ACMD

Advisory Council on the Misuse of Drugs

Alkyl nitrites (“poppers”) – updated harms assessment and consideration of exemption from the Psychoactive Substances Act (2016)

Contents

1. Introduction

1.1. Alkyl nitrites are volatile liquids (evaporating at normal temperatures) that, following inhalation, deliver a short, sharp 'high,' or sense of euphoria and relax smooth muscle, especially in blood vessels and sphincters [Haverkos et al, 1994]. The term 'alkyl nitrites' encompasses a group of substances that are chemically similar, with each member of the group differing in the alkyl group it contains (e.g., propyl, butyl, etc.). They can also be referred to using various synonyms (see Annex A). They have been used widely since the 1960s, especially by men who have sex with men (MSM), and since the late 1980s by teenagers, clubbers and festival attendees [Sigell et al, 1978; Measham, 1998; Palamar et al, 2023; Measham 2023]. Their use and harms have been previously reviewed twice by the ACMD [ACMD, 2011; ACMD 2016].

1.2. Alkyl nitrites are colloquially known as "poppers" because the first example used medically, amyl nitrite, was provided in small thin-walled glass vials, that made a popping sound when broken open. For consistency the term 'alkyl nitrite' is used to describe the group as a whole in this report. It should be noted that users may not be aware of the exact chemicals in the products they purchase and that the term 'amyl nitrite' may sometimes be used to describe any alkyl nitrite, not just amyl nitrite.

1.3. Alkyl nitrites are widely available for purchase from sex shops, festivals, convenience stores and on-line markets. They are often manufactured in small, colourful sealed bottles containing (at least initially) alkyl nitrite liquid only, although some of this may be converted with time to the corresponding alcohol (see below). These products are sold under numerous different brand names, some with sexual connotations, including *Amyl'*, *Kix*, *Liquid Gold*, *Ram*, *Rock Hard*, *TNT*, *Bang Aroma* or *Thrust*. These products may have information about their contents and include warnings about unsafe use printed on the label. More recently, brown screw-top bottles have been encountered, that sometimes contain a small white (probably plastic) ball which may be included as a desiccant or an agitator. 'Poppers' containers may or may not be tamper-proof and are relatively inexpensive, for example a 15 ml bottle can be obtained for less than £5, with cheaper deals available for bulk purchases. Sales of these products generate substantial income for manufacturers. For instance, in the United States the poppers retail industry has been estimated at $40 million [Mack, 2021]. This figure presumably refers to annual turnover, although this is not explicitly stated. Turnover from sales of one specific product in the European Union (*Jungle Juice*) was reported as €143,000 in 2020 [Funline International 2023].

1.4. Although intended for inhalation, they are labelled for a variety of uses that do not involve human consumption, in order for retailers to avoid contravening the law (see below). These include use as room deodorisers, nail polish removers or boot/leather cleaners. Labels often state "not for inhalation," adding to user confusion and potentially increasing the risk of ingestion, which is much more hazardous than inhalation (see below).

2. Legal Status

2.1. The legal status of alkyl nitrites varies in countries outside of the United Kingdom (UK), with information summarised in Annex B.

2.2. In the UK, alkyl nitrites have never been controlled via the Misuse of Drugs Act (1971). While use may be associated with harms (see Section 12), two previous ACMD reviews concluded that these were not common or severe enough to warrant control via the Act.

The Medicines Act 1968 makes it illegal to sell products for medicinal purposes without a product licence. Medicinal purposes include *'otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily'*. Similarly, the definitions of a medicinal product in the Human Medicines Regulations (2012) include *'any substance or combination of substances that may be used by or administered to human beings with a view to restoring, correcting or modifying a physiological function by exerting a pharmacological, immunological or metabolic action'*.

2.3. The Medicines Control Agency (now the Medicines and Healthcare products Regulatory Agency, MHRA) brought a prosecution against the directors of a company manufacturing and supplying isobutyl nitrite in 1999. This was on the basis that isobutyl nitrite had physiological effects and should therefore be considered a medicine, requiring a product license for sale and supply. The defendants, however, were found not guilty [ACMD, 2011].

2.4. The MHRA have recently stated that UK court judgments have made it clear that alkyl nitrites do not fall under medicines regulations and the requirement for medicinal products to have a demonstrable therapeutic purpose has been clarified by European Court of Justice case law. The MHRA have confirmed that there have not been any prosecutions for the period 2015-2023 under medicines legislation, but no information prior to 2015 has been provided.

2.5. The Dangerous Substances and Preparations (Safety) Regulations 2006, prohibits the sale of isobutyl nitrite as it has been classified as a carcinogen in the European Union and is listed in Schedule 2 of the regulations [EU, 2006]. As a result, manufacturers of alkyl nitrites now generally use other compounds in their products (see Section 9).

2.6. The Intoxicating Substances (Supply) Act 1985 (IS(S)A 1985), previously made it an offence for a person to *"supply or offer to supply a substance other than a controlled drug to a person under the age of eighteen"* (or to a person acting on behalf of such a person) *"if he knows or has reasonable cause to believe that the substance is, or its fumes are, likely to be inhaled by the person under the age of 18 for the purpose of causing intoxication."* This legislation, however, was repealed in 2016 by the Psychoactive Substances Act (Schedule 5, paragraph 1).

2.7. The Consumer Protection Act 1987, makes producers, importers and suppliers liable in the event of their products being found to be defective, without the need to demonstrate negligence. A defect in a product is something that makes it

unsafe compared to what a person is generally entitled to expect, for example producing personal injury or death. Surrounding circumstances, such as the manner and purposes for which the product is marketed, are taken into account, alongside warnings relating to use, and what the producer might reasonably expect to be done with the product.

2.8. The General Product Safety Regulations (2005) place obligations on those producing or distributing products for the British market, to ensure that these are safe and traceable and that consumers are provided with information about the risks associated with use. They must keep a register of complaints and inform distributors when a product does or may present a risk. Producers and distributors are also required to inform the enforcement authority if risks to consumers are incompatible with the general safety requirement. These regulations are enforced by trading standards authorities, which have powers to require additional warnings to be given to consumers or to suspend or withdraw products from the market. In Northern Ireland (NI) some of the provisions apply differently under the terms of the Windsor Framework [OPSS 2023].

2.9. UK REACH (Registration, Evaluation, Authorisation and restriction of CHemicals) regulates the majority of chemical substances that are manufactured in or imported into Great Britain (GB, i.e. England, Scotland or Wales). Businesses are responsible for identifying and managing the risks presented by substances they manufacture and place on the market. They also need to demonstrate how the substance can be used safely and communicate appropriate risk management measures to consumers. In addition, GB-based manufacturers, importers, professional users and distributors supplying the GB market must demonstrate that their classification, labelling and packaging (CLP) of substances and mixtures is compliant with the GB CLP regulation. Substances and mixtures placed on the market in Northern Ireland are subject to the EU CLP Regulation, from which the UK legislation was adapted. UK REACH and the GB CLP regulations are overseen by the Health and Safety Executive (HSE) in GB, while the Health and Safety Executive Northern Ireland (HSENI) is responsible for the relevant legislation in NI.

2.10. The Psychoactive Substances Act 2016 (PSA) made it an offence to produce, supply, offer to supply, possess with intent to supply, possess on custodial premises, import or export any psychoactive substance, if it is to be consumed for its psychoactive effects, unless specifically exempted. Currently exempted substances are listed in Schedule 1 of the Act as follows:

- Drugs already controlled via the Misuse of Drugs Act (1971);
- Medicinal products (as defined in the human Medicines Regulations (2012);
- Alcohol and alcoholic products;
- Nicotine and tobacco products;
- Caffeine and caffeine products;
- Foods that do not contain a prohibited ingredient[1];

[1] "food" includes drink; "prohibited ingredient", in relation to a substance, means any psychoactive substance which is not naturally occurring in the substance, and the use of which in or on food is not authorised by an EU instrument.

Activities listed in Schedule 2 of the Act are also exempted and are currently as follows:

- Healthcare-related activities (carried out by a healthcare professional acting in the course of his or her profession);
- Scientific research carried out by a person who has approval from a relevant ethics review body to carry out that research.

3. Government Commission

3.1. The ACMD were commissioned to provide an updated assessment of the harms of alkyl nitrites and advice on their psychoactivity in 2016. The ACMD's consensus view at that time, was that a psychoactive substance would have a direct action on the brain. The psychoactive effects of alkyl nitrites were thought to result from increased cerebral blood flow resulting from nitric oxide mediated vasodilatation [Kowaluk & Fung, 1991]. As the blood vessels involved are located outside the blood brain barrier, this was not considered by the ACMD to be a direct psychoactive effect. Consequently, the Council concluded that this would place alkyl nitrites outside their interpretation of the definition of psychoactivity and therefore there was no need to consider an exemption [ACMD, 2016].

3.2. The PSA as written, however, does not make any specific distinction between substances with direct or indirect psychoactive effects. A Court of Appeal judgment made in relation to a case involving nitrous oxide has since confirmed that substances which have an indirect psychoactive effect are captured by the 2016 Act (R v Rochester [2018] EWCA Crim 1936). Therefore, as alkyl nitrites are considered to have psychoactive effects, they are also subject to the PSA, irrespective of whether these effects are direct or indirect [Fortson, 2018]. This has resulted in the lawfulness of the supply of alkyl nitrites becoming uncertain, to the particular disadvantage of MSM, who choose to use them to facilitate intercourse. To address this, the then Home Secretary was minded to remove uncertainty by explicitly exempting alkyl nitrites from the 2016 Act. The ACMD's advice on an exemption was sought via a commissioning letter received in August 2020.

4. Scope of this report

4.1. The ACMD has not previously been commissioned to provide advice on possible exemptions to the Psychoactive Substances Act (2016). The ACMD has, therefore, sought clarification from the Home Office on the Council's role under the PSA and this has clarified the process that should be followed, including the appropriate format and scope of ACMD advice.

4.2. It has been agreed that the role of the ACMD in the PSA exemption process is to define the compounds affected, provide advice on their psychoactivity, legitimate uses and harms, make appropriate recommendations and, in the event of an exemption being made, assist with the wording of the exemption.

