Submission

A more direct and proportionate response to alkyl nitrite use

Prepared by the **Nitrite Action Group** for the TGA consultation on re-scheduling alkyl nitrites

Tuesday, January 15th 2019

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About the authors

The **Nitrites Action Group** is an ad-hoc coalition of gay men with expertise in public health, medicine, law and social science, formed to respond to the proposed rescheduling of alkyl nitrites. Our members are:

- **Daniel Reeders** BA LLB (Melb) Grad Dip Pub Hlth (Flin)
  PhD Candidate, School of Regulation and Global Governance, Australian National University and Principal Consultant, DNM Strategic Consulting (www.dnm.net.au)

- **Paul Kidd** LLB (Hons) (La Trobe) GDLP
  HIV and LGBTI community legal activist

- **Dr Vincent Cornelisse** BSc (Hons) (UWA) MBBS (UQ) FRACGP FAChSHM PhD (epidemiology)
  GP and sexual health physician, Melbourne

- **Julien Tran** BPsych (Hons) (VU) MPH (Sexual Health) (Melb)

- **Professor Kane Race** BA LLB PhD UNSW
  Department of Gender and Cultural Studies, School of Philosophical and Historical Inquiry, Faculty of Arts and Social Sciences, University of Sydney

This proposal was authored by Daniel Reeders, Paul Kidd and Dr Vincent Cornelisse.

1. Recap of our initial submission

1.1 Therapeutic purpose and value of alkyl nitrites

As we argued in our initial submission (Reeders et al., 2018), products containing alkyl nitrites have an important therapeutic purpose in facilitating safe and comfortable receptive anal intercourse, and they have been used by LGBTIQ people for this purpose for over forty years.

The supporting document for the third-round consultation argues that there is a distinction between *therapeutic use* and *therapeutic value*. Therapeutic use is a consideration relevant to the six matters set out in the *Therapeutic Goods Act 1989* (Cth) ('the Act') s 52E(1), while therapeutic value is a consideration relevant to the cascade analysis prescribed by the Australian Health Ministers' Advisory Council (AHMAC) guidelines. Both assessments must be carried out in order for the decision to be valid under s 52E sub-sections (1) and (2) of the Act.

We submit that alkyl nitrites have significant *therapeutic value* due to the lack of alternative therapeutic goods that can achieve the same effect without impairing the use of condoms for protection against HIV and STI transmission, and without significant side effects. This therapeutic value is recognised by many clinicians who work with the LGBTIQ community.

1.2 Assessment of the probability of risk is a legal requirement

The Act and the AHMAC guidelines require the Delegate to consider not just the seriousness and severity of adverse effects but how likely they are to occur. The supporting document refers to 'many people' using poppers and 'some people' experiencing adverse events, 'including' those in 'the most serious category of harms'. However, it contains no evaluation of how frequently these harms occur. The proportionality of the burden of regulation, we submit, requires an assessment of both the probability and the severity of the risk.

This assessment must be made on the best available evidence, and in our prior submission we noted that the National Health and Medical Research Council (NHMRC) guidelines for evidence assessment recommend considering observational studies and expert opinion where findings from prospective studies and systematic reviews are unavailable. Our submission is informed by observational studies and case reports published in the medical literature on alkyl nitrites since 1971, and by the accumulated experience of the LGBTIQ community and medical practitioners working with LGBTIQ patients who use poppers.

On numerous occasions in its notes on the cascade analysis, the TGA cites harms without responding to the elements of the criteria. Consideration of the AHMAC guidelines, including all the elements in each criterion, is required for a decision to be valid under s 52E(2). A decision made on the basis of the analysis presented in the Interim Decision and the cascade analysis outlined in the supporting documents would, in our opinion, be vulnerable to legal challenge.

1.3 The most serious risks can be prevented by a more targeted decision

In our earlier submission we presented a review of the published medical literature on adverse events associated with alkyl nitrite use and misuse. When the first and third authors presented to a joint meeting of the committees responsible for advising the Delegate on the decision, we were asked whether the recent spike in poppers maculopathy might simply reflect clinicians jumping on a publication 'bandwagon' after an earlier period of under-reporting.

As stated by Dr Cornelisse at the joint meeting, under-reporting of poppers maculopathy is inherently unlikely given the dramatic nature of its symptoms and morbidity, including phosphenes (bright 'lights' floating in the visual field) and permanent loss of visual acuity. Subtle adverse events often require active screening in order to be detected and may therefore be prone to reporting bias, but the dramatic symptoms of poppers maculopathy are very likely to cause patients to self-present to medical services.

