

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):

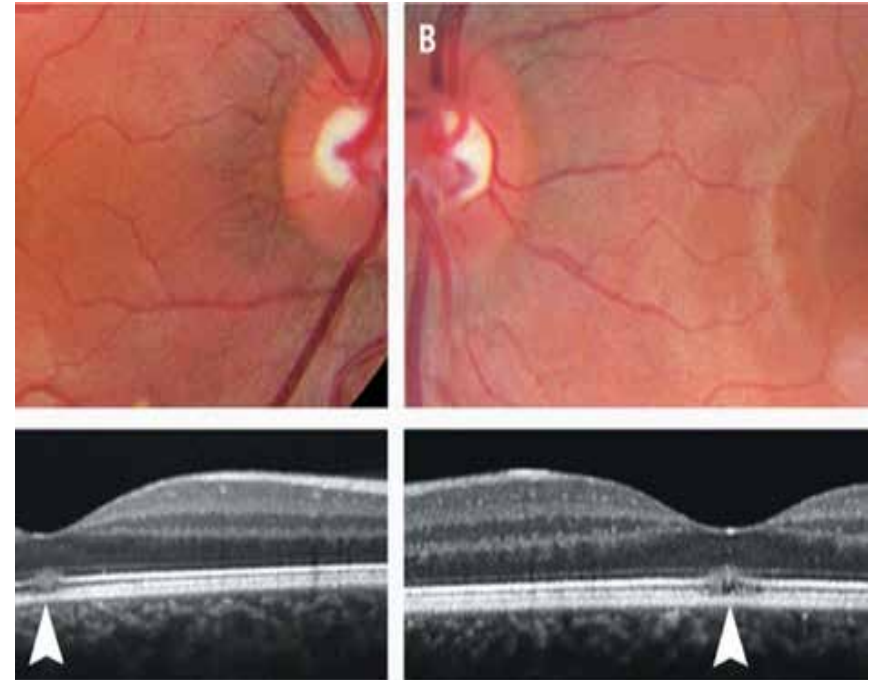
- **Loss of vision** (maculopathies or retinal damage) even after a single use - not common
- **Hospital emergencies** due to methaemoglobinaemia - loss of oxygen delivery to bodily organs
- **Interactions with many medicines and medical conditions** can worsen adverse events
- **Deaths** from oral consumption
 - 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**



Catherine Vignal-Clermont et al N Engl J Med 2010 (363) 1583



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Methaemoglobinemia - serious oxygen starvation³

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



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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



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Are some alkyl nitrites safer than others?

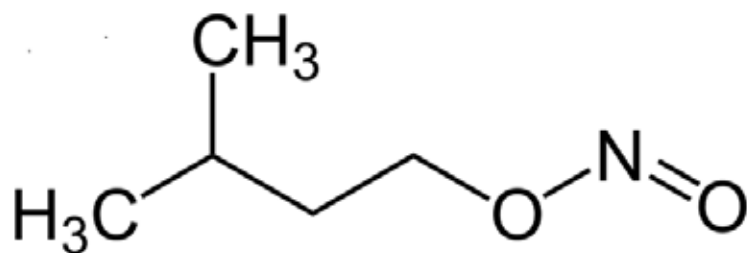
The composition of poppers has changed over time

- 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**



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Were 1970's poppers safer because they were pure(r) amyl nitrite?



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“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 dependencywhere 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 safely 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



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The legal situation varies internationally

US Consumer Products Safety Commission 1988

- 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)²¹ 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)



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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



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