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Inhalant Abuse: A Volatile Research Agenda

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In Memoriam
Sidney Cohen, M.D.
1910-1987

Throughout his distinguished career as a physician, researcher, mentor, author, and Federal administrator, to name some of the major roles he played, Dr. Sidney Cohen represented the highest level of integrity and commitment to truth. Perhaps it was that essential commitment that enabled Sid to avoid being seduced by the "psychedelic revolution" embraced so uncritically by some of his colleagues in the early 1960s. But he also never succumbed to the hysteria that maintained that all the problems of youths could be uncritically attributed to their drug use. His sense of proportion, good humor, and wide ranging knowledge of both science and history gave him a rare and wise perspective during a troubled era.

Sid Cohen's impressive skills as a communicator enabled him to make important contributions to both drug abuse research and to the public's understanding of the drug problem. Because he liked young people and was liked and respected by them, he was particularly effective in communicating with youths. And, since he did not shrink from asking himself the hard questions, he did not hesitate to ask them of the young as well. He was among the first to debate Timothy Leary, the self-styled "psychedelic drug guru," on college campuses, pointing out, "A pill does not construct character, educate the emotions, or improve intelligence. It is not a spiritual labor-saving device, salvation, instant wisdom, or a short cut to maturity." This was in the early 1960s when many who should have known better thought LSD and the other hallucinogens were all those things.

Sid was a gifted writer. Through hundreds of scientific articles as well as numerous books for lay audiences he conveyed the subtlety and complexity of psychoactive drugs and the hazards of their abuse. Sid's popular books included such classics as *The Beyond Within* and *The Drug Dilemma,* both of which went through several editions.

As a psychopharmacologist, Sid was very aware of the importance of not only the drug itself, but of its dosage and circumstances of use. Never a polemicist, Sid felt his greatest contribution to the drug dialogue was to make the public aware of the seductive hazards of drugs by acquainting them with the implications of scientific research. Some felt they knew all the answers. Sid was much more conscious of the unanswered questions. As a drug historian, Sid was very aware of how often a new analgesic, stimulant, or "recreational drug," intitially thought to be nonaddictive, was later found to produce dependency.

Sid Cohen's energies were legendary. To the very end of his life he was astonishingly productive as well as virtually a "commuter" between the west and east coasts in his many roles as administrator, consultant, or member of innumerable advisory boards on topics ranging from drug abuse to suicide prevention and schizophrenia. Drugs, and later psychopharmacology were, however, his basic preoccupation, beginning with his early training as a pharmacist (at Columbia University) in the early 1930s. He received his medical training in Germany (at Bonn University) during those turbulent—and for him potentially perilous—years in which the Nazis rose to power. In 1976, his alma mater, Columbia University, awarded him an honorary Doctor of Science degree in acknowledgement of his many contributions to psychopharmacology.

Toward the end of his life some of us sometimes wished Sid would find time to "enjoy life" more. But we forgot that for Sid to continue to work in his chosen field was more fun than anything else he could imagine. He had a small plaque on his desk that said, "It is not necessary to succeed in order to try." Surely he succeeded far better than he knew. We continue to miss his unfailing good humor, his wisdom, his perceptiveness, and his dedication to truth.

Robert C. Petersen, Ph.D.

Sidney Cohen and I entered the field of drug abuse at about the same time—more than 30 years ago. We also began by studying the same class of drugs, hallucinogens. One other point we shared was that we had both been trained in internal medicine, not psychiatry.

Although not specifically trained as a psychiatrist, Sidney could have been cast in such a role in any movie. His physical appearance was imposing. A leonine mane of graying hair swept back in pompadour style from his forehead, beneath which were a pair of piercing eyes. He conveyed an Old World charm legitimately obtained from his origin. His slightly raspy voice and the words he spoke showed empathy and compassion. I am sure that he must have been a good clinician.

His research efforts in the field of substance abuse spanned many years and were well recognized by his peers. However, his greatest service might have been as an administrator. When the drug abuse problem showed signs of becoming a national menace, Sidney was lured from his comfortable southern California existence to come to Washington to administer the program that later evolved into NIDA. As a result of his efforts, funding for drug abuse research grew rapidly and mechanisms were established to distribute controlled substances to qualified investigators. He was one of the first persons to recognize the importance of inhalant abuse. When things were finally going well, he rejoined his family in California.

Sidney was one of the most lucid lecturers I have ever heard. No fancy language, no jargon, but just good straightforward English. He was always careful with his facts but not afraid to slip in some sly humor. He was an excellent spokesman for the field of drug abuse and was active in many community activities as well as at the national level. He was a devoted husband who took good care of his wife, Elsa, after she had the misfortune to develop Parkinson's disease. He had many colleagues who also became his good friends.

No one is irreplaceable, but Sidney's death left a void that many of us still feel. It is entirely appropriate that this volume be dedicated to one of the pioneers in drug abuse research—a true scholar and gentleman.

Leo E. Hollister, M.D.

I respectfully conclude this tribute by noting that Sidney Cohen, a valuable colleague in the early period of the development of NIDA's Inhalant Program, was primary in supporting both my and the Institute's efforts. Not only because of his general knowledge and experience in the field of drug abuse, but also because of his interest in those abusing inhalants, he perceived the need for the investigation of the toxicology and drug dependence associated with solvent intoxication. Thus, he guided both me and NIDA in the early stages of this program and endorsed the accumulation of knowledge in this emerging field. Our efforts culminated in the first publication, *Inhalant Abuse: Euphoria to Dysfunction,* in 1977. Periodically thereafter, conversations often focused on recent advances in the field to which he contributed recent knowledge and relevant guidance, both of which were invaluable. He would be proud of the advances in the field which have been identified within this monograph, but always cognizant of, and quick to identify, the many challenges that lie ahead. I regret that he is not with us now to discuss the pertinent issues and thoughtfully approach and scientifically design studies to provide the necessary data that would allow us to reduce those tragedies associated with this state of drug dependency.

Charles W. Sharp, Ph.D.

Preface

In the fall of 1989, the University of Texas, Health Sciences Center, and the Texas Commission on Alcohol and Drug Abuse convened a meeting to review the present state of our knowledge concerning inhalant abuse and to stimulate increased inquiry into various aspects of this complex problem. During this meeting it became obvious that, unlike other areas of drug abuse research, no cohesive group of investigators has directly addressed research or treatment in the area of inhalant abuse. The lack of cohesion of inquiry into solvent abuse may result, in part, from both the unusual patterns shown by the abusers and the nature of the substances themselves. Many dimensions that differentiate inhalant abusers from other drug abusers are extensively described in this volume. Not only does this group of abusers utilize an enormous array of substances, the individuals themselves are a complex cross-section of many sociocultural and psychological dimensions. Many exhibit particularly dysfunctional behavior patterns, making them especially refractory to treatment. While volatile solvent abusers share a number of characteristics with other drug abusers, enough differences exist to make many researchers and treatment personnel reluctant to become involved with these populations and their behavior. Understandably, many investigators prefer to focus on less complex behaviors that offer greater promise for understanding and treatment.

The National Institute on Drug Abuse was pleased to cooperate with the Texas Commission on Alcohol and Drug Abuse in sponsoring this important meeting. The participants included established as well as new investigators from both the public and private sectors.

The format of the conference focused on broad fields of endeavor. Each section was introduced by a review of the state of our knowledge in a particular area followed by discussions and relevant short papers. Following the meeting, the papers were revised for the NIDA Research Monograph series and updated to present an intelligible review of the field.

It is hoped that this monograph will be a beginning step in the process of bringing more coherence to what heretofore has been an unfocused area of inquiry.

James V. Dingell, Ph.D.
Director
Division of Preclinical Research
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Introduction to Inhalant Abuse

Charles W. Sharp

The term "inhalant abuse" is used to describe a variety of drug abuse behaviors that cannot be classified by the associated pharmacology or toxicology, but only by the mode of administration. Yet, some other inhaled substances (e.g., tobacco, marijuana, and even heroin or "crack") do not fall into this classification. Leo Hollister has identified abused inhalants as groups of volatile substances used for altering mental status that are rarely, if ever, administered by routes other than inhalation. On this basis several subcategories can be established: (a) medical anesthetic gases, such as ether, chloroform, halothane, and nitrous oxide; (b) industrial or household solvents, including paint thinners or solvents, degreasers, and solvents in glues; (c) art and office supply solvents, including correction fluids and solvents in markers; (d) gases used in household or commercial products, e.g., in butane lighters, whipping cream dispensers, electronic equipment dusters and cleaners (e.g., for PCs), and refrigerant replenishers; (e) household aerosol propellants in items such as paint, hair, and fabric protector sprays; and (f) aliphatic nitrites. (There are substantive reasons for considering the nitrites as a special class. First, they act on vascular smooth muscle rather than as anesthetic agents on the central nervous system. Second, they are used as sexual enhancers, primarily by specific populations.)

Volatile substances (or "inhalants") are ubiquitous and their use as intoxicants extends well back into history. The practice of inhalation to produce euphoria can be traced to the ancient Greeks (Carroll 1977). As Hollister has noted:

> At the turn of the 18th century, Humphry Davy in England, experimenting with the newly discovered gas, nitrous oxide, discovered its mind-altering effects. He shared his fun with friends at a succession of private parties. Later, charlatans took the gas on the road, with travelling exhibitions at which for a fee, the audience might experience the effects of the gas.

Commonly called "laughing gas," the euphemism accurately describes one of the recreational uses of the anesthetic nitrous oxide. In the mid-19th century, after the discovery of the anesthetic action of ether and chloroform, these gases were also used nonmedically—e.g., chloroform and ether parties. These substances are still used today by inhalant abusers (Hutchens and Kung 1985; Kringsholm 1980). That these substances are abused by middle class professionals demonstrates the diversity of the groups that abuse inhalants (Nordin et al. 1988; Krause and McCarthy 1989; Jacob et al. 1989). Nearly all solvents produce anesthesia if sufficient amounts are inhaled. Although this is an important property, the ability to produce anesthesia does not seem to correlate with the extent of abuse of any given substance.

The 20th century brought on the use of gasoline and many other volatile compounds. Hollister notes that the present period of use of inhalants probably dates from the 1920s but expanded rapidly following World War II. These solvents can be found in numerous products that are everywhere—in industry, in the workplace, and in the home. Thus, in our industrial society, it is not difficult to find some substance to "get high on"—and at a bargain price.

Substances Inhaled

Despite the widespread abuse of these substances for years, it was not until the 1950s that nationwide attention focused on what was generally referred to as "glue sniffing" by the press (see Kerner 1988) and the judicial system. The term is still widely (mis)used to describe an activity involving a myriad of products that include not only glue but gasoline, paint thinner, spray paint, cooking spray, deodorant, hair spray, correction fluid, cleaning fluid, refrigerant gases, cooking gases, tobacco-lighter gases, anesthetics, canned whipped cream, dust remover aerosols, and fabric protector sprays. It is important to keep in mind that there are many different chemicals in these products, all of which have diverse physiological effects, toxicities, and

chemical properties. Sometimes the substances are listed on the container with or without the proportion of each.

Because of the diversity and complex composition of different products, there are often incorrect references to which particular solvents are being abused. Toluene, for example, is often cited as the substance involved when other substances may also be present and may contribute to the problem, or even be the primary substance at issue. Also, some reports associating toluene with a particular syndrome may have missed the substance that is the actual cause of that syndrome. To correctly identify the substance, it is critical that clinical measures of body fluids be conducted to correlate a clinical syndrome with a particular substance(s). Clues may be derived from containers, but that is often not helpful as many products do not identify all the substances and may often only refer to ingredients as "nontoxic hydrocarbons."

Some of the possible substances found in different products are listed in table 1.

Sociocultural Factors

The practices of "sniffing," "snorting," "huffing," "bagging," or otherwise inhaling to get high describe various forms of inhalation abuse. If the substance is glue or some other dissolved solid, the user will empty the product's contents into a plastic bag, hold the bag to the nose, and inhale ("bagging"). Another method is to soak a rag with the mixture and then stick the rag in the mouth and inhale the fumes ("huffing"). A simple but more toxic approach is to spray the substance directly into the oral cavity. Abusers can be identified by various telltale clues, including organic chemical odors on the breath or clothes, stains on the clothes or around the mouth, empty spray paint or solvent containers, and the presence of unusual paraphernalia. These telltale clues may point to a serious problem of solvent abuse, that may, in turn, lead to a serious health problem or death.

The bases for inhaling solvents are well described, as Sidney Cohen did a decade and a half ago (Cohen 1977). These substances are widely available, readily accessible, cheap, and legally obtained. As with other recreational substances they may make users temporarily forget their problems and relieve boredom—providing a quick high, with a rapid dissipation and a minimal hangover. Subjects who use heavily over short periods often complain of

Table 1. Chemicals commonly found in inhalants

Adhesives		
	Airplane glue	toluene, ethyl acetate
	Other glues	hexane, toluene, methyl chloride, acetone, methyl ethyl ketone, methyl butyl ketone
	Special cements	trichloroethylene, tetrachloroethylene
Aerosols		
	Spray paint	butane, propane (U.S.), fluorocarbons, toluene, hydrocarbons, ["Texas shoe shine," a spray containing toluene]
	Hair spray	butane, propane (U.S.), CFCs
	Deodorant; air freshener	butane, propane (U.S.), CFCs
	Analgesic spray	chlorofluorocarbons (CFCs)
	Asthma spray	chlorofluorocarbons (CFCs)
	Fabric spray	butane, trichloroethane
	PC cleaner	dimethyl ether, hydrofluorocarbons
Anesthetics		
	Gaseous	nitrous oxide
	Liquid	halothane, enflurane
	Local	ethyl chloride
Cleaning Agents		
	Dry cleaning	tetrachloroethylene, trichloroethane
	Spot remover	xylene, petroleum distillates, chlorohydrocarbons
	Degreaser	tetrachloroethylene, trichloroethane, trichloroethylene

Table 1. (Continued). Chemicals commonly found in inhalants

Solvents and Gases	
Nail polish remover	acetone, ethyl acetate
Paint remover	toluene, methylene chloride, methanol acetone, ethyl acetate
Paint thinner	petroleum distillates, esters, acetone
Correction fluid and thinner	trichloroethylene, trichloroethane
Fuel gas	butane, isopropane
Lighter	butane, isopropane
Fire extinguisher	bromochlorodifluoromethane
Food Products	
Whipped cream	nitrous oxide
Whippets	nitrous oxide
"Room Odorizers"	
Locker Room, Rush, Poppers	isoamyl, isobutyl, isopropyl or butyl nitrite (now illegal), cyclohexyl

headaches. Many solvent abusers, more than other drug users, are poor, come from broken homes, and do poorly in school (Korman et al. 1981; Oetting et al. 1988).

Oetting et al. (1988) have usefully categorized those who use inhalants into three groups: (1) inhalant-dependent adults, (2) polydrug users, and (3) young inhalant users. The first group will have the most serious health problems because they have used heavily for a long time; the last group will be those for whom treatment is most desirable to keep them from progressing to the first group and for whom there may be hope for successful intervention if caught in the early phases. Although all inhalant abusers use other drugs or alcohol, the first group predominately uses inhalants even though other drugs are available. The second group infrequently uses inhalants primarily in instances when they can not get their drug of choice; their problems will arise more from the use of other drugs and not be related to those discussed in this volume. The last group, young inhalant users, generally is in the experimentation period with solvents—having started with tobacco, alcohol, and possibly even marijuana as well as inhalants. Behavioral intervention is very important to dissuade members of this group from maturing into the first group.

One aspect of the inhalant abuse problem is often brought up but not answered to anyone's satisfaction. That is, why are certain specific substances inhaled? Some consider the odor to be important; others believe that the feeling one gets is most important. It is also difficult to say with certainty which substances are most preferred. Rankings of *ever-used* substances place glue and gasoline at the top (analysis of the National Household Survey data, 1991). Gasoline still topped the list upon analysis of *past-month-used,* which is followed by spray paint and other aerosols, nitrous oxide, correction fluid, and with glue being last. Additionally a Texas school survey (Fredlund et al. 1989) ranked correction fluids at the top with glue, gasoline, and spray paint being the next most frequent. A survey of delinquent children ranked paint sprays as the most frequently used substance (Fredlund et al. 1990) with nitrites also high on the list.

The now less-accessible fluorocarbons seem to be used very little (by general disclosures from the field and as per the Texas survey), possibly because they are available primarily only in the pressurized refrigerant replacement cans. However, there are still numerous deaths attributed to the abuse of fluorocarbons (Litovitz et al. 1990). The addictive nature of fluorocarbons is

exemplified by cases of asthma inhalers who inhale beyond the point of medication (Thompson et al. 1983). This is one of the few marketable forms of fluorocarbons in substances used by the general public other than the pressurized refrigerant refillers used for air conditioning systems. The United States banned the use of fluorocarbons as the propellant for most commercial applications at the onset of the 1980s because of the atmospheric pollution issue. There are new propellants being utilized in the anticipation that they will produce limited damage to the atmosphere (see Trochimowicz, this volume); however, little is known about their effects when used for recreational purposes. However, some of the new substitute fluorocarbons are singularly present without other ingredients in products used to clean contact points on electronic equipment. These products are apparently desirable to solvent abusers; this type of abuse has resulted in several reported deaths.

The more limited abuse of frying pan coaters today may suggest a lower desire for the butane and isopropane used by some inhalant abusers to replace the fluorocarbons. However, the abuse of butane lighter and other cooking gases here and in England (Anderson 1990, Ramsey et al. 1989; Mathew et al. 1989; Evans and Raistrick 1987*a,b;* Siegel and Wason 1990) refute that hypothesis. The availability of the pure gas in pressurized containers (such as lighters) nullifies the need for separating these gases from other substances in aerosols. It is indeed unusual that these very dangerous substances are inhaled, and it is hard to tell whether this is just a passing fancy or whether some really do like the dizzy effect they cause and will continue to use butane and propane gases. A recent report of deaths in the Cincinnati region (see Siegel and Wason's chapter, this volume) would indicate that the use of butane gas is a serious problem. The abuse of fuel gases, whether or not it will be a short-lived form of inhalant abuse, can be lethal (Siegel and Wason, this volume).

Evans and Raistrick (1987*a,b)* summarized a test group of sniffers' perceptions of butane gas vs. toluene. Moods, thoughts, hallucinations (except tactile), and colors appeared similar under both compounds; however, time passed slowly under butane and more rapidly under toluene. This one study would indicate that butane may be an acceptable substitute for one of the most widely abused substances—toluene—and will thus be a substance of concern. In an effort to reduce the undesired exposure to cooking gases, it is now mandatory to add thiols, a substance with an unpleasant aroma, to some portable gas containers such as propane tanks. It has also been suggested that

thiols be added to all forms of gas containers in a manner similar to that for the natural gas supply.

The bottom line is that a variety of substances are used, and the extent to which they are used may be based more on availability than individual preference. Yet, sniffers do seem to go out of their way to get their favorite, whether it is gold spray paint, whippets, lighter gas, "Texas shoe-shine" or another local or current favorite. All of these products, while apparently desirable to inhalant abusers, have resulted in deaths.

It is not the intent of this introduction to summarize the physiological, psychological, or social problems associated with this form of drug abuse; this information is provided and extensively discussed in the following chapters. One word of caution, however, to readers. Not all inhalants act alike. Some, for example, cause peripheral nerve damage (hexane) while others may act both centrally and peripherally (toluene, nitrous oxide) and others may not cause any irreversible neurological damage (butane, chlorofluorocarbons). Some solvents are toxic to the liver (chlorohydrocarbons) or kidneys (probably toluene). Only benzene has been associated with leukemia or oncogenic changes. Therefore, one should be very careful in globally stating that "inhalants" cause all of these medical sequelae. The fact that numerous exposures are necessary to cause any of these reactions can be reassuring to parents of youths "caught in the act." Time, however, will not be on the sniffer's side when overdose occurs and results in the rapid onset of death.

It is anticipated that this introduction will pave the way for the reader to more fully appreciate the in-depth discourse of the following chapters that enumerate our knowledge and ignorance of this subject. It is hoped that the reader will become more knowledgeable and thus be able to conduct further research and/or appropriate treatment that will help lead to a resolution of, and even more importantly prevent, the many tragedies surrounding inhalant abuse.

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Volatile Solvent Abuse: Trends And Patterns

Fred Beauvais

The study of the abuse of volatile solvents is hampered by a number of factors not usually found in the study of other drugs of abuse. Consequently, the quality of the research data is very uneven, and many contradictory findings appear in the literature. This chapter first discusses the problems encountered in this area of inquiry, then reviews the available data on the patterns, trends and distribution of volatile solvent abuse, and finally presents a series of recommendations for future research.

Definition and Terminology

Most drugs of abuse are grouped according to the effects experienced by users, and to a large extent, this is related to a specific biochemical action within the central or peripheral nervous system. For example, recent evidence has identified the euphoric and addictive effects of cocaine as emanating from disturbances in the neurotransmitter balance in certain midbrain areas, more specifically in the basic reward centers (Brown 1989). It is likely that methamphetamine has a very similar biochemical action, and thus, the clinical picture for its use and the use of cocaine could be similar. It is then useful to discuss both drugs as stimulants and to look for common factors in their use and consequences of use. In the same way, it is possible to categorize and discuss other categories of drugs, such as "downers," psychedelics, and tranquilizers, which have similar neurological activity.

The term "inhalants," however, has come to encompass a group of psychoactive chemicals that are defined by the route of administration rather than by their experienced effects or central nervous system (CNS) action. Thus, such diverse substances as toluene, ether, and the nitrites have been included under the rubric of inhalants because they are all taken in through the nose. This can lead to a great deal of confusion, since not only may the psychoactive properties be different, but the profiles of the typical users of the various substances are quite diverse. For example, it would be difficult to reconcile the motivational or behavioral pattern of a physician who chronically abuses anesthetics with that of a street huffer who is addicted to spray paint.

There is usually some understanding among those in the drug abuse field that the term "inhalant users" applies to those who use volatile commercial solvents. This convention, however, is not universal, and it is not unusual in the literature for anything that is sniffed or huffed to be considered an inhalant. The resulting discussion of epidemiological and clinical issues can only be ambiguous. The most common case of overinclusion occurs with amyl and butyl nitrites. These are very often considered the equivalent of industrial and household solvents and little distinction is made between the users of each type of substance. In a very large national data base collected over the past 3 years, we have been able to show significant differences between nitrite users and those who use common household solvents. (See Oetting and Beauvais [1990] for a description of the data base.)

The prevalence rates for nitrites and solvents for high school seniors are listed in table 1. Although it is apparent that some youths use both nitrites and solvents, the majority use only one or the other and are likely to differ on a number of important dimensions.

The lack of clarity as to what constitutes an inhalant leads to measurement problems in the assessment of incidence and prevalence rates. These problems arise from poor conceptualization of the questions included on surveys and from subsequent confusion on the part of the respondents. The inhalant question on the National High School Senior Drug Abuse Survey (Johnston et al. 1988), for instance, is broad enough to include the use of both solvents and nitrites, although nitrites are not specifically referenced in the question. From 1975 to 1979 this was the only question asking about drugs that are inhaled and was the sole basis for reporting inhalant rates. Subsequent to 1979

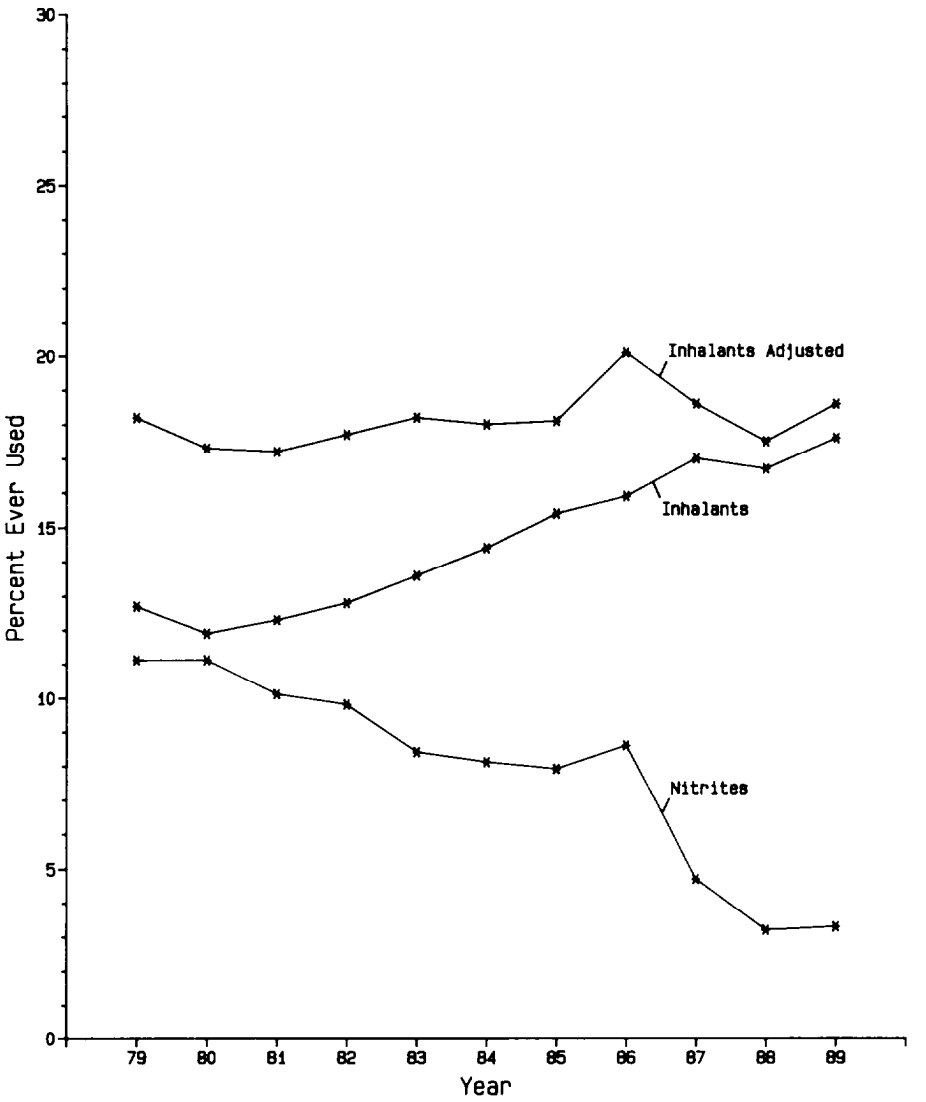
Table 1. Percentage of high school seniors (N=31,782) using volatile solvents, nitrites, and both substances.

	Ever used	Used in past 30 days	Used in past year
Volatile solvents	11.2	1.6	4.3
Nitrites	10.2	1.0	3.0
Both substances	4.8	0.3	1.0

a separate question was added asking about nitrites. Based on responses to this question the inhalant prevalence rates were adjusted upward. The reasoning on the part of the survey developers was that many students were not including nitrites when they responded to the inhalant question, so the inhalant question response rate needed upward adjustment. Obviously, these researchers consider inhalants to include nitrites. The net result is confusion when the long-term trends in inhalant use are examined—the unadjusted rates (including only volatile solvents) show gradual increases over time, but when adjusted for nitrite use, which their data show as decreasing, the long-term trends in inhalant use appear stable (figure 1). In combining solvents with nitrites (i.e., adjusting the solvent data), it appears that inhalant use has not changed over the past 13 years whereas, in fact, solvent use has steadily increased.

Poorly worded questions also lead to inaccurate results. Many surveys ask, "Have you ever inhaled anything to get high?" Without further qualification, many students will include the use of cocaine, powdered stimulants, or even the sniffing of heroin when responding to this question. The results are quite clearly confounded.

Figure 1. Lifetime prevalance for high school seniors for inhalants, inhalants adjusted, and nitrites



Adapted from Johnston et al. (1991)

Arriving at a Standard Definition

There have been several attempts to establish a convention regarding the nature of what constitutes inhalants. Beauvais and Oetting (1987) have argued that inhalant abuse should be restricted to the use of volatile solvents and should exclude the use of the nitrites and anesthetic gases. This is based on differences in both the neurochemical actions and the clinical profiles of the users of these three classes of substances. This convention is also followed in DSM-III-R, where the diagnoses "inhalant abuse" and "inhalant induced organic mental disorder" are restricted to the use of volatile solvents (American Psychiatric Association 1987). Abuse of nitrites and gaseous anesthetics is given a separate diagnosis.

The most consistent attempt to arrive at a common label was in the journal *Human Toxicology*. The entire July 1989 issue was devoted to various aspects of the abuse of volatile solvents. Throughout the issue, the term "volatile solvent abuse" (VSA) was used to denote the behavior. This not only provides a common terminology but also restricts the issue to solvents and excludes other psychoactive substances that are inhaled, in particular, the nitrites and anesthetic gases. This approach seems very reasonable as long as the label is used carefully and is not applied indiscriminately to all levels of solvent use. As is discussed later, it is very common for many young people to have a single episode, or a short period, of inhaling substances, and it would be inappropriate to refer to these as abuse. Perhaps another convention, "volatile solvent use," would be appropriate for these less severe patterns. As with any convention, there will be exceptions. Butane, chloroflourocarbon propellents, and certain forms of nitrous oxide have been used quite heavily in certain populations, and technically, they are not solvents. Because of their manner of use and the groups who use them, it would seem reasonable to classify people abusing these substances as volatile solvent abusers. There no doubt will be other exceptions in the future that will have to be considered on a case-by-case basis for classification.

Variability by Location

The use of volatile solvents is often characterized by short-term episodic patterns that occur in a school, community, or region. Periodically, a "new" solvent will be discovered by a small group of young people, and its use will quickly spread in a fashion very typical of teenage fads. The pattern of use for

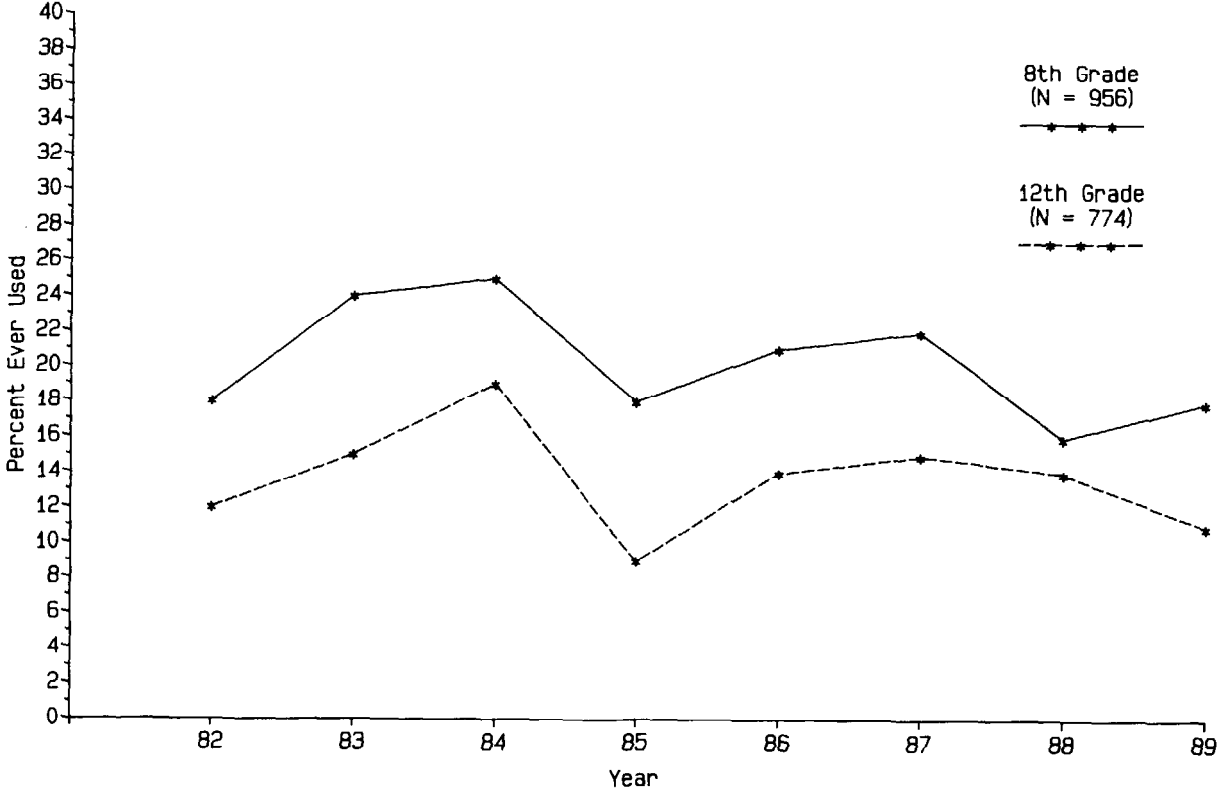
this substance will be widespread but not very heavy for any of the individuals involved. Just as abruptly, use will drop off and rates will return to low levels. While episodic patterns are noted for other drugs, they do not seem to be as dramatic as those patterns seen with solvents. The reasons for this are unclear, but they may be related to the unusual age period of solvent use, which is discussed below.

An example of an episodic pattern is presented in figure 2. These data come from a western U.S. community where drug use data have been available annually since 1982. For both grades (an aggregated sample of three high schools and six junior high schools) solvent use increased through 1984, followed by a sharp decrease in 1985 and then an increase for the next 2 years.

The important pattern here is the decrease from 1984 to 1985. For the 12th graders, the rate dropped by over one half. A number of methodological reasons for this were explored, including the wording and placement of the items on the survey from year to year. After this examination, however, the pattern still seems valid. As a further indication of validity, the age of first use of solvents for the various cohorts differed, suggesting that the factors influencing use had in fact varied from year to year. Large variations from year to year (i.e., from class to class) might be expected if the data were restricted to one school. In this instance, however, data from several schools were aggregated, and the lifetime prevalence rates for the other drugs asked about on the survey did not fluctuate. This suggests that attitudes toward solvents can shift very quickly and that information regarding acceptability or sanctions is rapidly communicated among youths.

This episodic pattern has important implications for the generalizability of survey results, especially in studies that are very local in nature. If a survey is conducted at the high point of an episode, it may lead to the conclusion that a massive intervention is needed. While it may not be wise to ignore the problem, it is equally inappropriate to overreact and not let the outbreak take its normal course. One of the problems with an overreaction is the possibility that the use of solvents could actually be exacerbated. Brecher (1972, p. 327) made this point 20 years ago in his description, "How To Start an Epidemic." In this analysis he felt that the extensive publicity given to a small outbreak of solvent use caused it to spread far beyond where it could have normally been contained. Many young people who were not aware that solvents could produce a euphoric effect learned the behavior through prevention activities.

Figure 2. Trends in lifetime prevalence of volatile solvent use among 8th and 12th graders in a western U.S. school district



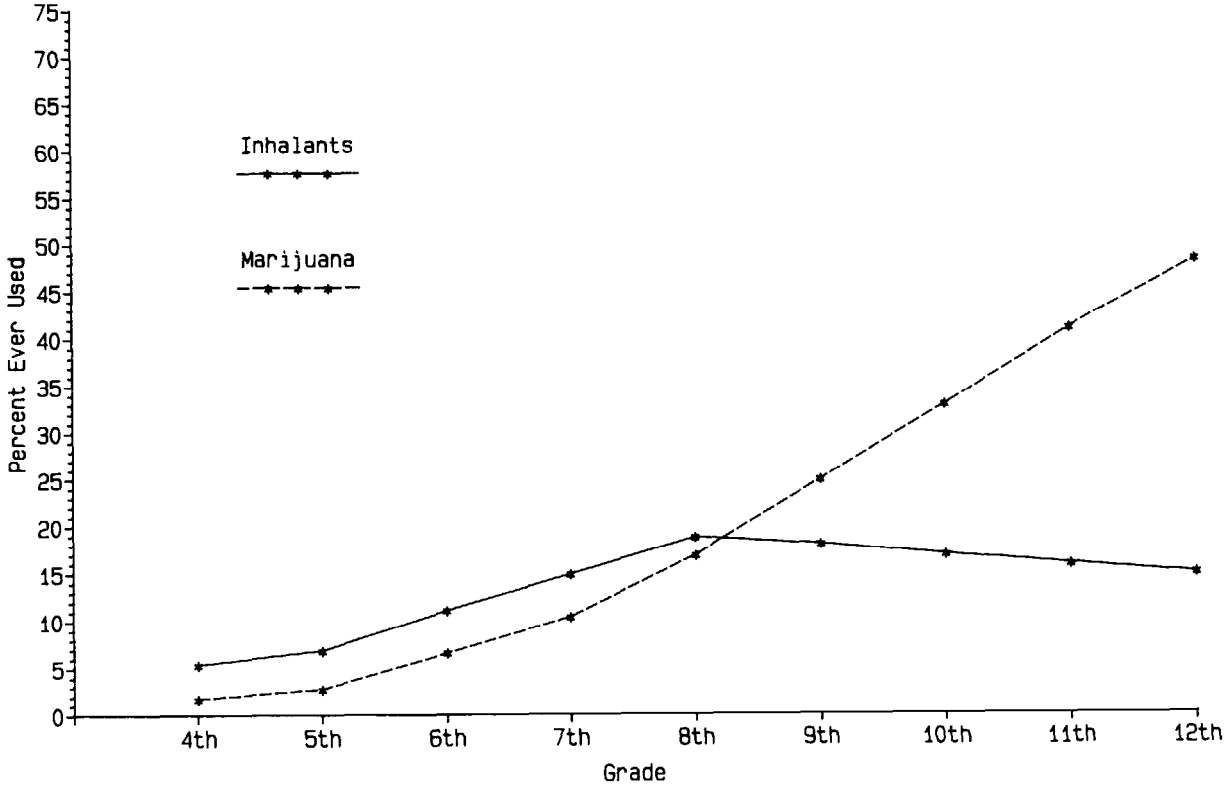
Another pattern that commonly occurs with volatile solvent abuse is localized endemics. Once again, the reasons for this are not known but may be related to isolation, availability, or simply a behavior that has few sanctions and that becomes entrenched in certain areas. Once established, the pattern is passed on from older to younger children. There is even a more insidious, intergenerational pattern consisting of parents teaching their children to use solvents as a means of making them more docile and tractable. (To date these reports are anecdotal and need more exploration.) If a survey happens to be conducted in one of these areas and high rates of solvent use are found, care must be taken to avoid erroneous generalization. As an example, a study over a decade ago in a Los Angeles barrio found that Hispanic children had rates of solvent use 14 times that found for Anglo youths (Padilla et al. 1979). Several subsequent studies in inner-city barrios reported similar findings, and it became well accepted that solvent abuse was a particularly serious problem among Hispanics. More recent studies, however, have sampled Hispanic youths in other geographic contexts and have not found these high rates (Oetting and Beauvais 1990). It appears that the rates for Hispanics may be a function of socioeconomic conditions, and as those conditions vary, so will the levels of solvent use. Hispanic youths in poor barrio environments may use solvents heavily, but Hispanic youths in less stressful environments do not.

Age Patterns of Solvent Use

Typically, lifetime prevalence rates for drug use increase with age throughout adolescence, peaking in late adolescence and then leveling off in young adulthood. The marijuana data in figure 3 illustrate this pattern. Current use of drugs, as measured by past 30 day prevalence, follows a similar pattern except that it tends to become lower as people move into young adulthood. Lifetime prevalence of solvent use has a peculiar pattern in that it peaks around age 13 and then drops off.

If a sample remains intact over a period of time, the lifetime prevalence should never decrease as age increases. A person may stop using a drug, but when asked whether they had ever used it, the answer should always be "yes," even though that use may have taken place many years before. Something unusual, then, must be happening with solvents. One possibility is that with school-based surveys, many of those younger students who admitted to solvent use are no longer around by the upper high school years and thus are not surveyed—that is, they have dropped out of school. This seems plausible

Figure 3. Lifetime prevalence by grade for inhalants and marijuana



since a great deal of research has shown that solvent abusers are a fairly dysfunctional group with a wide range of psychological and social problems that would include poor school adjustment and dropping out. (See Oetting and Webb in this volume.) Our laboratory has preliminary data which suggest that the dropout phenomenon is significant in accounting for the unusual lifetime prevalence pattern. In a project to assess drug use among school dropouts, we found that they have rates of solvent use much higher than two control groups. In this large-scale study, dropouts reported lifetime prevalence of 41 percent, while an in-school group defined as being at high risk of dropping out reported rates of 40 percent and the "normal" control group of students not at risk reported a rate of only 21 percent.

Another possible explanation for the dropoff in lifetime prevalence has to do with the differential perception of solvents by older and younger adolescents. Solvents may be seen as "kid" drugs, and older students who have had experience with other, more socially accepted, drugs may be unwilling to admit to the use of solvents—i.e., this is not seen as "sophisticated" behavior. A related factor may be the relative salience of solvent use at different age levels. An eighth grader who has recently had an episode or two of solvent use may have a clear memory of this and perceive those incidents as drug use. Four years later, however, the student may have totally forgotten the experience or may dismiss it as being unimportant in the context of a drug use survey.

Regardless of the reasons for the unusual age pattern for solvent use, it has important implications for determining the actual rates of use in a population and for making comparisons between populations. First, if an accurate measure of total exposure to solvents is needed, the measurement should be taken at the age of highest use; for solvents, that would be around age 13, but for marijuana, 17 to 18 would be more appropriate. Second, if one were to compare older students in one location with younger students in another, it would be wrong to conclude that the latter location had higher rates of solvent use since, in fact, the reported rates would probably decrease if older students in this group were queried.

Gender Patterns

The rates of solvent use for males and females have been converging over the past 20 years. In 1973 Cohen estimated that 10 times more males than females were involved with solvents. In a general review of this issue several

years later, Korman (1977) put the ratio at 3:1. One of the problems in making these types of estimates is in specifying the population being assessed. For example, it is possible that males who use inhalants are more frequently apprehended by the police than are females. Therefore, there would appear to be a discrepancy in use rates between the genders among police-involved youths. However, the picture in the general population is quite different. In 1988 the National High School Senior Survey reported lifetime prevalence rates of 19.5 percent and 14 percent for males and females, respectively (Johnston et al. 1989), while the 1988 National Household Survey of 12- to 17-year-olds reported rates of 9.2 percent and 8.3 percent (National Household Survey 1990).

Similar gender patterns, with males having only slightly higher rates of use were confirmed in large-scale surveys conducted in New York State (Frank et al. 1988) and in Texas (Fredlund et al. 1989). Interestingly, the ratio of males to females among the older National Household Survey group (i.e., 18- to 25-year-olds) was higher for all prevalence categories at nearly 2:1, suggesting that males continue use into adulthood much more than females.

One of the most comprehensive surveys of Hispanics, the HHANES survey (NIDA 1987), has shown that Mexican-American males are three times more likely than females to use solvents at any level and Cuban American males twice as likely. Rates for Hispanics in general are lower than those for Anglos.

In a study of American Indian adolescents, Beauvais, Oetting, and Edwards (1985) found nearly identical lifetime prevalence rates for males and females (31.8 percent vs. 32.9 percent) but surprisingly higher 30-day prevalence rates for females (9.1 percent vs. 7.6 percent).

The literature contains no data on gender differences for other United States ethnic groups. While the data from other countries are generally too sparse to interpret gender patterns, there is a tendency toward slightly higher use among males (Navaratnam, V.; Edmonson, K.; Smart, R.G.; Medina-Mora, E.; and Uchtenhagen, A.: Epidemiology section in Arif et al. 1988).

In general, it appears that females experience a little more protection from the use of solvents. This is consistent with the conclusion by Johnston and his colleagues with respect to drug use in general among U.S. adolescents and young adults: “Males are more likely to use most illicit drugs, and the

differences tend to be largest at the higher frequency levels" (1989, p. 11). However, they go on to say, "Insofar as there have been differential trends for the two sexes among any of these populations, they have been in the direction of a diminution of differences between the sexes" (p. 11).

Use of Other Drugs

It is common for volatile solvent users at any age or of any pattern of use to also use other drugs (Edeh 1989; Oetting et al. 1988, Crites and Schuckitt 1979). Exclusive use of solvents is rare. Young children who begin to use volatile solvents will also start experimenting with other drugs, usually alcohol and marijuana. Adolescent solvent abusers are typically polydrug users and are prone to use whatever is available, although they do show a preference for solvents. Adult solvent abusers also use a variety of chemicals although their tendency is to concentrate on volatile solvents and alcohol. There is some evidence that many adult users of heroin were once heavy solvent users, which is further confirmation that solvent abusers represent a particularly deviant group (D'Amanda et al. 1977). Little is known about adult patterns, and a great deal more research is necessary before they can be accurately characterized.

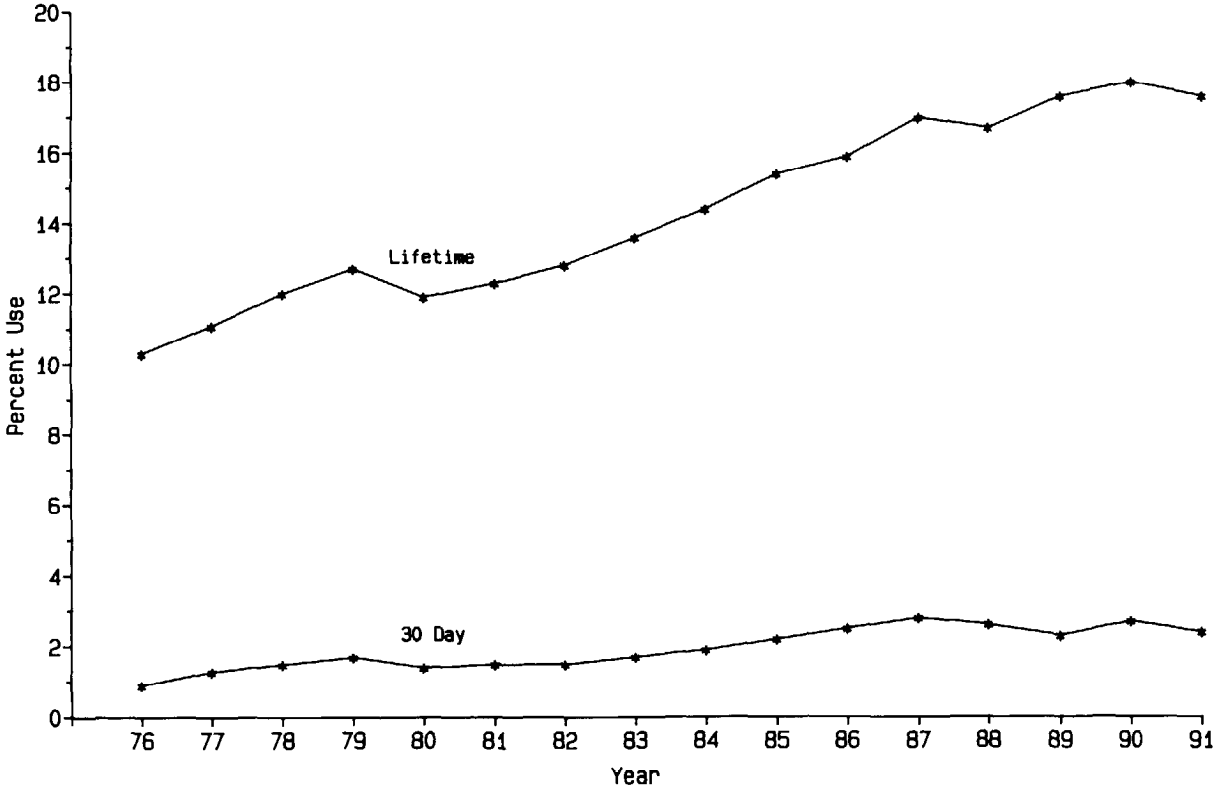
Trends in Solvent Use Prevalence Rates

There are only a few places where rates of solvent use have been accurately tracked over time, and by far the majority of studies have focused on adolescents. Although there seems to be general agreement that rates have increased worldwide over the past 20 years, the evidence for this is mostly anecdotal and may, in part, be a function of increased awareness and detection. In looking at the various studies, the lack of clarity of definition discussed above must be kept in mind.

United States

The most complete record at a national level comes from the National High School Senior Survey in the United States, which has been in progress since 1975 (Johnston et al. 1991; Most forms of drug use decline, NIDA 1992*a)*. Figure 4 shows the results for lifetime and past 30-day prevalence of solvent use for U.S. high school seniors since 1976. In both categories, use has been

Figure 4. Trends in lifetime prevalence (ever used) and use in past 30 days of volatile solvents for high school seniors in the United States



gradually increasing, although there is some indication that the rates may have leveled off in the past 2 years. The number of students using currently (i.e., within the past 30 days) is not exceptionally high. The 2.4 percent 30-day solvent rate for 1991 compares with 54.0 percent for alcohol, 13.8 percent for marijuana, and 1.4 percent for cocaine.