4.3. This report summarises, expands and updates the evidence on psychoactivity, use and harms previously provided by the ACMD [ACMD 2011; ACMD 2016], considers the advantages and disadvantages of an exemption to the PSA and makes recommendations to Government.

5. Anal sphincter physiology

5.1. Normal anal sphincter activity requires relaxation in response to rectal distension to allow defaecation. This is referred to as the rectoanal inhibitory reflex. Nitric oxide (NO) is a naturally occurring bioactive substance that acts as an inhibitory neurotransmitter within the internal anal sphincter and is integral to the process of nerve-related sphincter relaxation, which is abolished if NO synthesis is inhibited. NO-mediated sphincter relaxation is thought to be the mechanism by which the topical organic nitrate, glyceryl trinitrate (GTN, a NO donor), reduces anal pressure and can enhance healing of anal fissures. [O'Kelly, 1996; Lund 2006].

5.2. There are other potential pharmacological methods for promoting anal sphincter relaxation. Gastrointestinal smooth muscle tone is calcium-dependent and calcium channel blockers, including topical diltiazem, can reduce the resting pressure of the anal sphincter. Smooth muscle tone is also reduced by sacral parasympathetic cholinergic innervation and cholinomimetics, such as bethanechol also relax the anal sphincter when applied topically. [Carapeti et al, 1999].

5.3. The action on the anal sphincter of organic nitrates, calcium channel blockers and cholinomimetics has been explored because of their therapeutic potential for healing anal fissures. Topical GTN and diltiazem preparations have both been used for this indication but only GTN is licensed for this purpose in the UK.

5.4. It is possible that oral or topical preparations of the drugs described in this section might help prevent pain and trauma associated with anal intercourse. However, there is no specific evidence of this and the ACMD is not aware of any user experience for this purpose.

6. Chemistry, pharmacology and toxicology

6.1. Alkyl nitrites consist of easily synthesized liquid compounds containing a nitrite (–O–N=O) group linked to various hydrocarbon (alkyl) chains (Annex A). Within the body, the nitrite group can release NO, which is integral to the relaxation of smooth muscle, including in blood vessels to produce vasodilatation (widening) and in sphincters to produce relaxation, as described above. [Kapil et al, 2020]

6.2. Many alkyl nitrites are sufficiently volatile at room temperature to allow administration by inhalation. Volatility is determined by the alkyl group involved; those materials with lower boiling points have higher volatility (Annex A).

6.3. Limited information is available on the pharmacology of individual alkyl nitrites in humans. After inhalation they are rapidly absorbed via the lungs, with effects occurring promptly. There is more information available for amyl nitrite, because it has been licensed as a medicine in some countries. Effects occur within 30

seconds of inhalation and last between 3-5 minutes. Tolerance may develop to the effects of alkyl nitrites, requiring increased or repeated dosing to obtain the desired effects.

6.4. Alkyl nitrites can be detected and quantified using headspace gas chromatography [Seto, 2005] and/or Fourier transform infrared spectroscopy (FTIR). On contact with moisture, however, the alkyl nitrite degrades to its corresponding alcohol, so it is common to detect nitrite-alcohol combinations, for example amyl nitrite with pentanol (amyl alcohol), isopropyl nitrite with isopropanol or isobutyl nitrite with isobutanol.

6.5. Within the body amyl nitrite is metabolised rapidly, probably by hydrolytic denitration, although about a third of inhaled amyl nitrite appears in the urine [James Alexander Corp, 2012]. The alcohols resulting from metabolism of alkyl nitrites (e.g. pentanol, isopropanol, isobutanol) can be detected in blood, but for less than 30 minutes after use [Vogt et al 2015]. As a result, the measurement of organic or inorganic nitrite concentrations in blood is of little value in assessing their role in cases of toxicity [Seto, 2005]. This is one of the reasons screening for alkyl nitrites is rarely included in clinical or forensic toxicology testing. Another is that, although headspace gas chromatography is routinely used in forensic toxicology, the methodology is designed to detect other volatile substances and would need to be modified to detect alkyl nitrites. As a result, the involvement of these compounds in suspected drug-related deaths may not be recognised.

6.6. There is little published information available on the toxicology of alkyl nitrites in animals and this was not discussed in earlier ACMD reports. Some information on effects on the central nervous system is described in the section on psychoactivity below. Exposure of rodents to alkyl nitrites has been reported to cause methaemoglobinaemia, reduced haemoglobin and haematocrit, weight loss, and splenic or thymic atrophy [Soderberg, 1998]. The doses required to be inhaled over 4 hours to cause death in half the rats exposed (LD50) varied several fold between the six different alkyl nitrites tested (methyl-, ethyl-, n-propyl-, n-butyl-, isobutyl-, and isopentyl nitrite). The dose-mortality curves were characterized by extremely steep slopes. Toxic signs observed during exposure included cyanosis, prostration, and rarely, convulsions [Klonne et al, 1987]. The study did not include isopropyl nitrite and the relevance of these findings and the concentrations assessed to human use is uncertain.

7. Legitimate use

7.1. Amyl nitrite was first used as a treatment for angina in 1867, but was soon superseded by the organic nitrate GTN, which is easier to use and has a longer duration of action [Nossaman et al, 2010]. Currently several different organic nitrates are used widely in the treatment of angina pectoris. These are non-volatile compounds that are administered via sublingual, buccal, transdermal or oral routes. A topical GTN preparation is also available for treatment of anal fissure, as described in Section 5. Organic nitrates may cause low blood pressure and dizziness, but unlike organic nitrites, do not cause euphoria and, in spite of widespread prescribing for cardiovascular disease, are not used as

recreational drugs. The reasons why nitrites cause euphoria, but nitrates do not is unclear.

7.2. Amyl nitrite has also been used as an antidote for cyanide poisoning [Brazil, 2021] and is licensed as a medicine in some other countries. The MHRA have confirmed that there are no alkyl nitrites licensed as medicines in the UK and no clinical trials pending or authorised for any medicinal products containing any alkyl nitrite as an active substance. Neither are they aware of any products licensed or in development to reduce pain or trauma associated with anal sex.

7.3. In industry, alkyl nitrites can be used as reagents for chemical manufacturing, cleaning agents and solvents. To supplement any legislative changes, further information on use in the UK would normally be provided in an impact assessment by the Home Office.

8. Psychoactivity

8.1. The mood enhancing and intoxicating effects of alkyl nitrites have long been recognised. They include a 'rush' associated with dizziness, alongside a feeling of warmth and enhanced sexual arousal. These effects typically last a few minutes [Romanelli et al, 2004] and further doses may be needed for effects to be maintained.

8.2. The ACMD advised previously that these psychoactive effects were likely to be indirect [ACMD, 2016], resulting from increased blood flow from nitric oxide-mediated vasodilatation [Kowaluk & Fung, 1991]. There is, however, an increasing understanding of the complex effects of nitric oxide in the normal brain. This includesa role as a neurotransmitter [Picón-Pagès et al 2019; Pisani et al, 2019; Angelis et al 2020; Spiers et al 2021; Gambino et al, 2022; Solanki et al, 2022], so it is plausible that, by increasing nitric oxide concentrations within the brain, alkyl nitrites could exert direct psychoactive effects. One group of researchers has reported impairment in learning and of motor coordination [Cha et al 2016], as well as increased drug-paired place preference and striatal dopamine release in mice following alkyl nitrite administration [Jeon et al, 2016]. The mechanism for these effects and their relevance to the doses and modes of administration in typical human use are uncertain.

8.3. No information is available on the concentrations required to produce psychoactive effects in humans and how these relate to those needed for smooth muscle and sphincter effects.

8.4. Following the 2018 Court of Appeal ruling that, for the purpose of the PSA, psychoactivity can be either direct or indirect, the mechanism of psychoactivity now appears irrelevant to the legal status of alkyl nitrites.

9. Composition of products sold

9.1. A 2015 study in Germany involving 76 different 'poppers' flasks purchased online, found discrepancies between the alkyl nitrites declared and those analytically detected in 39 (51%). The declared contents were isopropyl nitrite, isobutyl nitrite or amyl nitrite, but butyl nitrite, isopentyl nitrite and isobutyl nitrite were also detected. In 41 (54%) products, more than one alkyl nitrite was

present [Vogt et al, 2015]. More recently in 2019, the Australian Therapeutic Goods Administration (TGA) analysed 8 samples of alkyl nitrite 'poppers', obtained from local adult stores. Isobutyl nitrite was detected as the single major ingredient in all of them. Analysis of 10 further products purchased from non-Australian websites, identified isopropyl nitrite in 5 samples and isopentyl nitrite in another 5 products [TGA, 2019].

9.2. More limited published information has been available on the specific alkyl nitrites currently used in products being sold the UK. A British study analysed products deposited in amnesty bins and bought from festivals before and after enactment of the Dangerous Substances and Preparations (Safety) Regulations (2006), which banned isobutyl nitrite. Those deposited prior to the regulations in 2006 contained mainly isobutyl nitrite, while those deposited in 2008 were all found to contain isopentyl nitrite [Davies et at, 2010].

9.3. UK stakeholders have provided updated information on the alkyl nitrites they have detected in drug seizures or forensic analysis of post mortem patient samples between 2018 and June 2023 for the purposes of this report. A total of 121 detections were reported including 91 for isopropyl nitrite, 11 for isobutyl nitrite, 3 for isopentyl nitrite and one each for amyl nitrite and amyl nitrate. There were also 14 unspecified alkyl nitrites detected. There were no consistent differences in the annual numbers of detections or in the pattern of substances identified over this time period (Annex C).

10. Use and reported benefits

10.1. Alkyl nitrites are usually inhaled directly from the bottle. A single prolonged inhalation is usually sufficient to produce psychoactive, cardiovascular and sphincter effects. These usually last for a few minutes and further inhalations are often required if prolonged effects are wanted. Alkyl nitrites have also been inhaled from an unlit cigarette dipped in the liquid or by inhaling from a cloth (e.g. a sock) that has had a small amount of liquid poured onto it [French & Power 1998]. These latter modes are potentially more hazardous, due to the highly flammable nature of the liquid. Other reported routes of administration include oral ingestion and intravenous injection [Reisinger et al, 2020]. These routes potentially involve larger administered doses and carry a much higher risk of adverse effects compared to inhalation.

