Alkyl nitrites

Appropriate access and safety controls

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What problem are we trying to fix?

We recognise that:

- Poppers have **significant use** in Australia (4.1% respondents used in last year - 2018 Global Drug Survey)
- Many people use inhaled alkyl nitrite products regularly without adverse effects

But there have been some very serious health impacts (including just from inhalation):

- **Loss of vision** (maculopathies or retinal damage) even after a single use - not common
- **Hospital emergencies** due to methaemoglobinemia - loss of oxygen delivery to bodily organs
- **Interactions with many medicines and medical conditions** can worsen adverse events
- **Deaths** from oral consumption
  - User base now wider than LGBTI community - more “less experienced” poppers users - more risks?

And there are legal problems - there is not a “loophole”:

- Supply or sale of several (S4) alkyl nitrites without the purchaser having a prescription is actually **illegal**
- Many products are imported into Australia **illegally** (no Industrials Chemicals (ICNA Act) registration)
Visual damage - retinal maculopathy

- Genuine side effect but not common - over 20 separate studies published in medical literature
- Only reported since 2010
  - Is this because of better eye tests?
  - Or due to switch from amyl to isopropyl nitrite?
- Many ophthalmologists or optometrists may not make a connection to poppers use
- Can be irreversible and **can occur after a single poppers use**

Methaemaglobinemia - serious oxygen starvation

Results in **impaired oxygen delivery to bodily organs**
• Resulting in chest pain, shortness of breath, altered mental state and possible permanent organ damage
• More likely in certain genetic conditions (e.g. G6PD deficiency)

e.g. NSW Poisons Information Centre reports
• About 90 poisonings reported in 2018 - double 2017 number
• Three quarters required hospitalisation - several from inhalation

e.g. Australian Poisons Information Centres
• 273 poisoning calls in 11 years to 2014 - 10 paediatric exposures
• Hospitalisation required in 73% of cases, almost all high risk level

23 deaths in the UK related to alkyl nitrites 1971-2009
• 14 claimed to be from inhaling (UK VSA mortality project)
• But some other reports claim the numbers of deaths are lower
And there are more common adverse but less severe reactions

- Skin irritation and burns
- Low blood pressure, tachycardia, dizziness, nausea and fainting
- Aggravated if individual is also taking prescription medicines such as sildenafil (Viagra®)
- Some reports of immune suppression and neurotoxicity
There are also legal problems with how the products are accessed …. leather cleaner and adult shops

Very hard to run education campaigns on safe use for a product that
• Is supplied illegally through adult shops or online
• Deliberate mislabelling to disguise use and circumvent laws
• Unknown composition and quality and may be promoted as not for human use

Can’t introduce formulation/packaging for safe use
• While there is anecdotal evidence that some brands / formulations are better, it is not possible to police counterfeiting or consistent quality standards
• So do access controls / controls on product quality have a role here?
Who would you trust for quality-assured products and advice on safe use of poppers?

- A pharmacist

  or

- Someone at an adult only shop or sex-on-premises venue
Are some alkyl nitrites safer than others?

The composition of poppers has changed over time

- from (1970s/80s) amyl nitrite (also known as isoamyl nitrite) TO isobutyl and isopropyl nitrite TO isopentyl and cyclohexyl nitrite
- affected by regulatory bans, what is readily available or manufactured in different countries

Composition of different nitrites in different poppers still varies

- Muscle relaxant effect due to the nitrite part of the molecule, differences in the alkyl part affect volatility
  - Also reports of contamination with ethyl chloride
    - Some evidence that isopropyl nitrite causes retinal damage more than other nitrites?

Variation in manufacturing quality
Were 1970’s poppers safer because they were pure(r) amyl nitrite?
“Scheduling” affects access and safety controls

• Medicines and chemicals are classified into **Schedules** according to the level of regulatory control required over the access to the substance to protect public health and safety.

• The **Schedules** in the **Poisons Standard** are given effect through state/territory legislation

• The **Scheduling Policy Framework** requires consideration of whether the alkyl nitrites have an established ‘therapeutic value’:
  – Whilst the muscle relaxant use for alkyl nitrites is its therapeutic use, its therapeutic value must also assess the associated risks of use, toxicity and the potential for abuse.