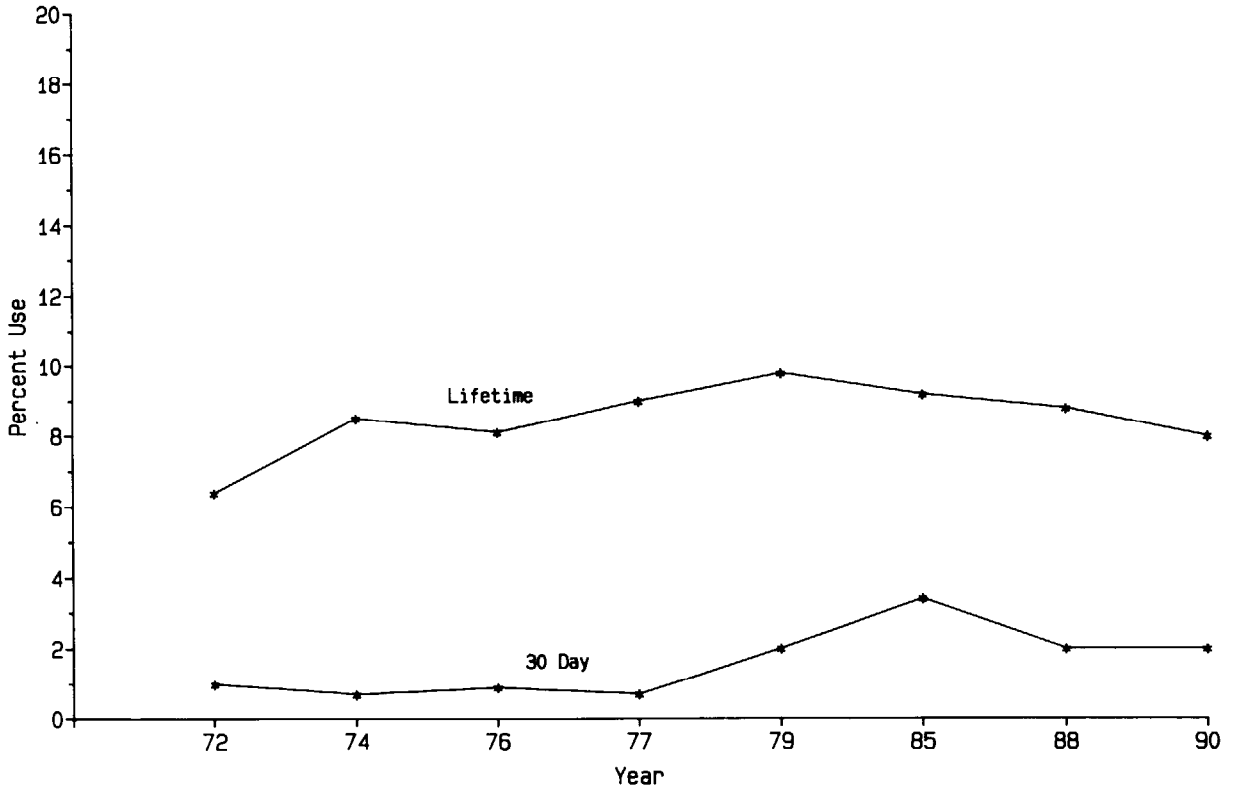
The pattern of increasing use of solvents is confirmed in a series of studies by Frank et a1. (1988) in New York State and Fredlund et al. (1989) in Texas. Since 1975, Frank et al. have found a quadrupling of solvent use rates (both lifetime and 30-day prevalence) among the State's high school students, while even more dramatic increases were found in the Texas study.

It is important to recognize that the trend toward the increasing use of solvents in school populations is in sharp contrast to the trends for other drugs. The National High School Senior Survey has shown substantial reductions in both lifetime and 30-day prevalence for nearly all drugs of abuse since 1981. It is quite possible that with increasing sanctions for other drugs and the relative lack of attention paid to solvents, youths are substituting solvents for other drugs.

The National High School Senior Survey results do not provide data for youths who are not in school or for younger children. Data are available for these groups in the United States from the biennial National Household Survey on Drug Use given since 1972 (NIDA 1990, 1991, 1992*b;* USDHHS press release 1990). The lifetime and 30-day prevalence rates are shown in figure 5. The pattern here is for increasing use through 1979, with essentially unchanged levels since then. The lifetime prevalence rates have been around 8 percent for the past decade. These results are not directly comparable with the National High School Senior Survey due to methodological differences; however, they show about the same order of magnitude of use. The lower rates for the National Household Survey are expected since these data are averaged for all 12- to 17-year-olds. It appears from both sets of data that a plateau in lifetime prevalence may have been reached, although it will take a couple of more years with the senior data to be more certain.

The peculiar age pattern for solvents, with higher use being reported at the younger ages, is not found in the National Household Survey. This survey reports data for four separate age groups, 12-17, 18-25, 26-34, and over 34. The lifetime prevalence rates for these groups in the 1988 survey were 8.8

Figure 5. Trends in lifetime prevalence (ever used) and use in past 30 days of volatile solvents for 12- to 17-year-olds in the United States



percent, 12.5 percent, 9.8 percent and 1.8 percent respectively. Thirty-day prevalence rates showed the same pattern. These data suggest a pattern similar to other drugs, with peak rates in the young adult groups. However, it must be kept in mind that the National Household Survey includes dropouts who likely have higher rates of use, and perhaps equally important, the solvent question specifically includes nitrites. The latter drugs have an older age of first use and may well be inflating the volatile solvent figures at the older ages. Once again, the lack of clarity in the definition of inhalants creates difficulties in interpretation of trends.

Minority Populations (United States)

Table 2 presents the lifetime prevalence rates of solvent use among minority U.S. high school seniors. While the table shows only lifetime prevalence rates, this statistic is the most stable across different surveys and allows an accurate comparison among groups. The Black American and Anglo samples are from the National High School Senior Survey (Johnston et al. 1987) while the two Hispanic-American samples and the American Indian samples are from two NIDA-sponsored projects currently in progress (Oetting and Beauvais 1990). The Indian and Hispanic-American studies are comprehensive for these groups and represent a highly reliable estimate of use in these populations. In the western Hispanic samples, the students were allowed to list their own ethnicity, with the majority calling themselves Mexican American and the others, Spanish American. **A** good part of this distinction comes from a historical pattern in which a subsample of the Hispanic people of the Southwest trace their heritage back several centuries to the original settlers of this region. These settlers came directly from Spain; thus they refer to themselves as Spanish-American. The more recent Hispanic-Americans of the area arrived from Mexico.

Table 2. Lifetime Prevalence of Solvent Use in Minority Populations

Anglo	African American	American Indian	Mexican American	Spanish American
(N=11,713)	(N=1,649)	(N=325)	(N=1,512)	(N=446)
17%	8%	17%	12%	16%

The highest rates of solvent use occured among Anglo and American Indian seniors, with the lowest rates found among blacks. The rates for Mexican-American youths were in between. This was the same basic pattern found in New York State (Frank et al. 1988) and Texas (Fredlund et al. 1989). While data on current use, that is use within the past 30 days, are not available, it is likely that these rates would occur in the same relative order among the various ethnic groups.

These findings are at variance with the commonly held belief that minority youths, particularly Mexican Americans, are at exceptionally high risk for solvent use. Since the data in table 2 are taken from school-based surveys, they are vulnerable to bias from excluding school dropouts. On the assumption that minorities have higher school dropout rates, we might expect that rates for these populations might be higher than those in table 2, and perhaps even higher than for Anglos. Arguing in favor of the lower rates for Hispanics, however, are data from the National Household Survey (1987) showing that Hispanic Americans at all ages had lower rates than Anglos and the HHANES survey (NIDA 1987) showing that Mexican Americans, specifically, had lower rates. The National Household Survey also confirmed the low rates for blacks.

Table 2 also shows the importance of accurately defining minority groups and not aggregating populations that may show important differences. Note the difference in prevalence rates for Mexican-American and Spanish-American seniors. Spanish Americans are very similar to their Anglo counterparts in contrast to the lower rates for Mexican Americans. If these two populations had been aggregated under the label "Hispanic American," potentially important information would have been lost. The significance of this pattern is unclear at this point, but the higher rates of use for Spanish Americans may well be related to their longer tenure in the United States, during which they have become more integrated into the Anglo culture and have adopted many of the behaviors, including similar rates of drug use. In fact, when all drugs are considered, Spanish-American youths are very similar in pattern to Anglo youths, whereas Mexican American youths show lower rates.

The picture for American Indians is different. While table 2 shows similar rates for Indian and Anglo seniors, other data show that Indian youths at other grade levels have much higher rates of solvent use. Beauvais et al. (1985) reported that 12- to 18-year-old Indian students had rates of solvent

use three times higher than those found for Anglo youths in the National Household Survey. This, however, was not the best comparison, since the methodology of the two surveys was quite different. More recent data are available that compare the two groups on similar surveys conducted in schools. (These are unpublished preliminary results from our ongoing studies.) These rates by grade are reported in table 3; it is clear that the Indian students at all grades are reporting higher lifetime prevalence rates. It is quite possible that the discrepancies for Indian youths between tables 2 and 3 are a function of higher school dropout rates among Indian youths.

Smart (1988) examined the available evidence regarding solvent use among Canadian Indians, and while use varied greatly from one community to the next, many Canadian Native bands appear to have a significant problem. In a number of instances, surveys of youths revealed that 50 percent or more could be classified as current sniffers. In examining the differences in conditions among the various communities, Smart concluded that the high rates were associated with extremely poor socioeconomic conditions and a very rapid rate of cultural change.

In summary, it appears that the findings of higher rates of solvent use for Hispanic Americans do not hold up when general population surveys are done, but that, indeed, Indian youths are more vulnerable to the use of solvents. One can only speculate on the reasons, but they may well be related to socioeconomic factors, which have been shown to influence the levels of solvent use in a population. (See Oetting and Webb in this volume for a discussion of these factors.) The previous studies on Hispanic Americans,

Table 3. Lifetime prevalence of solvent use by grade for American Indian and Anglo youths in U.S. schools.

	Grade in School					
	7	8	9	10	11	12
Indian	22.2	31.0	25.8	20.6	20.2	16.6
Anglo	14.9	18.8	18.0	16.9	15.9	14.9

showing high rates of use (e.g., Padilla et al. 1979) were conducted in impoverished areas where there was a great deal of social dysfunction. Not all Hispanic youths live in disadvantaged environments, and thus, as a group, are not subjected to the types of conditions that spawn the use of solvents. Indian populations, on the other hand, are more generally disadvantaged and may thus have higher rates of solvent use. Black youths appear to have the lowest rates of use while data on other United States minorities are too sparse to draw strong conclusions.

Trends in Other Countries

Three Canadian studies show possibly conflicting trends; however, they cover three different periods and were conducted in separate provinces (Smart 1988). One of the two earlier studies, covering 1970 to 1982, showed significant increases among 8th to 12th graders, while the other study during approximately the same time showed little or no increase. The most comprehensive study of this age group, although restricted to Ontario province, revealed some variance from year to year since 1977 in solvent use, but with a generally decreasing pattern. The annual prevalence rates were in the range of 2 percent to 5 percent.

Medina-Mora and Ortiz (1988) reported on more than two dozen studies done in Mexico since 1972 that covered general population, school, and special population samples (e.g., youths in treatment, street youths). The methodological differences make comparisons difficult, but it is evident that solvent use is quite low among school youths but exceptionally high among treatment and special populations and that use has increased since 1972. Given that only a minority of adolescents attend school in Mexico, and that most youths are at high risk, the authors concluded, "Solvent use is the main drug problem in Mexico" (p.166).

Research in the remainder of Latin America is quite disparate, making comparisons and the assessment of trends difficult. A review by Medina-Mora (1988) led to conclusions similar to those found in Mexico, with the higher rates of solvent use, by far, found among street and special populations. These conclusions were strongly mirrored in two studies in Brazil (Carlini-Cotrim and Carlini 1988*a,* 1988*b).* In the first of these studies, a sample of low socioeconomic students had solvent use rates of 24 percent for lifetime use and 5 percent for the past 30 days. The second study was of destitute

street youths, and the lifetime and 30-day rates for this group were 78 percent and 58 percent. Most importantly, nearly one third of these youths reported daily use.

The Latin American studies illustrate the difficulty in making sense of world-wide patterns and trends in solvent use. The age groups that are surveyed vary widely, the surveys themselves are not comparable, and the socioeconomic conditions of the groups studied are quite diverse.

Outside the Americas, the data become even more difficult to compare. Ramsey et al. (1989) reviewed a number of survey studies in the United Kingdom and concluded:

> Though it is generally acknowledged that the practice waxes and wanes in any particular area, it seems safe to conclude that somewhere between 3.5 and 10 percent of young people in the UK have at least experimented with VSA and that current users comprise some 0.5-1 percent of the secondary school population. (p. 262)

Although the survey data give no indication of trends in use, Ramsey et al. reported a dramatic increase in deaths due to solvent abuse. The numbers ranged from 2 deaths in 1971 to 111 deaths in 1987. It is unclear, however, how much of this increase is due to more accurate detection and increased reporting.

Data from Europe are usually limited to local studies, although there is some indication of a moderate epidemic of use in northern Europe in the 1960s and 1970s that has since subsided (Uchtenhagen 1988). A recent review, however, hints at another slight upsurge (Vaille 1988). In Southern Europe the rates have been extremely low, with one report from Spain showing a 0.11 percent 30-day prevalence rate for school children (Alvarez et al. 1989).

With the exception of Australia, where the pattern of use compares with Western industrialized countries, the use of volatile solvents in other parts of the world is a relatively new phenomenon (Navaratnam 1988). Use continues to be particularly troublesome among Australian aborigines, and there may be an emerging problem in Japan, where 40,000 arrests per year are recorded for solvent-related offenses (Tamura 1989).

If any sense can be made of the international scene, it is that solvent use became known in the early 1970s and appears to be increasing (with the exception of Europe). Most use occurs among children and adolescents, local epidemics are common, and solvents are typically between the third and fifth most common drug used by youths (Arif et al. 1988).

Solvent Use Among Adults

Although solvent use is generally seen as an adolescent phenomena, it must be recognized that some use extends into adulthood (Hershey 1982; Streicher et al. 1981). In the United States, the National Household Survey reports fairly high lifetime prevalence rates in the 18- to 34-year-old range, but current use in this group is very low at around 0.5 percent (National Household Survey 1990). It is generally felt that solvent use in adulthood is indicative of highly dysfunctional individuals and occurs when other drugs are not available. There are also anecdotal reports of isolated instances in which groups of adults have developed a pattern of solvent use that is extremely heavy and seems to have become endemic in that population. Adult use of solvents is an extremely underresearched problem and is deserving of much more attention. The highly deviant nature of these groups and their marginal living arrangements will make this work difficult.

The other adult pattern of solvent use occurs in industry, where workers come into contact with a wide range of commercial solvents (Parker 1989). Most of the concern in industrial settings is for workers who are inadvertently exposed to solvents, but it is also recognized that a small percentage of workers will seek out opportunities for inhaling chemicals in doses far above what is normally present in the work setting. It is likely that these people are also involved with other drugs and see this as one more opportunity for intoxication.

Conclusions And Recommendations

The state of knowledge regarding the epidemiology of volatile solvent use lags behind that of other drugs. This in part stems from lack of clarity in the definition of what are usually referred to as "inhalants." Another reason for the sparsity of data may lie in the relatively low rates of volatile solvent use when compared to other drugs, leading most researchers to focus on drugs with higher prevalence patterns. Other chapters in this volume describe the high levels and wide range of dysfunction found among volatile solvent abusers,

and it may well be that the research community would rather concentrate on populations with a higher probability for reduction in drug use. Solvents lack the glamour of other drugs and do not get the attention in the papers and news magazines afforded drugs such as crack, leaving many researchers reluctant to work in the backwaters of drug abuse.

The following recommendations derive from an assessment of the current state of research and the clear need for more precise data.

- Long-term surveillance is needed to detect and monitor trends and patterns of volatile solvent use and abuse.

While long-term trend data may be available for certain general populations, subpopulations may have different, and important, trends and patterns that indicate a need for special interventions and investigation. For instance, there is a strong indication that school dropouts and certain socioeconomic status groups are at high risk for volatile substance abuse.

Surveillance systems, other than general population surveys, are needed to assess the levels of solvent abuse in high-risk groups. It is well known that volatile substance abuse is more prevalent in marginal groups, which may not be easily accessible by the usual methods of field research. For example, monitoring emergency room admissions in public hospitals could give a more accurate picture of volatile substance abuse in a population. Alternately, longitudinal studies of potential school dropouts (i.e., those experiencing academic problems early in school) could be useful in determining the pattern of onset of volatile substance abuse.

It should be noted that basic epidemiology is the starting point for further investigative studies (see Oetting and Webb, this volume), and without this type of data for both general and special populations, it is difficult to establish a meaningful research agenda. Solid epidemiological data would also help focus attention on solvent abuse, leading to increased resources for further studies and interventions.

- Cross-national and cross-cultural studies, using comparable methodologies, would be useful in detecting conditions leading to use or nonuse of solvents.

It is clear that there are countries, or regions, of the world, in which solvent use is rare or may be declining. Analysis of the socioeconomic, political, or

other population variables in these locations could reveal factors that protect people from the use of solvents. The need for methodological consistency is obvious.

Studies of minority or ethnic populations should be designed to avoid broad labels that may obscure important differences among subgroups. For instance, in studies of Hispanic populations in the United States, it is important to distinguish between Mexican Americans, Spanish Americans, Cubans, Puerto Ricans, and other Latinos from Central and South America. Existing data show that there are significant differences between these groups in drug use behavior. Cognizance of these types of distinctions will lead to more precise and usable information.

- A common terminology is needed for what is meant by "inhalant abuse."

The lack of such conventions has hampered research in this field and has led to conflicting findings. It is recommended that the term "volatile substance abuse" be reserved for abuse of industrial solvents, or alternately, substances containing volatile hydrocarbons and that the use of other substances that are inhaled be excluded from this category (e.g., nitrites, anesthetics, and powdered stimulants that are used intranasally). The term "volatile solvent use" should be used for less serious patterns that do not lead to physiological or behavioral problems (e.g., patterns of experimentation or brief episodic use).

- More information is needed on the nature of episodic outbreaks of solvent use.

Although the majority of users during these outbreaks are not at risk, little is known about the possible effect on vulnerable individuals. Do outbreaks lead to volatile substance abuse for certain people where it otherwise would not have occurred? What are the dynamics of episodic patterns? How is knowledge of use and use itself transmitted? Does publicizing an outbreak lead to more widespread use? How can outbreaks be managed without exacerbation of the problem?

- What types of solvents are most commonly used?

Current research does not adequately assess the preference for different types of solvents. Knowledge in this regard could be helpful in determining the motivations to use solvents and could also be used to guide commercial regulation of the more popular or dangerous substances.

- More data are needed on the economic factors associated with higher population rates of volatile substance abuse.

The literature is very consistent in identifying poor economic conditions as being strongly correlated with higher levels of volatile substance abuse. However, the dimensions of poverty leading to use are unclear. Are solvents used because they are cheap and thus more available than other drugs? Is there a specific level of poverty associated with volatile substance abuse? Is there less stigma attached to volatile substance abuse in poor communities by community members? Do the law enforcement, health, and social service systems apply fewer sanctions against solvents in poorer communities? Since volatile substance abuse can also occur at any socioeconomic level, is use in poorer communities linked to the secondary effects of poverty, such as family dysfunction, which can also occur at higher socioeconomic levels?

- Most of the information available on prevalence rates is for adolescents. More data on adult patterns of use are needed.

With the exception of the National Household Survey in the United States, most of the data for adults is anecdotal, and adult use may be seriously underestimated. It is likely that adults who engage in volatile substance abuse are highly dysfunctional and are a difficult group to access and study, thus requiring substantial research monies.

- Knowledge of the relationship between levels of volatile substance abuse and social policy would be useful in assessing potential deterrents.

There is little consistency in national, State, and local laws regarding the use or sale of volatile solvents. While this may be an unfortunate situation in some respects, it does present the opportunity to study prevalence rates under various legal conditions. This may help in establishing policy consistent with lower levels of use.

- The distinct age pattern displayed by solvent use needs a more complete exploration.

Several explanations have been presented for why solvent use peaks at an earlier age than other drugs of abuse. However, these explanations are speculative and require more study. This is an instance where comparative studies across different populations could be useful, since age of onset is probably related to varying patterns of social control.

- Ethnographic studies of volatile solvent abusers would be helpful in designing more precise epidemiological studies.

Volatile solvent abuse is characterized by a number of anomalies when compared to other drugs of abuse. In particular, heavy users appear to be highly alienated from society, making a good deal of information inaccessible. Knowledge of their values, beliefs, routines, and the consequences of their solvent use would be valuable information in conducting accurate epidemiological studies.

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Epidemiology of Volatile Solvent Abuse: The Texas Experience

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Beauvais' synthesis of the epidemiology of volatile substance abuse highlights two conceptual distinctions critical for understanding patterns of inhalant use. The first differentiates volatile solvent abuse from that of nitrites and anesthetic gases. The second distinguishes acute volatile solvent abusers and chronic volatile solvent abusers.

Beauvais argues that it is a mistake to lump volatile solvent abuse and nitrite abuse in a single category, inhalant abuse. The two groups of substances have disparate pharmacological properties and are used by people with dissimilar socio-demographic characteristics and motivations. One of the primary goals of epidemiological research is to understand the process of substance abuse. When pharmacological characteristics, social settings, demographics, and motivations are different, the underlying process is also likely to be different. Yet the two primary sources of national information on substance use (the National High School Senior Drug Abuse Survey [Johnson et al. 1991] and the National Household Survey on Drug Abuse [NIDA 1992]) report a prevalence of inhalant use that subsumes volatile solvent abuse, nitrite abuse and anesthetic gas abuse.

The reporting protocols used in these surveys have tremendous influence on the choices made by investigators who research the epidemiology of substance

use. When we designed the Texas School Survey in 1988 (Fredlund et al. 1989), the first question asked was, "How can we produce information comparable to national data?" Such comparability was a consideration at every stage of the survey process from the selection of questions through protocols, including the decision to report the prevalence of inhalant use. Fortunately, the use of several additional questions enabled the differentiation of volatile solvent abuse from nitrite abuse.

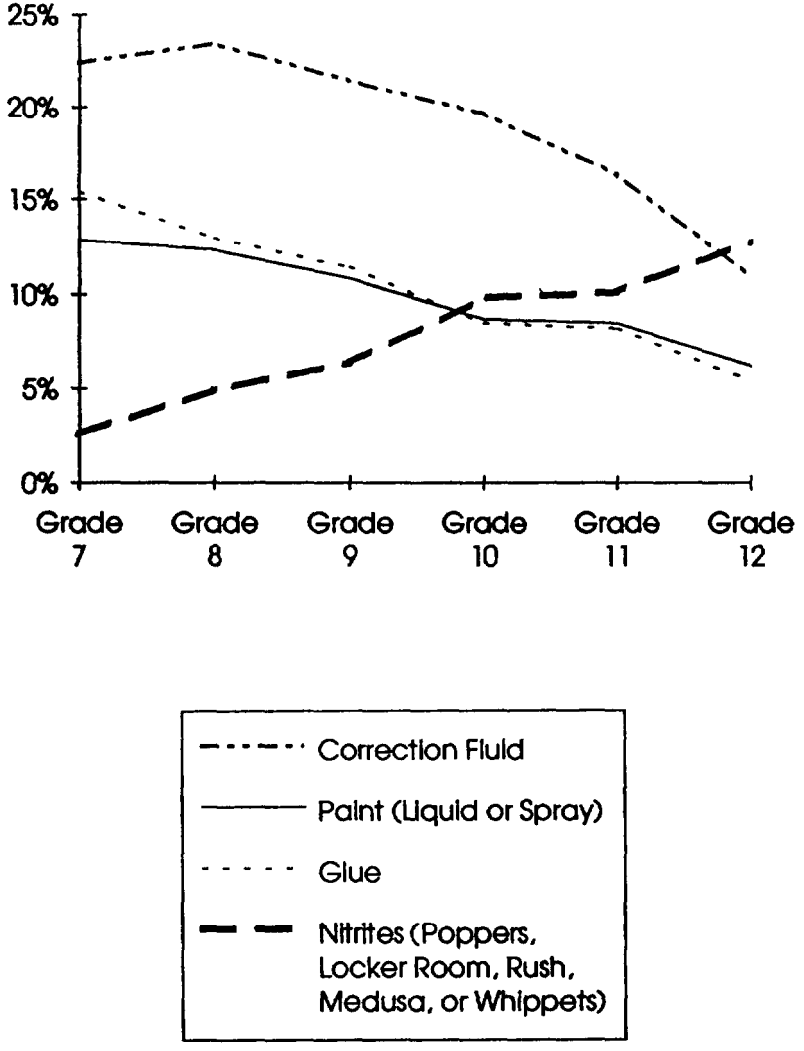
These Texas School Survey results clearly illustrate that students who primarily use volatile solvents are different from those who use nitrites. In 1988, younger students were more likely to report experience with volatile solvents than older students, and older students were more likely to report experience with nitrites than younger students (figure 1). Very few students reported experience with both volatile solvents and nitrites, which established that different substances tend to be used by students at distinct periods in their development. Moreover, similar age patterns of use were reported in 1990 (1990 Texas School Survey), building the case that these age patterns of use tend to persist through time.

One justification for combining nitrite use and solvent use under a single taxon might be that the users themselves call both these respective activities inhalant use. If this is true, one might argue that it is convenient to ask questions about inhalant use because the number of products that can be abused by sniffing (inhaling through the nose) or huffing (inhaling through the mouth) is very large. It is not practical to ask questions about every abused product. However, many who sniff or huff chemical substances for purposes of getting high have no idea they are using inhalants.

The 1990 Texas School Surveys included questions about the following substances students sometimes sniff or huff to get high:

Liquid or spray paint
Correction fluid or liquid paper
Gasoline
Freon
Shoe shine, Texas Shine
Glue
Paint thinner, toluene, other solvents
Other sprays (Pam, hair spray, etc.)

Figure 1. Lifetime prevalance of use of nitrites, correction fluid, glue, and paint by grade of respondent: The 1988 Texas school survey



Poppers, Locker Room, Rush, Medusa,
or whippets
Other inhalants

The question included an explanation that huffing or sniffing these things for purposes of getting high is called inhalant use. In 1990, 24 percent of seventh graders admitted using one or more of the substances listed above. Yet of the self-admitted users, one-half denied ever using inhalants when a general question about inhalant use was asked on the next page of the survey. The term "inhalant" is apparently not part of the lexicon of a significant proportion of those who abuse such substances.

These observations and experiences lead me to endorse Beauvais' call for a common definition of inhalant use, one that explicitly differentiates volatile solvent abuse from nitrite abuse. But in doing so, we must be careful not to throw out the baby, with the bath water. A significant number of individuals use nitrites and, regardless of whether or not we call them inhalant users, they are still a legitimate topic of epidemiological inquiry.

Volatile Solvent Users and Volatile Solvent Abusers

Beauvais distinguishes two groups of volatile solvent abusers on the basis of acute or chronic patterns of use. These groups have dissimilar demographic and social characteristics and manifest themselves in different ways. Different research questions are associated with each group. School surveys can be used to investigate acute volatile substance abusers, but this contributes little to the understanding of chronic solvent abusers.

The most common numerically are the acute abusers. They are usually young (13 or 14 years of age) and are experimenting infrequently with a variety of different industrial solvents. A surprisingly large percentage of youths may engage in this pattern of behavior. In the 1988 Texas School Survey (Fredlund et al. 1989), 22 percent of the seventh graders admitted sniffing correction fluid to get high, 11 percent used glue, 10 percent tried paint, and 8 percent used solvents and thinners. Additionally included in this reported lifetime inhalant use by seventh graders, an average of 4 (out of the list of 10) different inhalants were tried over a total of 18 different occasions.

Beauvais observes that outbreaks of acute volatile solvent abuse can be episodic. Marked short-term changes in the prevalence of inhalant use among Texas secondary students between 1988 and 1990 illustrate this point. Overall, the percentage of secondary students who huffed or sniffed any substance within the school year decreased from 19 percent in 1988 to only 12 percent by 1990 (TCADA 1990). Reported lifetime use of volatile solvents over all grades decreased between the 2 years with a corresponding diminution in the number of different volatile solvents used.

Beauvais also presents preliminary data associating early volatile substance abuse with an increased risk of dropping out of school. Again, the 1988 Texas School Survey data are consistent with these conclusions. For example, in both 1988 and 1990 surveys, volatile solvent-abusing youth had many characteristics associated with dropping out: poor academic achievement, high rates of truancy, and an excess of disciplinary problems. The survey results also consistently supported several other of Beauvais' observations about acute volatile solvent abuse, including patterns of use by race-ethnicity and gender.

The association between inhalant use and generally at-risk youth is also apparent from a 1989 survey of youth entering the Texas Youth Commission (Fredlund et al. 1990*a)*. Of these youths, 39 percent admitted lifetime use of inhalants, while 23 percent admitted use in the past month. These rates are approximately twice as high as those reported by Texas secondary students in 1988 (controlling for age, gender, and race-ethnicity).

According to Beauvais, relatively few individuals continue to use solvents into adulthood. Texas survey data generally support this observation. Less than 0.5 percent of Texas household adults reported current use of inhalants (Spence et al. 1989). Most adults who admitted current inhalant use reportedly used nitrites; use of volatile solvents was very rare. However, 27 percent of inmates entering the Texas Department of Corrections prison system (Fredlund et al. 1990*b)* reported a lifetime experience with such substances.

Recommendations for Research

Beauvais makes several important suggestions for future research in the epidemiology of inhalant use. Several are methodological and based on the observation that a plethora of substances are sniffed or huffed in order to achieve intoxication. While epidemiologists refer to substances taken in this

way as "inhalants" or "volatile solvents," those engaging in such behaviors are often unfamiliar with these terms. Ethnographic research is suggested as a source of basic information for constructing survey questions relevant to patterns of inhalant use.

Ethnographic research also has a potential role for helping us to understand the process that underlies geographic, demographic, and cultural diversity in patterns of inhalant use. Beauvais describes large differences among local communities and race-ethnic and age groups with respect to the incidence and prevalence of inhalant use. Moreover, patterns of inhalant use change rapidly as compared to other drugs. While epidemiological studies document differences in patterns of use among groups and rapid change in patterns of use through time, they contribute little with respect to understanding these patterns of difference and change.

Inhalant research is also needed to measure the risks associated with acute volatile solvent abuse—dropping out of school, subsequent illicit drug use, subsequent legal involvement, and progressing to a chronic pattern of inhalant use. What, if anything, is the significance of experimenting with volatile substances a few times at a young age? In areas where early experimentation with inhalants is common, the answer to this question has profound social and policy implications as well as scientific interest.

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Epidemiology of Inhalant Abuse: A Canadian View

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A review of the epidemiological literature on solvent or inhalant abuse is difficult, based on the limited subject matter. Special studies of solvent abusers are not usually available. The ones that are may be small, highly specialized, and based on a few cases for which results are difficult to generalize. Solvents and inhalants are included in a few large monitoring studies such as the National Institute on Drug Abuse *National High School Senior Survey* and the *National Household Survey* (e.g., Johnston et al. 1991; NIDA 1992). In Canada we include solvents at the school level but not in the household studies. When solvents are included in monitoring studies, usually relatively few relevant questions are posed or solvents are clearly not the focus of the research. It is also difficult to understand whether the category "solvents" includes the same substances in all studies. The chapter by Beauvais makes a good case for increasing our level of knowledge of solvents and outlines many of the important issues. I will add to the research agenda proposed and present a few different perspectives.

From my viewpoint, it is desirable to have more information along the following lines:

- A better definition of "solvent-inhalants"
- A standardization of solvent questions on surveys

- Studies of users' perceptions of solvent's effects
- More studies of high-risk populations of youths and adults
- More clinical epidemiology
- More studies of the natural history of solvent use
- More studies from other countries

Problems of Definition

The area of solvent-inhalants is a confused one. The concepts of solvents and inhalants are both too broad. The concepts could be narrowed by disaggregating and identifying all of the drugs and substances included; this may make for very long lists of individual products. Such lists would not be acceptable in many surveys if we attempted to get a use/nonuse response for each drug. It would be possible to differentiate the category into anesthetic gases, nitrites, and solvent-inhalants. Probably only the latter category is needed in most studies of youth, although nitrites may be necessary in some places.

It would also be of interest to know whether users see differences in the effects for the various solvent-inhalants, e.g., gasoline, glue, paint thinner. In our data from students, it is clear that glue users also use solvents. However, we do not make any effort to see whether users see any different effects from one substance or the other. Users seem to have definite preferences for some inhalants and not others but we know little about this area. If they view all as having the same effects, that would mean that they could be aggregated into the same question.

Standardization of Solvent-Inhalant Questions

Only a few surveys regularly ask about solvent-inhalant use in North America. Most of this research is supported by NIDA and a limited number of States. It should be possible to standardize the solvent-inhalant questions for most surveys and special studies. If this standardization occurred, it would be easier to rule out the possibility that students responded to the inhalant question by including crack or nitrites or anesthetic gases. This would also make trends easier to interpret. An assembly of researchers could propose a standard nomenclature and a standard set of questions for solvent-inhalants. Unless this is done by reputable scientific leaders or agencies, it would probably be

ignored by those doing the research. Also, it would be necessary for funding agencies to set standards on the use of some of these solvent questions wherever possible.

Users' Perception of Solvent-Inhalants

Unlike some abused substances, solvent-inhalants have never been very fashionable. Other abused substances have some sort of status or prestige. Hallucinogenic drugs and even cannabis are associated with mind expansion, enhanced perception, or various protest movements. Cocaine promises, according to some users, to be the champagne of drugs and to enhance sexual activities. However, solvent-inhalant abused substances have no mystique, no cachet, and they have never become "smart" or stylish. No one extols their virtues publicly, and yet they continue to be used by a number of young people and adults. It would help to understand solvent-inhalant use if we knew more about the perception of these drugs among users, such as the status that they have, the beneficial effects that users expect, and the health risks that they see from light and heavy use and from different products. Some psychologically perceived beneficial effects must be experienced for solvents to continue to be used. In our student study (Smart and Adlaf 1989), 13.7 percent of solvent-inhalant users who preferred glue inhaled the glue's vapors 40 or more times in the past year. This is much higher than for cannabis (9.7 percent), nonmedical barbiturates, stimulants, or tranquilizers (2.7 percent to 5.3 percent), LSD (3.5 percent), or cocaine (7.8 percent). Glue users were much more likely to be heavy users than were users of other solvents (6.4 percent vs. 13.7 percent).

Because of the relatively low status of solvent-inhalants, some users may tend not to report use of this substance on surveys. In our own student study, the nonresponse rate for the glue and solvent questions was rather high relative to most other abused substances (1.5 percent and 1.4 percent compared to a mean of about 0.8 percent). However, the retest correlations for the solvents (and glues) question was very high. Nonreporting of the limited glue and solvent use may be greater among adults than young people, especially for recent use. Inhalant use is disapproved of in adult society but not always among youths.

Solvent-Inhalant Use in High-Risk Adult and Young Adult Populations

In recognizing the need for more information on solvent-inhalant use by adults, I would emphasize high-risk groups and family-based studies. General population studies indicate that overall use rates are low, especially for recent use (about 1 percent). However, rates of use on some Canadian Indian reservations are very high (Barnes 1979). Family patterns of solvent-inhalant use have seldom been investigated. Some Indian reservations with poor social and employment conditions do not seem to have the serious inhalant problems others do; the reasons for this are not well understood. Acculturation may be one variable, but others are also likely to be important.

High-risk adult groups for solvent abuse could include the young homeless and also skid-row populations. Most studies of the homeless that examine solvent use appear to come from Mexico or Brazil. This youth homelessness appears to be increasing or at least is a more recognized problem than in the past. Estimates for the United States indicate that as many as 1.3 million youths may become homeless at some time during the year. A recent study of homeless youths in Hollywood, California (ages 13 to 17) showed no data on solvent use (Robertson et al., unpublished). Our recent study of homeless youth in Toronto found that 24 percent had used inhalants (all types combined) and about 1 percent used them daily. This is a rate 10 times as high as for comparable youths in school. It is interesting that, in this study, about twice as many females as males used solvents ever (35 percent vs. 18 percent) and in the past year (25 percent and 12 percent). These data suggest that solvent-inhalant use is a serious problem for homeless youths, especially females. We do not know why females in these groups should use more solvent-inhalants than males; further cross-tabulations are needed. This study does suggest that solvent questions should be put in studies of the homeless and that further study is needed to clarify the reasons for the high rates of use.

Clinical Epidemiology of Solvent-Inhalant Abusers

Most studies of solvent-inhalant abusers deal with relatively infrequent use. General population studies and those of students usually include too few heavy or addicted users for any serious analysis. The social and personality characteristics of solvent-inhalant abusers appearing for treatment are not well documented; however, solvents contribute significantly to the problems

among those getting drug abuse treatment. At the Addiction Research Foundation, solvent-inhalant abusers are the primary problem for about 1 percent of approximately 4,200 patients getting treatment each year. This may seem to be a small number; however, it is much larger than the proportions with hallucinogens, sedative-hypnotics, or amphetamines as their primary problem. Almost two-thirds of the inhalant problems arise from inhaling solvent products; about 30 percent from inhaling solvents of glue. A few patients have problems with gasoline sniffing (from the benzene, other solvents, and additives contained therein). There is no trend toward greater solvent abuse in our treated population than in the population as a whole.

Solvent abusers in treatment are older than the alcoholics in treatment and a greater percentage—about 80 percent—are male. Most of the solvent-abusing patients are aged 18 to 29, only a few are younger. About 10 percent are married, living with spouses, and employed. In general, solvent-inhalant abuse seems to occur with young, single male adults who are unemployed. We know relatively little about the smaller, more stable population of married, employed, solvent-inhalant abusers; a further study may be of interest.

More research into clinical epidemiology might also clarify the reasons why solvent-inhalants are chosen over the more popular drugs such as alcohol. It is possible that these are not preferred substances but begin as stopgap measures when other substances of abuse are not available or are too expensive. How solvent abusers progress to dependency that requires treatment is also not understood.

Natural History of Solvent Use and Abuse

Although many people try solvent-inhalants for a short time, few continue their use past the first few sessions. There are still many questions about why solvent abusers stop. Probably most were only experimenting and wanted to see what it was like. Perhaps some worried about health risks. It would be interesting to know the factors that contribute to stopping solvent use. Beauvais has noted that use peaks and usually stops about the age of 13, but no good explanation seems to exist for it. In our school study (Smart and Adlaf 1989) students' glue-and-solvents-use peaked at grade 7 (about 25-33 percent of the grade 7 level) or at the age of 12 or 13 and was lowest at the age of 18+. Concomitant changes that we see among students between the ages of 12 and 18 are a large increase in smoking tobacco (6.6 percent to 28.0 per-

cent), drinking alcohol (42 percent to 64.6 percent), and smoking cannabis (0.7 percent to 12.1 percent). These are the largest changes that occur in substance use among young people. When they get to be 14 or 15, their access to alcohol, tobacco, and cannabis increases greatly (as do their use levels) and that may reduce interest in solvents. Perhaps interest in illicit drugs is greatly increased around that age (tobacco and alcohol are illicit to these populations). However, physical access to drugs and peer pressure (from older teens) probably contributes to this problem as they move from lower or primary school to high school. More understanding of how and why 13- to 15-year-olds change their use patterns would be useful, rather than relying on hypothetical speculation.

International Perspective on Solvent-Inhalant Use

Almost all of the studies of solvent-inhalant abuse come from six sources—the United States, Canada, Mexico, the United Kingdom, Australia, and Brazil. With the low cost and universal availability of solvents and inhalants, it is surprising that so few countries have reported any solvent or inhalant abuse problem. Perhaps we are wrong in thinking that such abuse does not occur in other countries. It would be of interest to have an international study of solvent-inhalant abuse in many countries, perhaps sponsored by the World Health Organization or some other international body. This study might also help to clarify some of the enigmatic aspects of solvent abuse mentioned by Beauvais and others. It should focus on levels and frequency of solvent-inhalant use, the reasons for use, effects expected from the abused substance, reasons for quitting use and reasons for progressing to heavy use as well as use of other abused substances. This type of study could establish whether there is any validity to the concept that solvent abuse is related on a worldwide basis to poverty levels, low levels of acculturation among aboriginal groups, and aboriginal status. This type of study may also clarify the rates of solvent-inhalant abuse for different types of products.

Summary

The epidemiology of solvent-inhalant abuse is still not well understood. Problems with definition and questions about use remain. Many uncertainties still exist about solvent-inhalant abuse by high-risk adults and youths. Also, the clinical epidemiology of solvent abuse, especially the natural history of

abuse, remains to be studied. The reasons why solvent-inhalant use stops so early is also not well understood. The origins of such abuse in poverty conditions and among aboriginal groups could be studied on an international level.

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Psychosocial Characteristics and Their Links With Inhalants: A Research Agenda

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This chapter has two goals: (1) to assess the state of the art—to determine what is known about the relationships between psychosocial characteristics and inhalant use and (2) to suggest the next stages in psychosocial research.

Research Findings: The Psychosocial Correlates of Inhalant Use

Barnes (1979) thoroughly reviewed the early inhalant literature, noting particularly high levels of use in native peoples and attributing that to acculturation stress. He also indicated that (1) inhalant users were more likely to use other drugs, including alcohol, (2) their families were likely to be less stable, less successful, and more alcohol or drug involved, (3) their school adjustment may be poor, and (4) there were strong peer drug influences. The research reported in the decade since his review has expanded on, but not greatly altered, these conclusions.

Family Strength

One of the more frequent findings is that inhalant users have suffered from serious family dysfunction. They are more likely to come from broken homes,

from families with alcohol and/or drug problems, and from families that are marked by conflict and discord. Nearly every study that evaluated family structure found that inhalant users were more likely to come from homes where the primary family was not intact (Albaugh and Albaugh 1979; Berriel-Gonzalez et al. 1978; Carlini-Cotrim and Carlini 1988*b;* Crites and Schuckit 1979; Guitierrez et al. 1978; Jacobs and Ghodse 1988; Leal et al. 1978; Massengale et al. 1963; Nurcombe et al. 1970; Schottstaedt and Bjork 1977). The exceptions were comparisons of young inhalant users and young marijuana users on an Indian reservation (Oetting et al. 1988), young users and nonusers in prevention programs in two Texas barrios (De Barona and Simpson 1984), very young users and nonusers in an Indian village elementary school (Kaufman, 1973), and low socioeconomic status (SES) users and nonusers from a city in Brazil (Carlini-Cotrim and Carlini 1988*a).* In these reports, where there were no differences in intact family structure between inhalant users and others, the users were relatively young, and both users and nonusers were from groups with serious socioeconomic problems. It may be that in these situations, family breakdown was high for all groups, so inhalant users did not stand out. It may also be that a further and more detailed examination of family intactness would have shown more subtle differences. A study of opiate addicts in Berlin, for example, found that half of the families of both addicts who used inhalants and those who did not were broken, but the average age when the breakup occurred for inhalant-using addicts was only 8-9, compared with age 14-15 for the other addicts (Altenkirch and Kindermann 1986).

Family problems also show up in other ways. A number of studies indicate that families of inhalant users may be marked by discord, aggression, and/or hostility (Berriel-Gonzalez et al. 1978; Comstock 1978; Crites and Schuckit 1979; De Barona and Simpson 1984; Gilbert 1983; Korman et al. 1980; Matthews and Korman 1981). Frank et al. (1988) asked a slightly different question and found that the less close young people felt to their families, the more likely they were to use inhalants.

The families of inhalant users were also more likely to be deviant in other ways. Two studies found that more family members had prison records (Berriel-Gonzalez et al. 1978; Jacobs and Ghodse 1988). Where family drug or alcohol use was assessed, the families of inhalant users were more likely to be substance involved (Albaugh and Albaugh 1979; Bachrach and Sandler 1985; Berriel-Gonzalez et al. 1978; Carlini-Cotrim and Carlini 1988*a;* Crites

and Schuckit 1979; Guitierrez et al. 1978; Smart et al. 1972; Stybel et al. 1976). In a further analysis, Bachrach and Sandler (1985) found striking differences within their sample of inhalant users as a function of whether these individuals were from drug-using versus drug-free families. The inhalant users with drug-using families had used more types of drugs, perceived their friends as having a more favorable attitude toward drug use, had experienced more poverty, and were more likely to have disrupted families and parents who had been arrested.

Opportunity

Given the kinds of family problems that many inhalant users have, such as criminal records, alcoholism, drug use, and broken families, all of which should negatively influence socioeconomic status (SES), it seems surprising that there are not large and consistent differences, with inhalant users coming from families that are low in SES. Three studies showed no SES differences (Gossett et al. 1971; Press and Done 1967; Stephens et al. 1978), while several others did find families of inhalant users to be lower in SES (Altenkirch and Kindermann 1986; Berriel-Gonzalez et al. 1978; Ellison 1964; Guitierrez et al. 1978; Korman et al. 1980; Reed and May 1984, Sokol and Robinson 1963). The lack of consistent findings in all studies may be because measures of SES tend to be somewhat unreliable. It is more likely, however, that the difficulty lies in the comparisons that can be made in an individual study. Really low SES groups, for example, may be underrepresented in population surveys or in school based surveys, and population studies, therefore, may miss the groups lowest in SES and, possibly, highest in inhalant use. Studies done totally within low SES populations may have the same problem. When the majority of people involved in the study are suffering from unemployment and lack of opportunity, it is hard for one group to be identified as having more socioeconomic problems.

In fact, some relationship probably exists between low SES and inhalant use. The highest rates of inhalant use, for instance, are found in barrios, in this and in other countries, and on Indian reservations, places where unemployment, low education, poverty, and prejudice are endemic. A study that included both high SES and these low SES groups would almost have to show that SES is related to inhalant use.

The inhalant users themselves often show problems with employment (Berriel-Gonzalez et al. 1978; Comstock 1978; Korman et al. 1980). A seeming exception occurred in a study of low-income youths in Brazil, where more inhalant users had jobs (Carlini-Cotrim and Carlini 1988*a)*. This could, however, have meant that even among generally impoverished youths, the inhalant users were less involved in school and therefore more involved in jobs. It may also have meant that they needed the jobs more.

Perhaps the most telling quote comes from an unusual study of opiate addicts in Berlin, some of whom regularly used inhalants (Altenkirch and Kindermann 1986). All of these subjects were addicts, but the opiate addicts who also used inhalants could not even function well in the criminal drug scene. Inhalant users had less illegal income and "Chronic sniffers in adulthood do not show the social agility that is necessary in order to survive in the drug scene and procure the great amounts of money that would be needed each day for hard drugs" (p. 103).

School

Inhalant users also have serious problems in school. Beauvais (this volume) points out that inhalant users seem to disappear from school-based surveys beginning with the eighth grade. One hypothesis is that they drop out. The results of other research are strongly supportive of this hypothesis. When compared with either nonusers or users of other drugs, inhalant users tend to have greater difficulty in school. They are more likely to have high absenteeism, to have been suspended, to drop out, or to have been expelled (Altenkirch and Kindermann 1986; Bachrach and Sandler 1985; Berriel-Gonzalez et al. 1978; Carlini-Cotrim and Carlini 1988*b;* Comstock 1978; Coulehan et al. 1983; Galli 1974; Jacobs and Ghodse 1988; Matthews and Korman 1981; Reed and May 1984; Schottstaedt and Bjork 1977; Winburn and Hays 1974). They are also likely to have poor academic performance and lower grades (Ackerly and Gibson 1964; Annis et al. 1971; Barker and Adams 1963; Carlini-Cotrim and Carlini 1988*a;* Coulehan et al. 1983; Crites and Schuckit 1979; De Barona and Simpson 1984; Galli 1974; Guyer-Christie 1978; Kandel 1975; Korman et al. 1980, Matthews and Korman 1981; Massengale et al. 1963; Nylander 1962; Press and Done 1967; Schottstaedt and Bjork 1977; Smart et al. 1972; Stephens et al. 1978; Wingert and Fifield 1985). Among Australian aborigines, inhalant users showed more behavior problems in school and may have been less able in school (Nurcombe et al.

1970). Frank et al. (1988), in a New York survey of school children, found that one-third of the students in grades 7-10 who had either a "D" or an "F" average had recently used inhalants. The consistency in these results is unusually high; whenever a study looked at school adjustment, and many studies examined this variable, the inhalant users showed higher levels of school problems.

Deviance and Delinquency

As might be expected, since inhalant users have trouble adjusting to work and to school, they also have trouble adjusting to society in general. Inhalant use is drug use and is, therefore, a deviant act. But even among other drug users, inhalant users stand out as deviant.

Drug use. Inhalant users seem to be more likely to be involved with other drugs. Although some use inhalants exclusively or preferentially, the studies that have looked at a range of drug use often find that inhalant users are heavily involved with other drugs as well (Jacobs and Ghodse 1988; Mata and Andrew 1988, Carlini-Cotrim and Carlini 1988*a;* Dinwiddie et al. 1987; De Barona and Simpson 1984, Ellison 1964, Sokol and Robinson 1963). This heavier involvement with drugs in general may help to explain some other findings. Padilla et al. (1979), for example, found that the major predictor of inhalant use among barrio youths was knowledge about drugs, including information about their dangers. While this finding seems paradoxical, it may simply be a reflection of the inhalant users' greater total involvement in the drug scene, including involvement with other drugs.

Crime and delinquency. In most studies that look at deviant behavior, particularly in older youths, the inhalant users are not only more deviant than nondrug users, but are more deviant than users of other drugs. Bachrach and Sandler (1985) reported on youths referred by the juvenile court for treatment of inhalant abuse. While this study did not have an adequate comparison group of other drug users, it is notable that out of 40 inhalant users, 39 had been previously arrested, with a high number of arrests for a variety of crimes other than drug use. Among the inhalant users in a Texas youth program, chronic sniffers had been arrested an average of 9 times, 40 times more often than nondrug users, and twice as often as occasional sniffers (Stybel et al. 1976). In other studies: (1) of Mexican youths, two thirds of the inhalant users who were patients in a treatment program had been arrested compared

with only 3 percent of a control group (Berriel-Gonzalez et al. 1978); (2) among Mexican-American youths in Texas drug prevention programs, inhalant users were more likely to have been stopped and questioned by the police, to have been arrested, and to be on probation (De Barona and Simpson 1984); (3) among emergency room admissions, inhalant users were more likely to have had trouble with the law than both non-drug users and polydrug users who did not use inhalants (Korman et al. 1980); and (4) in a Seattle study of predominantly middle class white-Americans, inhalant users had more police problems and were more likely to be runaways (Crites and Schuckit 1979).

Inhalant users are also likely to get into trouble with the law earlier than users of other drugs. The Berlin opiate addicts who used inhalants had already had three offenses by the time other opiate addicts were arrested for their first offense (Altenkirch and Kindermann 1986). Among adolescent delinquents in London, on the average, the first arrest of inhalant users occurred about a year and a half before the first arrest of users of other drugs (Jacobs and Ghodse 1988). Reed and May (1984) found that inhalant-using delinquents from a city in the southwestern United States, when compared with other delinquents, had been arrested almost three times as often, were arrested more often for more serious crimes, and were younger at time of first arrest.

