Nitrite Inhalants: History, Epidemiology, and Possible Links to AIDS

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Nitrite inhalants have been commonly abused substances in the United States. Nitrite inhalants and AIDS was a popular topic in the early 1980s, when the cause of AIDS was not known. With the discovery of HIV, concern about nitrite use in the USA waned. However, nitrite inhalant use is associated with behavioral relapse and HIV transmission among gay men, with decreased lymphocyte counts and natural killer cell activity in a few laboratory studies, and it remains a candidate cofactor in the pathogenesis of AIDS-related Kaposi's sarcoma. Discouraging nitrite use continues to be a worthwhile public health goal. *Key words:* AIDS, HIV infection, immunosuppression, Kaposi's sarcoma, nitrite inhalants, sexual behavior. *Environ Health Perspect* 102:858–861 (1994)

Nitrite inhalants are commonly abused substances in the United States, primarily by homosexual men and others who use nitrites to facilitate sexual intercourse and/or produce euphoria (*1–4*). Scientific interest in nitrites increased in the 1980s due to their possible links to AIDS (*5–11*). In this paper we review the history, applications, and prevalence of use of nitrite inhalants. We present the hypotheses linking their use to AIDS. We provide suggestions to physicians, community leaders, policymakers, and researchers on what they can do to limit the use of nitrites.

History and Clinical Uses

The alkyl nitrites (e.g., amyl, butyl, isopropyl) are colorless or yellow liquids at room temperature and are highly volatile. They are esters of nitrous acid that have a fruity odor (often described as unpleasant) and have been nicknamed "poppers" because of the sound made when glass capsules containing amyl nitrite are crushed (*12*).

The vasodilatory effect following inhalation of amyl nitrite vapor was described in 1859 and led to the first report of its clinical application to provide relief for angina pectoris in 1867 (*13,14*). In the 1880s, butyl nitrites were found to have similar vasodilatory qualities, but these compounds were never developed for clinical use (*12*).

Amyl nitrite was initially marketed as a prescription drug in the United States in 1937 and remained a prescription drug until September 1960, when the Food and Drug Administration (FDA) eliminated the prescription requirement. In the 1960s, nitroglycerin sublingual tablets, dermally applied ointments, and, later, transdermal patches began to replace amyl nitrite as the preferred treatment for angina pectoris. In the late 1960s, pharmacists and drug manufacturers noticed widespread purchases of amyl nitrite by apparently healthy young men. These over-the-counter purchases became the impetus for the FDA to reinstate the prescription requirement in 1968. Since then an underground market for amyl nitrite has emerged (*15*). For the last few years, there has been no medical advertising for pharmaceutical-grade amyl nitrite, and it is no longer listed in the *Physician's Desk Reference* (*16*).

Amyl nitrite remains available by prescription. The clinical indication listed in the package insert is angina pectoris (*17*). Amyl nitrite is used experimentally to treat cyanide poisoning. The drug produces methemoglobin, which has a high affinity for cyanide, and leads to the production of cyanomethemoglobin, releasing cyanide from cell mitochondrial cytochrome oxidase sites, where it is otherwise destructive (*18*).

When amyl nitrite became difficult to procure for nonmedical or recreational purposes during the 1970s, there was a proliferation of butyl nitrite products by nonpharmaceutical manufacturers (*15*). Butyl nitrites were marketed as "liquid incense" or "room odorizers." Because the labels on bottles containing butyl nitrites stated that they were not to be inhaled and no health claim was made, the FDA never had jurisdiction over this product as it does medicine and many foods.

The legal status of some key nitrite preparations has changed in the past few years. One development prompting this change has been the description of several acute and chronic adverse effects attributed to the abuse of nitrite inhalants (*15*). In response to those reports, the U.S. Congress enacted a ban on the manufacture and retail sale of butyl nitrites (except when used in specified chemical commercial processes) in the Anti-Drug Abuse Act of 1988 (Public Law 100-690, Section 2404). The law specified that the Consumer Product Safety Commission (not the FDA) would enforce the ban. However, to circumvent the clear intent of the law, nitrite manufacturers began to sell other nitrite alkyl congeners, such as isopropyl nitrite, as "new and improved" room odorizers. In 1990, Congress outlawed manufacture and sale of alkyl nitrites in the Omnibus Crime Bill (Public Law 101-647, Section 3202). Since then, at least one manufacturer has developed a cyclohexyl nitrite inhalant and marketed it diversely. According to chemical nomenclature, cyclohexyl nitrites are not in the same class as alkyl nitrites and therefore may not be banned under current federal law. Underground manufacturers and importers continue to market butyl and isopropyl nitrites illegally.