Our review noted that there were two cases of vision loss reported between 1971 and 2007 and then 106 cases from 2007-2017. As we know, isopropyl nitrite (IPN) was widely substituted as the active ingredient in poppers products in the European Union and the United Kingdom as a result of EU regulations banning isobutyl nitrite in 2007 (Davies et al., 2008). However, isobutyl nitrite (IBN) continued to be used in poppers products manufactured and sold in North America. Indeed, it is the principal ingredient in all products sold by the world's largest manufacturer of poppers, Lockerroom Marketing in Canada. (The same company is also, we understand, the supplier of the vast majority of poppers products sold over-the-counter in Australia.) We repeated our literature search using the same search terms and were unable to identify any case reports involving poppers maculopathy from the United States or Canada.

This is not consistent with a 'bandwagon effect' following an earlier period of under-reporting, and could be interpreted as evidence from a 'natural experiment' (DiNardo, 2016; Friedman, 1980). It is consistent with the identification of isopropyl nitrite as the most likely cause of poppers maculopathy in published case series (Davies et al., 2012; Van Bol et al., 2017). It is noted that isopropyl nitrite is not currently listed on the Poisons Standard.

Given the strong ecological evidence that isopropyl nitrite is the agent responsible for poppers maculopathy, we support the Delegate's proposal to list isopropyl nitrite on Schedule 9 on the basis that it poses unacceptable risks to consumers' health and safety. We do not, however, support the listing of any other alkyl nitrite products on Schedule 9.

Although isopropyl nitrite can be used to achieve the therapeutic purpose of relaxing smooth muscle to facilitate receptive intercourse, we submit it has little therapeutic value specifically because of the availability of other alkyl nitrites that can be used for the same purpose without the same risk of maculopathy.

1.4 More direct and proportionate regulatory options for more frequent risks

The medical literature and clinical and community experience of poppers use all indicate that serious adverse events (such as poppers maculopathy, methaemoglobinaemia, and cardiovascular events) are infrequent when these products are used correctly (via inhalation).

However, there are also risks associated with misuse (e.g. oral ingestion), accidental exposure, or inappropriate use (by people for whom poppers use is contra-indicated due to pre-existing conditions or the use of medications that can interact with alkyl nitrites).

The ease of purchasing poppers online and the difficulty of detecting them in parcels mean that these products will remain available in the community despite being listed on Schedule 9.

Alternative regulatory action can be taken to directly adress the risks of misuse, accidental exposure and inappropriate use, through changes to packaging and the provision of product warnings and instructions for use. However, these steps cannot be taken if these products are made illegal and can only be obtained from overseas suppliers or ‘backyard’ manufacturers.

We also know that LGBTIQ patients are reluctant to discuss their use of illicit substances with their clinicians. Clinicians may be hesitant to discuss the correct use of illicit products with their patients and this is a barrier to identifying contra-indications and monitoring for adverse effects. Clinicians may feel pressure to choose between making a record of a conversation that could be used as evidence in a criminal proceeding, or omitting the record and accepting civil liability if the patient subsequently experiences harm.

We take seriously the risks and concerns the TGA has identified around the use of alkyl nitrites. However, we submit that these can be addressed in more direct and effective ways, without increasing the exposure of historically vulnerable populations to criminalisation.

2. Cascade analysis

2.1. Introduction

In this section, we work through the 'cascade analysis' outlined in the consultation documents, based on the criteria from the AHMAC *Scheduling Policy Framework for Medicines and Chemicals* (AHMAC 2018). Under s 52E(2) of the Act, these guidelines must be followed in order for the scheduling decision to be legally valid. We understand the 'cascade' principle as meaning the appropriate schedule is the first one in which all criteria are met. According to ordinary principles of legislative interpretation, for each criterion to be met, all of its elements must be met as well.

Some issues are raised in the criteria for more than one schedule, and we address these first under 'Common issues' below. In the analysis that follows, they are referenced by number: for example, "CI 2" refers to the discussion of dose control.

Common Issues		
#	Issue	Observations
CI 1	Therapeutic value	**Alkyl nitrites have an established therapeutic value.** Nitrite inhalants are used for an important therapeutic *purpose* — modifying a bodily process in order to facilitate comfortable receptive sexual intercourse. They are effective for this purpose. Their therapeutic *value* arises from the lack of any suitable alternative therapeutic goods that do not impair the use of condoms for HIV/STI prevention.
CI 2	Dose control	**Poppers containing alkyl nitrites are easy to dose.** Poppers are conventionally used by unscrewing the bottle, holding the bottle to one nostril, and briefly inhaling the 'headspace' — the gas between the liquid and the bottle-cap (see image below).