Psychological Characteristics

The picture thus far is that inhalant users are a group with serious social and societal problems. Do these problems result in, or are they accompanied by, high levels of psychopathology or other personal adjustment problems? The research that looks at psychopathology and personal/emotional characteristics is neither as extensive nor as consistent as that describing the social problems of inhalant users.

Early studies suggested that inhalant users might suffer from great emotional distress. Case studies, for example, indicated that inhalant users might be anxious and depressed (Weise et al. 1973). Smart and his colleagues found that inhalant users had higher scores on the Taylor Manifest Anxiety Scale, had been treated more often for emotional problems, and that they were more alienated (Fejer and Smart 1973; Smart et al. 1972).

A few recent studies have explored differences in emotional distress. Oetting et al. (1988) found that young Native-American inhalant users showed more

emotional distress than young marijuana users or controls, including depression, anxiety, feeling blamed, and anger. Jacobs and Ghodse (1987, 1988) found that more adolescent delinquents who used inhalants were depressed than adolescent noninhalant users who used other drugs.

There is some evidence that inhalant users are lower in self-esteem. De Barona and Simpson (1984) found lower self-esteem and satisfaction with social relationships. Annis et al. (1971) found inhalant users were lower in variables that would logically relate to self-esteem. A study of youths in Indian boarding schools found that inhalant users had lower self-appraisals, although the self-ideal difference was the same as that for other youths (Wingert and Fifield 1985). It might, however, pay to look in more detail at these self-ideal differences. In a study that did not examine drug use, Cole et al. (1967) found, on average, no self-ideal differences between a seriously disturbed group of adolescent girls and controls, but this statistical result occurred because the disturbed girls either had very high discrepancies or very low (and unrealistic) discrepancies; so the use of an average score covered up real and important differences in self-ideal discrepancy. This may have occurred in Wingert and Fifield's study.

When the populations studied are from inpatient psychiatric units, it is not surprising to find diagnosed psychopathology. For example, Dinwiddie et al. (1987) found that more than half of a small number of chronic solvent abusers met the criteria for antisocial personality disorder. Crites and Schuckit (1979) also found that the most common diagnosis for inhalant users was antisocial personality disorder. An exception was a Mexican study, where almost half of the inhalant users had a diagnosis of depression, but nothing is known about rates of diagnosed depression in other groups of Mexican drug users (Guitierrez et al. 1978).

Almost half of a group of adolescent inhalant users who were hospitalized for treatment in Texas were diagnosed as having adolescent adjustment reaction (Comstock 1978). The MMPI suggested less pathology in the inhalant users than in other drug users, but a more detailed examination of the findings suggest more pathology among inhalant users than the initial results suggested. For example, the MMPI profiles for other drug users had peaks on scales 4 and 9, suggesting primarily hostility, rebellion, and acting out behaviors somewhat typical of many adolescents. The profiles of the inhalant users, on the other hand, involved scales 4, 6, and 8, suggesting the presence of more

thought disorders. Further, if the adolescent norms that take into account the high levels of rebelliousness and acting out of adolescents had been used to profile the MMPIs instead of the adult norms, the inhalant group may have been judged to have more, instead of less, pathology. The inhalant users were also the only group to show more indications of pathology after treatment, a result the authors suggest may be due to uncovering of underlying pathology.

Inhalant users do seem to suffer from greater emotional distress, and some inhalant users may indeed have serious personality disorders. The evidence that inhalant abuse is caused by serious psychopathology, however, is not very convincing, at least at this time. **A** reasonably long-standing pattern of drug use, particularly when accompanied by other deviant behaviors—as it is in inhalant users—could, without any further information on psychological functioning, lead to a diagnosis of personality disorder or antisocial personality disorder. An adolescent reaction to the family problems that are often associated with inhalant use (broken families, family hostilty, and aggression) could easily lead to a diagnosis of adjustment disorder in an adolescent, another diagnosis that has been applied to inhalant users in some studies. Those diagnoses may accurately describe the behaviors, but a diagnosis of a personality disorder or an adjustment disorder can carry the implicit message that the behavior is caused by or rooted in that psychopathology. That conclusion is not really warranted, since the signs of emotional distress and the behaviors of inhalant users could equally be simply an outcome of the social and family problems and social environment of the inhalant user, and not a result of personal psychopathology. This line of reasoning is expressed well by Gilbert (1983), who argues that the "disordered existence" of inhalant users predates their sniffing, as inferred from the enduring nature of predisposing social and family problems more common to inhalant users.

Peer Drug Involvement

One stereotype of the heavy inhalant user is that of the social isolate or "loner." When people working with inhalant users get together, they often describe this kind of user, so they do exist. Research reports, however, are highly consistent in describing most inhalant use as a group activity. In an early report on inhalant-using youths in Texas, Stybel et al. (1976) stated that about three fourths of inhalant use occurred with other youths. Among London delinquents, 75 percent of users inhaled with friends (Jacobs and Ghodse 1988). Among adolescent users in Northern Ireland, nearly 80 per-

cent inhaled with friends (Lockhart and Lennox 1983). More than 80 percent of Brazilian "street kids" used with their friends (Carlini-Cotrim and Carlini 1988*b*). Among Native American children in a boarding school, sniffing was typically done in a group (Schottstaedt and Bjork 1977). Among poor Mexican youths, 90 percent used with their friends.

The kinds of friends that inhalant users have may be an important factor in their inhalant use. Inhalant users may have a narrower group of friends, with higher deviance among those friends. In one study, for instance, the friends of inhalant users all lived within their impoverished neighborhood, while many of the control group subjects had friends outside of the neighborhood (Berriel-Gonzalez et al. 1978). While family sanctions against inhalant use tend to be high, even in the families of inhalant-using youths (Bachrach and Sandler 1985; Beauvais et al. 1985; De Barona and Simpson 1984), sanctions against inhalant use by peers are much lower (Bachrach and Sandler 1985; Beauvais et al. 1985). Chronic inhalant users in Texas spent more time with their friends, and their friends were more deviant (De Barona and Simpson 1984). Friends of inhalant users may use more drugs (Mata and Andrew 1988), and the friends of inhalant users are also likely to be using inhalants (Bachrach and Sandler 1985; Oetting et al. 1988; Stephens et al. 1978).

In general, more than three fourths of inhalant use is probably with friends. This leaves a considerable gap, however, showing that a significant amount of inhalant use does occur when the user is alone. From general experience of those working with inhalant users, solitary users seem likely to be more disturbed and have more problems. Only one study compared those who use alone with those who do not. The authors felt there was more psychopathology in those who used alone (Guitierrez et al. 1978). Consistent with this general observation were findings from a recent case study (Mathew et al. 1989) of a young, heavy inhalant user who sniffed alone. This individual's extreme behavioral disturbances, especially aggressiveness, resulted in rejection by her peers and, eventually, social isolation.

Culture

The location of "hot spots" of inhalant abuse in Hispanic barrios and on Indian reservations suggests the possibility of cultural influences. Studies that point to differences in drug use rate related to ethnicity usually assume that the problems are occurring because youths are caught between two cultures

(Gilbert 1983; Guitierrez et al. 1978; Nurcombe et al. 1970). Gilbert (1983) expresses this clearly, stating that the Hispanic inhalant users in her study were "disengaged from the symbols and traditions of his/her culture or origin and concomitantly rejected by the culture of the dominant majority" (p. 82). There are, however, almost no actual studies of the cultural identification of minority youths and how that relates to inhalant use. The exception is a study of Native American "child polydrug" users (Oetting et al. 1980). The child polydrug pattern occurs in children 14 and under and involves use of both inhalants and marijuana. The study noted that children who were highly identified with Native American culture or who were bicultural were slightly less likely to be child polydrug users. Studies of older Indian youths, however, did not find this relationship between cultural identification and drug use, and in another study, these authors indicated that the relationship between cultural identification and drug use is not strong and is highly complex (Oetting and Beauvais 1990).

There is another application of the term "culture" that may be highly related to inhalant use—the fact that the most serious levels of inhalant use may occur in specific drug-oriented subcultures. The evidence that inhalant use is, predominantly, a group activity is discussed above. Perhaps the most extreme example of a subculture is reported in Leal et al.'s (1978) study of "street kids" in Mexico City, youths who have essentially severed all ties with their families and formed their own subculture, probably to replace the family, a subculture oriented around street survival and inhalant use.

Psychosocial Characteristics and Treatment Research

Experimental research aimed at altering psychosocial characteristics, either through prevention or treatment, could add to knowledge of the underpinnings of inhalant use. No studies have been specifically designed to address this kind of question, but some hints that are relevant to psychosocial characteristics are in the sparse literature on treatment. Barnes (1979) reviewed the early treatment case studies and reported mixed results. He also reviewed the one treatment study where various methods were tried (Rubin and Babbs 1970), noting that although solid data were not provided, a program that utilized intensive work with families, school, and the peer group may have had some success. The results agree with other literature, suggesting the importance of social environment. Carlini-Cotrim and Carlini (1988*b)* reported that some of the Brazilian street kids were able to get involved in a welfare in-

stitution. It provided leisure time activities, including creative crafts that they could sell. The youths in this program reduced their drug use, particularly those who stayed both day and night at the institution. The children who were able to get involved were self-selected, so alternative explanations cannot be ruled out, but the fact that a change in social environment was related to change in inhalant use should probably not be ignored. These studies are weak but consistent in suggesting that the social environment may be an important factor in the maintenance of inhalant use and that changing the social environment may be useful in treatment.

In contrast, psychotherapeutic approaches have not been notably successful (Comstock 1978; Guyer-Christie 1978), nor have traditional drug treatment programs. In one study, all 10 patients provided with inpatient drug rehabilitation had relapsed within 6 months (Dinwiddie et al. 1987). The ability of short-term treatment to alter relatively well-established psychological characteristics is questionable, but equally, social, rather than psychological, factors may be causative for inhalant use and essential for treatment.

Summary

In several ways, the research on inhalant use is remarkable. First, early research, prior to 1975, and research completed since then are essentially consistent and lead to the same conclusions about inhalant users. Considering that drug use has changed radically over this time span, differences in findings over time might be expected. Instead, the recent research has only expanded on and amplified the conclusions reached by Barnes in his 1979 review. Second, the research is remarkably consistent; within a psychosocial area, the studies show high agreement. Third, the research results lead to similar conclusions regardless of age of the study population—inhalant users are found among the subjects who have the fewest social resources at any age and in any group. Fourth, results are consistent across cultures. Research results from four continents and, within the United States, from a number of different cultural contexts, are fundamentally in agreement.

The most general conclusion is that inhalant users are likely to be marginal in society. Inhalant use is highest where poverty, prejudice, and lack of opportunity are endemic. Inhalant users are more likely to come from families that are unstable and dysfunctional. Youths who are failing in school, showing lack of ability to meet the requirements of that environment, are also among

those most susceptible to inhalant use. Inhalant users have friends who are also marginal; they are likely to be involved with drugs and are probably also using inhalants, since most inhalant use is a group activity. Those who do move on to solitary use, however, are probably the ones with the most problems. With all these social problems, it is not surprising to find that inhalant users are also likely to have problems with school authorities and to be involved in criminal behaviors. In addition, inhalant users may suffer from great emotional distress.

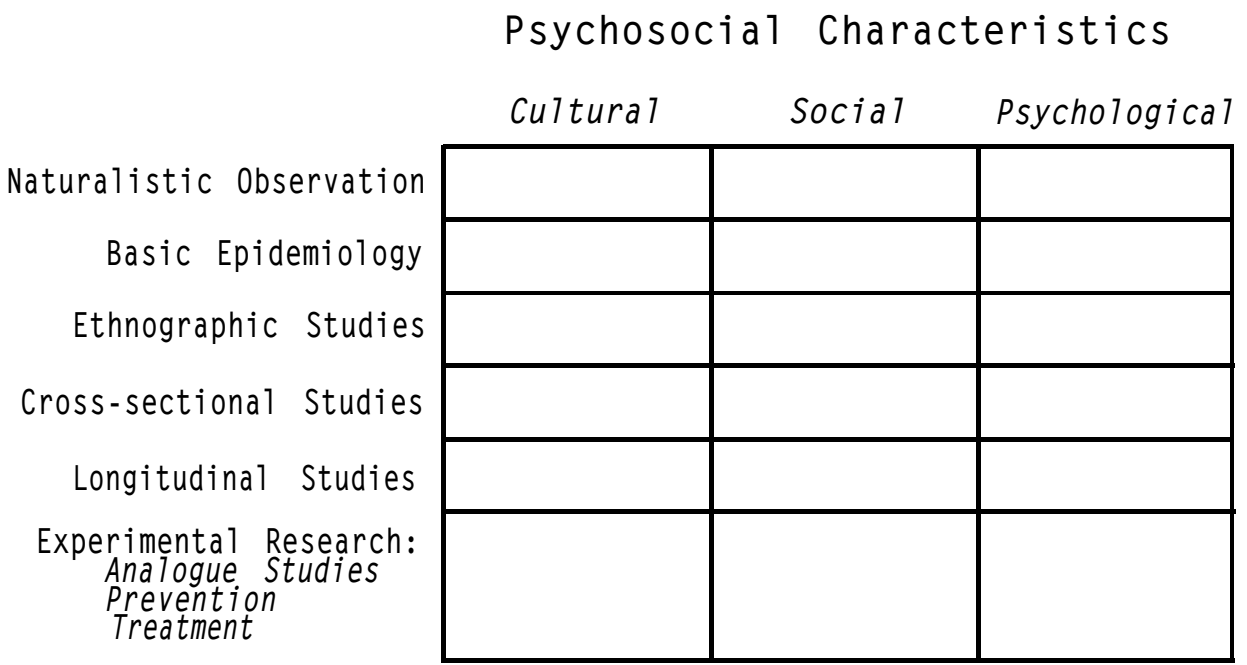
A Model For Psychosocial Research on Substance Use

A generalized model for psychosocial research can be visualized (figure 1). The columns list psychosocial characteristics—cultural, social, and psychological.

Culture provides a foundation of language, beliefs, values, and culturally approved or sanctioned behaviors. Social forces that affect the person include the community, the socioeconomic opportunity structure, school, work, religion, family, and peers. *Psychological* characteristics, traits, attitudes, and cognitions interact with these social characteristics to alter the probabilities of different behaviors.

The rows in figure 1 cover the types of psychosocial research and suggest a temporal order in a research agenda from naturalistic observation through experimental research. The general trend of research should follow this path, but the model is not meant to specify a rigid research agenda. The ultimate outcomes that derive from research are too unpredictable to warrant an inflexible policy. The model does suggest that, at certain stages in an overall research plan, particular types of studies may be more profitable than others.

Figure 1. A generalized agenda for psychosocial research



It also suggests that the value of the research at later stages may depend on progress made in different types of research at the earlier stages. The risks to subjects also increase through the stages in this research agenda. For example, cross-sectional research can be anonymous while longitudinal research cannot and therefore adds risk. Prevention or treatment involves manipulation of subjects, adding additional risk. With increasing risk there is increasing need to make sure that research results are likely to warrant that risk, and that need is usually met by research at an earlier stage in the agenda.

An overall planned research agenda should consider the state of scientific knowledge at any point in time, should determine what has been achieved at each of these stages, and then focus current efforts on filling in gaps and moving effectively to the next stage of development of knowledge. Research designs that fit into this overall plan at any stage of its evolution should, therefore, be sought out and given strong consideration, while proposals for other kinds of research should be questioned but not automatically rejected. As the knowledge base builds from successful efforts at earlier stages, new kinds of research become cost-effective, and the research agenda shifts and expands, moving on to the next stages.

To illustrate this point, when this chapter was first drafted, "ice," or smokable methamphetamine, had received considerable publicity predicting that it would be the next major drug problem. An expensive prevention research study could have been proposed at that time aimed at reducing use of ice. The model for forming a research agenda, however, would suggest caution. If prevention is undertaken before solid progress has been made in epidemiology, it could be aimed at inappropriate groups, populations, or ages. If reliable and valid measures of "ice" involvement and of intervening or process measures were not developed and tested, an expensive prevention study might be wasted because the measures it used were unstable or invalid. If data on psychosocial correlates of ice use were not available, a treatment program could easily be aimed at altering variables that would have no relevance to use of ice. In fact, the caution would have been well rewarded; the expected "ice age" never did appear on a widespread basis, and a major prevention research program would have been wasted.

The following sections take each row of the model in figure 1 in turn. They briefly discuss the nature and limitations of that type of research and how it fits into an overall psychosocial research agenda.

Types of Psychosocial Research

Naturalistic Observation

One stage must precede any other research—a problem has to be "noticed" before it can be studied. This naturalistic observation stage usually cannot be planned; it can only be identified after it has occurred. For example, Brecher (1972, p. 321) pointed out that, while it is likely that people sniffed glue, this practice is not mentioned in print prior to 1959. Until glue sniffing was noticed, further research could not take place. Once a problem is identified, the next studies may also fall into the general category of naturalistic observation. They may be case studies or studies that look at the behavior in small, not very generalizable, subsegments of the population. Many "one school" surveys are of this type.

From the point of view of psychosocial research, a major purpose of naturalistic observation is to identify a problem and feed that information into more formal epidemiology studies, suggesting what to assess, how to measure it, and what sampling frames may be important. This "we have a problem" function is not, however, the only use of naturalistic observation. It can be a powerful tool in the hands of the competent scientist, when observation leads to theory which is then tested through further observation to alter the theory. The most serious limitation of the method is the possibility of bias—of seeing only those facts that confirm the emerging theory. The accompanying advantage is that the door is always open for invention, discovery, and innovation.

Naturalistic observation does not end when other types of research start. New phenomena always need to be identified, and they point the way to further research needs. One example is a newly observed pattern in adult inhalant use. Inhalant-dependent adults are usually socially isolated and alienated, the use of inhalants may be obsessive and continuous, and unlike most use by younger users, inhalants are not usually used as a "social" drug. In one location, however, a group of adult inhalant users are getting together in groups, renting a motel room, and buying a case of spray paint for a weekend binge. This naturalistic observation clearly sets the stage for further research on a hitherto unusual pattern of use.

Basic Epidemiology

Once a problem has been noticed, epidemiological research needs to establish the characteristics of the problem, identifying its nature, extent, distribution, and how it relates to population demographics. Epidemiology may also provide an essential fuel for the research endeavor. If everyone knows that there is a problem, there may be no difficulty in obtaining political and policy support for work on that problem. But if a problem is obscure, if there are groups that would argue that there is no real problem, then solid data on epidemiology are needed to obtain support and funding for research.

Epidemiology forms a foundation for further research. It indicates what groups need to be included in future studies. The base rate of a behavior determines how many subjects may need to be included to obtain adequate data to determine the correlates of a behavior. Identification of at-risk groups or locations determines where ethnographic research should be done. Epidemiology studies are actually often combined with cross-sectional research on psychosocial correlates of use, a good illustration of the blurring across categories that is inherent in presenting a model that defines separate categories.

Use of drugs changes over time, and unless those changes are known, psychosocial research results may be confusing. Cross-sectional studies of correlates of use, for example, completed a decade apart, could easily show different relationships between inhalant use and psychosocial characteristics. Witness marijuana. In 1970, when its use was still relatively infrequent among younger adolescents, only the more deviant youths would be likely to have used it. In 1980, when adolescent drug use was at its highest level, many youths who were not particularly deviant would have used marijuana. Without solid data on trends in drug use, studies done at different times may appear to be in conflict, when in fact there is an underlying consistency.

Ethnographic Studies

Ethnographic studies, by their nature, can only obtain data from a limited number of subjects and may be at their best when they examine one specific and narrow subgroup. Until the distribution of the problem is known from epidemiological research, it is difficult to decide where an investment in these studies will be most valuable. There may be cogent theoretical reasons for studying a particular group that have little to do with the overall distribution

of the problem, and if so, those reasons provide sufficient justification for a personal research commitment. A research policy, however, may have to be more stringent, and those funding ethnographic research may need to be concerned with efficiency; in order to be funded, the results may have to be obviously generalizable to an "important" group, a group where the problem seems to be concentrated or where the consequences are most serious.

Ethnographic research provides a rich source of information about detailed behaviors, social and cultural contexts, meanings, attitudes, values, and beliefs. Certain kinds of questions can only be addressed by this type of study. In addition, other types of research may benefit from the rich detail and examples provided by ethnography. The value of research on correlates of use, for example, depends on the inclusion of measures of variables that are relevant to the problem, and without input from ethnographic studies, crucial variables may not be included. As an example from our own research, in the early stages of an ethnographic study of drug using adolescents, we found that a major component of their beliefs and attitudes centered around distrust. Although they tended to see anyone who used drugs as a friend, they had also been ripped off by these friends, who stole money, drugs, and property. Based on these interviews, measures to assess trust/mistrust are now being constructed for inclusion in our cross-sectional and longitudinal surveys.

One major limitation of ethnographic studies is the cost per subject in research time. Observations and interviewing take time, and the number of subjects must, therefore, be low. Observations are also usually restricted to one or two locations. To what extent will the results generalize to other groups? Another limitation is analysis. It is hard to describe and defend the analysis of the data, since the conclusions usually grow out of and gradually emerge from insight into the observations. The inability to describe analyses and predict results can prove to be a critical factor that prevents reviewers from being sure that a study warrants funding.

This early input into the research agenda is only one potential benefit from ethnographic studies. The ethnographer can sometimes provide information on subgroups that cannot otherwise be studied. An example is Terry William's ongoing study of crack houses, whose residents probably could not be reached in any other way (unpublished study). The ethnographer can also provide insights into complex interactions and cultural roots and can discover linkages between behaviors and contexts that could not be teased out of other

forms of data. The theoretical constructs that emerge from the best ethnographers are accompanied by rich descriptive detail that is a convincing image of real people in a real world—a balance for cold and formal drug statistics and abstract or arcane theories.

Cross-Sectional Research

Cross-sectional studies come in a variety of forms. Some are products that emerge from inclusion of psychosocial measures on instruments used to assess national epidemiology. Johnston, O'Malley, and Bachman's studies of drug use of high school seniors provide an important example (1989). Others are done in one location, such as Jessor and colleagues' valuable triethnic study (1968). Cross-sectional studies can have different purposes, such as research designed to examine factor or cluster structures, retrospective studies to find preliminary evidence of precursors of drug use, or path analyses that explore the intercorrelations of variables. Studies can be limited to one population or can compare groups, for instance by age, ethnicity and gender. The value of these studies is that they can provide useful information on how groups differ from each other—in this case, how inhalant users differ from other drug users and from those who do not use drugs. They can identity potentially salient characteristics, provide fundamental information on reliability and validity of measures of dependent and independent variables, and can lead to theories and hypotheses that guide further research. The studies do not have to be exploratory; cross-sectional studies can also provide confirmatory evidence for construct validity where a theory predicts that certain specific relationships should exist.

Their major limitation is that cross-sectional studies cannot yield direct evidence of temporal relationships. A psychosocial difference between inhalant users and nonusers could identify a trait that was a precursor of use, that was a result of use, or that might be a correlate of a factor that related to both that trait and inhalant use. There might be strong theoretical reasons to believe that a relationship does reflect a precursor of use or that it developed after use began; but until longitudinal or experimental studies are done, it is important to remain skeptical.

The major advantages of cross-sectional research are cost, flexibility, and immediacy. Large arrays of data can be obtained rapidly and analyzed immediately. Longitudinal, prevention, or treatment research are likely to be expen-

sive and to require extended time to get results and should usually be undertaken only after a proper foundation has been laid using cross-sectional studies.

Longitudinal Research

Longitudinal research adds a very important element. It provides direct data on temporal relationships that cross-sectional studies cannot. This additional information adds greatly to understanding how psychosocial characteristics relate to behavior. Longitudinal studies are usually aimed at one of two goals—determining the consequences of a behavior or identifying the precursors of a behavior. In some ways, a study of consequences appears to be easier; a group engaging in the behavior can be identified, a reasonably well-matched comparison group can be obtained, and after a period of time, the groups can be compared. The difficulty and the cost come in trying to track people over time. Inhalant users may present a particular problem in this regard, since they may be quite deviant and are likely to drop out of school, to be unemployed, and to move frequently.

Identifying precursors of a behavior with a relatively low base rate, such as inhalant dependence, can be difficult and costly. It requires assessing the psychosocial characteristics of large numbers of youths to be sure that, down the road, enough inhalant-using subjects are available for analyses. The problem is exacerbated because those few who do become inhalant dependent may not be found on followup.

Despite their problems, longitudinal studies are of great importance. Through longitudinal studies, it should be possible to determine whether a particular psychosocial characteristic appears before the behavior, along with it, or develops subsequent to the behavior. It is tempting to interpret these sequential relationships as causative, and in general, a temporal relationship is important evidence for causation. There are, however, other plausible alternative hypotheses that need to be considered. For example, the characteristic that appears earlier and the behavior that appears later may both be caused by some other underlying factor. The sequencing may occur for other reasons. For example, those who use cocaine almost always used marijuana first. Does marijuana use, therefore, cause cocaine use? Not necessarily. Youths with a relatively high general penchant for or attraction to drug use may end up using both drugs. They may have started with marijuana only be-

cause it is more available, because it is believed to be less harmful, or even because it costs less.

A historical trend could also account for results. Attitudes, beliefs, or drug use can change in society in general, and earlier and later results may derive from those changes. For example, a study tracking drug use in a group who were 10 years old in 1970 might find increases with age until they were 21 in 1981 and then decreases in drug use after that. But general drug use for the whole population shows exactly the same trends over these years, increasing until 1981 and then declining. How much of the result is age/drug related and how much is due to general social trends? Studying several age panels would answer the question, but as new panels are added, costs can soar.

Another critical problem with longitudinal studies is attrition; as many as half of the subjects may disappear over time. Would the results be different if all the subjects could have been found? When attrition is high, pretest results for those found and those not found are almost bound to be the same, since a small group of "different" subjects in either group would not have much effect on the mean scores of the large number of subjects in that group. Nonsignificant statistical pretest differences may not mean the groups are really equivalent.

Despite these problems, longitudinal studies are of great value. They do elucidate temporal relationships that are critical to understanding how psychosocial characteristics lead to and are influenced by drug use. The results must simply be treated with the same caution that is appropriate to all research results, with careful consideration of possible alternative explanations.

Experimental Research

All of the methods described to this point involve observing and assessing existing characteristics and behaviors and examining existing relationships. Experimental research involves altering or manipulating variables and determining the outcome. Three general types of psychosocial research involve changing or manipulating variables and, therefore, fall into the category of experimental research: (1) laboratory analog studies, (2) prevention research, and (3) treatment research.

A major advantage of experimental research is that it adds one more link to the chain of evidence needed to establish causation. A good experimental

design can eliminate many of the most common alternative explanations. Unfortunately, from the point of view of pure research, experimental psychosocial research must be done with humans, and because of ethical and practical considerations, must often use designs that are not optimal for eliminating alternative explanations.

Laboratory analog studies have the advantages of being relatively inexpensive and offering immediate results. They usually provide the most control over experimental conditions and utilize the best experimental designs, but sometimes because of this careful control, results may have minimal application outside the conditions of the laboratory. Prevention and treatment research programs are the most realistic; they deal with real people in real environments. They are, in one sense, "causal" research, since variables are manipulated, and outcomes of changing the independent variable can be assessed. They are, however, much less amenable to well-controlled experimental design. Their costs are so high that it is usually impossible to include all of the conditions that a good experimental design would suggest are needed, and they usually have little control over extraneous variables in the lives of participants that could influence results. If they fail, there are usually too many possible reasons for failure to allow isolating the causes. Findings can also be delayed, particularly if expected effects are long term.

Experimental studies in general are placed at the final stage in the research agenda, suggesting they should be strongly based on prior research. Actually, some types of analog studies probably do not have to await progress from other methods of research. They may be more applicable to the problem once there is considerable information about it, but at any time they might add small pieces to the equation that helps us understand behavior. The ethics of manipulating subjects are not likely to be a major issue, since studies almost always use fully informed volunteers and the procedures are unlikely to endanger subjects. More experimental studies of this kind should be done.

Prevention programs, on the other hand, need to be based on solid research to ensure that they are targeted appropriately and aimed at characteristics that may influence the outcome. Without a solid prior research base, prevention programs have to be based on beliefs about what ought to work, or on programs that worked for some other problem. The failure of so many prevention programs that used drug education may be a good example of the former; they ought to have worked, they just did not.

An example of trying to transfer a program from one area to another is the considerable research on prevention of smoking. One finding is that youths will, at least temporarily, reduce smoking when they believe that it leads to negative social consequences. But would this kind of program work for inhalant users, some of whom may be youths who see rejection by "good kids" as an asset, not a liability? Similarly, treatment programs that are not derived from research must be based only on prior treatment experiences with other problems, and generalizing from that experience may be unwise. If inhalant dependent adults, for example, have different psychosocial characteristics from alcoholics, why should a treatment based on Alcoholics Anonymous work for them?

Initiating prevention or treatment without a firm, data-grounded theory that suggests why it may work is questionable. There is always the excuse that something has to be done about the problem, but it must be remembered that prevention and treatment involve manipulation of people, and this manipulation can result in harm. The harm may even come simply from failing to be successful; what damage is done when prevention or treatment fails? Does it make people feel like failures? Does it lessen the chance that future interventions will succeed? Trying to change people without relatively strong evidence suggesting that they will be helped is probably not justifiable.

An Agenda for Psychosocial Research on Inhalant Use

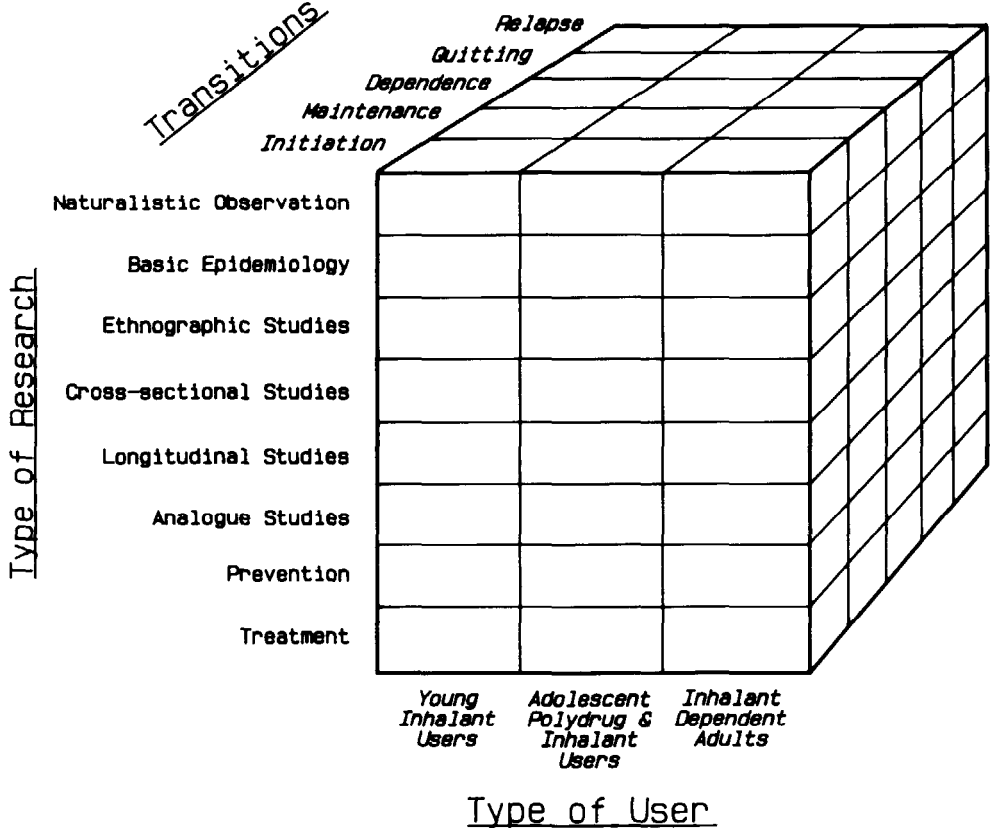
Checking the published research against the model for a research agenda presented in figure 1 shows considerable effort related to early parts of the agenda: naturalistic observation, epidemiology, and cross-sectional research. The noticing aspect of naturalistic observation occurred some time ago and was followed by a number of small studies that would fall in the same category. There is, however, no report of an in-depth set of naturalistic observations that involves strong theory development or hypothesis checking. In contrast, there is considerable knowledge of inhalant epidemiology, although, as Beauvais points out (this volume), gaps still need to be filled. Nearly all of the papers that deal with psychosocial characteristics present results from cross-sectional research. A few studies have an ethnographic flavor, but none are true ethnographic studies, and there are some minimal reports on treatment. No longitudinal, prevention, or laboratory analog studies were found.

A model research agenda on inhalant use is proposed. In figure 2 the rows indicate the different types of research discussed in the introductory section of this chapter. The columns list the three types of inhalant users (Beauvais and Oetting 1987), showing that a research agenda needs to cover three groups: young inhalant users, adolescent polydrug users who take inhalants, and inhalant-dependent adults. A third dimension lists the major transitions in drug involvement, showing that different psychosocial factors could be involved in initiation, maintenance, dependence, quitting, and relapse.

Another dimension could be added, showing that psychosocial research should explore cultural, social, and psychological characteristics. The most consistent findings in the literature indicate that inhalant use is strongly related to being socially marginal. The emphasis in this proposed research agenda, therefore, is placed on the social dimension. The finding that inhalant users are socially marginal across widely divergent cultures suggests that, despite finding high rates of use in some minority populations, no specific cultural content is a major factor in use. Future research on culture should, therefore, probably focus on marginality or lack of cultural stake rather than on cultural content. More research is probably also needed on psychological characteristics. Inhalant users may be more likely to suffer emotional distress, but that may be a result of their social problems rather than a proximal cause of inhalant use. While cultural and psychological characteristics should not be ignored in a research agenda, social characteristics are the most important definers of inhalant use and should probably be given more immediate priority.

If the additional dimensions involving cultural, social, and psychological characteristics were added, figure 2 would have 315 cells, each defining a different research project. Describing all of the possible research programs would be a formidable prospect. Fortunately, major studies cut out larger blocks of figure 2 that cover a number of adjacent cells, and based on what is known about inhalant use, some research projects emerge that should have high priority.

Figure 2. Model for an agenda for pshycosocial research on inhalent use



The first two rows of the figure are not dealt with in further detail here. The noticing aspect of naturalistic observation has already been accomplished, leading to a considerable body of research on epidemiology and correlates of use. As long as observers continue to witness new phenomena (and barring emergence of a new Darwin), no specific research agenda in this area is needed. The next row, basic epidemiology, has already been covered by Beauvais (this volume). Suggestions for a research agenda, therefore, begin with the next row in the diagram, ethnographic studies.

Ethnographic Studies

A number of possibilities exist for ethnographic studies, but the highest priorities should probably be given to studies of inhalant-dependent adults and polydrug users who use inhalants. The primary focus of these studies should probably be on the psychosocial factors involved in maintenance of inhalant use.

Inhalant-dependent adults. There are strong reasons to believe that inhalant-dependent adults are likely to be among the most disadvantaged and marginal people in society. They probably cannot be examined except through ethnographic studies. They are not likely to show up in surveys, and even if reached, many of them may not be able to accurately complete questionnaires. The studies should cover urban nonminorities, Hispanic barrio minorities, and Native Americans on reservations. Studies of inhalant dependent adults in black ghettos should also be done; although inhalant use is lower among blacks, some are inhalant dependent.

The questions that need to be answered center around the way that inhalant-dependent adults exist within the broader social structure, how they fit into the culture and the social environment. What are their patterns of substance use? Have they moved to essentially solitary use or are they still part of drug-using social networks? What are those networks like, and how do they support inhalant use? What were the transitions in use, and when did they occur? What are their beliefs, attitudes, and preferences in relation to drug use? Who are they? How do they survive? What social/personal interactions mark their days? How are they viewed by others in their environments? Does this vary by ethnicity/culture? What are the cultural roots of current attitudes of others in their environment to these inhalant-dependent adults? Most cultures have social roles for misfits. Do inhalant users now occupy these

niches? Are they scapegoats, the butt of jokes? Are they tolerated in certain locations and when engaged in certain activities and not tolerated in others?

Adolescent polydrug users who use inhalants. Polydrug users are more likely to use drugs within group contexts, and even their use when alone may be dictated by attitudes and beliefs formed in the group. Ethnographic studies of these youths will probably need to involve both interviews and observations of group behaviors and group dynamics. The same questions asked about inhalant-dependent adults would apply to these studies. Added would be questions about social structure and subculture of the groups. For example, heroin users in barrio gangs can form small subgroups within a larger gang of non-heroin users; is this true of inhalant users? Does group makeup and extent of solitary use differ on Indian reservations where travel is difficult? What role does criminal activity play for the individuals and the group? The probable high level of criminality in these youths suggests that the ethnographer will have to have unusual qualifications both to develop trust and to survive in a high-risk environment.

Cross-Sectional Studies

While nearly all of the existing published research is cross-sectional, there are still numerous opportunities for important additional studies. Young inhalant users appear more frequently among those who are failing in school, and polydrug users who use inhalants are also likely to have school problems. More information is needed about the details of that poor school adjustment. It might be assumed, for example, that youths who are doing badly in school also dislike school, but only one study actually examined liking for school, and it found no significant differences (De Barona and Simpson 1984). Since inhalant users may have high dropout rates, studies of the psychosocial characteristics that relate to inhalant use among school dropouts are also needed, particularly Hispanic and Native American dropouts, the ethnic groups where inhalant use is particularly prevalent.

Poor family adjustment is also a predictor of inhalant use, and there are indications that family problems when the child is younger may be particularly damaging. Studies comparing parenting styles, discipline, and role modeling as they relate to psychosocial characteristics and inhalant use of children might contribute valuable information. The high rate of broken families among inhalant users, and the importance of the extended family in the two

ethnic groups at highest risk for inhalant use, suggest studies of the potentially protective effects of roles played by the extended family.

Deviance is a major correlate of inhalant use, but more detailed information is needed. Among inhalant users, what kind of rebellious, hostile, or delinquent acts appear at what ages? How do tolerance of deviance and deviant behaviors interact? What patterns of deviance are engaged in by the peers of inhalant users? How do peer and individual attitudes and beliefs about deviance relate, and how are they related to beliefs and attitudes about inhalant use, particularly among polydrug users who use inhalants?

Other research findings suggest areas in which no research has been done that should be explored. The most important of these may be the role played by violence in the lives of inhalant users. Chavez et al. (1989) found surprisingly high levels of violence in the lives of dropouts, and this is worth exploring in inhalant users. There is evidence of family fights and family arguments, but to what extent are physical or sexual abuse factors that may underlie the general marginality that precipitates inhalant use? Have inhalant users been beaten, cut, shot, or raped? Violence could easily help create the marginal person who is most susceptible to inhalant dependence.

Another area of importance may be cultural identification. Oetting and Beauvais (1990) indicated that high cultural identification depends on having a stake in that culture, on the person's ability to obtain rewards and reinforcement from the culture. For youths, this stake is inextricably connected to the family's success in a culture. Identification with either minority or majority culture may be a protective factor, but the marginal families of inhalant users may not be able to provide the foundation for a strong identification with any culture. Oetting and Beauvais found that cultural identification is not highly correlated with drug use in general, in either Hispanic or Native American youths. There is, however, a high relationship between family marginality and both cultural identification and inhalant use, and poor cultural identification could be a major factor in inhalant use.

Longitudinal Studies

The research agenda for longitudinal research has to start with some negative considerations. Inhalant dependence is a relatively low base-rate behavior. Some research projects that would otherwise be of great interest, therefore, may become either too expensive or too impractical to make them worth at-

tempting. For example, initiation and maintenance of use by young inhalant users may have its roots in early family disturbance. A longitudinal study should obtain baseline data on family characteristics, parenting, child/adult interactions, the extended family, family involvement, success in the minority and majority culture, and handling of family crises. Of particular interest would be the interaction of family characteristics and developmental stages, since failure to complete very early developmental tasks may create the social marginality that marks the inhalant user.

A very large baseline sample would be needed to ensure having an adequate number of young inhalant users at followup to have sufficient power to assess the importance of and the interactions between the large number of variables involved. A study to determine the early markers of adolescent polydrug use with inhalant use would be valuable, but the base rate of this behavior is even lower. The length of these studies, and therefore their expense, would be even greater. If there were high rates of attrition, the original samples would have to be even larger. Convincing a funding source to support study of a sample large enough to look at low base rate behaviors can be difficult. The answer might be a national, multiagency, multidisciplinary, multicultural, longitudinal study of family characteristics and child development. Negotiating to make sure that the study included adequate assessment of drug involvement might be a problem. Multiagency studies in the past have often included only superficial measures of substance use.

There might be greater potential in structuring longitudinal studies of high-risk groups. For example, a list of family risk factors would include (1) broken family, (2) a history of family conflict, (3) criminal arrest of family member, (4) no member of immediate family with more than 5 years of continuous employment, and (5) a history of alcohol or drug abuse. A longitudinal study could include a high-risk group selected to have three or more of these family risk factors and, for comparison, a group matched only for ethnicity and neighborhood. The rate of inhalant use in the high-risk group could be high enough to allow the study to be completed at reasonable cost. A study following youths showing poor school performance, particularly those with records of disciplinary actions or arrest, might include significant numbers of youths who end up as polydrug users with inhalant use. These studies would also be expensive, because identifying, locating, testing, tracking, and continuing to get followup data on these youths, who are likely to become dropouts and who are on the fringes of society, would take large amounts of staff time.

A longitudinal study that determines the precursors of inhalant dependence in adults is probably not feasible. The base rate is simply too low.

Followup studies of users, to determine how psychosocial characteristics are related to consequences of inhalant use, should have a high priority and should be done for all three types of users. The results could lead to important information about psychosocial correlates of maintenance, quitting, and relapse. These studies would not suffer from base-rate problems. They are costly, but only because following marginal people over time is difficult. Inhalant users may be hard to find locally, but may not have the resources to move. Unless attrition is inordinately high, adequate power can be obtained with reasonable sample sizes.

A critical factor in any agenda for longitudinal research is making sure that the baseline data include reliable and valid measures of all critical variables. If variables have poor reliability or validity, the measurement models will not stand up, and if a key variable is missing, the final results can lead to conclusions that are inaccurate or misleading. Cross-sectional research is economical enough so that risks can be taken, since they can be expected to be self-correcting over a number of studies. Longitudinal studies are expensive and cannot be given the same latitude to err.

Laboratory Analog Studies

A useful set of studies that could lead to valuable information about inhalant users would involve determining how inhalant users differ from other youths, both users of other drugs and nondrug users, in their response to controlled, laboratory-imposed conditions. Studies can be aimed at any of the three types of inhalant users. The independent variables can range from highly theoretical to potentially practical. For example, these users are likely to be marginal in society. Do they, therefore, have inappropriate proxemic responses? Do they provide social nonverbal cues to others that lead to rejection or dislike? Response to standardized laboratory conditions can provide answers to these and other questions.

Many inhalant users have a history of family and authority conflicts. Do certain experimental conditions, therefore, such as presentations of family pictures or taped stories about family conflicts, lead to differing psychophysiological or behavioral responses? Do parents of inhalant users show different responses to standardized presentations of family crises?

Inhalant users consistently show high rates of school problems. Are there differences between inhalant users and other youths in learning style? Do they perceive problems in different ways? Do users show evidence of perceptual or learning disabilities? Do these change or disappear with time since the last episode of use? Do they respond accurately to some types of presentations of information and not to others? Do they differ from other youths in response to learning tasks or social/psychological situations? Do young inhalant users perceive and respond differently to messages about drug use? Is drug use grouped by gender, by age, by ethnicity interactions with the source of the message, the content, the style, the intensity, and so forth?

Obviously, a very wide range of laboratory studies might shed some light on the psychosocial characteristics of inhalant users and how they differ from other youths. If a researcher had access to inhalant users, most of these studies would be very economical. Only a few would even need external funding. The opportunity for an innovative and creative researcher with limited resources to make a contribution in this area of research is great.

Prevention

Simpson, and Jumper-Thurman and Beauvais (this volume) review the prevention and treatment research in detail and suggest a research agenda. Here we are concerned only with prevention and treatment as a form of experimental research that may shed some light on psychosocial links to inhalant use. The goal of a psychosocial prevention study would be to alter one or more psychosocial characteristics that are theoretically causes of inhalant use. The effect on inhalant use would then be determined.

The major psychosocial variables that the literature suggests are potential causative agents are family conflict and poor school adjustment. Prevention programs to alter these characteristics should probably be tried, because even if inhalant use did not change, the potential benefits might be great. But supporting a prevention study of this kind is a problem. Demonstrating success in preventing a low base-rate behavior would require large numbers of subjects, even more than a longitudinal study, since a control group is needed. More subjects must be added, because a prevention program, no matter how effective, cannot change everyone who is treated, and of those whose psychosocial characteristics are changed, only a portion will reduce inhalant use. As with longitudinal research, identifying and treating a high-risk group with

a high potential base rate of future inhalant use can improve the efficiency of the study, and psychosocial prevention research will probably have to take this form.

A second solution might be to increase subject numbers by developing methods for systemwide prevention, for example, using media to change psychosocial characteristics for whole schools or whole communities. This method would probably only work for prevention aimed at young inhalant users. The two other types of users would probably not be in the school system to be tested at followup.

Treatment

As a psychosocial experiment, treatment would look at the effects on the dependent variable, inhalant use, of altering psychosocial characteristics that either (1) maintain inhalant use, (2) enhance potential for quitting, or (3) prevent relapse. In establishing an agenda for psychosocial treatment research, a key question is what psychosocial characteristics should become the independent variables.

The research shows that inhalant use is related to peer drug involvement, and peers are likely to be a major factor in maintenance. Altering these peer relationships may be critical for quitting and prevention of relapse (Oetting and Beauvais 1987). Experimental approaches to change these relationships, either by separating the subject from the group or changing the group's behavior, probably should be tried, particularly for young inhalant users and adolescent polydrug and inhalant users.

Early and persistent family problems may be among the initial causes of susceptibility to inhalant use and may also be a factor in maintenance. Except when family breakdown is extreme, the young inhalant user is often still in touch with the family. Given the nature of the families of inhalant users, a highly structured form of family therapy and continued monitoring of the family to prevent abuse and deal with crises might alter the independent variable enough to see a result. A program like Vega's (1990) Projecto Bienstar, which used *servidora* to provide Hispanic women with cognitive-behavioral instruction on coping with family conflict, might be tried. It may be too late for family treatment to be useful for adolescent or adult users.

The underlying theme of psychosocial research on inhalant users is marginality. They are almost invariably found to be poorly adjusted to and incapable of functioning effectively in society. If an individual does not have the capacity to succeed in society, unless something can be done to alter that basic characteristic, treatment of inhalant users may prove to be futile. Even if they stop using, what does life have to offer? Without the capacity to adapt to and succeed in the world, they would be likely to return to inhalant use. For example, young inhalant users have problems in meeting the requirements of school. Even if they stop using inhalants, if they cannot succeed in school, they will drop out and continue to be marginal in society. In that case, the probability of relapse to inhalant use seems high. Experiments designed to alter their school adjustment should be attempted. Adolescent polydrug users who use inhalants may have similar problems, but as they get older and work becomes more relevant than school, alternative treatment possibilities may need to be explored such as job training or placement. Inhalant-dependent adults, from all reports, are likely to be unemployed and unemployable. Building their ability to function successfully in the work environment may also be essential if relapse is to be prevented. A treatment program to change work adjustment should take into account the fact that these inhalant users are likely to be very low on the work adjustment hierarchy (Oetting and Miller, 1977). Placing them on a job will not be enough. They may need help with many of the stages essential to developing work adjustment.

Summary: A Psychosocial Agenda

The descriptions of research show that every type of research can offer valuable potential insights into the psychosocial underpinnings of inhalant use. No one kind of research is preferable; each type of research answers different questions in different ways. Every type of research offers certain assets and has specific limitations. An overall research agenda should support a variety of studies, chosen to answer questions that are important given the current state of the art.

Tough minded cost/benefit decisions may need to be made. A difficult dilemma occurs because, even if a treatment program for inhalant-dependent adults were maximally successful, they tend to be so disadvantaged that it would likely lead only to entry level employment for a few of these people at a relatively low wage. Given their current status, this might be a major and beneficial outcome for them, but the result does not seem to be a major ben-

efit for society. Would the same funds lead to more societal benefits if they were devoted to an intensive research study to determine how altering school abilities of high-risk children changes their propensity for inhalant use?

Fortunately, since it will probably always be a costly endeavor, an investment in psychosocial research on inhalant use has benefits far beyond the immediate ones. The characteristics that we are learning about are important aspects of personal/social adjustment in general. Inhalant users are an extreme group, but because they are extreme, results may stand out more clearly. What we learn may help those who are tragically involved with inhalants. But more important, what we learn may be fundamental lessons about how cultural, social, and personal characteristics interact, either to develop resilience and enhance human potential or to create susceptibility to problems and destroy human potential.

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Ethnomethodology, Psychosocial Measures, and Inhalant Abuse Research

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In their chapter, Oetting and Webb set out two fundamental and somewhat ambitious objectives: (1) to assess and describe the psychosocial correlates of inhalant use and (2) to recommend a long-term series of highly focused research projects. In this comprehensive chapter, two basic themes subsume the actual thrust of his work. Specifically, Oetting and Webb emphasize the science of inhalant abuse research and, to a lesser extent, tantalize the reader with their emphasis on the role that culture and ethnicity play in the research. The isolation of these two salient themes stimulated me to focus my comments on selected psychosocial issues and the ethnomethodological[1] flavor of their writing.

