Joint submission

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Re: interim decision to amend the listing of alkyl nitrites within the Poisons Standard

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Overview

We first address the risk-benefit analysis and secondly consider the regulatory approach. This submission has been developed with the following objectives in mind:

1. Any decision on rescheduling alkyl nitrites should be deferred until the risk-benefit analysis mandated by s 52E of the *Therapeutic Goods Act 1989* (Cth) ('the Act') has been completed;

2. The TGA should seek expert advice and undertake targeted community engagement to assess the public health implications of the proposed rescheduling;

3. Consideration should be given to a more limited rescheduling of isopropyl nitrite to schedule 9, and as to whether other alkyl nitrites should be listed in schedule 2;

4. The TGA should adopt the process modelled by the Kava Expert Group for assessing the risks and appropriate response to low-risk substances with therapeutic uses and special cultural significance.

Risk benefit analysis

Requirements of the *Therapeutic Goods Act* (Cth) 1989

The proposal to move alkyl nitrites to schedule 9 of the Poisons Standard is made under section 52D(2) of the *Therapeutic Goods Act 1989* (Cth). The first subsection of s 52E lists matters the Secretary (or their delegate) must take into account in exercising this power:

Table 1 The matters required to be considered

SECT 52E Secretary to take certain matters into account in exercising powers

(1) In exercising a power under subsection 52D(2), the Secretary must take the following matters into account (where relevant):

(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.

The mandatory language ('the Secretary must') indicates that the TGA is legally bound to give consideration to, where they are relevant, in order for the decision to constitute a valid exercise of the s 52D power to amend the Poisons Standard.

The interim decision does not fully address the matters the Secretary is required to take into account under s 52D. We contend that the interim decision omits or excludes matters that are relevant to the analysis under s 52E(1). The additional matters are presented below, following the structure of that section.

The risks and benefits of the use of alkyl nitrites (s 52E(1)(a))

The terms used in s 52E(1) ('risk' and 'benefit') are not separately defined in the Act. In the ordinary meaning of the term, given by the Macquarie Dictionary, *risk* refers to 'exposure to the chance of injury or loss; a hazard or dangerous chance', and in the more technical meaning used in insurance, 'hazard or chance of loss' and 'the degree of probability of such loss.' In all of these senses, the emphasis is on the chance or probability or likelihood of an event, not the gravity or severity of the harm if it eventuates. Consistent with this, in judicial decisions on Peterson v Merck Sharp & Dohme Australia, risk is repeatedly and straightforwardly used to refer to the probability of injury. In *The TGA's Risk-Management*

Approach to the Regulation of Therapeutic Goods (version 4.0), the TGA itself describes risk as 'a measure of the combination of the likelihood and the consequence of an undesirable event' (TGA 2011, 6). This is consistent with the conception of risk adopted in negligence law, where the 'degree of risk' is determined via a calculus that incorporates both the probability of a harmful event occurring, and the severity of that harm: Wyong Shire Council v Shirt (1980) 146 CLR 40. We submit that this is the appropriate conception of 'risk' to be used by the TGA in determining the present case.

The interim decision lists a number of harms associated with alkyl nitrites, including methaemoglobinaemia, maculopathy, and injury or intoxication due to accidental exposure. However, the interim decision does not include any assessment of the probability of these events occurring. The probability may be expressed in conceptual terms as a fraction:

$$\frac{\text{frequency of adverse events (numerator)}}{\text{frequency of use (denominator)}}$$

No prospective cohort studies have been conducted to compare the incidence of adverse events between users of inhaled nitrites and non-users. A prospective study with an experimental design is considered the 'gold standard' of evidence (NHMRC 2009). However, for the purposes of the analysis in s 52E(1), the absence of this evidence does not mean there is no evidence at all regarding the risk of adverse events associated with nitrite inhalants. To assist the TGA in this assessment, we will briefly cite evidence on the frequency of nitrite inhalant use among gay and bisexual men in Australia. We will then present preliminary findings from a review of the literature to establish a general sense of the numerator: the number of adverse events associated with alkyl nitrites.

The denominator – frequency of use

Poppers products have been widely used in the gay community since the 1970s. The Gay Community Periodic Survey (GCPS), conducted by the Centre for Social Research in Health at the University of New South Wales, has been running on a yearly basis in major Australian cities since 1996. Use of poppers has remained steady at 35–40% among gay and bisexual male respondents over the past ten years (Mao et al. 2018). The Australian Study of Health and Relationships '2', a nationally-representative study of sexual behaviour and identity conducted via random digit dialling, found 3.2% of the adult male population identify as gay or bisexual (Richters et al. 2014). Applying that proportion to ABS estimates of the adult male population in Australia, we can estimate that around 90,000 adult gay and bisexual men have used poppers in the past six months in Australia.

