

Sector Summary Report:

Poppers

This sector summary report looks at the recreational drug poppers (nitrite-based inhalants), a substance with a long and contested history of links with HIV infection, immune suppression and AIDS. This report presents an overview of the evidence for links between HIV and poppers use. It also considers issues health promoters may encounter when addressing this with gay men.

What are poppers?

Poppers is the name for a range of chemical compounds belonging to the alkyl nitrite family. Available as a (flammable) clear or yellow liquid in small bottles, poppers (also known as 'aromas' or 'liquid incense') are inhalant drugs breathed in through the mouth (from a poppers-soaked cloth) or, more commonly, directly through the nose. They can be fatal if swallowed or injected. Poppers have a sickly sweet odour, described by some as resembling stale socks. They are sold under a variety of sexualised brand names.¹

Originally poppers contained amyl nitrite (in Australia they are still referred to as 'amyl'), a drug once used to relieve symptoms of angina pectoris by increasing blood supply to the heart and chest. The drug came in glass ampoules wrapped in gauze mesh which made a popping sound when crushed between the fingers prior to use, hence the name 'poppers'.

In the USA in the late 1960s *amyl nitrite* became a prescription only medicine available only from licensed retailers such as chemists. As a result poppers manufacturers replaced amyl nitrite with other formulations. Until recently most contained *butyl nitrite* and/or, more commonly, *isobutyl nitrite*. In the UK laws around the sale of these compounds have recently been tightened, and manufacturers have switched to *isopropyl nitrite*.

Nitrite or nitrate?

There is widespread confusion around the naming of the compounds found in poppers, frequently and incorrectly being referred to as 'nitrates', even by manufacturers. The correct term is nitrite. *Nitrates* are a related compound used in prescription medicines (usually in tablet form) to treat heart conditions.

It is thought that using poppers after taking erection drugs such as Viagra can cause a fatal drop in blood pressure, and their use together is contraindicated by the regulatory authority. But this may be based on the misunderstanding between nitrites and nitrates. There appear to have been no documented deaths as a result of use of Viagra and poppers together. However, there have been fatalities linked to Viagra use by men taking *nitrates* but it is not clear if this refers solely to nitrate-based medication for heart conditions. Warnings about poppers and Viagra stem from nitrates being confused with nitrites, or from believing that, as the two compounds are similar and both lower blood pressure, the same potentially deadly interaction is possible when either are used with erection drugs.

What do poppers do?

Poppers act as a vasodilator – they dilate (ie, open) blood vessels, increasing blood flow. They do this by relaxing the smooth muscle that the walls of blood vessels are made of. Smooth muscle is also found in other parts of the body that need to have an elastic quality, such as the bladder, digestive tract, vagina and anal sphincter.

As poppers cause blood vessels to relax and expand, this creates an inflow of extra blood, blood pressure drops and the heart must beat faster to maintain circulation.

Side effects of this drop in blood pressure last a few minutes and include:

- increased heart beat
- flushing of the face and chest
- very occasionally dizziness or fainting
- sense of (sexual) excitement, detachment and disinhibition
- headache some time after use (the after effect of expansion of blood vessels within the skull).

Despite being used as a sexual aid many men find poppers interfere with erections. A degree of tolerance builds to the drug but sensitivity returns after a few days of not using them. Poppers have no effect on pain receptors, but because of the drug's effect on relaxing the anal sphincter, are used to ease discomfort during sexual penetration, in particular anal intercourse and fisting.

Who uses poppers?

Widespread use of poppers among heterosexuals and especially gay men dates back to the 1970s. They are used as either an adjunct to sex or for use on the dance floor to boost the effects of music, lights or other recreational drugs.

Surveys show around 40% of gay men in the UK use poppers at least once a year, making it the most widely used drug after alcohol and on a par with tobacco.² In the 1990s poppers became popular on the heterosexual clubbing scene. Nearly 3 million Britons are estimated to have ever used poppers, 440,000 in the last year. This makes them the third most popular drug after cannabis, cocaine and ecstasy (excluding alcohol and tobacco).³

Legal status

The legal status of poppers is not clear cut.