10.2. Alkyl nitrite use is common under two circumstances:

(a) in nightlife contexts, to obtain a short-lasting ‘rush’, often during dancing [Romanelli et al, 2004] and usually as a secondary drug to primary dance drugs in polydrug repertoires that include methylene-dioxymethamphetamine (MDMA), amphetamines and cocaine [Measham et al, 2001; Measham et al, 2024].

(b) during or prior to sex, often by MSM in the context of receptive anal sex and/or chemsex. [Vaccher et al 2020; Giorgetti et al, 2017].

10.3. By promoting anal sphincter relaxation, use of alkyl nitrites is reported to enable easier and less painful anal penetration and may prevent spasm and injury (e.g. sphincter tears). This is not the only motivation for use by MSM, , as users also

report that alkyl nitrite use may prolong erection, increase libido and heighten the experience of pleasure including the duration and intensity of orgasm [French and Powers, 1998]. Commonly, there is overlap between motivations for use by MSM, to obtain a psychoactive 'high' and to enhance sexual experience and it is common for alkyl nitrites to be shared between the receptive and insertive partner.

10.4. No clinical trials have been identified that either quantify the effects of nitrites on the anal sphincter or confirm the reduction in pain and trauma associated with anal sphincter. Moreover,no evidence is available to establish dose-response relationships [Schwartz et al, 2023]. In a survey of 404 American MSM, 55 men (14%) reported frequent and severe pain during receptive anal sex (anodyspareunia), with most describing pain as lifelong, associated with psychological distress and causing avoidance of anal sex. Of those with anodyspareunia, 18% reported that not using poppers caused pain most or all of the time, compared to 4% of those not reporting this problem [Damon & Rosser 2005].

10.5. The benefits for receptive anal sex extend beyond making anal sex more pleasurable, to enabling some same-sex couples to engage in sexual intercourse without injury. The use of alkyl nitrites in this context enables sexual functioning for some coupled gay men and thus, has broader benefits to relationship satisfaction and well-being [Vaccher et al. 2020; Schwartz et al. 2023] which could be significantly impacted without access to them.

10.6. Alternative possibilities for relaxing the anal sphincter or otherwise reducing anal pain associated with intercourse are limited. Use of adequate lubrication is essential and anaesthetic lubricants may be useful for some. Nevertheless these reduce sensation for both partners and may increase the risk of injury. Topical preparations of GTN and diltiazem are available for treatment of anal fissure, although only the GTN preparation is licensed for this purpose in the UK as a prescription only medicine. No published data on use of these drugs to reduce pain and trauma associated with anal intercourse has been identified. Even if they did have benefits, those who might wish to use them would need to have them prescribed for an unlicensed indication by a doctor. To achieve this, they would need to disclose intimate details which would be a barrier for many.

11. Prevalence of use

Use overall

11.1. The Global Drug Survey (GDS) is an anonymous, international, online, self-selecting, cross-sectional drugs survey. In the most recently published report, covering 2021, the overall lifetime reported use of 'poppers' amongst 32,022 respondents was 15.8% and use in the last year was 5.8% [GDS, 2021]. This self-selecting population does not necessarily reflect the wider population and data were not provided in this report by age, sex or sexual orientation, but earlier data on this from the GDS are discussed below.

11.2. Current data on prevalence of use in the UK are limited. The Crime Survey for England and Wales last published data on use of 'amyl nitrite' for 2016/17, when reported use in the last year was 0.5% in people aged 16-59 years, equating to

approximately 169,000 people. Use in the last year was 2% of those aged 16-24 years [ONS 2017]. It seems likely that these figures represent use of any alkyl nitrite and not just amyl nitrite.

Use by MSM

11.3. Use of alkyl nitrites by MSM is common, although not confined to this group. According to a survey conducted by Stonewall in the UK in 2011, 31% of 6,861 gay and bisexual men surveyed had used “poppers” in the last year compared to 2% of men in general [Guasp A, 2013]. A survey in Australia in 2014-15 found that 1127 (66%) of the 1710 gay or bisexual men surveyed had used ‘amyl nitrite’ in their lifetimes and 577 (34%) within the previous 6 months [Jin et al 2018]. There is also limited evidence of increasing use in recent years. A cross-sectional survey of 3167 gay sexually active men recruited from a range of gay community sites in Sydney, reported use of alkyl nitrites increased from 40% in 2015 to 47% in 2019 [Broady et al, 2019]. In other countries, use of alkyl nitrites in the previous 3-12 months amongst MSM have been reported as 37% in the United States [Colfax et al., 2005], 34% in Germany [Deimel et al., 2016], 36% in Canada [Roth et al., 2018], 24% in Australia [Demant & Oviedo-Trespalacios, 2019], 15-98% in China [Li et al., 2014; Bae et al, 2018; Luo et al 2017], and 47% in France [Hambrick et al., 2018a]. In Australia, use was more common in older (41% of those 30-39 years) than younger men (23% of those 16-24 years) [Jin et al, 2018], reflecting similar findings from an earlier study performed in Scotland [Li & McDaid, 2014].

11.4. The GDS of 2013 provided information on drug use according to reported sexual orientation. Use of ‘poppers’ in the last 12 months was reported by 0.7% of 11557 heterosexual men, 17.5% of 1225 gay men and 8.3% of 842 bisexual men, with the differences between groups being statistically significant. Use in women was much less common than in gay or bisexual men, with reported use in the last 12 months being 0.4% of 4970 heterosexual women, 0.7% of 282 women who have sex with women and 1.1% of 962 bisexual women. Reported use of ‘poppers’ was positively associated with age and with respondents from the UK compared to those from the Eurozone, USA, Canada, and Australia. In this study, men rated the effects of poppers on intensity of orgasm higher than women, although the lower numbers of women reporting use of poppers limits the conclusions that can be drawn from the comparison [Lawn et al, 2019].

11.5. The Attitudes to, and Understanding of, Risk of Acquisition of HIV (AURAH) study of HIV-negative individuals attending sexual health clinics across England (2013–2014) and the Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study of HIV-positive individuals attending HIV outpatient clinics in England (2011–2012) reported use of alkyl nitrites in the past 3 months in those who were HIV negative as 33% of MSM, 1% of heterosexual men and <1% of women. For HIV positive people, reported use was 27% of MSM, 1% of heterosexual men and <1% of women. [Daskalopoulou et al, 2014; Miltz et al, 2021].

11.6. The European Men-Who-Have-Sex-With-Men Internet Survey (EMIS) study used a questionnaire administered to over 127,000 MSM in 50 countries. Use of poppers within the previous year, week or 24 hours was reported as 34.4%,

14.4% and 5.4% respectively. Amongst 43,000 men reporting drug use in the context of a sexual encounter, alcohol (28%), poppers (22%), erectile dysfunction medications (12%), cannabis (7%) and gamma hydroxybutyrate (GHB) or gamma butyrolactone (GBL, 3%) were the most common substances taken [Weatherburn et al, 2019].

11.7. A high prevalence of alkyl nitrite use was reported in a survey of 1478 men and women attending two sexual health clinics in London between December 2013 and March 2014, with use of poppers at least monthly reported by 4.0% overall and by 15.6% of MSM. [Thurtle et al, 2016]. Lifetime (71.4% vs 25.1%) and last month use of poppers (18.4% vs 0.6%) were higher in those identifying as MSM compared to those identifying as non-MSM [Hunter et al, 2014].

11.8. Of 1648 MSM aged 18 years or over in the UK recruited via a national, cross-sectional online questionnaire administered in 2018, 28% reported use of poppers immediately before sex [Hibbert et al, 2019].

Heterosexual use

11.9. Alkyl nitrites are sometimes used by heterosexual couples to enhance their sexual experience, including prolongation of orgasm. [French and Power, 1997]. Anal intercourse may occur during heterosexual encounters; in an American survey 35% of men and 30% of women had engaged in heterosexual anal intercourse within the previous year [Hess et al, 2016]. Little published information is available on the use of alkyl nitrites by women in the context of heterosexual anal or vaginal intercourse, but the overall low prevalence of alkyl nitrite use by women described in preceding paragraphs suggests that this is less common compared to use by MSM.

Use by nightlife populations and at festivals

11.10. High use of alkyl nitrites has been reported by clubbers attending electronic dance music (EDM) events in nightclubs and festivals. In New York City, use of alkyl nitrites within the previous year by attendees of these events was reported as 9.8% in 2017 and 24.5% in 2022 [Palamar et al, 2023].

11.11. In a survey involving 1345 EDM event attendees in Belgium (70% male), alkyl nitrites were used by 33%, with significant motivations including ‘to dance’ and ‘to look for sex’ [Van Dyck et al, 2023].

11.12. A late 1990s in-depth mixed methods study of young adults attending dance clubs in North West England found that 72% of respondents reported having used alkyl nitrites at least once and 30% in the last three months. Self-reported lifetime prevalence of use was 76% and 66% for male and female respondents respectively. A larger proportion of males (10.7%) than females (5.9%) had taken or were planning to take alkyl nitrites on the night the fieldwork for this study was done. Lifetime prevalence of use and use on the night the fieldwork was done were both statistically significantly related to respondent age and were also higher in those attending a predominantly gay city centre dance club (where one in five reported using alkyl nitrites that night) compared to other venues in the study [Measham et al, 2001].

11.13. Data on recent UK usage of alkyl nitrites comes from the English Festival Survey (EFS), conducted annually at music festivals as a partnership between universities, festivals and harm reduction charity The Loop. Teams of researchers conduct anonymous convenience sample surveys of festival attendees' current and previous alcohol and other drug use, policing and related issues onsite at festivals. Pooled data from 964 people surveyed at two English festivals taking place in 2016 and 2019, showed that 80 (8.3%) reported use of alkyl nitrites within the last year. For the whole sample surveyed, 46.5% were male, 52.6% female, and 0.3% transgender. Sexual identity was reported as 'straight' (89.4%), gay/lesbian (4.8%), bisexual (4.5%) or other (0.7%), with information missing for 0.6% [McCormack et al, 2022].

