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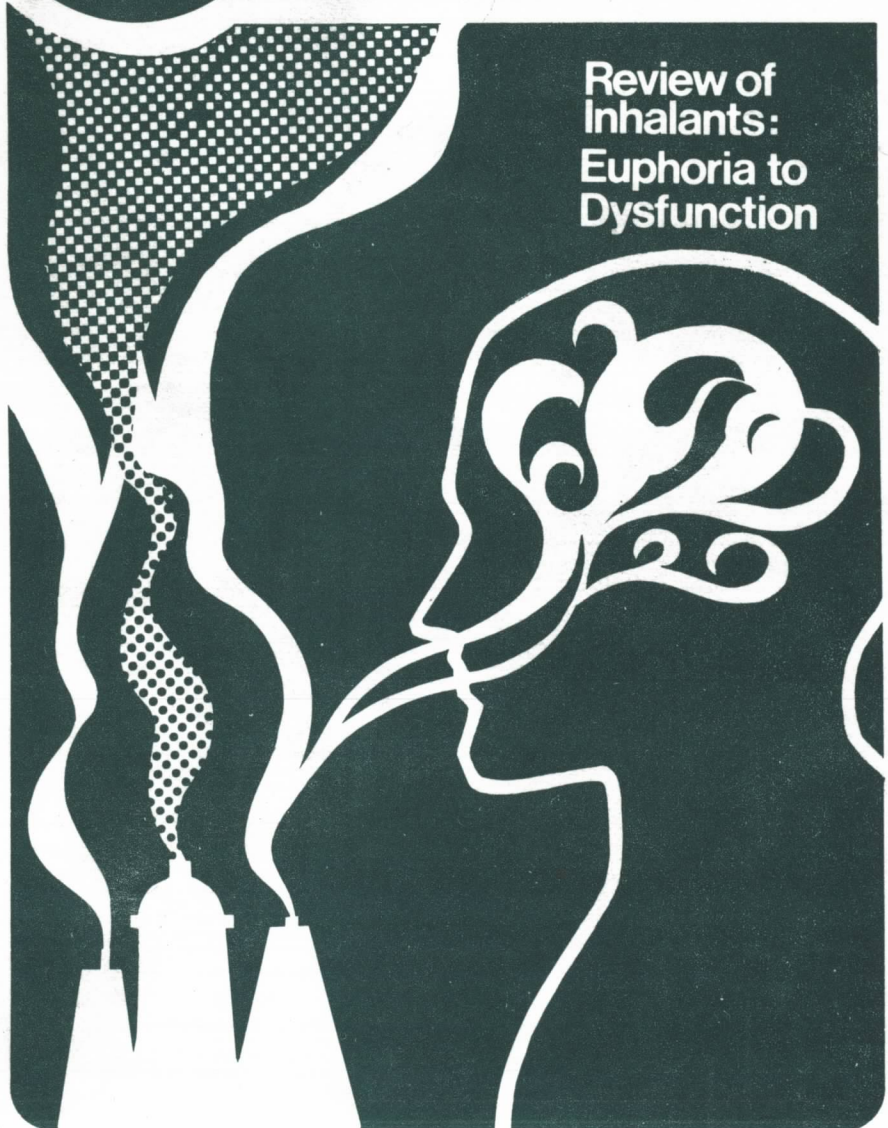
Review of Inhalants: Euphoria to Dysfunction



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Review of Inhalants: Euphoria to Dysfunction

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Review of Inhalants: Euphoria to Dysfunction

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FOREWORD

Inhalant abuse presents somewhat unique challenges to drug abuse research, treatment, and prevention. Inhalants, or volatile solvents, do not show up in large or alarming percentages in national surveys, nor until recently were they taken very seriously--"glue-sniffing" has been the rather innocuous sounding popular description of the practice.

But, such solvents are often the first drugs used by preteenagers to produce a state of altered consciousness (a "high"). Under certain conditions (poverty, minority, rural situations), solvents are the most readily available intoxicants. Users tend to be young (mean age 14, range 7-17), and the seriousness of the problem becomes apparent when one finds that continued inhalation of industrial solvents--including lacquer thinner--can result in paralysis or even death.

By virtue of the youth and vulnerability of the primary using population, the ready accessibility and increasing prevalence of these intoxicants for other common uses, and the nagging possibility that our survey techniques may not adequately be capturing the actual extent of use, we have a special responsibility, in my view, to be sure that we are doing all we can.

This monograph provides a thorough review of the literature and critical assessment of the state of our knowledge in the several papers presented, and an important post-1970 selected bibliography on the topic. It should prove a useful text and reference.

William Pollin, M.D.
Director
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PREFACE

Inhaling psychotropic substances and vapors for mind altering and recreational purposes is older than pharmacognosy. Although one of the oldest and simplest forms of producing an intoxicated state, inhalation of volatile solvents has provoked only limited efforts to define its basic elements, to evaluate the consequences, or to deal with the problem in a systematic way.

There are many reasons for this lack of interest and support. One of the primary reasons is a derogatory attitude towards the majority of the population of inhalers not only on the part of the general populace but also on the part of those from other drug cultures. Use of inhalants has no mystical or religious associations. Many users, themselves, refer to inhalants as a second choice of drug for producing an altered consciousness. Statements range from, “Anybody who would inhale that stuff must be a nut," to "I'd rather have alcohol or marihuana if I could get it." This view may be reinforced by frequent harassment and debasement by law officials, school authorities, parents, and even siblings or fellow drug users.

Another important reason for lack of focus on the problem may have resulted from calling the practice “glue sniffing.’ Although there was an apparent upsurge in the use of glue during the sixties, other forms of inhalant abuse were almost ignored and this labeling may have led to a limited approach to the problem. There is good reason to believe that most other substances which are being used today were used extensively then. Although the predominant product may change, the use of many mixtures may vary less than expected. A general attack on the use of glue led people to believe that this was an effective deterrent to "glue sniffing." However, distribution and availability may be more likely to influence the choice of substances used than the deterrent forces of press and legal attacks. Contributing to the availability of substances has been the capability of the petroleum, chemical, and related industries, to provide an increasing array of volatile organic substances to choose from during the past 50 some years. Also, the greater the diversity of substances, the less any one government agency or consumer group will be able to focus on the total problem. Although these different mixtures may have several uses in industry and in the home and may manifest distinctly different toxicological actions, most have a common chemical and biological action dependent on their lipophilic nature.

Another important reason for not focusing on inhalant abuse may be due to the type of products abused. Many of these "solvents"

have been used for several decades and are generally considered "safe" by the average user. Agencies charged to control their safety and hazard in industry and the home have been concerned mainly with the acute toxic phase of the physiological insult. Attention has been directed more recently towards chronic and continuous long-term exposure, especially towards carcinogenicity . Also, many other "pollutants" are considered more toxic, and therefore, less attention has been focused on the more common solvents. In drug abuse circles, opiates, barbiturates, amphetamines, hallucinogens, and, more recently, marihuana, cocaine, and phencyclidine have been considered the major drugs of abuse. Solvent abuse is still generally considered a "minor" problem. The data here show that its use may be as much or more prevalent than that of several of the substances mentioned above. Further, the toxicity of many of these solvents exceeds that of other drugs of abuse.

Possibly the oldest form of this type of abuse is associated with the field of anesthesiology. Although scientists in the field have studied most aspects related to these drugs, they have not carefully evaluated the recreational use of anesthetics. Not only are some of the abused inhalants used as anesthetics, the state of intoxication is comparable to Phase I-II (or "light") anesthesia. It is therefore very appropriate for those in this field to apply their techniques and knowledge to the study of inhalant abuse, especially now that they are concentrating on analogous problems associated with the repeated administration of anesthetics.

One of the first attempts to survey the inhalant problem was by Bass in 1970. Although the National Institute on Drug Abuse has included the use of inhalants in surveys, no thorough evaluation of the prevalence of solvent abuse exists. Despite these deficiencies , this publication has been assembled through the efforts of several qualified scientists to review that information which is presently available and to discuss the relevant issues associated with inhalant abuse. Hopefully, many investigators will be stimulated to study this problem. Also, clinicians and others in the community may be able to make use of this information and increase their efforts and cooperation in resolving the problem.

Because of the more complete treatment elsewhere, inhalants such as cocaine, marihuana, and other drugs taken intranasally or otherwise inhaled as a second route of administration are not covered here. Also not discussed is the misuse of many of the inhaled substances through accidental or purposeful ingestion.

This effort has been a culmination of many people's effort, thought, and reports. It is the intention that this compendium be the basis for energizing thought and action in this area not only in interest but also in support at all levels of our society.

Perhaps society can begin to look on this group, as it is beginning to look on alcoholics, with less disdain and view them as a group needing more positive consideration in home, school, and the community at large.

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INTRODUCTION

Chapter 1

INHALANT ABUSE: AN OVERVIEW OF THE PROBLEM

Sidney Cohen

HISTORY

The efficiency of the pulmonary absorption of gases and volatile liquids has been known since prehistoric times. The surface area of the pulmonary epithelium and the mucous membranes of the respiratory trace is large, and absorption is rapid. In addition to gases and volatile fluids, smokes, snuffs, and nonvolatile solutions in aerosol spray form can produce systemic effects through their absorption along the airway. Further advantages of respiratory tract absorption compared to the gastrointestinal route is that the material is delivered directly to the target organ without passing through the liver with its detoxifying enzyme systems. 'I'herefore, effects upon the brain, for example, are more rapid and more intense than by oral administration.

The advantages of pulmonary transfer of consciousness-altering substances have been widely exploited. The method of the ancient Greeks at Delphi was rather sophisticated. In order to invoke the gift of prophecy, an old woman known as the Pythoness was seated on a tripod placed over a vent in a rock from which carbon dioxide emanated, This induced a trance-like state during which the subsequent act of divination occurred.

When the carbon dioxide vent gave out, sacred laurel leaves were scorched in a copper bowl and inhaled by the Pythoness. A sufficient concentration of carbon dioxide was achieved to reproduce the trance and the prophetic experience (Cohen, 1967).

Nitrous oxide is another gas inhaled for analgesia, anesthesia, or fun. Ether and chloroform also had interesting histories of recreational usage before they came to be mundane anesthetics. Even ethyl alcohol can be inhaled in sufficient concentrations to produce inebriation.

Opium, dimethyltryptamine (DMT), and tobacco are smoked for the same various mind-altering changes they induce. Columbus encountered West Indian tribes that used snuffs (probably cohaba, Piptadenia peregrina) They had elaborate snuffing tubes for more efficient delivery of the powder. Virola, tobacco, and many other snuffs were and are used throughout Central 'and South America (Efron , 1967). Of course, cocaine and good quality heroin are also effective intranasally.

More relevant to the intentional use of commercial solvents, one of the earliest descriptions of the phenomenon is that of Clinger and Johnson (1951) who reported on a localized outbreak of gasoline sniffing in Warren, Pa. During the next decade articles appeared in the lay and scientific press about model airplane glue sniffing. The intoxicating effects of this substance apparently were accidentally discovered by a number of adolescents while working on their model airplane kits. Eventually, a long list of vaporizing liquids came to be abused. These included various contact cements and adhesives, paints, lacquers and their thinners, dry cleaning fluids and spot removers, transmission and brake fluids, liquid waxes and wax strippers, certain shoe polishes, lighter fluids, nail polish removers, degreasers, refrigerants, and other volatile products.

Not long after the aerosols became popular items on the marketplace, they also were found to be intoxicating, and their use for this purpose spread. These products contain not only a conventional solvent, but also one of the Freons, a chlorinated, fluorinated substituted methane or ethane derivative. In addition, of course, each has an ingredient that provides it with its specific commercial activity. Initially, the glass chillers and vegetable nonstick frying sprays were used. Eventually, it appears, almost every type of aerosol has been inhaled. A partial list would include cold weather car starters, air sanitizers, window cleaners, furniture polishes, insecticides, disinfectants, various spray medications, deodorants, hair sprays, and antiperspirants. More recently, the clear lacquers and the gold and bronze sprays have become increasingly popular.

It should not be assumed that the marketed products are simple solutions of one or a small number of solvents. Prockop (1975) analyzed a lacquer thinner and could identify 11 solvents. In addition, small amounts of unidentifiable impurities were found. It also cannot be presumed that any of the commercial formulations will remain constant. They change, often without notice, when improvements are made, when certain of the constituents increase in price, or when some of them come into short supply.

A special group of volatile substances require mention. Ampules of amyl nitrite ("poppers" or "snappers") are used medically to dilate coronary arteries during an episode of angina pectoris. Apparently, cerebral arteries are also dilated, rapidly producing a suffusion of blood to the brain. The perception of time is slowed. The recreational use of these solvents has been by adults, almost exclusively to prolong and intensify the subjective effects of orgasm.

More recently, advertisements for other products including Toilet Water, Locker Room, Vaporole, Rush, Kick, Bullet, and Joc Aroma have appeared in underground newspapers and magazines devoted to recreational drug use. These items contain isobutyl nitrite, isobutyl alcohol, and isopentyl nitrite. Siegel (1977), in a study of 85 cocaine snorters, found that 7 percent of them had used at least one of these products in 1975. Twelve months later 19 percent were found to be inhaling these "orgasm extenders"

The use of volatile substances for purposes of intoxication appears to be worldwide. Countries that have expressed special concerns include the United States, Canada, Mexico, a number of Central and South American nations, and many European and African countries. Reports from Japan and Sweden have described "thinner" problems among juveniles. Even the Australian aborigines (Norcombe, 1970) and the Indians of arctic Manitoba (Boecks et al. , 1976) are not exempted from the practice.

CLASSIFICATION

A list of the more common solvents that have been abused is provided in Table 1.

EXTENT OF THE PROBLEM

Although the prevalence and demographic nature of the problem of inhalation abuse will be dealt with in a later chapter, a few general comments at this time might be worthwhile.

School surveys that do not specifically inquire into solvent abuse, do not include grade and junior high schools, and do not sample dropout populations will under-report the prevalence of solvent inhalation. These drugs are often the first nonmedically used psychoactive agents, sometimes antedating tobacco and alcohol. Solvent usage tends to decrease with increasing age, one of the few substances showing this pattern in adolescents. The fact that the abuse of solvents occurs at an early age, and that they may be the first of the culturally unacceptable agents to be employed, suggests that they might serve as an introduction to a career of drug dependence.

TABLE 1

A CLASSIFICATION OF ABUSED SOLVENTS

1. Aliphatic and Aromatic Hydrocarbons:
   - Hexane
   - Naphtha
   - Petroleum distillates
   - Gasoline
   - Benzene
   - Xylene
   - Toluene

2. Halogenated Hydrocarbons:
   - Trichloroethylene
   - 1, 1, 1 , trichloroethane (methylchloroform)
   - Carbon tetrachloride
   - Ethylene dichloride
   - Methylene chloride
   - Chloroform
   - Halothane

   Freons:
   - Trichlorofluoromethane (FC11)
   - Oichlorodifluoromethane (FC114)
   - Cryoflurane
   - Dichlorotetrafluoromethane (FC12)

3. Aliphatic Nitrites:
   - Amyl nitrite
   - Isobutyl nitrite

4. Ketones:
   - Acetone
   - Cyclohexanone
   - Methyl ethyl ketone
   - Methyl isobutyl ketone
   - Methyl butyl ketone
   - Methyl amyl ketone

5. Esters:
   - Ethyl acetate
   - Amyl acetate
   - Butyl acetate

6. Alcohols:
   - Methyl alcohol
   - Isopropyl alcohol

7. Glycols
   - Methyl cellulose acetate
   - Ethylene glycol

8. Ethers

9. Gases:
   - Nitrous oxide

Since it is young children who tend to become involved with solvent sniffing, issues of their physical and emotional maturation arise. It is well known that growing tissues are more sensitive to toxic products than mature cells. Thus cellular damage can occur in pubescents at concentrations not as likely to cause impairment in older persons. It is also during these formative years that techniques of coping with life stress are learned. If, instead of dealing with the daily frustrations and problems. a youngster dissolves them in solvent fumes. then the techniques for coping with life's difficulties are never learned, and he or she may remain emotionally immature, perhaps for a lifetime.

WHY SOLVENTS ARE ABUSED

It is difficult for nonconsumers of solvents to undterstand why these materials would be deliberately inhaled for purposes of

intoxication. Industrial workers are usually protected from exposure to more than a few parts per million (ppm) of these agents, while young people will wittingly inhale concentrations 50 or 100 times greater than the maximum allowable concentration in industry. It is difficult for some people to understand why anyone would breathe in strange compounds whose potential for harm has hardly been studied, or if they have, art: considered unfit for human consumption at high concentrations over long periods of time.

In order to try to understand why the volatile inhalants are attractive to those who indulge in them, inquiries were made of the juveniles referred to me (1976) for interview because of a problem with solvent dependence. Their justifications for the use of solvents and aerosols appeared to fall into one or more of seven categories, and these will be described.

Peer Group Influences

The peer group is a very strong factor, perhaps the strongest, in initiating and perpetuating the use of specific intoxicants. Not only does the group dictate whether solvents or aerosols are to be used, but even which brand is currently favored, and how to use them. This does not mean that novel techniques and new products are not tried, but when the shift from paint thinner to clear lacquer spray to gold paint aerosols takes place, usually the whole group shifts over from one item to the other collectively. If the crowd one goes around with are all inhaling an intoxicant, it is very difficult for an individual group member to abstain.

Cost Effectiveness

An important factor in the decisionmaking process about whether to use one of the inhalants is cost. Many, but by no means all, inhalant abusers are from low income families, and the price factor is a decisive element for some of them. Remarks like "I can't afford anything else" or "It's cheaper than wine or pot" are made. A 75¢ can of varnish remover can intoxicate more people than a gallon of cheap wine. Furthermore, as one young man said, "If you're broke, there's always gasoline." Simply inhaling fumes from a car gas tank or a gasoline-soaked rag, or siphoning off some gas for later use are widely known methods of getting "stoned." When asked about the objectionable odor of gasoline, they claimed that it either wasn't so bad, or that they got used to it quickly.

Easy Availability

Although alcohol is commonly assumed to be the most widely available of all intoxicants, in fact, industrial solvents can be found even in places where alcoholic beverages do not penetrate. In poor households a stockpile of liquor hardly is to be expected,

but gasoline, paints, and a variety of aerosols are somewhere around. In very remote rural areas gasoline is the only intoxicant available to juveniles, The solvents are the easiest mind--altering substances for teenage youths to buy. In some communities there may be laws prohibiting the sale of model airplane glue to underage youngsters. But these same teenagers can readily purchase dozens of other solvent preparations in supermarkets, hardware stores, or pharmacies. Even the five and ten cent stores have a large selection to choose from. It is not even necessary to buy them; they are often displayed open shelves, and shoplifting them is not difficult. Among certain groups the theft of these substances is a routine practice. It is a point of honor not to pay for these products.

Convenient Packaging

"You can put a supply in your pocket, and nobody can tell." A tube of airplane cement or a bottle of nail polish remover can be concealed much more successfully than a pint of wine or a six pack of beer. The compact packaging is part particularly convenient for those who still attend school and like to sniff' between classes.

Mood Elevation

A number of the responses referred to the nature of the solvent-induced emotional experience. "It makes me feel good," or "I like the high," and "You aren't afraid when you're under" were some of the responses. The respondents seemed to be describing either a floaty euphoria or a blotting out of the unpleasant elements in their everyday lives. I asked them how it compared with alcohol intoxication, and it was usually described as similar but not identical.

It appeared to me that that the heavy, consistent users were, in effect, treating their feelings of frustration and depression with the state of oblivion that the vapors from some solvent can bring. They appeared unable to enjoy their life situation sober, either, because of some personal inadequacy, a miserable family situation, or a deplorable social setting.

The Course of the Intoxication

In one respect solvent inebriation was treated as superior to that produced by alcohol. "It's a quicker drunk." The inhalation route produces a more rapid onset than drinking, and this aspect is appreciated by those who want instant effect in their inebriant.

A further advantage mentioned by one client was that the drunk was over in an hour or so, rather than lasting all day as with alcohol. The solvent hangover is alleged to be less unpleasant than the postalcoholic state. Headache and nausea were the two

most common complaints noted during recovery from inhalant intoxication. It is considered more reliably intoxicating than marihuana.

The Legal Issue

Only one person mentioned the fact that buying or being in possession of some spray can or other solvent was not illegal. The legality of solvents versus the illegality of marihuana or alcohol for this age group did not seem to be an important consideration.

From the viewpoint of the consumer the use of solvents, therefore, becomes more comprehensible. They have certain advantages over other intoxicants: availability, inexpensiveness, rapid action, and desirable consciousness change. But what about the dangers involved? Certainly no prudent person would deliberately inhale these materials. Unfortunately, prudence or worry about what can happen to their future health does not seem to be a particular concern of those who use solvents for recreational purposes.

SOCIAL COSTS

The price that some inhalant abusers pay in the form of physical and psychological impairment will be presented in another chapter. The costs to society will be discussed here. It is not in its widespread use that the social losses should be counted. Cannabis, tobacco, alcohol, and the sedative-hypnotics are more. widely abused. But some disconcerting aspects of the abuser of solvents do exist. The youthfulness of the population involved is a matter of apprehension both in their added vulnerability to toxic chemicals and in their future tendencies to be overinvolved in future recreational drug-using practices.

The morbidity and mortality from acute cardiac arrest, asphyxiation, accidents . and organ failures are sufficiently numerous to cause concern. Particularly disquieting are the recent preliminary findings by Berry et al. (1976) that indicate a wide range of neuropsychological impairments in a group of chronic solvent abusers If these dysfunctions are established in further studies. it could have serious implications regarding the treatability of such individuals and their capacity to acquire the information and values that would enable them to be productive citizens.

The burden on the families of solvent abusers only increases what is often a tenuously organized or completely disorganized family group. The costs to the medical and social services and to the criminal justice system are visible, but they are not excessively high at present. Those in the immediate vicinity of solvent-intoxicated persons may be at risk because of their unpredictable, bizarre impulse-ridden behavior.

TRENDS

A number of trends in solvent-usage can be identified. Consistent with the increased involvement of females with all drugs of abuse, the male-female ratio for solvents is decreasing. There are greater numbers of users in the 21- to 30-year-old age group than previously reported.

In the past few years aerosols have become more popular as intoxicating agents, and these carry hazards beyond those accruing to the solvent itself. Among them are the inhalation of additional toxic ingredients (copper, insecticide, oil), and the cardiac arrhythmic properties of the propellant Freons

Another recently noted tendency is to add other drugs to a solvent habit. Alcohol and central nervous system depressants are usually those found in this form of polydrug abuse.

A favorable trend is the increased interest by the authorities in the solvent and aerosol problem. The National Institute on Drug Abuse (NIDA) has begun to fund projects designed to study the toxicity of various common solvents as used by juveniles. The first international symposium on the deliberate inhalation of industrial solvents took place in Mexico City, June 21-24, 1976. It was jointly sponsored by the Centro Mexicano de Estudios en Farmacodependencia (CEMEF) and NIDA . More recently a conference of Canadian clinicians and solvent industry representatives took place in Toronto, May 11, 1977.

There is little to report that is new in the areas of prevention and rehabilitation. Actually, developments outside the field of drug abuse may help the situation in time to come. If the public's concern with damage to the troposphere results in the fluorocarbon aerosols being taken off the market, they will therefore be unavailable for use as intoxicating agents. Whether new aerosol propellants will be developed that do not interfere with the ozone shield, or whether aerosols will eventually be abolished, is not known at this time.

A second current movement that will reduce toxicity is the removal of tetraethyl lead from gasoline. Instances of lead polyneuropathy and encephalopathy will decrease when leaded gasoline is no longer marketed.

In connection with gasoline, another development might also have a favorable impact. Now that it has become more expensive, more locks are seen on gasoline tanks. If locking gasoline tanks becomes fairly universal, a reduction in this form of sniffing should occur.

SUMMARY

Inhalant abuse, a youthful substance abuse problem of the past quarter century, is difficult for many adults to understand. When perceived from the perspective of the youth who tends to mimic the behavior of his peers, it becomes more comprehensible. The solvents are among the most available, inexpensive, and convenient of the intoxicants. They are effective in producing the desired state of transforming or obliterating sober consciousness. The fact that their dangers are either hardly studied or actually known to be serious, deters few consumers who indulge, because they seem to be more here and now, rather than future, oriented.

The person who experiments once or twice with some industrial solvent may simply be manifesting the natural curiosity or the mimicking behavior of the young. No particular treatment is needed for such individuals. It is the consistent consumer who is liable to the possible illnesses, injuries, and even fatalities associated with inhaling these unusual intoxicants. The unknown composition and the multiplicity of the products used make treatment difficult when such people appear at a medical installation. The management of the psychic and somatic disabilities is complicated, and rehabilitation is difficult to predict. It is in preventive measures that the greatest hope of making a real impact on the problem exists. Future strategies should focus on early, primary preventive efforts. However, it is acknowledged that these are the most difficult and challenging to achieve.

