The Acute Toxicity of Nitrite Inhalants

Ronald W. Wood

INTRODUCTION

Alkyl nitrites produce a variety of effects when inhaled. Except in the context of anginal pain or as an antidote to cyanide poisoning, these effects cannot be construed as having therapeutic utility. A number of demonstrable risks accompany the inhalation of these materials, and this chapter will review the acute hazards associated with the nonmedical use of these chemicals. Aside from the spectrum of effects desired by the user, there are less desirable “side effects” as well as frank injuries associated with the use of these products, including skin and tracheobronchial irritation; bum injuries; acute toxicity mediated by hypokinetic anoxia, methemoglobinemia, and associated disorders of blood and blood-forming organs; and the induction of a substance abuse disorder.

DESIRED ACUTE EFFECTS AND UNDESIRE SIDE EFFECTS

Inhalation of high concentrations of nitrites relaxes smooth muscle: the consequent intense peripheral vasodilation produces flushing, a fall in blood pressure, and a reflex increase in heart rate to maintain perfusion of vital organs (Haley 1980). These effects are accompanied by feelings of warmth, rapid pulse, and throbbing sensations. Volatile nitrites are frequently used as an adjunct to sexual behavior, because of their smooth muscle effects, nitrites can reduce sphincter tone and alter tumescence. The vasodilation is accompanied by heat loss and a subsequent chill. Headache, nausea, and fainting are common sequelae of nitrite inhalation.

Skin and Tracheobronchial Irritation

Skin contact with commercial products containing butyl nitrite can produce a crusty lesion at the site. Repetitive use of the material can lead to a proliferation of these lesions around the nose and lip (Fisher et al. 1981; Fisher 1984; Romaguera and Grimalt 1982) and has been reported around the penis, the scrotum, and elsewhere (Bos et al. 1985). The latter report suggests that a true allergic response to these materials may occur.

The irritating properties of these materials are not confined to the skin and have manifested themselves in tracheobronchitis with erythema of sufficient severity to require hospitalization, and with complaints of cough, fever, mild hemoptysis, and exertional dyspnea (Covalla et al. 1981). Subchronic toxicity evaluations support concern about lung injury (McFadden and Maickel 1985; Lynch et al. 1985).

Burn Injuries

Alkyl nitrites are flammable and explosive. At least one burn injury has been reported through the National Injury Information Clearing House (NEISS data base) of the Consumer Product Safety Commission (CPSC), following the use of a room odorizer product near a candle. "This incident involved a 26-year-old male who opened a small bottle on a stand when it ignited, flamed up, and burned him. During this accident, the victim spilled some of the gymnasium room odorizer onto parts of the living room furnishings. As a result, part of an ottoman and small sections of the carpet were damaged. It is believed that the liquid gymnasium room odorizer ignited, as its vapors came into contact with a lighted cigarette in a nearby ash tray. The victim received burns on the left side of his nose and an area of his left cheek. The victim was also singed on his right arm, forehead and some parts of his hair" (CPSC memo from Schmeltzer to Perez, July 11, 1977).

The materials are labeled with a warning of this hazard, which is not to be underestimated; small quantities have been responsible for refrigerator explosions in laboratories, and larger quantities have been implicated in the largest fire in San Francisco since the earthquake of 1980 (Turner 1981). Despite these hazards, many of the products packaged in small vials with shrink-fit plastic comply with U.S. Postal Service regulations for the shipment of small quantities of flammable and explosive materials.