11.14. Data submitted for publication from the same annual EFS involving 11,566 respondents surveyed between 2014 and 2023 indicated significant demographic differences in alkyl nitrites usage. Compared to a reference group of straight women, straight men were 1.56 times more likely to report ever using these products, while lesbians and bisexual women were respectively 1.43 and 1.80 times more likely to report ever having tried them. For gay and bisexual men, the effect was even stronger with gay men 5.81 and bisexual men 3.43 times more likely ever to have tried poppers than straight women, respectively. Past month use showed greater differences with gay men nearly twelve times more likely to report use of alkyl nitrites in the past month and bisexual men over three times more likely. Those aged 20-24 years were most likely to report poppers use in the last month and last year. Gay men who reported participating in anal sex in the past year were 14 times more likely to have taken poppers in the past year than straight women who reported not having engaged in anal sex in the past year [Measham et al, 2023].

Use by young people

11.15. Alkyl nitrites have been relatively easy for younger people (e.g., teenagers) to obtain and may be the first drug of initiation. In a study from the late 1990s age of first use was commonly 13-14 years [Parker et al, 1998]. In a survey conducted between 1991 and 1994, alkyl nitrites were the second most common substance reported to have been used by young people, after cannabis [Measham et al, 1998].

11.16. Limited more recent data on use in younger people has been published, but the proportion of school children aged 11-15 years who have taken "poppers" (i.e. any alkyl nitrite) in England declined between 2001 (3.7% boys, 3.1% girls) and 2021 (0.7% boys, 0.3% girls) [ONS, 2022a].

12. Health and Social Harms

Cardiovascular effects

12.1. As they relax smooth muscle and dilate blood vessels, alkyl nitrites can cause a fall in blood pressure and headache, with associated dizziness and tachycardia. Less commonly, bradycardia may occur. [TOXBASE 2023; Rosoff & Cohen, 1986].

12.2. Cardiovascular effects may be more prominent in those with underlying heart disease and those taking medicines that also cause vasodilation such as the

phosphodiesterase 5 (PDE5) inhibitors that are used to treat erectile dysfunction, including sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra). Because of the potential severity of the hypotension caused by this interaction, the combination of organic nitrates and PDE5 inhibitors is absolutely contraindicated [NICE, 2023]. The interaction with PDE5 inhibitors is also likely to occur with alkyl nitrites, whichis of particular concern because use of this combination by MSM is common [Li & McDaid, 2014; Aldridge & Measham, 1999]. It is not clear if users are aware of the potential severity of the interaction.

Effects on the blood

12.3. Alkyl nitrites convert ("oxidise") the iron in haemoglobin from ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) to produce methaemoglobin, which is less efficient at transporting oxygen in red blood cells. Normal amounts of methaemoglobin in blood are around 1-2%. If sufficient methaemoglobin is produced, the resulting reduced oxygen carrying capacity of the blood can cause breathlessness and rapid heart rate. Due to the dark colour of methaemoglobin, blood appears to be "chocolate coloured" when blood samples are taken. Individuals with high methaemoglobin concentrations can appear to have grey or blue peripheries (e.g. fingers and toes) and mucous membranes (e.g. lips) which look similar to cyanosis (blue discolouration due to lack of oxygen). Severe methaemoglobinaemia (usually >30%) can cause metabolic acidosis, respiratory depression, coma, convulsions and cardiovascular collapse and can be fatal in the absence of treatment. Ventricular fibrillation has been reported [Gooley et al, 2023].

12.4. Methaemoglobinaemia can be reversed by appropriate use of the antidote methylthioninium chloride ('methylene blue'), administered in hospital by intravenous infusion. The risk of severe methaemoglobinaemia increases with the amount of alkyl nitrite used and is particularly likely if the liquid is swallowed or injected rather than its vapour inhaled.

12.5. Haemolysis (breakdown of red blood cells) can also occur, especially in people with the congenital enzyme deficiency called glucose-6-phosphate dehydrogenase (G6PD) deficiency, causing anaemia associated with jaundice [Elshikh et al, 2021]. G6PD deficiency occurs in around 5% of the world's population, concentrated in those from areas affected by malaria.

Effects on the eyes

12.6. Visual loss associated with maculopathy including foveal damage may occur after use of alkyl nitrites ("poppers maculopathy"). When the alkyl nitrite involved is known, most cases have been associated with isopropyl nitrite and indeed maculopathy has only been recognised since 2010 when the use of isopropyl nitrite became more widespread following the ban on isobutyl nitrite. This apparent association may, however, result from the high prevalence of isopropyl nitrite in products sold over this period and there are also some reports of maculopathy with amyl and isobutyl nitrite [Bartolo et al, 2023; Rewbury et al, 2017].

12.7. Visual effects may occur within hours of a single use or may occur after multiple uses and include loss of visual acuity which is almost invariably bilateral

[González-Martín-Moro et al, 2022]. This is often associated with a central scotoma (loss of central vision), glare and phosphenes (sensation of light or colour that persist with the eye closed). Most patients have abnormal fundoscopic examinations, manifesting yellow foveal spots or foveal irregularities. Spectral domain optical coherence tomography (SD-OCT) commonly shows sub-foveal disturbance of the ellipsoid layer and less commonly vitelliform-like lesions, full thickness macular holes or micro-holes. Vision often improves over several weeks after stopping exposure, but recovery can be incomplete [Pahlitzsch et al, 2016; González-Martín-Moro et al, 2022; Bartolo et al, 2023]. Damage is likely to be related to excessive nitric oxide delivery to retinal cells, but the precise mechanism is not yet established.

12.8. The 2012 GDS reported that 5152 of 17,479 (29.5%) respondents from the UK, Australia, USA and Eurozone to a self-selecting online survey performed between November 2012 and January 2013 had used poppers within their lifetime and 1322 (7.6%) within the previous year. Of these 'last year' users, 29 (2.2%) reported that poppers use had affected their eyesight and there was increased prevalence of this symptom with age [Davies et al, 2017].

12.9. There is a single recent case report of central retinal vein occlusion associated with the use of amyl nitrite [Lam et al, 2022].

12.10. Alkyl nitrite vapours may produce transient lacrimation and stinging. Splashes in the eye usually cause only mild irritation but corneal damage has been reported [Mearza et al, 2001].

Effects on the skin

12.11. As alkyl nitrites are highly flammable, thermal burns can occur, particularly if cigarettes soaked in alkyl nitrites are then inadvertently lit or the liquid is spilled onto hands before lighting a match or cigarette lighter. Direct skin contact may also cause irritation, injury and/or wounds that resemble burns [French and Power, 1997; Moret et al, 2020].

12.12. Alkyl nitrites can result in contact and allergic dermatitis, particularly around the nose and lips. Risk can be reduced by ensuring no direct contact between the skin and the liquid being inhaled. Prolonged contact with the skin can also result in systemic absorption, with features as described above.

Effects on the lungs

12.13. Due to the irritant nature of nitrite compounds, haemoptysis (coughing blood) and respiratory complications including severe tracheobronchitis (inflammation of the airways) can occur with long term repeated use by inhalation.

Immunity, viral infections and cancer

12.14. In humans, inhalation of amyl nitrite in three-times daily sessions over 3 or 18 days was associated with a reduction in numbers of CD3+ T-lymphocytes and reduction in natural killer cell activity, effects which reversed after a few days [Dax et al, 1991].

12.15. Isobutyl nitrite has been listed as a human carcinogen but other alkyl nitrites are also potentially carcinogenic because of their potential to react with amines under acid conditions to form toxic and carcinogenic *N*-nitrosamines [Davies et al, 2010].

12.16. Use of alkyl nitrites has been associated with increased transmission of human immunodeficiency virus (HIV). This is likely to be because their use is associated with other behaviours that may increase HIV transmission, including condomless sex with multiple partners and receptive anal sex [Li & McDaid, 2014; Melendez-Torres et al 2017; Vaccher et al, 2020]. In men who were not living with HIV aged 50-70 years, long-term heavy alkyl nitrite use was associated with an elevated risk of some virus-associated cancers, with causative viruses being human papillomavirus, Kaposi's sarcoma associated herpes virus (HHV-8), and Epstein–Barr virus. Although reported as being independent of sexual risk behaviour the analysis did not include those factors most associated with increased risk. There was, however, no significant association found between heavy popper use and virus-associated cancers in HIV-infected men [Dutta et al, 2017]. It should be noted that, since earlier studies, risk of HIV transmission has been reduced by the use of pre-exposure prophylaxis (PrEP) using antiretroviral drugs. In one of the studies described above, the majority (57.7%) of HIV-negative men reporting recent poppers use were concurrently taking HIV pre-exposure prophylaxis [Vaccher et al, 2020].

Dependency

12.17. Alkyl nitrites do not appear to cause dependence in human users, however some studies have reported that a minority of users may rely on use for satisfactory sexual activity [Demant et al 2019].

Other effects

12.18. Mild effects that can occur after use include nausea and vomiting, headaches, sweating, chills, throat irritation, lethargy, euphoria, altered perception of time and aggressiveness [TOXBASE, 2023].

Drug combinations

12.19. Alkyl nitrites are commonly used in combination with other drugs, such as MDMA, cocaine, methamphetamine, mephedrone and GHB, especially when clubbing or during chemsex parties [Giorgetti et al, 2017]. There is evidence that polydrug use to enhance sexual pleasure has become more frequent internationally in recent years [Vaccher et al, 2020]. Users of alkyl nitrites were more likely to have engaged in group sex, chemsex, sex with casual partners and receptive anal sex compared to non-users [Vaccher et al, 2020]. This is likely to reflect that people having these types of sex use alkyl nitrites to reduce potential trauma and injury associated with anal intercourse, rather than alkyl nitrite use encouraging these higher risk sexual encounters.

12.20. Use of alkyl nitrites may be more hazardous if combined with use of other drugs, but, other than the interaction with PDE5 inhibitors described above, there is a lack of published information about this [Vaccher et al, 2020, Van Dyck, 2023].

