, even from health professionals.

This risks disincentivising the safe and constructive use of alkyl nitrites in facilitating receptive sex and encouraging an illicit market where the substances are more easily accessible.

It would be beneficial for consumers to speak to their doctors, but this can be encouraged through packaging prompting users to consult with their GP or clinician without restricting access to these therapeutic substances.

On that point, LGBTQI communities have a proven track record of public health initiatives and campaigns which enable individuals to address and manage risks to their health.

Proper packaging and regulated formulas could be effectively combined with peer education campaigns led by community organisations.

The discussion paper goes on to suggest that alkyl nitrites are difficult to dose which may lead to overdose. In fact, users can easily control the strength of inhalation and the frequency of re-dosing. The evaporation rate of alkyl nitrites is constant and the effects short-acting, and further, they do not inhibit cognitive function or decision making processes.

Overdoses are extremely rare and mortality almost always results from misapplication, usually ingestion. These harms could easily be minimised through accurate packaging, health warnings, prompts to consult with a GP and peer-based education.

Generally speaking, the conditions that alkyl nitrites are employed therapeutically to avoid require no or only minor medical intervention, and the substances themselves do not produce dependency.

The margin between safe use (e.g. occasional inhaling) and a toxic dose (e.g. ingesting a whole bottle) is extensive, and the general usage of the substance is informed by socio-cultural practices and norms around safe usage, particularly within the LGBTQI community.

Gay and bisexual men have been using alkyl nitrites for decades with relatively few harmful incidents even without medical monitoring or intervention. It may be appropriate to move some alkyl nitrites, excepting isopropyl nitrite, to Schedule 4 though this is likely excessive.

#### *Schedule 3 – Pharmacist Only*

There are benefits and disadvantages to placing alkyl nitrites in Schedule 3 which should be considered holistically.

Restricting alkyl nitrites to pharmacies carries similar benefits to restricting them to prescription only, however, it carries the same issues regarding shame, stigma, and judgement from some members of the medical profession.

As discussed above, the benefits of regulation could be achieved through clear packaging, regulation of formulas, intervention prompts, peer education campaigns and community organisation initiatives with a decreased risk of encouraging shame, stigma, over-policing or illicit markets.

Generally speaking, alkyl nitrites are substantially safe though may pose some harm if misused, and do not produce dependency at any dosage level. It may be appropriate to move most alkyl nitrites, excepting isopropyl nitrite, to Schedule 3.

#### *Schedule 2 – Pharmacy Medicine*

There are benefits and relatively few disadvantages to placing most alkyl nitrites in Schedule 2.

The available evidence, in addition to the experience of gay and bisexual men, indicates that the general use of alkyl nitrites for therapeutic reasons is substantially safe. Research indicates that consumers use infrequently, and irreversible harms and mortality are rare.

Labelling, packaging and other information sold with the product or available online can ensure the correct and safe use of these substances. It would be beneficial, though sometimes unnecessary, for a consumer to speak with a pharmacist or GP.



None of these substances produce dependency, and none of them are psychoactive. Misuse of alkyl nitrites is rare, and usually the result of incorrect labelling or unfamiliarity with the substance.

The ultimate aim is to promote public health through making therapeutic substances accessible relative to their safety. Restricting alkyl nitrites to prescription or pharmacy only may dissuade some particularly marginalised groups from employing these substances for therapeutic use.

One such group is men who have sex with men who may not identify as gay or bisexual. Members of this sub-group may be uncomfortable with approaching a GP or pharmacist candidly about their needs but might nevertheless approach peers in the setting of a restricted premises.

There are other groups such as LGBTQI migrants who may have a similar experience. The TGA might consider moving alkyl nitrites, excepting isopropyl nitrite, in a way that would allow them to be regulated and legally sold in pharmacies *and* restricted premises e.g. adult stores.

This approach would allow for appropriate packaging and labelling, as well as guidance about potential harms and correct usage, while avoiding the risk of encouraging illicit markets and marginalisation. It may be appropriate to move most alkyl nitrites to Schedule 2.

## **Summary**

Most alkyl nitrites have an essential therapeutic use in facilitating safe and healthy sex, particularly receptive anal sex, for which there are no other pharmaceutical alternatives. These substances are not psychoactive and carry no risk of dependency.

There is no reliable statistical or scientific research to support the claim that alkyl nitrites pose a significant threat to children. Similarly, the claim that alkyl nitrites are sweet-smelling is inaccurate.

Based on evidence such as Poisons Information Centre calls, it appears that many non-prescription medicines and common household items pose a much greater threat to public health than alkyl nitrites, with the exception of isopropyl nitrite.

On that point, the risk of maculopathy is relatively low and appears to be linked to one specific member of the nitrite family. Historically, negative side effects impairing vision were very rare and are only associated with isopropyl nitrite specifically.

Alkyl nitrites and a regulated sex-aid like sildenafil have comparable side effects, such as dizziness, vision impairment and, under extenuating circumstances, mortality. This might suggest that it would be consistent to move alkyl nitrites to a similar Schedule.

Examples of irreversible harm, overdose and mortality attributable solely to inhaling alkyl nitrites are exceptionally scarce given their ordinary and widespread use for more than 50 years, particularly within the LGBTQI community.

Generally speaking, the few cases of harm or mortality usually involve misuse or substituted substances resulting from prohibitionist regulation. The marginal risks can be adequately

addressed through regulation of formulas, clear packaging and peer-based community education.

Accurate labelling and packaging is a very sensible first step. Alkyl nitrite products should clearly state that they should not be swallowed and that safe use involves short and occasional use via inhalation for therapeutic purposes.

Packaging should include health warnings and a prompt to consult a GP. However, restricting access to pharmacies and prescription *only* may still nevertheless incentivise illicit markets or encourage the marginalisation of some groups, including the LGBTQI community.

With this in mind, the TGA should consider scheduling alkyl nitrites so that they can be legally sold in pharmacies *and* restricted premises such as adult stores. This would allow consumers to manage the risks to their health, receive guidance about correct usage and reap the benefits of regulation.

Moving alkyl nitrites collectively to Schedule 8 or 9 risks creating a black market for a therapeutic substance for which there is no ready alternative. Such a move would also promote the marginalisation of the historically over-policed LGBTQI community, compromising the physical and mental health of its members.

Given this, it may be appropriate to move isopropyl nitrite to Schedule 8 or 9 while moving other alkyl nitrites to schedules 2, 3 or 4. Schedule 2 is very appealing, as it offers the opportunity to capitalise on the therapeutic benefits of alkyl nitrites while avoiding the disadvantages of stricter prohibition.

Regards,

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