Oetting and Webb, in laying out a progressive series of social and behavioral science methodological approaches, remain somewhat faithful to their profession. They believe that psychology is a natural science and subscribe to the

[1]The term "ethnomethodology" was first coined by Garfinkel (1967) and refers to the study of the way ordinary people go about their daily lives. In this chapter, the term has broader implications and broadens the meaning to include the study of culture from an interdisciplinary perspective.

notion that the unit of analysis is the generalized individual. Unlike most of their colleagues, their perspectives are not locked in a segregationist ideology where culture is not viewed as a variable worthy of consideration (Pepitone 1987). Oetting and Webb are not steadfast in keeping to the fundamental guideposts that limit most investigators in the science of the social and behavioral science disciplines. For them culture is an important variable, especially in terms of the methods one chooses to use and the importance of the unique lifeways and thoughtways of the units of analysis. So it is no surprise that they recommend ethnographic approaches and devote space describing inhalant use among different ethnic groups.

Oetting and Webb jump right into the fray of the arguments surrounding appropriate substance abuse research models. They propose a model bounded by methodological and psychosocial dimensions. As intended, the model prompts close scrutiny and begs for analysis. The bait is not easily ignored. The methodological dimension follows a linear progression marked by presumed increasing scientific rigor. They note that scientific inquiry begins with naturalistic observations and ends with treatment research. The progressive dimension resembles the levels of analysis perspective introduced by the sociologist Talcott Parsons (1960) and advanced by the social psychologists Sherif and Sherif (1969).

The methodological dimension prompts me to make a few pointed suggestions. First, I would argue that the ethnographic method should immediately follow naturalistic observation; epidemiological procedures tend to be more quantitative, while ethnography and naturalistic observation lean more to the use of qualitative procedures. In fact, the emphasis a researcher places on quantitative and qualitative procedures fluctuates immensely as one progresses through various levels of research rigor. Second, Oetting and Webb's model can be readily expanded and might be made more useful since each method can be subcategorized into a variety of alternatives. Experimental research, for example, can be subdivided into quasiexperimental studies; this level of inquiry can be further divided into field studies, natural group experiments, etc. Third, there doesn't appear to be room in the scheme for economic, historical, physiological, and psychopharmacological methods. Oetting and Webb might argue that they are preparing a model for psychosocial research, but we cannot lose sight of the obvious fact that psychoactive substances are chemical compounds that interact with the human body in varied and complex ways that indeed influence consciousness. And we know

all too well that each individual reacts to the substances in a multitude of ways influenced by the history of usage, dosage levels, composition (especially for solvents) of the drugs, metabolic rates, and the availability of the substance. Methods are available to isolate the above listed variables. Without these additional methods of inquiry, the methodological dimension is incomplete and represents only a partial list of those methods necessary to comprehensively understand and predict the dynamic effects of drug use and abuse. Indeed, by including the methodological dimension as a psychosocial method, they omit other important aspects of human behavior.

Unfortunately, the three-part psychosocial dimension consisting of cultural, social, and psychological elements prompts even more stringent criticism. The social element presents very few problems and will not be discussed. The relationship of the psychological element is a bit more confusing. Do Oetting and Webb really mean the individual? Where is there room for the interactive roles of learning and genetics? What role does the findings of sociobiologists play in the psychological (or individual) element? Should the element be subdivided into more refined categories to include personality, psychopathology, and development?

The third element, culture, arouses the most concern. Oetting and Webb's discussion of culture is somewhat inaccurate and redundant. The social and psychological elements in the model, in themselves, are not acultural. In the discussion on culture, Oetting and Webb place the construct in an abstract domain; they state, "culture provides a foundation of. . ." Culture is a product and a process, not a foundation. Culture is the result of human interaction both at the individual and group level and therefore is inextricably woven in the fabric of all human activity. Furthermore, Oetting and Webb argue that major socialization forces are based on culture—they are not, as culture permeates those forces in every conceivable manner. For this and many other reasons I prefer to use the term "enculturation" in lieu of "socialization" as it is "the aspect of the learning experience which sets (humans) off from other creatures, and by means which initially and in later life (one) achieves competence . . . within the limits of a given body of custom" (Herskovits, 1948, p. 39).

The concept of culture is fraught with conjecture. Just a cursive review of its many definitions reveals its complex nature; one can find slightly over 100 attempts to define the seemingly elusive concept. But whatever definition one chooses, social and psychological processes will somehow be embedded in its

framework; that is, both processes will be implied by the definition or they will be stated directly.

Oetting and Webb's separate listing of culture also raises the inevitable research question: What research variable status should culture be given? Eckensberger (1979) pointed out that much of the early work in cross-cultural psychology treated culture as an antecedent and consequently provided no strategy for the interpretation of culture as a product of human action and behavioral change. Segall (1983) argues that social and behavioral researchers, rather than strive to comprehend culture, should "identify the various lower-order factors in the natural and man-made environments of humans which influence their behavior in a reliable manner" (p. 127). Hence, Segall believes that "culture cannot be one of these independent variables" (p. 127). Instead they suggest that it can be given the status of an overarching independent variable. Still others argue that the products of culture should be dependent variables, and, when that occurs, all sorts of measurement, sampling, procedural, and conceptual problems arise owing to a society's distinctive lifeways and thoughtways.

The psychosocial model put forth by Oetting and Webb is, however, appropriate for use in outlining a psychosocial research agenda. Because of the psychosocial domain, the model is somewhat limited in its inclusiveness. Huba, Wingard, and Bentler (1980) proposed a drug use framework that is a bit more comprehensive than that proposed by Oetting and Webb. The model is divided along four progressive dimensions, viz. biological, intrapersonal, interpersonal, and sociocultural. Linkages are established between various research element domains showing the interrelatedness of factors that summarily influence drug use. Oetting and Webb's measurement domains could be added to those of Huba, Wingard, and Bentler (1980) to add some guidance for the researcher.

While I have a partial fondness for comprehensive, ecologically grounded models, they do present horrendous research problems. Drug abuse researchers have been struggling with isolating causal relationships, contingencies, and correlates for decades. Some of the findings make sense; others are short lived as new, contradictory findings introduce alternative explanations. Comprehensive models like those proffered by Oetting and Webb and others are pushing researchers into using a potpourri of variables. We struggle to balance the precious time we have with our respondents and the number of

questionnaire items we can conceivably wedge in—each item or set of items is intended to give clarity to a variable and in some research efforts they end up as a latent variable in an intricate web of causal vectors in some recursive path model. As the causal vectors increase, so do our attempts to establish those significant paths that best predict drug use—in this instance inhalant abuse. After carefully considering all of the research questions and the model, Moncher et al. (1990) ended up with a questionnaire containing well over 200 items. The questionnaire, by prearrangement with our sampling units, could only be administered in a 60-minute session. We had to reduce the number of items, eliminate scales and variables, and thus erode the pretest reliability of some of our scales. The painful process of item reduction had to be reflected against our research agenda, commitments to research sponsors, and the integrity of our scientific mission. Some critics would argue that any predictive model we generated from our results would be only partially valid since there are many potent sources of causality that could not be included in our study. For example, of necessity we were obligated to ask a series of questions about polydrug usage—so for each drug (e.g., LSD, heroin, smokeless tobacco, crack, cocaine, marijuana) we had to repeat a series of interrelated questions that consumed about 60 percent of our questionnaire. Imagine a drug abuse study involving just one ethnic group where the researchers are driven to be inclusive of the many plausible array of interactive variables conducted with a few of the methods recommended by Oetting and Webb. All things considered, the effort could be enormous.

Few youths experiment with single psychoactive substances such as inhalants (e.g., solvents). Moreover, youths who integrate drugs into their lifestyle, however vigorously, usually are using other substances. Attempting single drug studies can obfuscate the use patterns and the accompanying vicissitudes of other drug use and argues against single method approaches to studying drug use. Certainly such isolated studies have merit and are worthy of consideration. As any drug researcher well knows, drug use patterns are not static phenomena. A temporal and historical factor intrudes on the drug use process that, to a large extent, is molded by changing attitudes, morals, values, drug availability, economics, and variable social sanctions. In a word, most drug studies are time bound. What might have been useful data two decades ago may only have an ounce of relevance for the last decade of the 20th century. To prevent our results from wearing out, do we wear out ourselves and our respondents by designing massive data mining ventures to accumulate and generate as much information as possible?

Oetting and Webb's chapter, especially the well written and thorough literature review, raises even more painful questions. A number of themes and findings could be isolated for further discussion; in keeping with the theme of this reply, emphasis will be directed toward the ethnic and cultural results.

Oetting and Webb's summary of cross-cultural inhalant abuse findings can be reflected against our review of the ethnic-minority drug abuse literature. Specifically: (1) drug abuse is presented as more of a problem for nonwhite ethnic groups; (2) these ethnics become users and abusers in response to the prevailing disorganization of the social climate; and (3) the study of drug abuse is only appropriate when comparing use and abuse patterns of different ethnic groups with whites. Consequently other ethnic groups, especially blacks, are "overrepresented," leading to the unfortunate conclusion that these groups have greater drug use problems than whites (Trimble and Bolek 1989). Moreover, Oetting and Webb's review and summary also echoes the review findings of Austin, Johnson, Carroll, and Lettieri (1977) of 13 years ago. Austin and colleagues maintained ethnic drug abuse research lacked any cogent theory to explain the results, that interpretations and theoretical generalizations were not convincing, and that the dimensions of the problem were still not well understood. The two sets of summary statements are not an indictment of Oetting and Webb's review; after all they merely organized and reported what was available to him. Instead, we have a series of psychosocial inhalant abuse findings that actually present more questions than answers and thus we have large gaps in our understanding of the problem.

One of the problems identified by Oetting and Webb concerns the near absence of studies attempting to isolate the correlates between ethnic and cultural identification of minority youth and inhalant use patterns. Oetting and Webb do summarize their own work on the identity-use relationship found in their work among American Indians. By their own admission the results are both mixed and highly complex. Part of the problem involves the psychometric characteristics of ethnic identification measures and the fact that most ethnic-minority drug abuse studies fail to assess the levels of ethnic identity of respondent populations.

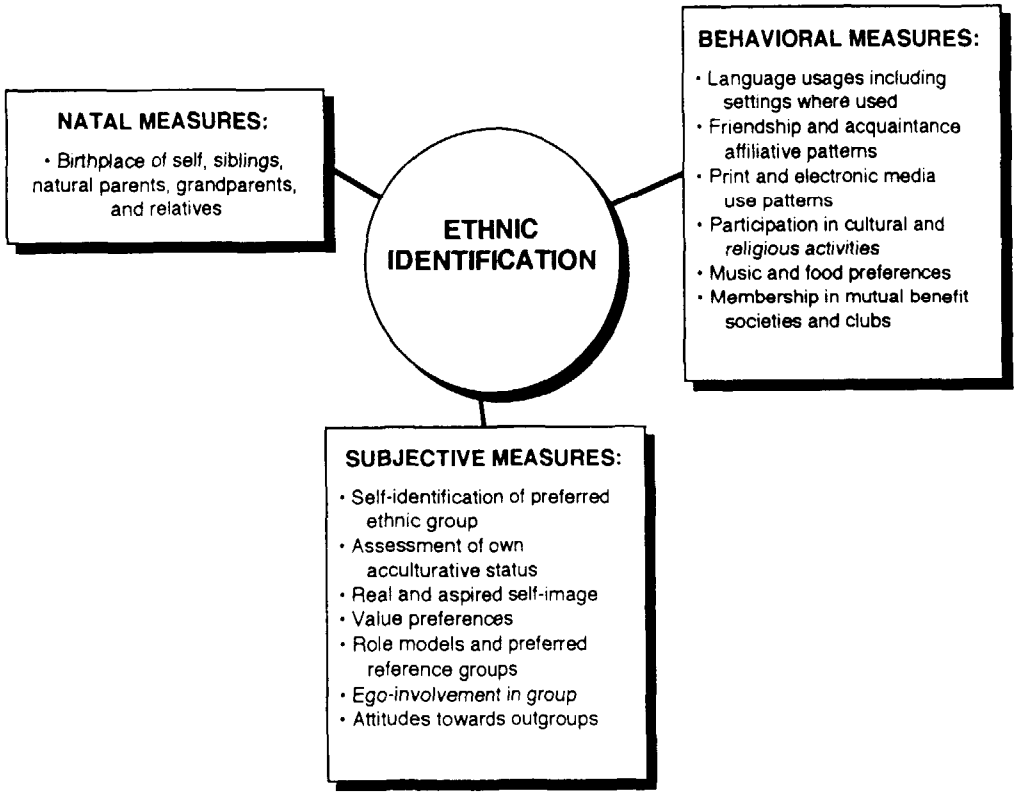
More often than not, drug abuse researchers seeking ethnic and cultural explanations select respondents as though they share a common modal understanding of their own ethnicity and nationalistic identification. Oetting and Webb's review of the literature bears out this assumption, as does the field of

ethnic minority substance abuse research. What we find are studies focusing on American Indians (or Native Americans), Asian and Pacific Americans, Blacks, Mexican Americans, Puerto Ricans, and even studies involving "Hispanics" (Trimble 1991). For a vast majority of the studies descriptions of ethnics tend to rely on the use of broad ethnic glosses, superficial, almost vacuous, categories that serve only to separate one group from another. Use of such glosses gives little or no sense of the richness of cultural variations within these groups, much less the existence of numerous subgroups characterized by distinct lifeways and thoughtways. Forbes (1990) maintains that use of broad ethnic designations in any form is insulting. Heath (1987) offers a more strident observation: "The insult arises from having to deal with someone else with the authority and aggressiveness to assault one's own ability to be one's self" (p. 48). "Even though such gross categories bear no relation to the reference groups with which people normally identify themselves," they claim, "one might expect them at least to yield useful statistics at the national level. Unfortunately, they are utterly useless in that respect as well" (p. 106). Use of ethnic glosses to conduct ethnic-comparative or ethnic-specific studies is not only insulting, it is very poor science. Consider the implications for external validity and replication studies (of which there are very few indeed in the drug abuse field).

So how do we assess ethnic-identity and marginality? The latter is a related construct that Oetting and Webb identified as a major theme. Most importantly, respondents should be given the opportunity to self-identify, a point emphasized by Trimble (1991) and Forbes (1990). Measuring ethnicity, however, "is not a simple all or nothing proposition. Researchers have long recognized that a person's level or intensity of identification with a particular ethnicity can vary from a weak-nominal association to a strong-committed association" (Smith 1980, p. 79).

Admittedly somewhat contradictorily in light of previous comments, I am recommending that ethnic identification be the mainstay of all studies involving ethnic groups. Self-identification by itself is not sufficient since it creates yet another variation of the ethnic gloss. Measures (which mean more questionnaire items and therefore more time) should tap into the depth and subtle layers of one's ethnicity. As a possibility I suggest that the tripartite measurement domains depicted in figure 1 serve as a guide. As currently

Figure 1. Ethnic identification measurement domains



conceived, ethnic identity consists of the subjective, behavioral, and natal domains. Suitable variables are listed beneath each domain that when aggregated across the measures would yield a unified index. Respondent indices most likely would vary across a continuum. Such variation permits numerous statistical manipulations not otherwise available to the researcher who uses ethnic glosses. Moreover, strong, reliable ethnic identification measures would increase external validity, offering the field a more valid array of findings (Trimble 1991).

Marginality, while an interesting concept, has not received the benefit of a good deal of research. That is, there are very few scales to assess it. In part, marginality is really a component of the acculturative process as determined by social class, socioeconomic status, ethnicity, and a few other salient but distinguishing characteristics. Oetting and Webb's claims that inhalant users are found among the marginal ones at any age and in any group and "are marginal in society" need more substantiation. Gist and Wright (1973) maintain that *groups* are marginal when: (1) members do not ordinarily qualify for admission into another group with which it is more or less closely associated; (2) these groups differ significantly in the nature of their cultural or racial heritage; and (3) between them there is limited cultural exchange or social interaction. Are there empirical data available to demonstrate indeed that inhalant users are marginal? Are some users more marginal than others? Can some form of intervention strategy be devised to chip away at the social and psychological factors that contribute to marginality? Are the users perennially marginal or do they sense their marginality when they feel excluded from groups to which they aspire to affiliate? Inhalant users may be at the edge, but it seems to me that some sense of belonging occurs through peer clustering and the correspondent use of inhalants and presumably other drugs. Scales should be developed to assess the marginality hypothesis. The continued use of the term without adequate substantiation provides the field with a thin excuse to explain away the problem.

Finally, I want to draw some attention to the notion that inhalant and polydrug users have something wrong with their sense of self. Many lay people and some researchers seem to be firmly committed to the idea that when youths use drugs, there one will find a distorted, negatively imbalanced relationship between ideal self and real self. Oetting and Webb did not find many studies examining the self-ideal notion among inhalant users. The ongoing drug use research being conducted at the National Center for American

Indian and Alaska Native Mental Health Research, which was conducted at an American Indian boarding school, yielded no significant statistical relationship for a measure of self-esteem and drug use (S. Manson, personal communication). In fact, self-measures are weak predictors in their regression analyses. Moreover, Moncher et al. (1990) found similar results among Indian youths in the State of Washington. Other researchers, too, have and continue to get mixed results in their studies relating self-perception or regard to the causes, prevention, and intervention of drug use. There may be a relationship. However, if we are going to continue to explore its possibilities, a good deal of solid psychometric research should be conducted. First, most drug researchers do not use the same measures of self. What is most often used are variations of Rosenberg's self-esteem scale. Hence, researchers are encouraged to settle on using comparable measures of self. Second, the concept of self is extraordinarily complex. Therefore, research is needed to isolate what self domain (e.g., esteem, understanding, control, alienation, mattering, acceptance, efficacy) is most associated with drug use. Third, we can no longer accept drug-related self-study results that are based on very short four to eight item scales. Whether the results are significant or not, use of small item scales tends to obscure observed relationships and general overall assumptions about the effectiveness of a prevention or intervention modality, and, in the main, can lead to gross exaggerations of statistically derived mean effects, especially if one has large samples. And, finally, a concerted, concentrated effort is needed to explore the theoretical relationship between the sense of self and what drug use really does to the general personality makeup of users. I have never quite understood why someone who ostensibly feels good about one's self would use a consciousness altering substance that would enhance that feeling.

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Comments on Psychosocial Characteristics

Daniel L. Creson

In clinical work with individuals who use and, in society's term, "abuse" street drugs (an interesting euphemism in itself), I am often reminded of George E. Valliants' words, used in a different context:

> If you have not the strength to accept the terms life offers you, you must in self-defense, force your own terms upon it (Valliants 1977).

This maxim is not unlike that of a 14 year-old inhalant user who said, in response to my persistent curiosity, "Man, look, me and my friend do what we do and that's just the way it is."

I don't know what Vaillants meant by the word "strength" when he referred to "strength to accept the terms life offers you." It is most certainly a subjective attribute, one that in human terms is needed to provide reason for why some individuals behave in one way and others in a very different way, why some individuals use inhalants as a mode of forcing their own terms on life, and others, from the same neighborhood, the same schools, and with similar experiences, do not. My inhalant using young friend chose a concept different than Valliants, but one just as deterministic. The use of inhalants was what he did, but was more than that—it was what he did with his friend.

For researchers, "That's just the way it is" and even "That's just the way it is with me and my friend" is just a beginning. Oetting and Webb have traced the

paths of researchers in their attempts to go beyond that beginning. In their comprehensive and exhaustive review of the inhalant abuse literature as we refer to it, they have described a multiplicity of variables that correlate with the use of inhalants, a multiplicity that is remarkably uniform from study to study. There are a few surprises—but not many. In the process of this review, inadvertently or perhaps with a clear intent, Oetting and Webb have done something more. They have uncovered something about the way the social scientist thinks about inhalant abuse. The evidence is indirect, but no more so than most social anthropological evidence. Oetting and Webb have given us some idea of our own preconceptions as they are implicit in: (1) the questions we ask about the use of inhalants, (2) the words and concepts we use in forming those questions, (3) the way those questions are asked, and (4) the sense we attempt to make out of the answers.

It may be that our mode of thinking presupposes a nonexistent smoking gun. The research literature Oetting and Webb have so carefully surveyed fails to disclose such an obvious linear cause-and-effect relationship that would make other questions redundant. I doubt seriously that they expected to find such an ultimate answer. Nor do I believe that anyone in this field is seriously committed to the idea that such a solution is possible.

As a direct result of these preconceptions, and sometimes even despite our own awareness of our own preconceptions, we continue to ask the same questions and, for the most part, get the same answers.

In a recent study of inhalant abuse among adolescents in a low socioeconomic Hispanic section of Houston, we (Creson and Welch, unpublished) were able to again confirm the correlations between inhalant abuse and such variables as (1) poor school performance, (2) high school dropout rates, (3) disciplinary problems, (4) polydrug use, and (5) peer influences.

I believe this incremental and conformational process of repeated similar findings is valuable, but I believe that Oetting and Webb's call for a comprehensive research strategy is much more important—and certainly more exciting. The elegant and sophisticated model they propose has much to recommend it. There are problems, however, and one of these Oetting and Webb recognize and define. It is a problem of resources. There is also a second problem, a problem of complexity.

With regard to resources, it seems unlikely that the talent and financial support are available for allocation to such a research effort, given the multiplicity of human dilemmas that social scientists are being asked to unravel. To provide such resources over time as they become available would be impractical. The time frame for the research effort could not be endlessly extended. In the rapidly changing social/cultural context of contemporary human life, research needs to be completed in a period during which previous findings remain relevant.

I do not believe Oetting and Webb meant the schema they proposed to be a road map, but rather a model for structuring our thinking, and in this way, it is extremely helpful. It is in this context that the second problem arises. It has to do with the necessary complexity the task requires. There are omitted parameters from their schema that must, at some point, be evoked if the schema is to organize rather than restrict our thinking. One can, for example, postulate additional second or third order categories of social variables, such as political and economic dimensions.

Further, and more importantly, the reciprocity between environment and biology, the consequences of social life acting on genetic potential, and the mediation of such feedback, all loop through an evolving awareness of self with attendant values and personas that contain implicit behaviors in given specific contexts. These complexities provide the greatest potential for useful understandings of why some use inhalants and others do not.

A recent incident puts this in perspective. A staff discussion of demographic and test data collected in a previous study (Creson and Welch, unpublished) left me dissatisfied, feeling that we had not significantly increased our understanding of what was going on in the youth culture of the Hispanic community in which we were working. The most significant finding was the results of neuropsychological testing of our inhalant abusing subjects. A striking finding to us was the discrepancies between performance and verbal I.Q.s in the inhalant abusing groups, where performance I.Q.s were significantly higher than in the noninhalant abusing group. The testing data were incongruent with our structured way of thinking about the problems. The demographic data were not.

Then I read Oetting and Webb's paper. My first thought was that only a prospective study could get us beyond what seemed to me to be a conceptual road block and clarify the interrelationship between the biological (presuming

the I.Q. discrepancies to be in some degree a function of biological and sociological interaction), and the social demographic data. But I have had some subsequent thoughts, less grandiose, but ones I want to share.

Paul Watzlawick wrote, "The belief that one's own view of reality is the only reality is the most dangerous of all delusions" (Watzlawick 1976). That thought is not a new one. It is not new to mystical speculation, and it is not new to scientific investigation.

The belief that substance abuse (in this case, the use of inhalants) "is 'caused'" is at the basis of much of the research that has been done. The very word "abuse" makes the assumption explicit. Richard A. Meisch (author of a chapter in this volume) once said to me, "What is amazing is that we are not all cocaine addicts." Much the same might be said about inhalants. Instead of exclusively looking for profound influences in the social cultural environment that predispose one to the use of inhalants, perhaps we should allocate some of our resources to an investigation of what may well be (based on animal studies) the abnormal state of "nonuse". It seems probable that the cause of nonuse can most profitably be pursued in the interaction of socio/cultural variables and biological processes. (Demographics interacting with the biological antecedents of I.Q. discrepancies).

It is impossible for science to answer all the questions that human creativity can formulate about inhalant abuse. Many of them would be nonsensical and beyond any answer. Most of them would be semantic puzzles rather than substantive issues. For this reason, scientific research strategies are necessary, and the first step in an existence of shifting reality is to ask what does one want to accomplish. This in no way negates basic research. Basic research goes where no one has gone before (or perhaps only a few). It is not basic research to ask the same questions others have often asked in another place, or with another group. In no way meaning to disparage replicating investigations, (our own included), it seems probable that there are other questions that might be assigned a higher priority.

It seems to me that a major motivation for asking questions about inhalant use is a desire to accomplish something, i.e., reduce the use of the inhalants. If this is accurate, then I would propose that direction (goal or goals) also be incorporated into Oetting and Webb's schema, that there be a measurable end point. One might propose a trial of successful interventions directed at social problems other than inhalants. The sophisticated targeted merchandising

strategies used to reduce HIV infection in the gay community of San Francisco might, for example, be directed against inhalant use in a defined population. This would fall into Oetting and Webb's category of experimental research, but the preimplementation merchandising surveys and trial would facilitate a more creative traditional research effort, including providing an impetus for studying the ethnologies that Oetting and Webb point out are missing from the literature.

Oetting and Webb's chapter is important. In it: (1) they provide us with a useful and thorough survey of relevant research, (2) underscore some of the prevalent research biases, (3) provide one heuristic model for conceptualizing future research, and, more importantly, (4) give us a basis for a stimulating and creative discussion that cannot help but improve our collective approach to find a better and more useful way of understanding the behaviors involved in the use of inhalants.

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Solvent Toxicity: A Neurological Focus

Neil L. Rosenberg
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Toxicology of Inhalant Abuse

Acute Intoxication

Most commercial products that are inhaled contain several distinctly different solvents, each with its own potential distinct toxicity. In addition, most "inhalant abusers" have inhaled a variety of products to excess before they appear in a treatment facility. One exceptional case would be a novice experiencing an overdose—usually resulting in anoxia and possibly death. The majority of inhalant abusers never reach a hospital or outpatient facility.

Many inhalant abusers use one or two "preferred brands," but this will change according to availability. For example, in the inhalant-abusing population in Denver, a clear spray lacquer of a particular company was the favored inhalant. However, when it became evident that the main use of this product was to get high, it quickly disappeared from store shelves. The inhalant-abusing population just as quickly focused their attention on a particular gold spray paint as the preferred brand.

To understand the solvent abuser, one can conceive of the intoxicated state as a quick "drunk," as many of the symptoms resemble alcohol intoxication. These individuals display several of the following symptoms: initial excitation

turning to drowsiness, disinhibition, lightheadedness, and agitation. With increasing intoxication individuals may develop ataxia, dizziness, and disorientation. In extreme intoxications, they may show signs of sleeplessness, general muscle weakness, dysarthria, nystagmus, and occasionally hallucinations or disruptive behavior. Several hours after, especially if they have slept, they are likely to be lethargic, hung over with mild to severe headaches. Chronic abuse is associated with more serious complications including weight loss, muscle weakness, general disorientation, inattentiveness, and lack of coordination.

Most reports have described the acute intoxication in heavy users of toluene vapors. Acute intoxication with toluene produces headache, euphoria, giddiness, and cerebellar ataxia. At lower levels (just over 200 ppm), fatigue, headache, paresthesia, and slowed reflexes appear (Benignus 1981; Von Oettingen et al. 1942). Exposure to levels over 600 ppm causes confusion or delirium, and euphoric effects appear above 800 ppm. Although solvent abusers have favorites, occasionally they use an unpredictable array of solvents. Multiple components in the mixtures may enhance the net toxicity in a synergistic or additive manner. More specific syndromes and details of the clinical features of the chronic inhalant abuser are described below and are related as closely as possible to specific substances.

General Considerations

Although treatments are usually not specific or designed for different solvents, it is important to identify the major contributing factors in understanding the prognosis and recovery of the individual and in the design of treatment. This is not easy, as it is difficult to identify the causative agents even if one obtains the container or product most often used.

Labels are often insufficient to identify even the major, let alone any minor elements, that could be contributory to the disease state. It is also common for the labels to identify toluene and some other solvents but yet ignore other substances. For example, one of the more toxic agents, hexane, affects the peripheral nervous system and has been identified in products that did not list it on the product's label. Only through an analysis of the products used (e.g., by quantitative gas chromatography) will it be possible to determine most of the volatile solvents in a product. Further, identification of one product sniffed by the user does not reveal all the toxicants that should be considered in the

user's diagnosis. A "sniffer's" repertoire is quite varied in the type of solvents as well as other drugs used.

In anticipation that the physician, forensic toxicologist, or others will be able to identify the major substances contributing to the disease state, we will attempt here to delineate the symptoms most often encountered in inhalant abusers and hopefully on a rational basis correlate them where possible with the substances that are most likely to be the cause. We will include where possible any specific treatments that will be used in addition to the provision of the usual basic supportive care.

To correlate those specific clinical symptoms that result from exposure to various volatile chemicals is not easy, as suitable animal studies have not corroborated many clinical evaluations. Also, months to years of exposure are often necessary for the expression of some disease states. As many inhalant abuse subjects are not admitted to hospitals, outpatient clinics, or drug treatment program for problems associated with inhalant abuse overdose or dependency, little information has surfaced detailing many of their problems. Therefore, this review will utilize clinical epidemiological studies of noninhalant abusers as well as retrospective clinical case studies of inhalant abusers and other solvent-related accidents, whether from abuse or occupational exposures, along with the information derived from animal studies, to identify particular hazards that may result from inhalation exposure.

Recognition of and Criteria for Defining Neurotoxicity

The nervous system may be affected at many levels by organic solvents as well as other neurotoxic substances. As a general rule, resultant syndromes are diffuse in their manifestations (Schaumburg and Spencer 1987). Because of their nonfocal presentation, neurotoxic disorders may be confused with metabolic, degenerative, nutritional, or demyelinating disease (Schaumburg and Spencer 1987). This principle is illustrated in the setting of chronic toluene abuse, which may resemble the multifocal demyelinating disease, multiple sclerosis, in the findings on neurological examination (Lazar et al. 1983; Hormes et al. 1986; Fornazzari et al. 1983). In addition, neurotoxic syndromes rarely have specific identifying features on diagnostic tests such as computed tomography (CT), magnetic resonance imaging (MRI), or nerve conduction studies (Schaumburg and Spencer 1987). As a result, mild cases of intoxication may be very difficult to diagnose. The most reliable information, in

fact, comes from documented cases of massive exposure, and details of low level exposure and presymptomatic diagnosis are vague at best.

Acute, high-level exposure to most, if not all, solvents will induce short-lasting effects on brain function, most of which are reversible. Acute incidents that are irreversible probably act by producing secondary systemic effects such as cerebral hypoxia or a metabolic acidosis (Rosenberg 1992) and none have been proved to act by inducing an irreversible functional abnormality. In general, both acute high-level and low-level exposure to organic solvents are associated with full reversibility, and the acute toxicity with high-level exposure in no way predicts whether chronic low-level exposure will lead to an irreversible neurological disease.

Chronic high-level exposure to organic solvents occurs only in the inhalant abuse setting, where levels several thousand fold higher than the occupational setting occur frequently. Chronic neurotoxic disease related to solvent abuse is slowly and incompletely reversible, is usually irreversible, and usually does not progress after cessation of exposure (Hormes et al. 1986, Fornazzari et al. 1983). Both acute and chronic neurotoxicity from organic solvents are functions predominantly related to the dose and duration of exposure.

There may be no relationship between the mechanism of acute neurotoxicity and the clinical manifestations of chronic neurotoxicity. For example, an acute effect of a particular organic solvent may be attributable to the parent compound, while a chronic effect may be associated with a metabolite of this compound. In addition, in several known cases, a solvent has been reported to either diminish or potentiate the neurotoxic potency of a second solvent (Altenkirch et al. 1982; Altenkirch et al. 1977; Saida et al. 1976).

There is little or no apparent individual variability or altered susceptibility to the neurotoxic effects of either acute or chronic exposure to organic solvents. Except for other toxic exposures or illnesses that also cause neurologic sequelae, individuals will be likely to develop a similar clinical picture when exposed to solvents at equivalent doses for equivalent durations of time.

Chemical structure usually does predict the neurotoxic effects. An example of this is seen with two closely related compounds: 2,5-hexanedione (the toxic metabolite of n-hexane) and 2,4-hexanedione. A fixed dose of 2,5-hexanedione produces axonal degeneration in a particular species very similar to that produced by hexane, whereas 2,4-hexanedione never produces these changes.

Thus a small but important change in the compounds structure elicits a change from a positive to a negative pharmacological action.

Treatment of the Inhalant Abuser

There is no accepted treatment approach for inhalant abusers. Many drug treatment facilities refuse treatment of the inhalant abuser, because many feel that inhalant abusers are resistant to treatment. In general, it is felt that longer periods of treatment are needed to be able to address the complex psychosocial, economic, and biophysical issues of the inhalant abuser. When brain injury, primarily in the form of cognitive dysfunction, is present, the rate of progression in the treatment process is even slower.

The inhalant abuser typically does not respond to usual drug rehabilitation treatment modalities. Several factors may be involved, particularly in situations of the chronic abuser, where significant psychosocial problems may be present. Treatment becomes slower and progressively more difficult when the severity of brain injury worsens as abuse progresses through transient social use (experimenting in groups) to chronic use in isolation.

Drug screening may be useful in monitoring inhalant abusers. Routine urine screens for hippuric acid (the major metabolite of toluene metabolism) performed two to three times weekly will detect the high level of exposure to toluene usually seen in inhalant abusers.

Neuroleptics and other forms of pharmacotherapy are usually not useful in the treatment of inhalant abusers. However, as alcohol is a common secondary drug of abuse among inhalant abusers, a monitored program for alcohol abuse may be necessary.

Neurological Sequelae of Chronic Inhalant Abuse

Organic solvents are widely prevalent compounds and inadvertent exposure, primarily industrial, as well as volitional abuse occurs primarily by inhalation, with significantly less absorption occurring via skin or gastrointestinal routes. These compounds are highly lipophilic, which explains their distribution to organs rich in lipids (e.g. brain, liver, adrenal). Unexpired solvents absorbed by the tissues are then eliminated through the kidneys following metabolism of the solvents to more water-soluble compounds. In addition, metabolism of

some solvents may create additional compounds that are sometimes more toxic than the parent chemical (Allen 1979; Goetz 1985; Spencer and Schaumburg 1980).

Although most organic solvents produce nonspecific effects following absorption of extremely high concentrations (i.e., encephalopathy), a few produce relatively specific neurologic syndromes with low level, chronic exposure. Table 1 lists those syndromes associated with organic solvent exposure. Most of the early animal studies, which served as the basis for the setting of tolerance levels in industry, utilized acute studies to measure the effects, often including high level exposures that produced lethality. More recent clinical and experimental studies have focused on chronic low-level exposures to solvents that result in slowly developing peripheral and central nervous system syndromes. Two major neurotoxic syndromes occur in individuals chronically exposed to select organic solvents: a peripheral neuropathy and an encephalopathy. Less commonly, a cerebellar ataxic syndrome, parkinsonism, or a myopathy may occur alone or in combination with any of these clinical syndromes. In some instances, solvents interact and cause synergistic effects, resulting in multifocal central and peripheral nervous system damage.

As noted above, many organic solvents are, at high levels of exposure, capable of inducing an acute, reversible encephalopathy. Few induce chronic, long-lasting, or irreversible changes in nervous system structure and/or function. For organic solvents with proven neurotoxic properties, the type of neurological damage is often closely related to the structure of the chemical agent, while the degree of impairment and the extent of reversibility are related to the potency, dose, and duration of exposure (Spencer and Schuamburg 1985). Examples include n-hexane and methyl butyl ketone, which produce peripheral neuropathy, both related to voluntary inhalation of solvents and accidental exposure in the occupational setting. Chronic inhalation abuse of toluene produces an irreversible multifocal central nervous system syndrome characterized by dementia, cerebellar ataxia, spasticity, and brainstem dysfunction (Hormes et al. 1986). However, similar changes have not been found in workers exposed to toluene in the occupational setting.

Table 1. Clinical classification of inhalant abusers

Transient Social	**Transient Isolate**
Short history of use	Short history of use
Use with friends	Use alone
Petty offenses while intoxicated	No legal involvement
Average intelligence	Average/above intelligence
Possible learning disabilities	No learning disabilities
10 to 16 years of age	10 to 16 years of age
Chronic Social	**Chronic Isolate**
Long history of use—over 5 years	Long history of use—over 5 years
Daily use with friends	Daily use alone
Legal involvement—misdemeanors	Legal involvement—assaults common
Poor social skills	Poor social skills
9th grade education	9th grade education
Brain damage	Brain damage
Mid 20s to early 30s	Mid 20s
Mental retardation prevalent	Pre-use psychopathology prevalent

Solvent Abuse in Occupational Settings

Most studies on the subject of solvent abuse focus on adolescents (Ron 1986). It has been observed that adults at risk for solvent abuse include those whose work brings them into contact with these substances, including shoemakers, painters, individuals working in gas stations, those involved in the refinement of petrochemicals, degreasers, and others. However, few attempts have been made to identify the prevalence of solvent abuse in industry. One study reviewed the cases of industrial accidents due to exposure to chlorinated hydrocarbons. Of 384 case of industrial accidents due to either trichloroethylene, perchloroethylene, or 1,1,1-trichloroethane, nine (2.3 percent) were in individuals identified as habitual solvent abusers by the person investigating the

accident (Cherry et al. 1982). Although 2.3 percent seems to be a small number, one needs to consider that the number may be much higher, especially in those industries in which solvents with higher abuse potential (e.g., toluene) are used, such as in the paint industry. In addition, considering the millions of individuals exposed to solvents in the workplace, even 2.3 percent represents a large number of individuals. Finally, when discussing abuse in industry, one needs to consider issues of personal protection. If an individual worker is instructed on the proper use of protective devices (respirators) on the particular job being performed, and that individual chooses not to comply, the complaints of injury should be considered self-inflicted (i.e., abuse) rather than occupational injury, provided the employer has observed its part of the rules and instructions are in force. This last issue has been ignored in the occupational literature but needs to be addressed in a critical manner in future studies.

Table 2. Major neurologic syndromes produced by organic solvents

A. ***Encephalopathy***
1. Acute encephalopathy—nonspecific; high level exposure
2. Chronic Encephalopathy—seen with repeated high level exposure over years
B. ***Cerebellar ataxia***
C. ***Peripheral neuropathy*****—**distal axonopathy
D. ***Cranial neuropathy*****—**primarily cranial nerves V and VII
E. ***Parkinsonism***
F. ***Visual loss*****—**optic neuropathy
G. ***Multifocal***
1. Central nervous system (e.g., toluene)
2. Central and peripheral

Exposure to organic solvent mixtures either in the occupational or abuse setting is far more common than exposure to a single solvent. Numerous papers, primarily from Denmark and other Scandinavian countries, allege that chronic occupational exposure to organic solvents induces irreversible changes in neurological function that has been described by various terms including psycho-organic syndrome (POS), neurasthenic syndrome, chronic painters' syndrome and chronic toxic encephalopathy. This syndrome is characterized by personality change, memory loss, fatigue, depression, and loss of interest in daily activities, headache, forgetfulness, insomnia, difficulty in concentration, loss of initiative, and depression. Most studies of the POS have utilized epidemiologic techniques to compare and contrast findings in solvent-exposed and unexposed reference groups. Methods applied have included self-administered questionnaires, neuropsychological tests, and clinical neurophysiologic and neuroimaging tests. Most reports consider that 10 or more years of exposure is required to produce the POS; however, one study has suggested that only a 3-year period may be required (Flodin et al. 1984). Few papers have even suggested either dose-effect (Gregersen et al. 1984) or duration-effect (Lindstrom 1980) relationships, obviously critical issues in establishing a toxin-induced syndrome. Virtually all of the studies on this subject have been written by scientists and physicians from Denmark, Sweden, and Finland, who are of the opinion that organic solvents, as a class, have chronic neurotoxic properties. In these countries, permanent neurological deficit of the type described as the POS is a recognized and compensatable occupational disability. Scientists and physicians from other European and from North American countries do not recognize this entity and have instead attempted to understand the chronic effects of individual organic solvents.

Many of these studies were done in a retrospective fashion on individuals already diagnosed as having chronic toxic encephalopathy, psychoorganic syndrome, or solvent poisoning (Seppalainen et al. 1980; Flodin et al. 1984; Juntunen et al., 1980*b;* Gregersen et al. 1987; Axelson et al. 1976). The obvious difficulties inherent in any retrospective data analysis are compounded when individuals have been diagnosed as having the syndrome and often given disability pensions for this problem.

Reports of this syndrome have been in workers, from various industries where exposure to solvent mixtures is common including printers (Iregren 1982), aviation fuel workers (Knave et al. 1979; Knave et al. 1978), and painters (Iregren 1982; Hanninen et al. 1976; Hane et al. 1977; Linz et al. 1986; Baker

et al. 1988; Husman and Karli 1980, Husman 1980; Elofsson et al. 1980; Lindstrom and Wickstrom 1983; Orbaek et al. 1985; Valciukas et al. 1985; Fidler et al. 1987). Although the majority of reports have focused on symptoms and neuropsychological testing, there have been a few uncontrolled reports showing abnormalities on vestibular function testing (Arlien-Soborg et al. 1981; Binaschi and Cantu 1983; Hodgson et al. 1989), electroencephalography (Seppalainen et al. 1980; Seppalainen 1973, 1982), electromyography and nerve conduction testing (Seppalainen 1982; Mutti et al. 1982), visual evoked potentials (Seppalainen 1982; Elofsson et al. 1980), cerebral blood flow (Hagstadius and Risberg 1983; Arlien-Soborg et al. 1982), pneumoencephalography (Juntunen et al. 1980*a)* and computed tomography (Jensen et al. 1984) in both symptomatic and asymptomatic individuals.

However, recent studies have begun to cast doubt as to whether long-term occupational exposure to solvents causes any permanent neurological dysfunction (Grasso et al. 1984; Errebo-Knudsen and Olsen 1986; Juntunen et al. 1985; Triebig et al. 1988; Gade et al. 1988; Errebo-Knudsen and Olsen 1987). **A** detailed review of this current literature does not support previously published studies relating chronic occupational solvent exposure to any permanent central or peripheral nervous system injury. Occupational solvent exposure literature discusses the inadvertent exposure of an individual to these compounds; however, the issue of abuse of these substances in the workplace is also of concern.

Specific Compounds of Interest

The listing of organic solvents, which are described in detail below, is not intended to be a complete listing of compounds with associated neurotoxicity. Represented are those organic solvents that have been more commonly associated with abuse or where clear neurotoxicity is associated with exposure.

N-hexane and methyl butyl ketone. These two organic solvents are classified together because both n-hexane and methyl butyl ketone (MBK) are metabolized to the same neurotoxin, 2,5-hexanedione (2,5-HD) and produce a similar peripheral neuropathy. 2,5-HD is responsible for most, if not all, of the neurotoxic effects that follow exposure to n-hexane or MBK (Spencer and Schaumberg 1980; Spencer et al. 1980; Graham et al. 1982; Perbellini et al. 1981). Methyl ethyl ketone (MEK) alone produces neither clinical nor pathologic evidence of a peripheral neuropathy in experimental animals

(Spencer and Schaumberg 1980). MEK's importance is related to a synergistic effect between MEK and MBK and MEK and n-hexane detected in experimental animals and probably in humans (Altenkirch et al. 1982; Altenkirch et al. 1977; Saida et al. 1976). This potentiation of toxicity of one compound (MBK or n-hexane) by an otherwise nontoxic compound (MEK) underscores the difficulty with sorting out toxic effects of individual solvents contained within a mixture, and suggests that occupational exposure to solvent mixtures should be minimized or avoided altogether.

Methyl butyl ketone. MBK had limited industrial use until the 1970s, when it became more widely used as a paint thinner, clearing agent, and a solvent for dye printing. Soon afterward, numerous outbreaks of polyneuropathy associated with chronic exposure to MBK were being reported (Menkes 1976; Billmaier et al. 1974; McDonough 1974; Allen et al. 1975; Mallov 1976). Originally, MEK had been used as a solvent, followed by a mixture of MEK (90 percent)/methyl isobutyl ketone (10 percent). When the methyl isobutyl ketone was replaced by MBK (10 percent), reports of polyneuropathy began to appear in the literature. The route of exposure is usually inhalation, but the oral route has also occurred by ingesting contaminated food in work areas, and cutaneous contact has also occurred.

The clinical syndrome is characterized by the insidious onset of an initially painless sensorimotor polyneuropathy, which begins several months after continued chronic exposure. Even following cessation of exposure, the neuropathy may develop or may continue to progress for up to 3 months. In severe cases an unexplained weight loss may be an early symptom. Sensory and motor disturbance begins initially in the hands and feet, and sensory loss is primarily small fiber (i.e., light touch, pin prick, temperature) with relative sparing of large fiber sensation (i.e., position and vibration). Electrophysiologic studies reveal an axonal polyneuropathy and pathologically multifocal axonal degeneration, multiple axonal swellings, and neurofilamentous accumulation at paranodal areas (Spencer et al. 1975). Overlying the axonal swellings, thinning of the myelin sheath occurs. These findings are typical of a distal axonopathy or "dying-back" neuropathy described in other toxic and metabolic causes of peripheral neuropathy.

Prognosis for recovery correlates directly with the intensity of the neurologic deficit before removal from toxic exposure, with mild to moderate residual

neuropathy seen in the most severely affected individuals up to 3 years after exposure.

N-hexane. Until relatively recently, n-hexane has been considered an innocuous solvent. N-hexane is used in the printing of laminated products, extraction of vegetable oils, as a diluent in the manufacture of plastics and rubber, in cabinet finishing, as a solvent in biochemical laboratories, and as a solvent for glues and adhesives.

Cases of n-hexane polyneuropathy have been reported both after occupational exposure (Herskowitz et al. 1971) and after deliberate inhalation of vapors from products containing n-hexane, such as glues (Gonzales and Downey 1972; Shirabe et al. 1974; Goto et al. 1974; Prockop et al. 1974; Korobkin et al. 1975; Oh and Kim 1976; Towfighi et al. 1976). Clinically and pathologically, the neuropathy occurring with n-hexane is that of a distal axonopathy (Schaumburg and Spencer 1976), indistinguishable from that associated with MBK.

When glues have been analyzed in past reports of polyneuropathy occurring after glue sniffing, n-hexane has been a major component of the products' composition (up to 50 percent by weight). Another major component of these glues has been toluene; however, polyneuropathy does not occur from inhalation of toluene alone, and in previous reports of n-hexane neuropathy, the neuropathy did not appear until the subject switched to a product containing n-hexane. In contrast to toluene, n-hexane does not usually induce significant signs of central nervous system dysfunction, except with high-level exposures where an acute encephalopathy may occur.

Both clinical and experimental studies have shown evidence of central nervous system effects from n-hexane. Experimental animal studies have shown n-hexane to cause axonal degeneration in the central nervous system (Schaumburg and Spencer 1976; Frontali et al. 1981). Clinically, cranial neuropathy, spasticity and autonomic dysfunction occasionally occur (Altenkirch et al. 1982). Abnormalities on electrophysiologic tests of central nervous system function have also been seen, including electroencephalography, visual evoked responses, and somatosensory evoked responses (Seppalainen et al. 1979; Mutti et al. 1982). In spite of these finds, clinical effects of chronic low level exposure to n-hexane is restricted to the peripheral nervous system.

Toluene (methyl benzene). Toluene is one of the most widely used solvents and is employed as a paint and lacquer thinner, and as a cleaning and drying agent in the rubber and lumber industries, and in the motor and aviation fuels and chemical industries. It is a major component in many paints, lacquers, glues, and adhesives, inks and cleaning liquids. As with other solvents, inhalation is the major route of entry, though some absorption occurs percutaneously. Of all the solvents, toluene-containing substances seem to have the highest potential for abuse (Press and Done 1967; Fredlund et al. 1989; Spence et al. 1989).

In 1961 Grabski reported the first patient with persistent neurological consequences of chronic toluene inhalation. Since then, several reports of severe neurotoxicity have appeared in the literature (Kelly 1975; Knox and Nelson 1966; Boor and Hurtig 1977; Keane 1978; Sasa et al. 1978; Malm and Lying-Tunell 1980; Streicher et al. 1981; Takeuchi et al. 1981; King 1982; Metrick and Brenner 1982; Ehyai and Freemon 1983; Lazar et al. 1983; Fornazzari et al. 1983; Hormes et al. 1986; Rosenberg et al. 1988*a,b*).

The effects of chronic exposure are even less well understood than the acute dose-related neurotoxicity of toluene (Benignus 1981; Von Oettingen et al. 1942). Experience is still not sufficient to determine the incidence or pattern of chronic effects of toluene and other volatile hydrocarbons. Complete resolution of signs and symptoms has been reported after chronic abuse with prolonged abstinence and no significant treatment (Boor and Hurtig 1977; Von Oettingen et al. 1942). Syndromes describing severe and persistent neurotoxicity include cognitive dysfunction (Knox and Nelson 1966; Streicher et al. 1981; King 1982; Lazar et al. 1983; Fornazzari et al. 1983*a,b;* Hormes et al. 1986; Rosenberg et al. 1988*a,b;* Berry et al. 1977; Channer and Stanley 1983; Tsushima and Towne 1977), cerebellar ataxia (Grabski 1961; Kelly 1975; Boor and Hurtig 1977; Malm and Lying-Tunell 1980; Streicher et al. 1981; Takeuchi et al. 1981; Lazar et al. 1983; Fornazzari et al. 1983), optic neuropathy (Keane 1978; Ehyai and Freemon 1983), sensorineural hearing loss (Ehyai and Freemon 1983), and an equilibrium disorder (Sasa et al. 1978). The most common syndrome is that of multifocal CNS involvement (Streicher et al. 1981; Metrick and Brenner 1982; Lazar et al. 1983; Fornazzari et al. 1983; Hormes et al. 1986; Rosenberg et al. 1988*a,b).* Despite the many instances of "persistent" neurological deficits, in only one study was abstinence documented prior to clinical evaluation (Hormes et al. 1986). This point is of great importance, since it has already been noted that some individuals will go

into complete remission with prolonged abstinence (Boor and Hurtig 1977; Wiedmann et al. 1987).