Social harms

12.21. Very little evidence of social harms from use of alkyl nitrites has been identified by this review. There may be some littering from used glass or plastic bottles which can have a particular impact in areas used for outdoor sexual activity. Psychoactive effects are short lived and unlikely to be associated with accidents or aggression. The potential economic impact of regular use for the individual, their families or society as a whole appear limited and the relatively low cost of poppers products is unlikely to prompt acquisitive crime, There is a risk of accidental ingestion by children but this appears very low (see sections 13.1 and 13.4).

13. Harms in the UK

13.1. The National Poisons Information Service (NPIS) has received 7531 TOXBASE accesses and 159 telephone enquiries concerning alkyl nitrites from healthcare professionals (HCP) since 2018. The specific alkyl nitrite involved was not known or reported by patients or their HCP in most cases, but specific alkyl nitrites most commonly reported were amyl nitrite and isopropyl nitrite (Annex D). None of the telephone enquiries involved children aged under 16 years.

13.2. Deaths involving use of alkyl nitrites appear uncommon. Statistics by year are not published but there were 25 deaths registered as involving alkyl nitrites in the 20 years from 2001 to 2020 in England and Wales. [ONS 2022b]. An earlier report documented 23 deaths involving alkyl nitrite use in the overlapping period from 1971 to 2009 [Ghodse et al, 2012]. A further 3 deaths were registered in Scotland between 2000 and 2022 and there has been 1 death recorded in Northern Ireland in the period 1997 to 2016.

13.3. Information on the specific alkyl nitrites involved in fatalities is available for only a limited number of cases. The National Programme on Substance Abuse Deaths (NPSAD) receives information from coroners (on a voluntary basis) on deaths related to drugs in England and Wales, Northern Ireland, the Channel Islands and the Isle of Man. NPSAD has identified 5 deaths associated with isobutyl nitrite and 4 associated with isopropyl nitrite since 1999. The EUropean-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging pSychoactiveS study study (EU-MADNESS) also identified 2 deaths (2011 and 2021) and a further death associated with “amyl nitrate” (2020).

13.4. Information is available about a single death in a child aged between 19 and 21 months who died in 1993 after apparently swallowing ‘amyl nitrate’ that was left within her reach. No other evidence of serious harms involving children has been identified.

13.5. The risk of death from alkyl nitrite use has recently been evaluated as ‘quite low’ (1 in 50,001 to 1 in 500,000) [Newcombe, 2023]. Risk of death, however, is higher if alkyl nitrites are ingested rather than inhaled, although fatalities following inhalation alone have been recorded [French and Power, 1997]. Using a range of sources including NPSAD and Re-solv, 5 UK deaths have been identified where alkyl nitrites were swallowed since 2002, including 2 of the 9 deaths identified by NPSAD. There may, however have been others as the route of administration is often not reported.

13.6. Overall, serious harms from alkyl nitrite use appear to be uncommon. A recent study using Multi-Criteria Decision Analysis that assessed poppers against 16 harm criteria found a very low overall weighted harm score, lower than all 21 other substances assessed in this and previous studies using the same methodology [Ferreira et al, 2022].

14. Conclusions

14.1. There continues to be significant use of alkyl nitrites in the UK, especially (but not exclusively) by MSM and by those attending dance clubs and festivals. Motivations include to enhance sexual experience by facilitating and reducing pain and trauma associated with receptive anal sex, to obtain a short term high and/or to enhance the effects of controlled drugs used for recreational purposes.

14.2. The information available on the components of products being sold in the UK is limited, but most of those analysed in the UK since 2018 have contained isopropyl nitrite, with isobutyl nitrite and amyl nitrite less commonly identified.

14.3. Health harms can occur as a result of use of alkyl nitrites and occasionally these are severe, including methaemoglobinaemia which in extreme cases can be fatal and maculopathy which can cause visual loss, although this is usually temporary. Considering the apparently high numbers of users, severe health harms are uncommon and the previous ACMD advice against control via the MDA remains appropriate. Risks may be further mitigated by provision of advice and information to users, including the importance of avoiding swallowing the liquid (contrary to labelling advising not to inhale) or direct contact with skin as well as the risk of fire and of drug interactions, especially those with PDE5 inhibitors such as sildenafil (Viagra).

14.4. The psychoactivity of alkyl nitrites has not been in doubt, especially considering their use as secondary dance drugs in clubbers' polydrug repertoires, but little information is available on the precise mechanism of psychoactivity. This could be an indirect effect of vasodilatation and increased blood flow, but the possibility of direct effects, for example via elevated concentrations of nitric oxide in the brain, cannot be excluded.

14.5. The mechanism of psychoactivity, direct or indirect, now appears unimportant in determining the legal status of alkyl nitrites following the 2018 Court of Appeal ruling concerning nitrous oxide. Therefore, currently the PSA would appear to provide legislation enabling the prosecution of those importing, exporting or supplying alkyl nitrites for human consumption for their psychoactive effects. This potentially places those who supply (e.g. by selling or sharing) alkyl nitrites to reduce trauma and injury associated with anal intercourse at risk of prosecution. To our knowledge, however, this has not been tested in court and we are not aware of any prosecutions made via the PSA in relation to alkyl nitrites.

15. Options for legislation

15.1. Options for legislation are discussed in further detail below and a summary of advantages and disadvantages is provided in Annex E.

Do nothing

15.2. If alkyl nitrites are not exempted from the PSA, it would remain an offence to produce, supply, offer to supply, possess with intent to supply, possess on custodial premises, import or export alkyl nitrites if the person knows, or is reckless as to whether these are likely to be consumed by some other person for their psychoactive effects. This means that shops or on-line sites selling alkyl nitrites could face prosecution.

15.3. For those who are not in custody, purchasing, possessing or using alkyl nitrites does not contravene the PSA, but individuals could be committing an offence if they gave (including sharing) or sold alkyl nitrites to others.

15.4. There are some potential arguments that could be considered in defending a prosecution via the PSA in relation to manufacturing, importing or supply of alkyl nitrites:

(a) ***They are not directly psychoactive and therefore the PSA does not apply***. Even if the psychoactive effects of alkyl nitrites are exclusively indirect, the judgement in R v Rochester [2018] in relation to nitrous oxide has removed this potential defence. Those who produce, distribute, sell or supply alkyl nitrites are therefore open to prosecution.

(b) ***They are not being provided for their psychoactive effects.*** A defendant might seek to avoid criminal liability for an offence under sections 4 or 5 of the PSA by asserting that the product was supplied, not for its psychoactive effect, but only to facilitate intercourse. The prosecution might have little difficulty in proving that a manufacturer or supplier objectively "ought to know or suspect that the substance is a psychoactive substance" (ignorance of the law being no defence). But a defendant would then be put in a position of asserting that he did not know or was not "reckless" (i.e. did not foresee the risk which he went on to take anyway / did not turn a blind eye) that the likely use was for its psychoactive effects. To prove this a retailer would be well-advised to take steps on each sale to demonstrate proof – enquiry of a purchaser as to what use the product is being put to; written assurance to that effect from customers; written assurance that it would not to be passed to a third party who might be taking it for a different purpose than the original purchaser, etc. Such steps seem unrealistic, unworkable and undesirable. They also involve enquiries and disclosure of an extremely personal nature. In order to avoid liability they may, however, be necessary. Manufacturers should seek similar assurance from retailers, however artificial this may seem. Current law also prohibits the commonly-encountered use of alkyl nitrites for both effects - to facilitate intercourse and for the psychoactive reaction.

(c) ***They are medicines and therefore already exempted from the PSA via Schedule 1***. Use for smooth muscle relaxation to facilitate sex could be

considered a medicinal effect by *'restoring, correcting or modifying a physiological function by exerting a pharmacological, immunological or metabolic action'*. If alkyl nitrites were considered medicines, their supply would potentially contravene the Medicines Regulations. No alkyl nitrites, however, are licensed as medicines in the UK (although amyl nitrite is licensed as such in some other countries) and no prosecutions using medicines legislation have been successful in the UK. The MHRA have stated that UK court judgments have made it clear that alkyl nitrites do not fall under medicines regulations.

15.5. Those who contravene the PSA currently face further jeopardy. An adverse outcome from the use of alkyl nitrites, for example a fatal accident in which the use might be one of a number of causative elements, could render a supplier, importer and manufacturer liable to be prosecuted for unlawful act manslaughter.

15.6. The fact that there may not have been any prosecutions under the PSA with respect to alkyl nitrites is arguably a reflection on the lack of danger that they pose. Nevertheless, however unlikely it may be, should serious injury or death occur where use of alkyl nitrites might be a contributory factor, the Crown could feel compelled to litigate.

15.7. It is therefore not possible to exclude the possibility of successful prosecutions via the PSA and this disadvantages MSM who use them to facilitate sex and also places those importing, manufacturing or supplying alkyl nitrites at legal risk. Continuing uncertainty about the legality of supply of alkyl nitrites would likely be interpreted as an attack on the LGBTQ+ community, and MSM specifically, with the potential to further marginalise a group based on their sexuality (a protected characteristic). Recent partial or complete bans on alkyl nitrites in other countries have been interpreted as targeted against gay men [Demant & Ovideo Trespalascios, 2019].

15.8. It could be argued that keeping alkyl nitrites as subject to the PSA might reduce consumption and consequently health harms. Evidence from Canada, however, suggests that legislation to make alkyl nitrites illegal does not reduce access or use. Instead, users turn to illicit sources, placing them at risk of harms related to an illicit and unregulated drug supply, including the opportunity for suppliers to sell them other drugs [Schwartz et al, 2023]. In Australia, only 15% of gay or bisexual male users indicated they would stop using alkyl nitrites if they were criminalised [Vaccher et al, 2020].

15.9. Currently, in the UK, the manufacture and sale of alkyl nitrites for human use is illegal. It seems clear that most people are ignorant of this. Should the status quo be maintained, as awareness of the current position spreads, it is unlikely that reputable retailers and manufacturers would risk continued illegal manufacturer and sale. This would bring a consequent disadvantage to those wishing to use them as an aid to atraumatic sexual intercourse.