Acute Toxicity

Whether inhaled or swallowed, nitrites can produce anoxic states. The administration of nitrites by any route can produce profound methemoglobinemia. Tissue anoxemia can result from methemoglobinemia (Darling and Roughton 1942; Lester and Greenburg 1944). Ascorbic acid and methylene blue may be effective prophylactic agents for nitrite poisoning if administered promptly, but laboratory studies offer little support for this in the case of isobutyl nitrite ingestion (McFadden and Maickel 1982). Prolonged administration of the materials may lead to several disorders of the blood and blood-forming organs, including Heinz-body hemolytic anemia and splenomegaly (Romeril and Concannon 1981); increased spleen weight has been observed in mice chronically exposed to butyl nitrites (McFadden and Maickel 1985). The administration of nitrites can also produce hypokinetic anoxia, an oxygen starvation of vital organs secondary to sustained profound peripheral vasodilation, pooling of blood in the extremities, and impaired vascular return (Wilkins et al. 1937).

A number of human anecdotes report on the acute toxicity of volatile nitrite "room odorizer" products and provide correlative observations that substantiate concern aroused by experimental work with laboratory animals. Severe methemoglobinemia can result from deliberate inhalation of room odorizer products (Home et al. 1979; Shesser et al. 1981; Guss et al. 1985). Ingestion can produce a more rapid and malignant methemoglobinemia than can inhalation and can be lethal (Dixon et al. 1981; Shesser et al. 1980; Shesser et al. 1981; Smith et al. 1980; Wason et al. 1980).

The acute toxicity of the alkyl nitrites has received attention in the laboratory and is relevant to the regulation of these materials in interstate commerce, including packaging and labeling requirements. A summary of these experimental findings is presented in table 1. Room odorizer products are currently considered to be "toxic" by inhalation or ingestion, although the oral toxicity of the material has not been evaluated adequately according to the CPSC. The materials display an unusually steep lethality function so that, in the effective range, small increments in dose produce large changes in the number of resultant deaths (Wood and Cox 1981; Klonne et al. 1987). In addition, there is a very narrow margin of safety between behaviorally effective and lethal concentrations (Rees et al. 1986).

Users estimate they can derive 40 “doses” from a typical room odorizer, yielding approximately 0.2 ml per self-administration (Israelstam et al. 1978). This estimate is neither a dose nor an exposure concentration, but a rate of loss of a volatile material from an open container. There have been no studies that describe either the absorbed dose or the exposure concentrations that are effective in producing smooth muscle relaxation, alterations in cardiovascular function, behavioral impairment, or self-administration under the brief exposure conditions typical of self-administration. However, Pryor et al. (1989) did expose rats to isobutyl nitrite for 15 to 60 seconds, at concentrations that increased gradually in the exposure chamber. The LC50s expressed as a peak concentration ranged from 4.5 to 4.8 percent. The slope of the lethality function was influenced by the rate of change of concentration. A constant concentration-time product relationship was not obtained in this study, or in that of Klonne et al. (1987), suggesting that the dramatic acute effects of the agent may alter the pharmacokinetics and exaggerate the toxicity of these agents.

For some of the aliphatic nitrites, the alcohol from which they are synthesized may contribute significantly to their toxicity when injected or ingested. In addition, the alkyl nitrites are metabolized to nitrite ions and the corresponding alcohol, which may lead to delayed deaths or hepatotoxicity. n-Butyl alcohol has an oral median lethal dose (LD₅₀) for the male rat of 790 mg/kg (Purchase 1969), in contrast to 13,600 mg/kg for ethanol (Smyth et al. 1941). In an investigation of several highly pure butyl nitrites and their alcohols given to mice intraperitoneally, sec- and tert-butyl nitrites were found to have significant delayed toxicity; the toxicity of the alcohols by the same route was also delayed, and the LD₅₀ ranged from 254 (n-butyl) to 544 mg/kg (isobutyl) 7 days after administration (Maickel and McFadden 1979).

SUBSTANCE ABUSE DISORDERS

There is clear evidence that volatile nitrites are used as drugs of abuse. National surveys indicate that high school seniors and adults not only have used alkyl nitrites as drugs, but also that 7.9 to 11.1 percent of high school seniors from 1979 to 1985 reported having tried these drugs in their lifetime (Johnston et al. 1986). The incidence of deliberate use by homosexual men has been greater and is discussed in more detail shortly. Lowry (1980) conservatively estimated that 250 million recreational doses a year were consumed in the United States (Lowry 1982).