In a recent study of 20 chronic abusers of spray paint, which consisted almost entirely of toluene, abstinence was documented for at least one month prior to evaluation (Hormes et al. 1986). In these 20 chronic solvent abusers, 65 percent showed neurological impairment. This was a small and unselected sample, so the findings probably do not reflect the true prevalence of neurologic damage. However, there was a fairly consistent pattern of neurologic abnormality. As others have suggested, the central nervous system is selectively vulnerable. In fact, no peripheral neuropathy was found, and there is no convincing evidence that pure toluene or other aromatic hydrocarbons cause peripheral neuropathy. Aliphatic hydrocarbons such as n-hexane, as noted earlier, cause predominantly peripheral nerve damage.

Neurologic abnormalities varied from mild cognitive impairment to severe dementia associated with elemental neurologic signs such as cerebellar ataxia, corticospinal tract dysfunction, oculomotor abnormalities, tremor, deafness, and hyposmia. Cognitive dysfunction was the most disabling and frequent feature of chronic toluene toxicity and may be the earliest sign of permanent damage. Dementia, when present, was typically associated with cerebellar ataxia and other signs (Hormes et al. 1986).

Other investigators have found a similar syndrome after chronic exposure to toluene (Boor and Hurtig 1977; Malm and Lying-Tunell 1980; Lazar et al. 1983; Fornazzari et al. 1983). Although some emphasized the cerebellar disorder, most cases also showed that they were impaired in a variety of cerebral functions. In one study, there was a similar pattern of cognitive impairment with neurologic abnormality, but the individuals were studied as soon as three days after the last exposure and there have been no data on long-term cognitive outcome long after cessation of prolonged toluene abuse. It should be noted, however, that many chronic toluene abusers have had no persistent cognitive impairment, despite approximately calculated cumulative doses equivalent to those individuals with cognitive impairment (Hormes et al. 1986; Rosenberg et al. 1988*b)*. This suggests either that the abuse histories obtained were not accurate or that other factors possibly play a role in those individuals.

Other types of neurologic dysfunction can be seen in many subjects, especially pyramidal and cerebellar signs (Hormes et al. 1986). However, in one study,

this pattern was observed in only one patient who was not also cognitively impaired or demented (Hormes et al. 1986). Oculomotor dysfunction, deafness, and tremor were seen only in severely affected individuals. Cranial nerve abnormalities were confirmed to olfactory and auditory dysfunction. Toluene-induced optic neuropathy, previously reported (Keane 1978), was not reported in the larger studies (Hormes et al. 1986; Rosenberg et al. 1988*a)*.

The clinical data suggested that the cognitive, cerebellar, corticospinal, and brainstem signs are due to diffuse effects of toluene on the central nervous system. In one prior report of an autopsy of a chronic solvent abuser, there was prominent degeneration and gliosis of ascending and descending long tracts with cerebral and cerebellar atrophy (Escobar and Aruffo 1980). Unfortunately, as in most reports of toluene neurotoxicity, this patient was abusing many solvents contained in several different mixtures, so the effects of individual solvents could not be determined.

A recent report has demonstrated that chronic abuse of toluene containing substances causes diffuse central nervous system white matter changes (Rosenberg et al. 1988*a)*. This was based on the findings on magnetic resonance imaging (MRI) of the brain in six individuals and the neuropathologic changes in one abuser not studied by MRI. All individuals abused the same toluene-containing mixture which contained primarily toluene (61 percent) and methylene chloride (10 percent). MRI of the six individuals revealed the following abnormalities: (1) diffuse cerebral, cerebellar, and brainstem atrophy; (2) loss of differentiation of the gray and white matter throughout the central nervous system; and (3) increased periventricular white matter signal intensity on T2-weighted images. The brain of the individual studied pathologically revealed diffuse, ill-defined myelin pallor, which was maximal in the cerebellar, periventricular, and deep cerebral white matter. Neurons were preserved throughout, axonal swelling or beading was not seen, gliosis was minimal, and occasional, scant perivascular macrophage collections were seen. These findings suggest that toluene is a white-matter toxin; the mechanism of action, however, remains to be explained.

Another recent study attempted to find correlation between the severity of the clinical involvement in 11 chronic toluene abusers and the findings on brainstem evoked responses (BAERs) and MRI (Rosenberg et al. 1988*b)*. Neurological abnormalities were seen in 4 of 11 individuals and included cognitive, pyramidal, cerebellar, and brainstem findings. MRI of the brain was

abnormal in 3 of 11 individuals, and all 3 also had abnormalities on neurological examination. Abnormalities on MRI were the same as those reported previously (Rosenberg et al. 1988*a)*. BAERs were found to be abnormal in 5 of 11 individuals, and were similar to those previously reported in toluene abusers (Metrick and Brenner 1982; Lazar et al. 1983). In this study (Rosenberg et al. 1988*b),* all three individuals with abnormal MRI scans and neurological examinations also had abnormal BAERs. Two of five individuals with abnormal BAERs, however, had normal neurological examinations and MRI scans. This study suggests that BAERs may detect early CNS injury from toluene inhalation even at a time when neurological examination and MRI scans are normal. These results also suggest that BAERs may be a sensitive screening test to monitor individuals at risk from toluene exposure for early evidence of central nervous system injury.

Although an exact dose-effect relationship cannot be drawn yet for chronic toluene exposure, it is clear that all severely affected individuals have had heavy and prolonged exposure. The lack of correlation between the type or duration of exposure and neurologic impairment may be due to unreliable histories or other factors, such as genetic predisposition (unlikely) or hypoxemia due to huffing or bagging. Nutritional factors and other concomitantly used substances may also be involved. Gradual resolution of acute toxicity and absence of withdrawal symptoms were probably due to slow elimination of toluene from the central nervous system.

Unlike the solvents that cause peripheral neuropathy, such as n-hexane, for which there are animal models of classical target organ neurotoxicity, no adequate animal model exists for all aspects of toluene-induced neurotoxicity. Several recent studies have addressed the behavioral effects of both acute and chronic toluene exposure in laboratory animals (Miyake et al. 1983; Lorenzana-Jimenez and Salas 1983; Pryor et al. 1983, 1987; Wood et al. 1983; Rees et al. 1987). Most noteworthy are the studies of Pryor et al., which demonstrate persistent irreversible high-frequency hearing loss by cued behavioral responses, auditory brainstem evoked responses, and pathology. This is produced as early as 2 weeks of exposure to 1,200 ppm or 1,400 ppm of toluene. This was attributed to cochlear dysfunction rather than the central conduction pathology found in the human studies noted above (Pryor et al. 1983, 1987; Rebert et al. 1983). Other studies from this group have measured a toluene-induced motor syndrome that is characterized by a widened landing foot splay and a short and widened gait that may relate to the cellebellar syn-

drome in humans (Pryor et al. 1991). However, as the pharmacodynamics, distribution, and bioavailability of toluene and its metabolites have been studied in animals but are poorly understood in humans, the basis for comparing toluene's effects in experimental animals with those in humans is not an easy task.

Trichloroemethylme (TCE). TCE is an important organic solvent used extensively in industry in metal degreasing, extracting oils and fats from vegetable products, cleaning optical lenses and photographic plates, in paints and enamels, dry cleaning, and as an adhesive in the leather industry. Although its use in recent years has diminished somewhat due to concern that it could be a human carcinogen (Lloyd et al. 1975), NIOSH estimates the total number of individuals exposed to TCE to be in excess of 3.5 million (NIOSH 1978).

TCE has been recognized as an industrial hazard with neurotoxic properties for over 50 years (Feldman 1979). It was once commonly used as an anesthetic agent despite early reports of toxicity (Humphrey and McClelland 1944; McClelland 1944; Enderby 1944; Firth and Stuckey 1945). TCE, however, was abandoned as an anesthetic agent, apparently not because of its toxicity, but because its anesthetic action was weak and eventually better agents became available (Atkinson 1960). Clinical experience suggested that it was safe in minimal concentrations, and useful because at the time, it was one of the few nonexplosive agents that could supplement nitrous oxide and did not produce significant respiratory depression (Atkinson 1960, Hewer 1943).

The major neurological manifestation is related to a slowly reversible trigeminal neuropathy (Feldman 1979; Humphrey and McClelland 1944; McClelland 1944; Buxton and Hayward 1967; Glaser 1931; Defalque 1961*a;* Mitchell and Parsons-Smith 1969), although involvement of other cranial nerves and peripheral nerves have also been described (Feldman 1979; Gwynne 1969; Feldman et al. 1970). The trigeminal neuropathy associated with TCE intoxication was recognized as characteristic and for a time intentional exposure was considered a useful treatment of trigeminal neuralgia (Glaser 1931). Cranial neuropathies were noted after general anesthesia with TCE over 40 years ago (Humphrey and McClelland 1944; McClelland 1944; Firth and Stuckey 1945). Of 13 cases of multiple cranial nerve palsies following general anesthesia, 2 were related to TCE anesthesia. Twenty-four to forty-eight hours after general anesthesia, individuals developed paresthesia around the lips which then spread to involve the entire trigeminal distribution

bilaterally over the ensuing 2 to 3 days. Motor weakness also occasionally occurred in the trigeminal distribution and other cranial nerves including facial (VII) and optic (II) nerves; other lower cranial nerves also became affected (Feldman 1979; Humphrey and McClelland 1944). Resolution of the trigeminal neuropathy occurs slowly in an "onion-peel" distribution, felt to be indicative of segmental or nuclear trigeminal involvement (Feldman 1979; Feldman et al. 1970).

Most importantly, much of the earlier literature on the neurotoxicity of TCE includes observations that were most likely due to decomposition products (e.g., dichloroacetylene) rather than TCE itself (McClelland 1944; Firth and Stuckey 1945; Defalque 1961*b;* Waters et al. 1977). Dichloroacetylene, produced most prominently under alkali conditions, reacts violently with air to produce two noxious gases, phosgene and carbon monoxide (Waters et al. 1977). Dichloroacetylene disrupts the region of the brainstem where the trigeminal nucleus is located in experimental animals and is therefore probably responsible for the neurotoxic properties of TCE (Schaumburg et al. 1983). Short-term exposure to narcotizing levels of TCE in the industrial setting has also been reported to induce a transverse myelopathy (Sagawa 1973). This report is of interest because it has also been shown that a transverse myelopathy can be experimentally induced in the rat with dichloracetate, which is a possible metabolite of TCE/dichloroacetylene (Spencer and Bischoff 1982). Attempts to experimentally reproduce the neurotoxicity associated with the industrial use of TCE have not been successful with pure grades of TCE (Adams et al. 1951; Utesch et al. 1981; Tucker et al. 1982; Dorfmueller et al. 1979). Recent studies of rats have identified a high-frequency hearing loss similar to that observed for toluene exposure (Rebert et al. 1991). This is the first study of pure TCE in animals documenting a neurotoxicity that may also be peripheral, i.e., cochlear in origin.

Little data are available on the neuropathologic changes after TCE exposure. A single autopsied case of an individual who died 51 days after industrial exposure to TCE and TCE decomposition products (probably dichloroacetylene), revealed bilaterally symmetric brainstem lesions (Buxton and Hayward 1967). These changes were most prominent in the fifth nerve nuclei, spinal tracts, and nerve roots. The fifth nerves both within and outside the brainstem showed extensive myelin and axonal degeneration. Other neuropathologic changes were seen but were less prominent.

Although higher level exposures to TCE and its decomposition products are well described, reports of long-term, low-level exposure occurring in the industrial setting are relatively few. These reports have focused on neuropsychiatric and behavioral effects including a neurasthenic syndrome with subjective complaints of dizziness, headache, nausea, fatigue, anxiety, and insomnia (Andersson 1957; Bardodej and Vyskocil 1956; Grandjean et al. 1955; Lilis et al. 1969; Salvini et al. 1971; Smith 1970). Although these disorders reportedly become more severe with length of employment and degree of exposure, the neurobehavioral and neuropsychological literature on the toxic effects of TCE is so fragmented and poorly documented that it is impossible to come to any firm conclusions regarding low-level, chronic exposure to TCE and its neurotoxic potential (Annau 1981). Neurobehavioral disturbances to acute, high-level exposure have included severe psychiatric presentations (Todd 1954; Harenko 1967).

Several studies have been performed in order to study the behavioral effects of single short-term exposure to TCE (Salvini et al. 1971; Stewart et al. 1970; Ferguson and Vernon 1970; Winneke 1982; Vernon and Ferguson 1969). These studies have indicated that while fatigue and sleepiness occur in humans following exposure to concentrations above 100 ppm for 2 hours, no deterioration in performance or manual dexterity occurs following exposure to levels up to 300 ppm. In one study, adverse effects on performance were seen at 1,000 ppm, but no significant effects were seen at lower concentrations (Kylin et al. 1967). In a frequently cited study, detrimental effects of 8 hours exposure to 110 ppm TCE on performing tests of perception, complex reaction time, memory, and manual dexterity were found (Salvini et al. 1971). Others have been unable to replicate this study (Stewart et al. 1970; Vernon and Ferguson 1969). In a study where subjects were exposed to 1,000 ppm TCE and optokinetic nystagmus measured, minimal effects were seen and found to persist for only up to 2 hours (Kylin et al. 1967). Somewhat increased effects are seen when ethanol ingestion is added to the TCE exposure (Ferguson and Vernon 1970; Winneke 1982), and it has been demonstrated that ethanol will inhibit metabolism of TCE to its breakdown products, trichloroethanol and trichloroacetic acid, thereby increasing TCE concentration in blood (Muller et al. 1975). In general, however, these studies have shown that the behavioral effects of ethanol are more pronounced than TCE.

In summary, there is no compelling evidence that exposure to TCE at or below 300 ppm has an adverse neurobehavioral effect.

Methylene chloride (dichloromethane). Methylene chloride is widely used in industry for paint stripping, as a blowing agent for foam, as solvent for degreasing, in the manufacture of photographic film, as the carrier in rapid-dry paints, and in aerosol propellants. It is also used in the diphasic treatment of metal surfaces, in the textile and plastics industry, and for extracting heat-sensitive edible fats and essential oils. It is estimated that almost 100,000 individuals are exposed to methylene chloride in the workplace alone.

As with other solvents, methylene chloride has CNS depressant properties at high levels of exposure and may lead rapidly to unconsciousness and death (Moskowitz and Shapiro 1952; Winek et al. 1981; Tariot 1983; Sturmann et al. 1985; Horowitz 1986). This has been reported both in industrial settings (Moskowitz and Shapiro 1952; Tariot 1983) and as a result of solvent inhalation abuse (Sturmann et al. 1985; Horowitz 1986).

Methylene chloride has generally been considered safer than other chlorinated hydrocarbons and has not attracted the attention it deserves as a possible cause of chronic CNS dysfunction. Methylene chloride is metabolized to carbon monoxide (Stewart and Fisher 1972; Kubic et al. 1974; Ratney et al. 1974; Astrand et al. 1975) and therefore both its hypoxia effect as well as its narcotic actions must be considered regarding methylene chloride's CNS-depressant effects. Carbon monoxide, at high levels, and other forms of cerebral hypoxia are known to cause permanent neurological sequelae.

The acute effects of exposure to methylene chloride have been studied in controlled experiments in humans (Stewart et al. 1972; Gamberale et al. 1975; Winneke 1981). In one study, 11 healthy nonsmokers were exposed to levels of methylene chloride up to 1,000 ppm for 1 to 2 hours (Stewart et al. 1972). Inhalation of methylene chloride at 500-1,000 ppm for this length of time was followed promptly by a sustained (at 24 hours post-exposure) elevation of carboxyhemoglobin. These levels, however, never reached above 10 percent saturation. Visual evoked responses in the three subjects tested showed an increase in peak to peak amplitudes after 2 hours of exposure and returned to baseline 1 hour after termination of exposure. No untoward subjective symptoms occurred at levels of exposure below 1,000 ppm. At exposure to concentrations of 1,000 ppm, two of three subjects reported mild light headedness, which promptly resolved after cessation of exposure.

The effects of methylene chloride exposure on three tests of cognitive function (reaction time, short-term memory, calculation ability) were tested in 14

normal subjects (Gamberale et al. 1975). Repeated tests at exposures to 870, 1,740, 2,600, and 3,470 mg/m^3 methylene chloride showed no statistically significant impairment in performance of these tests, although at the highest exposure levels, a greater variation in the responses was obtained for reaction time than under control conditions.

Controlled exposure of normal volunteers for up to 24 hours to various concentrations (up to 800 ppm) of methylene chloride in five separate studies showed the following abnormalities: After 2.5 hours of exposure to 500 ppm, complaints of general uneasiness were noted. After 4 hours of exposure to 300 and 800 ppm mood rating scales were noted to be significant for depression in only one experiment. There was no impairment of cognitive performance as measured by tests of short-term memory and calculation ability in any of these studies after 2.5 hours of exposure to methylene chloride at levels up to 1,000 ppm. Some impairment was noted in psychomotor performance and vigilance after 3 to 4 hours of exposure to 800 ppm.

Overall, studies of controlled human exposure to methylene chloride do not show effects of central nervous system toxicity, except at higher levels of exposure, and even then, the effects are minimal and rapidly reversible. The one exception may be in those inhalant abusers described where methylene chloride is a major component of the compound that they are abusing (Hormes et al. 1986; Rosenberg et al. 1988*a,b)*.

There have been few attempts to address the issue of chronic exposure and permanent neurological sequelae to methylene chloride. A group of 46 men working in a factory making acetate film reported an excess of neurological symptoms when compared to a nonexposed referent group (Cherry et al. 1981). These individuals were exposed to a methylene chloride:methanol (9:1) mixture, and methylene chloride concentrations were below 100 ppm. Although neurological symptoms were increased in the exposed group, no abnormalities were detected on neuropsychological tests. No evidence was found of long-term damage that could be attributed to exposure to methylene chloride. In a larger study to assess the potential chronic health effects of methylene chloride, no increase in the number of expected deaths due to diseases of the nervous system were seen among 1,013 workers chronically exposed to methylene chloride (Hearne et al. 1987).

In summary, the evidence suggests that methylene chloride does not produce permanent neurological sequelae except with massive acute exposures that

are associated with hypoxic encephalopathy. No evidence exists that chronic low-level exposure causes any long-term CNS injury.

1, 1, 1-trichloroethane. 1, 1, 1- trichloroethane is widely used as an industrial degreasing solvent and is relatively less toxic than other solvents, although several reports of severe toxicity and deaths exist in the literature (Jones and Winter 1983; Silverstein 1983; McCarthy and Jones 1983; Gresham and Treip 1983). Its acute toxicity has made it unsuitable as a volatile anesthetic, and its use as a carrier in aerosols was abandoned in the United States in 1973.

In those cases in which post-mortem examination of the brain was undertaken, the pathologic changes suggested cerebral hypoxia related either to a primary CNS depressant effect (Jones and Winter 1983), or secondary to cardiac or respiratory arrest (Jones and Winter 1983; Gresham and Treip 1983). The possible mechanisms of the effects of 1, 1, 1-trichloroethane have been postulated to be related either to its effect on the autonomic nervous system (Kobayashi et al. 1987) or central sleep apnea (Wise 1983). Chronic cardiac toxicity and possible sensitization to other inhalation anesthetics has also been suggested as a possible mechanism of 1, 1, 1-trichloroethane toxicity (McLeod et al. 1987).

There are several reports of the acute behavioral and neuropsychological changes after voluntary exposure of humans to 1, 1, 1-trichloroethane (Stewart et al. 1969; Salvini et al. 1971b; Gamberale and Hultengren 1973; Mackay et al. 1987). There was no impairment on a series of psychomotor tests following several days of exposure to 500 ppm of 1, 1, 1-trichloroethane (Stewart et al. 1969). In another study, no behavioral effects were seen after two 4.5 hour exposures to 450 ppm of 1, 1, 1-trichloroethane (Salvini et al. 1971*b)*. Two studies demonstrated some performance deficits (Gamberale and Hultengren 1973; Mackay et al. 1987). In one study, after 3.5 hours of exposure to 0, 175, and 350 ppm of 1, 1, 1-trichloroethane, abnormalities were seen on some behavioral tests, most notably those tests concerned with attention and concentration and those concerned with analysis of grammatical statements (Mackay et al. 1987). Overall, these studies suggest mild if any acute effects of exposure of individuals to levels of trichloroethane up to 500 ppm.

With regard to low-level, chronic exposure to 1, 1, 1-trichloroethane, a clinical, neurophysiological, and behavioral study of female workers chronically

exposed to this agent at levels of 110 to 990 ppm found no differences when compared to a reference solvent-unexposed group (Maroni et al. 1977).

It appears that 1, 1, 1-trichloroethane is not associated with either acute or chronic neurotoxicity at levels below 990 ppm, and that the only permanent neurological sequelae are related to cerebral hypoxia after massive exposure. In contrast to trichloroethylene, equivalent doses of trichloroethane do not produce hearing loss when administered to rats (Pryor, this volume).

Gasoline. Gasoline is a complex mixture of organic solvents and other chemicals and metals. The sniffing of gasoline is common among various solvent abusers, especially on some remote Native American reservations. Although some CNS or peripheral neuropathies may occur due to the solvents in gasoline, other toxicities may result from the tetraethyllead (or its metabolite triethyllead) (Coodin et al. 1980; Remington and Hoffman 1984; Goldings and Stewart 1982; Prockop and Karampelas 1981; Eastwell 1985; Valpey et al. 1978; Robinson 1978; Hansen and Sharp 1978). In all cases in which high lead levels are observed, hallucinations and disorientation, dysarthria, chorea, and convulsions have been reported. The symptoms also have included moderate to severe ataxia, insomnia, anorexia, slowed peripheral nerve conduction, limb tremors, dysmetria, and sometimes limb paralysis. In most cases the EEG is normal but in severe states, an abnormal to severely depressed cortical EEG is observed. Only in one lethal case was there any kidney damage noted; electrolytes are usually in the normal range. Because many of these symptoms in the early stages of the disease can be reversed by chelation therapy with EDTA, BAI, and/or penicillamine, it is important to check the serum lead levels in any chronic inhalant abuser to see if this treatment should be prescribed.

Alcohols and solvents. One interesting phenomenon has been observed following the exposure to two or more solvents. Degreaser's flush was ascribed to a flushing of the face when occupational workers left their degreasing vats and drank alcohol after leaving work (Pardys and Brotman 1974; Stewart et al. 1974). Also heavy drinking has been associated with toluene exposure (Antti-Poika et al. 1985. More recently, both humans and rats have been noted to be thirsty when exposed to toluene and alcohol (Kira et al. 1988; Pryor et al. 1985). Also, animal studies have shown that solvents alter the metabolism of alcohol and prolong its action (Takahashi et al. 1987; Cunningham et al. 1989). This might explain the "flushing phenomenon" but may or may not

relate to the psychological dependence on solvents or to the development of thirst. An attempt to study the acute effects of alcohol and toluene, at low exposures in human volunteers, failed to produce any interaction by their behavioral measures. This may be indicative that the interaction takes some time and/or high levels of exposure to develop.

A recent report (McCormick 1990) identifies methanol intoxication as a problem in an individual intoxicated on a spray can of carburetor cleaner containing toluene (42 percent), methanol (23 percent), and methylene chloride (20 percent). Although mild acidosis did occur, the main concern was the high blood level of methanol. Ethanol therapy was utilized to prevent formation of high levels of formic acid. The above mixture is common (very similar in composition to paint thinner) and available to and used by solvent abusers; yet the repercussions of prolonged use are unclear.

Nitrous oxide. Although nitrous oxide is not an organic solvent, it is discussed here because of its potential for abuse. Nitrous oxide is a commonly used anesthetic and has been noted for some unusual toxicities. This substance is not usually thought of when one discusses inhalants, as it is unique both chemically and in its physiological action. Although it is abused by youthful experimenters, it is also abused by medical personnel. This substance, nitrous oxide (N_2O), is used as an anesthetic and as a propellant primarily for whipped cream. "Laughing gas," as it is euphemistically called, was abused soon after it was discovered in the late 18th century. More recently it was shown that central and peripheral nerve damage resulted following high levels of N_2O exposure, even in the presence of adequate oxygen (Layzer 1978). The symptoms include numbness and weakness in the limbs, loss of dexterity, sensory loss, and loss of balance. The neurological examination indicates sensorimotor polyneuropathy. There is also a combined degeneration of the posterior and lateral columns of the cord that resembles B12 deficiencies (Layzer 1978). Studies focusing on the mechanism of action indicate that cobalamins (vitamin B12) are inactivated by N_2O; more recent studies have focused on the methionine synthase enzyme which needs vitamin B12 to function (Nunn 1987). Although vitamin B12 (or folinic acid) does not aid recovery from this disease (Chanarin 1980; Nunn 1987), dietary methionine might. Rehabilitation proceeds with abstinence and is relative to the extent of neurological damage. Recent reviews cover many of the medical aspects of the adverse effects of and the pros and cons of using nitrous oxide (Brodsky and Cohen 1986; Nunn 1987). Despite the widespread distribution of this

information to the medical community and the reduced availability of pressurized cylinders, cases are still being observed (Schwartz and Calihan 1984). In regard to dependency, animal studies on selectively bred mice for alcohol dependence showed a cross-dependency on nitrous oxide (Belknap et al. 1987). Belknap and colleagues also observed handling-induced convulsions shortly after cessation of nitrous oxide, which could be prevented by either alcohol or nitrous oxide. This might indicate a physical dependence on nitrous oxide that needs to be dealt with in treatment of this drug abuse state.

Nonnervous System Toxicity of Inhalant Abuse

Most of the adverse clinical effects of inhalant abuse are on the nervous system. There are however, other significant adverse effects on other organ systems, including the kidney, liver, lung, heart and blood.

Renal Toxicity. Inhalant abuse has also resulted in the hospitalization of indiviuals for various kidney disorders (Streicher et al., 1981; Will and McLaren 1981; Davidman and Schmitz 1988, Lavoie et al. 1987; Patel and Benjamin 1986; Baerg and Kimberg 1970; Bennett and Forman 1980; Ravnskov 1978; Daniell et al. 1988; Jone and Wu 1988; Sarmiento Martinez et al. 1989; Marjot and McLeod 1989; Mizutani et al. 1989; Nelson et al. 1990; Taverner et al. 1988). One of the primary conditions leading to hospitalization has been such severe rhabdomyolysis that some subjects are nearly paralyzed. These subjects often have associated gastrointestinal (GI) involvement, including nausea, vomiting, and severe abdominal cramps. Lauwerys et al. 1985 have recently reviewed the reports on nephrotoxicity in humans.

In one of the early reports, Streicher et al. (1981) examined several cases and described them in detail. Distal renal tubular acidosis occurred in groups of paint and/or glue sniffers from the Southwest and Hawaii. They and others have noted the recurrence of renal dysfunction associated with solvent abuse; the disease state reappears in many individuals who return to their habit after release from the hospital. They develop hyperchloremic metabolic acidosis, hypokalemia, hypocalcemia, and other electrolyte imbalances. Solvents usually cause a unique distal type tubular acidosis, but proximal tubules may also be affected.

A slightly different kidney dysfunction, glomerulonephritis, has also been identified in workers using solvents (Harrison et al. 1986). This has been noted in painters (Ravnskov 1978) and has been recently reviewed (Daniell et

al. 1988). In addition, an interstitial nephritis leading to renal failure has been recently reported (Taverner et al. 1988). Although toluene is often proposed as the toxic agent and is present in most of the substances abused by these subjects, there have been no animal data to verify that toluene is the primary agent or even one of a group of substances that can cause renal dysfunction.

There are also reports that halohydrocarbons—chloroform and others (Lock 1989); methylene chloride (Rioux and Myers 1988); trichloroethylene (Kimbrough et al. 1985); methoxyflurane (Brown and Gandolfi 1987); and dichloropropane (Pozzi et al. 1985)—may contribute to, if not cause renal damage. The pathologic changes in the kidney include tubular necrosis and calcification. The reversibility of these changes is unknown and is likely dependent on the extent of the damage. Others (Keogh et al. 1984; Nathan and Toseland 1979) observed signs of Goodpasture's syndrome. Animal studies have identified the nature of some of these nephrotic changes (Lock 1989; Kimbrough et al. 1985). Animal studies have also shown mild nephrotic changes following exposure to hydrocarbons (Short et al. 1987). In most cases more than one substance is present; this may indicate that the most severe nephrotic changes occur in the presence of two or more of these substances.

Thus several kinds of solvent mixtures are associated with either glomerulonephritis, distal renal tubular acidosis, or other nephrotic changes. Usually, these different kidney disorders do not occur in the same individual. Although metallic spray paints are frequently used by these subjects, they also use paint thinners and glues. It would appear reasonable to conclude that toluene may account for some but not all of these renal abnormalities, which are likely due to a combination of toxicants in these toluene products—possibly including the metals contained in the spray paint such as cadmium and lead, which are known to be nephrotoxic (Wedeen 1984) or concurrent alcohol use (Jone and Wu 1988; Sarmiento-Martinez et al. 1989) and/or infections (Ravnskov 1978; Yamaguchi et al. 1985; Farrell et al. 1985). As more cases of renal toxicity are being reported, it is important that individuals exposed to high doses of solvents be checked for renal changes and metabolic imbalance.

For most of these subjects, correction of the electrolyte disturbance and proper fluid management usually restores the proper renal function and eliminates the rhabdomyolysis, even in the more severely affected patients,

within a few days. Caution about the use of bicarbonate early in the treatment of these subjects has been discussed by Lavoie et al. 1987. Correction of salt and electrolyte imbalance, including potassium, calcium, magnesium, and chloride, should be considered in the treatment of solvent abusers for muscle fatigue even in the absence of more severe kidney disorders.

Renal toxicity in pregnancy. One report emphasizes the need to be especially alert for solvent abuse in pregnant women in regard to nephrotoxicity. Goodwin (1988) reported live cases of renal tubular acidosis in pregnant women. Although these mothers responded to treatment for their metabolic imbalance after 72 hours and abstinence of solvent abuse, other individuals may prove more difficult to treat for this metabolic disturbance.

Hepatotoxicity. Chlorohydrocarbons (e.g., trichloroethylene, chloroform, halothane) have been known for years to produce hepato-toxicities (Baerg and Kimberg 1970; Clearfield 1970; Dossing 1986; Hutchens and Kung 1985; Farrell et al. 1985; Cordes et al. 1988; McCunney 1988; Hodgson et al. 1989; Brown and Gandolfi 1987; Benjamin et al. 1985). Any individual who is chronically exposed to these compounds would expect to develop hepato-renal toxicities depending on the dose and length of exposure (Benjamin et al. 1985). Buring et al. (1985) evaluated the effects of low levels of exposure measured retrospectively by several investigators. They concluded there is increased risk for operating room personnel where these chlorohydrocarbon anesthetics are used. However, Brown and Gandolfi (1987) have questioned whether liver toxicity occurs very often after use of halothane as an anesthetic. Shaw et al. (1989) review these rare occurrences and their etiological factors. In addition, the situations in which halothane hepatitis occurs has been reviewed by Neuberger and Davis (1983), who have proposed a hypoxic model to explain those occurrences of hepatitis.

The recent increase in the inhalation of typewriter correction fluids that contain trichloroethylene and tri-, tetrachloroethanes increases the likelihood of observing more of these toxicities in inhalant abusers (Greer 1984). This disease state is exemplified in two recent reports of apparent occupational (poorly ventilated areas) overexposure. Nephronecrosis and/or hepatotoxicity were observed after exposure to mixtures containing methylene chloride and other solvents (Miller et al. 1985; Mizutani et al. 1988; Cordes et al. 1988) and trichloroethane (Keogh et al. 1984; Hodgson et al. 1989). Methylene chloride has been considered not to be hepatotoxic (Rioux and Myers 1988).

However, a recent report may have identified an upper limit that may occur in inhalant abuse (Cordes et al. 1988) where hepatotoxicity does occur. Ketones, including acetone, potentiate halocarbon hepatotoxicity (Plaa 1988).

So far there have been few inhalant abusers noted to have irreversible liver damage. For example, subjects with altered liver function, as noted by elevated serum liver enzymes, have recovered in a few weeks (Fornazzari et al. unpublished). The low incidence of liver damage so far noted for this group may be due to a low rate of use of chlorinated solvents. However, the frequent heavy use of alcohol concurrently with inhalants should be of concern for this group, especially as they become older and will have used these substances for many years. When these patterns of "drug" exposure are known, it would be advisable to conduct liver function tests.

Hepatocellular and other carcinomas are observed at high doses of trichloroethylene (Kimbrough et al. 1985) and halothane (Redfern 1990). Anesthetic chlorinated hydrocarbons (halothane, trichloroethylene, chloroform) are also considered to be carcinogenic (Cohen 1979).

Cardiotoxicity. Many solvent abusers may die from direct or indirect cardiotoxic actions of solvents without note of any public or private record. More specifically, several recent reports have identified ventricular fibrillation and cardiac arrest in hospitalized patients (McLeod et al. 1987; Cunningham et al. 1987; Wiseman and Banim 1987; Boon 1987; Wright and Strobl 1984; Ong et al. 1988, Wodka and Jeong 1989). Some of the subjects had inhaled trichloroethylene (Mee and Wright 1980) or trichloroethane containing solvents (Wodka and Jeong 1989; McLeod et al. 1987) and some were additionally compromised by anesthesia (halothane—McLeod et al. 1987). Fluorocarbons have been shown to cause arrythmias in animals (Taylor and Harris 1970). Chenoweth and colleagues have shown that butane, hexane, heptanes, gasoline, some anesthetics, and toluene also produce these arrythmias (Chenoweth 1977).

More recently, two reports (Cunningham et al. 1987; Wiseman and Banim 1987) have linked glue sniffing to arrythmias and dilated cardiomyopathy. However, the linkage of arrythmia to glue sniffing is not well supported by animal studies. Glues usually do not contain halocarbons but do contain toluene and other hydrocarbons. The somewhat different cardiotoxicities noted above are not all easily explained, but congenital or other environmental causes were not ruled out. When observed, antiarrythmic therapy should

be used (McLeod et al. 1987). Exercise and adrenaline exacerbate these cardiotoxicities, and efforts to minimize these situations should therefore be instituted. Also, anesthesia should not be induced in patients shortly after intoxication, and one should probably avoid the use of halogenated hydrocarbons in other circumstances where heavy solvent exposure is suspected.

Hematologic toxicity. There are three areas of concern in regard to solvent inhalation and the hematopoietic system. Two of these relate to blood dyscrasias as the result of the abuse of solvents. Methylene chloride exposure can increase the carboxyhemoglobin levels (Horowitz 1986), a change that also occurs with cigarette smoking. The levels of carboxyhemoglobin may become sufficiently high to cause brain damage (Barrowcliff and Knell 1979) or death (Manno et al. 1989). A second group of substances, the organic nitrites, produces methemoglobinemia and hemolytic anemia (Wason et al. 1980, Brandes et al. 1989). A third substance, benzene, has been identified as causing aplastic anemia and acute myelocytic leukemia (Lauwerys et al. 1985, Austin et al. 1988). Benzene is present in thinners, varnish removers, and other solvents and in varying proportions in gasoline.

Nitrite intoxication. One group of substances, the volatile liquid "amyl" and "butyl" nitrites, deserve special discussion. During the late 19th and early 20th centuries amyl nitrite was used in clinical practice as a vasodilator to treat angina pectoris. Although this use of the drug is uncommon today, it is used for diagnostic purposes in echocardiogram examinations (Rosoff and Cohen 1986) and for cyanide poisoning (Klimmek and Krettek 1988). These drugs are not the typical solvents previously described; however, they are often included in the "inhalant abuse" category. As with nitrous oxide, some individuals abuse isoamyl (amyl) or isobutyl nitrites, and the propyl nitrites. Homosexuals have been reported to use these substances for sphincter dilation and penile engorgement. Use by others for nonsexual purposes is unclear. A recent study could not correlate changes in regional blood flow with any psychological measures or somatic changes (Mathew et al. 1989a). These studies do not offer any explanation for why individuals become dependent on nitrites. However, the finding by Mathew and colleagues that nitrites reduce anger, fatigue, and depression may offer a clue.

The nitrites are not usually considered toxic during inhalation because of syncope (fainting). However, Guss et al. (1985) noted a dangerously high 37 percent methemoglobin level in a normal subject who had used isobutyl nitrite.

This methemoglobinemia is the major identified toxicity and is considered the cause of several deaths (Wood and Cox 1981). There is a specific treatment for nitrite overdose. The high and slowly reversible reduction of methemoglobin can be aided by the use of methylene blue (Smith et al. 1980).

Organic nitrites have also been reported to produce bradycardia (Rosoff and Cohen 1986), reduce killer cell activity (Lotzova et al. 1984), produce allergic reactions (Dax et al. 1989), and be potentially carcinogenic (Osterloh and Goldfield, 1984). These latter effects are of special concern in the development of AIDS in that there is an association between the development of Kaposi's sarcoma and high amyl-butyl nitrite use (Newell et al. 1984; Haverkos et al. 1985; Moss et al. 1987). The ability to produce nitrosamines has fueled the speculation that nitrites are carcinogenic (Osterloh and Goldfield, 1984; Mirvish and Haverkos 1987; Yamamoto et al. 1987). Yet, in contrast to sodium nitrite, organic nitrites produce methemoglobin instantly in vitro (Klimmek et al. 1988) and may therefore not be around long enough to produce nitrosamines. Thus, the rapid oxidation of organic nitrites by hemoglobin and the fact that detectable levels of organic nitrites in blood are noted only briefly after administration (Osterloh and Goldfield 1985) call into question this hypothesis. Also, organic nitrite effects only the isolated immune or bacterial cells (Dunkel et al. 1989) and in a nonspecific manner (Lewis and Lynch 1988; Jacobs et al. 1983), and not the immune state of the whole rodent. While mutagenicity appears possible under special conditions, carcinogenicity is far from proven.

Neonatal syndrome. There is little direct information regarding a "fetal solvent syndrome" or related teratogenic changes as a result of solvent exposure during pregnancy. However, authors of studies of infants of mothers who chronically abuse solvents (Hersh et al. 1985; Hersh 1989; Goodwin 1988) cite this as a possibility. (Also note Tenenbein's discussion of this issue in this volume.) Subjects in some of the above studies inhaled paint thinner and paint sprays and drank various quantities of alcohol. Whether the toluene (stated to be pure toluene in the "thinner") and alcohol or other environmental factors are responsible is open to question. Toluene may augment the fetal alcohol syndrome such that a fetal alcohol syndrome occurs at lower than usual levels of alcohol consumption. It is also worth noting that the mothers of the infants in Hersh's study showed ataxia, mild tremors, and slurred speech, while the mothers in Goodwin's study presented with severe renal tubular acidosis. The concomitant influence of undernutrition, other substance

abuse, or even genetic predisposition needs to be clarified through further studies.

With so little knowledge, and yet with all the potential dangers, it is very important that pregnant women not be exposed to very high concentrations of solvents. It is encouraging to know that a critical prospective study of workers exposed to low levels of solvent showed no more abnormalities than the carefully matched controls (Eskenazi et al. 1988). This does not, however, diminish the need for the avoidance of exposure of pregnant women to moderate to high levels of solvent.

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Clinical/Biophysiologic Aspects of Inhalant Abuse

Milton Tenenbein

While inhalant abuse is known to produce dysfunction and damage affecting several of the body's organ systems, Rosenberg and Sharp have appropriately decided to focus upon the nervous system and have provided a comprehensive review. My chapter will chiefly focus upon the methodologic barriers impeding research into the neurologic aspects of inhalant abuse and identify other relative aspects of solvent toxicity. Especially, I will briefly discuss a clinical aspect of inhalant abuse that is barely discussed in the literature, the teratogenic effects of this practice. Because there are many methodological barriers, I have chosen to conclude somewhat provocatively by suggesting a need to prioritize inhalant abuse research by proposing that research into causation, prevention, and rehabilitation be emphasized.

Investigating the Neurotoxicity of Inhalant Abuse

Neurotoxicity as an outcome of volatile solvent abuse is predictable. In order for a product to be favored as an agent for inhalant abuse, it must rapidly enter the central nervous system in quantities high enough to produce the desired effect: a pleasurable change in affect. Therefore, some alteration of central nervous system function, or perhaps even structure, must be occurring. Since the affective change is transitory, it is expected that this associated functional or structural alteration is reversible. However, it is reasonable to assume that at some point after chronic exposures, irreversible changes may occur. A stronger case for this speculation is made when one considers that a

major use of these chemicals is to dissolve various nonpolar organic substances. The central nervous system is richly endowed with organic lipids; thus, from an overly simplistic perspective, there is the potential for portions of the brain to be dissolved away over time.

Traditionally, the pathophysiology of a condition is studied and characterized in order to devise effective treatments and perhaps even a cure. If the condition is known to be produced by a drug or a chemical, then the investigation would include a study of the pharmacokinetics and pharmacodynamics of the agent of concern. The former describes the rates of absorption, distribution, metabolism, and excretion of the compounds in question, while the latter deals more with the interrelationships of these states and with dose-effect relationships. Both require knowledge of the actual dose of the drug or chemical and accurate methods of measuring its concentration within the body. Additionally, pharmacodynamics requires the measurement of the induced effects.

There are several potential methods for measuring the effects of a drug or chemical within the body. In general, these include clinical and functional assessments (often subclinical) and structural alterations. From the perspective of the clinical and biophysiologic effects of inhalant abuse upon the human nervous system, actual methods could include a neurologic medical history and physical examination (clinical); various electrophysiologic and psychometric assessment modalities (functional); and advanced organ imaging techniques (structural). There is obvious overlap within this classification because of the interrelationship between structure and function.

Assessment of the Pharmacologic Agent

Establishing the causative agent is the first priority, but for volatile solvent abuse, this is problematic. Historically, toluene was one of the first chemicals to be implicated (Grabski 1961) and several other convincing reports of toluene-induced neurotoxicity have appeared (Boor and Hurtig 1977; Lazar et al. 1983; Malm and Lying-Tunell 1980). These descriptive human examples, especially when supported by strong controlled animal studies (Pryor et al. 1984), establish a cause-and-effect relationship between chronic toluene abuse and neurotoxicity. This has led to considering it as the etiologic agent whenever its presence is known, and at times just assumed, despite the presence of other potential neurotoxins. This has been commented upon else-

where (Cavanagh 1983). The gold standard for attributing neurotoxicity to toluene in a chronic inhalant abusing patient is chemical analysis of all inhalants abused by the individual in order to rule out other neurotoxins. This is absent from most reports of neurotoxicity attributed to toluene (Fornazzari et al. 1983; Kelly 1975; King 1982; Schikler et al. 1982).

While not attempting to minimize toluene as a neurotoxin, the attention paid to it may give the impression, especially to the lay public, that the other abused inhalants are less toxic or even nontoxic. This has resulted in specific legislation against toluene-based products, which then further creates the impression of relative safety of the "nonregulated" substances. Furthermore, favored products vary from community to community and are not necessarily toluene based in each or sometimes any area. In our catchment area we have three distinct cohorts. In the inner city, toluene and halogenated aliphatic hydrocarbon based products are chiefly utilized. In small settlements in a remote area east of us, n-hexane based products are commonly abused (Tenenbein et al. 1984), while in similar settlements to the north, gasoline is favored (Boeckx et al. 1977). In the United Kingdom, butane is a popular substance of inhalant abuse (Anderson et al. 1985), and this is currently becoming prevalent in the United States. Propane is abused in the far Canadian North and in remote areas of Australia. Significant morbidity and mortality are not limited to toluene and also occur in these cohorts.

Thus there is a need to study other agents. Considering the virtually endless number of chemicals involved in inhalant abuse, this becomes an impossible task. However, a starting point would be examining some of the more common ones from each class. The goal of this endeavor would be the identification of safer agents that could then replace the more toxic ones currently in consumer products.

The pharmacokinetics and pharmacodynamics of these abused substances at doses that produce euphoria in humans are unknown and will almost certainly remain so. Such data would be helpful in determining the doses and duration of inhalant abuse required to produce chronic toxicity. This information could also address the perplexing question as to why some individuals seem to be more sensitive to the neurotoxic effects of chronic inhalant abuse through the related discipline of pharmacogenetics. Some individuals metabolize drugs and chemicals at different rates than the rest of the population (Vesell 1984).

Assessment of Effects

Clinical assessment includes medical history and physical examination. The volatile solvent abuser cannot be considered as a reliable historian. Reasons for inaccurate information regarding the types of abused products, the amount abused over a period of time, and the frequency and duration of abuse range from frank lack of recollection to fear of self-incrimination. Responses to inquiries regarding potential acquired disabilities may be inaccurate because of denial or lack of recognition. While physical examination is straightforward, demonstrated abnormalities are only detectable late in the clinical course. Furthermore they may not result from chronic solvent abuse but relate to coexisting confounding variables such as the abuse of other substances and poor nutrition.

Two methodologies that have been used to assess subclinical functional abnormalities are evoked potential and psychometric testing. There have been many anecdotal reports of abnormal evoked potentials in patients with frank central nervous system damage. Of perhaps even greater interest are the findings of abnormalities in brainstem auditory evoked potentials (Rosenberg et al. 1988) and in visual evoked potentials (Cooper et al. 1985) in apparently neurologically normal solvent abusers. This is supported by our own data (Tenenbein and Pillay, in press). Auditory, visual, and somatosensory evoked potentials were obtained from 15 neurologically normal solvent abusing children. This cohort abused a wide variety of products, and abnormalities were found in just over one half of them. Thus evoked potential testing may be an objective marker of early neurologic damage with potential usefulness for counseling and intervention. While this appears to be a promising tool, considerable work is required to determine if it can fulfill this goal.

Much has been written regarding psychometric evaluation of solvent abusers, and this topic has been reviewed elsewhere (Ron 1986). Some shortcomings of the published research utilizing this method of investigation are that it is frequently uncontrolled; there is often a lack of differentiation between acute and chronic effects, there are concerns about the many tests used, and there are concerns regarding the validity of these tests and the lack of normative data for specific ethnocultural groups under study. These issues, along with confounders frequently present in solvent abusers, such as preexisting psy-

chologic morbidity and the effects of other substances of abuse have not surprisingly led to confusing and conflicting results.

Structural central nervous system abnormalities are now simply and noninvasively assessed by modern diagnostic imaging techniques. Abnormalities in both computerized tomography (Fornazzari et al. 1983) and magnetic resonance imaging (Rosenberg et al. 1988) have been demonstrated in solvent abusers who were overtly neurologically abnormal. While the limitations of the latter techniques have not been fully characterized, these modalities would seem to be relatively insensitive for subclinical abnormalities, and their expense is a further limiting factor.

Teratogenic Effects of Inhalant Abuse

The effects of inhalant abuse upon the unborn child are unknown. Since chronic abuse produces functional and structural damage in the mature individual, it is reasonable to expect that the developing fetus would be at particular risk. Dysmorphic features, as well as physical and neurologic impairments have been reported (Hersh et al. 1985; Hersh 1989; Hunter et al. 1979). Anecdotal unpublished personal observations include acute neonatal withdrawal, transient neonatal renal tubular acidosis, intrauterine growth retardation, developmental delay, and impairments of vision and hearing. Much more information is needed to characterize the consequences of solvent abuse during pregnancy in order to devise effective strategies for dealing with this problem.

Clinical Effects of Inhalant Abuse: Future Research

There are many barriers for research into this problem. There are too many chemicals and mixtures to consider. We lack the tools to reliably measure the early subclinical effects. Controlled human volunteer studies cannot be done; therefore, research will likely remain descriptive in nature—largely descriptions of individual cases and small groups of individuals. Case controlled studies provide a more powerful methodology; however, when dealing with solvent abuse, the matching of appropriate controls is particularly problematic because it is virtually impossible to verify that an individual has not abused volatile solvents.

Since inhalant abuse has its beginnings in childhood, the ethical issues of research on children compound this problem. Prospective studies are not possible because of the need to intervene when this practice is discovered. Retrospective studies are flawed by incomplete and inaccurate data. In the case of volatile solvent abuse, key information that is often of questionable accuracy includes the identity of the abused substances, and the dose, frequency, and duration of abuse.

One could take the position that research directed toward identifying specific pathophysiology of volatile solvent abuse induced neurotoxicity is unlikely to achieve its goal. But, perhaps this may *not* be so unfortunate, because the likelihood of finding a specific treatment or cure for neurologic damage, whatever its etiology, is not great. Efforts may be better directed toward the early identification of those individuals at particular risk for permanent damage. A simple, noninvasive, and inexpensive screening test would be ideal. In this way, those in need of intervention could be identified prior to the onset of irreversible damage. It would seem that more would be gained from a better understanding of risk factors in order to formulate preventive strategies, and that the inhalant abuser would be better served if we gained more insight into appropriate rehabilitative strategies prior to the onset of neurologic damage.

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Death Among Inhalant Abusers

James C. Garriott

Inhalant abuse is a significant problem among youth in the Southwestern United States. A number of studies have addressed the potential adverse effects of the practice to include psychological and medical effects (Bass 1970; Hayden et al 1977; Comstock and Comstock 1977; Bruckner and Peterson 1977; Prockop and Couri 1977; Korman 1977; Korman et al. 1978; Boeckx and Cooding 1978; De La Garza 1978). In the late 1960s and early 1970s, sudden death among inhalant abusers was frequently observed (Bass 1970; Garriott and Petty 1980) and was found to be primarily related to the use of fluorocarbons and a few solvents that were found to induce cardiac arrythmias (Aviado 1977). After the prohibition of the use of fluorocarbons in aerosol spray products, these agents became more difficult to obtain, and deaths among teenagers from this source greatly diminished (Garriott and Petty 1980).

The practice of inhalant abuse has not ceased, however, and the preferred agents in south Texas have become primarily spray paints, lacquers, or other toluene-containing products, which are readily available to the public.

This chapter follows from an investigation of all deaths occurring in Bexar County, Texas, between 1982 and 1988 in which recent inhalant abuse by the decedent could be ascertained. Prior studies of inhalant-involved deaths have focused on deaths believed to have resulted directly from inhalant abuse. This was the focus of an early study carried out in the 1970s in Dallas County, Texas in which 35 deaths were found to be directly caused by inhalants (primarily fluorocarbons) (Garriott and Petty 1980). In contrast, only 18 per-

cent of the deaths in the current study were directly attributable to inhalant abuse. Although few deaths were found to be due to inhalant toxicity, many inhalant users met with a violent death, possibly related to but not directly caused by these volatile substances. Suicide and homicide were the most prevalent means of death in inhalant abusers, and the predominant method of suicide was hanging. This new analysis demonstrates a potential association between inhalant use and violent death and implies a new relationship to suicide.