Exempt from PSA

15.10. Exempting all or selected alkyl nitrites by addition to Schedule 1 of the PSA would remove the risk of prosecutions via this Act. Provision for human consumption, however, might under some circumstances contravene the General Product Safety Regulations (2005) or other legislation described in Section 2 of this report.

15.11. Exemption may be seen as an endorsement of use or safety, in the absence of clinical trial data providing a high level of evidence on efficacy, safety or quality of products that might be used. There is much less information available on which to base advice on the optimum doses and methods of use and the risks of adverse consequences compared, for example, to medicines that are licensed for human use.

15.12. There is also the possibility that adding an exemption for alkyl nitrites would create a precedent encouraging exemption requests for other psychoactive substances (not already controlled via the Misuse of Drugs Act) used by other minority groups, although the ACMD is not currently aware of specific examples where this is likely to occur.

15.13. An exemption would make alkyl nitrites available with fewer legal barriers for use specifically for their psychoactive effects, for example by clubbers taking dance drugs. This may be seen as inconsistent with the current or planned control via the Misuse of Drugs Act of other psychoactive substances associated with a relatively low risk of health harms, such as nitrous oxide and khat. There is a risk that the publicity associated with an exemption for alkyl nitrites, coupled with the recent control of nitrous oxide via the Misuse of Drugs Act, might encourage substantial increases in the use of alkyl nitrites as alternative 'legal' psychoactive substances. Prior to its control, nitrous oxide was sold at festivals in high volumes and the same could occur for alkyl nitrites in the absence of legislation to prevent this.

15.14. The information available on the comparative effectiveness or toxicity of different alkyl nitrites is extremely limited. If an exemption was planned, there is uncertainty about which specific alkyl nitrites it would be appropriate to exempt. Most information on human use is available for amyl nitrite, which is licensed as a medicine in some countries (although not the UK), but the limited information obtained for this report indicates that this compound is infrequently found in products currently sold in the UK and it could take some time for sufficient supplies to become available should this be the only compound exempted. Isobutyl nitrite has been listed as a carcinogen but it is also quite possible that other alkyl nitrites have carcinogenic potential. The most common alkyl nitrite used in the UK at present is isopropyl nitrite, but this is also the compound most commonly reported to have been used by people with poppers-related maculopathy. This may simply reflect the current frequency of use of isopropyl nitrite, but the possibility that the risk of maculopathy is higher with this specific compound cannot be excluded. Reflecting this, the government of Australia recently placed isopropyl nitrite in a more restrictive schedule than some other alkyl nitrites including amyl, isopentyl, butyl and isobutyl nitrite. (Annex B)

15.15. In view of the incomplete information available on short- and long- term safety for individual alkyl nitrites, further research is needed, with the priority being those compounds most commonly sold.

15.16. The ACMD also considered the possibility of an exemption for specific sexual activities by listing in schedule 2 of the PSA. This, however, was considered inappropriate as it would exempt those using any uncontrolled psychoactive substance in that context.

Exempt from PSA with additional legislative actions

15.17. It is likely that if alkyl nitrites were exempted from the PSA, they would continue to be sold in containers marked ‘not for inhalation’ with inadequate information on safe use and an absence of quality control, as they were prior to 2016 and sometimes still are. It would be important for Government to consider what further legislation is needed to regulate the market and to give the responsibility for regulation to an appropriate government agency which would ensure that appropriate information and advice is provided to users and that use and harms in the UK are monitored. This would be consistent with the position for the other exemptions listed in Schedule 1 of the PSA, which all have their own policy areas, regulatory regimes and guidance.

15.18. An exemption by listing in Schedule 1 of the PSA would allow those under the age of 18 years to purchase alkyl nitrites, an age group that were unable to do this legally prior to the enactment of the PSA and repeal of the ISSA in 2016. This would enable increased access for younger people for their psychoactive effects and not just to reduce trauma associated with anal sex. The need for age-related legislation should therefore be considered to prevent purchase of alkyl nitrites by younger people for their psychoactive effects, for example via safety regulations linked to schedule 12 of the Consumer Protection Act. The Secretary of State has the powers to make such provision as (s)he considers appropriate to ensure that goods which “are unsafe, or would be unsafe in the hands of persons of a particular description”, are not made available to persons generally or, as the case may be, to persons of that description. This would be analogous to the Cigarette Lighter Refill (Safety) Regulations (1999) which made it illegal to supply any cigarette lighter refill canister containing butane or a substance with butane as a constituent part to any person under the age of eighteen years. It should be noted, however, that there was not a sustained reduction in deaths from volatile substance abuse in this age group after that legislation was enacted [Butland et al, 1999].

15.19. Currently, while purchase of alcohol, tobacco and butane by those younger than 18 years is illegal, the age of consent for sexual activity is lower at 16 years. Legislation to prevent purchase by those aged under 18 years would disadvantage younger MSM in particular and potentially make them reliant on older adults to obtain supplies, so an age limit of 16 years for legal purchase of alkyl nitrites is considered more appropriate.

16. Recommendations

The ACMD advises that the following recommendations be considered by the Government as a package of interventions. If recommendation 1 is accepted, the Council stresses the importance of recommendations 2-4 also being adopted.

Recommendation 1: Remove the risk of prosecution under the PSA of those importing, selling or supplying alkyl nitrites to those who wish to use them as an aid to atraumatic sexual intercourse.

The ACMD recommends that alkyl nitrites should be exempted from the PSA 2016 by addition to Schedule 1 of the Act.

The ACMD does not recommend that the exemption should be limited to specific alkyl nitrites as there is currently inadequate information about the efficacy and safety of individual products and such a limitation could also cause supply issues in the short to medium term.

The ACMD acknowledges that the exemption would also remove the risk of prosecution under the PSA for those importing, selling or supplying alkyl nitrites for their psychoactive effects.

This recommendation should not be seen as an endorsement of the use of alkyl nitrites for their psychoactive effects, or of their efficacy and safety when used to aid intercourse. Further recommendations are therefore also made with respect to other salient legislation, monitoring of unintended consequences (including health and social harms) and research.

Suggested text for the exemption, after the current paragraph 7 is shown below:

Alkyl nitrites ('poppers')

8. Alkyl nitrite compounds.
In this paragraph 'alkyl nitrite compound' means any product which
(a) Contains any alkyl nitrite compound
(b) does not contain any other psychoactive substance
(c) is not prohibited by other legislation

Note that (c) would prevent the exemption of isobutyl nitrite.

Leads: Home Office

Measure of outcome: The inclusion of appropriate text in Schedule 1 of the PSA 2016.

Recommendation 2: Ensuring appropriate regulation, safeguards and guidance.

If Government is minded to exempt alkyl nitrites from the Psychoactive Substances Act 2016, as with all existing exemptions under the Act, Government should ensure that:

a) appropriate safeguards are in place for use of alkyl nitrites,
b) appropriate regulation is in place to govern the quality of alkyl nitrites products sold (purity, dose, use of childproof containers etc),
c) appropriate regulation is in place to govern the import and sale of alkyl nitrites, including the amounts that can be sold. In particular, sales of alkyl nitrites to children and young people should not be permitted, focussing on those under the legal age of consent for sexual activity (16 years). The opinion of the ACMD

is that alkyl nitrites would be unsafe in the hands of children and young people under this age. Government should consider what alternative legislation to the PSA or MDA should be used to prevent widespread sales of alkyl nitrites to those over 16 years of age for their psychoactive effects.

d) appropriate guidance is in place for safe use by consumers (e.g. provision of appropriate information on methods and routes of use, interactions with medicines, potential adverse effects, risks of fire etc.

Leads: Home Office, Health and Safety Executive, Department for Business, Energy and Industrial Strategy, Office for Product Safety and Standards, Department for Business and Trade)

Measure of outcome: Cross-government review of current regulations, guidance and safeguards, updating these where necessary.

Recommendation 3: Monitoring and evaluation

The impact of legislative changes in the UK should be monitored to ensure that these do not result in unexpected increases in use for psychoactive effects or in other unintended adverse consequences, including health or social harms. Effects on use of other substances should also be monitored.

Use of alkyl nitrites should be included in the Crime Survey for England and Wales (CSEW). Health harms can be monitored by quantifying and publishing annual episodes of severe toxicity recorded by the National Poisons Information Service (NPIS) and registered deaths before and after legislative changes involving alkyl nitrites recorded by the Office for National Statistics (ONS), National Records of Scotland (NRS) and the Northern Ireland Statistics and Research Agency (NISRA). The Royal College of Ophthalmologists (RCO) should also be consulted on the feasibility of tracking episodes of poppers-related maculopathy.

Leads: CSEW, NPIS, ONS, NRS, NISRA, RCO

Measure of outcome: Annual reporting of data for 5 years before and after legislative changes

Recommendation 4: Further research

In the event of an exemption being enacted, research should be commissioned to better establish the safety of short and long-term exposure to specific individual alkyl nitrites, including carcinogenicity and effects on vision.

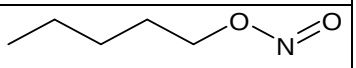
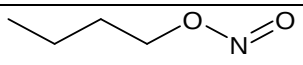
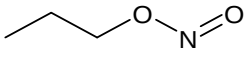
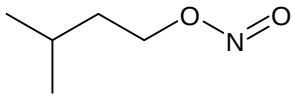
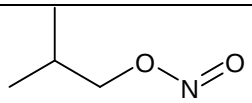
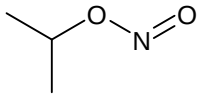
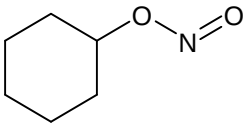
This should include systematic reviews of currently available evidence, with further primary research commissioned to address those evidence gaps identified.

Although unlikely to be identified as a research priority by funding bodies, it would be irresponsible for government not to ensure that the NIHR or other funding bodies commission appropriate research to ensure that legislative changes do not result in health harms that are currently unrecognised.

Leads: Department of Health and Social Care, National Institute for Health and Care Research

Measure of outcome: Published systematic review(s) within 3 years including recommendations for further primary research and a commitment to appropriate research funding.