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SOCIOCULTURAL-EPIDEMIOIOGICAL ASPECTS

Chapter 2

NOTES ON THE EPIDEMIOLOGY OF INHALANTS

Eleanor Carroll

About twenty-five years ago, Aldous Huxley began an address to the New York Academy of Sciences with the striking words, "pharmacology is older than agriculture." He went on to say that primitive man knew how to exploit every root, twig, berry, and grain in his environment for their possible uses. This was not only to satisfy such basic and fully acknowledged human needs as hunger and thirst, but also to satisfy another human need not so fully acknowledged, but perhaps just as basic, the need for alteration of one's state of consciousness. Perhaps just as basic because the Human Relations Area Files (coded for easy retrieval of information about drug use, as well as other types of basic information such as family organization, subsistence patterns, treatment of illness) indicate that there are only three societies which have not made some use of mind altering plant substances.

ETHNOGRAPHIC DATA

Even this small number of three may yet be reduced, given the burgeoning interest in ethnopharmacology, by scholars drawn from such diverse disciplines as botany, archaeology, and art history. This diversity of interest is exemplified by the recent establishment of the Ethnopharmacology Society through the joint efforts of a psychiatrist and an anthropologist Only in about the last 10 years have anthropologists, aided by botanists, psychopharmacologists, and psychiatrists, begun actively to record the

use of mind altering plant substances in communities ranging from the fairly primitive to modern Western industrial societies. These uses are as diverse as those of the Jivaro of Ecuador, who use psychoactive drugs in child rearing, and the quest for greater creative expression that has captivated some users in our own society. Among the Jivaro, the rebellious young must use these substances to discern the will of their ancestors, which oddly enough corresponds to the ideas of their tribal elders. Among our own rebellious youth, it is probably safe to say that the use of hallucinogens less frequently results in discovering views corresponding to those of their elders!

Psychoactive plant substances may be used to place oneself in communication with supernatural beings, to help with divination, to aid in the diagnosis and treatment of certain types of illnesses, or simply to give individuals a culturally acceptable mode of escape from everyday life. In most societies that we know of, this way of escape was not one open to all; usually it was reserved for priests and shamans. That situation could and did change, however, in response to certain outside economic and social pressures--one of the best examples is the post-Conquest spread of coca use to the common Indians after the defeat of the Inca.

The altered state of consciousness which many of these psychoactive plant substances could produce has been perceived as such a benison that only a god could have given the means to achieve it. Dionvsus was worshipped in Greece because of his gift of the grape, and in Mexico the hongos magicos are often called the flesh of the gods. In our own time, which has been aptly called the age of pharmacological Calvinism,' it is difficult to imagine any drug, either natural or synthetic, being given a divine origin. In fact, the polar, or at least the nether, opposite would probably be true.

Richard Evans Schultes, the eminent ethnobotanist of Harvard University, has often pointed out that the New World has many more narcotic and hallucinogenic plants than the Old World, and we have archaeological records to document their existence and employment for centuries before the Conquest. In addition, there are undoubtedly many plants, known at least at the time of Sahagun , which now seem to have disappeared, or, at least, to await further careful ethnographic work to document their present use. Of particular interest are the narcotic and hallucinogenic plants which depend on nasal ingestion, that is, sniffing, snuffing, or snorting, to produce their effects.

One of these is tobacco. In prehistoric and early historic times, tobacco achieved fairly extensive distribution through large parts of the tropical forest, the Andes and the Caribbean, and was used primarily as a psychotropic agent, usually in a magico-religious context. Tobacco can be used in many ways through

smoking, chewing, licking, in a liquid form, or through snuffing. Smoking, as a method of consumption, was probably a much later development. Of course, tobacco snuff achieved widespread distribution in the Western world after the Conquest. In addition to tobacco, several varieties of hallucinogenic cacti are ingested through sniffing in various parts of South America. Sometimes, as among the Yamamomo shamans of Ecuador, a long blowpipe is used to deliver the drug into the nostrils of another. In many parts of the Old World, as well as in the Far East, various cannabis preparations were inhaled.

This brief series of examples serves to indicate that the urge to alter one's psychological state to secure a state of consciousness deemed desirable is a well nigh universal phenomenon, and that snuffing or sniffing to secure this perceived blissful state is extremely widespread. It is ironic that we may have more widespread knowledge concerning the nature, extent, and correlates of inhalant use in some isolated primitive groups than we do about those in our own society. In at least one of these groups, the Yamamomo, thanks to remarkable film footage by two anthropologists, we not only have films of shamans using the hallucinogenic drug blowpipes, but we also have scenes of young boys imitating their elders by blowing from the fire into the nostrils of their same age companions. Following this, the youngsters give an earnest, if not entirely convincing, demonstration of the effect of the drug on the bodily movements of the male adults. Here, at least, is one society where we do not have to worry about the relative influence of parents or peers in the induction into this kind of drug using behavior.

DOMESTIC ISSUES AND INHALANTS

The extent of use/abuse of inhalants in the United States, the age, sex, racial and ethnic identification of the users, the physiological and psychological risks (either short or long term) involved in using various kinds of inhalants, with varying degrees of intensity of exposure--all of these are areas in which solid epidemiological data are lacking. There are several reasons for this.

1. For too long, the generic description for inhalant use has been "glue sniffing," because of the popularity of that particular substance. In reality, "glue" in this context actually alludes to a variety of substances which are sniffed and which pose a wide range of hazards. Unfortunately, "glue sniffing" to most of the general public does not sound terribly serious. Most, hearing it, are more likely to dismiss the problem as one of childish behavior, something easily outgrown and, like the smoking of corn silk cigarettes, not a matter for serious concern. Use of the term "inhalants" in the Mexico City Conference of 1976 was in itself a breakthrough, because it opened the door to a much broader and more serious consideration of the nature and extent of the problem.

2. Another reason is the nature of the problem with which we are concerned. There is little doubt that preoccupation with the abuse of heroin and the opiates has tended to dominate our thinking concerning drug abuse, prevention, treatment, and research for almost a decade. Allied with our concern about opiate abuse has been a fear regarding the crimes which opiate abusers commit to support their habits. Today, as we begin to assemble and analyze scattered clinical and control study reports from a variety of research sites, we begin to realize that the kind of aggression displayed by heavy inhalant users, aggression directed either against themselves or at others,. also makes these users a population which may have impact beyond their numbers.

3. A third problem, initially of interest primarily to those social scientists trained in the development and administration of gathering instruments, is that of wording questions about drug use (see contribution from Jack Elinson). Operational Definitions in Socio-Behavioral Drug Use Research, a 1975 Publication resulting from the combined interest of major NIDA grantees and the Special Action Office, is entirely devoted to the different kinds of answers one can predict, depending on how we ask about drug use. What, for example, does the concept "ever used" mean? And where do we place the cutting points for designating "light," "moderate," and "heavy" use of drugs? When dealing with inhalants, should there be provision for looking into the pharmacologically different attributes of the various inhalants used, so that the potential severity of outcome of their use can be anticipated?

4. A fourth difficulty has to do with the division of bureaucratic responsibility. Who, in what parts of the bureaucracy, has the major responsibility for dealing with inhalant use and abuse? In the U.S. government, for example, responsibility and knowledge regarding various facets of the problem are to be found in such agencies as the Food and Drug Administration, the Environmental Protection Agency, and the National Institute on Drug Abuse, to name but three of the many.

Such distinctions between agencies and their responsibilities become important when we consider such aspects as prevention, which may entail regulatory or legislative restrictions on the availability, packaging, and distribution of potentially abusable inhalants. It is also relevant to the assessment of the abuse potential and hazards posed by the various inhalants. Possible adverse effects of most industrial substances, for example, are assessed at levels of exposure likely in industrial settings and not under the conditions of concentrated inhalation involved in their deliberate abuse.

EPIDEMIOLOGY OF INHALANTS

When we turn to the various surveys that have been conducted in the United States in recent years, we are confronted with several

problems and sources of confusion. Many of' the surveys conducted have focused on illicit drug abuse or with the addition of alcohol and tobacco use, but have frequently omitted inhalant abuse or have restricted the questioning specifically to "glue sniffing." As we have already indicated, however, glue sniffing is but one form of inhalant abuse, the actual range of inhalants that may be utilized is very large. It includes such diverse substance:; as spray paints, spray shoe polish, gasoline, paint thinner, various other industrial solvents and many other products packed in aerosolized form. Thus, it is by no means certain that even the individual responding to a questionnaire with every intent of being open will divine the intent of the questionnaire and report his or her inhalant use accurately

There have been informal clinical reports of especially high incidence of inhalant abuse among younger minority group members, school dropouts, truants. and others who may not be adequately reached by the usual household survey or questionnaire administered in the school. Thus, national or even more narrowly focused surveys may omit important abusing groups or underreport their actual level of abuse. Lower class, minority members are also probably less likely to seek medical attention for adverse reactions to inhalants or, if they do, their symptoms may not be connected with inhalant abuse. This may well explain the very small number of mentions of inhalants in the DAWN system, which is a national drug abuse warning network to monitor emergency rooms, drug abuse crisis centers, and other treatment facilities that deal with drug-related emergencies,

Despite some limitations, the figures that are available concerning inhalant abuse do provide some useful information. In the United States, nationwide drug abuse surveys based on household interviews with a stratified random sample of the population have been conducted since 1972. Unfortunately, the form in which the questions regarding inhalants were posed varied in each of the three surveys involved (1972. 1974, and 1975/76) The 1972 survey asked about "glue or other things you breathe in." In 1974, it talked about "glue or some other inhalant," but by 1975/76, the questioning was considerably more explicit. It was then phrased "glue or some other substances that people inhale for kicks or to get high. Besides glue, there are things like gasoline, some aerosols, nitrous oxide, amyl nitrite which is also called 'poppers,' and other solvents." Among youth from 12-17, the most recent 1975/76 survey found that slightly less than one in twelve (8.1 percent) reported having used inhalants with less than one percent (0.9 percent) reporting current use. Among those over eighteen, 3.4 percent report ever having used inhalants and only one-half of one percent report current use, defined as use within the month preceding the survey. When one looks at the 18-25 group of young adults, generally the peak drug using age group, 9 percent of this group report having ever used with again one half' of one percent reporting current use.

Rates for inhalant use are on about the same level as those fore the use of such drugs as LSD and cocaine. Although the small percentages involved make tracing trends somewhat hazardous, the most recent rates appear to be higher for those who have ever used than were reported in 1972 (for youth 12-17, ever used figures were 6.4 percent in 1973 rising to 8.1 percent in 1975/76; among adults, comparable figures were 2.1 percent in 1972 and 3.4 percent in 1975/76). Current use rates for both youth and adults have shown no dramatic change at less than one percent for youth and one half of one percent in all three survey years. However, the rather low prevalence of current inhalant use found in the national survey samples coupled with the sample variation likely from year to year make it difficult to be certain if small changes are the result of sampling or reflect real changes in national use patterns (Abelson et al. , 1976).

Data obtained from a national cross section of high school and college students conducted from mid-1973 through 1974 (Drug Abuse Council, 1975) are generally consistent with the three major U.S. national surveys described. Among the high school students, the figure for ever having tried inhalants was 7 percent as compared with the 8.5 figure obtained for youth 12-17 in the 1974 National Survey. The figure for college students, 9 percent reporting having ever used, is identical with that found for the 18-25-year-old group in the most recent 1975/76 National Survey. Current use figures are also comparable, lending some confidence that the figures from these two independent sources are probably reasonably good estimates of the actual rates of use.

Despite these rather consistent national results, it should be emphasized that they may obscure considerable variability in the level of use within specific communities, schools, and quite possibly various ethnic groups. Figures from another national high school drug study conducted in 1973 illustrate this (Columbia University, 1973). Two of the high schools which were included had rates for ever having used inhalants that were considerably higher than those reported above. One of these was a large black or ethnically mixed city school on the West Coast which reported 16.6 percent had tried inhalants; another was a large city, predominantly white, East Coast school, which reported a figure of 17.1 percent. However, the percentage now using (defined as "used 3 or more times in last two months") was one half of one percent in the West Coast school and 4.1 percent in the East Coast, predominantly white school. Such figures illustrate the probable complexity of inhalant use and suggest a need to have considerably more detailed understanding of the patterns and implications of inhalant use for different groups.

There has been a diversity of local surveys of drug use including that of inhalants over the past several years (summarized in Glenn, 1976). Unfortunately, the highly varied form of the

questionnaires used, the times at which the studies were conducted, and the varying conditions of administration all make firm conclusions about differences noted dubious. A set of comparable studies of drug use which focused on the general population over the age of 14 in several States reported former inhalant user rates ranging from 0.1 percent in Mississippi to 1.3 percent in Arizona. The very low rates detected in these general populations and the small numbers of users in each make questionable any interstate comparisons, however (Chambers et al., 1973).

Two New York State studies are of interest for the light they cast on area differences within the State and differences in ethnicity of adolescent users. The lowest rate of ever having used "solvents" was in New York City (3.1 percent reported having used). Upstate New York was highest at 6.4 percent and the New York City suburbs were intermediate at 5.8 percent of 7-12 grade students having used inhalants (New York State, 1975). A second statewide study of 8,206 secondary school students in 18 public schools found American Indian youth had the highest rate of inhalant use at 12 percent and blacks the lowest at 3 percent having ever used, White inhalant use was intermediate--S percent reported having done so (Kandel et al. , 1974).

In addition to less precise impressionistic evidence that inhalant abuse is more common among poorer minority group children, there is some data to support this assertion. A study of 457 lower class Mexican American children living in four East Los Angeles public housing projects found inhalant use considerably higher than among the national survey of adolescents alluded to above. The children involved were randomly chosen and were interviewed by specially trained adolescent bilingual interviewers, themselves residents of the area studied. By contrast with the national adolescent sample, the Mexican-American adolescents were three times more likely to have ever used inhalants. In terms of current use, again compared to the national sample, teenagers in the barrios were fourteen times more likely to be currently using inhalants. As compared with the national sample in which less than one in a hundred (0.9 percent) reported inhalant use in the month preceding the survey, more than one in eight (13.1 percent) of the barrio youngsters in the same age range reported having used inhalants in the week prior to the Los Angeles survey. While current use of marihuana and of alcohol was also higher than in the national sample (on the order of twice as likely), the differences in inhalant use were much greater. Although inhalant users were often found to also use marihuana and alcohol, users of marihuana and alcohol reported little use of inhalants (Padilla et al., 1976).

Basing their report on interviews with 75 respondents in Arizona "who might be expected to have experience, contact, and knowledge about inhalant abuse," Varges and Kjolseth report that Mexican-Americans predominate among Arizona inhalant abusers

with Indians, and blacks also are more commonly abusers than are whites. Their respondents, who were predominantly drug treatment program administrators, counselors, or parole and probations officers, also described inhalant abusers as typically of lower class origins (Vargas and Kjolseth, 1976).

Inhalant use has also been systematically studied among the Pueblo tribes of New Mexico. Goldstein, based on a sample of nearly 2,200 junior and senior high school age Indian children found inhalant use in this group also far more common than in the national sample of adolescents. Twice as many in his sample (17.2 percent vs. 8.1 percent in the national sample) had tried inhalants and fifteen times as many (13.9 percent vs. 0.9 percent) were currently using these substances. In this group, female users were nearly twice as common as male users, a finding the author attributes to males have greater access to alternatives such as alcohol and to traditional prejudices against women drinking. Those youngsters who belonged to the Native American Church, which makes extensive use of peyote, a hallucinogenic cactus , as a sacrament, were much less likely to abuse inhalants. This is probably due to the Church's strong proscriptions against the abuse of any drug (Goldstein, 1976).

CONCLUSIONS

The overall picture of inhalant abuse that emerges from the admittedly incomplete data available may be summarized as follows: Use encompasses a rather large range of substances with an almost equally wide range of potentially toxic effects. National survey figures for inhalant abuse report levels of abuse roughly comparable to that for the major hallucinogens such as LSD and for the stimulant cocaine. Because such national data do not adequately sample special populations at higher than average risk, it is likely that these figures understate the extent of the problem, especially as it affects such minority populations as Mexican-Americans and Indians. Data from these groups as well as from other sources suggest that chronic inhalant abuse is a phenomenon of the young (late childhood-early adolescence) and the very poor. This is probably because of the widespread low cost availability of substances that can so readily be abused in this fashion.

Present deficiencies in the epidemiological data concerning inhalant abuse argue for more systematic study of the problem especially in high risk groups. The diversity of substances employed makes it desirable that the specific substances used by better identified and their possible toxic effects more clearly specified.

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Appendix

SUMMARY OF EXPLORATORY STUDY OF INHALANT USE AND TREATMENT

A report under NIDA contract 271-76-4409 on a Summary of Exploratory Study of Inhalant Use and Treatment has recently become available (General Research Corporation, Westgate Research Park, McLean, Virginia, 22101, 1977). In this preliminary effort, nine programs in seven field sites were visited, clients and staff were interviewed, and the following impressions were obtained.

1. There are two major types of inhalant abusers: (1) experimenters or transitional users who move on to other drugs, and (2) chronic abusers.

2. Chronic inhalant abuse is a phenomenon of the young and the very poor.

3. Inhalant experimentation is extremely widespread among young people--i.e., nearly everybody tries it.

4. Among the general population, committed inhalant abuse is extremely rare.

5. As an established drug problem, inhalant abuse occurs in certain neighborhoods and not in others.

6. Where inhalant abuse becomes popular, a system of not-for-profit distribution of the preferred product is developed.

7. Inhalant abusers are invisible to the educational and health care delivery systems, but visible to the criminal justice system.

8. Within their own neighborhoods, chronic inhalant abusers come from the most unstable, disorganized, and problem-ridden families.

9. Chronic inhalant abuse in children and parental alcoholism are related.

10. Black children are sniffers less frequently than other ethnic groups.

11. The prevalence of sniffing is stabilized or increasing.

12. Sniffing among girls is increasing. But girls don't get caught as often as boys.

13. Children start sniffing with peers--either siblings or friends.

14. Chronic inhalant abusing children generally have been abused and/or neglected by their parents.

15. Children without siblings rarely sniff.

16. Inhalant abusers do not develop ritual or jargon--they are not part of a drug subculture

17. In each of the sites visited, inhalant abusers number at least in the several hundreds.

The table (on the following page) indicating regional differences in solvent recreational use reproduced from the report. Fashions change in the solvent employed from time to time so that repeated surveys will show new products appearing and old ones disappearing.

PREFERRED SUBSTANCE(S) AND STATED REASON FOR PREFERENCE, BY SITE

Site	Favored Product	Reason for Use, Comments
New York	Plastic cement, amyl nitrite ("Locker Room")	"Gives longest high"
Miami	Transgo transmission fluid	"Made in the area-goad high"
Louisville	Spray paint ("Toohey's Gold")	"Gives longest high-made in the area"
Los Angeles	Clear plastic spray paint, glue, "PAM"	No reason given
Houston	Spray shoeshine ("Texas Shoeshine"), paint	Shoeshine made in area
Albuquerque	Spray paint ("5-Star Gold")	"Gives longest high"
Sandoval Pueblos	Gasoline, spray paint, spray acrylic	No reason given
Denver	Clear plastic spray	"Gives longest high"

CLINICAL EVALUATION

Chapter 3

CLINICAL EVALUATION OF PSYCHOLOGICAL FACTORS

Maurice Korman

INTRODUCTION

This section will review selected relevant literature describing psychological factors predisposing to use; mental status of users; personality studies of users; long-term effects; and psychological treatment and prevention. Emphasis will be on recent research, much of it presented at the First International Symposium on the Voluntary Inhalation of Industrial Solvents, Mexico City, June 1976.

Characteristics of inhalant users have been described in an impressive number of studies, with major review articles by Cohen (1973), Done (1973), and Wyse (1973). Unfortunately, the bulk of the literature is marred by serious methodological flaws. There is excessive emphasis on retrospective studies; many investigators content themselves with a purely descriptive approach, control groups are frequently lacking, and when present, are inadequate in that other-drug use in particular is seldom properly matched for. Sampling problems abound with few careful attempts to delineate the nature of a particular sample or to evaluate its representativeness. Informational sources are nearly exclusively restricted to the inhalant user himself; few investigators have used an explicit theoretical framework. These methodological considerations will be expanded upon passim.

PSYCHOLOGICAL FACTORS PREDISPOSING TO USE

Much of the literature on licit and illicit drug use attempts to pinpoint the antecedent conditions that lead to substance use and abuse. Most of this research has dealt with alcohol, psychedelics, and narcotics (Braucht et al., 1973; Lettieri, 1975; Gorsuch and Butler, 1976) and has led to a considerable amount of speculation concerning causal relationships between psychological and social factors on the one hand and substance abuse on the other.

The use of inhalants can be viewed in the context of overall drug use. It is possible, of course, that no significant specific etiologic agents are at work here. Except for the very young age distribution (which, incidentally, appears to be rapidly changing--see Faillace and Guynn, 1976, for instance), Done (1973) finds that "the similarity of psychosocial factors in sniffers and in narcotic addicts or alcoholics (Coodley, 1961) suggests that there is nothing unusual about this form of abuse from the standpoint of possible etiology and epidemiology" (p. 112). Nonetheless, it seems a reasonable procedure that inhalant users be contrasted to other-drug users when one is investigating predisposing factors, since there may be particular circumstances or specific characteristics that set the stage for inhalant use, quite aside from the forces that lead youngsters to chemical coping generally (Gorsuch and Butler, 1976). A critical heuristic question is: What does the research on drug use in general tell us about such antecedent conditions and to what extent are inhalant users different? Such background information is particularly important with regard to alcohol, tobacco, and marihuana , drugs which appear in the lives of adolescents at about the same time as inhalants. We will, therefore, try to set our discussion of the predisposing factors to inhalant use against the background of the research literature on the predisposing factors to the use of other such drugs.

Personality Factors

Published speculation on personality factors involved in an increased likelihood that a youngster will use inhalants has relied primarily on information collected from confirmed sniffers. It is likely, however, that sniffers will frequently show personality characteristics which are the result, direct or indirect, of the physical, psychological, or social impact of inhalant use. Under some circumstances, sniffers will come to the attention of legal or medical personnel during or after a crisis. As a result, some of the data is suspect to an unknown degree. One should note that the inhalant literature does not yet contain longitudinal studies of the type exemplified by certain investigations on the use of marihuana and alcohol to which we now turn.

Haagen (1970) found that students who 3 years later became marihuana users were originally more dissatisfied and nonconformist; they were typically bright hut disaffected with school and unconcerned about the future. Smith (1973) reported that self and

peer ratings of rebelliousness were both predictors of subsequent marihuana use. Jessor (1976) found that high school students who became marihuana users later on, initially placed a lower value on achievement and a concurrently greater value on independence; they were more given to social criticism and more tolerant of deviation.

Somewhat similar results are reported in the longitudinal investigation of alcohol use. For example Jones (1968) found that problem drinkers were initially seen as being more unpredictable, unstable, and impulsive than control subjects. These findings, it is interesting to note, parallel to an appreciable extent ad hoc studies of personality variables in young problem drinkers such as those reported by Williams (1970). If the same holds for inhalants, one can perhaps assume, as a working hypothesis, that the descriptive studies cited below may be borne out by future longitudinal or developmental investigations, especially those that deal with young users observed under "everyday" conditions.

In an early study of 27 sniffers, Massengale et al. (1963) conjectured that inhalants were helpful in controlling the anxiety that would otherwise have accompanied strong sexual and aggressive impulses. Press and Done (1967) inferred from their study of 16 inhalant users that the principal personality factors at work in inhalant users include a sense of inadequacy, bashfulness, and feelings of frustration over inability to reach high standards set by parents. Nylander (1962) described an "emotionally disturbed background" in many of 20 intensively studied youngsters in Stockholm. Nurcombe et al. (1970) studied gasoline sniffers who came from traditionally belligerent clans in a remote part of Australia. They posit a higher than average need for discharge of tension associated with sexual, aggressive, and acquisitive drives. Inhalant-promoted disinhibited behavior thus aids in establishment and assertion of masculinity. Some confirmation of this hypothesis was obtained through a technique based on teacher ratings (presumably not on a blind basis) which resulted in higher Tension Discharge scores and higher Anxiety Index scores for inhalant users in contrast to a control group.