Complementing the cross-sectional data provided by the GCPS, the FLUX study is a six-monthly cohort study conducted by the Kirby Institute for Infection and Immunity at the University of New South Wales since 2014 (Hammoud et al. 2017). The FLUX study investigators have provided data on the frequency of use of nitrite inhalants. It found the same proportion of respondents (42.1%) had used nitrite inhalants in the past six months as in the GCPS findings. Among those respondents, 41.7% had used them once or twice, 34.4% used them less than monthly, 22% used them every week, and 1.6% used them daily (Mo

Hammoud, personal communication, 2018). Research undertaken by Prof Kane Race at the University of Sydney, presented later in this submission, indicates that 'poppers' have been in use in the gay and bisexual community since the 1970s. Taken together with data from behavioural surveys, this suggests the denominator – the number of people who use the substance – is substantial.

The numerator – the number of adverse events

In the absence of a systematic review or prospective study, the next-best available evidence consists of case series and case reports. These are ranked higher on the NHMRC pyramid of evidence than the opinion of experts, which the TGA has relied upon extensively in its interim decision. To inform the decision of the delegate, we conducted a rapid review of the English-language medical literature, looking for peer-reviewed publications reporting adverse events associated with nitrite inhalant products. The preliminary findings are presented here.

Review methods

To conduct the review, electronic databases including PubMed and Google Scholar were searched using the terms listed in Table 2 below. Search results were imported into Endnote vX7 (Thomson Reuters, New York, U.S.A.) and titles and abstracts were reviewed for relevance. The inclusion criteria were any publication with an abstract available in English (including translated abstracts) that describe an adverse event affecting an individual person or series of persons. This generated a list of 52 publications. The fulltext was reviewed by the first author of this submission and references were hand-searched to identify additional references, resulting in a total of 45 included papers. The results were tabulated (see Figure 1 and Table 3 below).

Where a publication presented a series of cases, the total number of persons involved is reported against the year of publication. The de-identified reporting of results makes it difficult to assess whether the same individuals were reported on multiple occasions. It is possible that a small number of publications were missed, particularly publications in languages other than English or publications in journals not indexed by PubMed. It is possible the results of this review are affected by under-reporting, particularly of cases where the harm was less severe or clinical management was uncomplicated.

Table 2 Search terms
'amyl nitrite' OR 'amyl' OR 'poppers' in combination with the following keywords: abuse, adverse, amphetamine, blindness, bronchitis, carcinogen, cardiac, cardiovascular, damage, death, heart, hospitali*, impact, lung, macular, retinal, [redacted] and vision

Findings of the literature review

Cases identified in the literature review were categorised as fatal events (cardiovascular, haematological and other) and non-fatal events (cardiovascular, haematological, optical and other) and recorded by year (see Table 3). Findings are summarised in Figure 1 (below).

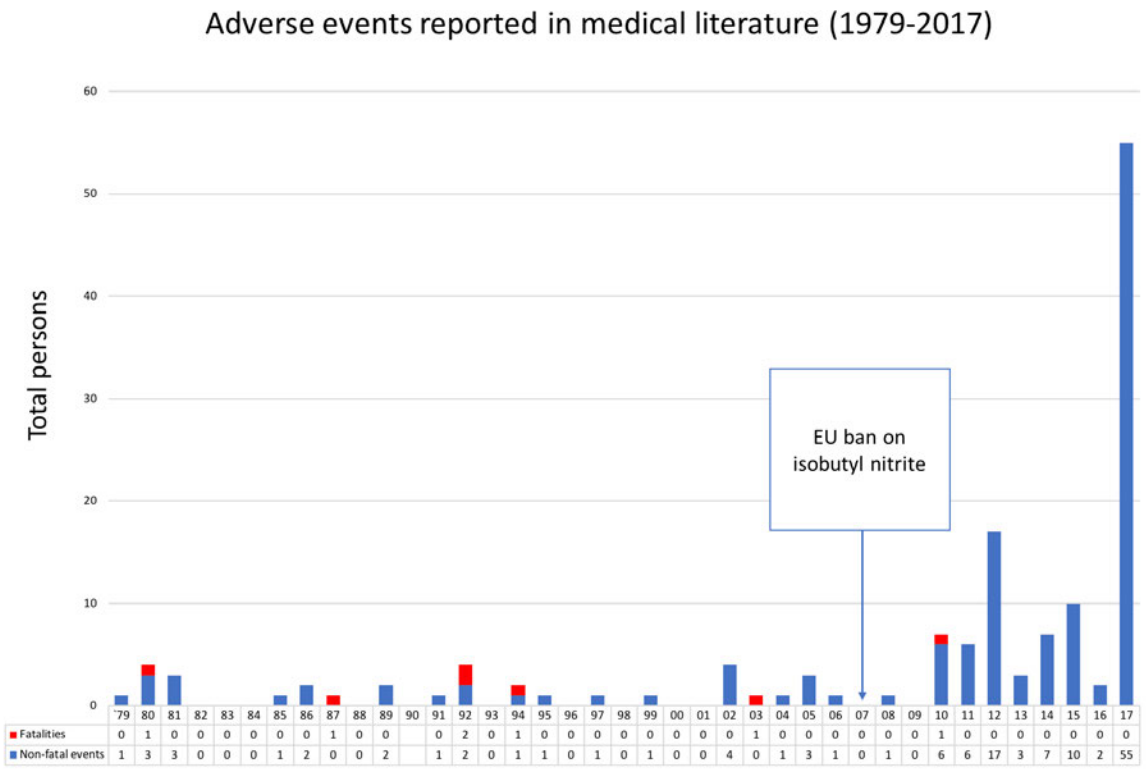
Table 3 Allocation of adverse events by individual publication