The acute toxicity of inhaled and ingested nitrites in humans includes skin irritations (especially around the nose and lips), tracheobronchial irritation, headache, hypotension, cyanosis, methemoglobinemia, intoxication, and, rarely, death (*15*). Other effects include development of habitual use patterns, tolerance, and burns resulting from inadvertent ignition of the vapor. The National Toxicology Program of the National Institute of Environmental Health Sciences evaluated mice and rats exposed short term (6 hr/day for 14 days and 13 weeks) to inhaled isobutyl nitrite at concentrations ranging from 0 to 800 ppm and noted several adverse effects. Rats exposed to greater than 600 ppm died during the 14-day studies. At lower exposure levels, the most striking lesion seen in mice was hyperplasia of the nasal mucosa and bronchial and bronchiolar tree. Methemoglobinemia was confirmed. Other adversely affected organs included the liver, spleen, thymus, and bone marrow (*19*).

Prevalence of Nonmedical Nitrite Use

Alkyl nitrites are among the most commonly used inhalants in the United States. Other commonly abused inhalants are nitrous oxide, gasoline, glues, and solvents, such as paint thinners. The National Institute on Drug Abuse has collected information concerning nitrite inhalant use among high school seniors since 1979. Eleven percent of high school seniors interviewed in 1979 reported ever using nitrites. Use has decreased consistently among seniors since 1980, to 1.5% for the class of 1992 (*20*).

According to national surveys, self-reported amyl and butyl nitrite use varies by gender, region, and race. Male high school seniors reported higher rates of

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inhalant use and nitrite use than females. The proportion of males who used nitrites at least once was typically twice the percentage of females reporting lifetime use (*20*). The highest rate of nitrite use reported by high school seniors in 1979 was in the Northeast, and the lowest rate was reported in the West. Rates have decreased markedly in all regions, with the highest rates in 1992 reported in the North-Central United States and the lowest rates in the Northeast (*21*).

Nitrite use varies by race/ethnicity as well as geographic area. Although racial/ethnic data are not available for high school seniors, the Public Health Service-sponsored National Household Survey provides limited population-based estimates. Self-reported nitrite use in 1991 was highest for white males in each of six selected metropolitan areas for which data were analyzable. National estimates of use by females was 1.3% for white females in 1991, 0.7% for black females, and 0.8% for Hispanic females (*22*).

Nitrite use has been commonly reported among homosexual men for several decades, but less so for self-identified heterosexual adolescents and adults. In 1981, Centers for Disease Control and Prevention (CDC) investigators surveyed 420 men attending sexually transmitted disease clinics in New York, San Francisco, and Atlanta and found that 242 of 279 (86%) homosexual/bisexual men compared with 21 of 141 (15%) heterosexual men reported any use of nitrite inhalants within the previous 5 years (*6*). Almost all gay men enrolled in an AIDS case–control study conducted by CDC in 1981 reported use of nitrites (*23*). Other studies of gay men in the United States, Canada, and Europe found high rates of nitrite use (*24–29*). A multisite study demonstrated a marked decrease of nitrite use among gay men from 66% to about 35% between 1984 and 1989 (L. Jacobson, personal communication). Possible explanations for this trend include increased awareness of adverse effects, including concern about nitrites' possible links to AIDS, and decreased availability after nitrites were banned as consumer products (*30*).

Hypotheses Linking Nitrites and AIDS

At least four separate hypotheses have been proposed that suggest a role for nitrites in the pathogenesis of AIDS. When AIDS cases were first recognized in 1981, nitrites were proposed as a possible cause of the new syndrome (*5,6*). Nitrite abuse was virtually universal among the gay men diagnosed with AIDS in 1980–1983. However, this hypothesis was dismissed when the disease was recognized among drug injectors, hemophiliacs, and other heterosexual men and women who did not consistently report using nitrites. In 1983 and 1984, human immunodeficiency virus (HIV) was discovered and reported as the cause of AIDS (*31,32*). Subsequently, three other hypotheses suggesting nitrites as promoting factors in AIDS have been proposed. First, nitrites have been proposed to enhance HIV transmission by their association with risky sexual behaviors and HIV infection among gay men. Second, nitrite use has been associated with immune suppression and thus might hasten the onset of symptomatic disease. Third, nitrite inhalant use has been associated with the development of AIDS-related Kaposi's sarcoma.