In the USA in the 1980s, in the wake of concerns about links to AIDS, the use of poppers in public places such as bathhouses was banned in cities like San Francisco. Retailers were obliged to display health warnings at the point of sale (this practice had disappeared by the end of that decade).

In 1990 poppers were banned in the US as a hazardous product and it became technically illegal to manufacture, import, distribute or sell any alkyl nitrite-based products for inhaling or otherwise introduced into the body for euphoric or physical effects (use and possession were not made illegal). Manufacturers consequently marketed their poppers as products not intended for human consumption such as 'leather cleaners', 'room odourisers' or 'tape head cleaners'. The ban is not widely enforced and poppers are advertised in the American gay press and are available by mail order, over the internet or in some venues.

In the UK in 1984, 1987 and 1991, enquiries into poppers by the Advisory Council on the Misuse of Drugs found insufficient evidence of harm to the individual or society to warrant including poppers in the Misuse of Drugs Act. Instead, when poppers have been the focus of legal proceedings it has been in connection with the 1968 Medicines Act.

In 1994 the Royal Pharmaceutical Society (RPS) began investigating poppers, under pressure from Positively Healthy, a gay health rights group concerned about a link between poppers and Kaposi's sarcoma.⁴ In 1996 the RPS took a case under the Medicines Act against a North London shopkeeper for selling poppers. It is likely that most of the poppers in this case were butyl or isobutyl nitrite and not technically subject to the Medicines Act, which only covered amyl nitrite. The RPS argued that all poppers should be treated in law as if they were amyl nitrite. The case was not contested and the retailer was fined £100. A further prosecution in 2001 involving butyl and isobutyl nitrite failed.

The Medicines and Healthcare Products Regulatory Agency (which administers the Medicines Act) has stated that it regards all poppers as a medicine and a substance covered by the Act, which means only licensed outlets such as chemists should be able to sell them. By 1997 the Medicines Act had been amended to make amyl nitrite a prescription only drug. Possession of amyl nitrite without a prescription remained legal but supply became an offence. This was largely irrelevant as amyl nitrite had long been replaced by butyl nitrite and isobutyl nitrite as the main ingredients of poppers. As neither of these have any medical use it was thought they did not come under the control of the Medicines Act.

As in the USA, poppers have often been sold in the UK as a 'room deodoriser', 'video tape head cleaner' or 'leather cleaner' to get around restrictions against their sale for human inhalation. Indeed, some poppers' labelling carries warnings stating they are harmful if inhaled. Until August 2007 isobutyl nitrite, traditionally the most common chemical compound used in poppers, was freely on sale.

August 2007 saw isobutyl nitrite come under tighter control as a result of two developments. A 2006 European Union directive classed it as a Class 2 carcinogen (a cancer-causing substance),⁵ making its sale prohibited. In addition, the UK Medicines & Healthcare Products Regulatory Agency decreed that all psychoactive or mind altering substances, including poppers, were now covered by the Medicines Act.

Within a few weeks poppers made of *isopropyl nitrite* appeared on the shelves. Advertisements appeared in the gay press drawing attention to the change in law regarding isobutyl nitrite and the introduction of isopropyl nitrite. The new formulation is being marketed as stronger (anecdotal reports claim its effects are weaker). Some manufacturers are even promoting isopropyl nitrite poppers as 'safer'.⁶ Poppers remain freely available in the UK from sex shops, bars, nightclubs and over the internet.

Impact on health

Because of their impact on blood pressure and heart rate, poppers use is advised against for people with glaucoma (high blood pressure in the eye) or breathing, heart and blood pressure irregularities. Excessively high doses can cause the potentially fatal methaemoglobinaemia (excess of the protein methaemoglobin in the blood).⁷

Poppers can burn the skin if not washed off immediately, although a 'poppers burn' (usually seen around the nostril) lasts only a few days and leaves no scar. If swallowed poppers can kill as they interfere with heart function. Long term cancer-causing effect in humans remains to be established, although a recent EU directive classes isobutyl nitrite as a potential carcinogen.