• **The decision-maker** is a senior public health physician (not the Minister), who must consider:
  – Section 52E of the Therapeutic Goods Act 1989 and the **Scheduling Policy Framework** (SPF)
  – Not a process of comparing substances, but reviewed individually against 52E and SPF criteria
  – Information obtained through public consultations and meetings, public submissions received
  – Recommendations of Advisory committees plus any additional evidence
Matters to be taken into account (in reaching the decision) in accordance with section 52E, *Therapeutic Goods Act 1989* are:

- the **risks and benefits** of the use of a substance
- the **purposes** for which a substance is to be used and the extent of use of a substance
- the **toxicity** of a substance
- the **dosage, formulation, labelling, packaging and presentation** of a substance
- the **potential for abuse** of a substance
- any other matters that the Secretary considers necessary to protect public health

…however issues of “human rights” are out of scope in law…
Current scheduling status

Schedule 4 (Prescription only medicines) applies to 5 nitrites

- AMYL NITRITE, BUTYL NITRITE, ISOAMYL NITRITE, ISOBUTYL NITRITE and OCTYL NITRITE
  - Some nitrites - such as isopropyl and cyclohexyl nitrite are currently not scheduled

- **In law** “A person, other than a medical, dental or veterinary practitioner in the ordinary course of their professions or a pharmacist dispensing a legal prescription must not sell or supply”
  - i.e. as prescription medicines they need to be dispensed by a pharmacist based on a prescription
  - Additional state and territory laws can apply e.g. in NSW “must be stored in a part of the premises …. to which the public is not permitted to have access”

- Currently there are **no commercial alkyl nitrite medicine products available in Australia** but patients **who are prescribed** alkyl nitrites could access them either
  - through a compounding pharmacy
  - or by personal importation with a doctor’s prescription
Public submissions - most wanted three outcomes:

A safer product to use - could this be achieved through

- Changes to formulation
- Changes in labelling of products to describe safe use, emphasise the risks, and provide advice about child-safe storage; mandating child-proof caps or other caps to prevent ingestion but not inhibit inhalation

Regulation that is proportional to the risks involved with the use

- Is there consensus on the risks?
- Prohibition could drive the market underground and remove the opportunity to potentially regulate the formulation and packaging of alkyl nitrites
- Is requiring a prescription to legally access poppers realistic?

Education on how to use alkyl nitrites safely

- Possible point of sale restrictions such as minimum age for purchase
- Perhaps making them available via pharmacies where people could access quality advice
Possible options for access controls to alkyl nitrite containing products

- **Very significant polarisation of views** … and most submissions **did not comment** on most options in the discussion paper

- Options for a **product with therapeutic** use range from
  - general (unrestricted) sale
  - access in pharmacies, pharmacist only access
  - prescription only access or prohibited substance status

- Need to consider whether it is appropriate to apply different access controls to **different alkyl nitrite substances**

- Options need to consider management of risks to health in **communities wider than LGBTIQ communities** need to be considered
Scheduling options - analysis against the factors

Sale, supply or use forbidden except research or educational purposes (Schedule 10)
• If a substance is harmful and has no valid therapeutic or industrial use

Prohibited substances (Schedule 9)
• Substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use.
  Would not allow supply, even under prescription
  Countervailing factors influence “therapeutic value” - Sale currently illegal, does make use “illicit”?

Controlled drugs - available on doctors’ prescription (Schedule 8)
• 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
  Not recognised to produce dependence
  Sale currently illegal but the use may not be
  S8 would significantly increase penalties for possession without a prescription in several states
Prescription only medicines (Schedule 4)

- The ailments or symptoms that the substance is used for require medical intervention
  Medical review beneficial before use to diagnose underlying cardiovascular disease, glaucoma or an enzyme deficiency
- The use of the substance requires … specialised handling for administration
  Difficult to control how much is inhaled so people can accidentally overdose. Swallowing can be fatal
- Use…. may produce dependency, moderate propensity for misuse, abuse, illicit use
- The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical practitioner is required to minimise risk
  Medical advice on adverse events (low BP, tachycardia, dizziness, nausea and fainting, methaemoglobinaemia) beneficial
  Unlikely that loss of vision (maculopathies or retinal damage) could be avoided even with medical advice
- Margin of safety between the therapeutic and toxic dose of the substance
  Risk profile of alkyl nitrites is not well defined
- Seriousness, severity and frequency of the interactions of the substance with other drugs
  Combination with other vasodilators, anti-hypertensives, certain migraine drugs, and high doses of aspirin serious
- The experience of the use of the substance under normal clinical conditions is limited
  Little clinical experience with alkyl nitrites other than for angina treatment
Pharmacist only medicines (Schedule 3)

• The medicine is substantially safe with pharmacist intervention …may be potential for harm if used inappropriately

   Pharmacist guidance could include counselling about the adverse event profile, interaction with other medicines and serious side effects

• Use … not expected to produce dependency ….where risk of misuse, abuse or illicit use is identified, the risk can be minimised through pharmacist-consumer consultation

   Pharmacist advice could be given on avoiding excessive inhalation, skin contact or swallowing

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

   Presently, the risk profile of alkyl nitrites is not well defined.