Most of the inhalant-related deceased were teenagers, with 21 (54 percent) under 20 years of age (see table 1). It is interesting to note, however, that nearly half were adults, demonstrating that inhalant abuse is not confined to teens and adolescents. The average age was 19.3 years; the youngest was 8, and the oldest was 32 years of age. Males outnumbered females 34:5. Also, 79 percent had Hispanic surnames but were classified as "white" by the medical examiner. (In Bexar County, it is estimated that 53 percent of the population is of Hispanic origin.)

Table 1. Ages/sex of inhalant abusers

Age/sex	No.
up to 13	2 (5%)
13-19	19 (49%)
20-29	16 (41%)
Over 30	2 (5%)
Total	39 (100%)
Males	34 (87%)
Females	5 (13%)

The inhalants identified in all cases are listed in table 2. As reflective of the incidence of use in this community, the great majority (82 percent) had used toluene-containing products; toluene was detected in their blood at autopsy. The next most frequently used solvents were a combination of trichloroethylene plus 1,1,1-trichloroethane (10 percent), resulting from the use of typewriter correction fluids. The remaining abused substances included dichlorodifluoromethane (Freon 12), gasoline, and nitrous oxide. If present in sufficient amounts, the toxicological procedures would have also detected alkane gases (e.g. butane), benzene, methylene chloride, and most anesthetic gases (Foerster and Garriott 1981). In addition, conventional toxicological tests determined the presence of most drugs and/or alcohol. Ethanol was commonly observed and ranged from 0.07 to 0.28 g/dl in 49 percent of the cases.

Table 2. Chemical agents measured at autopsy

Substances measured	Possible products	Prevalence of substances
Toluene	Spray paints, lacquers	32 (82%)
Trichloroethylene and 1,1,1-trichloroethane	Typewriter correction fluids and solvents	4 (10%)
Dichlorodifluoromethane	Refrigerants	1 (2.7%)
Gasoline	Commercial gasoline	1 (2.7%)
Nitrous Oxide	Nitrous Oxide tanks	1 (2.7%)
Total		39 (100.1%)[1]

Alcohol was also present in 19 (49%) of the cases.

[1]Total does not equal 100 percent due to rounding.

Table 3. Elements of autopsied subjects

Manner of death	Number (%)	Products used	Major solvents	Other drugs
Suicide:	11 (28)			
Hanging	10	Spray paint	Toluene	Ethanol
Gas (CO)	1		Toluene	
Accident:	10 (26)			
Vehicle—passenger	1	Unknown	Toluene	
Pedestrian	3	Spray paint	Toluene	Ethanol
Fall	2	Fluid*	Trichl* Toluene	
Overdose	3	Unknown	Toluene	Heroin Phenothiazine Ethanol Cannabis Propoxyphene
Train	1	Spray paint	Toluene	Ethanol
Homicide:	9 (23)			
Gunshot	4	Spray paint	Toluene	Phenothiazine
Stabbing	3	Spray paint	Toluene	Ethanol Cannabis Cocaine
Other	2	Spray paint	Toluene	Heroin Ethanol
Accident: Inhalant	7 (18)			
Arrhythmia	4	Gasoline Fluid* Refrigerant	Gasoline Trichl* Dichlorodi-fluoromethane	
Other	3	N_2O tank	N_2O Toluene Methylene chloride	Ethanol
Undetermined	2 (5)	Spray paint	Toluene	Ethanol
Total	39(100)			

*Fluid = typewriter correction fluid; Trichl = trichloroethylene and 1,1,1-trichloroethane

Deaths Resulting From Inhalant Abuse

Among all cases where inhalants were suspected, there were 39 cases in which solvents or gaseous inhalants were detected. In only seven cases (18 percent) were the deaths considered to have been directly the result of inhalant toxicity (table 3). Only one death was directly attributable to *toluene* exposure, probably from spray paint abuse. That product also contained methylene chloride, a substance that could have contributed to the cause of death (arrhythmia). Toluene has been implicated in a few deaths (Baselt and Cravey 1990); those cases reported in the past may not all be attributable to toluene, as authors often did not critically rule out other substances. Toluene has been demonstrated to induce heart block at high concentrations in mice (Taylor and Harris 1970), but human death from toluene abuse is quite rare. The mean blood concentration in the 32 toluene cases reported here was 3.78 (±5.1) mg/L. These concentrations do not appear to have been indicators of lethality nor of any specific toxicity, as much higher concentrations of toluene have been observed in the blood (greater than 30 mg/L) of inhalant abusers without any observable toxicity (Garriott et al. 1981).

Gasoline inhalation also has not been frequently reported to cause death, although in some studies, severe toxicity and death have been reported from the accompanying lead poisoning (Boeckx and Cooding 1978, Poklis and Burkett 1977; Kurt et al. 1982). In this study, the death was believed to have resulted from cardiac arrythmia due to gasoline inhalation.

Abuse of *nitrous oxide* also has caused deaths; the lethal mechanism here was most likely anoxia (as is the case in most nitrous oxide related deaths), rather than a direct toxic effect of nitrous oxide (DiMaio and Garriott 1978). This gas can be inhaled in very high concentrations under controlled circumstances without causing harm (Marshall and Wollman 1980).

Dichlorodifluoromethane (Freon 12) from a refrigerant regenerator was directly responsible for one death due to cardiac arrhythmia (Aviado 1977).

The solvent combination found in typewriter correction fluid (e.g., *trichloroethylene* and *1, 1, 1-trichloroethane)* was the next most frequently detected inhalant after toluene. A much higher percentage of deaths was attributed to toxicity from these solvents (2 of 4) than for toluene (1 of 32). The lethal mechanism is considered to be cardiac arrythmia due to myocardial sensitization, as described for the fluorocarbons (Aviado 1977).

Deaths Resulting From Suicide

The most prevalent manner of death in these inhalant abusers was suicide (28 percent) (table 3). The age range of these suicides was 12 to 32, with 7 of the 11 being teenagers. These were compared to a cohort of 38 suicides in noninhalant-abusing teenagers during the same period. In the latter group, only 7 of 38 (18 percent) died by hanging, while most (66 percent) died from gunshot (see table 4). This contrasts with 91 percent of the inhalant abuse suicides choosing hanging as the method of suicide.

Table 4. Type of suicides in noninhalant abusing teenagers

Gunshot	25 (66%)
Hanging	7 (18%)
Drug overdose	4 (11%)
Carbon monoxide	2 (5%)
Total	38 (100%)

Alcohol was present in 12 cases (32%)

Delta^{9}-THC was present in 4 cases (10%).

Deaths Resulting From Accident and Homicide

Deaths resulting from accidents (26 percent) and homicides (23 percent) were other major categories of violent deaths among inhalant abusers. These tended to result from aberrant aggressiveness or bizarre accident-prone behaviors (e.g., challenging auto or train traffic).

This analysis provides a new perspective of the consequences associated with inhalant use, that is, an association with violent death and especially suicide. Almost two thirds of these deaths resulted from nondrug related causes. The majority of the individuals had used products containing the solvent, toluene, as evidenced by its detection in bodily specimens at autopsy. This relationship with violent death may be similar to that observed for alcohol, a central nervous system depressant that is also highly associated with violent death. Effects such as general central nervous system depression, impaired thinking and judgement, and slowed reaction times are common to both intoxicants.

Inhalants also have been associated with aggressive, especially self-aggressive, behavior (Korman 1977), as with alcohol. The high proportion (28 percent) of inhalant abusers committing suicide and the number of homicides (23 percent) may be related to that phenomenon. Suicide is a common outcome of severe clinical depression, and chronic solvent abusers have been reported to have higher rates of depression (Zur and Yule 1990). However, the high rate of suicide by hanging (10 of 11 solvent abusers) is not explainable, especially since less than 1 in 5 noninhalant abusing suicide victims chose this method (table 4). Both the high incidence of suicides, as well as violent or bizarre behavior leading to violent death as occurred in some homicide and accident victims in this study, may be evidence of neuropathy and cerebral dysfunction in chronic inhalant abusers, described in clinical studies (Comstock and Comstock 1977; Filley et al. 1990; Rosenberg et al. 1988).

Future Research on Inhalants

Evaluation of Solvent Mixtures and Other Toxic Additives

Most research on inhalant abuse toxicity has focused on pure solvents and select solvent mixtures. Although a wide variety of solvent-containing products are available, a large portion of solvent abuse involves only a few preferred products. Predominant are: (1) those that contain a high concentration of toluene with or without other solvents, (2) those that contain trichloroethylene and/or 1,1,1-trichloroethane, and (3) less commonly used agents such as alkyl nitrites, alkane gases (butane, propane), hydrocarbon mixtures (e.g., gasoline, paint removers) and anesthetic gases (including nitrous oxide).

Product formulators do not always provide the exact composition of the solvents on their products, and minor components, or even contaminants unknown to the manufacturer may be present and not recognized. Minor components can be extremely important, however, as exemplified by the relatively small amounts of organic lead in leaded gasoline responsible for severe lead encephalopathy in gasoline sniffers and the relatively low levels of hexane that can induce polyneuropathy. Also, paint sniffers' lung tissue at autopsy sometimes contains metal-containing pigments (Garriott and DiMaio unpublished). Since sniffers, rarely, if ever, use the pure solvent, one can not be sure whether the neuropathies or other forms of toxicity are primarily due to the solvent or to other substances in these abused products, or even to other related substance abuse.

Research can be focused on those few substances most often occurring in commonly abused products (toluene, trichloroethylene, 1,1,1-trichloroethane), and combinations of these with or without alcohol—especially since alcohol is commonly ingested along with solvents. Additionally, methylene chloride, another common solvent, as well as other components uncovered in commonly abused products could be evaluated. More comprehensive analyses of abused products should be performed, with the goal of identifying known toxic agents, especially if and when unexplained toxicity occurs following inhalant exposure.

Clinical Studies

Many physiologic systems are known or reported to be affected by inhalants and can be evaluated by standard medical testing. The evaluation should include screening for a broad range of toxic effects to include nervous system, liver and kidney damage, effects on the blood-forming organs, respiratory system effects, and effects on the immune system.

Testing for neurological and behavioral effects should also be carried out, as this form of toxicity may be the most serious and irreversible of all the potential toxic effects of solvents. To determine nonacute irreversible toxicity, analyses must be done in a controlled fashion, using analytical techniques to rule out recent use of inhalants. Toluene, for example, has an approximate half-life of 72 hours in the body (Baselt and Cravey 1990), so some acute effects may persist for a week or longer.

The role of other factors, such as noninhalant drug abuse and environmental factors, should also be evaluated in any clinical studies. A recent study of previous inhalant abusers tested for drug abuse (other than alcohol and inhalants) found that 81 percent were positive for one or more of the commonly abused (for nonmedical purposes) drug groups (Joe et al. 1991). These tests can determine drug use within the past 1-5 days (depending on the drug). Liver damage from other sources and poor nutrition may also contribute to poor health of these subjects.

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Sudden Sniffing Death Following Inhalation of Butane and Propane: Changing Trends

Earl Siegel
Suman Wason

Volatile substance abuse has been noted as a serious problem in Britain since the 1970s (Editorial, *Lancet* 1988). In the United Kingdom two deaths from solvent abuse were reported in 1971 and almost 1,000 deaths since then (Ramsey et al. 1989; Johns 1991). One fifth of these deaths were apparently first-time users (Johns 1991). Among products abused by the British teenager, in order of decreasing frequency, are toluene-containing glues, chlorinated hydrocarbons (cleaning fluids, paints, varnishes, lacquers, dyes), acetone (nail polish remover, polystyrene cements), and gasoline, butane, and propane (lighter fuels and bottled gases) (Editorial, *Lancet* 1988). The largest number of deaths resulted from exposure to butane and propane (gas fuels or propellants) (Johns 1991). In a survey from the United Kingdom, deaths due to abuse of volatile substances occurred primarily in male teenagers (95 percent) of all social classes. Twenty-five percent were due to butane or propane. The causes of death were direct toxic effects (51 percent), asphyxia (21 percent), aspiration of gastric contents (18 percent) and trauma (11 percent) (Anderson et al. 1985).

The profile of American teenagers who abuse volatile substances fits a slightly different pattern (see chapters by Beauvais, Smart, and Fredlund in this volume). A recent U.S. survey indicated almost one in five eighth-graders have

experimented with inhalant abuse (Johnston et al. 1992). By contrast with the United Kingdom, experience with propane and butane inhalation appears to be more limited in the United States. There are only limited reports of deaths in the United States due to inhalation abuse. However, reports of the American Association of Poison Control Centers annual data, which reflects the experience of approximately 70 poison control centers across the United States from 1987 to 1990, are an indicator and are summarized in table 1 (Litovitz et al, 1988, 1989, 1990, 1991). Details were provided for only four cases (table 2). They were all young adults aged 14 to 20 years. We believe that this and other published data underrepresent the true numbers of fatalities related to propane and butane abuse for the following reasons: (a) the circumstances surrounding death may be misrepresented to coroners, (b) volatiles are not easily or routinely screened for in cases of sudden sniffing death, and (c) there, is no formalized registry of this form of drug abuse.

Death resulting from deliberately inhaled aerosol propellants for the purpose of getting high was first reported in 1970. The cause of death was attributed to cardiac dysrhythmia induced by the fluoroalkane propellants, trichlorofluoromethane (Freon 11) and dichlorodifluoromethane (Freon 12) (Bass 1970). Because evidence indicated that continued discharge of these fluoropropellants would lead to a decrease in atmospheric ozone concentrations, and result in climatic changes and skin cancer, the Food and Drug Administration called for a ban of chlorofluorocarbons in aerosol products in 1978 (Molina and Rowland 1974). Most manufacturers replaced the Freon propellants with isobutane, n-butane, isopropane, and isopentane. In 1986, we reported the first human case of ventricular tachycardia after the accidental inhalation of n-butane and isobutane, suggesting that these replacement propellants, too, had potential for inducing fatal dysrhythmia in humans and animals (Wason et al. 1986; Final report of the safety assessment, 1982).

Teenagers have continued to seek products other than fluorocarbons, for their “highs.” Inhalation of gasoline, previously a well-known problem among American Indians and lower socioeconomic teenagers, has become more prevalent among all teenagers (Edminster and Bayer 1985). Also, the use of

Table 1. American Association of Poison Control Center inhalant abuse related deaths

Year	No. of inhalant abuse related deaths	No. caused by butane/propane
1987	10	1
1988	12	7
1989	25	9
1990	20	10

Table 2. Details of sudden sniffing deaths due to propane and butane

Age	Sex	Product	Symptoms/Signs	Post mortem drug
17	M	Nail-enamel dryer	Collapse	Propane/ isobutane
16	M	Air freshener	Coma Ventricular fibrillation	Not reported
16	M	Butane lighter fluid	Collapse	Butane
16	M	Butane lighter fluid	Collapse/electro-mechanical dissociation	Butane

typewriter correction fluids frequently occurs and has resulted in sudden sniffing deaths among teenagers following deliberate inhalation (King et al. 1985); this fluid contains trichloroethane and trichloroethylene.

Although not a comprehensive sample, table 3 identifies several cases brought to the authors' attention from the Tristate area surrounding Cincinnati, in the latter part of 1991. These and those in table 2 compile only a portion of the total deaths in the United States due to these replacement hydrocarbon propellants.

Two recent fatalities attributed to propane and butane abuse serve to emphasize the potential for sudden death. The ready availability of these products makes it imperative that health care providers and youth counselors across the United States are aware of this problem (Siegel and Wason, 1990).

> March 1990: An 11-year-old boy collapsed in a movie theater bathroom. A butane cigarette lighter fuel container and a plastic bag were found next to him. He also had several bottles of typewriter correction fluid in his pocket. Cardiopulmonary resuscitation was instituted; efforts proved unsuccessful and he was pronounced dead shortly thereafter. Post mortem examination showed no evidence of organic disease or anatomic cause of death. Toxicologic analysis confirmed the presence of butane in the patient's blood and lung tissue. Trichloroethane and trichloroethylene were not detected in the patient's blood or tissues.
>
> April 1990: a 15-year-old boy was found unconscious in a backyard. Three companions related that the four teenagers had taken a 20-gallon propane tank from the family gas grill, placed some of the gas in a plastic bag and were inhaling it in order to get high. They also engaged in "torch breathing" whereby they purposefully exhaled the propane gas and ignited it. The subject collapsed soon after inhaling the gas; fumes, ignited by a match, resulted in a flash fire. The patient did not sustain any burns. He could not be resuscitated and died en route to the hospital. Post mortem examination in this case, too, failed to reveal an organic cause of death. Propane was detected in the blood and lung tissues.

Table 3. Other selected Midwestern cases

Date	Age	Sex	Origin	Comments
7/91	16	M	Kokomo, IN	Inhaling lighter fuel while driving with friends, held his head out of the window gasping for air and then crashed. Autopsy showed no anatomic or traumatic cause of death
8/91	16	M	West Michigan	Died after inhaling butane lighter fluid
10/91	16	M	Dayton, OH	1 of 4 boys inhaling butane lighter fuel died
10/91	15	M	Noblesville, IN	Died after inhaling aersolized* shoe protectant
11/91	14	M	Madisonville, KY	Died from inhaling aerosolized* solvent
11/91	29	M	Portsmouth, OH	Died after sniffing aerosolized* paint
12/91	17	M	West Michigan	1 of 3 boys inhaling butane lighter fuel died

*Aerosol blends usually contain isobutane, n-butane, and propane.

Also, in January 1991 four teenagers huffing butane in a parked car in Jefferson County, Kentucky, sustained facial and upper body burns from an explosion ignited by a spark from the car lighter.

In addition, in October 1991 a 6-year-old boy imitating his older brother huffing aerosolized room deodorizer was hospitalized.

Interviews with friends and school officials revealed that sniffing of butane lighter fuel is a common practice among many children at upper middle class schools in Cincinnati. The second subject was avowedly antidrugs and did not consider sniffing to be "drug abuse." Ironically, his mother had discussed the first fatality with him. His response was that the dead teenager was "probably doing it wrong," again attesting to the unfortunate, uneducated familiarity with this form of abuse. Many empty butane canisters were subsequently found in this teenager's bedroom.

There are few reports of nonfatal incidents with "butane abuse". Inhalation of butane lighter fluid by a 15-year-old boy, reported in the British literature, resulted in severe anterior chest pain, agitation, and collapse. In the emergency department, ventricular fibrillation occurred; this condition reverted to sinus rhythm after cardioversion and lidocaine treatment (Gunn et al. 1989).

There is also some reported experience with "fire breathing" or "torch breathing" after butane inhalation. Cartwright reported a 19-year-old fire breather who inhaled butane gas from a cigarette lighter and then ignited it after forcible exhalation (Cartwright et al. 1983). The subject suffered dyspnea, fever, malaise, and hypoxia and had extensive pulmonary infiltrates. Marsh (1984) reported the case of a 14-year-old boy who developed hemorrhagic esophagitis and gastritis after repeated fire breathing.

A recent report details a 17-year-old adolescent's propane abuse practices (Wheeler et al. 1992). The authors speculate that the practice may be widespread.

Several sudden sniffing deaths due to propane and butane have been presented. Since the abandonment of fluorocarbons, replacement fuels and propellants (such as butane and propane) probably represent the most common sudden sniffing death hazard. Health care providers need to be aware that the profile of the teenager who inhales volatiles does not include only the ethnic lower socioeconomic classes. Reported investigations and many other communications lead us to believe that abuse of these readily available inhalants has reached epidemic proportions, indicating an urgent need for preventive efforts directed at teenagers and their parents with emphasis on the risk of sudden sniffing death.

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Treatment of Volatile Solvent Abusers

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Even a cursory reading of the chapters in this volume leads to an inescapable conclusion: Volatile solvent abusers are among the most difficult and refractory people to deal with from a treatment perspective. The research on background and psychosocial characteristics show this group to typically have serious, multiple problems that lead to dysfunction in a wide range of social and personal contexts. Most treatment programs are not equipped to deal with the intensity of problems that solvent abusers present. Further adding to the difficulty in the treatment of volatile solvent abuse is the lack of even a rudimentary treatment model. Solvent abusers present a rather unusual clinical profile, and in many respects they do not fit well within existing treatment regimens. The lack of knowledge about solvent abuse treatment is reflected in the routine and often frantic appeals for information from drug abuse treatment programs. Drug abuse professionals who have an interest in volatile solvent abuse or who have conducted even minimal research are routinely queried for any information that would be helpful in addressing treatment issues. These pleas are commonly from remote areas that are experiencing extremely high rates of solvent use and are nearly devoid of effective resources. The lack of good information, also, is widespread and even well-established drug abuse treatment programs are often at a loss as to how to approach solvent abusers.

From time to time, there is an effort to build a volatile solvent abuse treatment program that will serve these populations, but it is our estimate that these programs rarely survive for more than 9 months. The expense of this type of treatment, the lack of trained treatment staff (in fact, little is known about what training should consist of), and the staff demoralization over the ineffectiveness of treatment seem to be the major elements leading to the failure of these program efforts. Generally volatile solvent abuse has low visibility in most communities and even among treatment professionals, resulting in a lack of funds for targeted treatment. It is quite possible that this will change in the coming years if the trend toward increasing use of solvents among adolescents continues. (See Beauvais, this volume.)

In this chapter we will attempt to outline the critical elements that should be included in volatile solvent abuse treatment. These recommendations are not derived from any particular theory of treatment, nor are they based on a theory of volatile solvent abuse. Indeed, as already pointed out, such a theory does not exist. The basis of what follows will be the characteristics of solvent abusers as they have been discovered through research and upon which there is some consensus among the various studies. It is hoped that, as more experience and knowledge are gained in volatile solvent abuse treatment, we will arrive at a point where treatment efforts can be more theoretically grounded and more effectively focused.

Treatment of volatile solvent abuse has a great deal of overlap with drug abuse treatment in general, and many of the techniques and approaches used in the usual treatment programs do have a place in volatile solvent abuse treatment. Those general treatment approaches, however, will not be addressed here; rather, the focus will be on the specific issues that are related to volatile solvent abuse treatment.

Assessment and Detoxoification

Oetting and Webb (this volume) make it abundantly clear that volatile solvent abusers are typically beset by numerous psychological and social problems in addition to their abuse of chemicals. If treatment is to be effective it must address each of these problem areas.

At the outset it is important to make the distinction between solvent abusers and those individuals who may have used solvents once or twice, or who may

have experimented with them for a brief period of time. The ubiquity of commercial solvents and the natural curiosity of youths make it likely that most young people have had a least a passing encounter with inhaling chemicals for their euphoric effects. For the most part, however, this is time limited and there are no lasting negative consequences. (The exception to this is the naive experimenter who may die from the use of a particularly lethal solvent.) The picture for solvent abusers, however, is much different and their lives become consumed with the obtaining and use of solvents. Oetting and Webb (this volume) and the DSM-IIIR (American Psychiatric Association 1987) provide some guidance in making the distinction between "benign" solvent users and chronic solvent abusers who are in need of treatment.

While physical examinations are normally a part of the intake procedure in most drug abuse programs, they take on added importance for solvent abusers. There are a number of specific medical complications that must be assessed. Sharp and Rosenberg (1991) point out that renal and hepatic abnormalities are often associated with chronic solvent abuse and, where leaded gasoline is still widely in use, lead poisoning is common. Furthermore, there is also a possibility of cardiac arrhythmias and pulmonary distress. Many solvent abusers are lacking in basic life skills, including personal hygiene, leading to potential problems with skin diseases and poor nutrition. In general, a thorough medical examination is needed with special attention to those conditions resulting from chronic solvent abuse. Clients brought in to treatment during acute intoxication may have other immediate medical crises that need attention.

The families of abusers are quite often highly dysfunctional, and it is not uncommon for the abuser to have been raised in a home without a father. This raises the need for a thorough assessment of family stability, structure, and dynamics so that treatment can be focused on such needs as therapeutic intervention with the family or providing reparenting or social bonding skills for the client. In many cases the family situation may be so chaotic that one of the treatment goals may be to work toward foster care for younger abusers or halfway house placement for older adolescents.

One of the common findings in research studies of solvent abusers is the presence of neurological impairment. Unfortunately, much of this research is flawed in that there is no control for the possibility that these problems may have predated the use of solvents. It would be important to know if there are

underlying conditions such as learning disabilities that may have contributed to the constellation of premorbid dysfunctional behaviors. There is some speculation that solvent abusers are self-selected in the sense that their early neurological and behavioral problems are somehow implicated in their later choice to use solvents. A thorough examination of records of any early neuropsychological testing and of school records would help frame the need for the remediation of specific problems during the course of treatment.

Unfortunately, not a great deal is known about the extent and duration of neurological damage caused by solvents. (See reviews by Rosenberg and Sharp, and Tenenbein, this volume.) There are a number of studies that reveal that heavy solvent users do indeed incur damage; however, the duration and/or reversibility of this damage is unclear. The majority of volatile solvents are lipophilic, meaning that they are stored in fatty tissue in the body and are eliminated much more slowly than most other drugs. One consequence of this is that solvent users may be experiencing residual effects from the drugs for quite some time (due to the deposit of solvents in the white matter of brain), including altered affect and dullness of intellectual functioning. The implication for treatment is that the period of detoxification for solvent abusers may need to be longer than that of other drugs of abuse. It is quite possible that much of the frustration with treating solvent users is that very few short-term treatment gains can be achieved. Solvent abusers simply are not able to capitalize on the therapies that are typically used in treatment programs until the abusers have recovered sufficient cognitive and emotional functioning. There are absolutely no data to indicate how long it will take solvent abusers to recover to the point at which they are capable of actively engaging in the recovery process. This no doubt will be subject to individual differences, the level of premorbid functioning, and the duration and level of solvent abuse. Any neurological or neuropsychological testing done early in the course of treatment should be repeated in several months to assess the possibility that any measured deficits have improved with time in treatment.

Peers have been consistently implicated as the most powerful influence on adolescent use of drugs (Oetting and Beauvais 1986). This influence may be even more salient for solvent abusers since the peer clusters (see Oetting and Webb, this volume) of solvent abusers can be highly deviant, thus making them more impervious to positive social influences. Assessment should take into account both the structure and norms of the abuser's peer cluster so that a treatment goal can be established to break those social bonds and replace

the cluster with a more constructive group of peers. Achievement of this goal can be enhanced if there is knowledge of the particular dynamics that attracted the client to the peer cluster. Leal et al. (1978), for instance, describe groups of street children in Mexico City who have left their homes at early ages and have joined other groups of children in a structure that basically recreates the family. The older adolescents provide protection and direction for the younger children, but they also direct much of the street crime that is utilized to acquire solvents, the use of which is the norm in the group and is quite extensive. While this is an extreme example, it does illustrate that the peer structure has a basic meaning for these youths and that certain primary needs are being met by the group. It should be possible to discern similar meaning by examination of the peer cluster structure of solvent abusers in treatment.

The role played by siblings of solvent abusers should not be overlooked. In many instances there is a pattern of use by brothers and sisters or even cousins, a case in which treatment must be extended to all members of the family involved with solvents. This pattern has been found quite often among minority children where the extended family may live within close proximity.

Older adolescent solvent abusers are also most likely using other drugs. It is important to obtain an accurate drug use history in order to assess any problems created by this use and to understand the drug taking motivation of individuals. It is useful to know if the use of solvents has a different meaning for the individual than the use of other drugs. The drug history should also involve as thorough a knowledge as possible of the types of solvents that have been used. Most of the time it is not possible to link a specific solvent with a specific neurological or behavioral symptom, but in some instances important insights can be gained. For instance Pryor (this volume) reports essentially irreversible peripheral neuropathies from exposure to hexanes, toluene, and other solvents. As stated, this type of assessment is very difficult due to the wide range of solvents and solvent mixtures that may have been used as well as denial or poor recall from the patient.

Length of Treatment

Treatment programs for solvent abusers, then, should be prepared to engage their clients in an extended period of supportive care marked by abstinence from solvents, nonconfrontation, and an emphasis on developing basic life

skills. Initial intervention should be very brief (e.g., 20-minute sessions as opposed to 60 minutes) and concrete. Attention span and complexity of thinking are greatly reduced for many solvent abusers when they first enter treatment. Clients should be monitored to assess their changing level of functioning to determine at what point they are cognitively ready for increasing levels of therapeutic intervention. Data on the optimum length of treatment are nonexistent, although some programs are recommending as long as 2 years (Driver 1991-92).

One of the drawbacks to extended periods of treatment is the possibility of bringing people together who are likely to form deviant peer clusters within the treatment environment. Given a sufficient amount of time, like-minded people will tend to coalesce and create peer clusters that can subvert treatment. Staff need to be aware of these dynamics and develop strategies for intervening when relationships form that are detrimental to the therapy goals.

Intensive aftercare and followup are essential for volatile solvent abusers. They need particular assistance in creating a healthy social milieu, since in all likelihood their social contacts have been limited to other solvent abusers and otherwise deviant peers. For younger abusers the school environment may be especially difficult to readjust to. There they will find it difficult to avoid many of the people they previously associated with, and it is likely that they have developed poor relationships with the school teachers and staff. It is important to have a school counselor or other staff person who will be involved in discharge planning and who will act as an advocate for the client in the school. In addition, it is advisable that someone be responsible for closely monitoring the behavior of treated abusers so that help can be made immediately available at the first sign of relapse into previous behavior patterns. Big Brother/Sister programs are especially helpful for previous solvent abusers.

Inpatient Versus Outpatient Treatment

In the treatment of substance abusers, there is always the question of whether inpatient or outpatient treatment is the most appropriate. There are no clear-cut guidelines for this. However, there are several characteristics of solvent abusers that make inpatient treatment the most appropriate choice. The typically chaotic family situations make it unlikely that the abuser will receive adequate support from the family for treatment goals. Quite the opposite, it

is more likely that family members will subvert therapeutic efforts. In particular, these families often have very little control over the behavior of the abuser, making abstinence from solvents very difficult.

The highly deviant and powerful peer clusters of solvent abusers also make behavior change unlikely in an outpatient setting. The solvent abuser has typically restricted his or her relationships to other solvent abusers, leaving these peer clusters as the only source of socialization. The antisocial nature of these groups makes adherence to therapeutic aims nearly impossible. Furthermore, solvent abusers spend the great majority of their time either obtaining solvents or being under their influence. This leaves little time for positive or socially acceptable interactions.

As a group, solvent abusers are very impulsive and elusive, making treatment compliance very difficult. As outpatients they may avail themselves of treatment for short periods of time but they soon "disappear" into their previous milieu where they are extremely difficult to locate (N. Rosenberg, personal communication, July 1990). Inpatient treatment provides the structure and control needed to get abusers through the extended detoxification period and to a point where they can begin to experience the positive effects of treatment.

The elusiveness of solvent abusers contributes to making them a "hidden" population in need of treatment. They rarely volunteer to come into treatment, and their disenfranchisement from the family makes it less likely that the family will bring them into treatment. Case finding for solvent abusers is difficult, and a great deal of reliance must be placed on referral sources such as the police, welfare workers, homeless shelters, hospital emergency rooms, and runaway shelters. Hospitals are a source; however, few subjects are referred by this process as they seldom seek or require treatment in a hospital setting.

More so than other drug abusers, it is necessary to have some type of leverage to keep solvent abusers in treatment. Neither the abusers nor their families have the motivation to endure the effort and extended time that is necessary for effective treatment. Ironically, the highly dysfunctional behavior of the families of solvent abusers can often provide the route to treatment. These families are quite often abusive and have a history of contact with police or welfare agencies. This record can often provide the leverage for placing a young person in treatment.

The law itself, that is, the existence of penalties for the use of solvents, is another common source of leverage. Whether or not one believes that laws can control drug abuse, in instances like this, legal clout can at least provide the vehicle by which highly dysfunctional individuals can be brought into treatment. Reed and May (1984) provide evidence that solvent abusers, even more so than other drug abusers, have a greater history of criminal involvement. Unfortunately, the legal status of solvent inhalation is highly variable, with some jurisdictions having no legal controls or interdiction directly relevant to solvent abusers.

Designated Treatment Programs

Solvent abusers appear to present enough differences in their clinical profile to suggest that they cannot be treated in the context of programs that work with drug abusers in general. The extended period of detoxification and recovery of neurological function, the relative unresponsiveness to early treatment efforts, and the multitude of collateral problems dictate that, in general, solvent abusers need to be treated in separate programs.

One of the problems in treatment of solvent abusers to this point is the frustration on the part of treatment staff over the slow rate of recovery. If staff expectations are not appropriate to the level and pace of progress that can be reasonably achieved, there will undoubtedly be low morale.

Specific treatment programs for solvent abusers are undoubtedly an expensive proposition; yet, given the nature of this problem, this seems the only logical and effective approach.

Special Emphases in Treatment

Adding to the expense of solvent abuse treatment is the broad array of intervention strategies that are required if lasting change is to be effected. Solvent abusers are typically deficient in a variety of skills needed for effective living. While most drug abusers needing treatment also have personal/social problems that need attending to, solvent abusers are marked by the extent and depth of these characteristics. Following are areas where special attention is needed in the treatment of solvent abusers.

1. Extensive involvement of the family to ensure compliance with treatment goals after treatment. Alternate placement should be explored.

2. Remediation of academic deficits to ensure adequate posttreatment school adjustment for younger abusers.

3. Vocational training for older abusers to promote self-sufficiency.

4. Training in basic life skills including personal hygiene and nutrition.

5. Advocacy with the justice system.

6. Restructuring of social environment to exclude peers who are detrimental and include nondeviant peers.

7. Extensive aftercare and followup.

Summary

Those contemplating treatment of solvent abusers must be prepared to work with individuals who have a greater breadth and depth of personal and social problems. Treatment can be expected to be long term, possibly up to 2 years with an extended period of detoxification before any specific therapeutic interventions can be attempted. A wide range of interventions will be necessary to address the multiple social problems experienced by the typical solvent abuser.

The effective treatment of solvent abusers is likely to be an expensive proposition, yet, given our current level of knowledge of treatment, there is no alternative. The cost of volatile solvent abuse treatment must be weighed against further costs for this high risk population, including incarceration, medical expenses, and welfare support.

Research Agenda

The above discussion leads to a number of gaps in our knowledge of solvent abuse treatment that can be addressed in future research. They are as follows:

1. Are there specific neurological deficits caused by solvents that can be remedied with specific treatment techniques? Can these be discerned by the type of solvent?

2. Can guidelines be developed that would indicate when reversibility of neurological damage will occur? Can a timetable or list of benchmarks be developed that would indicate when higher order cognitive therapies would be effective?

3. Are there specifiable premorbid characteristics that lead to solvent abuse? Can these be addressed in treatment?

4. Are there certain therapeutic approaches that are more appropriate for solvent abusers?

5. What are the family characteristics that indicate that discharge back to the family would or would not lead to continued therapeutic progress?

6. Are there socioeconomic factors that contribute to solvent abuse?

7. Are there highly structured outpatient settings where there is sufficient control to provide treatment?

8. What incentives/leverage can be applied to ensure treatment compliance?

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A Longitudinal Study of Inhalant Use: Implications for Treatment and Prevention

D. Dwayne Simpson

Evaluation of prevention and treatment paradigms for dealing with inhalant users has received limited attention. As described elsewhere in this volume (see chapters by Octting and Webb and by Beauvais) and earlier by McSherry (1988) and Santos de Barona and Simpson (1984) these drug users are typically young and have poor life management skills. They are at high risk for drug use and deviant behaviors due to their low socioeconomic opportunities, poor educational background, disrupted family environment, poor psychological and emotional adjustment, and social discrimination. Treatment agencies face a major task in dealing with these youths, compounded further by the common problem of disintegrated families with parents who are emotionally despondent and have "given up on their kids." As a result, counselors at community-based intervention programs often become friends, school teachers/tutors, role models, and surrogate parents for their clients, but the emotional weight of these responsibilities leads to frequent burnout. Even though there appears to be short-term gains for many clients while the therapeutic relationship is maintained, sustained progress is difficult and long-term outcomes are frequently poor for these youths as a whole.

Little is known also about the etiological aspects and natural history of toxicant inhalant use. Sniffing or huffing of solvents and other inhalants often appears to be part of a broader pattern of drug use, but the duration of use

and its role in the general psychosocial development of youths remains largely unknown. Prospective research on the social and psychological correlates of inhalant use is important for examining long-range consequences and implications of these factors for intervention efforts. This chapter therefore summarizes major findings from studies conducted based on the Texas Prevention Management and Evaluation System (Santos de Barona and Simpson 1984), a multisite data base that included followup research on Mexican-American youths admitted to intervention services for inhalant users (see Simpson and Chatham 1991).[1]

Description of the Sample

A total of 175 Mexican-American youths aged 13 to 17 when they entered the Youth Advocacy (YA) Program in Austin, Texas, from 1981 to 1985 were targeted for followup. Their history of preadmission inhalant use showed that 20 percent used at least weekly in the 2 months prior to entering this program, another 24 percent used at least once a month, 19 percent had used previously but not in the prior 2 months immediately before admission, and 37 percent had never used inhalants. This heterogeneous mix of high-risk youths represented an appropriate sample for the longitudinal study of drug use changes and related outcomes over time. These clients stayed in the program an average of approximately 13 months, during which time they received individual counseling and participated in a variety of recreational activities, cultural enrichment, academic tutoring, and related life-skills training. However, detailed client participation records were not available in this study for specifically evaluating these services.

Private face-to-face followup interviews were conducted during October 1987 to April 1988, an average of over 4 years after admission to the YA program. Of the 175 cases in the target sample, 150 (86 percent) were successfully traced; 110 (63 percent) gave informed consent and were interviewed, 9 (5 percent) refused to participate, 3 (2 percent) were deceased, 13 (7 percent) were in prison and unavailable for interview, and 15 (9 percent) had moved

[1]The Texas Prevention Management and Evaluation System data collection forms for intake and followup are available from the author; also see Simpson and McBride 1992.

outside the Austin metropolitan area. The remaining 25 (14 percent) could not be located. Of the 110 completed cases, 79 percent of the mothers were also interviewed.

Average age at program admission was just under 15, and 65 percent were male. Reasons for coming to the YA program showed that 35 percent were referred by legal authorities, 22 percent by school officials, 19 percent by parents or family members, and 12 percent were self-referrals; 68 percent had friends who had been in the program before. They came predominantly from low socioeconomic background (less than one in four of their parents had finished high school), and only a third reported their parents were living together.

Behavioral Changes From Program Intake to Followup

When followed up—at average age 19—a third of the sample was either married (10 percent) or living as married (25 percent), and 8 percent were separated or divorced. Half had one or more children (68 percent for females). Marital relationships of their parents had become further impaired, compared with the time of intake. This was especially true among females; only 13 percent said their natural parents were living together.

When admitted to the YA program, two thirds of the youths were in school (most had reached the eighth grade) and one third were suspended or had quit school. Of those still in school, however, 41 percent had mostly failing grades on their last report card, and over half had either skipped classes or been in trouble at least once a week. Attitudinal ratings also showed that school was not generally considered to be a high priority by these youths.

It was therefore not surprising to find that at followup, 71 percent of this high-risk sample had dropped out of school. Only 9 percent had graduated or received their GED, and 15 percent were still enrolled in school or a formal vocational training program. Only half had been employed at a full-time job for 1 or more months in the year before followup (including 56 percent of males and 37 percent of females).

Before entering the YA program, most youths (85 percent) had been picked up by the police at least once, and 77 percent had been arrested (which was

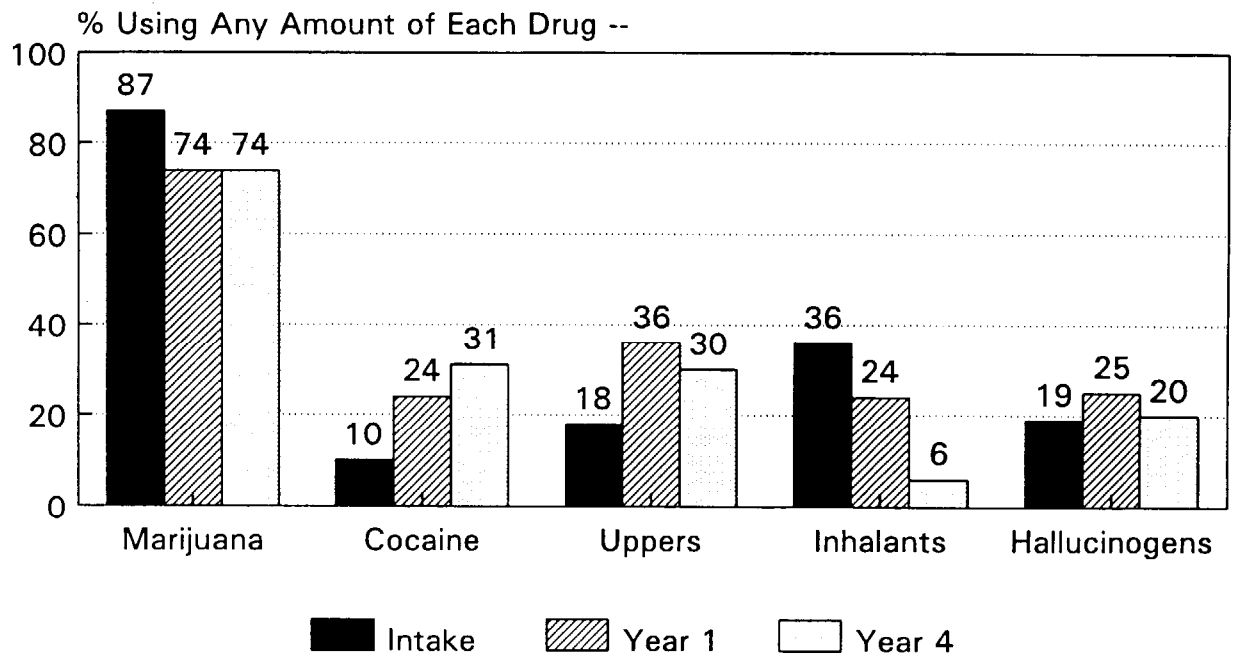
consistent with the high rate of legal referrals to the agency). During the year immediately prior to the followup interview, the youths still were involved in a high level of criminal activity. Over half (54 percent) had been arrested at least once during the year, and 26 percent were arrested two or more times; 12 percent had spent at least 30 days in jail. Approximately one third of the youths (31 percent) admitted to having committed serious crimes such as theft, robbery, mugging, fighting with a weapon, or rape.

Historically, marijuana was typically used first (at about age 13, on average), followed 6 months later by alcohol and then inhalants at age 14. Cocaine use was initiated, on the average, after turning age 16. Almost all of the sample (93 percent) had used alcohol before entering the YA program, and information on specific drinking patterns immediately before the followup interview suggested there was a continuation of heavy alcohol involvement. That is, one third drank on 15 or more days of the last month before followup, 26 percent consumed an average of 4 ounces or more of 80-proof liquor equivalent per day, and 40 percent had been drunk in the past month.

Prevalence of marijuana and inhalant use decreased somewhat from before YA program intake to followup, but usage of several other drugs increased. Figure 1 shows that marijuana was the drug used most often in the first year—referred to as year 1—after termination from the YA program. Seventy-four percent reported using it in the first year (and about 45 percent of the sample reported using it at least weekly); this was down from a level of 87 percent of those using marijuana in the 2 months before entering YA program. The second most frequently used drug category in year 1 was uppers (36 percent), while hallucinogens, inhalants, and cocaine were each used by approximately one-fourth of the sample. Opiates and downers/depressants were the least frequently used drugs (and are not shown in figure 1).

In the last year before the followup interview—referred to as year 4—marijuana was again the most frequently used drug (74 percent). However, cocaine and other uppers were next in prevalence of use (31 and 30 percent), which was assumed to be due in part to their increased popularity and availability during the time of this study. On the other hand, inhalants were used by only 6 percent, and along with opiates and downers, were the drugs used least frequently.

Figure 1. Drug use in years 1 and 4 after leaving YAP



The major reasons youths gave for using inhalants were easy availability, curiosity, and the "high" resulting from sniffing or huffing (see Joe and Simpson 1991). Personal adjustment problems as well as parental absence and family relations were also important. Fortunately, very few individuals continued long-term use of inhalants, and their reasons for quitting were found to be primarily associated with family or social pressures and attitudinal changes about its use (including concerns about health).

Followup Outcomes in Relation to Inhalant Use at Intake

One important aspect of this study was the comparison of followup outcomes according to level of baseline (preadmission) inhalant use. These data are summarized in table 1, but the small sample sizes call for caution in making interpretations. Preliminary analyses indicated these four groups were generally comparable at intake in terms of sociodemographic characteristics. Most interestingly, the use of alcohol and other drugs as well as legal involvement measures were directly associated with the level of inhalant use. At followup, the data presented in table 1 show these trends remained intact; thus, the youths who were heavier inhalant users at intake continued to have more negative outcomes 4 years later.

In particular, the group of weekly users had lower employment rates, higher prevalence of arrests and illegal activity, and more drug use than the other groups. At least two thirds of each group used illegal drugs in year 4 of the followup; this was true of 95 percent of the weekly users. Furthermore, 45 percent of this group were also heavy drinkers who on the average consumed over 4 ounces of 80-proof liquor equivalent per day.

The only exception to the continued tendency toward more general polydrug use by the weekly inhalant use group is cocaine. Overall, preadmission use for cocaine was 10 percent for the total sample, and it increased to 31 percent at followup. In contrast to all other drug categories, the preadmission group of weekly inhalant users had the lowest level of cocaine prevalence in year 4 (although the group differences were small and statistically insignificant).

Youths with more extensive inhalant use histories reported more cognitive problems involving clarity of thinking, decisionmaking, concentration, and remembering details. Depression, anxiety, and thoughts of suicide were also common (see Smith et al. 1991). Almost half of the youths, for instance, showed evidence of clinical depression and were highly anxious. Over one

Table 1. Behavioral outcomes at year 4 followup by preadmission inhalant use

Outcomes in past year	Level of preadmission inhalant use				Total
	Weekly	Monthly	Experimental	Never	N
Days Employed (%)					
Over 90 Days	38	52	48	63	54
Legal Involvement (%)					
Arrested	76	58	43	49	54
Jailed	71	53	38	41	48
In illegal activity	76	50	52	55	59
Alcohol and Drug Use (%)					
> 4 oz./day*	45	26	30	16	26
Using any illegal drug	95	79	67	77	79
Any marijuana	90	74	62	73	74
Any cocaine	24	36	29	33	31
Any other uppers	38	37	24	26	30
Any hallucinogens	29	27	24	12	20
Any inhalants	24	5	0	4	6
Sample Sizes	21	19	21	49	110

*Refers to ounces of 80-proof liquor equivalent drunk in the past month.

fourth had experienced suicidal thoughts, and one fifth had made at least one suicide attempt. Psychological problems, including depression and low self-esteem, tended to be accompanied by other health problems or symptoms.

Integrative Prediction Model of Outcomes

Several measurement domains representing major conceptual areas (often considered important in measuring drug use among youths) were examined as part of a general multivariate prediction model, similar to previous efforts by Huba et al. (1980), Jessor and Jessor (1977), Kandel (1978), Kaplan (1980), and Oetting and Beauvais (1987). In particular, Joe et al. (1991) included cultural, socioeconomic, and other factors using causal modeling procedures (Joreskog and Sorbom 1988) with the 4-year followup data. The results showed that a conceptual path model in which influences of drug availability, family relations, sociodemographic, and cultural domains are assumed to operate exclusively through peer and psychological mediators to explain drug use was inadequate. Instead, a more integrated model allowing both direct and indirect effects on the drug use criteria provided a better fit to the data. At the same time, however, deviant peers exerted a primary influence on inhalant and other drug use at followup; family and environmental variables tended to operate indirectly through this link. It was also found that measures of psychological adjustment or vulnerability (such as self-esteem, depression, self-derogation, and learned helplessness) were not directly predictive of drug use outcomes.

With respect to inhalant use history, one of the strongest predictors was education; lower education levels were associated with more extensive inhalant use, especially total days of lifetime use and starting at an earlier age. Inhalant use by other family members, usually older siblings, was another predictor for heavier use. Finally, indicators of perceived availability of inhalants and acculturative stress also failed to demonstrate significant direct or indirect effects on inhalant use (also see Barrett et al. 1991).

Evaluations of Intervention Effects

Using during-program data from the YA program and three other similar programs primarily serving Mexican-American youths, Barrett et al. (1988) found that favorable changes occurred on behavioral indicators for alcohol and drug use as well as legal and school problems during the first 3 months in

treatment. In particular, the results reflected the positive influence of traditional social bonding—as represented by family support and commitment to religious involvement—on reducing problem behaviors over time. Decreased exposure to drug-using peers during treatment was even more important as a positive influence, however, supporting the widespread evidence for the role of peer pressure and support networks. Severity of problems at the time of intake was also associated with the outcomes 3 months later, but these effects appeared to be moderated by the impact of positive family and peer influences.

Another important (and therapeutically encouraging) finding was that client interest and motivation at the time of program intake were positively related to level of participation in treatment, which in turn was related to improved performance during the program. The results confirmed the frequent observations in the epidemiological literature that family, friends, and religion are related to adolescent behaviors, but more importantly, these findings indicate that the same relationships operate in the context of a therapeutic environment as well. The implications are that intervention efforts should (1) enhance efforts to capture family involvement and emotional support for the youths, (2) increase contacts and rapport with positive peer and role models while diverting relations with drug-using friends, and (3) focus efforts on ways to maximize client interest in and commitment to the therapeutic enterprise. These are not new goals, but it is important to explore new ideas for implementing ways to reach them.