Year	Ref	Non-fatal events				Fatalities		
		CVD	Haem	Optical	Other	CVD	Haem	Other
1979	[1]		1					
1980	[2]		1					
1980	[3]						1	
1980	[4]	1	1					
1981	[5]						1 [a]	
1981	[6]		3					
1985	[7]		1					
1986	[8]	2						
1987	[9]						1	
1989	[10]				2			
1991	[11]		1					
1992	[12]		1					
1992	[13]							2 [b]
1992	[14]		1					
1994	[15]						1 [c]	
1994	[16]		1					
1995	[17]		1					
1997	[18]		1					
1999	[19]			1 [d]				
2002	[20]		2					
2002	[21]		2					
2003	[22]							1 [e]
2004	[23]			1 [f]				
2005	[24]		2					
2005	[25]		1					
2006	[26]		1					
2008	[27]		1					
2010	[28]		1					
2010	[29]					?	?	1 [g]
2010	[30]		1					
2010	[31]		4					
2011	[32]			6				
2012	[33]			7				
2012	[34]			10				
2013	[35]			1				
2013	[36]			2				
2014	[37]			7				
2014	[38]			1				
2014	[39]			1				
2015	[40]			10				
2016	[41]			1				
2016	[42]			1				
2017	[43]			4				
2017	[44]			39 [h]				
2017	[45]			12				

Superscript letters indicate notes in Table 4 (following page).

Table 4 Notes to Table 3		
Note	Reference	Remarks
a	Dixon (1981)	Fulltext is unavailable but possibly a duplicate of Shesser (1980) (coauthors, similar circumstances in description).
b	Sarvesvaran (1992)	Alkyl nitrite reported as a factor in two deaths by misadventure (one involving ingestion).
c	Bradberry (1994)	Reports the first and apparently only fatality due to inhalational use.
d	Fiedelius (1999)	Total, irreversible blindness in a 15-year old following a single exposure
e	Bungardt (2003)	Death due to autoerotic strangulation; poppers flask found beside body, assumed accidental hanging due to vasodilation.
f	Pece (2004)	Single case, vision loss with foveal 'yellow spot' characteristic of poppers maculopathy; attributed to isobutyl nitrite but unclear how determined.
g	Stefanidou (2010)	Death with methaemoglobinaemia (22%), one old and one recent heart attack, COPD, and head injuries suffered in car accident, with poppers flasks found on his person.
h	Van Bol (2017)	Case series over ten years.

Figure 1 Adverse events reported in the medical literature



Discussion of findings

Subject to the limitations discussed under 'Methods' above, we can make a number of observations based on the preliminary findings of the review:

1. Deaths related to volatile nitrite use and misuse are very uncommon. A systematic review by Hunter (2011) found only one death caused by methaemoglobinaemia following inhalation of volatile nitrites and a further two deaths associated with ingestion. This stands in contrast to the 1,289 deaths attributable to alcohol in 2013 in New South Wales alone (HealthStats NSW 2018), or the 92 deaths attributable to caffeine use globally (Cappelletti et al. 2018).

2. The overwhelming majority of reported cases of methaemoglobinaemia were quickly identified and cured by treatment with methylene blue, often with discharge on the same day as admission. Our preliminary findings do not support the conclusion that alkyl nitrites are poisons within the meaning of s 3 of the Act as 'an ingredient, compound, material or preparation which, or the use of which, may cause death, illness or injury.' These findings suggest that the conventional inhalational use of volatile nitrites poses very low risk of death, illness or injury.