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

   Use of alkyl nitrites is unlikely to be safe to use in people with undiagnosed cardiovascular disease
Pharmacy only medicine (Schedule 2)

- Quality use can be achieved by labelling, packaging, and/or provision of other information. But should it be available without first having to speak to a pharmacist about safety/warnings/use?
- Use of the medicine is substantially safe ….. and the potential for harm from inappropriate use is low.
  - No - potential for harm from ingestion, spilling on skin or excessive inhalation
- Use is very unlikely to produce dependency…very unlikely to be misused, abused or illicitly used.
- Risks can be identified and managed by a consumer through appropriate packaging and labelling.
  - Safety of alkyl nitrites not well characterised in comparison with commercial medicines
- Use … is not likely to mask the symptoms or delay diagnosis of a serious condition.
  - Use of alkyl nitrites unlikely to be safe to use in people with undiagnosed cardiovascular diseases

General sale (e.g. supermarkets, convenience stores)
- Substance would need to be unscheduled - i.e. not raise any safety concerns
Other options?

• **Can’t treat as household / industrial chemical** as this use not permitted under the ICNA Act
  – Since there appears to be no genuine industrial uses in Australia
  – Schedule 5 (Caution) and Schedule 6 (Poison) categories are not used for human medicines
  – Thus cannot use these schedules to enable label warnings or packaging changes

• **Submissions have emphasised the importance of government safety controls on composition, contents, packaging (to prevent swallowing and limit spills) and labelling (safety warnings)**

• Is a **Mandatory Safety Standard under Australian Consumer Law** an option?
  – Not usual for products where they are able to be used safety by a significant majority of users
  – Standards are around design and manufacture rather than preventing inappropriate use or on the composition or quality of the alkyl nitrites
  – Limited monitoring ability for standards of this type

• Prohibitions on **sale to children** or of **advertising** are matters for state/territory governments
The legal situation varies internationally

• Banned butyl and other volatile alkyl nitrites for human use
• Amyl nitrite is a prescription drug, so other nitrites have become readily but illegally available
• Some US states have made alkyl nitrite purchase or possession illegal

Canadian Government 2013
• sale of poppers is illegal as they are “unauthorised drugs”

Required to hold a prescription in UK to legally possess alkyl nitrites
• UK Psychoactive Substances ban not implemented as poppers do not directly affect the central nervous system
• Isobutyl nitrite classified in the EU as cancer-causing in 2006
Safety benefits of provision as a medicine

If poppers were legally sold as medicine, it would be possible to
• Have controls on safety, quality and efficacy of the products
• Provide guidance on safe use, possible adverse effects, directions in the case of overdose
• Packaging to prevent/minimise accidental or deliberate swallowing
• Require identification of the manufacturer so that complaints can be directed appropriately
• Report adverse events to the TGA

Main challenges
• No currently-registered products in Australia (some in USA); available through pharmacy compounding
• Company would need to apply to TGA
• Would people go to their doctors if a prescription medicine were available?
• Would people go to their pharmacist?
Only amyl nitrite is available as a pharmaceutical (in USA) e.g. as a unit dose inhalant of 0.3mL

Options for legal Australian access (if alkyl nitrites are scheduled as a prescription or pharmacist only medicine)

- Organisation becomes the **Australian sponsor** of the product and obtains TGA approval
- **Compounding pharmacy** prepares the product (but labelling and packaging laws don’t apply)
- **Personal import** with a prescription (if prescription only)
Next steps

- These public forums in Sydney and Melbourne
- Review public submissions from latest consultation round (closed 15 Jan 2019)
- Discussions with other product safety regulators
- Joint meeting of Advisory Committees on Medicines and Chemicals Scheduling in mid March 2019
- Delegate’s decision/s June 2019