Richek et al. (1975) administered the Bown Self Report Inventory to 190 middle class high school juniors and seniors. The Bown Inventory measures positiveness of attitude towards self and milieu. Richek reported low negative correlation coefficients between self-reported incidence of inhalant use and the Bown Inventory scales. The pattern of correlation coefficients was roughly similar to those involving the use of other drugs. Meloff (1970) reports on intergroup differences on the California Psychological Inventory: inhalant users scored lower on scales reflecting poise, ascendancy, self-assurance, socialization, maturity, and responsibility. Control groups, however, were not fully adequate, and it is unclear, as it is in most of the research here reported, whether these differences reflect drug use in general or inhalant use specifically.

The most telling criticism here is the absence of comprehensive studies based on a useful theoretical framework rather than on happenstance observations of a sample's salient personality characteristics. A potentially promising approach, for instance, might attempt to examine unsuccessful adaptation in response to important developmental tasks of adolescence. Might, for instance, the decision to inhale be a function of repettitive failures of this type? Alternative models (and easily more comprehensive ones) could be evolved. Future research needs to be guided by potentially useful notions rather than adding still more descriptive studies of small samples. Since the antecedent conditions to marihuana and alcohol use are beginning to be known with some reliability, they represent a useful point of' departure for inhalant research, As a start, one might try to replicate the work of Haagen (1970) or Jessor (1976) with experimental and compulsive sniffers.

Familial Disorganization and Pathology

Much of the research in this area, basically descriptive in nature, is focused on the level of intactness of the family and overall judgments of the family's effectiveness of functioning. In a sample of nine glue sniffers admitted to a psychiatric state hospital, Jackson et al. (1967) found no child living with both parents at the time of admission, Ackerly and Gibson (1964) reported that most of the families in their small sample of inhalers were "multipe problem families" that had gone through considerable periods of turmoil and discord. In a sample of 32 sniffers living as illegal squatters in Mexico, De la Garza et al. (1976) found that nearly half of the families had a parent. missing through abandonment or death, Massrngale et al. (1963) report on a sample of 27 sniffers. Only seven families had both parents living at home; one or both parents were alcoholic in a total of 13 families. Press and Done (1967) similarly note the incidence and extent of family disorganization. They point to the excessive use of alcohol in one or both parents. The greater use of alcohol in sniffers' families suggested by some of these investigators is, of course, paralleled by the literature on the families of alcohol abusing youngsters (mcKay, 1961; Maddox, 1970; Gusfield, 1970)

Some studies report information regarding parallel control groups. Barker and Adams (1973) found that sniffers resembled control youngsters in a training school setting in that signs of family disintegration were present in both groups, although they concluded that the sniffers' families showed a greater level of clinical deterioration, Meloff (1970) reported that over half of the families of inhalers included separated marital couples; two control groups yielded 25 percent and 9 percent split families respectively. A sample of sniffers in the remote north of Australia was reported by Nurcombe et al. (1970) to be slightly, though not significantly, more often separated from their fathers than a control group. The better controlled studies are less conclusive on the issue of family intactness than the clinical reports.

The literature generally provides little insight into the actual pathology beyond pointing to the general turmoil and ineffectiveness of family functioning. Bonnheim and Korman (1977) videotaped structured interactions among family members of sniffers and other-drug controls. Blind ratings of the tapes by professionals reflected a significantly more conflictual, anxious atmosphere in sniffer families, with particular problems in communication and organization. It should be noted that it is especially important (though difficult) to differentiate family reactions to a child's sniffing from antecedent family conditions. Comstock (1976), for instance, reports on a sample of families of hospitalized sniffers and describes the outrage and rejection by the sniffers' families in comparison to other-drug controls.

Because no longitudinal studies are available which study the initiation of sniffing behavior, it is not possible to evaluate the extent to which the lack of parental control and support, which Jessor (1976) reports as antedating the use of marihuana, is likewise present in the case of inhalants.

Furthermore, is it possible that factors that presumably precede drug use generally, such as family instability, over- and under-domination, parental rejection, harsh physical punishment by one or both parents (see Gorsuch and Butler [1967] for an extended review) are present initially in the case of inhaler families to the same extent, but are then amplified by the almost reflexive negative response that sniffing specifically seems to bring out in most parents?

Future research clearly needs to focus on the possible relationship between the personality variables and familial conditions. An adolescent's psychological vulnerability may eventuate in an increased likelihood of inhalant use only in the context of a familial impasse, or when accompanied by a specific constellation of sociocultural pressures. Multivariate research that examines such variables additively, and perhaps interactionally, is needed.

Environmental Pressures

School adjustment represents one of the most frequently reported troublesome areas for the sniffer. Ackerly and Gibson (1964) and Massengale et al. (1963), among others, describe samples of sniffers noted for their poor school performance and adjustment. More recently, a number of controlled studies have suggested much the same pattern. Barker and Adams (1973) found that inhalant users were more significantly retarded educationally ($p < .01$) than a comparable control group even though they were roughly of the same intelligence. Meloff (1970) found that inhalant users were approximately one grade below a comparison group; he further reports that three of the four variables that best discriminated sniffers from others were school-related: days absent from school last year; grade point average last year; and school-related attitudes. Nurcombe (1970) likewise found a ten-

dency for sniffers to be slower learners than control children. Korman et al. (1977) found that inhalant users appeared to be significantly discriminable ($p < .05$) from other drug using children on the following variables: lower grades on last report card; more suspensions at school; and overall severity of school problems. In addition, teachers were perceived by them as being significantly stricter and controlling.

As was noted above with reference to family pathology, schools and teachers may react to the visible signs of sniffing at least as much as they set the stage for alienation and disaffection. Thus, they become involved in the etiology and the consequences of inhalant use. Such a dual role for schools, frequently noted clinically, needs to be confirmed experimentally, particularly in Mexican-American communities where increased inhalant use and unsatisfactory educational situations coexist.

Another environmental condition present with some frequency in the life space of inhalant users is boredom or idleness. Medina-Mora and Terroba (1976) stressed their subjects' "state of idleness" in their epidemiological survey of inhalant users in the Federal District (Mexico City). A sociological study of sniffers in Phoenix, Arizona (Montiel, 1976), reports a high incidence of inhalant use when there is "nothing to do." Stybel et al. (1976) concluded from similar data that community programs emphasizing recreation should be initiated. Korman et al. (1977) report simultaneously a significant lack of socially appropriate current activities in inhalant sniffers in comparison to a control group of other-drug users and negligible interest in new activities being made available.

Peer use represents a significant environmental press directed towards inhalant use in that reference is persistently made to the role that peers play in introducing youths to sniffing (Ackerly and Gibson, 1964; Cohen, Chapter 1, this volume; Berry et al., 1976). At the same time, it appears that only a minority of a sniffer's reported "best friends network" may themselves be sniffers or even approve of sniffing (Korman et al. , 1977), which may leave the door open to the use of "counter-models."

No definitive information is currently available regarding the extent to which substance use may differentially characterize the families of eventual sniffers. In this they may parallel (or exceed) families of alcoholics (Maddox, 1970) or marihuana users (Kandel, 1973) . Of most interest here would be longitudinal controlled studies comparing sniffers with other-drug using groups.

MENTAL STATUS OF USERS

Cognitive Difficulties

In the 50's and 60's a number of small sample clinical reports were published suggesting a relationship between inhalants (particularly gasoline) and signs of acute brain damage (Courtin, 1955; Faucett and Benson, 1952; Lawton and Malmquist, 1961; Satran and Godson, 1963; Brozovsky and Winkler, 1965; Chapel and Taylor, 1968). Many of these studies, with some exceptions such as Massengale et al. (1963), found abnormal EEG's and occasionally reported on psychological test results suggesting impaired memory and concentration, perceptual motor difficulties, and disorientation.

Barmen et al. (1964) evaluated 15 glue sniffers, 8 of whom were given the Bender Gestalt test shortly after inhaling; they reported gross deviations from normal. The subjects' performances had much improved a week later, leaving the investigators to conclude that the visual-motor distortions were transitory in nature. No controls fot either initial performance or practice effects were included. Torres-Ruiz (1976) reported on a larger sample of 30 sniffers and found attentional and memory disturbances on the Psychopathological Appraisal Form.

Because many of the youngsters evaluated in the studies listed above had disturbed backgrounds characterized by polydrug use, it is impossible to ascribe findings of organic brain syndromes to inhalant use alone without the availability of appropriate controls. A number of investigators, however, did investigate brain changes in inhalant users in the context of parallel data on control subjects and/or objective behavioral measures of brain involvement. Dodd and Santostefano (1964) gave 12 glue sniffers a series of tests of concentration, continuous performance in the face of distraction, and visual-motor coordination some 14 hours postinhalation. These subjects had inhaled a median number of 82 times. The authors concluded that their "performances were strikingly similar to those of the controls" (pp. 568-569).

In a well designed study still in progress, Berry et al. (1976) evaluated 37 chronic inhalers (average number of inhalations in excess of 7,000) with the Halstead-Reitan Neuropsychology (NP) Battery. These subjects, who inhaled primarily metallic paints, were compared to a control group matched on ethnicity, education, sex, age, and drug histories. On nearly half of the tests making up the NP battery, inhalant users scored significantly lower than controls; 40 percent of the inhalant subjects scored in the brain damaged range on impairment indices, while none of the control subjects did. These results were corroborated by Korman et al. (1977), likewise reporting on work in progress. Approximately 60 percent of 59 moderate sniffers, primarily aerosal paint

users (average number of inhalations in excess of 50), yielded NP battery results that were initially rated as brain damaged, in contrast to "experimental" sniffers and other-drug controls whose NP batteries were rated as brain damaged 30 and 35 percent of the time, respectively. Finally, two studies report on mental status evaluation of organic brain syndrome. Comstock (1976) found that 55 percent of a sample of 22 primarily toluene users demonstrated an acute organic brain syndrome characterized by memory impairment, poor retention, and inability to perform simple calculations. Korman et al. (1976) compared 162 inhalant. users seen in a psychiatric emergency room to a group of 162 controls matched on age, sex, ethnicity, and drug use, and found that they differed significantly on the following characteristics: loss of immediate recall ($p < .05$); greater abstraction deficit ($p < .05$); greater judgment deficit ($p < .001$); and greater insight deficit ($p <. 001$).

Research on the impact of inhalants on the higher brain functions has been beset by a number of deficiencies. Among these are the frequent lack of samples of sufficient size, appropriate controls, and systematic approaches to the measurement of dependent variables. At the very least, careful specification of type, amounts, and duration of inhalant and other drugs used is critical. It would be desirable if subjects were sought out whose inhalant history is limited to severe abuse of only one inhalant. Contradictions in the literature may simply resolve themselves to issues of sampling and types of inhalants. Also, too little is known regarding the natural course and long-term reversibility of brain-related behavior deficiencies; as the age range of inhalant users becomes greater, such follow-up will become both critical and feasible.

Danger to Self and Others

Sniffers have frequently come to the attention of authorities because of their involvement with some form of antisocial behavior. Many clinical studies have stressed the sniffer's sense of grandiosity and invulnerability (Wyse, 1973) which is seen as frequently leading to self-directed destructive behavior; others (Cohen, 1975) have pointed out that inhalants may, like alcohol, diminish behavioral control capabilities long before motor activity is diminished. A representative clinical study (Press & Done, 1967) detected sniffing behavior to be "a precursor to criminality" in about a third of the subjects. These individuals were seen as suffering from serious deficits in their judgment and reality perception which led them to be accident prone and to indulge in antisocial and self-destructive acts. It is interesting to note that in Kalogerakis' (1971) report on a series of patient assaults at Bellevue Hospital in New York, only one incident was due to an intoxicant, and that was glue.

Tinklenberg and Woodrow (1974) contrasted groups of youthful assaultive and nonassaultive incarcerated offenders with reference to their history of drug use. Although inhalants were used with low frequency by both groups, their prevalence in the assaultive group was of suggestive proportions in contrast to the control group.

Friedman and Friedman's (1973) large sample studies on drug use and delinquency yielded self-reports of greater violence and aggression on the part of drug users in contrast to non-drug-using controls.

Within-drug-group analyses suggested that "users of inhalants reported the greatest overall amount of violence, both in order to obtain drugs and while under the influence of drugs" (p. 468). They also noted that, among boys with police records, some 40 percent attributed their loss of control leading to violence to drug use. Official records implicated solvents more frequently than any other drug.

In a psychiatry emergency room study, Korman et al. (1976) found that their sample of 162 inhalant users differed significantly from matched controls in that they displayed significantly more self-directed destructive behavior as well as some degree of recent suicidal and homicidal behavior. Mean differences in clinical ratings, however, were small. Some interactive effects were suggested: the non-Hispanic, postadolescent inhalant user is particularly at risk. Another aspect of this study investigated the question, what combination of drugs best predicts self-directed, destructive behavior? Inhalants, and no other drug with it, appeared to be the significant predictive drug variable.

The relationship between inhalants and aggressive behavior represents an important current research issue: What psychological mechanisms are involved? Is the problem primarily a predisposition to aggress or is it a failure of internal controls? What role do inhalant-produced internal states play? These are some of the important, unresolved questions.

Mood and Affect

Massengale et al. (1963) found that nearly all youths in a sample of sniffers showed chronic depression and passive aggressiveness. Brozovsky and Winkler (1965) summarized an investigation of 17 sniffers by postulating basic feelings of helplessness and depression which inhalers replace with euphoria. De la Garza et al. (1976), in a careful psychiatric evaluation of 32 inhalant users in Monterrey, Mexico, found that depression was the most frequently exhibited symptom, being characteristic of 40 percent of the subjects. Using the Brief Psychiatric Rating Scale, Torres-Ruiz (1976) described a sample of 30 sniffers as being high on emotional shyness, flattening of affect, motor retardation, and depression.

Three studies are of particular interest because they involve comparison groups. Comstock (1976) found that a sample of 22 hospitalized sniffers were significantly lower on the anxiety, depressive mood, motor retardation, excitement, and suicidal ideation components of the Brief Psychiatric Rating Scale. Furthermore, the sniffers' Minnesota Multiphasic Personality Inventory (MMPI) neurotic triad scores tended to be lower than that of users of barbiturates, stimulants, and psychotropics. Berry et al. (1976) reported on a sample of 37 sniffers who had significantly higher Depression (D) scores on the MMPI than a control group. It should be noted, however, that D was not elevated by absolute standards (average T score of 62), and was lower than five of the remaining seven clinical scales. Korman et al. (1976) found that inhalant users and other-drug users were both rated higher on depression than the general population of individuals visiting a psychiatric emergency room. In addition, there were no significant between-group differences on any of seven other rating scales reflecting various dimensions of mood and affect. There seems little question that inhalant users are more depressed than the population at large, and that they present themselves as having lowered mood and poor morale, particularly if seen at a time of personal crisis. The issue of whether they show greater affective disturbance than drug users in general is very much open to question.

Diagnosis and Prognosis

The modal prognostic picture that any group of professionally evaluated patients presents is primarily a function of the selection (or self-selection) process with reference to a particular health setting. Not surprisingly, the literature reveals much variability on this issue. For example, Brozovsky and Winkler (1965) found that three quarters of a small sample of sniffers are schizophrenics. By contrast, Alapin (1972) evaluated sniffers in Britain and Poland and reported about a third of them to be schizophrenic. Comstock (1976), describing a sample of sniffers hospitalized in a polydrug treatment center, reports a diagnostic breakdown as follows:

Sociopathic personality	23%
Adolescent adjustment reaction	45%
Depressive neurosis	23%
Schizophrenia	9%

In a setting that accommodates a wide range of patients, the prevailing base rates for both "drug" and "non-drug" patients are fundamental to an assessment of the diagnostic picture of inhalant users. Shown in the table at the top of the next page is the diagnostic structure of inhalant (I), other-drug (O.D.), and non-drug groups (N.D.) taken from a recently completed study by Korman et al. (1976). Interestingly, the three groups do not differ in the incidence of psychosis. The inhalant group appears

	I	O.D.	N.D.
Psychotic Organic Brain Syndrome (O.B.S.)	7%	6%	1%
Non-Psychotic O.B.S.	4%	2%	2%
Affective Psychosis	4%	4%	4%
Non-Affective Psychosis	23%	19%	26%
Neurosis	15%	15%	15%
Personality Disorder	20%*	0%	0%
Sexual Deviation	2%	1%	1%
Alcoholism	6%	1%	1%
Drug Dependence	35%*	17%	1%
Psychophysiological Disorder	0%	0%	2%
Transient Situational Disturbance	10%	15%	19%
Behavior Disorder of Childhood or Adolescence	15%	10%	7%
Mental Retardation	1%	6%	6%
No Diagnosis Made	2%	5%	15%

Note: Based on N=162 psychiatric emergency room patients per group; percentages include primary and secondary diagnoses.

*Significantly different from O.D. group.

to include a relatively large number of persons noted for their lifelong pattern of maladaptive behavior. Does the difference in drug dependence diagnoses reflect a more committed drug orientation on the part of inhalant users than non-sniffing polydrug users?

Prognosis appears to be poorer for inhalant users than for other-drug users. In Comstock's (1976) study, for instance, sniffers responded to a total hospital therapeutic program with "an apparent mobilization of agitation, impulsiveness, and of antisocial manifestations as well." As seen in the emergency room (Korman et al., 1976), inhalant users differed from other-drug users in that the duration of their illnesses was significantly longer ($p < .01$), as was the index episode's duration ($p < .05$); furthermore, the typical disposition was more frequently to hospitalize the patient and less frequently outpatient treatment or no further treatment ($p < .05$).

Other Drug Use

A number of problems exist with reference to determining the use of other drugs by sniffers. Other-drug use is a function of the age of the respondents, the number of years of drug use, the current extent of involvement with inhalants and, most of all, the "type" of sniffer--a determination most influenced by considerations of sample selection. It is instructive to look at the variability of information regarding other drugs ever used as reported in three studies describing different samples of sniffers:

Berry et al. (N=37; $\bar{x}$ age=18.3)		Comstock (N=22; $\bar{x}$ age=17.7)		Korman et al. (N=162; $\bar{x}$ age=21.5)	
Alcohol	100%	Alcohol	18%	Alcohol	51%
Marihuana	100%	Marihuana	36%	Marihuana	65%
Barbiturates	54%	Sedatives	59%	Sedatives	39%
Amphetamines	73%	Stimulants	23%	Stimulants	18%
Heroin	24%	Narcotics	27%	Narcotics	29%
Hallucinogens	54%	Psychedelics	14%	Hallucinogens	41%
Cocaine	38%	Psychotropics	14%		

Studies such as these seem to corroborate the view that inhalant users are a heterogenous group when it comes to other-drug use. Perhaps, as Glaser (1966) notes, they are confirmed in their primary drug orientation much like narcotic and alcohol addicts. Reliable data are lacking on this score.

The issue of possible progression up the "drug ladder" is an important one for inhalant users since it is a drug of early initiation. Kramer (1972) reported that nearly half of a sample of 47 heroin addicts began their drug abuse with glue sniffing. Unfortunately, so little is known about the incidence of sniffers who do stop short of using narcotics that causal arguments derived from studies of heroin addicts cannot be taken seriously.

In spite of the wide panoply of drugs used by most sniffers in the samples discussed above, the prevalence of heroin ("ever used") does not exceed 30 percent. Done's question about a "graduation" from early inhalant use to heroin (Done, 1973, p. 114) is far from conclusively answered.

What is the order in which inhalant users move from one drug group to another? Some preliminary findings on a sample of 37 sniffers (average age 18), would appear to give the following sequence (Berry et al., 1976):

	Age of First Use	% Ever Used
Alcohol	10.7	100%
Amphetamines	11.3	73%
Marihuana	12.8	100%
Solvents	12.8	100%
Barbiturates	15.0	54%
Hallucinogens	15.8	54%
Cocaine	16.6	30%
Heroin	16.9	24%

A younger group of sniffers (N=61; average age 15) show the following progression: (Korman et al., 1977)

	First Tried (Months ago)	% Ever Used
Beer	41.7	77%
Marihuana	38.3	92%
Spray paint	33.9	77%
Liquor	33.0	39%
Gasoline	30.5	29%
Wine	26.4	21%
Glues or cements	25.7	21%
Lighter fluids	20.6	21%
Heroin	19.5	3%
Hallucinogens	11.7	57%
Barbiturates	17.5	30%
Stimulants	15.5	66%
Other Sedatives	13.4	13%
Cocaine	10.4	33%
Hashish	6.5	3%
Other Narcotics	5.3	10%

Alcohol and marihuana seem to precede the beginning of inhalant use by very little, if at all; a year and a half or more, however, appears to elapse before the appearance of most street drugs.

It is interesting to note that whereas only 3 percent of the 15-year-old inhalers tried heroin, the parallel figure for the 18-year-old is 24 percent. It will be significant if further research supports the notion that this figure is close to the maximum level of penetration of heroin for samples of sniffers.

PERSONALITY STUDIES OF USERS

Although some group data have been published which utilized the California Psychological Inventory (Meloff, 1970), the most useful data derived from objective personality tests appear to come from studies using the Minnesota Multiphasic Personality Inventory (MMPI). MMPIs of individuals primarily identified as sniffers that have been collected by two investigators (Comstock, 1976; Berry et al., 1976) were pooled into a composite profile (see Figure 1) for the purposes of this section because of their essential similarity This composite sample (mean age of 18) includes mostly men (85 percent), and is half Anglo and half Mexican-American or Indian, while including slightly more nonhospitalized than hospitalized individuals.

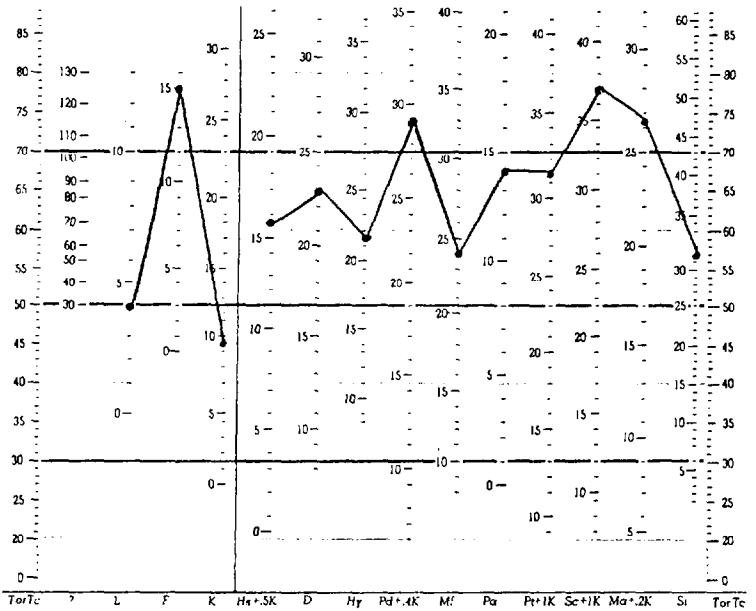

Figure 1. Mean MMPI profile of 59 inhalant users.

A personality description for this profile, as derived from actuarially constructed interpretation devices for adolescents (Marks et al., 1974) and adults (Gilberstadt and Duker, 1965; Hovey and Lewis, 1967), might include descriptors such as (a) a predisposition to exhibit strange and not very well organized beliefs, occasionally of a delusional (persecutory) caliber, and to report sense organ disturbances occasionally; (b) a tendency to under-control impulses, to act out, to resist or derogate others, particularly authority figures.

In Lachar's extensive review of polydrug use and the MMPI (Lachar et al., in press), he concludes that "most studies reported Pd-Sc/Sc-Pd or a Pd spike with a moderate elevation on Sc mean profile." MMPI profiles that include SC/Ma elevations have typically been regarded as reflecting somewhat greater psychopathology in patients in general (Lachar, 1974). Research that will contrast inhalant users MMPIs with those of selected properly matched comparison groups will be of interest in this regard.

Lachar and his colleagues (in press) clearly demonstrate the usefulness of using the MMPl as the tool of choice for the objective assessment of personality and psychopathology of groups of poly-drug users generally. Profile analysis, however, is called for since mean profiles or even code types are far from adequate. Profiles in turn will need to be related to patterns of use and prognosis on a longitudinal basis; a number of critical variables should be looked at, such as the context in which the inhalant user presents himself (voluntary vs. involuntary) as well as the customary demographic variables of sex, age, and ethnicity. One interesting research question deals with a possible typology of inhalant users. The MMPI might be used as the vehicle for differentiating and then describing subtypes if they exist (Marks et al., 1974). As Lachar et al. (in press) point out, identifying subgroups differentiated by the success of various treatment approaches would be an especially useful contribution.

LONG-TERM EFFECTS

The development of an apparent tolerance for inhalants, particularly toluene-based compounds, has been noted by a number of investigators (Glasser and Massengale, 1962; Brozovsky and Winkler, 1965; Press and Done, 1967; Preble and Laury, 1967). Borzovsky and Winkler, for instance, noted an increase of up to 25 tubes per day in one child. A more typical progression is that "over a one or two year period the user may experience less effect with eight to ten tubes of plastic cement, for example, than was noted initially with one or two" (Done, p. 109).