Common Issues		
		 *Figure 1 'Amyl Nitrite' from Fischer, 1977* Users can control how much they use in a single dose by inhaling shallowly or deeply, and they can decide whether or how often to re-dose. The rapid onset of action and short duration of effect of poppers allow users to easily titrate their dose until the therapeutic effect is achieved. Side effects from overuse, such as headache or softening of the erection, can make poppers use 'self-limiting' in sexual contexts (Morin, 2010). Many experienced users only use poppers for initiation and completion of sex (Morin, 2010) with a study of Australian users reporting an average of 3.2 doses per episode (Mullens et al., 2011).
CI 3	Risk profile	**The risk profile of inhaled nitrites is well understood.** The TGA itself lists the known side effects and risks associated with conventional use and misuse (or accidental exposure) in the cascade analysis, which also identifies patient groups who should be counselled against the use of products containing alkyl nitrites. The risks and side effects of alkyl nitrites are shared by nitrite donors as a class, and this includes glyceryl trinitrite products currently available as pharmacist-only medication (eg. 'Rectogesic' cream) or prescription medication (e.g. GTN sublingual spray). The same effects identified by the TGA as toxicities of alkyl nitrites are listed as 'common side effects' for these other substances. We support the listing of isopropyl nitrite (IPN) on Schedule 9, based on emerging evidence of a risk of ophthalmic injury associated with the recent substitution of this substance in 'poppers' products (Davies et al., 2012; Van Bol et al., 2017). We submit, however, that no such evidence exists in relation to other commonly-used alkyl nitrites. The over 40-year history of widespread use of poppers among gay and bisexual men indicates a very low frequency of serious adverse events. There is, moreover, extensive clinical experience of patient use of inhaled nitrites among HIV and sexual health practitioners

Common Issues		
		working with this patient group. This experience could be codified in clinical guidelines. The risks identified by the TGA in the cascade analysis are already discussed in resource materials produced by community education agencies, along with strategies for minimising these risks and recognising symptoms that warrant clinical investigation. The demonstrated capacity of LGBTI community organisations to develop robust and culturally appropriate educational resources to assist users to employ poppers safely should be taken into account by the TGA.
CI 4	Dependency	**Inhaled nitrites are not dependency-forming.** As acknowledged by the TGA in the supporting documents (p. 14) as well as technical sources and community education, alkyl nitrites are not dependency-forming.
CI 5	Propensity for misuse, abuse, or illicit use	**There is some potential for misuse or accidental exposure.** The listing of alkyl nitrites on Schedule 4 means that products have historically been sold without correct warnings and instructions for use. If alkyl nitrites were 'down-scheduled' the risks of ingestion or accidental exposure can be managed by product packaging and labelling, with access to pharmacist advice on quality use. **There is little or no potential for abuse or illicit use.** Alkyl nitrites are not dependency-forming and use is generally self-limiting due to common side effects such as headache. There is no 'street value' that could lead to diversion.
CI 6	Overdose	**There is no description of a risk (or even the possibility) of overdose in either the medical literature or community education materials.** Some of the consultation materials suggest adverse events like methaemoglobinaemia result from overdose. These events are rare, despite some people using nitrite inhalants frequently. It has been observed that a small number of individuals bear a heterozygous deficiency of the NADH-dependent methaemoglobin reductase enzyme, making them more susceptible to forming methaemoglobin when exposed to inducing agents, which include nitric oxide (NO) donors as a class and other medications (Hall et al., 1986) .

2.2 Cascade analysis by schedule

2.2.1. Illicit substances

	Schedule 9	
#	Criterion	Observations
9.1	Relevant UN conventions	**Not relevant as alkyl nitrites are not included in these conventions.**
9.2	The substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use.	**Alkyl nitrites have an established therapeutic value (CI 1).** Inhaled nitrites permit safe and comfortable receptive anal intercourse. They are often recommended by HIV and sexual health physicians as an option for patients experiencing difficulty with receptive anal intercourse. **Inhalant use of alkyl nitrites is acknowledged not to produce dependency (CI 4). The substance itself does not present a high propensity for misuse, abuse or illicit use (CI 5).** The risk of misuse via ingestion or accidental exposure is currently increased due to the lack of product warnings, instructions for use and child-safe packaging, rather than being inherent in the substance itself. Because these products are available at low cost online or via restricted premises, and are not dependency-forming, there is no risk of diversion of licit purchases to a secondary market for illicit use.
	General observations	**Alkyl nitrites do not fit the regulatory aims of this category.** Products containing alkyl nitrites have an important therapeutic value, unlike other substances in Schedule 9. Possession, use or trafficking of substances in schedule 9 potentially attracts serious criminal sanctions. For example, listing alkyl nitrites on Schedule 9 mean possession and use would attract a $75,000 fine and up to 5 years imprisonment in the ACT and NT. Products containing alkyl nitrites have been in wide use for an important purpose for over forty years. Like many substances, there are risks associated with misuse and occasionally with conventional use, however poppers are not associated with significant harm to individual users, their family and friends or the community at large.