Volatile nitrites are persistently self-administered by people. Israelstam et al. (1978) interviewed 150 users of isobutyl nitrite and reported that users who administered nitrites did so from three to six times per "occasion"; the number of occasions ranged from only once to four times a week. The duration that this frequency of self-administration was maintained was unspecified. Goedert et al. (1982), in an attempt to determine if volatile nitrites alter immune function, studied 17 men; 10 were described as regular users, inhaling nitrites from 1 to 20 times per month; 4 had used nitrites for longer than 6 years. Romeril and Concannon (1981) presented two cases, each of which reported 20 sniffs per occasion, two to three times per week, for either 3 or 24 months. Fisher et al. (1981) reported on two men who stated that they were "in the habit" of inhaling butyl nitrite and continued to do so during the 6-week period that they were seen by a physician.

According to the nosological scheme of the Diagnostic and Statistical Manual (DSM III) of the American Psychiatric Association, one definitional criterion of "substance abuse" is a duration of pathological use for at least 1 month; several of the cases described above meet this criterion. Other than the duration of use, definitional criteria for "pathological use" vary with the substance abused but may include episodes of complication due to substance intoxication, e.g., alcoholic blackouts, opioid overdose; need for daily use of the substance for adequate functioning; and continuation of substance use despite a serious physical disorder that the individual knows is exacerbated by use of the substance. Examples from the literature fulfilling these criteria follow.

Complications Due to Substance Intoxication

Shesser et al. (1981) report a hospital admission following several hours of continuous inhalation of an isobutyl nitrite preparation. The patient was alert and combative, and the parents sought to have the patient admitted to the hospital because of mental status change and cyanosis. The patient admitted to having had several drinks of alcohol. Treatment of the patient with oxygen and intravenous methylene blue and ascorbic acid resulted in alleviation of the cyanosis; with the patient becoming calmer and reoriented. Covalla et al. (1981) report a hospital admission for severe tracheobronchitis following the patient's inhalation, with a friend, of two bottles of LockerRoom in a week's time. His friend developed a similar but less severe illness. The cases in the following paragraph also constitute complications of substance intoxication.

Continuation of Substance Use Despite a Serious Physical Disorder Exacerbated by Use of the Substance

Home et al. (1979) report emergency room admission on two separate occasions of a 25-year-old man after he inhaled butyl nitrite. The occurrence of clinically significant methemoglobinemia was not sufficient to deter self-administration in this individual. In a survey of 255 experienced users (Lowry 1979), 10 percent had experienced nasal irritation at least once, and 5 percent had experienced nausea or temporary loss of erection. These negative effects were associated with "overuse" (emphasis Lowry's). Fisher et al. (1981) report several cases of facial dermatitis due to butyl nitrite inhalation. Two of the three cases reported that they were "in the habit of inhaling butyl nitrite," and continued to do so during the 6-week period in which the dermatitis was evident. The skin lesions cleared when nitrite use was terminated.

Need for Daily Use of the Substance for Adequate Functioning

Sigell et al. (1978) interviewed an unspecified number of users, some of whom claimed that they were no longer able to perform sexually without the use of these drugs. Everett (1975) has made a similar assertion.

CONCLUSION

Research funded by the National Institute on Drug Abuse (NIDA) has demonstrated that drugs abused repetitively by humans are self-administered by animals; drugs that are abused sporadically by humans (most hallucinogens), or not at all (major tranquilizers), are not taken by laboratory animals. Thus, there is a pharmacologic *sine qua non* for the ability of drugs to maintain self-administration: in the absence of intrinsic abuse potential, humans will not persistently abuse a drug. Although there have been no laboratory investigations using animal self-administration preparations, volatile nitrites have abuse potential because they would not generate persistent human self-administration in its absence.