Although users cannot become physically addicted, they may become psychologically dependent.

Poppers and AIDS

In the early 1980s, before HIV was identified as the infectious agent responsible for AIDS, poppers were suspected as causing the syndrome. This was based on widely reported use of poppers in the gay men who made up the bulk of early AIDS cases. After the identification of HIV, credible opinion dismissed poppers as the cause of AIDS. Some who deny HIV causes AIDS continue to present poppers as a cause or co-factor in immune system damage.

In the mid 1980s poppers were also linked to the AIDS-related skin cancer Kaposi's sarcoma (KS), again because a large proportion of those developing KS used poppers. However, in 1994 infection with a previously unknown herpes virus (HHV-8) was identified as the cause of KS in people with weakened immune systems. The false link between poppers use and KS is a good example of concluding a causal link between one thing and another when there was in fact none.

Although poppers use in itself was not shown to cause KS, doubts remain over whether the drug plays a role as a co-factor in acquiring HHV-8 and/or developing KS in the immune-suppressed. Studies are inconclusive. It may be that poppers use acts as a marker for other factors linked to the development of KS. However, it may be possible that among people already infected with HIV and HHV-8, poppers use may increase the likelihood of developing KS.

Poppers and immune suppression

There is an absence of robust evidence for poppers weakening the immune system. The great majority of studies involve animal, not human subjects, and much of this research is open to criticism for poor methodology. In studies suggesting a negative impact on immunity, there appears to be a modest suppression of CD4 cells (in mice) or natural killer cells (in humans) for 4-7 days following poppers use.^{8,9} However, many factors affect immune function or CD4 count, including diet, exercise, smoking and time of day.

Many of the research studies investigating the impact of poppers on immunity come with caveats or methodological flaws such as:¹⁰

- studies may be conducted on blood cell cultures in the test tube, not in live subjects
- studies frequently involve rodents (some genetically altered to have no immune defences), not humans
- adjustments are often not made for the difference in body mass between rodents and humans
- quantity and duration of exposure to poppers can be much greater than typical in recreational use¹¹
- poppers may be injected into the bloodstream, not inhaled
- study samples are usually small
- study results may include preliminary, unconfirmed data or findings not obtained in repeated trials
- data is not published in respected peer-reviewed medical journals.

There is research suggesting poppers have no lasting significant effect on the human immune system,¹² and certainly no conclusive research shows any significant impact on human immunity. In fact, inhaled nitrites break down easily and quickly leave the body.

Poppers and acquiring HIV

Simply because two behaviours occur together (eg, using poppers and becoming HIV positive) does not mean one causes the other. Poppers use may just be a marker of another behaviour or factor that is more relevant to the infection such as (unprotected) anal sex, rough sex, use of other drugs, STI acquisition or a generally less healthy lifestyle.

However, a link between using poppers and acquiring HIV has been suggested by numerous studies over the last two decades,^{13 14} including those that have looked directly at poppers use during the act of unprotected anal sex. Increasingly studies have attempted to take into account other factors that might also play a role in acquiring HIV. By controlling for these confounding factors using multivariate analysis (looking at several statistical variables at a time) the role played by poppers in acquiring HIV has become clearer.

The disinhibiting effect of poppers is unlikely to be the explanation for greater HIV transmission seen in poppers users in these studies. Many other drugs with similar or stronger disinhibiting effects often do not emerge as significant risk factors in these studies. Several studies have found no association between poppers use and non-condom use.^{15 16}

It is believed that the physiological effect of nitrite inhalants on the blood vessels of the rectum accounts for the observed increase in HIV transmission. As a vasodilator, nitrite inhalants increase blood flow to the rectum and engorge blood vessels. As the walls of these expand this may provide a greater and thinner surface area through which HIV might pass. This may also result in a higher likelihood of blood vessels breaking, leading to anal bleeding and an easier way for HIV to enter the bloodstream. In addition, although poppers do not have an effect on pain receptors, they may also facilitate easier anal penetration and possibly increase friction and trauma.