Not enough is reliably known concerning the antecedents of increased tolerance for the major classes of inhalants. There are indications (Easson , 1962) that the sniffing of gasoline, for instance, may likewise involve eventual tolerance buildup. As increasing numbers of adults are reported to be returning to occasional or compulsive inhalant use (cf Faillace and Guynn, 1976). prospective and retrospective research on tolerance needs to be undertaken.

A number of investigators have commented anecdotally on sniffers' symptoms of psychological dependency primarily in terms of the persistence with which the goal of inhaling is pursued (Clinger and Johnson? 1951; Ackerly and Gibson, 1964). There have also been reports of a negative psychological state induced in confirmed inhalers when prevented from sniffing. Some investigators (Ackerly and Gibson, 1964; Preble and Laury, 1967; De la Garza et al., in press) have reported increases in irritability, restlessness, excitability, and anxiety under such conditions. Frequently, it has been difficult to establish the causal relationship between the inaccessibility of the drug and such psychological states. This is particularly true when the sniffer comes to the attention of professionals because he is apprehended or needs

medical care. Further research is also needed that will chart the extent to which the deprived inhaler departs from an optimal state of well being as a result of the nonavailability of inhalants, and under what conditions the urge to use, or fantasize about use, are most frequently experienced.

There has been disagreement in the literature over the existence of a withdrawal syndrome upon abrupt cessation of long and frequent inhalant use. Some authors specifically point to its absence (cf Done, 1973) although there have been reported observations of a syndrome resembling delirium tremens under conditions of abrupt cessation (Merry and Zachariadis, 1962; Nylander, 1962; Lindstrom, 1973)

In an interesting study, De la Garza et al. (1976) described an abstinence syndrome in 22 percent of a group of sniffers characterized not only by dysphoric symptoms but by physical signs as well: abdominal pain, general paresthesias , leg cramps, headaches, and other discomforts. Furthermore, a small group (9 percent) kept some plastic cement to inhale early the next day to counteract deprivation symptoms. Since this is an unusual finding, its replication and further explication is highly desirable, particularly in populations other than the one investigated.

PSYCHOLOGICAL TREATMENT AND PREVENTION

Psychological Treatment

Anecdotal accounts abound regarding the difficulties in modifying sniffing behavior (Clinger and Johnson, 1951; Ackerly and Gibson, 1964; Chevaili, 1976). Comstock (1976) reports fewer favorable pre-post changes on psychometric instruments for a sample of inhalant users in contrast to groups of other-drug users following a period of hospitalization during which psychotherapy, social work, and vocational rehabilitation were available.

Laury (1972) describes his experience with a sample of 30 sniffers, 10 of whom were seen in outpatient psychotherapy. He stresses the need for careful diagnostic evaluation and points out that removal of the sources of glue is insufficient. He emphasizes the importance of helping the child secure new peer relationships, of investigating community resources in order to find alternative "square" activities, and particularly of changing the family interaction with the aim of increasing communication and heightening reinforcement for appropriate behavior. Unfortunately, no outcome information is provided.

Chevaili (1976) finds inhalant users to be unreachable by traditional therapeutic methods because of the lack of verbal ability and the unavailability of basic support systems usually provided by family, school, and work institutions. Like Laury, he stresses the need to work with the family, the school, and the

work setting while providing for an integration of verbal therapy and corporal exercises. Campuzano (1976) focuses on the utilization of psychodrama and the inclusion of paramedical personnel in alternating group therapy sessions. A somewhat similar attempt to avoid the pitfalls of the verbal therapies through a very active "reality therapy-confrontation" approach is outlined by Bratter (1973).

A series of studies have been reported which are based on conditioning principles and other learning paradigms. Although most of these efforts are based on very small samples, they reflect increasing interest in a specific delineation of the therapeutic procedures and a concern with information regarding outcome.

Mecir (1971) reports on an attempt to pair inhalation of a cleaning liquid containing trichloroethylene with discomfort produced by an injection of apomorphine. Twenty such trials were given to a 17-year-old boy in the space of a month, followed by five booster shots. The author reports success over a 7-year follow-up. Skoricova and Molcan (1972) treated 22 adolescents and 10 adults with aversive therapy, following a period of detoxification and symptomatic treatment. They report therapy as being successful in 50 percent of their treated cases, using resumption of sniffing as the criterion.

Kelvin (1967) reports on the treatment of a 15-year-old gasoline sniffer by the use of relaxation and aversive imagery techniques. Self-report information during a 17-month follow-up period showed no resumption of sniffing. Blanchard et al. (1973) treated a patient with a 7-year history of spray paint inhalation with a combination of covert sensitization and apneic aversion, with apnea induced by an injection of succinylcholine chloride (Anectine) . Dependent variables included two types of free access measures. Follow-up for a year indicated a discontinuation of sniffing and an appreciable degree of social rehabilitation.

Maletzky (1974) treated ten Army drug abusers, one of whom was a spray paint user, with covert sensitization assisted by the inhalation of a foul but safe odor. Behavioral measures included self-report information (incidence of drug abuse and urges to abuse drugs), reports from the authorities, and randomly scheduled urinalysis. The experimental group improved more than a control group receiving counseling on all three sets of criteria; follow-up lasted 6 months.

A group of Mexican researchers (Perez de Francisco et al. , 1976) report useful results obtained in treating hospitalized inhalant users with prolonged action neuroleptics (pimocide, penfluridol, and pipotiacina) in conjunction with a total rehabilitation effort.

Other Control Techniques and Prevention

A number of authors reporting on psychological treatment have indicated the importance of adjunctive methods involving the school, the home, and work (Bratter, 1973; Laury, 1972; Chevaili, 1976).

Additional reports deal with the effectiveness of such other approaches in the absence of psychological treatment. Unfortunately, these are largely anecdotal accounts that do not report outcome evaluation data.

Silberberg and Silberberg (1974) focus on the role of the school and point out that a spurt in arrests for glue use sometimes follows on the heels of a school drug education program, a fact that seems to be in keeping with difficulties occasionally encountered with drug information programs. They emphasize the need to initiate programs that develop self-worth within the context of the schools. They conclude that the typical sniffer can succeed most easily in an alternative school setting of the type where traditional skills are not the only aptitudes necessary for success.

De Hoyos (1975; 1977, in press) organized youth groups designed to develop positive status on the basis of attainable achievements in sports and the arts, particularly in relationship to peers. Simultaneously, workers facilitated the formation of formal neighborhood groups of parents (concilios) who interacted with youth groups in drug abuse seminars. This community group also developed audio-visual and written materials (e.g. , comic books) as a preventative measure.

A number of attempts at prevention have been reported (Barker and Adams, 1973) stressing the need to appeal to merchants to control in some fashion the sale of the more popular inhalants in a particular community. Such efforts, complicated by the patchwork of local laws regulating the sale of various inhalants, appear not to have changed inhalant-related behavior materially. Attempts to control inhalant use through unpleasant additives or chemical replacement (Cohen, 1973) have been thwarted by sniffers' discoveries of other intoxicating solvents.

It might be useful, in conclusion, to review criteria for improving inhalant treatment research, adapting recommendations suggested by Callner (1975) among others:

1. Include more representative inhalant users by type of inhalant used, history, and typical dose, as well as by subject characteristics likely to interact with treatment approach.

2. Use a larger variety of reliable and representative dependent measures--including behavioral components of

2. sniffing, unobtrusive or nonreactive variables, ongoing program performance measures, reports by collateral informants.

3. Increase experimental control through the utilization of baseline data and carefully chosen control groups whose characteristics and alternate "treatment" are throroughly described.

4. Improve follow-up procedures--adding to self-report approaches through the use of informants and in vivo assessments, and collecting dependent measures similar to those used during and at the conclusion of the experiment.

5. Apply appropriate data analysis, both graphical and statistical.

6. Provide detailed analysis of variables affecting both therapeutic successes and failures as a preliminary step to refiing treatment and patient selection procedures.

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MEDICAL EVALUATION OF INHALANT ABUSERS

Eric G. Comstock and Betsy S. Comstock

INTRODUCTION

Inhalant abuse describes a pattern of behavior which involves the voluntary inhalation of gases or vapors in order to achieve a modified state of consciousness. The usual intent is to achieve a state of euphoria or "high." A sensation of dizziness, light-headedness, or floating ordinarily is associated with the euphoria. The state of dissociation from one's environment allows temporary escape from the troubles, concerns, and stresses of everyday living. The response induced by inhalation is dose-related and cumulative over short periods of time. The desired alteration in consciousness may be achieved by high concentrations of gas or vapor in air within 1 to 2 minutes, while lower concentrations may require 5 to 10 minutes to achieve the desired effects. Depending upon the substance and the dose, an altered state of consciousness may persist for a few minutes to several hours. With poor control of exposure, the intended effects may become excessive, leading to general central nervous system (CNS) dysfunction, depression, sedation, coma, and death due to respiratory depression or major cardiac arrhythmias. Depending upon the technique of administration, hazard exists for reduction of oxygen content of inhaled air with anoxia leading to unconsciousness and for death from respiratory failure.

Toxicity

The deleterious acute effect of inhalant abuse represents a pharmacologic progression beyond the response desired by the host and occurs as a result of excessive doses. Because the respiratory tract provides a portal of entry into the blood stream for lipophilic substances that is almost equivalent to intravenous injection, elevated concentrations of inhaled substances in the blood are achieved almost immediately. The blood brain barrier is readily penetrated by lipophilic substances. The concentration in the central nervous system reflects the concentration of substances in inhaled air delayed only by the circulation time from the lungs to the brain. The combination of ease of administration and rapidity of response allows immediate feedback. While induction is very rapid, disappearance of effects is relatively slower because of retention of lipophilic substances in lipid pools in the body from which there is gradual release over a period of hours to days. Recurrent use of inhalants over a time interval shorter than the time required to clear fat depots of their retained substances may result in a gradual accumulation requiring many days for dissipation after the last use of the substance.

The effects of inhaled substances may be immediate, delayed, or remote with respect to the time frame within which the effects are manifest . Alteration of consciousness is an immediate effect as are cardiac conduction abnormalities. Delayed effects are manifest by persistent organic brain syndrome, peripheral nerve injury, reduction in hematopoietic activity, and liver and kidney damage. Remote effects may not be manifest for 10 to 30 years and consist of increased rate of cancer and genetic changes in germinal tissue.

Exposure and Clinical Effects

The medical literature is spotted by case reports and reports of series of epidemiologically related cases of injury associated with the use of inhalants. The available medical literature cannot be construed as representative of injury associated with the use of inhalants alone. Publication in medical literature requires the occurrence of a clearly identified injury within reasonable temporal proximity of the use of inhalants. Consequently , medical literature is weighed heavily toward the more dramatic clinical manifestations that occur as an immediate or early effect of inhalant use. Chronic or delayed effects of inhalant use are not likely to be recognized clinically as associated with inhalants, and remote effects, by definition, require 10 to 30 years to be manifest. There exists no comprehensive data base emerging from the careful, systematic investigation of inhalant users with regard to their state of continuing health or disability. Much of the published literature on inhalant effects comes from inadvertant occupational exposure. While such exposure is assumed to be accidental, patients occasionally indicate the vapors inducing euphoria

are not actively avoided. Table 1 summarizes published reports stating briefly the circumstances of exposure and the clinical effects.*

n-Hexane

n-Hexane exposure by inhalation clearly is associated with polyneuropathy , which is predominantly motor. A latent period of 6 to 10 weeks is usually necessary but months to years may elapse between initial exposure and clinical effects following lower levels of exposure. The question of persistent cerebral dysfunction following n-hexane polyneuropathy has not been addressed. Injury to other organ systems has not been identified.

Toluene

Toluene ($C_6H_5CH_3$; methylbenzene, toluol, phenylmethane) is a substance preferred by many inhalant users. Commercial products containing toluene are sought after and used for long periods of time. Since commercial products containing toluene usually contain a wide variety of other volatile organics, generalizations from single case reports have precarious validity. In contrast with n-hexane there is no single predominating target organ system that shows a response to toluene. The diversity of responses associated with toluene suggests that other substances, either alone or in combination, are the primary toxic agents. Toluene users who do not develop significant injury are grossly underrepresented in the literature. Selected case reports are summarized in Table 1. Central and peripheral nervous system, liver, and kidney injury have occurred in association with toluene use.

Gasoline

Gasoline (petrol) vapor inhalation occurs primarily among younger children or in isolated cultures where a very limited variety of volatile substances is available. Various gasoline additives present special hazards. Triorthocresyl phosphate (TCP) is an established cause of both upper and lower motor neuronal degeneration with spastic muscle wasting disorders. Benzene, a common ingredient, is an established cause of subacute and chronic disorders of the hematopoietic system, including various combinations of cytopenia and delayed occurrence of leukemia. Organic lead additives may cause acute and chronic lead encephalopathy. The diversity of clinical effects reported in gasoline inhalers is consistent with the effects of these various additives.

*Although the inhalants described in the following paragraphs and in Table 1 are listed by categories of major or identified constituent, the physiological effects may not be associated solely with this agent or may be due to an action of this and other agents present in the commercial mixture.

TABLE 1
SUMMARY OF CLINICAL SYNDROMES OF SELECTEO CASES FROM THE LITERATURE*

Chemical Compound/Product	Neurologic CNS Effects: Clinical Effects	Neurologic CNS Effects: Diagnostic/Pathologic Findings	Other Effects
NHEXANE PRODUCTS			
Yamamura, 1969:			
Author presents a study checking 1,667 workers in Japanese industries with exposure to n-hexane	Quadriplegia, muscle weakness, dysesthesia, muscle atrophy, hypesthesia	Polyneuropathy. axonal degeneration	
Herskowitz et al., 1971:			
A report of 3 cabinet workers who developed neuropathy while exposed to n-hexane	Muscle weakness, hypesthesia, areflexia	Neuropathy, increased number of neurofilaments, axonal degeneration	
Gonzalez and Downey, 1972:			
Case history of 20-year-old male with 15-month history of glue sniffing (80% n-hexane) who presented with progressive polyneuropathy. Improvement occurred after 2-6 months of admission	Muscle weakness, hypesthesia, paresthesia, muscle atrophy	Polyneuropathy, neurogenic atrophy	
Goto et al., 1974:			
Report of 4 cases primarily motor polyneuropathy caused by inhalation of an adhesive agent. Weakness and sensory impairment developed in 7-30 months with symptom progression noted after cessation of activity. Glue also contained toluene	Muscle weakness, muscular atrophy, flaccid quadriplegia, hypesthesia, areflexia, foot and wrist drop	Polyneuropathy, axonal degeneration, neurogenic atrophy. decreased nerve conduction rates	
Shirabe et al., 1974:			
Report of 2 patients involved in glue sniffing: one for a 3-year period, one for 2 years plus. Glue first used contained small amounts of n-hexane (0-30% n-hexane. 70-100% toluene)	Paresthesia, flaccid paralysis of extremities, muscular atrophy, hypesthesia	Polyneuropathy, axonal degeneration, denervation atrophy	

*Although the inhalants described in Table 1 are listed by categories of major or Identified constituent, the physiological effects may not be associated solely with this agent or may be due to an action of this and other agents present in the commercial mixture.

TABLE 1
SUMMARY OF CLINICAL SYNDROMES OF SELECTEO CASES FROM THE LITERATURE (con.)

Chemical Compound/Product	Neurologic- CNS Effects: Clinical Effects	Neurologic- CNS Effects: Diagnostic/Pathologic Findings	Other Effects
N-HEXANE PRODUCTS (con.)			
Korobkin et al., 1975:			
Case report of 29-year-old male with 5-year history of contact cement inhalation. Several months prior to symptom onset, patient changed to brand containing n-hexane. Improvement followed avoidance of n-hexane exposure	Muscle weakness, paresthesia, muscle atrophy of distal extremities	Peripheral neuropathy, axonal abnormalities, decreased nerve conduction rates	
Paulson and Waylonis. 1976:			
Authors review situation in a small plant using n-hexane in which at least 8 of 50 employees (in 25-year period) developed mild neuropathy. Four patient summaries are presented.	Muscle weakness, hyporeflexia	Polyneuropathy	
Towfighi et al., 1976:			
Report of 2 cases exhibiting chronic glue sniffing behavior. Both patients initially used glues containing no n-hexane (pt. 1, 5 yr. hx., pt. 2, 10 yr. hx.) and experienced good health. Both changed to brand containing n-hexane with onset of symptoms appearing in 1-2 months.	Paresthesia, muscle weakness, atrophy of distal extremities, arefiexia	Neuropathy, neurogenic-atrophy, axonal swelling, decreased nerve conduction rate	
TOLUENE PRODUCTS			
Grabski, 1961:			
Author presents case of irreversible cerebellar degeneration following continuous pattern of toluene sniffing lasting several years.	Ataxia, intention tremor posterior column signs adiadochokinesis	Cerebellar degeneration	Hepatomegaly

TABLE 1
SUMMARY OF CLINICAL SYNDROMES OF SELECTED CASES FROM THE LITERATURE (con.)

Chemical Compound/Product	Neurologic - CNS Effects: Clinical Effects	Neurologic - CNS Effects: Diagnostic/Pathologic Findings	Other Effects
TOLUENE PRODUCTS (con.)			
Massangale et al., 1963:			
Summary of 27 children chronically habituated to inhalation of cement vapors. Toluene was major component of glue used. Two detailed case histories are presented.			Microscopic hematuria
Satean and Dodson, 1963:			
Summary of patient presenting with 10-year history of toluene inhalation who presented because of loss of consciousness. No systemic abnormalities were found.			
Knox and Nelson, 1966:			
This paper discusses the report and conclusion of Grabski, 1961.	Ataxia, nystagmus tremor, diffuse EEG, Babinski's reflex	Permanent encephalopathy, corticobulbar damage, diffuse cerebral atrophy, corticospinal damage	
O'Brien et al., 1971:			
Case history of 18-year-old male with 6-year history of glue sniffing. Presentation followed 6-hour sniffing of a liquid cleaner.			Jaundice, hepatocellular damage; anuria. hematuria, proteinuria
Taher et al., 1974:			
Two case histories are presented, one patient with a 3-year history of glue sniffing, with a 1-year history of toluene sniffing, other patient with 5-6 day history of sniffing paint (60.4% toluene)	Muscle weakness, flaccid quadriplegia, areflexia		Renal tubular acidosis

TABLE 1
SUMMARY OF CLINICAL SYNDROMES OF SELECTED CASES FROM THE LITERATURE (con.)

Chemical Compound/Product	Neurologic - CNS Effects: Clinical Effects	Neurologic - CNS Effects: Diagnostic/Pathologic Findings	Other Effects
TOLUENE PRODUCTS (con.)			
Kelly, 1975:			
Presentation of case history of 19-year-old female with 1-year history of paint sniffing. Toluene was common in all brands she sniffed.	Intention tremors, impossible tandem gait, ataxia	Cerebellar-dysfunction	
GLUE SNIFFING GENERAL			
Glaser and Massengale, 1962:			
An overview of glue sniffing among children. The authors note that in a 2-year period in Denver, 130 (average age 13) were arrested for glue sniffing. Six detailed case histories are presented.			
Merry Zachariadis, 1962:			
Case history of 20-year-old man presenting with an 18-month history of glue sniffing. Presentation was precipitated by the inhalation of 6 tubes of cement glue which resulted in a semi-comatose state.	Tetany		
Powars, 1965:			
Paper describes 5 adolescents (all with sickle cell disease) who developed hematologic disorders associated with glue sniffing.	Wallerian degeneration, neuronal death		Septicemia; Apiastic anemia, reticulocytopenia, hypoplasia. pancytopenia
GASOLINE PRODUCTS			
Easson, 1962:			
Two cases of gasoline inhalation in children (ages 11 and 14) are presented in which a degree of physical tolerance is indicated.	"Borderline EEG"		

TABLE 1
SUMMARY OF CLINICAL SYNDROMES OF SELECTED CASES FROM THE LITERATURE (con.)

Chemical Compound/Product	Neurologic - CNS Effects: Clinical Effects	Neurologic - CNS Effects: Diagnostic/Pathologic Findings	Other Effects
GASOLINE PRODUCTS (con)			
Tolan and Lingl, 1964:			
Two cases of adolescents with history of gasoline inhalation are presented.	"Model psychosis"		
Karani, 1966:			
A case report of a 20-year-old mechanic with a 3-year history of gasoline consumption and inhalation. Author attributes diagnosis to Triorthocresyl phosphate component of gasoline.	Muscle weakness, moderate-severe areflexia, bilateral foot drop, bilateral claw deformity, muscle atrophy, paresthesia	Peripheral neuritis, neurogenic muscular atrophy	
Law and Nelson, 1968:			
Report of a 41-year-old female presenting with 8-month history of leaded gasoline sniffing (3-4 hr/day) exhibiting a chronic psychosis.	Ataxia, tremor, psychotic behavior, recent memory impairment	Lead encephalopathy	Anemia
Carroll and Abel, 1973:			
Case report of chronic gasoline inhalation (6 years) in a 14.year-old male.	Choreiform movements, diffuse EEG delerium	Diffuse encephalopathy	Mild liver congestion
AEROSOL PRODUCTS			
Bass, 1970:			
The author discusses the incidence of sudden sniffing deaths (without plastic bag suffocation) in the 1960's. Details of 5 case histories are presented. In 4 of the 5 cases autopsies were performed which showed no anatomical cause of death. Death occurred after sniffing followed by some stressful situation, i.e., exercise.			

TABLE 1
SUMMARY OF CLINICAL SYNDROMES OF SELECTED CASES FROM THE LITERATURE (con.)

Chemical Compound/Product	Neurologic - CNS Effects: Clinical Effects	Neurologic - CNS Effects: Diagnostic/Pathologic Findings	0ther Effects
AEROSOL PRODUCTS (con.)			
Traffert, 1974:			
The author discusses sudden sniffing death problem and the mechanism of death.			Hypercapnia; sever cardiac arrhythmia, ventricular fibrillation
Wenzl et al., 1974:			
Discussion of 4 teenagers who sniffed PAM.			Acute renal tubular necrosis, proteinuria, uremia; azotemia
Kamm, 1975:			
Report of a 18-year-old male who inhaled Arid Extra Dry deodorant. Death followed immediately after inhalation.	Cerebral edema		Pulmonary edema, mild to moderate pulmonary vascular congestion; ventricular fibrillation
Poklis, 1975:			
Report of case history of adolescent death due to aerosol propellant inhalation.			Pulmonary and laryngeal edema at autopsy
Standefer, 1975:			
Case history of 13-year-old male who died following inhalation of fluorocarbons F11 and F12 in cooking spray.			Lung congestion; cardiac arrhythmia
Wilde, 1975:			
Discussion of inhalation of spray paints with particular reference to those which contain metals, i.e., zinc and copper.	Stepping gait		Systemic absorption of metal:
Carlton, 1976:			
Discussion of 12 cases of death due to fluorocarbon inhalation from 1971-1975 Postmortems am nonspecific, excitation precedes death.	Anesthetic		

TABLE 1
SUMMARY OF CLINICAL SYNDROMES OF SELECTED CASES FROM THE LITERATURE (con.)