3. There is a very clear signal in the evidence that cases of vision loss are attributable to substitution of isopropyl nitrite as the principal ingredient in 'poppers' products, resulting from a European Union ban on isobutyl nitrite introduced in 2007 (S. Davies et al. 2008). In the 37 years prior to 2007 there are only two cases reporting vision loss; in the ten years from 2007 to 2017 we identified 102 cases.

Conclusions of the review

As previously acknowledged, there is no prospective study available to estimate the incidence rate or probability of the adverse events identified in the interim decision. However, there is evidence for a very large denominator, with behavioural surveillance and cohort study data indicate use of nitrite inhalants by 35–40% of the gay and bisexual community, up to 90,000 persons, in the past six months. Our review of the literature identifies fewer than five deaths unambiguously attributable to volatile nitrites globally since 1970. A larger number of cases involving methaemoglobinaemia were identified, and the overwhelming majority were identified and successfully treated without incident. The major concern arising from this review of the literature is the number of cases of vision loss involving poppers maculopathy since 2007. This is addressed later in this submission.

Benefits of use and therapeutic uses (s52E(1)(a) and (b))

The interim decision fails to consider the balance between the risks and benefits of use as required by s 52E(1)(a). Perhaps reflecting a prejudgment of the scheduling decision, the interim decision *lists the benefits of use as risks of use.* The interim decision therefore, we argue, has failed to carry out the balancing assessment required by the Act. Additionally, the decision identifies the risks of use as 'illicit use for euphoric (perceived due to dilation of blood vessels in brain and periphery), analgesic and muscle relaxant effects.' This

contradicts the later assertion in the interim decision that 'Alkyl nitrites have little to no therapeutic use.' For the sake of clarity the benefits and therapeutic uses of nitrite inhalants will be considered together in this section.

Under s 3 of the Act ('Interpretation'), *therapeutic use* means use in connection with 'influencing, inhibiting or modifying a physiological process in persons' or 'preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons.' The research literature and the interim decision itself acknowledges that inhaled nitrites influence or modify a physiological process in humans: they induce the relaxation of smooth muscle and cause the dilation of blood vessels in the brain and periphery. As a result of the first effect, inhaled nitrites prevent and alleviate spasm and prevent tearing of the inner sphincter during receptive anal intercourse. There are two rings of muscle in the anus, the outer under voluntary control, while the internal sphincter is activated by involuntary reflex.

In one study of sexual dysfunctions and concerns among gay and bisexual men, 61% of participants reported ever having had painful receptive anal sex and 16% reported this was currently a problem (Rosser et al. 1997). A study of anodyspareunia (pain experienced during receptive anal intercourse) found 59% of gay and bisexual men (n=1190) indicate some degree of anal pain during and after sexual intercourse, with 6% reporting moderate or severe pain (Vansintejan, Vandevoorde, and Devroey 2013). A study of heterosexual women (n=2002) found 62.3% of respondents reported two or more episodes of anal intercourse in the past 12 months, with 8.7% reporting severe pain during every occasion (Štulhofer, Kuljanić, and Buzina 2011).

In that study, the inability to relax was the most frequently-given explanation for the difficulty. Micro-tearing and muscle spasm caused during initial difficulties with penetration can make the entire sexual encounter painful and this may increase anxiety during subsequent encounters. While phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil are available for individuals who have trouble with insertive sexual intercourse, there are no therapeutic goods – other than nitrite inhalants – available for use by individuals who experience difficulties during receptive sexual intercourse.

The interim decision notes that there are no products on the Australian Register of Therapeutic Goods (ARTG) that contain alkyl nitrites. However, in s 3 of the Act, the definition of *therapeutic goods* is not limited to products listed on the ARTG. It includes goods 'that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be: (…) for therapeutic use.' Among gay and bisexual men and other members of the queer community, nitrite inhalants are widely understood as facilitating receptive sexual intercourse via the very same euphoric, analgesic and muscle relaxant effects acknowledged in the interim decision. HIV prevention materials available via internet search describe in clear and simple language how alkyl nitrites are conventionally used, as well as the potential downsides of use and how they can be managed.

In conclusion, the interim decision fails to properly balance the risks and benefits of the use of nitrite inhalants as required by s 52E(1)(a). The interim decision prejudges the question of the proper scheduling of alkyl nitrites, by treating the benefits of use as risks, and use as

abuse. These are conclusions that only make sense if the delegate were already convinced that nitrite inhalants fit the definition of a schedule 9 poison. We contend that interim decision errs in failing to consider the benefits, purpose and extent of use of nitrite inhalants to facilitate receptive sexual intercourse, as required under s 52E(1)(b).