Nitrites and Sexual Behavior/HIV Transmission. Several studies have linked nitrite use with risky sexual behavior and/or HIV infection among gay men. Ostrow et al. found these associations in the Multicenter AIDS Cohort Study (*29,30*). A similar correlation was not found for other substances of abuse, including alcohol (*30*). Stall et al. (*33*) linked nitrite, alcohol, marijuana, and other drug use during sex with increased likelihood of "risky" sexual behavior for HIV infection among gay men in San Francisco. They did not identify a unique risk for nitrites independent of several other drugs studied (*33*). In a longitudinal study of 249 gay men in Toronto, Calzavara et al. (*28*) found a significant decline in sexual activities associated with HIV infection and that nitrites and other drug use during sex are strong predictors of continuation of high-risk behaviors for HIV infection. Among all the variables tested, Penkower et al. (*34*) found that nitrite inhalant use was the most strongly associated with HIV seropositivity among a cohort of 1045 gay men.

Nitrites and the Immune System. The hypothesis that nitrite inhalants might induce immune suppression was first advanced by Goedert et al. in 1982 (*8*). T-lymphocyte abnormalities were reported in 9 of 10 gay men who reported regular nitrite use compared to 1 of 7 who did not use nitrites (*8*). This study came under criticism because of its small numbers and lack of evaluation for many potentially confounding variables, including HIV infection.

Several other investigators have evaluated the effects of nitrites on human immune function. Hersh et al. (*35*) cultured venous blood with up to 1% isobutyl nitrite in alcohol and, after 24 hr, observed irreversible effects on various lymphocyte functions, including blastogenesis, cell-mediated cytotoxicity, and monocyte adherence. Dax et al. (*36*) at the Addiction Research Center studied the effects of three inhalations at various concentrations per day for 3 or 18 days on the immune systems of 18 male volunteers. One inhalation of amyl nitrite (0.18, 0.36, or 0.48 ml) was administered from a closed 4-l flask at 3-hr intervals each day of study. After full exhalation, the subject inhaled from the flask through the mouthpiece with the nose "clipped" and held at full inspiration for 5 sec before exhalation. Blood was drawn for immune profile immediately after the last inhalation and 1, 4, and 7 days later. Modest depression of T-lymphocyte counts and natural killer cell activity were noted with a rebound to at least baseline levels several days after the last inhalations. Cell proliferation responses to phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM) were unaffected by amyl nitrite inhalation (*36*).

Ross and Drew (*37*) interviewed 97 gay men in Australia and measured T-cell counts and mitogenesis responses to PHA, Con A, and PWM. T-lymphocyte counts did not differ between nitrite users and nonusers. Mitogenesis in response to the three antigens was significantly higher in users compared with nonusers after cells were incubated for 72 hr, but the differences disappeared for PHA and Con A by 96 hr (*37*).

Studies of the immune system of mice following nitrite challenge are even less consistent than those among humans. Studies evaluating nitrites' effects on immune parameters have been hampered because formulations and dosages vary greatly, and routes of administration and immunologic outcome measures have not been standardized.

CDC investigators evaluated the effects of isobutyl nitrite on the immune system of BALB/c mice (*38,39*). The mice were exposed to either 50 or 300 ppm isobutyl nitrite for 6.5 hr/day, 5 days/week for up to 18 weeks. Mice were sacrificed at various times and antibody-producing cells were enumerated; mitogenesis responses were evaluated to PHA, Con A, PWM, and lipopolysaccharide and skin test reactions to purified protein derivative of immunized mice were observed. No immunotoxic effects were discerned, although decreased thymic weights were noted for female mice at the highest dose levels (*38,39*).

Other investigators have noted decreases in natural killer cell activity, helper lymphocyte counts, and/or body weight in mice exposed to nitrites. Lotzova et al. (*40*) injected mice with 0.50 ml isobutyl nitrite and noted significant depression of natural killer cell activity in female C57BL/6 × DBA/2 mice. Administration of isobutyl nitrite by inhalation (2- to 3-min exposures twice daily) also suppressed natural killer cell function in mice (*40*).

Ortiz and Rivera (*41*) exposed CD-1 mice to increasing amounts of amyl nitrite by nasal administration for up to 21 weeks. The total T-cell and suppressor cell counts did not differ from mice exposed to saline solutions. However, helper cell counts, body weight, and weight gain rates were significantly decreased in nitrite-exposed versus control mice (*41*). Soderberg and Barnett (*42*) exposed female C57BL/6N mice to 900 ppm isobutyl nitrite by inhalation chamber for 45 min per day for 14 days. Body weight was reduced 4%, mixed-lymphocyte reaction (MLR) was reduced 50–60%, and mitogen response to Con A was reduced was reduced 33% (*42*).