Chemical Compound/Product	Neurologic - CNS Effects: Clinical Effects	Neurologic - CNS Effects: Diagnostic/Pathologic Findings	Other Effects
AEROSOL PRODUCTS Icon.)			
Crawford, 1976:			
Report of the death of en adolescent following inhalation of fluorocarbons.			Cardiac arrhythmia
LACQUER THINNER			
Prockop et al., 1974:			
Seven cases of severe peripheral neuropathy are reported as seen in 7 males (ages 17-22 years) with history of chronic inhalation of lacquer thinner. Syndrome progression was predominately motor.	Muscle weakness, hypalgesia, hypesthesia, decreased nerve conduction, acute denervation paralysis, paresthesia	"Huffer's" neuropathy. neurogenic muscular atrophy, corticobulbar neuropathy	Respiratory distress, diminished vital capacity
Oh and Kim, 1976:			
Summary of findings in case of 20-year-old male with 2-year history of "huffing" lacquer thinner.	Muscle weakness, hyperesthesia, moderate areflexia, decreased nerve conduction	Peripheral neuropathy, giant axonal swelling	
LIGHTER FLUID			
Ackerly and Gibson, 1984:			
Summary of 12 cases of lighter fluid inhalation among children in the San Antonio, Texas, area. Duration of involvement ranged from limited to continuously for 3 years.	Minimal EEG abnormality	Convulsive disorder	
CHLOROFORM			
Storms, 1973:			
Case report of a 10-year-old male who participated in a "chloroform party" in which large amounts of chloroform were inhaled.	Coma	Severe hepatic damage	

TABLE 1
SUMMARY OF CLINICAL SYNDROMES OF SELECTED CASES FROM THE LITERATURE (con)

Chemical Compound/Product	Neurologic - CNS Effects: Clinical Effects	Neurologic - CNS Effects: Diagnostic/Pathologic Findings	Other Effects
TRICHLOROETHYLENE			
Mitchell and Parson-Smith, 1969:			
Case description of 33-year-old male who worked as a metal degreaser in which ha lowered a basket containing metal into warm trichloroethylene.	Loss of taste, vertigo, analgesia in all divisions of RT. Trigeminal nerve	Neuropathy	
Seage and Burns, 1971:			
Report of male with history of cardiac disease who drank alcohol following inhalation of trichloroethylene.			Pulmonary edema
Hayden et al., 1976:			
The authors cite three sources of inhalation of cleaning fluids which contain trichloroethylene.	Vertigo, trigeminal analgesic, decreased visual field.	Neuropathy	Jaundice, centrilobular necrosis, hepatomegaly; anuria, hematuria, oliguria, proteinuria (tubular necrosis)
TRICHLOROETHANE			
Travers, 1974:			
Case report of an 16-year-old male seaman who collapsed on ship; 24 hr later death occurred. Evidence in his bunk indicated he had been sniffing the substance.	Cerebral edema		Hematuria; ventricular fibrillation, tachycardia, cardiac arrest
Guberan et al., 1976:			
Case report of a 20-year-old mechanic who inhaled trichloroethane in en episode which led to his death. Autopsy showed no anatomical cause of death.			Ventricular fibrillation

TABLE 1
SUMMARY OF CLINICAL SYNDROMES OF SELECTED CASES FROM THE LITERATURE (con.)

Chemical Compound/Product	Neurologic - CNS Effects: Clinical Effects	Neurologic - CNS Effects: Diagnostic/Pathologic Findings	Other Effects
BENZENE			
Vigliani and Saita, 1964: A review of the history of benzene exposure resulting in leukemia. Plus 6 case reports from personal observation in which all worked with benzene.			Epistaxis, hemocytoblastic leukemia; mucosanguineous diarrhea
Forni and Moreo, 1967: Case report of a 38-year-old female who worked for 22 years as a cable cleaner using solvents containing benzene.			Hyporegenenerative anemia, leukemia
Winek and Collom, 1971: Case report of 16-year-old male who died following inhalation of reagent grade benzene. Boy's head was found inside a plastic bag.	Cerebral edema		
Aksoy et al., 1972: Four case histories are reported in which shoemakers using benzene-containing adhesives developed acute leukemia.			Pancytopenia; apiastic anemia, acute myeloblastic leukemia, thrombocythemia
Aksoy et al., 1974: Two case reports of leukemia following exposure to benzene are discussed with particular reference to the familial factors in this case.			Acute lymphoblastic leukemia, acute myeloblastic leukemia
Hayden et al., 1976: The authors enumerate several sources of principally industrial exposure resulting in hematologic damage.			Erythroleukemia, pancytopenia, thrombocytopenia, myeloid metoplasia. apiastic anemia

Aerosols

Abuse of freon-pressurized aerosol products is common. (Not all aerosols contain freons and many contain solvents other than freon.) The great variety of clinical manifestations attributed to these products is not surprising because of the diversity of contents. The consistently recognized syndrome is sudden death associated with vigorous exertion immediately after inhaling freon. Myocardial sensitization to endogenous epinephrine with ventricular fibrillation is one accepted mechanism. A number of case reports and reviews of freon use appear in the current literature (Carlton, 1976; Crawford, 1976; Kamm, 1975; Poklis , 1975; Standefer, 1975; Treffert, 1974; Wenzl et al, 19'74; Wilde, 1975).

Chlorinated Hydrocarbons

Among the chlorinated hydrocarbon solvents there is a potential for injury of various organ systems especially neuropathy and liver and kidney injury. These substances also sensitize the myocardium to epinephrine-induced dysrhythmia.

SURVEY OF MEDICAL EFFECTS OF INHALANT ABUSE

During the 2 years of existence of the Houston Polydrug Abuse Research and Treatment Program, 22 patients among 241 admissions *were* identified as having sustained intense and long-term exposure to inhalants. Among these 22 patients, 8 patients were identified as primarily inhalant users with minimal and sporadic involvement with other drugs. The patients were admitted primarily for drug abuse sufficient to be significantly disruptive of their life style and not selected on medical criteria. This population provides an opportunity to assess the health status of heavy and long-term inhalant users.

All patients in this data base had been using inhalants up to and including the day prior to admission. Seven of the eight patients presented with an acute organic brain syndrome as the predominant finding on the day of admission. Several days were required for the acute organic brain syndrome to clear, and it is assumed that this represents the time required to clear accumulated residual lipophilic vapors from fat depots in the body.* Completion of any examination dependent on subjective data was difficult during the initial 2 to 3 days of admission because of the confusion, disorientation, and general lethargy manifested by the patients. Neurologic examinations during the initial stages of admission also are unreliable, particularly with regard to ataxia and dysmetria, characteristic findings in acute organic brain syndrome which clear after several days of inhalant-free living.

*Editor's note: Further work needs to be done to assess whether the amount persisting in tissues can cause these symptoms or whether this is a metabolic: process of regeneration or reorganization.

CASE ABSTRACTS

Patient #9238

The patient is an 18-year-old white male who presently is on probation. Drug history includes marihuana three to four times a week, methaqualone once a week for one month and spray paint inhalation for more than 5 years with use occasionally as much as 12 hours per day. The patient dropped out of school after the tenth grade and presently is living with his family. He had been employed intermittently. Psychiatric diagnosis: Acute organic brain syndrome. The patient was released to his parents against medical advice after 5 days in the inpatient treatment program. Past history reveals a suicide attempt with drugs.

Patient #9258

The patient is a 23-year-old white female with a 10-year history of drug abuse who considers herself to be physically dependent on Plasticoat aerosol spray. Over the past 2 years she has used Plasticoat, plastic enamels, and toluene from paint thinner. She estimates daily use up to 5 hours. The patient completed the twelfth grade. She has made two suicide attempts with drugs. The patient is married but separated from her husband whose location is unknown. The patient's parents are divorced and the patient has lived in at least five households since the divorce. Both parents are alcoholics. The patient has had approximately 30 arrests with charges currently pending for assaulting a police officer. In 1969 she was hospitalized for 5-1/2 months at the Austin State Hospital. Admission diagnosis: Acute organic brain syndrome. The patient was discharged after 16 days on an inpatient program. Her typical pattern of abuse was to inhale the toluene-based acrylic spray paint for up to 5 hours a day. She managed to remain almost continuously intoxicated during this period by saturating a cloth with the spray paint, placing the cloth in her mouth, and inhaling the vapors through her mouth. Routine physical examination revealed no neurological deficit in either motor sensdry function; however, the patient complained of continual muscle pain and loss of sensation distally in her extremities. With the exception of a slightly elevated alkaline phosphatase, her laboratory values were all within normal limits. A routine toxicology screen failed to detect the presence of any common 'drugs of abuse in her blood or urine. Electromyography and nerve conduction tests failed to indicate evidence of

either peripheral neuropathy or myoneural transmission defects; however, borderline myopathic changes consistent with a low-grade myopathy were observed. A deltoid muscle biopsy was performed and microscopic examination of the muscle specimen indicated the presence of minor pathological changes including isolated rare atrophic skeletal muscle cells with increased sarcolemma cell activity. In general, however, there was no evidence of gross changes that would account for the patient's symptomatology.

Patient #9279

The patient is a 15-year-old Mexican-American male who has used clear plastic acrylic sprays, Texas Shoeshine, and other aerosols three times a week for approximately 1 year. The patient completed the ninth grade and is not in school presently. There were several suspensions for fighting and he has been arrested more than ten times having spent 7 months in Gatesville Prison for automobile theft. The patient's father is an alcoholic who is frequently drunk and belligerent. The patient has never been employed. Psychiatric diagnosis: Acute organic brain syndrome. The patient remained 13 days in the inpatient treatment program.

Patient #9281

The patient is a 21-year-old white male who has been using inhalants for 4 years and now considers himself to be psychologically dependent. Substances used include Texas Shoeshine, clear acrylic spray, and toluene The patient completed the twelfth grade and currently is on probation by both the county and the state. There have been six arrests with a total of 67 days in Harris County jail. The patient entered the program as an alternative to incarceration. Family background reveals parents divorced and the parents state that they have "given up on him." The patient has had four jobs with 4 months being the longest at any one job. He states his present occupation is "getting high." There have been two previous psychiatric admissions with a tentative diagnosis of paranoid schizophrenia. Psychiatric diagnosis: Acute organic brain syndrome. Duration of hospital stay was 17 days.

Patient #9285

The patient is a 13-year-old Mexican-American male who has been using gold spray paint and Texas Shoeshine every other day for approximately 4 months. The patient was abandoned at birth and reared in foster

homes. Presently he is in the seventh grade and has been suspended from school for disciplinary problems and truancy. There have been two drug-related arrests. Psychiatric diagnosis: Adolescent adjustment reaction and depression neurosis. The patient remained in the inpatient treatment program for 22 days.

Patient #9289

The patient is a 2l-year-old Mexican-American male with a history of using glue, paint thinner, and Texas Shoeshine over the past 11 years, three or more times daily. The patient states that he is dependent upon these substances. The patient completed the seventh grade of school and was suspended and has not. returned to school. Presently he is unemployed but has been employed intermittently over the past 4 years. The patient has had nine juvenile arrests and four adult arrests with no charges pending currently. Parents are separated. Psychiatric diagnosis: Acute organic brain syndrome with mild retardation. The patient remained in the treatment program for 16 days.

Patient #9308

The patient is a 16-year-old white male who has been using paint thinner and clear acrylic plastic sprays on a daily basis for 2 years. The patient completed the ninth grade and was suspended for poor attendance, inattentiveness, and truancy. The patient has held one job for 14 months and has no arrest record. Both natural parents are dead. Presently being reared by a stepmother and maternal grandparents. Psychiatric diagnosis: Organic brain syndrome. Patient remained in the program 14 days.

Patient #9312

The patient is a 17-year-old white male who has been using clear acrylic paints several times a week for 3 years. The patient completed the eleventh grade and dropped out of school. He has been arrested twice for driving while under the influence of drugs and currently has charges pending for the possession of marihuana. The patient has been in jail on three different occasions. Both parents are alive. Mother is an alcoholic who has had psychiatric hospitalization twice. Father is an epileptic with asthma. Psychiatric diagnosis: Acute organic brain syndrome. Patient remained in the treatment program 14 days.

DATA SUMMARY

Table 2 summarizes the history of inhalant use for these patients. Table 3 presents positive responses to questions in the review of systems for six of these primary inhalant-using patients. (Case #9238 was excluded becausce of other drug involvement; data for case #9279 are missing.) Their responses are compared with those of 95 non-inhalant polydrug abuse patients admitted to the Houston Polydrug Abuse Research and Treatment Program. Serum chemistries included: total protein, albumen, calcium, cholesterol, glucose, blood urea nitrogen, uric acid, creatinine, total bilirubin, alkaline, phosphatase, lactic dehydrogenase, glutamic-oxaloacetic transaminase, and glutamic-pyruvic transaminase. These were found to be within normal limits, Other admission evaluation included physical examination, EKG, chest X-ray, complete blood count, and urinalysis. None of these procedures yielded clinically significant findings.

DISCUSSION

The clinical assessment of the eight inhalant-abusing patients on whom data are presented was not designed prospectively specifically for evaluation of inhalant users, but was the routine clinical assessment performed on all Polydrug patients. The data illustrate that no abnormalities of clinical significance were detected by the approaches used for medical assessment. The only exception is the acute organic brain syndrome which was manifest characteristically by a vast majority of inhalant-using patients on their admission to the unit. This was manifest by varying degrees of ataxia, lethargy, irritability, confusion, and in some cases disorientation and impaired short-term memory. The acute organic brain syndrome characteristically disappeared in a time frame consistent with the metabolism and/or excretion of accumulated lipid soluble psychoactive volatiles.

These data are remarkable for the absence of abnormalities. In this population selected for heavy and prolonged inhalant use, there was no evidence of neuropathies, liver injury, kidney injury, anatomical lung changes, or hematopoietic abnormalities. The opinion that frequent and prolonged inhalant use does not commonly result in significant tissue injury is supported by this investigation. These data do not address the issue of more subtle abnormalities detectable by neuropsychological testing and their etiology. Neither do they address the problem of delayed increase in incidence of neoplastic disease requiring 10 to 30 years to be manifest. They also comprise a small sample and may not be very representative of the inhalant pollulation.

MEDICAL EVALUATION OF INHALANT USERS

Medical evaluation of inhalant users may have to be performed in several stages or repeated several days after the patients have

TABLE 2

INHALANT USE HISTORY OF SELECTED CASES*

Case No.	Age, Ethnicity and Sex	Substance	Duration	Frequency
9238	18 WM	Spray paint	>5 yr	Daily up to 12 hr
9258	23 WF	Acrylic spray Enamel spray Toluene	2 yr	Daily X3 up to 5 hr
9279	15 M-AM	Acrylic spray Texas Shoe Shine	1 yr	Weekly X3
9291	21 WM	Acrylic spray Lacquer Toluene	4 yr	Daily X3
9285	13 M-AM	Gold spray paint Texas Shoe Shine	4 mo	Weekly X 3-4
9289	21 M-AM	Glue Paint thinner Texas Shoe Shine	11 yr	Daily X3+
9308	16WM	Acrylic spray Paint thinner	2 yr	Daily
9312	17 WM	Acrylic spray	3 yr	Weekly

*Age, ethnicity, sex, substances used, duration of use, and frequency of use for eight patients (selected from 241 polydrug admissions) for primary solvent abuse without significant simultaneous abuse of other substances.

WF = White female.
WM = White female.
M-AM = Mexican-American male.

TABLE 3

REVIEW OF SYSTEMS OF SELECTED CASES*

	9258	9281	9285	9289	9308	9312	No. Positive	% Positive	95 Drug abuse admissions, % positive
Ear disease									20
Nose, sinus, throat	+				+		2	33	49
Fainting spells									27
Loss consciousness									32
Convulsions									17
Paralysis									5
Dizziness	+						1	16	63
Frequent severe headaches	+	+		+	+		4	66	66
Depression, anxiety	+	+		+			3	50	76
Difficulty concentrating		+		+			2	33	46
Memory problems		+		+			2	33	69
Enlarged glands									16
Skin disease									10
Chronic or frequent cough	+	+		+	+		4	66	29
Chest pain or angina	+	+			+		3	50	29
Cough blood	+			+	+		3	50	20
Night sweats					+		1	16	37
Shortness of breath	+	+					2	33	55
Palpitations, heart fluttering									28
Swelling hands or feet									27
Back, arm, or leg problems									23
Varicose veins									8
Extreme tiredness or weakness	+	+		+				50	57
Kidney disease									22
Bladder disease									4
Urine albumin, sugar									2
Urine pus or blood									4
Difficulty urinating									19
Abnormal thirst		+				+	2	33	27
Stomach trouble, ulcer				+			1	16	38
Indigestion		+		+			2	33	42
Appendicitis									15
Liver-gall bladder disease									5
Colitis or bowel disease									7
Hemorrhoids-rectal bleeding									18
Constipation or diarrhea		+							42

*Review of systems on six primary solvent abuse patients showing number and percent of positive responses; percent of positive responses on 95 drug abuse patients not primarily solvent users (Case 9238 was excluded because of other drug involvement; data for case 9279 are missing).

been free of inhalant use. This is necessary in order to differentiate effects due to the influence of volatile substances in the body in contrast with residual effects present after the substances have been cleared from the body. Aspects of the examination which require responsiveness from the patient or subjective assessment may vary substantially from the first day of admission to a drug-free program as compared with similar assessment after 3 to 4 days.

Clinical Assessment

Chief Complaints

The chief complaint should review in brief form the principle immediate health concerns of the patient along with a statement of the duration of each health concern. For example, a usual complaint would be headache. A brief simple statement should indicate the location, the quality, the frequency, and duration of headaches experienced by the patient. Other chief complaints may be dizziness, loss of memory, inability to think, cough, easy bruising or easy bleeding, abdominal pains, menstrual disorders, urinary pain, muscle cramps, weakness in extremities, numbness or tingling in the extremities, or spotty paralysis. These are examples of typical chief complaints and not an exhaustive enumeration. Each statement of a chief complaint should give the location, the duration, the frequency, and the quality of the health concern involved.

A patient experiencing an acute organic brain syndrome secondary to the immediate effects of inhaled substances may not have a chief complaint upon his admission to a treating program. Several days may be required before the confusion clears.

Present Illness

The present illness consists of a careful, detailed chronological development of circumstances leading to the illness enumerated in the present illness. In the case of inhalant users, the present illness should include a statement as to first involvement with inhalants, the types of inhalants used and the manner in which they were used; for example, head in a plastic bag, inhaled through a saturated cloth, inhalation from a rigid container. A description of the present illness may well be developed from exploring with the patient the most recent time that he felt himself to be normal or well. The time of onset of all symptoms should be recorded and the chronological development of symptoms explored. The present illness should include detailed description of therapeutic intervention undertaken during the course of the present illness. This should include doctors or other health care persons visited and nature of therapy undertaken, particularly the use of prescription drugs. Attempts at self-treatment should be explored and enumerated, especially with reference to use of

over-the-counter drugs or use of other home remedies. The present illness should consist of the patient's description of the chronological development of his current clinical status. Examiner should avoid extensive probing in a manner such as to be suggestive of manifestations which the observer injects into the patient's account of his illness. When a patient complains of such symptoms as chills, fever, headache, gastrointestinal disturbances, cough, regional pain, or any other general or local symptoms, then these should be documented with respect to their time of first onset and changes in the quality and duration of these symptoms as the present illness has progressed. The relationship of any complaint to the pattern of use of inhalants should be documented since the use of inhalants is intermittent and cyclic. Some disabilities may occur only while under the influence of volatile substances while others persist through the non-use period.

Review of Systems

In order to determine the presence or absence of specific significant manifestations, a review of systems as detailed in any standard text on internal medicine should be documented.

Past Medical History

Inquiry into past medical history should include documentation of physician visits wherever possible, with identification of the name and address of the physician to facilitate obtaining past records. Any hospitalization should be identified as to date, duration, principle reason for admission, and name of the attending physicians so as to facilitate obtaining hospital records. Consent forms for obtaining past medical records should be signed by the patient at this time. Inquiry should be made as to childhood diseases, acute or chronic infections with description as to nature, duration, treatment, and complications. Any injuries sustained should be documented, described, and resulting disabilities enumerated.

Employment History

Any jobs held by the patient should be documented as to time the job began, duration of employment, nature of work with special regard to potential for exposure to occupationally related toxic substances, especially solvents and metals. Reasons for discontinuing each job should be documented.

Personal and Social History

A complete social and personal history should be documented.

General

At this point in the clinical assessment, there is a 70 to 80 percent chance of identifying probable areas of disability associated with inhalant use. The remainder of' the examination should be guided by the findings evoked in the preceding assessment. The remainder of the examination is predominantly confirmatory although an additional 20 percent of existing disability may remain to be discovered by subsequent procedures.

Physical Examination

Physical examination must be performed by meticulous, consistent adherence to predetermined protocol. The general physical examination may lead to areas of special concern requiring more elaborate diagnostic procedures to investigate variation from normal. Physical examinations must be performed in a compassionate and considerate manner; a cursory lo-minute physical examination is totally unsatisfactory. Although reasonable consideration of the patient's modesty must be observed, a complete physical examination cannot be performed on a partially clothed patient. The physical examination should be quantitative not qualitative; for example, descent of the liver edge below the costal margin should be stated in centimeters not finger breadths. Identified masses should be measured rather than described in qualitative terms. Pupillary size should be measured in millimeters. Data recovered from physical examination should be objective and stated without interpretation. For example, the identification of the left upper quadrant mass should be indicated as to size, consistency, mobility, and not necessarily construed as splenomegaly, since it may well be another abnormal intra-abdominal mass. Assessment of liver size must not be performed exclusively on the basis of palpation of the liver edge below the costal margin since a patient with chronic emphysema may have enlarged chest capacity, depressed diaphragm, and abnormal liver position rather than an actually increased liver size. The physical examination, however, must not be rigid to the extent of exclusion of diversion for more comprehensive assessment of particular findings. The alert physician will pursue, in depth, abnormalities presented in the routine physical examination. For example, discovery of a dusky or bluish discoloration of the skin and nails may lead to a false assumption of representing hypoxemia secondary to lung pathology, whereas in fact the discoloration may be secondary to methemoglobinemia induced by inhalation of aromatic substances in patients with a glucose-6-phosphate dehydrogenase deficiency which impairs ability to correct methemoglobinemia. The discovery of an abnormal heart sound should lead to examination at rest, after exercise, and in varying positions in order to complete its assessment.

Before the performance of hands-on examinations, basic data on the patient should be obtained by observation of his activity.

The patient is asked to stand, to walk toward and away from the observer and to sit on the edge of the examining table. This permits recognition of characteristic abnormalities in body posture, gait, associated movement, ataxia, gross defects in motor neurologic control, gross limitations of motion as well as assessment of the patient's mood and cooperativeness,. and assists in development of initial rapport with the physician. A hasty, inconsiderate attitude on the part of the physician will lead to an irritable, uncooperative patient preventing the performance of an effective, maximally informative physical examination.

Neurological examination. The neurological examination of the inhalant-abusing patient is probably the most difficult part of the physical examination. If performed in a cursory manner, many abnormalities will be missed. Because of the frequency with which subtle neurological abnormalities are associated with the commonly inhaled substances, neurologic assessment must be comprehensive. Suitable outlines for further neurologic examination occur in most text books of neurology. The neurologic assessment of these patients is addressed in the following chapter of this volume.

Genetic defects. Certain preexisting genetic defects are known to influence to toxic substances, many of which appear among the volatiles to which inhalant abusers are exposed. The best example is the occurrence of a glucose-6-phosphate dehydrogenase deficiency, especially common among the non-Caucasian races. The presence of this deficiency increases the sensitivity to lead poisoning, increases sensitivity to intravascular hemolysis induced by aromatic solvents in drugs and increases sensitivity to methemoglobinemia induced by a number of toxic substances. Other genetic abnormalities influencing response to toxic substances include the hemoglobinopathies. Presence of sickle cell and thalassemia hemoglobin may significantly influence response to commonly inhaled vapors (Powars, 1965) The area of genetic predisposition to toxicologic injury is still in an investigational stage and future research is sure to yield additional examples.

Extended clinical examinations. 'The medical workup of inhalant abusing patients should include chest X-ray. EKG. EEG, and EMG. A screening electromyographic assessment, particularly in the lower extremities. should be an essential component of all clinical assessment of inhalant-abusing patients. It is equally as important to document normal nerve conduction and normal EMG as it is to document an abnormal result. Data are not sufficient at this time to permit a logical decision upon which to base the need for electromyographic assessment. If in the course of physical examination obvious abnormalities in motor function, deep tendon reflexes, or peripheral sensory perception are identified, there is no doubt that an EMG should follow. However, accumulated clinical experience is not yet sufficient to determine whether electromyographic abnormalities might be present in the absence of clinical detectable abnormalities.

Laboratory examinations. Clinical laboratory examination of the inhalant-abusing patient should include a CBC, serum iron, iron binding capacity, and a bone marrow in the event peripheral hematologic abnormalities are identified A routine urinalysis is required and this examination should include a careful microscopic assessment of sediment performed within a few hours of collection in order to assure reliable identification of formed elements in the sediment. Serum chemistry should include the usual SMA 12 battery on serum collected while the patient is in the fasting state, and minimally should include a total protein, albumin, cholesterol, glucose, blood urea nitrogen (BUN), uric acid, creatinine, bilirubin, alkaline phosphatase, lactic dehydrogenase (LDH), glutamic-oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), and should be supplemented with creatinine phosphokinase. A glucose-6-phosphate dehydrogenase activity of red blood cells should be determined on non-Caucasian patients minimally, Laboratory assessment also is valuable to determine the chemical nature of the substances the patient has been using. In order to achieve this, exhaled air, blood, or urine is suitable for examination of particular substances. Almost all commonly used inhalants can be identified by one or more of these specimens if they are collected within 24 hours of the last inhaling episode, In some instances volatiles may be identified as long as a week or more after their last use.

CONCLUSIONS

The literature documents numerous episodes of individual and/or sporadic outbreaks of significant injury associated with the abuse of inhalant substances. Clinical assessment of chronic inhalant users not presenting with primary medical complaints has revealed remarkably little in the way of objectively documentable impairment. The overall health significance of inhalant abuse can be assessed only by elaborate and detailed examination of a cross section of long-term inhalant users. Only this type of research will determine whether inhalant abuse constitutes a general hazard to health as opposed to sporadic outbreaks of significant injury secondary to an unusually toxic component in a particular product .