The toxicity of the substance (s 52E(1)(c))

When used conventionally via inhalation, alkyl nitrites have very low toxicity. The interim decision lists a number of potential adverse events associated with nitrite inhalants, but, again, does not consider *how likely* inhalation of alkyl nitrites is to cause these events.

Dosage, formulation, labelling, packaging and presentation of the substance (s 52E(1)(d))

The delegate has omitted the s 52E(1)(d) consideration altogether, possibly taking the view that it is not relevant. As the preliminary findings of our literature review indicate, the *formulation* of nitrite inhalant products is highly relevant to the risks of harm. In particular, two UK papers identified isopropyl nitrite as the ingredient associated with vision loss seen in 'poppers maculopathy' (Davies et al. 2008; Davies et al. 2012) . As we observed in our own review, reports of vision loss were exceedingly uncommon prior to the substitution of isopropyl nitrite. The risk of vision loss could be more or less eliminated by rescheduling this substance on its own. In addition, there is considerable scope for regulation of the labelling, packaging and presentation of products containing alkyl nitrites to address the risks and concerns listed in the interim decision. This issue will be considered further below (see 'Regulatory practice').

The potential for abuse of a substance (s 52E(1)(e))

The interim decision again lists the benefits and therapeutic uses of nitrite inhalants as 'misuse and abuse' of these substances. It is certainly the case that poppers products, as a direct result of their listing on Schedule 4 of the Poisons Standard (and similar regulatory schemes worldwide), are described as cleaning products or 'room odorisers' and state 'Do not inhale' on their packaging. However, information about their conventional use is instantly available via internet search. Again, consideration of their benefits and therapeutic uses, as required by s 52E(1)(a) and (b), suggests that 'use as sex aids due to their muscle relaxant properties' should not be considered 'misuse and abuse' of these substances. We argue that these are legitimate, beneficial and therapeutic uses of these substances.

Any other matters that the Secretary considers necessary to protect public health (s 52E(1)(f))

The interim decision describes consultation with industry stakeholders about the potential impact of losing access to alkyl nitrite-based lubricants. It refers to the use of nitrite inhalants by 'particular sections of the community.' This can be taken as a reference to the community of lesbian, gay, bisexual, trans and nonbinary people (the LGBTIQ community). However, the interim decision does not indicate that the TGA made any attempt to engage with the LGBTIQ community or seek advice from experts on LGBTIQ health and wellbeing. In

this section we invite the TGA to consider additional matters necessary to protect public health. These matters include the risk of product substitution, the impact on affected communities, and the loss of opportunities to regulate these substances in more effective ways.

Risk of product substitution as a result of regulatory action

The history of the regulation of nitrite inhalants reveals the risk of product substitution occurring as a result of regulatory action. The same risk is present in the proposal to list alkyl nitrites as a class on Schedule 9 of the Poisons Standard. This risk should be considered as one of the matters relevant to the decision and necessary to protect public health.

In 2007 the European Union and the United Kingdom banned isobutyl nitrite, the principal ingredient in most poppers products on the market at the time. Davies (Davies et al. 2008) conducted a before-and-after evaluation of the ban, which found 100% of poppers products tested via spectrophotometry contained isobutyl nitrite in 2006, while 61.3% contained isopropyl nitrite in 2008. As our preliminary results demonstrate, EU regulation exposed users of inhalant nitrites to drastically increased risk of permanent vision loss.

The apparent justification for the ban was the 2006 publication of findings from a study of protein expression in mice exposed to isobutyl nitrite via inhalation (Tran et al. 2006). They report increased expression of vascular endothelial growth factor (VEGF), which the authors claim might explain the 'tentative' association of nitrite inhalant use and a particular kind of skin lesion, Kaposi's Sarcoma (KS). KS is a lesion of very limited clinical relevance: it is seen occasionally in patients with HIV. It is known to be caused by a sexually transmitted infection, human herpesvirus 8 (HHV-8), and its causation did not require additional explanation. However, seemingly on the basis of these two publications, isobutyl nitrite was classified as a Class II carcinogen in the EU and UK.

We are concerned that the proposal to reschedule alkyl nitrites in Australia poses a similar risk of product substitution. There are already products for sale online, via Australian suppliers, that dispense ethyl chloride from aerosol canisters (see Figure 2). These products are marketed as 'Jungle Juice Gold', referencing one of the largest brands of poppers products. These products do not contain alkyl nitrites and would not be restricted by the current proposal. By removing safer competing products from sale, however, the current proposal would increase the market for these products and exposure to the risks they pose.