Annex A: Alkyl nitrite chemistry

Nitrite stem	Synonyms	Formula	BP (ºC) [1]	Structure
Amyl-[2]	n-Pentyl-	$C_5H_{11}NO_2$	96-99	
Butyl-	n-Butyl-	$C_4H_9NO_2$	78	
Propyl-	n-propyl	$C_3H_7NO_2$	46-48	
Isopentyl-	Isoamyl- 3-methylbutyl-	$C_5H_{11}NO_2$	99	
Isobutyl-	2-methylpropyl-	$C_4H_9NO_2$	68	
Isopropyl-	propan-2-yl -	$C_3H_7NO_2$	40	
Cyclohexyl- -		$C_6H_{11}NO_2$	139	

[1]Boiling point at 760 mmHg atmospheric pressure

[2]The term ‘amyl nitrite’ may also be used colloquially to refer to isopentyl (isoamyl) nitrite or as a collective term for alkyl nitrites in general.

Annex B: International legislative control of alkyl nitrites

Legislative control of alkyl nitrites is often a ‘grey area’, with materials being sold under ambiguous product descriptions such as ‘room de-odouriser’ or ‘leather cleaner’ to avoid the implication of intent of use for human consumption. In some jurisdictions, amyl nitrite itself is classified as a medicinal product. Other alkyl nitrites are regarded as chemicals and sales are subject to consumer protection legislation. However, there are some examples of more specific controls on alkyl nitrites.

The following gives an overview of legislative approaches taken by selected countries.

European Union (EU)

Isobutyl nitrite was classified as a Carcinogen, Category 2 in January 2006 and member states were required to implement appropriate controls by August 2007 (European Union, 2006]. Individual EU countries have differing laws related to other alkyl nitrites, for example:

France: France has banned poppers on three occasions. In 1990 butyl and pentyl nitrites and their isomers were banned and in 2007 and 2011 aliphatic, cyclic and heterocyclic alkyl nitrites and their isomers were banned. However, on each occasion the ban was subsequently overturned by France’s Council of State following representations from suppliers and user groups so that, with the exception of the EU-banned isobutyl nitrite, alkyl nitrites continue to be available. The most recent Council of State decision, issued in 2013, stated that *“products containing alkyl nitrites have low toxicity at usual inhaled doses”* and that there was an absence of *“scientific study or investigation making it possible to establish that these substances present a risk of drug dependence or abuse”*

Germany: Possession and consumption of alkyl nitrites is not illegal, except for isobutyl nitrite.

Netherlands: Sales of alkyl nitrites are prohibited.

Non EU countries

Switzerland

Alkyl nitrites are subject to the complex Chemicals Act ChemG. Possession and consumption are not illegal, but sales are only permitted under specific conditions.

United States of America (USA)

Amyl nitrite is controlled as prescription drug in the USA [National Archives, 2023]. Other volatile alkyl nitrites are banned hazardous products under consumer product safety legislation if present in consumer products *"that may be used for inhaling or otherwise introducing volatile alkyl nitrites into the human body for euphoric or physical effects". [USC 1990].*

However, alkyl nitrite-containing products continue to be available, described as nail polish removers etc. In June 2021, the US Food and Drugs Administration (FDA) issued a warning to consumers advising them not to purchase or use alkyl nitrite "poppers" following an increase in reports of adverse effects and stating that the FDA will continue to monitor reports with a view to the possibility of taking *"appropriate actions to protect the public health"* [FDA, 2021].

Canada

In Canada, alkyl nitrite poppers have been classified as drugs within the definition of the federal Food and Drugs Act since 2013:

"[In] *Canada, products containing alkyl nitrites are considered drugs under the Food and Drugs Act and must be authorized by Health Canada to be legally sold. "* [Government of Canada 2017].

However, as no alkyl nitrite products have been approved by Health Canada, there are no materials which can be prescribed. Although action is taken against retailers selling unauthorised health products, products continue to be available via illicit on-line and in-person retail outlets and there are concerns about harmful formulations. Health Canada continue to issue warnings that unauthorised products, including alkyl nitrites, may pose serious health risks, including the following text:

"Poppers" is a slang term for products that contain alkyl nitrites. Despite being labelled for various uses such as leather cleaners, room odourizers or liquid incense, these products are inhaled or ingested by consumers for recreational purposes.

Alkyl nitrites, such as amyl nitrite, butyl nitrite and isobutyl nitrite are prescription drugs and should be used only under the supervision of a health care professional. Products containing alkyl nitrites may pose serious risks, including death, depending on the amount used, how frequently they are used and how long they are used for, as well as the person's health and the other medications they may be taking. Since it is difficult to control how much is inhaled, people can accidentally overdose. Swallowing these products can lead to serious medical complications and may be fatal. People with certain medical conditions (including recent head trauma, bleeding into the head, glaucoma, or heart disease) and those taking certain medications (particularly drugs used to treat erectile dysfunction, and other drugs such as high blood pressure medications,

certain migraine drugs, and high doses of aspirin) or illicit drugs are at particular risk [Government of Canada 2019].

Alkyl nitrites are currently only available through illicit online and person-to-person sales, but this has not led to a significant reduction in poppers use in Canada. Additionally, the products which are available are provided with reduced information on content and safe use [Schwarz et al 2022].

Australia

Alkyl nitrites have, since 2020, been treated as pharmaceuticals regulated by the Australian medical regulator, the Therapeutic Goods Administration, currently via the Therapeutic Goods (Poisons Standard) Instrument 2023 [Australian Government, 2023]. The rationale for this is described in detail elsewhere [Australian Government, 2019]. The Instrument divides controlled therapeutic materials into a series of 10 Schedules and alkyl nitrites appear in three of these:-

Schedule 3: Pharmacist only medicines

- Amyl nitrite, if for human therapeutic use and in child-resistant packaging.

Schedule 4: Prescription only medicines

- Alkyl nitrites not scheduled elsewhere
- Amyl nitrite (other than as specified in Schedule 3)
- Butyl nitrite
- Isopentyl nitrite
- Isobutyl nitrite
- Octyl nitrite

Schedule 10: Substances of such danger to health as to warrant prohibition of supply and use

- Isopropyl nitrite
- Propyl nitrite

Some alkyl nitrites are therefore theoretically available to the public, as long as acquisition is authorised by a medical professional, either via purchase from a pharmacist or by a prescription being issued. However, this requires that products either approved for medicinal use in Australia or approved elsewhere to be imported are available. In the absence of approved products, materials presented as room de-odourisers, etc continue to be available.

New Zealand

New Zealand has adopted the same approach as Australia, which is for alkyl nitrites to be available as medicinal products accessible via medical professionals.

Japan

In Japan, six alkyl nitrites (isobutyl nitrite, Isopropyl nitrite, Isopentyl nitrite, tertiary-butyl nitrite, cyclohexyl nitrite and butyl nitrite) were listed as ‘Designated Substances’ in 2007. This category of controlled materials was established as a mechanism to control New Psychoactive Substances, as an alternative to materials being listed in the ‘Narcotics’ category.

Designated substances are prohibited from manufacture, import, sale, display, possession or use, other than for scientific purposes. [MHLW Japan, 2023].

Annex C: Results of analysis of alkyl nitrite products in the UK

Collated results from stakeholders that reported at least one detection of an alkyl nitrite in a drug seizure or post mortem sample analysis (Eurofins, SOCOTEC, Scottish Police Authority, EU-MADNESS study and The National Programme on Substance Abuse Deaths). There were nil returns from NHS Grampian, DSTL/FEWS, the PHS Drugs Radar, the IONA study, the Scottish Prison Service and WEDINOS.

	2018	2019	2020	2021	2022	2023*	TOTAL
Amyl nitrite	0	0	0	0	1	0	**1**
Butyl nitrite	0	0	0	0	0	0	**0**
Propyl nitrite	0	0	0	0	0	0	**0**
Isopentyl nitrite	0	0	1	2	0	0	**3**
Isobutyl nitrite	2	2	5	0	2	0	**11**
Isopropyl nitrite	20	8	17	24	18	4	**91**
Cyclohexyl nitrite	0	0	0	0	0	0	**0**
Amyl nitrate	0	0	1	0	0	0	**1**
Unspecified alkyl nitrite	0	1	3	6	2	2	**14**
TOTAL	**22**	**11**	**27**	**32**	**23**	**6**	**121**

*Data to June 2023 (2023 data only available from 2 of the 4 stakeholders).

Annex D: Data from the National Poisons Information Service

The National Poisons Information Service (NPIS) is commissioned by the UK Health Security Agency to provide information and clinical advice to UK healthcare professionals (HCP) managing patients who may have been exposed to potentially toxic substances, including drugs of misuse. For most cases information is provided via an internet database called TOXBASE®, but a 24/7 telephone enquiry line is available with consultant support for more complex cases or when TOXBASE cannot be accessed. Number of accesses to TOXBASE® and NPIS telephone enquiries reflect (but do not measure directly) the frequency of contacts between health professionals and patients presenting following suspected exposures.

NPIS data for alkyl nitrites for the period 2018 to 2023 (June) is provided below.

NPIS Telephone Enquiries	**2018**	**2019**	**2020**	**2021**	**2022**	**2023[1]**	**TOTAL**
Amyl nitrite	7	9	11	3	6	2	38
Butyl nitrite	0	0	0	0	0	0	0
Propyl nitrite	0	0	0	0	0	0	0
Isopentyl nitrite	0	0	0	0	0	0	0
Isobutyl nitrite	0	1	0	0	0	0	1
Isopropyl nitrite	3	3	0	0	0	3	9
Cyclohexyl nitrite	0	0	0	0	0	0	0
Others (list below)							0
Unspecified alkyl nitrite[2]	15	17	31	12	16	19	110
Pentyl nitrate	0	1	0	0	0	0	1
TOTAL	25	31	42	15	22	24	159

TOXBASE online accesses	**2018**	**2019**	**2020**	**2021**	**2022**	**2023[1]**	**TOTAL**
Amyl nitrite	205	216	313	214	262	347	1557
Butyl nitrite	1	3	3	5	2	9	23
Isobutyl nitrite	19	10	16	34	17	20	116
Isopropyl nitrite	97	49	35	52	67	103	403
Unspecified alkyl nitrite[2]	761	827	1004	853	958	1008	5411
Isopentyl nitrite	3	4	5	4	5	0	21
Total	1086	1109	1376	1162	1311	1487	7531

[1]Part year to July

[2]Including ‘poppers’

Note: No TOXBASE access data is available for propyl, isopentyl or cyclohexyl nitrites as no TOXBASE pages are available for these substances.