	Schedule 8	
#	Criterion	Observations
8.1	Relevant UN conventions	**Not relevant as alkyl nitrites are not included in these conventions.**
8.2	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 have an established therapeutic value (CI 1).** Inhaled nitrites permit safe and comfortable receptive anal intercourse. **Inhalant use of alkyl nitrites is acknowledged not to produce dependency (CI 4). As a class, alkyl nitrites do not have a high propensity for misuse, abuse or illicit use (CI 5).** We reiterate the commentary on these two issues under criterion 9.2, above.

2.2.2. Prescription medication

	Schedule 4	
#	Criterion	Observations
4.1	The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention.	**Inhaled nitrites are not used to treat a medical disorder that requires medical intervention.** They are primarily used to facilitate receptive intercourse that might otherwise be painful or impossible as a result of muscle spasm. While this has been labelled 'anodyspareunia' in sexological research (Damon and Rosser, 2005; Vansintejan et al., 2013), however, we argue this phenomenon is better described as an unpleasant physical difficulty not a medical condition requiring diagnosis and intervention.
4.2	The use of the substance requires adjunctive therapy or evaluation or specialised handling for administration	**Ongoing evaluation or adjunctive therapy is not required.** It is sufficient to provide information for the purpose of symptom recognition for adverse events, so that users can seek medical consultation if required. The same approach is taken with products containing glyceryl trinitrite that pose identical risks and side effects. **The medical literature on alkyl nitrite use does not describe any risk of overdose (see CI 6) or any dose-response relationship with side effects.** Users have a high degree of control over the dose of the substance (CI 2). Behavioural research indicates the average number of doses per episode of use at 3.2 (Mullens et al., 2011). There are no reports in the medical literature of 'overdose' from inhalation. Reviews of methaemoglobinaemia in glyceryl trinitrite users suggest the existence of an undescribed genetic susceptibility to nitrites, with methaemoglobinaemia occurring even after low doses (CI 6).

	Schedule 4	
		The risk of misuse (e.g. accidental overdose by oral ingestion) can be addressed in other ways. Package warnings and instructions for quality use of the substance can ensure users know not to drink the substance.
4.3	The use of the substance at established therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use	**Inhalant use of alkyl nitrites is acknowledged to not produce dependency (CI 4). The substance presents a low propensity for misuse, abuse or illicit use (CI 5).** The possibility of misuse via ingestion or accidental exposure can be managed via product warnings, instructions for use and child-safe packaging.
4.4	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	**The low frequency of adverse effects must be considered by law.** Section 52E(2) of the *Therapeutic Goods Act* 1989 (Cth) requires the decision-maker to consider guidelines published by AHMAC when revising the *Poisons Standard*. Under the guidelines for Schedule 4 listing, criterion 4 requires consideration not just of the seriousness and severity of the adverse effects but also their frequency. The best available evidence on the frequency of these effects is summarised in our earlier submission. We acknowledge that some of the adverse effects associated with nitrite inhalants are severe and serious (e.g. vision loss and methaemoglobinaemia). However, the best available evidence indicates they are infrequent. **Advice on symptom recognition is sufficient to enable consumers to consult their medical practitioner when this is required.** The risk profile of alkyl nitrite inhalation is well understood (CI 3). The symptoms and side effects that warrant GP consultation can be provided to consumers, either via pharmacist consultation (under Schedule 3) or patient information (under Schedule 2).
4.5	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	**There is no fine margin between a therapeutic dose and overdose.** In fact, there is no description of overdose risk in the clinical literature at all (other than via oral ingestion). The risk profile of use is well-understood (CI 3) and nitrite inhalants are easy to dose (CI 2). The risk profile is understood well enough to provide advice to consumers on when to seek medical attention after use. This could be done via pharmacist consultation (under Schedule 3), or on patient information sheets and product labelling (under Schedule 2).
4.6	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,	**There are potentially severe interactions that can be prevented via the provision of consumer information and packaging warnings.** There are well-known risks of co-administration of alkyl nitrites with prescription medication for erectile dysfunction (PDE-5 inhibitors such as sildenafil citrate) and high blood pressure. In addition, community educators warn against the use of alkyl nitrite inhalants with illicit drugs, such as cocaine or methamphetamines. In all cases, these risks can be managed by avoiding co-administration. There are no