The extrapharmacologic determinants of substance abuse are of great importance; in this case, the pattern of distribution, availability, and promotion of materials in commerce play predominant roles in elevating the abuse liability of the volatile nitrites. The pattern of distribution of volatile nitrites is typical of a free market with access to the mails and the right to advertise. The interruption of this

pattern of distribution would reduce the abuse liability of these agents.

TABLE 1. *Acute toxicity of alkyl nitrites*

	Compound	Species	LD ₅₀ /LC ₅₀	Reference
Oral	n-Butyl	Rat	83 mg/kg (79.5-86.5)	Wood and Cox 1981 Federal Hazardous Substances Act protocol Ethanol vehicle (50 mg/kg="highly toxic")
	n-Butyl	Mouse	180 mg/kg (0-288)	McFadden and Maickel 1982 (2-hour LD ₅₀)
	sec-Butyl		428 mg/kg (358-469)	
	tert-Butyl		336 mg/kg (292-447)	
	Isobutyl		279 mg/kg (0-610)	
	n-Butyl	Mouse	171 mg/kg (27-249)	McFadden and Maickel 1982 (7-day LD ₅₀)
	sec-Butyl		423 mg/kg (393-456)	
	tert-Butyl		308 mg/kg (220-426)	
	Isobutyl		205 mg/kg (5-311)	
Intraperitoneal	Amyl	Mouse	130 mg/kg (111-152)	Dewey et al. 1973
	n-Butyl	Mouse	158 mg/kg (127-197)	McFadden and Maickel 1979 (30-minute LD ₅₀)
	sec-Butyl		592 mg/kg (476-734)	
	tert-Butyl		625 mg/kg (520-750)	
	Isobutyl		169 mg/kg (139-199)	
Intravenous	Amyl	Mouse	51 mg/kg (38-68)	Dewey et al. 1973 (24-hours LD ₅₀)

TABLE 1. (Continued)

Compound	Species	LD ₅₀ /LC ₅₀	Reference
Inhalation			
Isbutyl	Mouse	1346 ppm (1219-1473)	Rees et al. 1986 (30-minute exposures)
n-butyl		949 ppm (897-1001)	
Isoamyl		1430 ppm (1302-1559)	
Isobutyl	Mouse	1033 ppm (843-1234)	McFadden et al. 1981 (60-minute exposures)
n-butyl		567 ppm (531-625)	
sec-Butyl		1753 ppm (1552-1964)	
tert-Butyl		10852 ppm (626-15408)	
Methyl	Rat	176 ppm (169-183)	Klonne et al. 1987 (4-hour exposures)
Ethyl		160 ppm (151-169)	
n-Propyl		300 ppm (293-308)	
n-Butyl		4210 ppm (410-431)	
Isobutyl		777 ppm (747-809)	
Isopentyl (Isoamyl)		716 ppm (702-731)	
n-Butyl		1470 ppm (1226-1823)	
Isobutyl		1000 ppm (815-1255)	
Isoamyl		1118 ppm (797-1493)	
			CPSC memo fro Perez to Preuss, September 24, 1979
			Federal Hazardous Substances Act protocol
			(1-hour exposures)

Note: LD₅₀=Median lethal dose (lethal to 50 percent of test subjects).
LC₅₀=Lethal concentration, 50 percent.

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AUTHOR

Ronald W. Wood, Ph.D.
 Research Associate Professor
 Department of Environmental Medicine
 New York University Medical Center
 550 First Avenue
 New York, NY 10016

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Editors:

Harry W. Haverkos, M.D.

Division of Clinical Research
National Institute on Drug Abuse

John A. Dougherty, Ph.D.