Although much laboratory work has been done to evaluate nitrites and the immune system, it remains unclear whether continued nitrite use by HIV-infected or uninfected individuals is immunotoxic.

Nitrites and AIDS-related Kaposi's Sarcoma. The epidemiology of Kaposi's sarcoma (KS), the most commonly reported cancer among AIDS patients, differs markedly from the other opportunistic diseases that have characterized the AIDS epidemic. KS has occurred much more frequently among gay men with AIDS and much less frequently among other AIDS patients. Furthermore, the rate of increase in KS cases has been lower than that of other AIDS indicator diseases (*43–46*). KS was almost never seen in HIV-infected blood-transfusion recipients, even when the presumed HIV donor developed KS (*47,48*). KS was reported about twice as often among white gay men with AIDS than among black gay men with AIDS, suggesting an association with increased socioeconomic status or some other factor (*49*). Women linked sexually to gay men were reported with AIDS-related KS more often than women infected with HIV by heterosexual contact with intravenous drug users (*50*). Wide geographic variations of KS rates were reported among gay men with AIDS in the United States (*50*). These observations suggested that some cofactor highly associated with gay lifestyle was operating in conjunction with HIV in the pathogenesis of AIDS-related KS. Nitrite inhalants were suggested as one possible factor (*10,11,51–56*).

There are several reasons to consider nitrite inhalants as a KS cofactor. First, the epidemiology of nitrite use in the United States parallels that of HIV-related KS. Nitrite inhalants are used more commonly by gay men than others (*6*); use has been declining since AIDS was first reported (*30*) and has roughly paralleled the pattern of reported KS cases, and use among whites is greater than among blacks, as is the incidence of KS (*22*). Second, some, but not all, epidemiologic studies have shown a statistical association between the development of KS among gay men with AIDS and the use of large quantities of nitrite inhalants when compared with gay men with AIDS, but without KS (*11,51–56*). Third, anecdotal reports of increased frequency of AIDS-related KS on the chest and face, especially the nose, and in the lungs are consistent with the body areas most heavily exposed to nitrite vapors when inhaled. Finally, plausible mechanisms of action have been proposed for nitrites and their metabolites, such as cholesteryl nitrite and nitrosamines, to be carcinogenic, and mutagenesis has been demonstrated in the Ames test (*7,57,58*). Nitrites are known to affect small blood vessels, the anatomic site presumed to give rise to KS (*12*).

Nitrite inhalants are one of several factors proposed as KS promoters in HIV-infected individuals. Other KS cofactors proposed include a second sexually transmitted agent and/or genetic factors (*48,59–65*).

Conclusions

In summary, nitrite inhalants are commonly abused substances in the United States. Nitrite inhalants are associated with behavioral relapse and HIV transmission among gay men, with decreased lymphocyte counts and natural killer cell activity in a few laboratory studies, and they remain a candidate cofactor in the pathogenesis of AIDS-related KS.

Encouraging the decline in nitrite abuse appears to be a worthwhile public health goal. The most effective ways to accomplish this goal are not clear. In the United States, laws banning nitrite manufacture and sale were enacted in 1988 and 1990. However, use of nitrite inhalants had started to decrease even before the laws were implemented. What impact did discussions of scientific findings suggesting a link between nitrites and AIDS, particularly as reported in the predominantly gay press, have on nitrite sales and use? What impact did grass-roots organizations discouraging nitrite use have? What alternative drugs of abuse will take the place of nitrites by those who discontinue use?

The search for cofactors in AIDS-related KS remains an important scientific challenge. If the KS cofactor(s) can be identified, it may provide important insights into the pathogenesis of AIDS and possibly some forms of cancer. Nitrite use is consistent with much of the epidemiology of AIDS-related KS. Further studies of nitrite use and other potential cofactors among gay men with KS as well as women and others with KS should be encouraged. Animal models exposed to retroviruses and nitrite inhalants should be pursued.

The possible links of nitrites with AIDS and the other known adverse effects of these inhaled substances suggest that more attention to these products by clinicians and researchers is warranted. Clinicians and community leaders should discourage the use of nitrite inhalants. Researchers should study further the associations between nitrite use and HIV infection and AIDS.

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