Concluding Comments

It appears that intervention efforts are increasingly difficult after youths become more heavily enmeshed in drugs and related problems. Low cost and easy access to toxicant inhalants facilitate and encourage their use, but educational efforts and family support seem to help change attitudes and reduce chronic or long-term usage. It is especially important to redirect adolescent ties with deviant peers and destructive friendships. Feelings of discrimination and alienation by youths need to be addressed through efforts to establish better social coping skills as well as reducing educational failures and school dropout rates (see Menon et al. 1990). This may require that attention be given to cultural heritage and identity for enhancing self-concepts, and considering alternative cognitive learning strategies that might be more effective with some minority youths. Care for physical health must also be emphasized,

along with education about the growing threat of AIDS and lowering the frequency of teenage pregnancies by unwed parents. As stressed by McSherry (1988), much of this effort revolves around the needs for basic life management skills and should help enhance socioeconomic opportunities and expectations that are critical for long-range solutions to many of the problems experienced by these youths.

It is important to sustain and systematically refine intervention services in community-based agencies that have the support and confidence of the neighborhood being served. Community trust, effective social service networking, and organizational stability are important attributes of most successful programs. To evaluate the efficacy of their services, however, clinical efforts must be carefully coordinated with comprehensive empirical assessments of the intervention process and longitudinal outcomes. Comprehensive data systems should include community epidemiological indicators over time, along with client and intervention process data collected throughout treatment. Posttreatment followup assessments are also essential components of this longitudinal evaluation model.

Toward this end, improved strategies are especially needed for involving parents and families of inhalant users, both behaviorally and emotionally, in the therapeutic process to create a supportive environmental atmosphere for positive change. Efforts to accomplish such family involvement and counseling have continued to prove difficult in some Mexican-American communities (Jesse Flores, personal communication), suggesting that culture-sensitive approaches may be required and that this represents a serious challenge for intervention efforts (see Szapocznik and Kurtines 1989).

These represent extremely complex sociological problems and psychotherapeutic goals, and their solution is not the unique responsibility of drug abuse prevention and treatment programs. In order for agencies to be realistic in the scope and focus of their intervention objectives, identification of priority concerns for their particular community and the planning of strategies requires careful thought, expertise, discipline, and community mobilization. Sustained attention and financial support for the progressive development of effective intervention efforts are required, particularly among low socioeconomic groups with limited access to drug treatment and related services.

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Treatment and Prevention Research Issues

Leo E. Hollister

I reflect on these issues from a broad perspective as a clinical pharmacologist studying various drugs of abuse for more than 30 years, yet with no direct experience with inhalants. Therefore, I bring that experience to this very important issue dealing with the prevention and/or treatment of inhalant abuse.

Inhalants have a great appeal because of certain advantages over other drugs of abuse. They are widely available and so important commercially that reducing or controlling supplies has never been seriously proposed. Some are conveniently packaged, often in ways that appear innocent. The cost for each intoxication is low, often measured in pennies. The intoxication can be quick in onset and relatively short-lived, allowing multiple repetitions. Peer group influence appears to be a stronger factor in promoting inhalant use than with other drugs.

The study reported by Dr. Simpson is one of the few systematic approaches to gain some idea of the natural history of inhalant use. Actually, studies of the long-term course of all drugs of abuse are unusual.

When it comes to long-term evaluations of treatment outcome, the literature is sparse indeed. Yet such studies are basic requirements for the development of a strategy aimed at prevention or treatment. One might try to imagine some of the characteristics of an ideal prevention-treatment program. We

should like to identify for such a program youths at high risk for becoming compulsive users.

Future Directions

The many sociological studies already accomplished, and reinforced by Dr. Simpson's findings, suggest various characteristics to identify such persons. They come from low socioeconomic levels, have many problems with their families and at school, and associate with drug- or inhalant-using peers. Using such criteria, one might decide on the characteristics of a prevention-treatment program. It should remove the at-risk person from the proselytizing of peers and the instability of their families. At the same time, it should try to minimize access to inhalants as well as other drugs. Education would be important but should be directed at practical goals: vocational training to prepare the youths for a job and provide some ray of hope in an otherwise hopeless future. Less important, but included mainly because it is part of most existing drug treatment programs, would bc education about the potential harm from drugs of abuse. Based on the notion that physical fitness enthusiasts are the least likely to use drugs, emphasis should be placed on personal hygiene, athletics, and physical fitness. Efforts should be made to raise self-esteem, either by the learning of a new skill or by improving physical development. One might think of many other aspects that could be incorporated into a curriculum.

The word "curriculum," with its implications of school, was used deliberately. I would propose that a study be established along the following basis in a research setting. Inhalant-abusing youngsters should be separated from their peers and their families by attending a kind of boarding school. One might think of it as having a character between that of Marine Corps boot camp and Outward Bound. It might be situated on one of the growing number of underutilized military bases, which afford enough security to prevent wholesale elopements. The schooling might be of variable length, up to 2 years. If possible, students should not be returned to their friends and family on discharge but to some semiindependent type of living. These might be the rough elements of a formal prevention-treatment program.

Assuming that such a program might be feasible to establish, it should be critically evaluated. Too often in the area of drug abuse, treatment programs are used without any attempt to assess their worth. It should be possible to

make a controlled evaluation by randomly assigning identified at-risk youths to either the school program or to remain in their present situation. One would like to follow each group for at least 3 years, using a variety of end-points of success to compare the two groups. What Dr. Simpson's study has shown is that it is possible to follow inhalant users for substantial periods of time with reasonable degrees of completeness as well as obtain the kinds of information that would permit a valid assessment of treatment.

Inasmuch as inhalant abuse might be considered, at least for those who use these substances, as a possible "gateway" drug, such a program of prevention-treatment, were it effective, might be adapted and applied to youths in impoverished areas at risk for becoming cocaine or heroin abusers. The same principles of rehabilitation that might be used for inhalant users might be appropriate for potential users of other drugs.

Such a demonstration project would be expensive, both in terms of dollars and time. However, the fact that we have the ability to undertake such a study with available techniques obliges us to try to find what may help this group of ill-fated youths. We have precious little else to offer.

Conclusions

Followup studies of inhalant abusers have been shown to be feasible for obtaining the kinds of information that can be used to evaluate a prevention-treatment program. Enough sociological information has been gained over the years to identify at-risk youths and to define some characteristics of a prevention-treatment program for inhalant abuse. Simple techniques can be used to establish comparison groups to permit objective assessment of treatment. Such a treatment program for users of one of the earliest used drugs might provide guidance in the development of similar rehabilitative efforts for youngsters at risk for cocaine or heroin abuse. The time is propitious for testing.

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Animal Research on Solvent Abuse

Gordon T. Pryor

Many solvents have been evaluated to establish safe exposure levels and to set industrial standards. However, in the context of solvent abuse, conclusions reached from the results of classic toxicologic evaluations may not apply. Indeed, even in the case of mild to moderate (and sometimes heavy) solvent abuse, the incidence of verified persisting organ toxicity and/or functional damage is relatively rare. Moreover, the unambiguous identification of the agent and/or agents responsible in such cases has been very difficult because (1) the substances involved are typically mixtures, (2) the formulations and choices of the mixtures change over time, and (3) the history of the subjects involved often includes a variety of factors (not the least of which may be the use of other drugs) that might be partly or primarily responsible for any observed disorders. Thus, laboratory experiments designed specifically to address the issue of human solvent abuse are essential if any significant progress is to be made in our understanding of this phenomenon and its consequences.

The purpose of this chapter is to review some of the literature and to describe various toxicological findings from this laboratory on the effects of exposure of animals to those solvents most commonly found in abused products and suspected of being involved in the neurologic consequences of heavy solvent abuse. The discussion will focus on the evidence that implicates specific solvents in relatively severe and persisting neurologic sequelae. The discussion will be restricted to those solvents found in abused commercial products that

are reportedly associated with neurologic dysfunction (anesthetics such as halothane and the volatile nitrites will not be considered here). Issues of physicochemical characteristics, pharmacokinetics, and biochemical/neurochemical consequences of the solvents involved, all of which are important in understanding the mechanisms by which such agents may cause damage to the nervous system and/or other target organs or tissues, will not be covered (see Arlien-Sϕborg 1992 for a recent review).

Recognition of the problem of solvent abuse began emerging in the 1960s. However, aside from scattered case reports and the results of a few isolated laboratory studies, very little was known about the extent of the problem or the hazards involved. An important milestone was the monograph by Sharp and Brehm (1977). This review was especially important because it signaled the recognition of the problem by the newly formed National Institute on Drug Abuse (NIDA). Subsequent reviews addressed specific solvents such as toluene (Benignus 1981*a,b),* trichloroethylene (Annau 1981), dichloromethane (Winneke 1981), methyl chloride (Repko 1981), and hexacarbons (Spencer et al. 1980). These reviews often depended heavily on scattered reports from the toxicologic literature, and definitive conclusions were elusive (see especially Benignus 1981*b,* p. 413). A more recent discussion of the problem, including an update of the relevant biologic research (Pryor 1986), was sponsored by the World Health Organization in Mexico City in 1986. By that time some experimental results more relevant to the human abuse problem were beginning to appear.

In the Sharp and Brehm (1977) monograph the number of solvents and chemicals that might be considered potentially hazardous in the context of solvent abuse was relatively large. Since then studies of the solvents of major concern have focused mainly on toluene and its related analogs xylene and styrene; dichloromethane (DCM), trichloroethylene (TCEE), 1,1,1-trichloroethane (TCEA), methyl ethyl ketone (MEK), *n*-hexane and its related analogs, and various mixtures containing one or more of these solvents. The major focus in this chapter will be on toluene because of its central role in human solvent abuse.

Acute Behavioral Effects of Exposure to Solvents

Most solvents found in various abused commercial products are CNS "depressants" at high concentrations and lead to unconsciousness and death

with prolonged exposure. However, behavioral manifestations of "excitation" are seen after short durations of low-level exposure, and during various stages of emergence after high levels of exposure. On the other hand, a few solvents such as *n*-hexane, *n*-heptane, and some of their analogs (e.g., methyl cyclohexane) often found in commercial products are convulsants at high concentrations.

The literature describing the acute behavioral effects of various solvents in animals is not extensive and provides limited insights into the possible persisting neurologic consequences of heavy human solvent abuse that is the major concern of this chapter. Nevertheless, in reviewing this literature, at least one broad, albeit unsurprising, generalization emerges. That is, exposure to sufficiently high concentrations of these solvents for sufficient durations of time can markedly affect ongoing behavior and impair performance in various species of animals, including humans. From the industrial toxicologist's perspective, this generalization has important ramifications, and the determination of "threshold" limits for such effects is a goal for establishing safe exposure standards. From the perspective of solvent abuse, such lower limits dramatically serve to reemphasize the acute hazards, in terms of potential for accidental injury, that can be associated with this practice.

Having just made this broad generalization, it is just as important to point out that the behavioral manifestations of acute exposure to various solvents are not uniform. This point is important for at least three reasons: First, qualitative differences are probably more important in product selection by solvent abusers than quantitative differences. Second, such qualitative differences may provide clues as to mechanisms of action that would not be apparent from differences in potency. Third, classification schemes based on qualitative differences are a necessary step toward understanding the basic structure-activity relationship among various classes of solvents.

An example of the dissimilar pharmacologic effects among various solvents is provided by the results of some early experiments investigating the effects of a mixture containing DCM, toluene, commercial heptane (itself a complex mixture), and methanol (Pryor et al. 1977; 1978*b;* 1980). Acute exposure of rats to this mixture for 10 minutes caused a concentration/time-related behavioral syndrome characterized by ataxia, falling, hindlimb flaccid paralysis, sporadic aimless scratching movements, head jerking, and, finally, prostration and unconsciousness. When the components were studied alone, the hindlimb

flaccid paralysis and head jerking were associated exclusively with exposure to DCM, whereas the abnormal, aimless scratching was caused by the toluene. Exposure to the commercial heptanes caused full tonic-clonic seizures that were subsequently found to have been blocked in the mixture by toluene. Methanol had only sedative properties, with none of the unusual characteristics noted for the other solvents.

More recently, Rebert et al. (1989*a,b,c)* examined the acute, concentration/time-related effects of toluene and DCM on the spontaneous electroencephalogram (EEG) and a battery of sensory-evoked responses. Clear and dramatic differences between the pattern of effects of the two solvents were observed. Moreover, when the two solvents were combined in various proportions, the results were complex and generally unpredictable from the results obtained with the separate solvents (Rebert et al. 1990).

These behavioral and electrophysiologic results serve to emphasize the markedly different pharmacologic characteristics of various solvents, even though they may all be generally described as CNS depressants. They also clearly demonstrate that the effects of exposure to a solvent mixture cannot be predicted simply from the known pharmacology of its components or vice versa.

Why Solvents?

Various reasons have been proposed to account for why humans use and abuse psychoactive substances, including inhalants. Whatever the reasons, the substances selected must have pharmacologic properties that satisfy the user's perceived psychologic/psycho-social needs. The actual choice of a substance may depend on diverse and sometimes fortuitous factors, not the least of which include availability and cost. Because of the complexity of human psychosocial behavior, identification of the causative use factors and the properties of the substance(s) involved present formidable difficulties for the clinical researcher. Fortunately, there are animal models that can be used to identify the properties of the substances that make them attractive to humans. Two such models are drug self-administration and drug discrimination. These models were developed for evaluating the abuse potential of a variety of psychoactive substances, but their application to inhalants has been very limited thus far.

Drug Self-Administration

The principle underlying this model is that an animal is permitted to perform some act (e.g., pressing a lever) to deliver a substance into its body where it can then exert a "rewarding" effect. This model is a mainstay in the evaluation of the abuse liability of psychoactive substances such as opiates and psychomotor stimulants.

Yanagita et al. (1970) first reported that monkeys would self-administer chloroform, toluene, and ether through intranasal cannulae, thus demonstrating the reinforcing properties of these solvents in animals. This important observation was pursued further by Wood and colleagues who developed inhalation methods for use in squirrel monkeys (Wood et al. 1977; Wood 1979). They showed that nitrous oxide and toluene would serve as positive reinforcers, thus confirming the observation of Yanagita et al. (1970). Other solvents have not been examined for their abuse potential in this model. A more extensive examination of a variety of solvents in this model could have important practical applications. For example, if toluene were removed from a product and another solvent was substituted, it would be unfortunate indeed if the substitute was as reinforcing, or more so, than toluene itself and/or had greater toxic consequences. Moreover, this model might be used to find additives that would mask or counteract the reinforcing properties of a solvent like toluene, either by making the product aversive (see Wood 1979) or by antagonizing the pharmacologic effect responsible for the target solvent's appeal.

Drug Discrimination

This model is based on the principle that chemically induced internal stimuli can be used to train an animal to make one response (e.g., press a lever) when the chemical is present and to make another response (press another lever) when it is not. This model has its roots in the concept of state-dependent learning (e.g., Overton 1966) and, like the self-administration model, has been used extensively (Stolerman et al. 1985; 1989 for bibliographies). Its importance is derived from the substitution of a new compound for the compound used to train the animal. This substitution allows the investigator to determine if the subjective effects of the new compound are similar to or different from those of the training compound. Thus, in the context of solvent abuse, this model can be used in animals to explore the extent to which a solvent may

have similar subjective effects to those of another solvent or other, perhaps better understood, psychoactive substances (e.g., opiates, barbiturates, stimulants, alcohol).

Balster and his colleagues have used this model to evaluate the discriminative stimulus properties of toluene, 1,1,1-trichloroethane (TCEA), halothane, isoamyl nitrite, and flurothyl and compared them with a number of psychoactive drugs (Rees et al. 1985; 1987*a,b,c)*. They initially trained mice to discriminate pentobarbital from saline. When inhaled toluene was substituted for the barbiturate, the mice chose the response lever associated with the barbiturate (Rees et al. 1985). They then trained mice to discriminate toluene (injected) from saline. The cues generalized to toluene (inhaled) and pentobarbital (i.e., these compounds generated similar internal stimuli), but not to morphine (Rees et al. 1987*a)*. Subsequent results indicated that the pentobarbital cue also generalized to the anesthetic halothane, TCEA, and the anxiolytic oxazepam, but not to isoamyl nitrite or the convulsant flurothyl (Rees et al. 1987*b)*. Similarly, mice trained to discriminate ethanol from saline also generalized to toluene, halothane, TCEA, and oxazepam (Rees et al. 1987*c)*. More recently, this group reported that rats trained to discriminate ip-injected toluene from saline generalized to methohexital and oxazepam, but not to chlorpromazine (Knisely et al. 1990).

As a result of these experiments, the authors concluded that inhalants such as toluene, halothane, and TCEA share some of the discriminative stimulus properties of other CNS "depressant" drugs. Thus, they suggest that humans might abuse volatile substances for the same reasons that they abuse other commonly abused drugs. Moreover, their experiments demonstrate that the stimulus properties of the inhalants examined are not simply the result of discriminating something from nothing, because generalization did not occur to other CNS depressants such as morphine and chlorpromazine.

Solvents as Therapeutic Drugs

Reports suggest that some users might inhale solvents to alleviate a perceived psychologic disturbance by the user. For example, a 14-year-old states that sniffing toluene relieved a state of chronic anxiety (Press and Done 1967). Based on such statements, Geller et al. (1983) tested inhaled toluene in a standard preclinical test in rats designed to identify potential anxiolytic drugs and compared it with diazepam. Both agents reinstated lever pressing that

had been suppressed by punishment (i.e., experimentally induced conflict). A similar anxiolytic effect of toluene was reported by Wood et al. (1984). These latter investigators also demonstrated that ip-injected toluene and m-xylene antagonized pentylenetetrazol-induced tonic-hindlimb-extension seizures in mice and prevented or delayed death. As noted above, we showed that toluene effectively antagonized seizures caused by exposure to heptanes. Thus, these results (1) suggest a possible motivation for the use of such solvents by some humans and (2) provide clues as to the acute mechanisms of action of these solvents. Another potentially interesting report by de Ceaurriz et al. (1983) indicated that a number of solvents, including toluene, TCEE, TCEA, xylenes, and styrene, appeared to have antidepressant effects in mice in a "behavioral despair" swimming test. The interpretation of these results is difficult because the test is not very specific. Nevertheless, they suggest the need for further study in the context of solvent abuse.

Chronic Effects of Exposure to Solvents

As noted in the introduction, the toxicologic profiles of many of these abused solvents have been fairly extensive. With few exceptions, the results of these studies have generally been negative for those organs and tissues examined and at the doses and routes of administration tested. For example, there was no evidence of chronic toxicity or oncogenicity in rats exposed up to 300 ppm toluene for 6 hr/day, 5 days/week, for up to 24 months (Gibson and Hardisty 1983). Results of various studies with xylenes and its separate isomers were also unremarkable (reviewed by Low et al. 1989). Some evidence for liver toxicity was reported for DCM in rats (Serota et al. 1986*a)* and mice (Serota et al. 1986*b),* and mild nephrotoxicity was found in male, but not female, rats exposed chronically to "white spirits" or C10-C11 isoparaffinic hydrocarbons (Phillips and Egan 1984).

The ability of these industrial toxicologic studies to detect persisting neurologic deficits is questionable. Behavioral, electrophysiologic, and appropriate neuropathologic measures are rarely included in such studies. Even in those studies in which neurobehavioral tests have been included, the ability of the tests to detect specific and/or subtle CNS deficits can be questioned (see the discussion below). Moreover, the exposure protocols for such studies are typically not designed to reveal effects more relevant to the human abuse problem. A particularly striking example is provided by the results of two studies that examined the effects of exposure for 13 weeks to *n*-hexane, a

known neurotoxicant that causes severe peripheral neuropathy (Spencer et al. 1980). In the first study (Cavender et al. 1984), rats were exposed to concentrations up to 10,000 ppm *n*-hexane for 6 h/day, 5 days/week to simulate a worst-case occupational exposure regimen. No clinical evidence of neuropathy was observed, and histologic examination of sections of tibial and sciatic nerves were unrevealing. Only teased nerve preparations showed evidence of the developing neuropathy. In the second study (Dunnick et al. 1989), mice were exposed similarly with equally mild consequences. The failure of these two studies to reveal any but the slightest signs of neuropathy probably can be accounted for by the pharmacokinetics of *n*-hexane and the exposure schedules used (as suspected by Cavender et al. 1984 and demonstrated earlier by Pryor et al. 1982 and Howd et al. 1982). Just as brief, high-level exposures may not be an appropriate model for the workplace, the toxicologic studies just mentioned, which were designed to mimic the 5-day workplace environment, may be irrelevant to the excesses seen in substance abuse and cannot be used to draw conclusions about the potential hazards of a given solvent in the hands of a dedicated "sniffer."

Do Solvents Cause Brain Damage?

General concern about the possible toxic effects of chemicals on the nervous system led to the emergence and development of behavioral toxicology in the 1970s. This concern was motivated to a great extent by the assumption that the nervous system, because of its complexity and high metabolic demands, is especially vulnerable to toxic insult, and that behavior, reflecting the integrated output of the nervous system, would be especially sensitive to such insults. These notions were reinforced by Scandinavian investigators who reported that the main symptoms encountered in workers chronically exposed to low levels of industrial solvents were psychologic in nature (e.g., fatigue, attentional disorders, memory problems). Taken together with the scattered case reports of "brain-damaged" heavy solvent abusers, one might have expected an explosion of new findings from animal studies demonstrating the neurotoxic hazards of low-level as well as high-level exposure to solvents. Few such studies appeared.

In retrospect, some of the reasons seem obvious. First, only a few laboratories worldwide took up the challenge of intensively investigating the possible persisting neurotoxicity of solvents—chronic inhalation studies are technically difficult, time-consuming, and expensive. Second, the exposure proto-

cols were still geared to the industrial setting and for regulatory purposes. Third, the test methods used were generally designed for screening purposes and, as such, could not be expected to detect any but the grossest manifestations of nervous system dysfunction.

Thus, in spite of the increased concern about the potential neurotoxic consequences of solvent exposure, these industrial-type toxicology studies have not provided much evidence that the solvents encountered in human abuse are especially hazardous. For example, Kulig (1987, 1989) recently examined TCEE and styrene in well-designed chronic inhalation studies aimed specifically at detecting neurobehavioral deficits. Although behavioral deficits were found during the exposure phase, they rapidly returned to normal during the recovery phase. Even the *n*-hexane studies cited above would not have identified the severe deficits caused by *n*-hexane and related solvents in humans that were well known by then. Because toluene is the solvent most often associated with reports of neurologic deficits in human solvent abusers, several investigators attempted to demonstrate its neurotoxic effects in animals. For example, Dyer et al. (1984), using sophisticated electrophysiologic techniques, reported a subtle effect of a 30-day exposure to toluene on the second of two flash-evoked potentials that might represent an increase in nervous system excitability. However, the persistence of this effect was not examined. At about the same time the author and co-workers exposed young rats to high concentrations (1,400 ppm) of toluene 14 h/day, 7 days/week for 14 weeks (Pryor et al 1983*a).* However, using a battery of behavioral and electrophysiologic tests, no convincing evidence for persisting neurologic damage was found. Interestingly, Naalsund (1986) reported that exposure of rats to 500 ppm toluene (8 or 16 h/day, 5 days/week) for 12 weeks caused a decrease in the frequency of theta electrical activity recorded from the hippocampus that was still present 1 month later. However, the reproducibility and functional significance of this effect is still unknown.

The majority of case reports of solvent-induced nervous system damage and/or disorders have been associated with products containing large amounts of toluene. This circumstantial evidence led many clinicians to conclude that toluene, as the common solvent, was the responsible agent. Yet the animal experiments did not appear to corroborate this conclusion. Also, actual measurement of the contents of the abused products has rarely been reported, even if they were available for analysis. Therefore, the possibility exists that some other substance in the products (another solvent or solvents, heavy met-

als, etc.) could, even in small amounts, be responsible. A few reports involving the use of pure toluene (e.g., Grabski 1961; Knox and Nelson 1966) provided stronger evidence to support the assertion that toluene was the responsible agent in the product mixtures. If the human studies were correctly identifying neurotoxic consequences of toluene, then why were they being missed in the animal studies?

The approaches taken to study the safety of solvents and those used to study the consequences of solvent abuse are markedly different. The author and his co-workers have been the only investigators who have maintained a continuing program that has attempted to define the neurotoxicologic consequences in animals of heavy solvent abuse at the laboratory level. Therefore, the remainder of this chapter will focus on these studies conducted over the past 13 years.

Some Solvents Are Ototoxic

When these studies began there were very little scientific data on solvent-induced neurotoxicities. There was considerable speculation about the solvents being used and their hazards, but mostly, solvents, especially toluene, were guilty by association. The peripheral neuropathy seen in some industrial workers and in some solvent abusers had been identified as being caused by *n*-hexane and methyl-*n*-butyl ketone. Demonstration of the syndrome in animals soon followed, thus opening the way for a systematic investigation of the mechanisms involved. Therefore, studies in this laboratory began by assuming that most (if not all) solvents found in abused products were potentially capable of causing irreversible nervous system damage.

Early studies were designed to mimic the human abuse situation, i.e., brief, repeated exposures to high concentrations. Such exposures might be more hazardous or have different qualitative consequences than equivalent doses administered under a low-level, continuous exposure schedule comparable to those used by industrial toxicologists. A mixture containing dichloromethane (DCM), toluene, heptanes, methanol, and small amounts of xylenes was studied initially to mimic abused products. These experiments with weanling rats employed a battery of behavioral and electrophysiologic tests (Pryor et al. 1983*c;* Rebert 1983) and provided a large amount of new information about the acute pharmacologic effects of this mixture, the individual components thereof, and their interactions (Pryor et al. 1977; 1978*a,b;* 1980). However,

with the exception of *n*-hexane (Pryor et al. 1982; Rebert et al. 1982; Howd et al. 1983; Rebert and Sorenson 1983), attempts to demonstrate any progressive and/or persisting neurotoxicity caused by repeated exposures to the mixture or the various individual solvents were negative.

In one chronic experiment (Pryor et al. 1983*a),* exposures to toluene were sufficient to cause an inhibition of weight gain, a slightly slower acquisition of a multisensory conditioned avoidance response (MCAR) and a tone-intensity discrimination, a depression of a component of the brainstem auditory-evoked response (BAER), and a transitory decrease in motor activity during the exposure phase. However, these changes did not persist after the exposures ended. The slower acquisition of the MCAR was suggestive of a cognitive deficit. However, because the rats were trained during the exposure phase, residual acute effects could have been responsible. The results of an experiment with rats trained at various times after the last exposure demonstrated that the deficit was, indeed, transient (Pryor et al. 1983*b)*.

Fortuitously, these rats were not sacrificed at the end of the experiment and were used in an experiment 2 months later that required them to perform the MCAR using a 20-kHz tone as the auditory stimulus (instead of the 4-kHz tone used previously). The tolucne-exposed rats performed the response to light and footshock stimuli admirably, but they showed a marked deficit in performance of the auditory MCAR, as though they were unable to hear the 20-kHz tone! Subsequent behavioral and electrophysiologic (Rebert et al. 1983) experiments, in which the intensity and frequency of the tone were varied, confirmed a marked hearing loss at frequencies above 4 kHz. Auditory dysfunction was also one of the symptoms reported in some workers accidentally exposed to high concentrations of toluene (e.g., Biscaldi et al. 1981) and in some solvent abusers (e.g., Ehyai and Freeman 1983; Mctrick and Brenner 1982).

These results provided the first clear and indisputable evidence in animals that exposure to relatively high levels of toluene (e.g., 1,000 ppm) could cause persisting damage to the nervous system. The results of subsequent experiments (Pryor and Howd 1986; Pryor et al. 1984*a,b;* 1987) showed that (1) weanling rats are more sensitive to the effect than young adults; (2) the hearing loss was frequency dependent, being greater at higher than at lower frequencies; (3) damage resulted from loss of receptor (hair) cells in the cochlea; (4) the effect is concentration, duration, and exposure-schedule dependent;

(5) subcutaneous injection of toluene was as effective as inhalation exposure; and (6) related solvents xylene and styrene also cause hearing loss. However, this effect is not a common characteristic of solvents (see below). The major finding of a hearing loss caused by exposure to toluene has been confirmed by a group in Sweden (e.g., Johnson et al. 1988) and in the United States by Sullivan et al. (1989), the latter investigators using the oral route of administration.

A Solvent-Induced Motor Syndrome in Rats

Although the hearing loss associated with exposure to toluene and related solvents was well established by 1987, neurologic deficits associated with solvent abuse other than hearing loss had not been demonstrated in animals. Reports continued to appear in which groups of solvent abusers displayed persisting neurologic symptoms that the clinical investigators attributed to toluene. Fornazarri et al. (1983) described the symptoms of a group of solvent abusers in Toronto who mainly used a specific brand of contact cement. The investigators attributed the deficits to toluene. Rosenberg and coworkers (Hormes et al. 1986; Rosenberg et al. 1988) described similar, but not identical, symptoms associated with abuse of particular brands of paint thinner and spray paints in Denver that they also attributed to toluene. The Denver reports were especially important because the sample size was relatively large and the patients studied had been abstinent for at least 4 weeks before examination, a time when residual pharmacologic effects had most likely dissipated. However, unambiguous assignment of toluene as the causative agent could not be made since the contact cement from Toronto was found to contain not only toluene but also hexanes, MEK, and a complex mixture of hydrocarbons. The spray paint from Denver contained toluene, DCM, xylenes, and propellant gases (recognized by the investigators). Nevertheless, the common, and major, solvent in both products was toluene. Therefore, toluene was reexamined using tests designed to reflect some of the symptoms reportedly associated with toluene abuse.

Table 1 shows a list of symptoms commonly reported in humans who have abused various products containing toluene. Some of the symptoms do not have obvious and measurable counterparts in rats. However, symptoms such as “wide-based ataxic gait,” “staggering or stumbling in trying to walk,” and “nystagmus” suggest involvement of sensory-motor systems controlled by the cerebellum and associated pathways. Therefore, tests were selected that

Table 1. Signs and symptoms most frequently reported in heavy, long-term abusers of toluene-containing solvents

Short-term memory loss
Emotional instability
Cognitive impairment
Slurred and "scanning" speech
Wide-based ataxic gait
Staggering or stumbling in trying to walk
Nystagmus
Ocular flutter
Tremor
Optic neuropathy
Unilateral or bilateral hearing loss
Loss of sense of smell
Diffuse slowing of the EEG
Abnormal or absent brainstem auditory-evoked response
Diffuse cerebral, cerebellar, and brainstem atrophy
Enlarged ventricles and widening of cortical sulci, especially in the frontal or temporal cortex

might be reflective of this syndrome in rats. The battery of tests selected consisted of measurements of motor strength (fore- and hindlimb grip [Meyer et al. 1979]), locomotion (gait analysis [Jolicoeur et al. 1979]), reflexive response to sudden loss of support [landing hindlimb foot splay (Jolicoeur et al. 1979)], and sensorimotor balance (rotorod [Christensen 1973]).

Weanling rats were exposed to high concentrations of toluene, *n*-hexane, or a mixture of toluene, *n*-hexane, and MEK 8 h/day, 7 days/week, for 11 weeks (concentrations ranged from 2,000 to 5,200 ppm). The data were subjected to discriminant function analysis to identify possible differential syndromes associated with the two solvents and the mixture (figure 1). By 7 weeks there were clear differences among the groups. These differences were still evident when the rats were tested 6 weeks after the last exposures.

Examination of the data from the individual tests in the battery showed that the syndrome associated with exposure to *n*-hexane was, as expected, mainly the result of decreased grip strength reflecting the emerging peripheral neuropathy. The syndrome associated with exposure to toluene was characterized by a shortened stride length and a widened stride width resulting in a marked increase in stride angle and an increase in landing hindlimb foot splay. The group exposed to the mixture first took on some of the characteristics of the group exposed to toluene, but then as the peripheral neuropathy caused by the *n*-hexane in the mixture progressed, the effects on grip strength predominated. The rats were also trained and tested for visual, auditory, and somatosensory sensitivities, and, as expected, the rats exposed to toluene, either alone or in the mixture, had a frequency-dependent hearing loss, whereas those exposed to *n*-hexane did not.

The results of this and other experiments (Pryor 1991) provided the first evidence for a persisting motor syndrome in animals caused by exposure to toluene. Moreover, the syndrome in the rat appeared to resemble the "wide-based ataxic gait" described in human solvent abusers. An example of this effect is shown in figure 2.

Figure 1. Centroids of groups of rats exposed to toluene, n-hexane, or a mixture of toluene, n-hexane, and MEK on the first two discriminant functions derived from the results of a battery of behavioral tests of motor strength and coordination

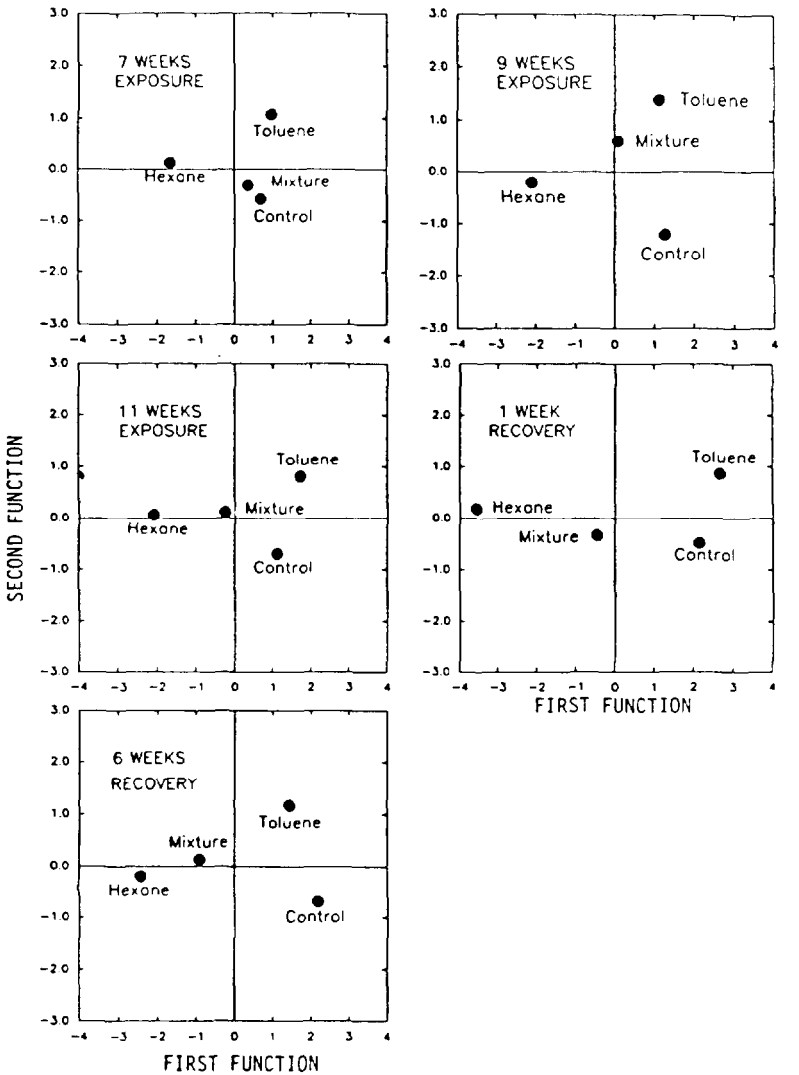
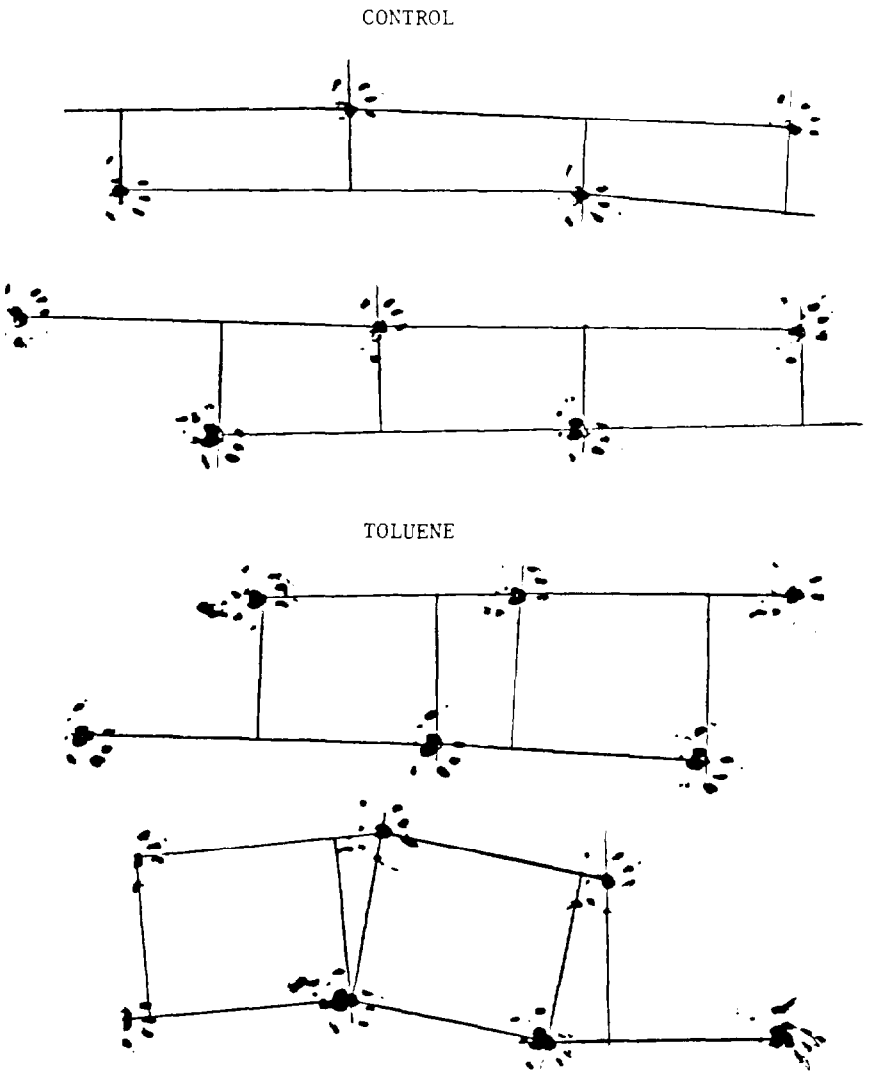


Figure 2. Examples of patterns of locomotion by rats exposed chronically to toluene. Measurements were made several months after the last exposure to toluene.



Other solvents were examined for this syndrome (table 2). Thus far, of the solvents tested, only xylenes and TCEE have shown a motor syndrome similar to that of toluene. From the results of this series of experiments, there is now clear evidence that toluene can cause persisting neurologic dysfunction in rats, thus confirming its alleged role in human solvent abuse in an animal model. With such a model it may now be possible to identify toluene's sites of action and the mechanisms involved in this effect. Further examination of other solvents may also give clues about the critical chemical structures involved as well.

Recommendations

Most, if not all, abused psychoactive substances, including solvents and other inhalants, may impair performance and/or result in socially unacceptable behavior because of their acute pharmacologic effects. Compulsive use may also result in behavior that is morally and legally unacceptable and cause a progressive deterioration of family, work, and social relationships. However, the issue of persisting and/or permanent damage to the nervous system resulting from such abuse has been less clear. Spencer and Schaumburg (1985) suggested the following criteria for definitively identifying a substance as the causative agent suspected of being responsible for persisting nervous system damage in humans:

1. There is a consistent pattern of neurologic dysfunction in humans associated with well-documented exposure to the substance.

2. The syndrome (all or in part) can be mimicked in animals by appropriate exposure to the substance.

3. Neuropathologic "lesions" can be demonstrated in the nervous system and/or the peripheral sense organs that satisfactorily account for the dysfunction in humans and animals.

In their view, and in the author's as well, "failure to satisfy any of these criteria leaves room for doubt that the suspect agent is capable of impairing the structure or function of the nervous system" (p. 53). When these investigators proposed these criteria, they were able to identify only five solvents—carbon disulfide, *n*-hexane and methyl n-butyl ketone, toluene (only in terms of abuse), and impure trichloroethylene—that minimally met their criteria based

Table 2. Summary of effects of various solvents on hearing and motor coordination

Solvent	Hearing loss	Motor syndrome
Toluene	Yes	Yes
Xylenes	Yes	Yes
n-Hexane	No	Not toluene-like*
Dichloromethane	No	No
Methyl ethyl ketone	No	No
Trichloroethylene	Yes	Yes
Trichloroethane	No	No
Ethanol	No	No

*The peripheral neuropathy caused by *n*-hexane is different from the motor syndrome caused by toluene.

on the evidence available. Indeed, their inclusion of toluene in this list was only possible at that time by our finding of hearing loss in rats associated with hair cell loss in the cochlea. The case against toluene now has more substance because of the recent work described briefly above. Nevertheless, considerably more work is needed before we have a comprehensive animal model of the biomedical consequences of toluene abuse (see table 1).

Although this review focuses on the neurotoxic consequences of solvents in young animals, an equally important concern is the potential effects of in utero exposure. This area was not reviewed because so little is known about solvent abuse in pregnant humans or animals. Preliminary experiments with toluene suggest that long-lasting motor effects occur in the offspring and are similar to those described above. Interestingly, no hearing loss has been observed in prenatally exposed rats, although this effect was evident in the

dams. Clearly the issue of in utero exposure to solvents under conditions of human abuse during pregnancy deserves further attention.

Another area of considerable concern is that of the reported nephrotoxic effects of solvents containing toluene. Although fairly well documented in the human abuse literature, this issue has received little attention by animal expcrimentalists. Again, the question of the causative agent (toluene or some other component of the abused product) can be raised. Although this may be an acute overdose phenomenon, further work focused on mimicking the human abuse situation in appropriate animal models will be needed to make this identification with any confidence.

Finally, as noted above, considerably more work is needed to better define the characteristics of solvents that make them targets of abuse. Self-administration and drug-discrimination models should be expanded to evaluate a variety of solvents and their relative abuse potentials. Such models may also offer opportunities to discover therapeutic measures that might be effective in counteracting the pharmacologic effects of such solvents that make them attractive and promote continued abuse.

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Basic Science Solvent Abuse Research Issues

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Pryor's chapter gives an excellent overview of basic science research findings concerning inhalant abuse. He also describes his own innovative research program. Pryor and colleagues pioneered research in this area, and his description of how this research evolved is very interesting. In fact it is a classic case history of the development of a research program. It is hard to overemphasize the difficulties encountered when attempting to begin research in a new area: Essentially no one knows how important variables should be manipulated and no one knows what measures should be made. Initial progress is often slow, and results can be discouraging. In spite of these difficulties, Pryor and his colleagues persisted with their studies, and the results are very important and form the foundation for future studies.

I want to discuss three aspects of this area of research. The first relates to the identification of solvent abuse as a member of a larger class of behavior, namely, drug reinforced behavior. The second suggests some differences in emphasis on research goals, and the third reemphasizes some of Pryor's recommendations.

Solvent Abuse as a Drug Reinforced Behavior

There are a number of views about drug abuse. Often drug abuse is considered to be illegal behavior. If the essential feature of drug abuse is illegal behavior, then the major approach should be law enforcement. Others con-

sider drug abuse to be immoral behavior, and if drug abuse is primarily immoral behavior, then a change in the individual's morals or character would be an appropriate approach. Others see drug abuse as an outcome of poverty or stress, and still others view drug abuse as an attempt to self-medicate a disorder such as anxiety. These different views are not simply of academic interest because each view suggests very different ways of conceptualizing and correcting the problem.

Laboratory research over the past 30 years has led to an interpretation of drug abuse that differs from the ones I mentioned. This interpretation is that drug seeking behavior is an instance of operant behavior, and that abused drugs can function as reinforcers (or less technically as rewards). The basis for this interpretation is that in laboratory experiments a wide range of animals self-administer the drugs that humans abuse, and they do not self-administer the drugs that humans do not abuse.

Food and water often function as reinforcers, and the reasons for this undoubtedly have to do with evolution. Why do drugs serve as reinforcers? At present there is no accepted answer to this question. However, it has been noted that drug reinforcement is a case of a normal biological process, namely reinforcement, that has by accident gone awry much like an autoimmune disease is a case of normal biological process that has gone off kilter and attacked the organism's own body. This interpretation holds that drug abuse is a biomedical disorder, and that the appropriate approach is the same as that in other biomedical disorders, namely, treatment and prevention based on research in a wide range of disciplines. Such research will lead to an understanding of etiology and will provide the rational basis for prevention and treatment. The fact that laboratory animals routinely self-administer abused drugs, including solvents, indicates that it is ridiculous to characterize drug taking as simply immoral behavior, since moral concepts are inappropriate in characterizing the behavior of laboratory animals. Moreover, it is now unequivocally clear that cigarette smoking is an instance of drug reinforced behavior, and yet most of us would not characterize cigarette smoking as immoral. Like certain other chemicals, solvents can serve as reinforcers for animals, and solvent taking should be considered drug reinforced behavior.

Levels of Analysis

Drug abuse is a disorder that occurs at the behavioral level, and it is at this level that primary analysis should be done. Brains or nervous systems do not self-administer drugs, and this level of analysis should not be the primary focus in drug abuse studies. One can have an intact nervous system and still have disordered behavior. In fact, toxicity at the behavioral level can result from abnormal functioning of a variety of organ systems.

To understand the determinants of solvent self-administration, one has to manipulate behavioral variables. Further, to adequately characterize the adverse effects of solvent abuse, one needs to examine the resulting deficits in behavior and then relate these deficits to possible organ pathology. It is interesting that in Pryor's studies, important progress resulted from careful consideration of the clinical findings. The point is that the behavior level should be the primary level of analysis and not the nervous system.

Animal studies of drug self-administration have frequently been described as models of human drug abuse. I disagree with this view because the animal studies do not fit the definition of a model: They are not a small-scale replica or a simulation of something. In animal studies one uses real animals, real drugs, and obtains real drug reinforced behavior. The animal studies are more analogous to experimental preparations used in physiology such as the heart-lung preparation. The use of the term "model" can lead to misunderstandings and to posing the wrong questions. Humans as well as other animals show drug reinforced behavior. The important question is to assess whether similar variables act in similar ways with both humans and other animals.

Recommendations

First, the actions of the solvents may have important similarities with the actions of ethanol and also with those of gaseous anesthetics. Consequently, research with solvents may have important implications for these other drugs and vice versa. Second, in biology, genetic effects are pervasive. Such effects need to be studied with solvents. The use of genetic tools may also be a powerful way to analyze mechanisms of solvent actions.

I agree with most of Pryor's recommendations for future research. Among these are the importance of studying high levels of solvent exposure when analyzing the consequences of solvent abuse. Pryor has noted that findings from studies designed to evaluate acceptable exposure levels in industry may have little relevance for understanding the effects of solvent abuse. He has also emphasized the importance of looking at qualitative as well as quantitative differences among solvents. Studies are needed with a variety of solvents. It is important to characterize both similarities as well as differences in the effects of these agents, and it is also important to study their relation to other CNS drugs. The characteristics of solvents that lead to their abuse need to be identified, and more intensive drug self-administration and drug discrimination studies should be conducted. Such studies are necessary for developing rational treatment and prevention strategies.

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Animal Research as a Guide to Regulation and Prevention of Solvent Abuse

Ronald W. Wood

Issues of Solvent Dependency

Inhalant abuse is arguably the most toxic of all substance abuse practices. Consequently, as discussed by several conference participants, biomedical research has focused on the adverse consequences of this form of substance abuse, particularly for the nervous and other organ systems. Such work is of interest not only because of its relevance to inhalant abuse, but also because it contributes to understanding occupational and environmental health problems, and to a basic understanding of the nervous system and its pathophysiology.

Identification of the sequelae of inhalant abuse guides one only in the prevention and treatment of organ toxicity; it adds little guidance to prevent the substance abuse practice itself. If society can devise strategies for preventing inhalant abuse, by definition this will prevent not only solvent-induced organ system toxicity, but also the displacement of socially productive activities. Youths sniffing glue are not learning skills or earning money, but are producing behavior impairment that is incompatible with productive activity and social and intellectual development.

To devise prevention strategies requires us to address the basic issues of abuse potential and abuse liability. Abuse potential is that portion of a chemical's intrinsic pharmacologic activity, without which there would be no self-administration. Drugs vary in their ability to support self-administration—cocaine and haloperidol being on opposite ends of this spectrum. The Controlled Substances Act embodies this relationship between chemical structure and biological activity in its scheduling process. Abuse liability encompasses both the pharmacological and extrapharmacologic determinants of the substance abuse practice; the availability of the substance, its pattern of distribution and marketing, and social milieus that foster patterns of substance abuse.

Most inhalant products have useful functions in the home and workplace. Although our society may be able to accomplish a reduction in the abuse of cocaine by interdiction, we are no more likely to remove from modern life the volatile chemicals subject to abuse than to give up our dependence on the motor vehicle. We cannot ban gasoline in order to prevent its abuse. However, that does not imply that inhalants are beyond regulatory interventions that might reduce both the incidence of inhalant abuse and its toxic sequelae.

One might hope that the more toxic materials would not be marketed in consumer products and that consumer product formulation might be guided by the intent to reduce abuse potential. Nonetheless, we still find neurotoxicants like hexane in some consumer products. "Poppers," butyl nitrite products, were sold in this country from 1971 until 1988 as room odorizers even though they were subject to abuse and smelled like dirty sweat socks (e.g. "Locker Room, Aroma of Men") and were toxic (Wood 1988). Despite many deaths associated with the deliberate inhalation of chlorofluorocarbon propellants, only the threat of stratospheric ozone depletion resulted in the removal of chlorofluorocarbon propellants from most commercial products. Thus, reduction of abuse potential and toxic sequelae through regulation of commercial products has not been foremost on the agenda of the Federal Government. The difficulties in implementing these types of regulations are apparent in the public records and hearings associated with regulation of the volatile nitrites. Eventually, legislation removed alkyl nitrites from the market place. Unfortunately, these products have been replaced with other "designer nitrites" that apparently fall outside the legislative definition. It might have been easier to control volatile nitrites if the Consumer Product Safety Commission had the discretion to weigh the benefits of the product

against its abuse liability and risk of bodily injury, and the authority to impose measures ranging from labeling and packaging requirements to an outright ban of selected product formulations.