Veterans Administration Medical Center
Lexington, KY

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Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

National Institute on Drug Abuse
5500 Fishers Lane
Rockville, MD 20857

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Preface

The National Institute on Drug Abuse (NIDA) is concerned about the acquired immunodeficiency syndrome (AIDS) for two reasons. First, intravenous drug abusers constitute approximately 25 percent of reported AIDS patients in the United States. Human immunodeficiency virus (HIV) infection is transmitted among intravenous drug abusers primarily when contaminated needles and other paraphernalia used to inject drugs are shared. Infected drug abusers are capable of transmitting HIV to their sexual partners during sexual contact and to their unborn children during pregnancy. Second, the use of drugs may expedite disease progression by further decreasing immune function or by acting as the vehicle of transmission of other infectious agents, such as hepatitis B virus, which may also be immunosuppressive. Drugs of abuse may promote the development of malignancies. Nitrite inhalants, commonly used by homosexual men, have been associated with Kaposi's sarcoma (KS) in AIDS. The mechanism of action of nitrites as a cofactor in KS, if any, has yet to be elucidated.

On March 31, 1987, NIDA sponsored a technical review entitled "The Extent of Use and Health Hazards of Nitrite Inhalants." Approximately 25 scientists attended the meeting in Rockville, MD. The purpose of the workshop was to review the status of research regarding nitrite inhalants and their potential public health implications and to set directions for future studies. In part, this meeting was called to provide up-to-date information about nitrite inhalants for NIDA to respond to a congressional request for information as part of the Anti-Drug Abuse Act of 1986.

This monograph is a collection of presentations delivered at the meeting. The chapters are organized to present the history of nitrite use; the basic biochemical, pharmacologic, and toxicologic effects of various forms of alkyl nitrites; the effects of nitrite use on the

immune system; and epidemiological findings associating nitrite use with KS in AIDS. The purpose of this introduction is to provide an overview of issues and controversies raised at the meeting that are covered in more detail in individual chapters.

There are many controversial issues surrounding nitrites, not the least of which are their current regulatory status. As Guy Newell discusses in his historical presentation, amyl nitrite is a prescription drug, but butyl nitrite, with effects very similar if not identical to the amyl congener, is not considered to be a drug because it is marketed as a "room odorizer." Proposals to regulate the sale of butyl nitrites have been periodically considered by various agencies of the Federal Government.

A series of metabolic and toxicity studies of four nitrite butyl esters in mice was presented by Roger Maickel. The lethality of these compounds was related to rapid hydrolysis to nitrite ions with the subsequent oxidation of hemoglobin to methemoglobin. However, methemoglobin formation cannot account for all toxic effects. While there were wide differences in toxicity, the relative toxic potencies of the four butyl nitrite isomers found in "room odorizers" were maintained under a variety of experimental conditions and routes of administration.

The acute toxicity of nitrites in animals and man was reviewed by Ronald Wood. Skin and tracheobronchial irritations (especially about the nose and lips), burns from accidental ignition, headaches, hypotension, cyanosis, methemoglobinemia, intoxication, and the development of habitual use patterns are possible adverse effects of nitrite inhalation.

Much of the discussion at the meeting focused on two possible pharmacologic mechanisms by which nitrites may be involved in the genesis of KS in AIDS: carcinogenicity and immunosuppression.

Although dependent on an unproven and controversial mechanism, nitrites have been hypothesized to interact with organic amines and amides in vivo to form significant amounts of highly carcinogenic N-nitrosamines. Direct data on the carcinogenicity of nitrites in animals are sparse. However, the in vitro studies of lipid peroxidation and the finding of route-dependent in vivo formation of nitrosamines from amyl nitrite and methylaniline in mice, reported by

Sidney Mirvish, suggest that the possibility warrants serious investigation. Interestingly, the areas where absorbed concentrations of volatile nitrites would be expected to be highest--the skin surrounding the nose and in the nasal/pulmonary mucosa--are also reported to be the areas in which KS occurs in persons with AIDS. This association logically leads to the hypothesis that there is a causal relationship between nitrites and KS, perhaps mediated by the formation of N-nitroso compounds. How HIV infection initiates or promotes this process is not clear.