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Chapter 5

SPECIFIC NEUROLOGICAL EVALUATION OF INHALANT ABUSERS: CLINICAL AND LABORATORY

Leon Prockop

INTRODUCTION

Volatile hydrocarbons are inhaled in the abuse situation in order to produce an altered mental state, which may be an elevation of mood (euphoria) or may be an escape from depression, anxiety, or other unpleasant or distressing emotional states. In any case, an alteration of cerebral or central nervous system (CNS) function is desired. In addition to the positive effect which the abuser seeks, a variety of other effects may also occur. These include: dizziness; malaise; tearing, conjunctival injection, diplopia, or other visual symptoms; altered hearing; rhinorrhea , altered smell, and other nasal symptoms; symptoms referable to the oral mucosa and facial skin; gastrointestinal symptoms such as nausea and vomiting; and cardiopulmonary symptoms such as tachycardia and cough. In most instances these symptoms, whether desirable or undesirable, are transient in nature. The CNS effects, in particular, are usually a temporary alteration of CNS function. However, as is the case with virtually all exogenous agents which alter general systems and/or CNS function temporarily, permanent functional alteration may occur. This leads to a pathophysiological or diseased state of CNS function. In fact, death can be a direct result of solvent inhalation (Alha et al., 1973; Press and Done, 1976). Although adverse effects to other organ systems have been reported rarely, e.g., cardiac arrhythmia (Reinhardt et al., 1971) and renal tubular acidosis

(Taher et al., 1974), permanent adverse effects to both the central and peripheral nervous systems after inhalation of volatile hydrocarbons is not uncommon. This occurs in both the abuse situation (Shirabe et al., 1974; Korobkin et al., 1975; Prockop et al., 1974; Grabski, 1961; Oh and Kim, 1976) and after "normal use," such as in the occupational setting (Billmaier et al., 1974; Prockop, 1977; Mendell et al., 1974; Davenport et al., 1976). Other sections of this monograph provide reference to a variety of these toxic effects to the nervous system including "glue sniffer's neuropathy" (Shirabe et al. , 1974; Korobkin et al., 1975)) "huffer's neuropathy" (Prockop et al., 1974; Oh and Kim, 1976; Means et al., 1976), optic nerve damage (Prockop, 1977; Benton et al. , 1953; Berg, 1971), cerebellar involvement (Grabski, 1961; Prockop, 1977), cranial nerve damage (Prockop, 1977; Feldman et al., 1970), and encephalopathy (Prockop, 1977; Knox and Nelson, 1966). Furthermore, data derived from animal experiments involving inhalant exposure are beginning to accumulate (Schaumberg and Spencer, 1976; Saida et al., 1976). They indicate that a CNS dysfunction, measured by a variety of parameters, can be documented. Some of these experimental data were reported at the First International Symposium on the Voluntary Inhalation of Industrial Solvents held in Mexico City, June, 1976.

NEUROLOGICAL EVALUATION

General Comments

Because inhalant abuse may lead to temporary and/or permanent alteration of the function of both the central and peripheral nervous systems, special attention must be paid to the neurological evaluation of inhalant abusers. In fact, proper neurological evaluation may disclose more evidence of disease than the remainder of the medical evaluation.* The neurological dysfunction suffered by the inhalant abuser may lead to further psychiatric problems as well as medical, social, economic, and legal problems. For example, an individual suffering from a peripheral neuropathy secondary to inhalant abuse may become depressed because of the physical disabilities and the inability to obtain employment because of this disability. Therefore, further inhalant abuse as well as other drug abuse may occur.

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* A footnote is used here to emphasize a factor common in the medical and/or psychiatric evaluation of inhalant abusers and others in contact with potential toxins, whether drugs or otherwise. Organically caused neurological deficits such as ataxia and weakness are often ascribed to sloppiness, laziness, or hysteria. Signs of dementia or an organic mental syndrome are often ascribed to a lack of cooperation or other psychological factors or to psychomotor retardiation, i.e., a heredito-familial cause for poor performance on mental status testing.

Neurological Physical Examination

The neurological evaluation form attached as an appendix to this chapter is useful to document the neurological status of the inhalant abuser. In some cases an initial evaluation should be performed followed by serial evaluation over the course of time. Futhermore, the dysfunction documented on this form may lead the clinician to obtain laboratory and other diagnostic studies which may further quantitate and delineate the dysfunction suffered. It should be stated that this neurological evaluation should follow the general medical evaluation as described in the preceding section. The neurological history and examination forms are self-explanatory. At their conclusion an assessment and plan should be formulated by the clinician. The assessment should consist of a summary of the history and the positive neurological findings as well as a diagnostic formulation followed by a treatment and/or management plan which would include any further diagnostic tests indicated.

Diagnostic Assessment

In the diagnostic formulation, specific consideration must be given to the disease categories of: peripheral neuropathy , cranial nerve neuropathy, cerebellar degeneration, and cerebral degeneration or encephalopathy . Because these disease categories may have etiologies other than that of inhalant abuse, specific consideration must be given to other pathophysiological mechanisms. It is not possible to detail all of these sometimes rare diseases in this section. The reader is referred to standard neurological textbooks (Merritt, 1973; Gilroy and Meyer, 1975; Walton, 197'7). Some common entities which might be seen in the inhalant abuser and might be a causative or contributory factor to their neurological dysfunction, should be enumerated. When peripheral neuropathy is documented clinically, special consideration is given to the possibility of diabetes mellitus and alcohol abuse with nutritional deprivation as etiological factors. If an inhalant abuser is weak without clearly demonstrable signs of peripheral neuropathy, consideration must be given to primary muscle disease or disease of the myoneural junction. Therefore. consideration must be given to polymyositis, myasthenia gravis, muscular dystrophy, and periodic paralysis. Special laboratory tests may be required to evaluate these possibilities (e.g., a Tensilon Test). When a cerebellar dysfunction is documented, the toxic effects of a variety of heredito-familial diseases must be considered. When encephalopathy is documented, a variety of considerations must be made. Most prominent is the potential effect of hypoxia or anoxia on the brain. During the course of inhalant abuse the individual participating in the activity is inhaling a gaseous mixture low in oxygen, particularly if the abuser uses a paper or plastic bag during the course of the procedure (Alha et al., 1973, Press and Done, 1976) . Since death from asphyxia can occur if the abuser inserts his head in a plastic bag and then becomes unconscious

during the course of the inhalation, the possibility of less catastrophic, but nonetheless serious, brain damage due to oxygen deprivation must be considered. Practically speaking, it may be impossible to separate the effects of potential hypoxia from the direct toxic effects of the volatile solvents being used by the inhalant abuser. When a multifocal neurological deficit is documented, e.g., multiple cranial nerve deficits including optic nerve damage, the possibility of a demyelinating disorder such as multiple sclerosis must be considered.

The possibility that the inhalant abuser is suffering the effects of more than one toxin within a mixture being inhaled must be considered. For example, leaded gasoline may be inhaled. Lead itself causes peripheral neuropathy and also encephalopathy , alone or together. Appropriate laboratory analysis for such neurotoxins must be conducted.

ANCILLARY TESTS FOR FURTHER NEUROLOGIC EVALUATION

It is not within the scope of this section to discuss in detail the neurologically pertinent laboratory diagnostic tests which may be indicated in a particular patient. However, they will be discussed briefly with reference to relevant, more detailed publications (De Jong, 1967; Toole, 1969; Kiloh and Osselton, 1976; Ramsey, 1977; Lenmon and Pitchie, 1973).

Mental Status Evaluation

The mental status examination frequently requires significantly more detail than called for in the neurological examination form. Richard L. Strub and F. William Black, in their book, The Mental Status Examination in Neurology, provide a recent and relevant approach to this problem. In addition to the aspects of mental status outlined in the attached examination form, they stress the following: constructional ability. higher cognitive function, and related cortical function. Criteria for further neuropsychological evaluation including speech and language evaluation and psychiatric consultation are delineated. An appendix to the book outlines the standard psychological tests available for the assessment of: intelligence; memory; constructional ability and perception; aphasia batteries; auditory perceptions; other tests of cognitive dysfunction; achievement; and personality. A second appendix provides a "Composite Mental Status Examination" arranged as a form which could be completed by any clinician in his evaluation of an inhalant abuser.

Several other laboratory techniques for quantitation of neurological dysfunction will be pertinent to the inhalant abuser in selected circumstances as indicated by the assessment and plan formulated. These include: electroencephalography (EEG); electromyography (EMG); nerve conduction velocity studies (NCV); lumbar puncture; and computerized axial tomography (CAT or EMI scan).

Other neurologically oriented diagnostic procedures such as plain X-ray studies, angiography, pneumoencephlography, myelography, echoencephalography , and isotope brain scan will be of little use in the evaluation of the inhalant abuser.

Electroencephalography

The EEG records the amplified voltage difference between two points on the head. The brain normally has continuous electrical activity which can be analyzed by EEG. In the case of the inhalant abuser it can be used to determine whether there is a local or generalized slowing or disorganization of electrical activity or whether there are local or generalized spontaneous epleptiform discharges (Kiloh and Osselton, 1972).

Electromyography and Nerve Conduction Velocity Studies

The EMG is the amplification of electrical discharges from the muscles. A needle electrode is inserted into the muscle; abnormal muscle discharges at rest and during activity can thus best be detected by audio and visual display. This technique is useful for the determination of diseases of the muscles, nerves, and anterior horn cells, all of which may be impaired secondary to inhalant abuse. NCV is determined by measuring. the length of time it takes a stimulus applied at one point on a nerve to travel to another point on the same nerve. This technique is particularly useful in the evaluation of the peripheral neuropathy which may occur as a result of inhalant abuse (Lenmon anti Pitchie, 1973).

Lumbar Puncture

The lumbar puncture performed in the inhalant abuser may indicate an increased pressure which may be related to cerebral edema or an elevated protein content which may indicate CNS degeneration. Various other special analyses may be performed on the cerebrospinal fluid obtained at the lumbar puncture (Toole, 1969).

Computerized Axial Tomography

The CAT involves small-dose X-ray penetration of the head in multiple directions with quantitations of the uptake. Through a process of triangulation with beams from other angles, the exact density or hindrance of the X-ray beam for each point is obtained. By computer, an entire cross section of the brain can thus be mapped with clear differentiation of density in all areas. This technique will show differences in density between skin, skull, dura, spinal fluid, gray matter, white matter, and vrntricles, and is useful in detecting tumors, infarcts, hemorrhages, and ventricular abnormalities (Ramsey, 1977). In the inhalant

abuser, particular attention would be placed upon the ventricular size and the size of the subarachnoid space over the cortical mantle in an attempt to assess whether any disturbances in the mental status as determined clinically can be correlated to cerebral atrophy.

Nerve Biopsy

Under special circumstances muscle and peripheral nerve biopsy may be performed. Nerve biopsy, in particular, may provide valuable information to document the etiology of the peripheral neuropathy which had been disagnosed clinically. The characteristics of peripheral neuropathy caused by volatile hydrocarbons has been well documented by light and electron microscopic studies (Shirabe et al. 1974; Oh and Kim, 1976; Mendell et al., 1976; Means et al., 1976; Saida et al., 1976; Kaeser , 1970). Therefore, this study would not be performed routinely but only if it is essential to verify a clinical diagnosis or as part of an investigative effort of potential benefit to the patient involved. In that case the studies should be performed only at a medical facility equipped to use the proper techniques and appropriate processing and analysis of biopsy material obtained (Dyck and Lofgren, 1968).

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APPENDIX
NEUROLOGICAL EVALUATION FORM

NEUROLOGICAL HISTORY

A. Record onset (sudden, gradual, insidious) and course (acute, subacute, chronic, with exacerbation and remissions) of problem(s) and/or symptoms(s) and whether they are focal or generalized. This should be recorded for:

Pain

Weakness
(including swallowing and breathing)

Stiffness
(or other muscle complaints)

Numbness
(or other sensory symptoms)

Syncope or
Seizures

Visual Change

Hearing Change

Memory Loss

Personality Change

Incoordination
(including ataxia)

Abnormal movements
(e.g., tremor)

Automatic functions
(bowel, bladder, sexual)

B. Record significant elements of systems review (ROS)

C. Record significant past medical history, especially, surgery; trauma; medications; systemic illness, e.g., diabetes mellitus; hypertension; mental illness.

D. Record significant history of heredito-familial illness

E. Record significant social history, especially. dietary habits ; alcohol; tobacco and drug use; education; environmental emotional stresses; marital and family status.

F. Record vocational and avocational history, including. exposure to toxins.

NEUROLOGICAL EXAMINATION

(Items to be completed always are in capital letters. Items in small letters are done when appropriate. Some items may be completed as N1=Normal or Abn=Abnormal; others must be defined.)

A. MENTAL STATE

STATE OF CONSCIOUSNESS
ORIENTATION
ATTENTION
BEHAVIOR
INTELLECTUAL PERFORMANCE (Rate as excellent, good, fair, poor, absent)

MEMORY — PAST — FACTUAL FUND

RECENT

CALCULATIONS (e.g. SERIAL 7'S) — DIGITAL RECALL (5 forward, 4 backward)

AFFECT AND MOOD: (Circle appropriate term and/or add other designations)

APPROPRIATE INAPPROPRIATE DEPRESSED EUPHORIC FLAT

THOUGHT CONTENT : SPONTANEOUS THOUGHT - YES NO

SPEAKS IN APPROPRIATE SEQUENTIAL SENTENCES -

YES NO OTHER (e.g, paranoid, incoherent, evasive, tangential, etc.)-

LANGUAGE (Including aphasia)-

B. CRANIAL NERVES

I. OLFACTORY (Record odors used)

II. OPTIC

GROSS VISUAL ACUITY - NORMAI, ABNORMAI,

RE

best visual acuity

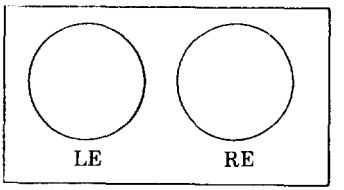
LE:

FUNDUS EXAM

DISC : A/V Ratio =

VESSELS :

CONFRONTATION FIELDS



III, IV, VI. OCULOMOTOR, 'TROCHLEAR, ABDUCENS

PALPEBRAL FISSURES ORBIT lids, conjunctiva, iris, cornea

eye position at rest (diagram if abnormal)

EYE MOVEMENTS - INDIVIDUAL & CONJUGATE NYSTAGMUS optokinetic

PUPILS SIZE (mm) & SHAPE DIRECT CONSENSUAL, ACCOMMODATION

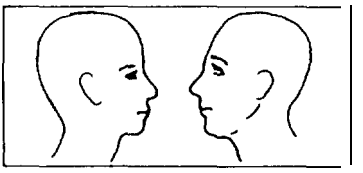
R

L

V. TRIGEMINAL

MOTOR (temporalis L R *masseters)*

CORNEAL



SENSORY (diagram if abnormal)

VII. FACIAL

MOTOR (VOLITIONAL, EMOTIONAL)

taste (note test materials) hyperacusis

lacrimation

VIII. ACOUSTIC

HEARING - AD AS

LATERALIZATION (WEBER)

AIR/BONE CONDUCTION (RINNE) RIGHT (B = A)
LEFT (B = A)

calories - cold water
warm water

IX., X. GLOSSOPHARYNGEAL, VAGUS

GAG REFLEX SWALLOWING PHONATION

XI. SPINAL ACCESSORY

XII. HYPOGLOSSAL

C. REFLEXES: (0 = absent; 1 = trace; 2 = active;
3 = very active; 4 = unsustained clonus;
5 = sustained clonus)

R L R L R L R L

D. MOTOR :

GAIT - POSTURE -

COORDINATION - left right

finger to nose
heel to shin
rapid alternating movement

INVOLUNTARY MOVEMENTS -
(tremor, chorea, athetosis , ballism)

MUSCLE EVALUATION - STRENGTH (100% = normal; 75% = full range of motion (ROM) vs. some resistance; 50% = full ROM vs. gravity; 25% = full ROM without gravity; 10% = contraction; 0 = no contraction, no movement)

UPPER EXTREMITIES : LEFT RIGHT

PROXIMAL

DISTAL

LOWER EXTREMITIES :

PROXIMAL

DISTAL,

MUSCLE TONE:
(whether normal; decreased, e.g., flaccid; increased, e.g., spasticity)

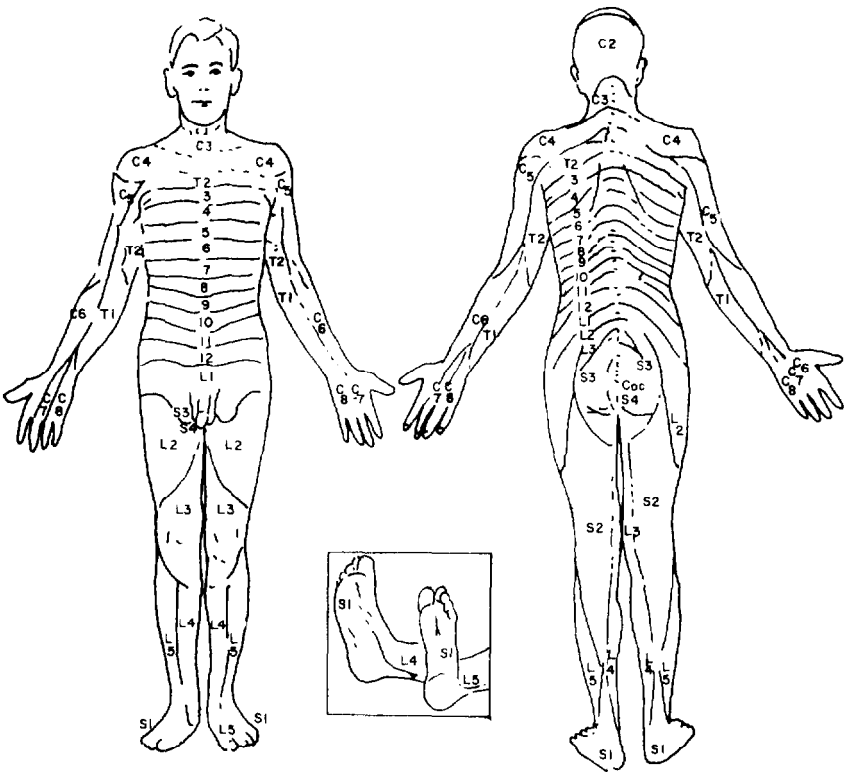
FASCICULATION:
(whether present and where)

ATROPHY:
(whether present and where)

MYONTONIA

TENDERNESS & INDURATION

E. SENSORY: Chart deficits in: Pain Touch Temperature Vibration Position when present.



Describe the following when tested:

two point	extinction
stereognosis	localization
traced figures	

F. ASSESSMENT AND PLAN: This should be a summary of history, a summary of positive neurological findings, and a diagnostic formulation and further diagnostic, treatment and/or management plan (on separate sheet).

PRECLINICAL: PHARMACOLOGY AND TOXICOLOGY

Chapter 6

INTRODUCTION

Daniel Couri

This section will be devoted to the characterization of volatile agents used as inhalants. Significant aspects of the physical and chemical properties as well as the known biological effects will be highlighted. It is important to recognize that each of these agents will be described and discussed in proportion to the data available. Since most materials of solvent abuse consist of mixtures of varying composition, the effects noted in studies of single solvent vapor exposure may, at best, suggest likely target organ specificity, or more so, minimal toxicity (Couri and Abdel-Rahman, 1977). Furthermore, most of the literature dealing with volatile agents is derived from studies of single agent exposure (or administration) aimed at providing safety data and hazard evaluation for the work environment. Consequently, these often describe results of either acute high dose mortality data (LD_{50}, LC_{50}) or long-term (chronic) low concentration exposures. In either case, the data obtained provide guidelines for establishing relative hazard indices. Animal studies coupled with any known human exposures at various safe (and sometimes lethal) levels of chemical agents are compiled, evaluated, and used as a basis for recommended maximal allowable concentrations (MAC) or the Threshold Limit Value (TLV), i.e., an average exposure level a worker can be exposed to for an 8-hour workday over an indefinite period of time without any hazard to health.

OCCURRENCES OF VOLATILE AGENTS

The volatile solvents are often used in combinations which are arrived at based upon the most desirable properties of mixtures to achieve an industrial or commercial purpose. Thus, a composition of paint thinners or brush cleaners or degreasing agents will vary greatly from region to region and from manufacturer to manufacturer. A selected group of mixtures of commonly available compounds is depicted in Table 1 according to chemical class.

PHYSICAL AND CHEMICAL PROPERTIES OF VOLATILE SOLVENTS

Most of these compounds are liquids at room temperature and inhaled toxicity is dependent upon their physical properties. For example, a compound which has a relatively high TLV can still be hazardous if it readily vaporizes at room temperature. Table 2 includes physical and chemical properties of the compounds discussed in this section. The table includes vapor pressure, a measurement of the partial pressure the solvent exerts at 25° C. Vapor pressures which have higher numerical values are more easily volatilized than those with lower values, e.g., acetone is about twice as volatile as methyl ethyl ketone. The more volatile substances will be more concentrated in inhaled fumes. The absorption of these compounds through alveolar membranes and into tissues is enhanced by their organic solubility and diminished, in general, by their water solubility. This may be an oversimplification of these properties and many exceptions occur. However, these data may be utilized in this manner to determine the relative toxicity and absorption that would occur from humans exposed to these vapors.

For further information on many of these compounds in relation to their hazards, the reader is referred to the numerous Criteria Documents on individual substances that are listed (under "C") in the Bibliography of this volume.

REFERENCE

Couri, D., and M. Abdel-Rahman. Toxicological evaluation of intentionally inhaled industrial solvents. Presented at The First International Symposium on Voluntary Inhalation of Industrial Solvents, Mexico City, June 1976.

TABLE 1

OCCURRENCES OF VOLATILE SUBSTANCES

Compounds	Anti-freeze	Gasoline	Paint Thinner	Degreasers	Windshield Washers	Adhesives and Rubber Cement	Model Cements	Aerosol Sprays	Spray Shoe Polish	Room Odorants	Foem Dispensers
Alcohols											
Methanol	X		X		X						
Ethanol			X				X	X			
Iropropanol	X		X	X			X	X	X		
Esters											
Ethyl acetate			X								
n-Propyl acetate			X								
n-Botyl acetate				X							
Ketones											
Acetone			X				X				
Methyl ethyl ketone			X	X							
Methyl butyl ketone			X								
Aromatic Hydrocarbons											
Benzene		X		X		X					
Toluene		X	X	X		X	X	X	X		
Xylene		X	X	X		X	X	X			
Stryene						X	X				
Naphthalene		X	X			X					
Aliphatic Hydrocarbons											
n-Hexane		X				X	X				
n-Heptane		X	X			X					
Anesthetics											
Methylene chloride			X	X							
Trichloro-ethylene				X							
Tetrachloro-ethylene				X							
Nitrous oxide											X
"Freons"								X			
Aliphatic Nitrite											
Isoamyl nitrite										X	

TABLE 2

PROPERTIES OF VOLATILE SOLVENTS

Compound	Molecular Weight	Boiling Point °C, 760 mm Hg	Solubility* g/100 ml Water, 25 °C	Vapor Pressure mm Hg, 25°C
Alcohols				
Methanol	32	65	∞	160
Ethanol	46	78	∞	50
Isopropanol	60	82	∞	44
Esters				
Methyl acetate	74	57	32.0	235
Ethyl acetate	88	77	8.6	100
n-Propyl acetate	102	102	1.9	35
n-Butyl acetate	116	125	1.0	1.5
Methyl formata	60	32	30.0	600
Ethyl formats	74	54	11.8	200
Ketones				
Acetone	58	56		226
Methyl ethyl ketone	72	80	25.6	100
Methyl propyl ketone	86	86	5.5	16
Methyl butyl ketone	100	128	1.6	3.8
Methyl hexyl ketone	128	173	0.1	1.2
Di-isobutyl ketone	142	142	vss	2.4
Methyl amyl ketone	114	114	0.4	1.6
Aromatic Hydrocarbons				
Benzene	78	80	vss	76
Toluena	92	111	vss	36.1
Xylenes	106	141	I	10
Stryene	194	145	I	6.5
Naphthalene	128	211	I	0.1
Aliphatic Hydrocarbons				
n-Pentana	72	36	I	409
n-Hexane	86	68	I	103
n-Heptane	100	100	I	41
n-Octane	114	114	I	10.2
Aliphetic Nitrite				
Isoamyl nitrite	117	97-99	I	0.11
Anesthetic Agents				
Nitrous oxide	30	-89	NA	Gas
Chloroform	119	61		200
Di-ethyl ether	74	35		439
Halothane	197	50		240
Ethyl chloride	67	12	NA	Gas
Trichlomethylene	131	87		77

*All compounds listed in this table are miscible at all proportions in organic solvents.