Figure 2 'Jungle Juice Gold' (active ingredient: ethyl chloride) on-sale in Australia

The risk of these products being mistaken for nitrite inhalants is identified by Hall et al (2015). The authors observe a failure to distinguish between nitrite inhalants and 'huffing' volatile solvents like ethyl chloride:

> lumping these disparate agents together based on mode of administration obscures substantial differences in both mechanism and typical risk between alkyl nitrites, which act on a specific NO [nitric oxide] pathway, and inhaled solvents and propellants that exert their effect through combinations of mild hypoxia, direct chemical interaction with neuronal membranes, and agonism at various receptors. Moreover, huffing solvents or halogenated alkanes, such as the aerosol propellant ethyl chloride (also known as chloroethane), can induce a rare fatal arrhythmia in some individuals, known as "sudden sniffing death." More common serious side effects include delirium in the short term, as well as potentially permanent impairment in memory and executive functioning, and neuropathy.

Public mental health promotion

There is widespread recognition that public health includes mental health promotion and population-level initiatives for the prevention of mental illness. A review conducted by the National LGBTI Health Alliance (Sally Morris 2016) indicates that same sex attracted and sex and gender diverse (SSASGD) people are significantly more likely to experience mental illness. There is nothing inherent in SSASGD identity that drives this difference: it is due to increased exposure to stigma, discrimination, marginalisation, criminalisation and trauma. Community health advocates have been working for decades to undo that history.

We encourage the TGA to consider the public health implications of a decision that would, overnight, criminalise the practice of an estimated 90,000 adult gay and bisexual men, as well as an undetermined number of queer women, nonbinary people, and heterosexual men and women who currently use nitrite inhalants. In 2015 the Victorian Government launched a scheme to expunge historical convictions for consensual homosexual activity, which had been criminalised under offences such as buggery, gross indecency with a male

and offensive behaviour. An apology made in the Victorian Parliament in May 2016 acknowledged the harms caused by criminalisation:

> Those convicted were publicly shamed in newspapers. As a result, they lost jobs, were forced to withdraw from study, and were ostracised by family and friends. The burden of a criminal conviction affected their full participation in the workforce and community, and inhibited their freedom to travel. (Martin Foley, Minister for Equality, 24 May 2018)

Research by Prof Kane Race at the University of Sydney, published in his book *Pleasure Consuming Medicine* (2012), has described the personal and cultural significance of dance parties and sexual intimacy in helping LGBTIQ people to survive mental and emotional challenges associated with the HIV/AIDS epidemic as well as the ongoing experience of stigma and discrimination towards homosexual and transgender people in Australia.

Impact on education and help-seeking behaviour

Listing alkyl nitrites on Schedule 9 of the Poisons Standard will have the practical effect of making their possession and use illegal under state and territory laws. This may deter people who have concerns about their use of these substances, particularly in settings that involve HIV risk, from talking with their clinicians or with educators about strategies to manage the risks involved. This effect has been clearly demonstrated in research studying the impact of HIV-specific criminal laws in Australia and around the world.

Missed opportunity to regulate in more effective ways

These risks are discussed further in the following section (‘Regulatory approach’).

Regulatory approach

As we have argued, the proposal to reschedule alkyl nitrites as a class has important public health implications, on which the Secretary and their delegate are authorised, by s 52E of the Act, to consult and seek expert advice. In this section we invite the Secretary and their delegate to consider the risks that may be posed by the proposed regulatory approach, not just the risks associated with the substance in question. We argue that the proposed rescheduling has consequences which are disproportionate to the risks and arbitrary in effects, and suggest that an approach based on responsive regulation would enable a more direct and effective response to the risks and concerns identified in the interim decision. Finally, we identify a precedent for a process using expert assessment and community consultation to assess the risks and identify an appropriate response to adverse events involving a substance with therapeutic uses and special cultural significance.

Responsive regulation

In a statement at the National Press Club on 25 September 2018, a former commissioner of the Australian Federal Police, Mick Palmer, noted that banning alkyl nitrites will not reduce

their availability; rather, it will simply drive the market underground. This is likely to be counter-productive, as it is not possible to regulate the formulation and packaging of an illegal product.

Rescheduling alkyl nitrites would be a missed opportunity to adopt a regulatory approach that responds more directly and effectively to the risks and concerns identified in the interim decision. Such 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; educational messages about risk reduction; and point of sale restrictions such as minimum age limits for purchase and restricting sale to adult stores.

In particular, we encourage the TGA to consider listing *only* isopropyl nitrite as an individual substance on Schedule 9 of the Poisons Standard. This would drive *positive* product substitution in favour of less-risky constituent substances. It would address the substantive concern raised by ophthalmologists about increases in maculopathy and associated vision loss. These are adverse events which have been directly and exclusively attributed to isopropyl nitrite in the published literature.