	Schedule 4	
	veterinary or dental practitioner.	circumstances where co-administration is medically necessary and therefore no requirement for monitoring by a medical practitioner.
4.7	The use of the substance has contributed to, or is likely to contribute to, communal harm.	**Not applicable.**
	General observations	**We submit that alkyl nitrites are not a good fit with Schedule 4.** The risk profile of alkyl nitrite products is well-understood (CI 3) and while consultation with a GP is something that we would encourage, the risks of misuse, accidental exposure and inappropriate use are manageable through pharmacist consultation, and via product warnings, child-safe packaging and instructions for use. Notwithstanding this, we acknowledge that, due to historical scheduling decisions, most currently-available poppers products fall within Schedule 4, and there may be practical or policy obstacles to our preferred option of downscheduling them to Schedule 3 or 2. If downscheduling is not possible, we submit that Schedule 4 listing is preferable for alkyl nitrites other than isopropyl nitrite, as this permits the adoption of measures that more directly reduce the risks while removing isopropyl nitrite from the market.

2.2.3. Pharmacist-only or pharmacy-only medication

	Schedule 3	
This is our recommended listing for alkyl nitrite products, with the exception of isopropyl nitrite.		
#	Criterion	Observations
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.	**Alkyl nitrite products are substantially safe.** Substantially safe does not mean no risks at all. The risk profile of alkyl nitrites is well understood (CI 3). The more than 40-year history of their widespread use among gay and bisexual men, in the absence of significant rates of adverse events or deaths, indicates that alkyl nitrite products are substantially safe. **The risks are primarily associated with inappropriate use.** In this analysis we define inappropriate use as misuse (e.g. oral ingestion) or use by people with contraindications (such as those identified by the TGA in the supporting document). If rescheduled to S3, pharmacist consultation and the provision of consumer information can prevent or substantially reduce these risks. Consumer information can describe symptoms and side effects that require clinical follow-up. The risk of poppers maculopathy can be prevented by listing isopropyl nitrite on Schedule 9.

	Schedule 3	
3.2	The use of the medicine is not expected to produce dependency at either the established therapeutic dose or at supratherapeutic doses. Where risk of misuse, abuse or illicit use is identified, the risk can be minimised through pharmacist-consumer consultation	**The use of alkyl nitrites is not associated with dependency (CI 4) and there is no description of the possibility of overdose by inhalation in the medical literature (CI 6). The identified risks of misuse involve ingestion or accidental exposure (CI 5).** These risks can be minimised by requiring pharmacist-consumer consultation prior to purchase, and further prevented via child-safe packaging, warnings for storage and instructions on correct use.
3.3	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.	**The risk profile of alkyl nitrites is well understood (see CI 3).** The TGA itself lists the potential risks, side effects, contraindications, drug interactions and patient groups who should not use the product. Knowledge about the risk profile exists among HIV and sexual health clinicians as well as LGBTI community educators, and could be codified and made widely available via clinical guidelines for healthcare workers including specialists, GPs and pharmacists, and product information sheets available for consumers at point-of-sale.
3.4	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	**The medication is not intended for treatment of a chronic condition where pharmacist intervention is required to monitor safe use.** We would submit that ongoing monitoring is generally not required to ensure safe use of products containing alkyl nitrites. However, ongoing pharmacist consultation would provide opportunities for any patients who have concerns about their use, or their experience of side effects, to be referred to their medical practitioner for follow-up.
3.5	The use of the medicine at established therapeutic dosage levels may mask the symptoms or delay diagnosis of a serious condition	**There is no indication in the literature that use of the substance may mask symptoms or delay the diagnosis of any serious condition.** We understand this criterion to be concerned with determining whether ongoing monitoring of use by a pharmacist is necessary to ensure the use of the substance would not mask the symptoms or delay the diagnosis of a serious condition. There is nothing in the medical literature to support this.
	General observations	**The Schedule 3 criteria do not require that the substance is completely free of risk. It is enough for a substance to be substantially safe, with some risks of misuse or inappropriate use that are manageable via pharmacist consultation and product information.** In our submission, listing alkyl nitrites on Schedule 3 for use as a therapeutic product to assist with discomfort or pain associated with receptive anal sex will be beneficial to public health and to the social

	Schedule 3	
		and sexual wellbeing of the gay and bisexual communities. It will reduce the risk of accidental misuse and provide opportunities for pharmaceutical oversight and medical intervention to promote safe use and minimise adverse events. We strongly urge the TGA to consider rescheduling poppers products containing alkyl nitrites (other than isopropyl nitrite) to Schedule 3.