∞ = Miscible at all proportions.

VSS = Very slightly soluble.

I = Insoluble.

NA = Not applicable.

Chapter 7

ABUSE OF INHALATION ANESTHETIC DRUGS

M. B. Chenoweth

HISTORY

It is generally accepted that surgical anesthesia with all its blessings arose out of the abuse of the earliest materials available, diethyl ether and nitrous oxide. "Ether frolics" and "laughing gas demonstrations" were common events and the absence of reactions to painful injuries noted during the effect of these substances led directly to their use in surgery. Yet not five years after his introduction of nitrous oxide in 1844 to dentistry and surgery, Dr. Horace Wells died, a victim of chloroform abuse (Brown, 1967.) The literature on abuse of anesthetic vapors begins at about that time and is largely anecdotal.

Although there is no way other than inhalation to obtain the effects of nitrous oxide diethyl ether is sufficiently liquid at cool room temperatures to be drunk. Such use of ether progressed concomitantly with its surgical uses, especially in certain geographical regions (Connell, 1965). It seems that ether was used both as an alternative to the more expensive alcohol and as a drink with its own special "desirable" properties. The waning of its usage warrants more study of the mechanisms used to discourage ether drinking in Ireland. A combinaition of control of sales and social pressure: seems to have been responsible, but these forces seem not to help much in the United States today in attacking the drug abuse problem in general

AGENTS AND ACTIONS

The inhalation anesthetics available in the United States are now numerous and may be classified in numerous ways; for example, by usefulness or popularity among anesthesiologists, or by price, availability, color, boiling point, etc., etc. Perhaps a useful categorization is between gases and liquids as it at least distinguishes the containers and the portability of the system. Some features are gathered in Table 1 which are particularly relevant to the problem of abuse.

The inhalation anesthetics as a class are presented to the legitimate user as extraordinarily pure and powerful drugs. They are singularly low in organ toxicity and generally safe when used properly. Much is known of their pharmacology and/or toxicology and the desirable and undesirable features of each are massively documented and updated in texts, treatises, and periodical scientific literature. Table 2 summarizes the pharmacological characteristics of some standard materials. Table 3 contains some chemical information. A synopsis of anesthestic drug action may be of value to readers not familiar with it.

ANESTHESIA AND ITS PROBLEM

With the exception of ethylene and nitrous oxide, the materials listed in Table 3 are "complete anesthetics." That is, they will produce complete narcosis characterized by complete unconsciousness, total muscular relaxation, and respiratory and/or cardiac arrest. This cannot be accomplished with 80 percent nitrous oxide or ethylene in oxygen, the maximum concentration that can be used safely.

The induction of anesthesia progresses in four stages classically demonstrated by use of ethyl ether. Stage II is of importance to the abuse problem for in this stage excitement, struggling, and vomiting often occur. Stage III, divided into four planes, is that of general anesthesia and in this stage reflexes become increasingly obtunded, ending with Stage IV--cessation of everything. A special hazard to the abuser is the extreme relaxation of the throat which occurs, occluding the respiratory passages. The combination of vomitus, relaxed tongue and throat muscles, and feeble breathing efforts is a likely cause of death in many abusers.

TOXICITY OF ANESTHETICS

Although possibly less toxic in terms of organ damage potential than most commercially employed solvents, the anesthetics are not free of unwanted effects. Sensitization of the myocardium to the catecholamines can lead to abruptly fatal ventricular fibrillation, and hepatic damage is reported in abusers as well as patients. Although nitrous oxide is known to produce leukopenia, this has

TABLE 1
FEATURES OF ANESTHETIC RELEVANT TO ABUSE

Name	Source (See Footnote)	Comment
GASES		
Nitrous Oxide	1,2,3	Great volumes used in anesthesia Abuse increasing.
Ethylene	1,2,5	Unpleasant odor. Explosive. Weakly active. No record of abuse.
Cyclopropane	1,2,5	Explosive. Costly. No record of abuse.
VOLATILE LIQUIDS		
Chloroform	1,2,4,5	
Diethyl Ether	1,2,3	Explosive, irritating.
Halothane	1	Very dangerous to abuser.
Ethyl Chloride	1,2,5	Unusual for abuse.
Methoxyflurane	1	Notable odor. Slow acting. Rarely abused.
Enflurane	1	Excitatory properties may influence ebuse.
Fluroxene	1	No longer marketed. Explosive. No record of abuse.
Divinyl Ether	1,2,5	No record of abuse.
Trichloroethylene	1,2,3,5	Special interaction with ethanol to cause flushing.

[1]Pharmaceutical channels.

[2]Commercially available.

[3]Found in consumer products.

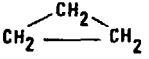
[4]Specifically excluded from consumer products.

[5]Can be had in anesthetic grade but is used in anesthesiology in the United States very rarely, if at all in 1977.

TABLE 2
CHARACTERISTICS OF SOME STANDARD GENERAL ANESTHETICS

Anesthetic	Flammable	Rate of Induction	Rata of Emergence	Analgesia	Respiration	Cardiovascular System	Liver Function	Kidney Function	Postop. Nausea & Vomiting
Cyclopropane	Yes	Rapid	Moderately rapid	Good	Depressed	Supported	Depressed mildly	Depressed	Moderate
Ether	Yes	Slow	Slow	Good	Light-not depressed Deep-depressed	Moderately well supported	Depressed mildly	Depressed	Moderate
Methoxyflourine	NO	Slow	Slow	Good	Depressed	Depressed	Depressed mildly	Depressed	Moderate
Halothane	No	Moderately rapid	Depends on duration	Poor	Depressed	Depressed	Depressed mildly	Depressed	Mild
Nitrous Oxide	No	Rapid	Rapid	Good	Not affected	Not affected	Not affected	Not affected	Minimal

TABLE 3
CHEMICAL DATA ON ANESTHETICS

Generic Name	Trade	Chemical Structure	Boiling Point	Flammability	Miscellaneous
Nitrous Oxide	None	N_2O	-88.46 °C.	None (supports combustion however)	Blue tanks
Ethylene	Nom	$CH_2=CH_2$	-102.4 °C.	Explosive limits in air, 3.02-34%	Violet tanks
Cyclopropane	None		-34.5 °C.	Explosive limits in air, 2.41-0.3%	Orange tanks
Chloroform	None	$CHCl_3$	61.0 °C	Nom	
Diethyl Ether	None	$CH_3CH_2OCH_2CH_3$	35.0 °C.	Explosive limits in air. 1.85-100%	
Halothane	“Fluothane”	$CF_3CBrClH$	50.0 °C.	None	
Ethyl Chloride	Several*	CH_3CH_2Cl	12.3 °C.	Burns. Explosive limits in air, 3.6-14.8%	Pressurized glass containers
Methoxyflurane	“Penthrane”	$CH_3OCF_2CCL_2H$	104.6 °C.	Lower explosive limits in oxygen 5.4%, usually unreachable in clinic	
Enflurane	“Ethrane”	F_2CHOCF_2CClFH	56.5 °C.	Nom	
Fluroxane	“Fluoromar”	$F_3CCH_2OCH=CH_2$	42.5 °C.	Explosive Lower limit in oxygen, 4.0%	
Divinyl Ether	“Vinethene”	$H_2C=CH-OCH-CH_2$	30.0 °C.	Explosive. Slightly less so than diethyl ether	Contains 4% ethanol
TrichloroMhylsne	"Trilene"*	$Cl_2H=CHIH$	86.7 °C.	None.	

*See Merck Index 3713,9319, 9th Ed.

not been a feature of abuse. Malignant hyperthermia is potentially a serious threat to abusers who possess the genetic requirements for this oft-fatal phenomenon.

Although the acute effects of anesthetic vapors have been very extensively studied, the effects to be expected from long-term low level inhalation are only now under study (Chang and Katz, 1976). Furthermore, as with all the abused materials, next to nothing is known about the long-term results of repeated, brief sub-anesthetic self-dosing. The self-dosing aspect is important because of the risks of partial anoxia and occasional overdosage. The details will be difficult enough to ascertain for the cases of single drug abuse, but there are probably far more persons who abuse two or more drugs simultaneously.

SOURCES OF ANESTHETIC CHEMICALS

Some compounds are available in commerce as general chemicals, but for others the system of distribution is almost entirely that of prescription drugs (Table 2). Indeed, because almost all inhalation anesthesia is carried out in hospitals, the disbribution pattern is even more narrowed. A practicing physician wishing, for whatever strange but legitimate reason, to keep inhalation anesthetics in his offices must be quite insistent *to* obtain a supply. Dentists, however, make use of nitrous oxide as an analgesic and often they are equipped to use it regularly.

The veterinarian makes considerable use of these drugs and may have a sizeable supply. Biological and chemical laboratories often have large supplies of these drugs.

Fortunately, even the cheapest of the chemicals is costly and the best are downright dear, so storage generally tends to be more secure than casual. Several are flammable and this, too, limits the carelessness with which they are stored.

In short, the abuser must have legitimate access to these drugs or he must be a thief. Roth occur.

ADDICTION AND ABUSE OF ANESTHETICS

Some case reports showing the details of usage by addicted anesthesiologists and by inexpert thieves are instructive (see annotated bibiography) As a generality, the anesthesiologist addicted to anesthetic “sniffing” is careful not to exceed the social tolerance of his peers, but as with ethanol, excess occurs. He is, then, in the position of the alcoholic physician and may end in disgrace or in another area of work. The inexperienced thief frequently ends on a slab in the morgue. These latter cases often appear in the medical literature; the former do not.

INCIDENCE AND CONTROL OF ANESTHETIC ABUSE

It is difficult to get a grasp on the incidence of anesthetic abuse by professionals. The old practice of testing the anesthetic mixture upon oneself is fading due to better instrumentation of anesthesia machinery but it is not gone. The bottles of halothane, methoxyflurane, or enflurane are small and easily secreted. In a busy hospital only the administrator really worries about the cost and numbers of such bottles which must be at hand at all times. Some operations use more, some less, and the anesthesiologist is buried at the end of the table alone behind the drapes. "Sniffing" may go undetected. With most eyes riveted to the table, it is easy for an intern, a circulating nurse, or an orderly to drop a bottle for future use into a pocket or cache. The National Institute for Occupational Safety and Health (NIOSH) estimates 214,000 workers are exposed to anesthetic vapors in 1977. In addition, total strangers in white coats, grabbed from a handy coat room, can walk boldly into the drug room, as often hospitals have little in the way of security measures.

A "bottle count" similar to the classical sponge count at the end of the operation could discourage hospital staff thefts or at least increase their chances of being detected.

Why does a professional turn to inhalation anesthetics as a drug of abuse? It is speculated that perhaps they are already alcoholic in that they drink to excess while off duty and the anesthetic "sniffed" in the operating room merely tides them over until they can get to a bottle. Later, the balance swings more to the anesthetic than to alcohol. However, there are "pure" anesthetic addicts who do not use alcohol. Perhaps they rationalize that the anesthetic is less toxic and in any case, they "are not alcoholics."

The rapid move to regard the surgical suite as a "workplace" in the meaning of the Occupational Safety and Health Act, together with the previous findings of hazard to the workers in such places (Van Stee, 1976), is leading to air monitoring and a profound decrease in the ambient vapor concentrations. NIOSH, in a recent Criteria Document, proposes a 2 parts per million (ppm) limit on halogenated anesthetic vapors in the workplace and 25 ppm for nitrous oxide. This can only be generally salutory. Furthermore, a sudden rise in concentration may then reveal "on-the-job" abuse to some extent. Theoretically, the absence of clouds of vapors may also decrease the number of persons experiencing an effect which might later lead to deliberate abuse.

A recent popular magazine article put the proportion of alcoholic physicians at about 12 percent of the total (Robinson, 1977).

Therefore, it is perhaps fair to guess the proportion of 214,000 persons who abuse anesthetic vapors at around 1 in 10, a frightening figure the author hopes is wildly erroneous. Several dis-

tinguished anesthesiologists have assured the author that the incidence among anesthesiologists is less than 1 or 2 percent, but they fear it may be higher among other groups having access to these substances. Thievery can be reduced by commonplace measures but the old problem remains, "nam quis custodiet ipsos custodes?"

SUMMARY

Abuse of inhalational drugs used to produce anesthesia has progressed pari passu with their evolvement and may exist far into the future. It occurs among both professional and lay people and is fraught with toxicological and sociological hazard in excess of many other forms of substance abuse.

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Chapter 8

TOXICOLOGY OF ALCOHOLS, KETONES AND ESTERS--INHALATION

Daniel Couri and J. P. Nachtman

ALCOHOLS

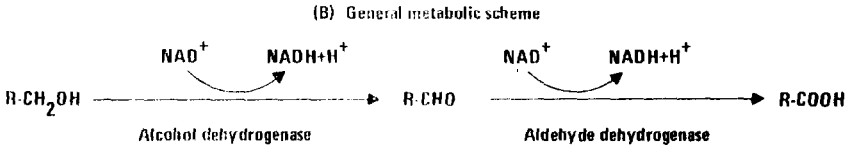
Although alcohols as solvents are not generally inhaled, their occurrence in solvent mixtures makes it important to describe their known toxicities. Oftentimes, when alcohols occur in these mixtures, the cautionary label on the product refers to symptoms of ocular damage especially referable to methanol.

Alcohols are synthesized from natural gas, wood and grain distillation, and petroleum distillates. Most water soluble of the organic solvents, they are poorly eliminated from the lungs, are metabolized to acetate and/or excreted by the kidney. Much is known about alcohol metabolism because of its ingestion toxicity and addiction.

The general metabolic pathway for alcohols is outlined below.

(A) Alcohol and corresponding metabolites

R	Compound	Metebolite-1	Metabolite-2
H-	Methanol	Formaldehyde	Formic acid
CH3	Ethanol	Acetaldehyde	Acetic acid
CH3CH2	n-Propanol	Proprionaldehyde	Proprionic acid



Methanol

Symptoms of Exposure

Methanol (CH_3OH) is used as a solvent for paints and varnishes, resins, films, antifreeze and inorganic synthesis and extraction. High concentrtrations occur during beer vat cleaning, varnishing of ship engine rooms, shellacking, and dye preparations, often causing fatalities Thus, inhalation of methanol can be lethal similar to that following oral intoxication.

Early symptoms of methanol poisoning are headache, weakness, vertigo, and occasionally nausea, vomiting, and abdominal pain. Symptoms due lo acidosis (formic acid metabolite) can be treated with bicarbonate.

Delayed symptoms occur in the visual system: blurred vision, loss of acuity (spots or gray mist seen), photophobia, and eye tenderness. Pupils dilate and lose their reflexes. The high rate of oxidative metabolism of the retina is thought to produce formaldehyde in situ with resulting edema, blurring of the optic disk, and permanent damage to ganglion cells. Infused formaldehyde cannot produce this injury, which appears from 6 to 30 hours after exposure to methanol.

Delayed retinal toxicity can be treated by infusion of ethanol until plasma ethanol levels reach about 0.1 g% (grams per 100 ml blood). Ethanol is a better substrate than methanol for alcohol dehydrogenase, thereby preventing the formation of formaldehyde; methanol is excreted unchanged by the kidney.

Retinal and Central Nervous System Toxicity

Methanol intoxication has been studied in primates (Potts and Gonasun, 1975), since they are the only species showing this retinal and central nervous syte (CNS) toxicity. Potts et al (1955) showed three disease processes in primates given a 90 percent fatal dose of methanol:

1. Organic solvent poisoning,
2. Systemic acidosis (cause of fatalities due to methanol), and
3. CNS and eye toxicity.

The time course of effects shows a minimal initial solvent depressant effect followed by a lucid interval. This reversal was transient as systemic acidosis would be fatal if base (sodium bicarbonate) were not infused. CNS effects, primarily in the putamen, were noted in animals who survived the first two stages, only to die from the CNS toxicity of methanol.

To determine whether methanol, a metabolite, or acidosis is responsible for these effects, Potts et al. (1955) administered methanol, formaldehyde, or formate to rhesus monkeys. Control monkeys were given ammonium chloride by stomach tube to serve as acidotic controls. All the animals given methanol died despite reversal of acidosis by sodium bicarbonate. At autopsy, only one animal showed retinal changes of any kind. This exception survived the longest (9 days vs. 23 hours) and had fixed, dilated pupils with apparent blindness but no retinal edema at the time of death.

Examination of the brains of methanol-treated animals showed the caudate nucleus and putamen with hemorrhagic infiltration and necrosis. Controls treated with ammonium chloride, formate, or formaldehyde showed no such lesions.

Electroretinograms (ERG) showed the absence of ß wave and accentuated α wave in methanol animals with comparable results for formate- and formaldehyde-infused monkeys. The methanol-treated group showed symptoms and ERG changes 20 to 30 hours after administration, while formate and formaldehyde produced effects at 45 and 90 minutes, respectively.

Similar effects have also been observed in humans, including the basal ganglion disease. These ERG changes have been observed in man, suggesting ERG would be of diagnostic value in measuring the severity of methanol poisoning.

Metabolism

Inhalational toxicity data in humans arc inadequate, yet lethal levels of methanol and formic acid ingestions in humans are as follows:*

	Methanol mg%	Formic Acid mg%
Bood	74-110	9-68
Urine	140- 240	216- 785
Liver	106	60-99

Urine methanol is approximately twice blood levels.

*A principal source of these data is Lund (1948).

Ethanol

Symptoms of Exposure

Inhalation of ethanol (CH_3CH_2OH) will produce irritation of mucous membranes and upper respiratory tract, headache, nervousness, and narcosis. Asthma patients inhaling an ethanol mist to control bronchospasm do not show ethanol toxicity. About 90 percent of inhaled ethanol is metabolized to acetaldehyde, acetate, and ultimately CO_2. Concentrations that produce drowsiness in humans range from 6,000-9,000 parts per million (ppm) (Loewy and Von Der Heide, 1918) and are accompanied by an intense odor which would normally cause an individual to escape.

Metabolism

The rate of metabolism of ethanol is about 1/3 oz. of 200 proof per hour.

A lethal level of ethanol in blood (by ingestion) is around 0.4 g%. Exposure to 8,000 ppm for 6 hours produced only 0.05 g% in blood, indicating how difficult it is to inhale a lethal dose of ethanol (Lester and Greenberg, 1951).

Ethanol also will induce tolerance. Also, chronic ingestion will increase the activity of drug-metabolizing enzymes in liver microsomes (Rubin and Lieber, 1971).

Isopropanol

Isopropyl alcohol ($CH_3CHOHCH_3$) is synthesized from propylene, a product of petroleum cracking. Like methanol, it is found in many formulations including perfumes, lacquers, preserving solutions, and rubbing alcohol.

Symptoms of Exposure

Isopropanol becomes irritating to the eye and nose at concentrations of 800 ppm, well below that of lethal effects. Isopropanol produces narcosis and death in high concentrations (12,000 ppm for 4 hours). Hemodialysis is recommended for acute intoxication.

Metabolism

Isopropanol is metabolized to acetone which has been found in urine. Acetone is more readily excreted in expired air (10:1 over isopropanol).

Acute Toxicity of Alcohols

Data are available on the effects of alcohol vapor exposure in a variety of species; a principle source of the data in Table 1 is Patty (1963).

TABLE 1

ACUTE TOXICITY OF ALCOHOLS

TLV (ppm)	Compound	ppm/Duration	Effect	Species
200	Methanol	31.600/18-21 hr	Lethal 100%	Rat
		22.500/8 hr	Narcosis	Rat
		8,800/8 hr	Lethargy	Rat
1,000	Ethanol	32,000/8 hr	Some deaths	Rat
		22,000/8 hr	Deep narcosis	Rat
		6,400/8 hr	Lethargy	Rat
400	Isopropanol	12,000/8 hr	Lethal 50%	Rat
		12,000/4 hr	Narcosis	Rat

ESTERS

General Features of Toxic Exposure

Esters are synthesized from organic acids and alcohols as follows:

The loss of polarity evidenced by this reaction causes the ester to have a higher lipid solubility, liquid phase at. room temperature, and lower boiling point than the alcohols. Because esters are liquids and have high nonpolar solubility they can be used as plasticizers and lacquer solvents.

As with the ketones, esters are capable of producing eye, skin, and mucous membrane irritation. In this, the lower molecular weight esters are more potent than the corresponding alcohols. For example, ethyl acetate is more irritating than ethanol. However, chronic exposure does not produce observable eye disease. Halide esters are the most potent eye and skin irritating compounds of this class. It is thought that these halide esters bind sulfhydryl groups,

Central nervous system depression is the primary effect of volatile esters. esters of highest molecular weight having the greatest anesthetic. effect Because esters have higher solubility than ketones, they are not excreted as readily through the lungs.

Metabolism

Esters are converted in the body to the original alcohol and acid. Whole blood can metabolize ethyl acetate to ethanol and acetate.

However, the biological half-life of ethyl acetate in rat whole blood in vitro is 65 minutes versus only 5 minutes in vivo. The pseudo-cholinesterase of blood is thought to be responsible for the whole blood breakdown of ethyl acetate, whereas the liver is thought to contribute to the short in vivo half-life. Inhalation of 20,000 ppm and above causes increased ethylacetate over ethanol, suggesting saturated biotransformation.

Acute Toxicity of Esters

Data are available on the effects of exposure to esters in a variety of species; a principle source of the data in Table 2 is Patty (1963).

TABLE 2

ACUTE TOXICITY OF ESTERS

TLV (ppm)	Compound	ppm/Duration	Effect	Species
200	Methyl acetate	22,000/2-1/2 hr 10,000/22 hr	Lethal 100%	Cat
400	Ethyl acetate	12,000/5 hr	Lowest narcotic concentration	Cat
		20,000/3/4 hr	Oeep narcosis (recovered)	Cat
200	n-Propyl acetate	24,500/1/2 hr	Narcosis/death	Cat
150	n-Butyl acetate	17,500/1/2 hr	Narcosis some lethal	Cat
100	Methyl formats	50,000/l/2 hr	Lethal 100%	G. Pig
100	Ethyl formate	10,000/80 min	Narcotic and lethal 100%	Cat

KETONES

General Features of Source and Exposure

Ketones are largely produced from petrochemicals by dehydrogenation of a secondary alcohol. Their use ranges from solvents for inks, paints, and resins, to intermediates in organic synthesis, to specialty products such as perfumes.

The current threshold limit value for aliphatic ketones is based primarily on an irritation threshold. Subnarcotic levels of ketones produce eye, nose, and mucous membrane irritation sufficient to prevent acute overexposure.

Industrial exposure to ketones occurs in painting, printing, cleaning, and plastic processing operations. The extreme flammability of ketones has caused their replacement by higher flash "Safety Solvents" and thus has tended to reduce defatting injuries to the skin. Eye irritation is a common complaint in situations where high concentrations are volatilized.

Generally, narcotic effects occur in animals exposed to high concentrations of ketones with death due to respiratory depression. Animals will recover from otherwise lethal concentrations if they are removed to fresh air, indicating that excretion of the inhaled solvent is mostly through the lungs.

Acute Toxicity of Ketones

Data are available on the effects of exposure to ketones in a variety of species; a principle source of the data in Table 3 is Patty (1963).

TABLE 3

ACUTE TOXICITY OF KETONES

TLV (ppm)	Compound	ppm/Duration	Effect	Species
1,000	Acetone	46,000/1 hr	Lethal 100%	Mouse
		20,256/1-1/2 hr	Narcotic	Mouse
200	Methyl ethyl ketone	3,000/2 hr	Lethal 50%	Rat
200	Methyl propyl ketone	30.000/3/4 hr	Lethal 100%	G. Pig
25	Methyl n-butyl ketone	5,000/3/4 hr	Lethal 100%	G. Pig
75-100 (range)	Methyl hexyl ketone	1,300/1 hr	Narcotic	G. Pig
50	Di-isobutyl ketone	2,000/8 hr	Lethal 100%	Rat
100	Methyl amyl ketone	4,800/4-8 hr	Narcosis/death	G. Pig

Methyl Ethyl Ketone

Methyl ethyl ketone (MEK; $CH_3COCH_2CH_3$) is used as a solvent for cellulose products in the plastics industry and in paints and lacquers. It is a CNS depressant and causes irritation of the mucous membranes. Nelson et al. (1953) reported slight nose and throat irritation at 100 ppm and mild eye irritation at 200 ppm. Their recommendation for exposure limit was 200 ppm based on these irritant properties.

Acute toxicity of MEK vapors is low: Guinea pigs survived l-minute exposures to 100,000 ppm and l-hour exposures to 10,000 ppm. The latter produced irritation of the eyes and nose soon after the start of exposure with narcosis after 4 to 5 hours.