Arbitrary effect

The TGA is responsible for administering and amending the Poisons Standard, but the criminal liability for supply, possession and use of a Schedule 9 substance comes from state and territory laws that refer to the Poisons Standard. As a result, listing alkyl nitrites on Schedule 9 will have legal consequences that vary enormously between jurisdictions. Table 5 (below) lists the jurisdiction, the relevant legislative provisions, and the maximum penalty for breach of those provisions. That liability ranges from a $1600 fine for possession in Victoria to a $75,000 fine *and* up to five years' imprisonment in the Australian Capital Territory. As a consequence of this variation, the proposed regulation is arbitrary in its effects – imposing radically different liabilities on people depending on location. A person could catch a domestic flight with a bottle of nitrite inhalants in their checked luggage and unwittingly go from liability to a relatively small fine to liability to five years in prison. Our argument here is that possession and use of nitrite inhalants do not pose the kind of risks or involve the kind of wrongdoing that could justify such significant criminal penalties.

Table 5 Offences relating to Schedule Nine poisons		
Jurisdiction	**Legislation**	**Penalty**
ACT	*Medicine, Poisons and Therapeutic Goods Act 2008* (ACT) s 13 defines a "prohibited substance" as one listed on Schedule 9 of the Poisons Standard. Section 25 defines a "declared substance" as including any "prohibited substance". S26(1) defines use as 'supply to yourself' and s 26(2) supply to another.	Both offences attract a maximum penalty of 500 penalty units (approx $75,000), imprisonment for 5 years or both.
NSW	*Drug Misuse and Trafficking Act 1985* (NSW) s 18B(2) a person who supplies a Schedule 9 substance (not listed elsewhere in the Act as a prohibited drug, and inhaled nitrites are not) is guilty of an offence (penalty unclear). Under s 18B(3) a person who has in their possession a Schedule 9 substance (not listed as a prohibited drug) is guilty of an offence.	For s 18B(3): 20 penalty units (approx $2200) or imprisonment for 12 months or both.
NT	*Medicine, Poisons & Therapeutic Goods Act 2014* (NT) s 12(a) a *prohibited substance* includes a Schedule 9 substance. Section 52 applies to possession, s 53 to supply, and s 54 to use of a prohibited substance.	Section 52 and s 54: 200 penalty units or imprisonment for 2 years (each). Section 53: 500 penalty units (approx $77,500) or imprisonment for 5 years.
QLD	*Health (Drugs & Poisons) Regulations 1996* (Qld) appendix 7 defines any substance listed in the Poisons Standard Schedule 9 as a *regulated poison*. Reg 271(1) 'A person must not dispose of, dispense, manufacture, obtain, possess, prescribe, sell or use a regulated poison…'	80 penalty units (approx $10,400).
SA	Under *Controlled Substances Act 1984* (SA) s 12(7) the Governor can declare substances 'volatile solvents', and Controlled Substances (Poisons) Regulations 2011 reg 8(a) includes all the alkyl nitrites and their isomers. Controlled Substances Act 1984 s 19(1) is an offence applying to sale or supply of a volatile solvent if there are reasonable grounds for suspecting it will be used for inhalation; s 19(2) applies to purchase on behalf of another person for inhalation purposes.	Both offences separately attract a fine of $10,000 *or* 2 years' imprisonment.
Tas	*Poisons Act 1971* (Tas) s 55 a person who imports, sells, supplies, possesses, or uses a *prohibited substance* (defined in s 3 as schedule 9 of the Poisons List) is guilty of an offence.	Fine of 50 penalty units (approx. $8150) or 2 years' prison or both. The same occasion of use could ground multiple charges.
Vic	*Drugs, Poisons and Controlled Substances Act 1981* (Vic) s 36B(2) 'A person shall not have in his possession a Schedule 8 poison, Schedule 9 poison or Schedule 4 poison unless he is authorized by or licensed under this Act or the regulations to do so.'	10 penalty units (approx.. $1600).
WA	*Medicines and Poisons Act 2014* (WA) s 17 'A person who manufactures, supplies, uses or is in possession of a Schedule 9 poison commits an offence'.	In s 115(1)(a)(ii), if the offence relates to a schedule 9 poison, the penalty is a fine of $45,000 ***and*** 3 years imprisonment.