Annex E: Summary of advantages and disadvantages of exempting alkyl nitrites from the PSA (2016)

	Advantages	**Disadvantages**
No exemption **(PSA applies)**	Consistent with situation for other **uncontrolled** psychoactive substances	Unlikely to reduce use as products can be procured from illicit sources. (Canadian data suggests legislation does not reduce access/use) Introduces harms related to an illicit and unregulated drug supply, including opportunity to sell users other harmful substances Places suppliers and importers at risk of prosecution/criminal record. Reduced access would disadvantage MSM populations (anal sex more physically difficult/damaging) and clubbing populations (criminal record damaging to educational and employment prospects) No legal alternative products/medicines available for use by MSM to reduce trauma associated with anal sex.

	Advantages	Disadvantages
Exemption **(PSA no longer applies).**	Allows access for MSM with fewer legal barriers Eliminates risk of prosecutions for supply or import via PSA Increases possibility of supply with appropriate quality control and information for users	Can't separate sales to facilitate MSM sex with those for psychoactive effects Inconsistent with policy on other drugs used for their psychoactive effects or in clubbing contexts May be seen to endorse safety of use of unregulated products for which limited safety information is available No/limited info on • which chemicals to exempt • Optimum doses and methods of use • Risks of adverse consequences, drug interactions etc. Sets precedent for other psychoactive drugs and minority groups Supply may still contravene medicines or consumer protection legislation Legalises sales to children in the absence of further legislation to prevent this

Annex F: List of abbreviations used in this report

ACMD	Advisory Council on the Misuse of Drugs
ASTRA study	Antiretrovirals, Sexual Transmission Risk and Attitudes study
AURAH study	Attitudes to, and Understanding of, Risk of Acquisition of HIV study
CLP	Classification, labelling and packaging
CSEW	Crime Survey for England and Wales
DSTL	Defence Science and Technology Laboratrory
EDM	Electronic dance music
EFS	English Festival Survey
EMIS	European Men-Who-Have-Sex-With-Men Internet Survey
EWCA Crim	England and Wales Court of Appeal (Criminal Division)
EU	European Union
EU-MADNESS study	EUropean-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging pSychoactiveS study
FDA	Food and Drugs Administration (USA)
FEWS	Forensic Early Warning System
FTIR	Fourier transform infrared spectroscopy
GDS	Global Drug Survey
G6PD	Glucose-6-phosphate dehydrogenase
GTN	Glyceryl trinitrate
HSE	Health and Safety Executive
HSENI	Health and Safety Executive Northern Ireland
HIV	Human immunodeficiency virus
IONA study	Identification Of Novel psychoActive substances study
IS(S)A 1985	The Intoxicating Substances (Supply) Act 1985
LD50	Lethal dose for 50% exposed animals
LGBTQ+	Lesbian, gay, bisexual, transgender, queer, and/or questioning (the + sign recognises other sexual orientations and gender identities)
MDMA	Methylenedioxymethamphetamine

MHRA	Medicines and Healthcare products Regulatory Agency
MOJ	Ministry of Justice
MSM	Men who have sex with men
NICE	National Institute for Health and Care Excellence
NISRA	Northern Ireland Statistics and Research Agency
NO	Nitric oxide
NPSAD	National Programme on Substance Abuse Deaths
NPIS	National Poisons Information Service
NRS	National Records of Scotland
ONS	Office for National Statistics
OPSS	Office for Product Safety and Standards
PDE5	phosphodiesterase 5 enzyme
PHS	Public Health Scotland
PrEP	Pre-exposure prophylaxis
REACH	Registration, evaluation, authorisation and restriction of chemicals
PSA	Psychoactive Substances Act (2016)
RCO	Royal College of Ophthalmologists
SD-OCT	Spectral domain optical coherence tomography
TGA	Therapeutic Goods Administration
UK	United Kingdom
USA	United States of America
USC	United States Code
WEDINOS	Welsh Emerging Drug & Identification of Novel Substances

Annex G: ACMD membership, at time of publication

Dr Kostas Agath	Consultant psychiatrist (addictions), Change Grow Live Southwark
Professor Judith Aldridge	Professor of criminology at the University of Manchester
Professor Owen Bowden-Jones	Chair of Advisory Council on the Misuse of Drugs, Consultant psychiatrist, Central North-West London NHS Foundation Trust
Dr Anne Campbell	Reader in substance use and mental health and co-director of the Drug and Alcohol Research Network at Queens University Belfast
Dr Emily Finch	Clinical director of the Addictions Clinical Academic Group and a consultant psychiatrist for South London and Maudsley NHS Trust
Mr Mohammed Fessal	Chief pharmacist, Change Grow Live
Mr Lawrence Gibbons	Head of drug threat – National Crime Agency Intelligence Directorate – Commodities
Dr Carole Hunter	Lead pharmacist at the alcohol and drug recovery services at NHS Greater Glasgow and Clyde
Dr Hilary Hamnett	Associate Professor in forensic science, University of Lincoln
Professor Graeme Henderson	Professor of pharmacology at the University of Bristol

Professor Roger Knaggs	Associate professor in clinical pharmacy practice at the University of Nottingham
Dr Ann Sullivan	Consultant physician in HIV and sexual health
Mr Harry Shapiro	Director – DrugWise
Dr Paul Stokes	Senior clinical lecturer in mood disorders, King's College, London
Dr Richard Stevenson	Emergency medicine consultant, Glasgow Royal Infirmary
Professor David Taylor	Professor of psychopharmacology, King's College, London
Professor Simon Thomas	Emeritus professor of clinical pharmacology and therapeutics, Newcastle University
Dr Derek Tracy	Medical director of West London NHS Trust
Dr David Wood	Consultant Physician and Clinical Toxicologist, Guy's and St Thomas' NHS Foundation Trust and Honorary Reader in Clinical Toxicology, King's College London
Ms Rosalie Weetman	Public health lead (alcohol, drugs and tobacco), Derbyshire County Council - (currently on secondment to Office for Health Improvement and Disparities, as programme manager, Drug and Alcohol Improvement Support Team)

Annex H: ACMD NPS Committee membership, at time of publication

Dr Kostas Agath	**Consultant psychiatrist (addictions), Change Grow Live, Southwark**
Mr Paul Bunt	Director of Casterton Event Solutions Ltd, Former Drug Strategy Manager for Avon and Somerset Constabulary
Mr Peter Cain*	Drugs Scientific Advisor, Eurofins Forensic Services
Dr Caroline Copeland	Lecturer in Pharmaceutical Medicine at King's College London, and the Director of the National Programme on Substance Abuse Deaths
Mr John Corkery*	Senior Lecturer in Pharmacy Practice at University of Hertfordshire; mortality and epidemiological lead for EU-MADNESS project
Mr Lawrence Gibbons	Head of drug threat – National Crime Agency Intelligence Directorate – Commodities
Dr Hilary Hamnett	Associate Professor in Forensic Science, University of Lincoln
Professor Graeme Henderson*	Professor of Pharmacology at the University of Bristol
Professor Stephen Husbands	Professor of Medicinal Chemistry, University of Bath
Professor Roger Knaggs	Associate Professor in clinical pharmacy practice at the University of Nottingham
Professor Fiona Measham*	Professor and chair in criminology, University of Liverpool; co-founder and co-director, the Loop

Mr Harry Shapiro	Director – DrugWise
Dr Richard Stevenson*	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Ann Sullivan*	Consultant physician in HIV and sexual health
Professor Simon Thomas*	NPS Committee Chair, Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Mr Ric Treble*	Retired Laboratory of the Government Chemist (LGC) expert
Dr Derek Tracy	Medical director of West London NHS Trust
Dr David Wood*	Consultant physician and clinical toxicologist at Guy's and St Thomas' and reader in clinical toxicology at King's College London

In addition to members of the NPS committee listed, significant contributions were made by co-opted members of the alkyl nitrites Working Group:

Carl Fletcher*	Dstl Porton Down
Stephen Ream*	Director, Re-Solv
Mark Lay*	NPCC National Drugs Co-ordinator Lead
Mark McCormack*	Professor, College of Business and Social Sciences, Aston University
John Simmons*	Barrister, The 36 Group, 4 Field Court, Greys Inn, London

*Alkyl nitrites working group members

Annex I: Quality of evidence

Range of Evidence

Evidence gathered was considered in line the ACMD's standard operating procedure (SOP) for quality of evidence [ACMD, 2020].

To evidence the identification and prevalence of alkyl nitrites in the UK, the ACMD's NPS Committee wrote to stakeholders requesting available data on the substances listed in Annex A in June 2023. Responses were received from the following (which include submissions of 'no data held' and anecdotal evidence:

External agencies:

- Eurofins
- EU-MADNESS
- FSNI
- IONA
- Leverhulme Research Centre for Forensic Science, University of Dundee
- NISRA
- National Programme on Substance Use Mortality (NPSUM, formerly known as NPSAD)
- NPIS
- NHS Grampian and Crown Office and Procurator Fiscal Service
- Scottish Police Authority
- SOCOTEC UK
- TICTAC
- WEDINOS

Government Departments:

- DSTL FEWS Project
- MHRA

- OHID
- ONS
- Public Health Scotland Rapid Action Drug Alerts and Response (RADAR)

This report also draws on evidence from peer-reviewed literature (UK and international publications) and government reports. The ACMD also considered international approaches when drafting its recommendations.

Quality of evidence (design, limitations, bias)

Many agencies and departments may return ‘no data held’ for the substances considered in this report. It is important to note that due to difficulties detecting alkyl nitrites and their metabolites in biological samples due to rapid metabolism, the value of forensic testing is limited and as a result often not done. As a result the role of alkyl nitrites in episodes of toxicity may not be recognised.

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