The role of scientific research is to improve our basic understanding of the phenomena and its determinants, so that society may be able to predict and control the substance abuse practice and its consequences. Although research agendas are readily drawn, the institutional contexts in which such research programs can be conducted remain limited. This is a generic problem in neurobehavioral toxicity evaluation, and was discussed in a recent Office of Technology Assessment report on neurotoxicity (U.S. OTA 1990).

There are few academic environments that consider studies of commercial product formulations to be an appropriate research activity. An academician would not study a proprietary volatile polymerizing agent used in the fiberglass industry in order to determine whether or not it is neurotoxic or has abuse potential. However, if workers have experienced neurotoxic injury by such a material, (e.g. LUCEL7, trimethyltin, carbon disulfide, methylbutyl ketone), then a study of the compound might lead to a new understanding of the structure and function of the nervous system. One should not expect very much product safety evaluation or toxicity screening to be conducted in the university context.

Fundamental research can be conducted in universities to further our understanding of (a) why inhalants are subject to abuse; (b) the nature of their acute and chronic effects; (c) what other drugs of abuse they resemble; (d) the underlying mechanisms of action; and (e) whether abuse potential and toxicity can be predicted in advance of distribution, and with what techniques.

Private research institutes and contractors can explore problems of concern to NIDA, and Pryor's research program is an example of how the contracting mechanism can be used productively to focus on questions that would otherwise not be addressed in academic or industrial contexts. In addition, the contracting mechanism should be used to support projects that are sufficiently challenging or expensive that they will not be undertaken under any other circumstances. Such a project is outlined below in the context of the sequelae of inhalant abuse.

Finally, the corporate and regulatory sectors have a responsibility to address these issues as well. Although the Consumer Product Safety Commission and

the Food and Drug Administration have been able to regulate inhalants when specific products have led to death *(Federal Register* Vol. 38, p. 10956, 1973), these two agencies apparently have limited ability to regulate commercially available solvents based on inhalant abuse properties. This is principally because the problem of inhalant abuse has not been interpreted to be within their jurisdiction or mandate. Perhaps this will change if Congress continues to express concern about this problem as it did in the Anti-Drug Abuse Acts of 1986 and 1988. The primary concern of these agencies has been on adequately labeling and packaging products.

Comprehensive premarket toxicity evaluation of commercial chemicals currently falls within the purview of the Environmental Protection Agency (EPA) under the Toxic Substances Control Act (TSCA). The constrained activities of all of these authorities were discussed in detail in a recent U.S. OTA report (1990). On July 18, 1981, EPA solicited comment on the need for testing and appropriate methods for evaluating the abuse potential of an industrial chemical *(Federal Register* Vol. 45, pp. 48538-48539, 1980). Later in 1981, EPA prepared a test standard for evaluating the abuse potential of inhaled substances under the Toxic Substances Control Act. However, as of now, little useful information has been collected for guiding consumer product formulation or for setting occupational exposure limits for this purpose.

In spite of the magnitude of the challenge to society to cope with this largely ignored substance abuse problem, the research and testing needs are clear. The National Research Council's report on toxicity testing (1984) made it clear that society is not in a position to perform even a minimal toxicity evaluation of 90 percent of the 50,000-plus chemicals in commerce. Among the areas to be evaluated, neurotoxicity was among those of highest priority. Most of the chemicals that are subject to abuse by inhalation fall within the class of chemicals for which occupational exposure limit values have been recommended by the American Conference of Governmental Industrial Hygienists or set by the Occupational Safety and Health Administration. For approximately 30 percent of these chemicals, the recommended exposure limits cite the nervous system as the basis for the recommended exposure limit values. Thus, the adverse effects of volatile chemicals on humans remains one of the principal sources of information used to prevent subsequent injuries, despite the ready availability of techniques to screen for adverse effects using laboratory animals. Frequently, studies in laboratory animals follow the detection of adverse effects in humans, rather than vice

versa. In this respect, it seems that solvent abusers, who push the dose to extraordinary levels, serve as a special sentinel population for workers and consumers exposed to such chemicals.

Approaches to Addressing the Problem

Solvent encephalopathy. No large-scale evaluation of the neurotoxicity of organic solvents has been undertaken despite several important prompts, including clear-cut injuries to the nervous system of inhalant abusers, calls for more work by a consensus conference on solvent neurotoxicity (Cranmer and Golberg 1986), and a report of the neurotoxicity of automotive emissions and fuel constituents (Wood 1988*b)* expressing the need for further solvent neurotoxicity evaluation, the recognition of a psycho-organic syndrome by some European authorities, and the magnitude in the exposed population. Also, most laboratory studies evaluating chronic solvent neurotoxicity have not conformed to the testing guidelines promulgated by EPA and have not employed the appropriate techniques of modern neuroscience to detect and quantify the behavioral and neurological consequences of solvent exposure.

Although appropriate first-tier evaluation of solvent neurotoxicity with rodents would serve to steer the selection of solvent classes for more detailed evaluation, primates are often the most appropriate subjects for detailed study. A series of chronic studies should be considered. These could be conducted in two phases. The first phase would identity the hazards by using concentrations and durations of exposure that are maximally tolerated; then a series of chronic studies using multiple concentrations would provide guidance on the magnitude of the risk. Primates have been recommended for such studies (Cranmer et al. 1986). Studies should include magnetic resonance imaging studies, brain stem auditory evoked responses, evaluation of simple neurological function and conditioned behaviors, and post-mortem quantitative morphometry. The second phase should focus on the sensitive endpoints demonstrated in the first studies, as well on complex conditioned performances for the assessment of "cognitive" impairments and sensory dysfunction.

Abuse potential evaluation. Techniques exist for the evaluation of the abuse potential of inhaled materials (Yanagita et al. 1970; Wood et al. 1977; Wood 1978 1979*b;* Grubman and Woods 1982). By permitting animals to self-administer solvents one can identify compounds subject to abuse by inhalation.

These studies also identify the range of concentrations that are effective and can permit the estimation of relative potency, a matter of particular importance in the context of incidental exposures leading to the discovery of intoxicating effects. Although simple self-administration experiments do identify the existence of the hazard, they do not permit the evaluation of relative reinforcing efficacy (i.e., relative risk) from simple rates of response because of the interactions of direct effects and duration of action of the agents. Progressive ratio or choice experiments, where animals are permitted to choose between different concentrations and different agents, are necessary to evaluate relative efficacy. These are slow and labor intensive experiments that are of considerable interest and importance.

Characterizing direct effects with schedule-controlled behavior and other techniques. Techniques used for the characterization of the acute effects of psychoactive drugs can be used to further our understanding of the nature of the effects of inhalants. This strategy relies on using experimental protocols that have been well characterized with particular drugs of abuse, and evaluating the effects of inhalants in a similar manner to develop a profile of action. Using these techniques, some aromatic hydrocarbons have been demonstrated to be anticonvulsants (Wood et al. 1984) or anxiolytics (Wood et al. 1984; Geller et al. 1983), while others produce barbiturate like increases in the frequency of conditioned and unconditioned behavior (Wood and Colotla 1990) and have stimulus properties that resemble barbiturates and anxiolytics (Rees et al. 1987*a,b,c).*

Drug discrimination studies have proved to be rapid techniques for characterizing unknowns against reference compounds, and broad surveys of solvent classes should be encouraged in this area, with an eye to detecting different patterns of activity. Drug discrimination experiments do not directly address abuse potential, but address the extent of shared stimulus properties with such agents. Tolerance is a hallmark of most drugs with abuse potential. Schedule-controlled operant behavior is appropriate for studying tolerance and its determinants in the context of inhalants (Rees et al. 1989).

Conditioned stimulus effects related to persistence of substance abuse disorders and relapse. Stimuli associated with drug administration or within the context of drug administration can exert powerful control over behavior, both in increasing its strength, exerting powerful control over tolerance development, exposing individuals to exaggerated risks associated with administration in

unfamiliar environments, and in inducing craving and promoting relapse. Furthermore, the drugs themselves may exert direct effects on the process by which conditioned stimuli become effective or exert their control, e.g., effects on stimulus control or effects on conditioned reinforcing properties.

Irritancy evaluation. Physiological (Kane et al. 1980, Nielsen and Alarie 1982) and behavioral techniques (Wood 1979*a;* Wood 1981) are available to characterize the irritant potency of inhalants. The initial irritancy of materials may correlate well with their abuse potential (Bowman 1977). Several studies have been performed for related solvents, but major classes have not been examined. Irritancy increases with lipophilicity within a family of related solvents.

Structure-activity determinations. The relationship between an inhalant's structure, associated physicochemical properties, and its pattern of neurobehavioral activities remains poorly known, despite the passage of a century since the promulgation of the Meyer-Overton hypothesis (Overton 1901; Seeman 1972). Systematic research activity of this nature would be of great benefit because it enables the prediction of relative potency and the identification of unusual activity by a solvent that merits more detailed evaluation. By its sensitive nature, such work usually must rely on simple assay systems; nonetheless, work of this nature can also make a significant contribution to occupational and environmental health. Pharmacokinetic determinations have been quite limited in this context. Attempts should be made to determine the nature of the disturbances of neuronal and synaptic function associated with solvent exposure.

Complex performances predictive of cognitive, sensory, and intellectual impairment. Techniques suitable for the detection of gross neurobehavioral toxicity may not detect more subtle impairments produced with chronic exposure. Therefore, research efforts need to be directed at developing procedures that can characterize such impairments in detail, as well as techniques that can detect their occurrence relatively inexpensively in rodents.

Adverse effects on neurobiological development. The fetal alcohol syndrome is now a recognized entity of great concern. There have been several clinical anecdotes suggesting the existence of a fetal solvent syndrome. This deserves further examination to determine if such effects are related to membrane disturbances during development or are attributable to specific compounds or metabolites.

Tolerance, physical dependence, and withdrawal phenomena. The nature of repeated exposure effects, the extent of tolerance, and its dependence on environmental variables has received only limited attention (e.g., Rees et al. 1989). Withdrawal from solvents has produced only limited evidence of a withdrawal syndrome, and this may be attributable to the duration of action of solvents. Ethanol is illustrative of the difficulties associated with producing sustained nervous system concentrations of inhaled agents. Some solvents may accumulate with repeated exposure (Rees et al. 1989) and may clear slowly enough so that withdrawal signs are not expressed. Work with benzodiazepines has indicated that significant dependence potential exists with compounds that mask their own withdrawal (Lukas and Griffiths 1982). Comparable phenomena are likely to occur with solvents.

Human studies of direct solvent effects. Cross-species extrapolation is of principal concern for many toxicity evaluations. By its very nature, the study of potentially neurotoxic chemicals in humans has been quite limited, and has been restricted to the study of smaller marginal effects. Studies of higher level exposures characteristic of human solvent abuse have not been undertaken, but would be of great interest, just as is the study of relatively high doses of cocaine in human subjects. Attempts might be made to gather more information at high and low levels of exposure to relatively innocuous solvents in human subjects.

Mechanistic studies. We have little information about the biochemical and neuropharmacologic consequences of inhalant abuse. In the case of demonstrable ototoxicity, we have little insight into the mechanism of this injury. Is the injury due to the parent compound or a metabolite? Is the hearing loss attributable to an acidotic change in the inner ear overcoming the buffering capacity of the endolymph? Mechanistic studies become of great importance once the hazards associated with a particular solvent or solvent mixture have been identified.

Concluding Remark

Substance abuse practices are dependent on a biological substrate of susceptibility to reinforcement by chemicals, a pharmacologic "original sin." Focusing on populations that are at risk is of importance because it can identify the familial, social, and cultural factors that predispose to substance abuse. However, to characterize inhalant abuse as "perverted use" appears to

imply a moral or personality defect in the user. Despite the fact that the population at greatest risk is below the age of consent, such stigmatization of the user works against the effectiveness of therapeutic interventions intended to promote the adoption of behaviors incompatible with substance abuse and the reintegration of the user as a useful member of society. Products with intrinsic toxicities are regulated to minimize injuries, and that regulatory authority should be extended to minimize inhalant abuse and its toxic sequelae.

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An Industrial/Economic Perspective of Inhalant Abuse

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In 1967, the problem of inhalant abuse and the related health hazards were abruptly brought to the attention of the industrial world. At that time, the Federal Trade Commission and the consumer products industry became aware of seven deaths allegedly involving a consumer product, the "cocktail chiller." This product contained only the propellant dichlorodifluoromethane (Propellant-12). Everyone was, therefore, at a loss to see an association, since these propellant systems were considered to be "pharmacologically inert." This raised the question: Could this propellant or similar propellant systems be pharmacologically active and cause, at some concentration or set of conditions, death? Three pharmacological concepts developed. They were: (1) the propellant freezes the larynx, (2) the propellant replaces oxygen in the blood stream and produces asphyxiation, and (3) the propellant possibly affects cardiac muscle and, more specifically, the cardiac conduction system (Levy 1911, 1912-13, 1913-14).

During this period there were reports in the literature that tended to demonstrate a cause-and-effect relationship with asthmatics and the increased use of aerosol bronchial dilators (Speizer et al. 1968; Inman and Adelstein 1969; Gandevia 1968; Scott 1971). Later in 1972, it was demonstrated that the increased concentration of isoproterenol in the nebulizers marketed in certain countries was positively correlated with increased asthma mortality (Stolley 1972). But, also during this period, 110 sudden sniffing deaths were reported allegedly from the abuse of consumer products (Bass 1970).

Immediately the question was raised: Are aerosol products safe with repeated use? The Consumer Product Safety Commission held hearings on the subject of consumer product safety. Sniffing was considered just aberrant behavior (CPSC 1974). Many parents wanted such products removed from the market or closely controlled. No one at that time realized the number and types of products that would be involved if such an approach was taken. Also, the industry never, at that time, focused on the abuser. Defending the safety of the products was the issue that had to be resolved.

The Aerosol Inter-Industry Safety Committee was formed, as was a peer review group of nonindustry scientists to answer these questions (Giovacchini 1972, 1973, 1975). Six studies were commissioned at a cost of nearly $10 million. They included: (1) human exposure to halocarbon gases under controlled conditions (Stewart et al. 1973), (2) animal exposure to halocarbon gases to examine for possible metabolic byproducts (Blake and Mergner 1974), (3) the effect of fluorocarbon propellants on the cardiac conduction system of the heart (Flowers et al. 1975), (4) effects of propellant gases on the upper respiratory system's defense mechanisms (tracheobronchial mucociliary clearance) (Bohlen et al. 1975), (5) the effect of propellant gases on the clearance of bacteria from the lungs (Guarneri et al. 1976), and (6) an occupational health study of cosmetologists—a retrospective epidemiology study (Disher and Hall 1979).

In addition, the Federal Trade Commission had concluded that the "cocktail chillers" should carry a warning label. Examples of the warning were: "Warning: use as directed—inhalation of concentrated vapors of this product is harmful and may cause death," or "Warning: use only as directed—misuse of this product by inhaling its concentrated vapors is harmful and may cause death" (Federal Trade Commission 1969). The cocktail chillers disappeared from the market over a short period of time.

Labeling was proposed by the Food and Drug Administration and also by the industry. It was believed that this would alert parents. But others argued that this approach would also identify, for the sniffer, those products that would give them a high. The FDA proposed label stated, "Do not inhale directly; deliberate inhalation of contents can cause death" (Food and Drug Administration 1973).

The proposed industry label stated, "Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or

fatal." The industry label was approved by the FDA (Food and Drug Administration 1975).

During this period, the consumer products industry became aware of deterrents. The sniffing of hobby cements during the 1950s had apparently been deterred by the addition of oil of mustard to the product. The use of deterrents had been mentioned by both regulatory and industry scientists. Here was a situation where apparently a deterrent (a known approved food additive) appeared to work, at least in some individuals.

Several hundred chemicals were reviewed for their olfactory abilities to create tearing, malodor, or nausea. None were really examined for any length of time because many were either too toxic, unstable, or not effective enough. Some companies tried to add oil of mustard to their products, where marketing of the products with deterrent was not a problem. But the majority of companies could not or did not add a deterrent to their products. Rather, they labeled the products.

During this period, a group from industry founded and financed the Aerosol Education Bureau (Aerosol Education Bureau 1970, 1984). This industry group was organized to disseminate information on aerosols to the science departments of schools. It was believed at that time that the incidence of sniffing would be reduced once a youngster recognized the hazards associated with this form of aberrant behavior. We do not know what effect this educational program had, but we do know that many teachers and parents first became aware of "sniffing" through this medium (Aerosol Education Bureau 1984). Several companies also hired film companies to make movies on sniffing and the detrimental effects it could have on the body. These films were never released. At the time, experts believed that the films would not deter sniffing and, in fact, might cause more youngsters to experiment with chemicals, using this technique.

Interestingly, during this period, sales of aerosol products did not drop. The consumer was satisfied with the products, and sniffing was seen as something done by a very small fraction of youngsters who were on the "fringe."

Legislation tried to deal with the symptoms of the problem. Was it product based, abuser based, or supply based? To deal with the product, companies used warning labels, deterrents, repackaging, and reformulation. Legislation attempted to remedy the abuser-based issue by making it: illegal to sniff, ille-

gal to purchase to sniff, illegal to be "high" from sniffing, and a treatable offense (through referral to drug treatment centers) if caught sniffing. In regard to the supply-based aspect of the problem, legislation was introduced and included limitations on the purchase of these products by minors, on the sales of certain products to minors for sniffing purposes, and on any sales of selected products.

From the viewpoint of the consumer products companies, the period of the later 1970s saw an end, or at least a great drop, in the abuse of their products. Many of us believed that the labeling of the product and the education of teachers and parents had caused the problem to retrogress. It was not until the early 1980s that we realized that the problem had not gone away. The abusers had found other legitimate products that they were now sniffing. The industry also found out that what was originally thought to be a U.S., and to some extent a Canadian problem, was, in fact, a worldwide problem. At that time most scientists and regulators believed the problem of sniffing should not be brought to public attention so as not to escalate the issue.

After years of working pro bono (most companies assigned one or two people to work on this problem), we seemed to be nowhere. But several facts had become clear: Every solvent had the ability to produce untoward effects when inhaled under perverted conditions, and it would be impossible to remove all products from the marketplace that could give a high. What was the answer? Well, it was not a question of product safety. Industry had to focus on the abuser. We had to focus on the social problem. Why would someone want to get a high by sniffing legitimate commercially available consumer products?

But our problem is much larger than just legitimate consumer products. Our problem is substance abuse, which is a worldwide social problem. The issue, then, is one of people, not one of product. When the industry first realized this in the late 1970s and early 1980s, we began to re-review our entire program and where it should be headed. This was necessary if industry was to meaningfully help in attacking the problem.

The world of the 1960s and 1970s was different from the world of the 1980s and 1990s. We are today facing a serious substance abuse problem that is attacking the very marrow of the country and the world.

Thus, while many years had been spent defending the safety of consumer products before various regulatory bodies, hindsight now demonstrates that if

that time and money had been spent on the societal issue, we might well be further ahead in dealing with this problem. The questions are: How do you stop destructive behavior? What causes destructive behavior? How do you turn that around? Why sniffing? Why not sniffing? How does all this relate to the abuse of either legal or illegal substances?

When I first became involved with the "sniffing" problem in 1968, the youngsters were of high school age. Today, younger individuals in the sixth and seventh grades are inhaling substances to get high, and high school age youths are using other substances as well as inhalants. It has been suggested that solvent abuse is the "gateway," implying that this is the highway to illegal substances. Further complicating the issue is the number of students that drop out of school. How does this reflect on the interpretation of the levels of substance abuse measured? Also, is there a relationship between dropouts and drug abuse?

Many have studied sniffers (Giovacchini 1985). What are their characteristics? The picture we see is one of high unemployment levels among parents, absent parents, single parent families, and belonging to a large family at the low end of the social economic scale. But sniffers are different from other drug users. They are often younger, more likely to be delinquent and disruptive, and usually in conflict with the justice system because of some delinquent or disruptive behavior. They have very low self-esteem and have a lack of motivation. They do poorly academically and have a higher than normal school dropout rate. They tend to come from minority low income families with all the attendant serious problems.

However, I believe that we also see the problem in middle and higher income families. I believe the real issue is not income, but rather the youngsters' perception of whether or not the future is worth fighting for. Do they have a chance of getting out of their present social situation? Where is the help that will give them the tools and the support to supply them with the necessary accouterments to develop positive, instead of destructive, goals—i.e., a plan and pathway to change their future? Is the problem that they have no one to turn to as guides to the development of the correct skills? If this is true, then they see no answer to their problems, and it is no wonder they get high, because they have to feel there is no future for them. Does this have anything to do with the increased teenage suicide rate?

The Federal Government has spent billions of dollars to fight substance abuse. There are basically two programs, one dealing with supply reduction (interdiction—about 70 percent of the funds) and the other with demand reduction (about 30 percent of the funds) (Bush 1990). The major feature of the demand reduction program is treatment and prevention. We seem to be recognizing that substance abuse is causing societal changes and that educational and community action programs are necessary. But the focus again is on illegal drugs, and less on the "perverted use" of legitimate products. While no one can disagree with approaches to deter and change illegal drug user attitudes, it is conceivable that the illegal drug user differs from the "sniffer" and that different approaches to prevention may be required (Mason 1979).

It has been stated that substance abuse has cost society $60 billion, $33 billion of which is due to lack of unrealized productivity (Mulcahy 1989). Others claim that substance abuse costs the business community as much as $100 billion annually through increased absenteeism, added health care costs, and accident rates that are 10 times higher for abusers than for nonabusers (Bacon 1989). The amount of money spent for mental health care appears to have risen from $34 billion in 1984 to about $70 billion in 1987 (Howard 1989). In a survey conducted by Marsh and McLennan Co., the conclusion was reached that substance abuse in the workplace costs employers from 1 percent to 5 percent of their payroll each year, and further, the annual cost of substance abuse to business and to State and local government is between $60 and 65 billion (Kiltrell 1989). It has been estimated that 17 million people in the United States have a substance abuse problem that is serious enough to warrant professional help and that if left untreated the insurance claims will cost nearly $48 billion annually (Carels 1987). Alcoholism costs industry over $25 billion annually, and workers who smoke cost the employer $624 billion more in annual medical costs (Williams 1986).

How much of these costs can we attribute to sniffing? I do not know, but I am guessing that very little of these costs are directly caused by sniffing. What we are seeing are the costs, in industry, basically due to alcohol abuse and illegal substance use. While there have been reports in the literature of adult solvent abuse, most of the literature suggests that solvent abuse is a problem in the young (Hershey and Miller 1982). Therefore, what are the costs of solvent abuse in industry? We do not know.

What are the costs to the Nation of solvent abuse? Why do we talk about employee assistance programs (EAPs) in industry to help the employee solve his or her problems, but do very little to provide programs to help the youngster? In 1985, it was reported that the costs of EAP programs, supplied by outsider contractors contracted on an annual per capita basis, ranged from $10 to $60 per employee per year. Further, keep in mind that such industry programs deal with more than alcohol and substance abuse. Industry has recognized that only about half of the employee problems are due to substance abuse (MacDonald 1985).

What are the costs to the Nation of solvent abuse in youngsters? Industry cannot give you this figure readily. Possibly insurance companies can give us an estimate based on the numbers and cost of incidences of alcohol, drug abuse, and mental illness (ADM) in dependents of employees. But, more than today's financial costs, what are we going to do with these youngsters when they become adults? How will they interact with society? If we allow this destructive behavior to continue throughout their childhood, what will they contribute to society as adults? There is the argument that we need more money for treatment centers and that treatment centers have been underfunded—and that is why there are so many nontreated substance abusers. That may be true, but that is not the total answer. Neither is the shortsighted answer that many officials give—that is, we must keep these kinds of products out of the hands of youngsters, the semi-interdiction approach.

We have to have sufficient treatment centers; there is no doubt about that. But, more important, we must have community education programs that give the tools to turn destructive behavior of children into positive behavior. If industry can have Employee Assistance Programs, then maybe communities can have Community Assistance Programs for youngsters in school in their formative years. The industry has supported the development of the Solvent Abuse Foundation for Education (SAFE) particularly aimed at reducing solvent abuse. A greater cooperation of the communities and industry can lead to even greater strides in resolving this problem in our youths. In this way local people can help solve local problems. The previously mentioned industry-supported programs are built to utilize the community as the active force working with youngsters to give them the support and proper goal setting to face today's challenges and crises. If something is not done now, the financial costs we will be reporting in the future will not only be higher, but industry will have a reduced pool of individuals available for employment. But the

bigger problem is, what impact will this have on the Nation if no changes are undertaken?

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Development of Alternative Fluorocarbons

Henry J. Trochimowicz

Introduction

Chlorofluorocarbons (CFCs) have been used as refrigerants, solvents, aerosol propellants and foam blowing agents over the past 50 years. Selected physical/chemical properties and uses of common, commercial CFCs are shown in table 1.

The main reasons for their wide acceptance in these uses were chemical stability, low toxicity, and a lack of environmental reactivity. However, CFCs appear to have one serious problem—an environmental stability in the lower atmosphere resulting in subsequent breakdown in the upper atmosphere, leading to ozone depletion. Suggested requirements for CFC replacements are shown in table 2.

Therefore, industry needs to create chemicals that are "less environmentally stable," and therefore more environmentally acceptable: with low ozone depletion potential, low global warming potential, and a low photochemical reactivity. These chemicals should still possess, however, a high degree of chemical stability in their end uses and be relatively low in toxicity. As these alternative fluorocarbons are introduced into the marketplace, it is important that deliberate abuse of these new chemicals does not occur. Manufacturers need to educate their workers and customers, but also they need to work through interindustry groups to teach parents, teachers and youngsters about

Table 1. Chlorofluorocarbons—properties and applications

CFC No.	Chemical formula	B. pt. °C	Vap. press. Bar A/25°C	Principal applications
113	CCl_2FCClF_2	47.6	0.45	Solvent, chemical intermediate
11	CCl_3F	23.8	1.07	Aerosols, foams, solvents
114	$CClF_2CClF_2$	3.8	2.18	Aerosols, foams, refrigerants
12	CCl_2F_2	-29.8	6.57	Aerosols, foams, refrigerants
115	$CClF_2CF_3$	-38.7	9.09	Refrigerants

Table 2. Requirements for alternatives to CFCs

- Environmentally acceptable
  - Low ozone depletion, low global warming potential, and negligible photochemical reactivity
- Low toxicity to humans and other life forms
- Non- or low flammability in products or other end uses
- Commercially applicable
- Commercially acceptable properties for end use applications
- Cost effective

the hazards of inhalant abuse. The education process starts with a knowledge of what the new CFC alternatives are and some information about their toxicity potential. This information is summarized in the subsequent tables.

Fluorocarbons in general have different properties and different applications. Therefore, when one looks for replacements, a good starting point is a comparison of the physical properties of old versus the new type of fluorocarbon (see table 3). Some alternatives that are already available, along with their uses, are listed in table 4. Selected chemical and physical properties of these compounds are listed in table 5 and a brief summary of their toxicities is shown in table 6.

There are several other chemicals under development as replacements for CFCs. These compounds, their uses and selected chemical and physical properties are listed in tables 7 and 8. On a worldwide basis, fluorocarbon producers have sponsored a cooperative program to expedite the acquisition of toxicology data on these compounds. It is called the Program for Alternative Fluorocarbon Toxicity Testing (PAFTT). The companies are: Akzo, ICI, Allied-Signal, Rhone-Poulenc, Asahi Glass, Kali Chemie/Solvay, Atochem, Montefluos, Daikin, Pennwalt, Du Pont, Hoechst, Showa-Denko, and Ulsan Chemicals. A testing profile proposed for these new alternatives is summarized in table 9. Currently, over 50 tests are underway or are completed. The goal is to complete these tests in about 5 years. The progress to date for compounds HCFC-123, HFC-134A, HCFC-141B, HCFC-124 and HFC-125 is noted in tables 10, 11, 12, and 13.

A comparative toxicity profile for CFC-11 and HCFC-123 is shown in table 14. In general, the HCFC replacement is of equal or lower toxicity. Similar findings were obtained for another alternative, HFC-134A, when compared to CFC-12 in table 15.

It appears from research to date that the replacement compounds (HCFCs) for the previously used aerosol propellants (or CFCs) will not only be better for the environment but will have a relatively low order of toxicity.

Relative to inhalant abuse in particular, the chemical industry will take the following actions:

1. Continue the development of low toxicity alternatives for CFC solvents, propellants, refrigerants, and blowing agents.

Table 3. CFCs and alternatives

Currently used CFCs			Alternatives	
Formula	CFC No.	Boiling Point	FC No.	Formula
$CCl_2F.CClF_2$	113	47.6		
		32.0	141B	CH_3CCl_2F
		27.8	123	$CHCl_2.CF_3$
CCl_3F	11	23.8		
$CClF_2.CClF_2$	114	3.8		
		-9.2	142B	$CH_3.CClF_2$
		-12	124	$CHClF.CF_3$
		-24.5	152A	CH_3CHF_2
		-25.0	DME	CH_3OCH_3
		-26.5	134A	$CH_2F.CF_3$
CCl_2F_2	12	-29.8		
$CClF_2.CF_3$	115	-38.7		
		-40.8	22	$CHClF_2$
		-49	125	$CHF_2.CF_3$

Table 4. Principal alternatives to CFCs (commercially available)

- Dimethyl ether (DME)—Propellant
- HCFC-22—Air conditioning agent, refrigerant, blowing agent, propellant
- HCFC-142b—Blowing agent, refrigerant blend component, propellant
- HFC-152a—Refrigerant blend component, blowing agent, propellant

Table 5. Properties of commercially available alternatives

	HCFC-22	DME	HFC-152A	HCFC-142b
Formula	$CHClF_2$	CH_3OCH_3	CH_3CHF_2	CH_3CClF_2
B. Pt. (°F)	-41	-13	-13	+14
V.P. (psig) 70 °F	121	63	63	29
Ozone Depletion Potential (ODP) (vs. CFC-11 = 1)	.05	0	0	.06
Global Warming Potential (GWP) (vs. CO_2 = 1)	.34	Negl	.03	.36
Volatile Organic Compound (VOC)	No	Yes	No	No
Flammable	No	Yes	Yes	Yes
Workplace Exposure Limit (ppm by vol.)	1,000 TLV	1,000 AEL	1,000 AEL	1,000 AEL
Toxicity testing	<----------Complete---------->			

TLV = Threshold Limit Value proposed by the American Conference of Governmental Industrial Hygienists (ACGIH)

AEL = Acceptable Exposure Limit proposed by the Du Pont Company

Table 6. Toxicological summary of commercially available alternatives (DME, HCFC-22, HFC-152a, HCFC-142b)

- Low order of acute and chronic inhalation toxicity
- Weak cardiac sensitizers
- Low order of skin and eye irritation/sensitization
- Pose no hazard to humans from the viewpoint of systemic toxicity, carcinogenicity, mutagenicity, or teratogenicity when used within their TLVs or Du Pont AELs

TLV = Threshold Limit Value proposed by the American Conference of Governmental Industrial Hygienists (ACGIH)

AEL = Acceptable Exposure Limit proposed by the Du Pont Company

Table 7. Principal alternatives to CFCs (not commercially available)

- HCFC-123 AND HCFC-141b
  Principal candidates for replacing CFC-11 in blowing agent applications
- HCFC-124
  Potential candidate for specific blowing agent, refrigerant uses
- HFC-125
  Potential candidate for air conditioning, refrigerant uses
- HFC-134a
  Potential candidate for CFC-12 in refrigeration applications

Table 8. Properties of noncommercially available alternatives

	HFC-125	HFC-134A	HCFC-124	HCFC-123	HCFC-141B
Formula	CF_3CHF_2	CF_3CH_2F	CF_3CHClF	CF_3CHCl_2	CH_3CCl_2F
B. Pt. (°F)	-55	-16	+12	+82	+90
V.P. (psig) 70 °F	165	70	33	—	—
Ozone Depletion Potential (ODP) (vs. CFC-11 = 1)	0	0	0.02	0.02	0.15
Global Warming Potential (GWP) (vs. CO_2 = 1)	0.84	0.28	0.1	0.02	0.15
Volatile Organic Compound (VOC)	No	No	No	No	No
Flammable	No	No	No	No	Yes
Workplace exposure (ppm by vol.)	1,000 AEL	1,000 AEL	500 AEL	10 AEL	500 AEL
Toxicity testing	<----------Underway through PAFTT---------->				

PAFTT = Program for Alternative Fluorocarbon Toxicity Testing

AEL = Acceptable Exposure Limit proposed by The Du Pont Company

Table 9. PAFTT proposed toxicity testing schedule

Phase I (6-8 months)
Acute inhalation (LC50, ALC)
Dermal and eye irritation/sensitization
Dermal toxicity (LD50 in 2 species)
Cardiac sensitization
Genotoxicity (AMES, lymphocyte, micronucleus)
Other (acute oral, human patch studies)
Phase IIa (6-8 months)
Subacute inhalation (4 weeks)
Preliminary pharmacokinetics (blood levels, uptake, elimination)
Teratology probes (2 species)
Environmental toxicity
Phase IIb (1 year)
Teratology (2 species)
Phase III (1 year)
90-day inhalation
Metabolism—CNS effects
Phase IV (4 years)
Chronic inhalation toxicity/carcinogenic study

PAFTT = Program for Alternative Fluorocarbon Toxicity Testing

Table 10. Present toxicity testing status on HCFC-123

- Low in toxicity on an acute basis
- Not mutagenic—based on in vitro and in vivo studies
- Not a developmental toxin—in rats or rabbits
- Low in toxicity on a subchronic basis
- Chronic inhalation toxicity study in rats—after 24 months exposure
  - Initiated 1/89 (doses of 0, 300, 1,000, and 5,000 ppm)
  - No adverse effect on survival
  - Liver weight (slight decrease)
  - Peroxisome proliferation (slight increase)
  - Triglyceride, cholesterol, and glucose (levels decrease)
  - Higher incidence of benign liver, pancreatic, and testes tumors

Table 11. Present toxicity testing status on HFC-134A

- A gas of low order of toxicity (acute and repeated exposure)
- Practically not metabolized; not accumulated; quickly eliminated
- Nongenotoxic
- Not a developmental toxic in rats or rabbits
- Inhalation
  - Subchronic low toxicity
  - Carcinogenic/chronic toxicity study in rat is in progress (initiated 10/89)

Table 12. Present toxicity testing status on HCFC-141B

- Not mutagenic or clastogenic
- Negligible acute toxicity/irritation potential
- Reversible anesthetic effects
- Low order of subchronic toxicity
- Not a developmental toxin in rats or rabbits
- Chronic toxicitykarcinogenicity study in rats in progress (initiated 1/90)

Table 13. Present toxicity testing status on HCFC-124 and HFC-125

HCFC-124

- Very low order of acute and subchronic toxicity
- Minimal CNS effects at $\geq$50,000 ppm
- Moderate cardiac sensitization potential
- Not mutagenic (in vitro or in vivo)
- Not a developmental toxin
- Chronic study—to be initiated in 1992

HFC-125

- Low order of acute inhalation toxicity
- Not mutagenic
- Subchronic inhalation toxicity studies in progress

Table 14. Comparative toxicity of CFC-11 and HCFC-123

	CFC-11	HCFC-123
Formula	$CFC1_3$	CF_3CHCl_2
Boiling point	23.7°C	27.1°C
4-hr LC50 (Rats)	26,200 ppm	36,000 ppm
10-min EC50 (CNS, Mice)	35,000 ppm	<40,000 ppm
AMES (Salmonella)	Negative	Negative
In vivo genotoxicity (rats)		Negative
Cardiac sensitization threshold (dogs; epi i.p.)	5,000 ppm	> 10,000 ppm
Subchronic noel (rats)	5,000 ppm	1,000 ppm
Teratology (rats)	Neg. at ≤ 20,000 ppm	Neg. at ≤ 10,000 ppm
Teratology (rabbits)		Neg. at ≤ 5,000 ppm
Carcinogenicity (oral, rats)	Negative	
Carcinogenicity (inhal., rats)	Neg. at ≤ 5,000 ppm	Produces benign tumors of the liver, pancreas, and testes
Metabolism (^{14}C-label, rats)	Not metabolized	Slight metabolism
Occupational limits	TLV = 1,000 PPM C AEL = 1,000 PPM TWA	TLV - NONE AEL = 10 PPM (8-hr TWA)

(TVL= Threshold Limit Value [ACGIH]; AEL = Acceptable Exposure Limit [Du Pont Company].)

Table 15. Comparative toxicity of CFC-12 and HFC-134A

	CFC-12	HFC-134A
Formula	CCl_2F_2	H_2CFCF_3
4-hr LC50 (rats)	760,000 ppm	500,000 ppm
AMES (Salmonella)	Negative	Negative
In vivo genotoxicity (rats)	Negative	Negative
Cardiac sensitization threshold (dogs)	50,000 ppm	75,000 ppm
Subchronic noel (rats)	10,000 ppm	50,000 ppm
Teratology (rats)	Negative	Negative
Carcinogenicity (oral, rats)	Negative	Negative
Metabolism (^{14}C-label, rats)	None	None
Occupational limits	1,000 ppm (TLV)	1,000 ppm (AEL)

(TVL = Threshold Limit Value [ACGIH]; AEL = Acceptable Exposure Limit [Du Pont Company].)

2. Utilize, at all times, the most effective warning language on labels, on material safety data sheets, and in product literature.

3. Continue to support, on an individual company basis and through interindustry efforts, education programs on the potential hazards of inhalant abuse for:

   - our own workers
   - our customers
   - parents, teachers, and young people at the earliest possible age

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Recommendations

The focus of the conference was to establish future areas of research worthy of support and necessary to accomplish the goal of a reduction in inhalant abuse, especially among young people. In preparing this set of recommendations, several specific as well as broader recommendations, which seem to be manageable research endeavors, have been identified and organized in this section according to the appropriate fields of research. The knowledge gained from new research identified by these recommendations should provide us with the needed elements to more successfully attack the inhalant abuse problem.

General Considerations

One issue was extensively discussed but not resolved. There is a need in the field for clearer definitions of the solvent-inhalants abuse area. At a minimum, greater differential clarity is needed between (a) solvents, (b) medicinal anesthetics, and (c) the nitrites. This is not only a problem for epidemiologists evaluating the extent of use but also for many clinical researchers. In addition, there are several recommendations that should be considered for future clinical and/or epidemiological studies. These are outlined here prior to the listing of more specific recommendations for research.

I. Case Studies

A. Investigators need to conduct more complete and accurate histories of drug/inhalant exposure; measure urine/blood/tissue levels where possible and apply other techniques to determine extent of exposure.

B. Researchers need to screen individuals for acute toxicity before being evaluated so acute intoxication can be differentiated from long-term

or chronic irreversible changes. Toxicity (medical or psychological) studies on humans should be conducted several days to weeks after the subject has been abstinent from inhalant use.

C. Future toxicity studies should utilize the most recent and sophisticated techniques to assess toxicity (especially neurotoxicity) of existing as well as newly introduced solvents and propellants. Establishment of the initial MRI parameters and other standardizations are essential for cross-study comparisons.

D. Researchers should perform independent chemical analyses of the compounds under study. Manufacturers' product ingredient labels are often incomplete for these complex compounds.

II. Case and Cohort Studies

E. Studies of minority and ethnic populations should be careful in distinguishing differences and unique characteristics among each of these groups. For example, in studies of Hispanic populations, differentiations should be made between Mexican Americans, Spanish Americans, Cuban Americans, Puerto Rican Americans, and other Latinos from Central and South America. As for any ethnographic study, detailed definitions for subgroups within an ethnic/minority group are needed.

F. Special attention must be paid to the role of mediator variables in studies of the etiology of inhalant use behaviors. Consideration of socioeconomic, political, or other population variables in different locales are important in discerning possible mediator variables and their effects.

G. In light of the low base rate of inhalant use compared to other drug use, special attention should be paid to inclusion of inhalant questions on general drug surveys. Many research endeavors fail to incorporate inhalant-specific components in their research protocols.

H. Standardization of solvent questions on surveys is much needed. For example, both the NIDA National Household Survey and the High School Senior Survey could disaggregate their overly inclusive ques-

tions on inhalants. At a minimum, volatile solvents must be clearly distinguished from nitrites. It is suggested that the appropriate agencies convene a panel of experts to aid in standardization.

I. It is important to obtain detailed histories of all the types of solvents and drugs used—not just the street names or other jargon—and an adequate description of the amounts used per episode and over time.

J. Special attention to cohort effects as well as historical trends is essential.

The following identify some specific areas of solvent, or other inhalant, abuse research identified by the participants as important to conduct.

General Studies

1. Long-term followup studies of users should be a prime focus. These studies are relevant to epidemiology, treatment, prevention, drug effects research, and outcome.

2. The development of comprehensive data systems can be useful repositories of inhalant abuse information.

3. Given the similarities of alcohol and toluene (and other solvents) actions, studies are needed on the incidence of alcohol use among solvent abusers, and a measure taken of the synergistic effects of alcohol and solvents (like toluene) when used together. Alcohol abuse may be a confounding cofactor in resolving solvent abuse questions and problems.

Pharmacologic and Toxicologic Studies (Animal)

4. There should be a variety of studies in different species evaluating the long-term cognitive outcome effects of prolonged solvent abuse.

5. Studies on the pharmacodynamics, distribution, and bioavailability of toluene and other abused solvents and their metabolites need to be

investigated to be able to compare the effects in experimental animals with those in humans.

6. Drug interaction studies (of different solvents as well as solvents and other drugs) are needed in light of the fact that inhalation of combinations of solvents is typical in occupational as well as drug abuse settings.

7. Several different acute and chronic neurotoxic studies concentrating on subhuman primate species as well as other animal models should be conducted. These studies should unambiguously identify the solvent and/or solvents responsible for specific toxic effects.

8. Drug-discrimination studies are needed to compare subjective (user experienced) effects across a range of abusable drugs and solvents. Such data can shed light on whether humans abuse volatile solvents for the same reasons they abuse other, noninhalant drugs. If so, can one predict which new "solvents" the user might select and any alternative use of drugs when inhalants are less desirable.

9. The issue of in utero exposure to solvents under conditions of human abuse during pregnancy (fetal toxicity) deserves further attention and study. It is becoming more apparent that toxic effects occur in neonates born of mothers who used inhalants while pregnant. Experimental animal and retrospective human studies should be conducted.

10. Studies to determine if alternatives for CFC solvents (chlorofluorocarbons), propellants, refrigerants, and blowing agents have suitably diminished toxicities.

Clinical Case and Cohort Studies

11. Cross-sectional and longitudinal studies on the problems associated with human use of inhalants in natural settings are needed. Such studies should collect information on the effects of dose, duration of exposure, analysis of the solvent mixtures, users' nutritional status, use of alcohol and other drugs, head trauma, psychiatric disorder, aging,

and other disease factors affecting the central nervous system, as well as more knowledge about preexposure cognitive functioning, and preexisting psychological dysfunction, with the deployment of appropriate reference, comparison, or control groups.

12. Prospective studies on neurotoxic and other toxicologic effects of solvents and other inhalants are needed. To date all studies are retrospective. Although these are difficult to visualize or design, it may be possible to follow up controls of other studies who become inhalant abusers.

13. More sophisticated neuroimaging studies, which combine metabolic evaluations with imaging technology such as positron emission tomography (PET), and single photon emission computed tomography (SPECT), should be employed to study both acute and chronic effects of solvent inhalation.

14. Post-mortem analyses can identify links between solvents and disease states or toxic effects on various tissues.

Psychosocial Studies

15. Studies on social marginality (viz., social problems such as poverty, prejudice, and lack of opportunity) are essential next steps in research. The focus on marginality may be exclusive of or inclusive of culture or age groupings.

16. Studies on the psychological motivations for death (viz., retrospective case histories) are needed among inhalant users. (For example, is there a basis for hanging?) Special attention on apparent suicides may reveal underlying inhalant use histories.

17. Exploratory studies on the motives for use of inhalants may utilize the user's perceived therapeutic effects of these inhalants (e.g., for their anxiolytic and antidepressant effects). These results could establish future research guidelines for the exploration of potential therapeutic compounds.

18. Both cross-sectional and longitudinal studies are needed on such variables as school adjustment; family characteristics; deviance by age and by peer group; violence and victims of abuse; and cultural identification factors, family risk factors, school risk factors, and psychosocial consequences of inhalant use.

19. Laboratory analog studies are needed on such variables as social responses of users; hostility and anger in both users and their families; and learning and perception abilities of users.

20. Detailed and thorough ethnographic studies are needed on inhalant dependent adults; such endeavors should encompass both intact and broken families as well as homeless persons.

21. Studies have emphasized primary inhalant users. New studies are needed on polydrug users who also use inhalants (secondary inhalant users).

22. Studies are needed on specific occupations and occupational settings and their influence on solvent abuse. For example, because of their high level of exposure to "solvents," tradespeople in the paint, cleaner, and degreaser processing professions are important first groups to study.

23. Select cultural studies are needed to focus on new solvent patterns in vogue in special locales. For example, why are propane and butane used by some adult populations, by some college students in the United States, and by other groups in Great Britain, but their use is unheard of in many other locales?

24. Studies are needed on the role of criminal activity and other deviant behavior (including rebelliousness and influence of peer-sanctioned deviance) in inhalant users.

25. Studies on school dropouts and the role of poor school adjustment are needed. Studies examining the differences in learning styles between inhalant users and others are potentially relevant for treatment and prevention endeavors.

26. Studies are needed to examine the etiological relationship between inhalant-using youths and learning disabilities.

27. The distinct age patterns displayed by solvent users need a more complete exploration. In particular, comparative studies across different populations could be useful since age of onset may be interdependent on varying patterns of social control.

28. More extensive studies on the role of the family and how it relates to inhalant use among children are needed. The focus of such efforts might include parenting styles, discipline, role modeling, family violence and abuse, and handling of family crises.

29. There is a need for more cross-national and cross-cultural studies.

30. Ethnographic studies on the user's values, beliefs, routines, and consequences of their solvent using behaviors are needed. These should include knowledge of the user's perceptions of solvents and their effects, and phenomenologic studies such as the settings, purposes, motivations and functions of use for the user. These naturalistic observation studies are an important prelude to epidemiological and experimental studies.

31. Studies are needed on the types of solvents used and the motives for use. Data from these studies may be helpful in determining the more popular and/or dangerous substances.

Treatment and Prevention Research

Treatment and prevention approaches should be individually tailored to the diverse inhalant-abusing target populations and should be critically evaluated for the efficacy/outcome of these programs. Also, the best prevention programs are those based on solid research of what has worked, not what "ought" to work. Adaptation rather than adoption of extant prevention approaches is needed.

32. Conduct studies on how drug using groups differ from nonusers in their perceptions and responses to drug prevention messages by

examining differences by age and by ethnicity, based on the content, style, intensity, and the source of the message.

33. Comparative studies are needed to examine the prevalence rates under various legal conditions, given that different locales have imposed diverse laws regarding the use or sale of volatile solvents.

34. Studies should be designed using controlled evaluations of prevention efforts with adequate comparison or control groups especially designed for inhalant abusing populations.

35. Studies are needed to see how community-based treatment settings, such as Community Assistance Programs (CAPs) can be adapted and deployed for assisting inhalant abusers with special attention to the unique needs of the target community, or target population, primarily focusing on youngsters in school in their formative years. Employee Assistance Programs (EAPs) may also be utilized to help the young (not just the adult) inhalant user/abuser.

36. Studies are essential to determine "threshold" limits for exposure concentrations that markedly affect ongoing behavior and/or induce self-indulgence in "sniffing" and impair performance in animals and humans, particularly in the workplace.

37. Evaluate the use of brainstem evoked responses (e.g., BAER's) as a sensitive screening test to identify individuals with early evidence of central nervous system injury who thus may need treatment intervention.

38. Determine if the lack of proper use of protective devices (e.g., respirators) in occupational settings encourages or relates to workers' abuse of commercial volatile substances.

39. Investigate conditions that lead to the cessation of heavy use of inhalants as well as initiation of inhalant use.

40. Studies to explore alternative treatments for young adult users should include training in vocational counseling and testing, job training and placement, training in employment interviewing skills, developing

methods for good work adjustment habits, and learning to conform to the work environment.

41. Develop treatment programs that would address changing social as well as psychological factors for the inhalant user. (Neither standard psychotherapeutic approaches nor traditional inpatient drug rehabilitation have been notably successful for inhalant abusers).

42. Studies are needed to enhance multifaceted delivery of comprehensive treatments for inhalant users, as inhalant users have extensive dysfunctions in many life domains.

43. Studies need to adapt treatment approaches to changing levels of functioning, as inhalant users often experience neurological and motor dysfunction that interfere with treatment.

Epidemiology

44. Longitudinal surveillance to detect and monitor trends and patterns of volatile solvent abuse—especially for detecting new fad drugs, the role of age-dependent use curves, and gender differences—are essential.

45. There is a need to study the outbreaks (endemics), the mode of spread, and the dynamics of episodic patterns of inhalant abuse.

46. Clinical epidemiological studies, especially those related to inhalant exposure, are essential.

47. Regional and local area epidemiological studies are desirable.

Economic Studies

48. Studies need to be conducted on the economic factors associated with different rates of volatile solvent abuse, including the relationships to specific levels of poverty; of availability and cost of solvents; or of stigmatization or, in economically depressed areas, sanction associated with solvent use.

49. Studies on the costs to industry of volatile solvent abuse (e.g., costs due to accidents, insurance, rehabilitation, and lowered productivity) would aid prevention and treatment.

50. Studies on the national costs of solvent abuse are desirable.

51. Cost benefit studies for treatment and prevention where analyses of the costs of inhalant-attendant criminal behavior should be compared with the costs of prevention, treatment, and criminal justice involvement.

While limited supplies last, single copies of the monographs may be obtained free of charge from the National Clearinghouse for Alcohol and Drug Information (NCADI). Please contact NCADI also for information about availability of coming issues and other publications of the National Institute on Drug Abuse relevant to drug abuse research.

Additional copies may be purchased from the U.S. Government Printing Office (GPO) and/or the National Technical Information Service (NTIS) as indicated. NTIS prices are for paper copy; add $3.00 handling charge for each order. Microfiche copies are also available from NTIS. Prices from either source are subject to change.

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