Regulating substances with therapeutic uses and special cultural significance

In Practicing Desire: Homosexual sex in the era of AIDS (1996), sociologist Gary Dowsett discusses how the 'physical relaxation' produced by amyl nitrite allows Australian research participants to 'enjoy receptive anal sex' (p. 175). The use of volatile nitrites for this purpose in particular, as distinct from other social and recreational purposes, is so well established that the substance is mentioned in *Anal Pleasure and Health* – the bestselling therapeutic self-help book by Jack Morin (PhD), first published in 1981 (now in its 4th edition) – which discusses the use of nitrite products to help the 'anal muscles to relax' and make it 'easier to receive a finger, object or penis into the anus and rectum' (2010, p. 116). Recent data on drug use among gay, bisexual and other men who have sex with men in Australia corroborate these findings. While nitrite inhalants are used in a range of sexual and social contexts, their use is found to be most pronounced in sexual contexts, where it is typically used to facilitate receptive anal sex (Hammoud et al. 2018).

The significance of poppers within modern gay culture is extensive and well documented. The practice of sniffing poppers features prominently in Hal Fischer's (1977) critically acclaimed account of US gay subcultural practices and codes in the 1970s, *Gay Semiotics*, which states:

> Amyl nitrite is a prescription capsule drug used in the treatment of angina pectoris (heart disease). Amyl nitrite, or "poppers" as it is known in slang terminology, is inhaled through either the nose or the mouth. After inhalation the user experiences a quickened heartbeat and the sensation of blood rushing to his head. Amyl nitrite is especially popular on dance floors and immediately prior to sexual climax. Since Amyl Nitrite is available only by prescription, manufacturers have created a number of commercial substitutes as well as a variety of inhalers. Although Amyl is used by heterosexuals, its immense popularity among gays has earned it the title "The Gay Drug."

References to the use of poppers for both sexual and social purposes abounds in hallmark depictions of the rise of urban gay culture in New York in the 1970s, including Andrew Holleran's (1978) novel *Dancer from the Dance* (11 references); Larry Kramer's (1978) novel *Faggots* (17 references); and William Friedkin's (1980) film *Cruising*. In each of these fictional but ethnographically precise depictions of modern gay culture, poppers are used variously within sexual settings and on dancefloors to promote relaxation and facilitate sex within a subpopulation recently liberated from decades of severe social and institutional oppression.

Social histories of homosexual life and culture in Australia reveal similar associations. In *Street Seen: A History of Oxford Street* (2000), Clive Faro discusses how

> Oxford Street became the site of a new, American-influenced, much more visible enactment of gay identity over the 1970s … matched by the adoption of many of the accoutrements of disco, including amyl-nitrate poppers, 'the drug that defined an era, fueling both the ecstatic twirl of dancers at nightclubs and … sexual hedonism' (p. 245).

There is a precedent in the recent history of the TGA for assessing the risk of adverse events in substances that are generally considered safe, and that have both therapeutic uses and special cultural significance. In 2005 the TGA published a fact sheet on the process it followed to evaluate the same issues and concerns in relation to kava, a substance with mild psychoactive properties that plays an important role in the cultural and community rituals of peoples from the Pacific Islands.

This process involved expert assessment and community engagement (see Table 6). It enabled the consideration of risks and benefits, therapeutic uses, purposes for and patterns of use, and the public health implications of the substance in question. We argue the same approach could and should be taken with regard to nitrite inhalants, with a view to regulating these products as Listed (low-risk) medicines.

Table 6 The Kava Evaluation Group

- In January 2003, the TGA established an expert committee, named the Kava Evaluation Group (KEG), to review the safety of kava-containing medicines and to report to the CMEC as to whether it was appropriate to allow kava (*Piper methysticum*) to be used as an ingredient in 'Listed' (or low risk) medicines.
- The KEG brought together regulatory, kava and liver experts to comment on the safety of kava-containing medicines. The TGA, New Zealand Medsafe and both the Australian and New Zealand industry nominated experts for membership of the KEG. The process also included consideration of public submissions.
- The KEG considered a safety review of kava prepared by the TGA in early 2003, as well as other relevant information and made a number of recommendations to the CMEC regarding the regulation of kava-containing medicines. These recommendations addressed the different preparations and dosage forms of kava.

Source: TGA (2005)

Outcomes sought

1. Any decision on rescheduling alkyl nitrites should be deferred until the risk-benefit analysis mandated by s 52E of the *Therapeutic Goods Act 1989* (Cth) ('the Act') has been completed;

2. The TGA should seek expert advice and undertake targeted community engagement to assess the public health implications of the proposed rescheduling;

3. Consideration should be given to a more limited rescheduling of isopropyl nitrite to schedule 9, and as to whether other alkyl nitrites should be listed in schedule 2;

4. The TGA should adopt the process modelled by the Kava Expert Group for assessing the risks and appropriate response to low-risk substances with therapeutic uses and special cultural significance.

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