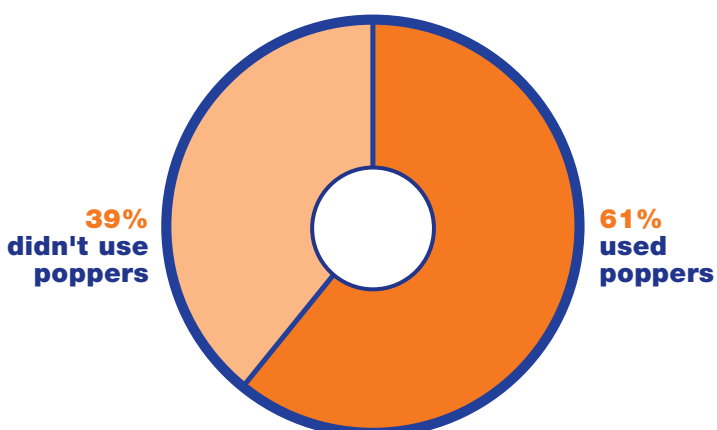
Poppers a major risk factor in INSIGHT study

INSIGHT was a three year research project funded by the Medical Research Council and the first England-wide multidisciplinary study to investigate new seroconversions among gay men.¹⁷ A major finding was that poppers use during receptive unprotected anal intercourse appeared to be a key risk factor in acquiring HIV. After multivariate analysis had taken into account such factors as men's sexual behaviour (eg, unprotected anal intercourse), poppers were the only drug men took that was associated with an additional risk of seroconversion.¹⁸

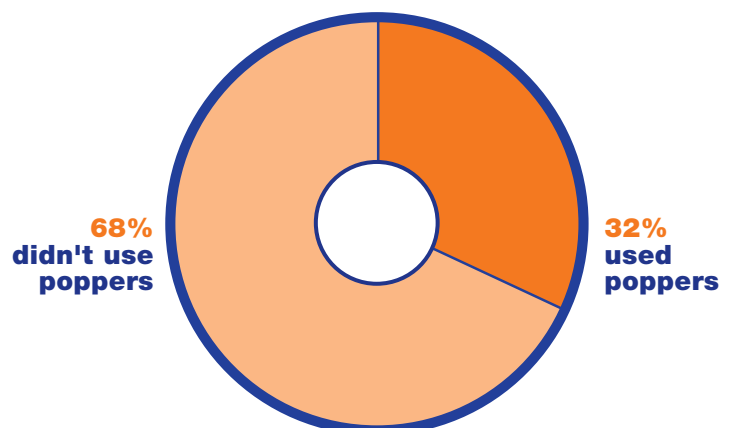
80% of men who tested HIV positive used poppers compared to 58% who remained HIV negative. Of men who had been fucked without a condom by someone they didn't know was HIV negative, 61% of men who tested positive had sniffed poppers during sex, compared to 32% of those who had stayed HIV negative.

The study's authors speculated that, in addition to how poppers affect blood circulation inside the rectum, the additional risk may be also partly the result of poppers facilitating anal trauma through more forceful anal sex, or that men attracted to such sex might be more likely to be poppers users.

Men who got HIV



Men who didn't get HIV



Issues for health promoters

Poppers as a potential co-factor in HIV transmission was widely recognised in the UK HIV health promotion field by the CHAPS partnership 19 in the 1998 and 2000 editions of its strategy document *Making it count*.²⁰ In CHAPS materials dating from 2003 poppers were acknowledged as making infection more likely during exposure to HIV.²¹

In December 2007 the CHAPS partnership launched a mass media campaign educating gay men about the role played by poppers in HIV transmission (as part of its ongoing programme of work on the biology of HIV transmission).²² Focus group pre-testing during the development of this campaign highlighted issues that might face health promoters wishing to engage gay men around nitrite inhalants. Findings from the focus groups²³ include:

Confusion

- Many men hold inaccurate beliefs about poppers (eg, 'they are illegal', 'raise blood pressure', 'kill brain cells', 'damage the liver', 'have a big risk of heart attack', etc). It cannot be assumed that all men understand in enough detail the biology of HIV transmission to accurately interpret messages about poppers.
- There is confusion over the role played by nitrites in HIV transmission stemming from the 1980s theory that poppers caused AIDS and Kaposi's sarcoma.
- Men are not clear how the HIV status of either partner and modality of intercourse (insertive or receptive) impact on the poppers-related risk of HIV infection during unprotected anal sex.
- Further confusion is generated by the lack of certainty about whether poppers affect immune function.
- Many men believe that the disinhibiting effect of poppers is a likely cause of increased HIV transmission, despite the lack of evidence for this.

Resistance and concern

- Gay men, especially poppers users, do not see nitrite inhalants as 'drugs'. Many are resistant to messages about poppers being harmful to health and are suspicious about the source and reliability of such messages. This is coupled with a general cynicism about health warnings.
- There is a concern that health interventions about poppers would 'demonise' both their use and individuals who use them (or increase stigma against gay men if heterosexuals see the interventions).
- Nitrite users had concerns that increased awareness of the link between poppers and HIV could lead to tighter restrictions on the availability of the drug.
- Some suspected health promoters are using 'scare stories' about poppers to further an agenda of achieving sexual behaviour change.
- Some men believe the authorities and 'Establishment' bodies wish to regulate or discourage any psychoactive or mood altering substance, even in the absence of evidence of significant harm.
- To some men a potential result of raised awareness of the poppers/HIV link was increased HIV transmissions. Men might give up poppers believing this would make unprotected sex of negligible risk, or health promoters might shift the focus from unprotected sex itself to poppers use.
- Men recognise the conflict between the health of gay men and the promotion of poppers by gay venues and the gay press.

Messaging

- In focus groups few gay men recalled previously encountering messages about nitrites inhalants and HIV.
- There were questions over how these new, potentially disquieting and relatively complex messages can be effectively communicated, particularly in gay scene settings. This was seen as especially difficult given the lack of consensus about the biological mechanisms involved and their precise impact on HIV transmission.
- Men wanted certainty or precision, often where this is difficult or impossible, eg, around the scale of increase in risk or how much and for how long poppers might cause immune suppression. Men are suspicious of uncertainty couched in terms of 'might' or 'could', and felt if health promoters do not know or are dealing in a theory they should stick to concrete facts and/or clearly state they are not sure (although some men say that allows them to disregard the message).
- It was felt to be important that messages clearly state that the negative health impact relates to poppers use during sex, not as a club drug.
- Men approved of messages couched in terms of multiplied risk, ie, to clearly state that sex without condoms is a risk but that the same sex on poppers is even more risky.
- Some poppers users want, in line with other drug education, a recognition of the positive effects of using the drug and not an 'anti-poppers' approach.
- There was a belief that, for good or bad, interventions about poppers and HIV act as direct or indirect condom reinforcement messages.

Notes

1 Brand names include Rush, Bolt, Ram, Thrust, Stag, Stud, Rock Hard and Locker Room.

2 Hickson F, Weatherburn P, Reid D, et al. *Consuming Passions: findings from the United Kingdom's Gay Men's sex Survey 2005*. London: Sigma Research; 2007. Available from www.sigmaresearch.org.uk Around 40% had used poppers at least once in the previous year – the same proportion reported smoking. About 1 in 10 used poppers once a week or more.

3 In the UK an estimated 2.9 million people, or 9.1 per cent, aged between 16 and 59 had ever used poppers. This included 766,000 young people, 103,000 of whom said that they had inhaled the drug in the past month. Overall 1.4% (4.3% of 16–24 year olds) had used poppers in the last year. Poppers use had remained stable over the previous decade. *British Crime Survey 2006–7*. London: Home Office; 2007.

4 www.posh-uk.org.uk/gmh/poppers.html

5 Group 2 carcinogens are substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of long-term animal studies or other relevant information.