	Schedule 2	
#	Criterion	Observations
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	**With the exception of isopropyl nitrite, we submit that a Schedule 3 listing is the best option for products containing alkyl nitrites.** We would recommend that every method available, including labelling, packaging, and provision of other information, be used to reduce the risks associated with use, misuse and accidental exposure. However, requiring a pharmacist consultation prior to purchase would provide ongoing opportunities to promote quality use of the products, and to check for any experience of symptoms or side effects that would warrant follow-up by the consumer's medical practitioner.
2.2	The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low	**Inappropriate use of alkyl nitrites does not have 'low' potential for harm.** The risk profile of alkyl nitrites is well-understood (see CI 3). This identifies certain patient groups for whom any use of alkyl nitrites would be 'inappropriate use' for the purposes of this criterion. This includes patients with cardiovascular disease, glaucoma, recent head injury, or who are taking high blood pressure or erectile medications. Again, listing alkyl nitrites on Schedule 3 offers a greater opportunity to check that consumers have no contraindications and have appropriate information on quality use of these products.
2.3	The use of the medicine is very unlikely to produce dependency (at either the established therapeutic dose or supratherapeutic doses) and the medicine is very unlikely to be misused, abused or illicitly used	**Alkyl nitrites do not produce dependency at any dose (CI 4), but it is not the case that alkyl nitrites are 'very unlikely' to be misused.** Misuse of alkyl nitrites via ingestion poses a serious risk of harm, and has resulted in two deaths in Australia since 1971. The risk is primarily caused by users not understanding that the conventional use is via inhalation. These risks could be managed via warnings and instructions for use on product packaging. However, again, listing alkyl nitrites on Schedule 3 offers a greater opportunity to check that users do not have any contraindications and have appropriate information on quality use of these products.

3. Alternative regulatory regime

Our earlier written submission argued that many of the risks described in the interim decision could be addressed by mandating child-safe packaging, correct usage instructions and product warnings, and through the provision of community education. This section will briefly detail the educational advice already available from Australian sources online, which describes the known risk profile of alkyl nitrites based both on published medical literature and LGBTIQ clinical and community experience over many decades. It will then describe the institutional capability that exists for promoting health and harm reduction among the LGBTIQ community. Finally, we present an indicative outline of activities for an integrated public health response to the risks and concerns raised by the TGA.

We submit that a public health response will be more direct, effective and proportionate than criminalisation, considering the risk profile of the substances involved.

3.1. Risks already identified in community education

The risks and side effects associated with alkyl nitrites are clearly identified in community education materials. The ACON *HowHard* resource targets 'sexually adventurous' gay and bisexual men (as they are described in research) with explicit advice about managing the use of drugs in sexual contexts.[1] It notes the practical benefit poppers provide for receptive anal intercourse, while also acknowledging their mild euphoric effects and their potential downsides. Specifically, the resource mentions the following risks that need to be kept in mind:

- the danger of combining erectile dysfunction drugs or heart medication with poppers, causing a risk of low blood pressure and passing out;
- the danger of combining use of stimulant drugs such as methamphetamine, ecstasy or cocaine with poppers, placing stress on the heart;
- erectile softening caused by poppers making it more difficult to use a condom for insertive anal intercourse;
- increased peripheral blood supply causing increased bleeding and increased risk of HIV transmission (although this advice pre-dates findings about pre-exposure prophylaxis, and is not likely to be relevant to people who use pre-exposure prophylaxis);
- the potential for superficial burns if the liquid gets on your skin.

The *HowHard* website refers users to another resource known as *TouchBase*, produced by the Victorian AIDS Council (now Thorne Harbour Health) for the mainstream (non-sexually adventurous) LGBTIQ community.[2] The *TouchBase* listing for 'amyl' (poppers) begins with the following message:

[1] http://www.howhard.com.au/.
[2] https://touchbase.org.au/.

> There is no such thing as a **safe** level of drug use. Substance use carries risk. It's important to be careful when taking any drug.

The website notes that the level of harm generally experienced from nitrite inhalation is low, but cautions that effects range from mild allergic reactions to life-threatening methaemoglobinaemia. It cautions against use by people with anaemia, pregnancy, glaucoma, or any history of high blood pressure. It warns that '[orally] Ingesting any [member] of the nitrite family is extremely dangerous and may result in death.'