Besides participating in the formation of carcinogenic metabolites, alkyl nitrites may increase the likelihood of KS by altering immune function. Dan Lewis, Jesse Ortiz, and Elizabeth Dax studied the effects of nitrites on immunologic function using variations on two basic strategies: first, examination of effects on immunologic components (lymphocyte numbers, thymus weight, etc.) and second, measurement of effects of nitrite pretreatment on the responsiveness of immune system components to challenge with various adjuvants, mitogens, and antigens. Given the complexity of the immune systems in mice and humans, the possible variations in nitrite exposure parameters, the large number of dependent variables and sampling times to choose from, and the diversity of analytic methods available, one might have predicted in advance the divergent results obtained. Lewis reported no significant detrimental effects on the immune systems of mice from exposures to 300 parts per million isobutyl nitrite vapor for 13 weeks. However, the other two researchers showed different patterns of decreases in T-lymphocyte numbers and changes in immune functions after 21 weeks of intranasal amyl nitrite in mice (Ortiz, this volume) or after 13 sessions of amyl nitrite inhalation in human volunteers (Dax, this volume). It is apparent that there is much to learn before the relevance of nitrites to disease processes, such as KS, is understood.

Much has been written about the extent of nitrite use among homosexual men. In addition, household and high school surveys have quantitated use of nitrites among adolescents and young adults, but these surveys have not distinguished use by sexual orientation. In this monograph two surveys of nitrite inhalant use by drug abusers are presented. Richard Schwartz presents data collected from adolescents at a residential drug treatment community in suburban Virginia. Schwartz also assesses the rates of acute toxicity attributed to nitrites among adolescent abusers. Robert Lange presents

data concerning nitrite use among intravenous drug abusers in treatment from six regions of the United States and among homosexual men in Baltimore. Lange suggests that nitrite use is decreasing among homosexual men because of the fear of an association with AIDS. Nitrite use among intravenous drug abusers is not as extensive as among homosexual men and is not apparently changing.

The unique epidemiology of KS in AIDS suggests that a cofactor is necessary to explain its pathogenesis. Harry Haverkos reviewed the existing epidemiologic studies of nitrite use and KS in homosexual men and found inconclusive results; nitrite use is associated with KS in some studies but not in others. In discussing the variables that may be responsible for the varied results, he ruled out bloodborne infectious agents and focused attention on drug use and sexually transmitted microbial agents as the most likely places to look for the KS cofactor. His discussion points out the difficulties of interpreting questionnaire data when sample sizes are small and methods, populations, and questions vary. Tighter control over survey conditions and standardized methods would make these studies more efficient, but may be impractical to achieve.

An open discussion moderated by Dr. Newell followed the presentations at the workshop. More epidemiologic and laboratory studies are needed to assess the role, if any, of nitrite inhalants as a cofactor in AIDS-related KS. There is a need to develop questionnaires for studies that assess nitrite exposure over one's lifetime, analogous to pack-years in cigarette usage. Despite the epidemiologic associations with KS, butyl nitrite has never been tested as a carcinogen. Such studies should be conducted. Studies of animal models infected with retroviruses and challenged with large quantities of nitrites before, during, and/or after retrovirus infection would be useful.

More research is needed to determine the dose-response curve of nitrite inhalation in humans. Many individuals use other drugs, such as alcohol, marijuana, and/or cocaine, with nitrites. What are the effects of these drugs in combination?

Nitrite inhalants are important drugs of abuse in the United States. Their association with KS and AIDS raises an important scientific question about possible synergistic reactions between viruses and chemicals in the development of cancer. It is our hope that this

monograph will stimulate interest in nitrite inhalant research and attract investigators who can conduct the multidisciplinary research necessary to address the scientific questions raised at this NIDA technical review.

Harry W. Haverkos, M.D.
Clinical Medicine Branch
Division of Clinical Research
National Institute on Drug Abuse
Rockville, MD

John A. Dougherty, Ph.D.
Veterans Administration Medical Center
Lexington, KY