6 One manufacturer's press advert attempted to put a positive spin on the law change: "New range of safer aromas," and "Get the new 'August 2007 compliant' (sic) room aromas...made from the new isopropyl Nitrate (sic) and classified in accordance with EEC (sic) directive:- 677548EEC." Aromasxpress advert, *Boyz*. London; 29 Nov 2007.

7 Nitrites enter red blood cells causing a chemical change in haemoglobin (the substance that takes oxygen around the body) with the result that the body becomes starved of oxygen with risk of death.

8 CD4 cells are the white blood (lymphocyte) cells that HIV attacks, also referred to as 'T-4' or 'helper T-cells'. Natural killer cells are another type of lymphocyte important in killing infected cells.

9 Dax E, et al. *Effects of nitrites on the immune system of humans. Health hazards of nitrite inhalants: NIDA Research Monograph 83*. 1988 Mar; 83: 75–80. PMID: 2902516

10 A critical overview of many of these studies was conducted by Lisa Ringold at www.virusmythpoppersmyth.org/hank_wilson_references

11 In some studies on mice the dose used was close to a lethal one

12 In a cohort of 715 Canadian gay men followed for over eight years CD4 counts remained stable in HIV negative men despite high levels of poppers use. Schechter MT, Craib K, Gelmon K et al. HIV-1 and the aetiology of AIDS. *Lancet* 1993; vol. 341, no. 8846, pp 658–659

13 Drumright L, Patterson T, Strathdee S, et al. Club drugs as casual risk factors for HIV acquisition among men who have sex with men: a review. *Substance Use & Misuse*, Volume 41, Numbers 10–12, 12/2006, pp.1551–1601. This review of 74 articles published between 1980 and 2005 found most evidence for methamphetamine and poppers as risk factors for HIV.

14 Buchbinder SP, Vittinghoff E, Heagerty PJ, et al. Sexual risk, nitrite inhalant use and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *Journal of Acquired Immune Deficiency Syndrome*. 2005 May 1;39(1):82–9. A cohort of 3257 men between 1995 and 1997 found poppers use a key independent risk factor for seroconversion.

15 Lampinen T, Mattheis K, Chan K et al. Nitrite inhalant use among gay and bisexual men in Vancouver during a period of increasing HIV incidence. *BMC Public Health*. 2007 Mar 15; 7:35

16 Plankey M, Ostrow D, Stall R, et al. The relationship between methamphetamine and poppers use and risk of HIV seroconversion in the Multicenter AIDS Cohort Study. *Journal of Acquired Immune Deficiency Syndrome*. 2007; 45(1):85–92. Study found stopping poppers use did not lead to increased condom use.

17 75 men were interviewed after recently testing positive for HIV as were 157 who had recently tested HIV negative. All 232 men had tested HIV negative in the previous two years. Neil Macdonald, Gillian Elam, Ford Hickson, et al. Factors associated with HIV seroconversion in gay men in England at the start of the 21st century. *Sexually Transmitted Infections*. Published online Nov 2007. Available from: <http://sti.bmj.com/cgi/content/abstract/sti.2007.027946v1>

18 Among other substances covered in INSIGHT were alcohol, LSD, ecstasy, crystal meth and cocaine.

19 CHAPS (Community HIV and AIDS Prevention partnership brings together community-based organisations, co-ordinated by Terrence Higgins Trust, to deliver HIV prevention and sexual health initiatives to gay and bisexual men in England and Wales.

20 Poppers as a facilitator of transmission were not included in the third and most recent edition of *Making it count* (2003). Poppers use as a population level target was not adopted due to insufficient evidence to convince the strategy development group (correspondence with Ford Hickson, November 2007).

21 *The Bottom Line* booklet on anal health, poppers section. CHAPS/Terrence Higgins Trust 2003, expanded and updated in 2006.

22 The campaign can be viewed at www.chapsonline.org.uk/biology

23 Pre-test data from CHAPS mass media campaign on poppers. Pat Branigan. *Formative Evaluation Report*. Cambridge: Cambridge Health Evaluation Consultancy; 2007.

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