Like the *HowHard* resource, *TouchBase* warns against combining alkyl nitrites with ED medication or stimulant drugs like amphetamines. Additionally, it encourages people living with HIV, and transgender, gender diverse and intersex people who take hormones, to check in regularly with their GP to monitor potential drug interactions. Finally, it describes a potential for psychological withdrawal when ceasing poppers use, and provides details for alcohol and other drug (AOD) counselling and peer support services.

The AIDS Council of New South Wales (ACON) also maintain a Facebook page for the *HowHard* resource with over 2000 followers.[3] In addition to running community forums and placing articles in LGBTIQ publications, this social media presence enables the organisation to update the community when new drugs (or new trends in drug use) pose additional risks. For example, the *HowHard* page has linked to articles about the danger of co-administration of Viagra and poppers; whether poppers pose a risk to recovery from methamphetamine addiction; and a 2015 article from respected San Francisco publication *BetaBlog* drawing attention to the risks posed by products claiming to be 'poppers' that contain the more dangerous ethyl chloride. (The latter article even mentions the risk of poppers use for people with G6PD deficiency.)

These are three resources available from the first page of a Google search. They draw on nearly four decades of educational capability built up during the AIDS crisis (Kippax and Race, 2003; Sendziuk, 2003). This capability includes the ability to engage with complex biomedical and scientific literatures and to distil the findings into appealing, accessible and culturally-appropriate language and imagery. A quarter of a century ago, the Victorian AIDS Council published a resource promoting safe use of poppers and cautioning against their use by those with 'a history of heart problems, stroke or epilepsy' (Benton et al., 1994).

Many of the risks identified in the cascade analysis, such as co-administration of alkyl nitrites with drugs for erectile dysfunction, were first identified by community educators whose role in providing HIV treatment support meant they were alert to drug interactions.

The take-home message from this summary is that community education *has already* addressed the risks identified by the TGA in the interim decision and cascade analysis. The advice reflects the accumulated experience of 'poppers' use in the gay community (and the clinical experience of HIV and sexual health physicians). It demonstrates that the risk profile of

[3] https://www.facebook.com/HowHard.com.au/.

alkyl nitrite products is well-known and relatively low, and we submit that this weighs against a regulatory approach based on criminal liability.

3.1.1. Organisational capability of the LGBTIQ community

The LGBTIQ community sector includes organisations that were founded in response to the HIV/AIDS crisis, as well as agencies and programs providing mental health services, drug and alcohol services, or health policy advocacy. These include state and territory AIDS Councils, such as ACON (formerly the AIDS Council of NSW) and Thorne Harbour Health (formerly the Victorian AIDS Council). They include organisations and programs for people living with HIV, such as Living Positive Victoria and Positive Life NSW. There are programs promoting harm reduction for LGBTIQ people who use drugs, such as the Party Rovers at ACON, formed as a rapid response to GHB overdoses at dance parties. Health promotion programs have developed campaigns and resources addressing drug use among gay and bisexual men and lesbian and bisexual women (such as *HowHard* and *Claude*, both initiatives of ACON). There are peer-based and community-run harm reduction organisations such as NUAA and Harm Reduction Victoria that have programs for LGBTIQ people who use drugs. Both AIDS Councils and mental health services such as Drummond Street Services offer alcohol and other drug services for LGBTIQ people, including one-on-one and group counselling and peer support.

In short, there is considerable established capacity to develop and promote robust and culturally appropriate messages about the safer use of poppers and to support users who have concerns about their use of any drug.

This capacity is based on skills and infrastructure that were built from the 1980s onwards as part of the Australian 'partnership' response to the HIV/AIDS crisis. A unique aspect of this approach was that prevention activities were delivered primarily by community-based organisations (with the exception of some high-profile campaigns like the 'Grim Reaper'). This can be contrasted with the United States, where prevention programming was developed and delivered by public health professionals — typically clinicians and researchers — according to normative models of health behaviour and communication (e.g. Ajzen and Fishbein, 1980).

The difference in approach meant that Australian programs were based on more in-depth understandings of the communities and cultures they sought to influence (Brown et al., 2015), and their activities were continuous and embedded in community life, rather than one-off or episodic mass communication and outreach initiatives. Clinical agencies like the Australasian Society for HIV Medicine (ASHM) and research programs like the Australian Research Centre in Sex, Health and Society (ARCSHS) learned to draw on knowledge from educators and community members' experience of health issues (Kippax and Race, 2003).

This is the background to our recommendation of an alternative to criminalisation for the regulation of the risks and concerns the TGA has identified around the use of alkyl nitrites. We are not arguing that we can just 'leave it to the market' to sort out, or that all consumers of these products are rational decision-makers who can assess the risks for themselves. Rather,

there is an organised infrastructure, comprising community organisations, clinical and research agencies capable of preparing and delivering an integrated public health response to alkyl nitrites as a health issue, without criminalising their possession and use. (Although we have focused on the LGBTIQ population in this submission we note there are peer-based organisations for non-LGBTIQ people who use drugs with equivalent capacity.) In the following section we provide an indicative outline of what this response might look like.

3.2. Alternative to Schedule 9 listing for alkyl nitrites as a class

In this submission, we encourage the TGA to consider a Schedule 9 listing for a single substance, isopropyl nitrite, on the basis of emerging evidence that it is the principal cause of the adverse event of greatest concern to medical specialists and the community, poppers maculopathy. We propose Schedule 3 listing for the remaining alkyl nitrites. This would enable the use of more effective strategies for the regulation of risks of misuse, accidental exposure and inappropriate use. There is no way to regulate the packaging and labelling of illegal products, and clinicians and their patients may be hesitant to discuss the proper use of an illicit substance. Our goal in this section is to provide an indicative outline of the potential components of an organised and strategic response to the risks and concerns the TGA has identified.

3.2.1. An integrated public health response to the risks

The indicative outline below identifies interventions that will complement and reinforce each other from the individual level up to the whole-of-population level. An agency leading the development of a public health response to a health issue would consider options for intervening at multiple points in the sequence of risks and harms. This includes primary prevention to prevent the condition, secondary prevention initiatives to detect the condition and tertiary prevention to slow or stop disease progression. In developing the indicative outline below, our focus was on primary prevention — messages and strategies that can prevent risks occurring in the first place. In addition, we have identified steps that could be taken to build capacity among the relevant clinical and community stakeholder groups to respond in an effective and coordinated way based on evidence and experience.

Indicative outline for an integrated public health response to alkyl nitrite risks	
Level	Interventions
Capacity building *Preparing an effective and coordinated response*	• Scoping review of the evidence on alkyl nitrites • Structured consultation (e.g. Delphi scan) with HIV and sexual health practitioners to characterise the clinical experience of alkyl nitrite use among LGBTIQ+ patients • Development of clinical guidelines for health professionals (including specialists, general practitioners and pharmacists) on contraindications and use instructions • Working group to monitor evidence and experience of 'poppers maculopathy' • Engagement with emergency physicians about managing accidental exposures
Primary prevention *Preventing the risk of harm*	• Schedule 9 listing for isopropyl nitrite (only) to prevent or reduce maculopathy • Child-proof packaging and storage warnings — reducing accidental exposures • Warnings against ingestion and skin contact — reducing risks of misuse • Package insert or labelling on the conventional use and potential risks and side effects, as well as information on symptoms that require medical follow-up • Contra-indications: warnings against use by people with particular conditions, or co-administration with particular drugs • Restrict sale to pharmacies and require pharmacist consultation prior to purchase regarding correct use and contra-indications • Development of social marketing campaigns and resources to promote awareness of correct use and contra-indications to use • Encourage GP consultation to check for undiagnosed conditions prior to use
Secondary prevention *Detecting symptoms*	• Campaigns and resources provide information to facilitate symptom recognition by popper users and encourage self-referral for medical follow-up • Opportunistic screening by GPs and pharmacists for symptoms (e.g. fatigue, vision changes) or recent emergence of contra-indications to use
Tertiary prevention *Preventing disease progression*	• Clinical guidelines for GPs and pharmacists facilitate the identification and referral of symptomatic patients for specialist follow-up • Working group comprising ophthalmologists, toxicologists, HIV and sexual health clinicians and LGBTIQ-friendly general practitioners to monitor the emerging evidence and clinical outcomes for poppers maculopathy

4. Conclusion

In this submission we consider the evidence and experience relevant to alkyl nitrites use in the LGBTIQ community. Together, these indicate that serious harm resulting from the use of poppers is rare. There is strong evidence, based on the timing and location of reports of poppers maculopathy, that indicates this risk could be prevented by listing isopropyl nitrite on Schedule 9. We support moving the remaining alkyl nitrites from Schedule 4 to Schedule 3, as this will permit the adoption of more direct, targeted, effective and proportionate measures to respond to the risks of misuse, accidental exposure and inappropriate use. These measures could be delivered and supported through an integrated public health response that engages with clinical and community stakeholders, including general practitioners, specialists, pharmacists, research agencies, community educators and community members. Such an approach would address the risks and concerns that have been identified by the TGA without exposing a historically-marginalised community to an increased burden of criminalisation.

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