In high concentrations MEK produces CNS depression, emphysema in lungs, and congestion of the liver and kidneys. Since MEK is less soluble in water than acetone, it is more rapidly eliminated in the lungs.

Little serious injury to humans from MEK exposure has been documented. Skin exposed to a solution of MEK or its vapors has developed dermatitis, and fainting occurred due to MEK exposure (300-500 ppm exposure) (Smith and Mayers, 1944). These authors also report a numbness of fingers and arms in workers exposed to MEK vapor and liquid.

Acetone

Acetone (CH_3COCH_3) is a common industrial solvent for resins, lacquers, oils, paints, acetylene, and fats. It is the most volatile of the aliphatic ketones and easily produces dermatitis by defatting the skin. Acetone is highly flammable and has a flashpoint of 0° F (-17.8° C).

Acetone is rapidly taken up by inhalation. Kagan (1924) found that 71 percent of inhaled acetone (9,300 ppm) is absorbed in a 5-minute exposure. Human exposures have shown acetone to be irritating to the eye, nose, and throat at 500 ppm. Exposure to 700 ppm produced severe irritation initially but shortly after initial contact, 700 ppm was undetectable by odor or irritation. After acclimation, 2,500-3,000 ppm caused only slight eye and nose irritation.

Acetone has a very high solubility in water. The distribution between alveolar air and blood (water) is 1:333 (Briggs and Shaffer, 1921), indicating a large amount of inhaled acetone would be retained. Since physiological dead space is 24 percent, the predicted retention of acetone would be 76 percent; this agrees well with Kagan's aforementioned 71 percent retention.

Once inhaled, acetone is largely excreted unchanged by the lungs with no reduction. Small (1.7 mg/kg) oral doses are found to be oxidized almost completely (Price and Rittenberg, 1950). ^{14}C-methyl-acetone has been found in choline, methionine, and the 1,6 positions of glycogen, suggesting that acetone can be cleaved to acetate and formate. Formate then enters one carbon pool to reappear in choline, methionine, and glycogen; ^{14}C-methyl-acetate appears in acetylated compounds and the 2,5 positions of glycogen.

Despite widespread use of acetone in commercial and industrial products. few cases of industrial poisoning have been reported. The most common effect is dizziness due to anesthetic concentralions and irritation to mucous membranes at lower concentrations. Lacrimation, salivation, and giddiness follow exposure to acetone.

A threshold limit value of 1,000 ppm is set for acetone.

Methyl n-Butyl Ketone and Ketones Derived from Hydrocarbons

Methyl n-butyl ketone (MBK; $CH_3CO(CH_2)_3CH_3$) has also been shown to cause peripheral neuropathy in man (Allen et al., 1975). In a study of 86 cases of peripheral neuropathy from a plastic coatin operation. 11 were severe with both motor and sensory involvement, 38 were mild, primarily showing sensory impairment, and 37 were virtually asymptomatic with characteristic electromyographic changes.

Incidence of these cases was highest for members of the printing shop (21.5 percent of employees there). Printing operators, with greatest contact with the printing inks and solvents, had an incidence rate of 36.1 percent, followed by pan washers (28.6 percent). No symptoms were noted before December 1972, indicating that the disease was of recent origin. In August 1972, MBK had replaced methyl isobutyl ketone as a printing ink solvent.

Airborne concentrations inhaled by printers averaged about 9 ppm MBK and 331 ppm MEK. Other plants which produced similar products using solvents other than MBK showed no neurotoxicity.

(Chief clinical signs are as follows: gradual onset of sensory loss, predominately distal proceeding to proximal regions. In more severe cases, motor invovement occurs with sparing of proprioception and reflexes (large fibers spared). Progression of symptoms persists in spite of cessation of exposure, but gradual recovery follows.

Electron microscopic examination of single teased nerves shows a paranodal denudation of myelin with focal internodal myelin loss. Axonal swelling with increased numbers of microfilaments appear, Schwann cells remaining intact.

Hexane is also described here since recent evidence indicates that hexane is biotrunsformed to hexanol and 2,5 hexanedione. The latter ketone can cause neurotoxicity similar, if not identical, to that of n-hexane. Yamamura (1969) found hexane to be neurotoxic to workers. Two workers using hexane as a glue solvent in the manufacture: of sandals became quadriplegic. Survey of other employees revealed 93 cases of polyneuropathy, all of whom were involved in gluing sandals in their own homes. Gas chromato-

graphic analysis of the rubber paste solvent revealed 70 percent n-hexane with a small amount of toluenc. Environmental concentrations of hexane varied widely, from 500 to 2,500 ppm.

Of the 93 workers in Yamamura's study, 53 experienced sensory polyneuropathy and 32 had sensorimotor polyneuropathy; 8 showed muscle atrophy upon examination.

Yamada (1927) found two plants where hexane was used and noted 17 workers showing evidences of polyneuropathy: fatigue and loss of appetite initially, followed by distal sensory paresthesia and difficulty in walking. Three months after cessation of exposure, the progression of disease was stopped with gradual recovery over the next 2 years.

Herskowitz (1971) investigated a polyneuropathy outbreak in cabinet-finishing workers. Air analysis revealed an average concentration of 650 ppm hexane with peak excursions of 1,300 ppm. Electron microscopy of muscle anterior tibialis showed two types of axonal changes:

1. Increased neurofibrils and abnormal membranous structures, and
2. Clumping and degeneration of mitochondria within the axon with many onion bulb structures.

These workers applied the solvent. in a small, poorly ventilated room (3.6 m by 3.6 m), taking the hexane from an open 189-liter drum. The dipping of rags into the drum and wiping of excess glue from finished cabinets also led to cutaneous exposure.

Swann et al. (1974) exposed mice to 64,000 ppm n-hexane and found respiratory arrest occurring within 2-1/2 to 4-1/2 minutes. These authors found that 32,000 ppm produced deep anesthesia (in mice) but 16,000 was not anesthetic. Truhaut et al. (1973) exposed Wistar rats to hexane (2,000 ppm) and heptane (1,500 ppm) for 1 to 6 months. These exposures reflected occupational contact 5 hours/day, 5 days/week. Technical grade hexane was used and consisted of only 15 percent n-hexane. Sciatic anti saphenous nerves were excised and removed after 1, 2, and 5 months of exposure. Electrophysiological analysis showed a decreased nerve conduction velocity and excitability with an increased refractory period.

SOLVENT MIXTURES

Most inhalation toxicity tests have been done with reagent grade (pure) substances. Little is known about the uptake, distribution, and retention of solvents when inhaled as mixtures.

It has been shown that methyl ethyl ketone will increase both plasma levels and toxicity of methyl butyl ketone.

Since no commercial or industrial preparations are so pure, inhalation will be of solvent mixtures. Therefore, attention should be paid to possible potentiation of toxicity of one solvent by mixtures (Couri and Abdel-Rahman, 1977).

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Chapter 9

TOXICOLOGY OF ALIPHATIC AND AROMATIC HYDROCARBONS

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AROMATIC HYDROCARBONS

The aromatic hydrocarbons are a series of cyclic compounds which are based upon benzene as the parent compound. They may be monocyclic or polycyclic and differ from one another not only in the number of rings, but degree and placement of alkyl substitution on the ring(s). Coal and petroleum are the chief sources of aromatic hydrocarbons. Various methods of catalytic reforming or fractional distillation are employed to obtain them from the crude products. Aromatic hydrocarbons are mostly insoluble in water, but freely miscible in other organic solvents. The aromatics are used individually as solvents and as synthetic substrates. A number of aromatics are also major components of common hydrocarbon mixtures.

Benzene

Benzene (C_6H_6; benzol, phenyl hydride, cyclohexatriene) is a volatile, highly flammable liquid with a characteristic odor. It is only slightly soluble in water, but freely soluble in alcohols and other organic solvents. Benzene is obtained as a byproduct from petroleum and coke oven emissions. Benzene is used as a substrate in the manufacture of many aromatic compounds, and as a solvent for waxes, resins, plastics, lacquers, varnishes, and paints. The use of benzene as a solvent has been more limited in

recent years, due to its recognized myelotosic potential. Benzene is nevertheless often present in varying quantities in hydrocarbon solvent mixtures, including gasoline (Parkinson, 1971; Runion, 1975) and assorted thinners and solvents (Carpenter et al., 1975-1976).

Absorption and Distribution

Inhaled benzene is rapidly absorbed into the blood and distributed throughout the body (Schrenk et al., 1941). In studies involving exposure to relatively low vapor levels (25-100 ppm), humans quickly approach a steady-state or equilibrium between inhaled and exhaled vapor concentrations (Srbova et al., 1950; Hunter, 1966). This equilibrium is largely governed by the solubility of benzene in the blood, as data discussed by Patty (1958) show rapid saturation of the blood in such circumstances. Approximately 50 percent. of inhaled benzene is retained in subjects in these studies, although individual variability is pronounced Because of its lipophilicity, benzene is distributed to tissues according to their fat content.. The highly perfused lipoidal tissues, including the brain. are anticipated to most rapidly accumulate benzene. This phenomenon would account. for the rapid onset of narcosis upon exposure to concentrated organic solvent vapors. The bone marrow possesses a quite high tissue/blood partition coefficient for benzene, due to a high neutral fat content (Sato et al., 1974). This is undoubtedly an important factor in consideration of benzene's myelotoxicity

Upon cessation of solvent exposure, benzene is eliminated from the body at a rate dictated by a number of interdependent factars, including alveolar ventilation, blood/tissue partition coefficients, blood/air partition coefficient, and metabolism. Benzene levels in the blood and exhaled air fall quickly during desaturation (Hunter, 1966; Sato et al. , 1974). The human studies of Srbova et al. (1950) and Sato et al. (1974) indicate that roughly 30-50 percent of systemically absorbed benzene is exhaled, which agrees with findings of Parke and Williams (1953) in orally dosed rabbits. Those tissues with greater blood perfusion and lower lipid content will lose benzene most rapidly, while the poorly perfused adipose tissue will most slowly release benzene. This concept is supported by findings of Hunter and Blair (1972) that more obese persons excrete larger proportions of inhaled benzene as urinary metabolites than do their "slimmer" counterparts. Adipose tissue apparently acts as a depot from which benzene is gradually released and subject to metabolism.

Metabolism

The majority of benzene which is not exhaled is metabolized in the liver to phenolic derivatives. These are excreted principally as urinary sulfates and glucuronides. In an early study with rabbits, Parke and Williams (1953) recovered approximately 35

percent of an oral dose of benzene as urinary metabolites within 2 days of dosing. Conjugates of phenol comprised the majority of these metabolites, while less significant quantities of catechol, quinol, hydroxyquinol, trans- trans-muconic acid, and phenylmercapturic acid were present. Cornish and Ryan (1965) found that 23 percent of an intraperitoneal (i.p.) dose of benzene was excreted within 24 hours by rats as free or conjugated phenols. Some variance in the metabolic fate of phenol in 19 species of animals including man has been demonstrated, with the major difference being in the preponderance of ethereal sulfate or glucuronide conjugates (Capel et al., 1972). The quantity of urinary phenols (Walkley et al., 1961; Hunter and Blair, 1972) and the urinary inorganic/organic sulfate ratio (Elkins, 1959; Gerarde and Ahlstrom, 1966) have been advocated as indices of industrial exposure to benzene. The in vitro metabolism of benzene by the microsomal mixed function oxidase system has been reviewed in detail by Snyder and Kocsis (1975).

Acute Toxicity

The acute toxicity of benzene resembles that of other hydrocarbon solvents. Exposure to high concentrations of benzene vapors may produce irritation of the eyes, nose, and respiratory tract. The nature and severity of symptoms depend upon the time and level of exposure. Effects seen in man (Gerarde, 1960) range from exhilaration, dizziness, and headache to fatigue, vertigo, dyspnea, and collapse. Svirbely et al. (1943) report a 7-hour LC_{50} for benzene in mice of about 10,000 ppm, while Drew and Fouts (1974) find the 4-hour LC_{50} in rats to be 13,700 ppm. Rabbits subjected to levels as high as 35,000 to 45,000 ppm live an average of 36 minutes before succumbing to benzene narcosis (Carpenter et al., 1944).

Marked individual variation in susceptibility to the acute lethal effect of benzene suggests that the solvent cannot only produce respiratory arrest in deeply anesthetized persons, but may predispose to cardiac failure. Early studies utilizing the cat and monkey (Nahum and Hoff, 1934) and the dog (Chenoweth, 1946) indicate that inhaled benzene sensitizes the myocardium to epinephrine, resulting in ventricular arrhythmias. This mechanism is implicated in numerous human fatalities in both occupational settings (Browning, 1965; Tauber , 1970) and in instances of solvent abuse (Winek et al. , 1967; Bass, 1970; Winek and Collom, 1971). Physical exertion and/or emotional excitement often associated with these fatal cases may contribute to the victim's demise by liberating epinephrine.

Organ Toxicity

General. Direct organ damage, other than myelotoxicity, has only rarely been attributed to acute or chronic benzene exposure in

humans and experimental animals (Browning, 1965; Snyder and Kocsis, 1975). Modest, variable effects on body weight gain, organ weight, and histology of the liver, kidney, spleen, and testes were occasionally seen in rats, guinea pigs, and rabbits subjected for 7 hours daily to benzene vapors for as long as 11 months (Wolf et al., 1956). Determinations of levels of various serum enzymes have failed to reveal significant organ damage upon chronic exposure of rats, guinea pigs, monkeys, and dogs (Jenkins et al., 1970), and upon acute exposure of rats (Wirtschafter and Cronyn, 1964) and guinea pigs (DiVincenzo and Krasavage, 1974) to benzene.

Myelotoxicity. The most significant toxic action of benzene is upon the blood-forming elements of the body. This toxic effect is thought to be unique, in that simple alkyl substitution of the benzene ring apparently negates myelotoxicity. Although susceptibility and hematologic findings vary markedly among individuals, classic benzene-induced abnormalities include anemia, leukopenia, and thrombocytopenia. These alterations in the circulating blood may also be elicited in a variety of animals, although leukopenia appears here to be the most sensitive and consistent manifestation of benzene exposure. Benzene is believed to produce chromosomal abnormalities in humans and animals, as well as induce leukemias in humans (Vigliani and Forni, 1976). It is beyond the scope of the present. discussion to relate in detail the majority of topics pertaining to benzene myelotoxicity . This subject matter is reviewed in detail in a Criteria Document (1974) and Snyder and Kocsis (1975).

A variety of factors have been considered as potentially important in benzene myelotoxicity Shils and Goldwater (1949) found that inadequate dietary protein intake by dogs and rats predisposed to benzene-induced blood dyscrasias, raising the possibility of altered formation, intracellular binding, and conjugation of toxic metabolites. Although a history of infection preceding symptoms of benzene poisoning has been recorded on occasion, it appears more likely that. increased susceptibility to infection will result from benzene-induced leukopenia. It has been widely held that women are more prone to chronic benzene poisoning than are men, and that. the young are more susceptible than adults. Animal studies have been conducted which support this concept (Hirokawa and Nomiyama, 1962; Ikeda, 1964; Nomiyama et al., 1965). These age and sex differences in experimental animals have generally been linked to differences in benzene metabolism. The relationship of animal studies to man is quite tenuous, however, since marked sex differences in chemical metabolism seen in animals (e.g., rats) likely (10 not occur in humans. Although certain epidemiologic studies and individual case reports have supported the belief that sex and/or age are predisposing factors in benzene myelotoxicity, sufficient numbers of findings to the contrary have largely discounted this concept at present (Criteria Document, 1974; Snyder and Kocsis, 1975). Nevertheless, marked

individuality in resistancce to benzene poisoning cannot be overlooked. Factors including genetic variation, differences in degree and duration of exposure. concomitant exposure to additional chemicals and drugs, nutrition. general state of health , smoking and drinking habits, age, sex, metabolic capability each may contribute to the final outcome of benzene exposure.

Metabolites of benzene are believed to play an important role in development of blood dyscrasias. Although the precise mechanism of toxicity is unknown, it is widely held that metabolites must interact with cellular constituents. Covalent binding of metabolites to DNA is advanced as a plausible explanation for such findings in the bone marrow as inhibition of RNA and DNA synthesis (Moeschlin and Speck. 1967) , chromosomal abberations (Kissling and Speck, 1969; Forni et al., 1971 a,b), abnormalities and decreases in mitotic figures (Pollini et al., 1965), and diminished incorporation of radiolabeled iron into hemoglobin (Lee et al., 1974). Lee and coworkers use this latter technique to demonstrate potentiation of benzene toxicity in phenobarbital-pretreated mice, and protection from benzene toxicity in mice concomitantly administered benzene and toluene. Under, these conditions phenobarbital is known to stimulate and toluene to competitively inhibit benzene metabolism (Ikeda et al., 1972; Snyder., 1971). Interestingly, Ikeda and Ohtsuji (1971) and Mitchell (1971) report that while phenobarbital stimulates metabolism of' benzene in rats, the rats are apparently protected against myelotoxicity. Mitchell (1971) also notes that piperonyl butoxide, a microsomal enzyme inhibitor, protects against benzene myelotoxicity.

Phenobarbital stimulates not only oxidation of benzene, but conjugation and excretion of benzene metabolites as well, thereby likely affording the bone marrow protection from metabolites formed in the liver. The metabolic changes measured by Ikeda and Ohtsuji (1971) and Mitchell (1971) reflect largely handling of benzene by the liver. Event:, occuring in the bone marrow, however. would appear to dictate whether myelotoxicity develops upon benzene exposure. Since large quantities of benzene accumulate in the marrow, it seems reasonable that highly reactive metabolites formed in situ may simply bind to marrow elements and exert a direct toxic effect. Parmentier (1953) did see abnormal mitoses and chromosomal aberrations in the bone marrow of hamsters within 6 hours of intraperitoneal injection elf hydroquinone, followed by appearance of pyknotic nuclei anti diminished numbers of leukocyte mitoses within 24 hours. Harrison and Randoll (1948) report that benzene is not toxic to cultures of bone marrow cells, while phenol and pyrogallol are moderately toxic and catechol and hydroquinone are very toxic. Nomiyama (1965) observes catechol to be the most myelotoxic of a series of metabolic given rats by subcutaneous injection. Findings of Mitchell (1971), that the major benzene metabolites are largely nontoxic to the marrow when given in vivo. suggest that these highly reactive and unstable agents may not reach the marrow before being inactivated and/or

excreted. In order to clarify this phenomenon, the techniques of Mitchell and Jollows (1975) might be employed to correlate covalent binding of benzene metabolites with toxicity in the bone marrow.

Development of myelotoxicity upon benzene exposure has been demonstrated to be both time and concentration dependent. Although it has been difficult. to accurately correlate clinical findings in victims with length and level of exposure, hematologic abnormalities have been noted in workers breathing vapor concentrations as low as 40 to 80 ppm (Hardy and Elkins, 1948) and 30 to 150 ppm (Juzwiak et al., 1969). The period of benzene exposure prior to onset of symptoms may vary from months to years (Hunter, 1939; Hardy and Elkins, 1948). Studies utilizing relatively high benzene vapor levels (600 to 1,000 ppm) have revealed leukopenia in rats after approximately 1 week (Deichmann et al., 1963; Nau et al., 1966; Ikeda and Ohtsuji, 1971). Deichmann et al. (1963) found 47 ppm to be the minimum toxic concentration, with 15 and 30 ppm exerting no leukopenic action within exposure periods of 90 and 215 days, respectively. Evaluations of more sensitive histological and biochemical parameters have revealed adverse effects within hours of administration of relatively high doses of benzene or its metabolites to animals (Parmentier, 1953; Wirtschafter and Bischel, 1960; Lee et al., 1974). Gerarde (1960) has stated that a single, high-level exposure to benzene may result in development of myelotoxicity, although concrete evidence appears to be lacking. Based on the foregoing evidence, the current standard for occupational benzene exposure was set at 10 ppm (Criteria Document, 1974), however, an emergency standard of 1 ppm has recently been implemented.

Potential Health Risks

Gasoline. Individuals who abuse solvents containing substantial quantities of benzene would appear to face the potential risk of myelotoxicity Many commercial solvent mixtures contain benzene in varying amounts, ranging from a trace to as high as 50 percent by volume (v/v). There are no present restrictions on the sale or use of commercial products or fuels containing benzene, other than precautionary labeling of household products. Benzene exposure is of particular concern in the gasoline industry, such that exposure standards for gasoline in the United States are now based upon benzene content. A recent study (Runion, 1975) relates that representative United States gasolines contain an average of about 1% (v/v) benzene, while European gasolines contain an average of 5% (v/v) or more. Runlon (1975). and others (Parkinson, 1971; Sherwood, 1972) conclude that it is unlikely industrial workers handling gasoline are at risk under properly controlled conditions. The gasoline abuser, however, may readily exceed the benzene threshold limit value, since he subjects himself to such high vapor concentrations. Based on responses seen in early human studies of Fieldner et al. (1921) and Drinker et al. (1943), the gasoline abuser could be expected

to intoxicate himself within 1 to 3 minutes by inhaling 20,000 to 30,000 ppm of gasoline. The degree of benzene exposure would of course depend upon a number of variables, including among others benzene content of the gasoline, inhalation time, and interval elapsed between inhalation periods and sessions.

Other mixtures. Myelotoxicity should also be considered a hazard upon abuse of benzene-contaminated solvents other than gasoline. Deichmann et al. (1963) exposed rats to vapors of a solvent containing 7% benzene in hexane and noted leukopenia within 3 weeks. Mean benzene vapor levels were found to be approximately 60 ppm. It should be recalled here that the majority of occupational cases of benzene-induced blood dyscrasias involved solvent mixtures. The role of other solvents in benzene myelotoxicity has yet to be elucidated.

Blood dyscrasias are observed in individuals who abuse solvents, although such findings are not commonplace in this population. Commercial products which have been associated with blood dyscrasias include plastic cements, glues, rubber cements, gasoline, and paint thinners. Hematologic abnormalities reported include eosinophilia (Massengale et al., 1963; Sokol and Robinson, 1963; Press and Done, 1967), lymphocytosis (Massengale et al., 1963), anemia (Edwards, 1960; Powars, 1965), hemoglobin reduction (Lawton and Malmquist, 1961; Powars, 1965), basophilic stippling of erythrocytes (Christiansson and Karlsson, 1957; Sokol and Robinson, 1963), and hypoplastic bone marrow (Christiansson and Karlsson, 1957; Powars, 1965). Individual responses to solvent exposure within groups of patients in each study are quite variable. Some patients demonstrate no hematologic abnormalities, while others show alterations of varying magnitude in one or more parameters. Such discrepant findings are typical of occupational exposure to benzene-contaminated gasoline (Amorati et al., 1952; McLean, 1960; Verwilghen et al. , 1975) and likely reflect not only individual susceptibility to benzene, but the length and pattern of solvent abuse and the composition of abused solvent(s). Benzene is generally considered to be responsible for blood dyscrasias in solvent abuse cases, although neither benzene content nor vapor levels have been accurately determined for commonly abused products under conditions approximating self-intoxication. Because benzene myelotoxicity is so variable and insidious, the condition may go largely unrecognized and undiagnosed in the solvent abuser. There is an obvious need not only for control and recognition of benzene content of commercial products, but for delineation of the nature and conditions under which myelotoxicity can result from abuse of benzene-contaminated solvents.

Toluene

Toluene ($C_6H_5CH_3$; methylbenzene, toluol, phenylmethane) is a volatile, flammable liquid at room temperature, with a benzene-like odor. It is very slightly soluble in water, but freely soluble in

alcohol, acetone, chloroform, and other organic solvents. Toluene is used as a starting material in the manufacture of a variety of organic compounds. It is also commonly employed as a solvent or thinner for paints, varnishes, enamels, lacquers, gums, fats, and resins.

Absorption and Distribution

Toluene is rapidly absorbed upon inhalation and distributed throughout the body, with lipids in the various tissues acting as an extensive reservoir (Sato et al., 1974). Despite inhalation of as high a vapor concentration as 4,000 ppm for 3 hours, saturation in the liver and brain of the mouse is not reached (Peterson and Bruckner, 1976a). Toluene that is not exhaled is largely metabolized by the liver to hippuric acid and excreted by the kidneys. The measurement of urinary hippuric acid is used as an index of human exposure to toluene in industrial settings (Ikeda and Ohtsuji, 1969; Ogata et al., 1971).

Acute Toxicity

Relatively little animal experimentation has been conducted to delineate the toxicologic properties of toluene. Svirbely et al. (1943) report that the LC_{50} for a 7-hour inhalation exposure of mice to toluene is 5,300 ppm, while Kimura et al. (1971) report the oral LD_{50} for adult rats to range from 6.4 to 7.4 ml/kg. Toluene, like other hydrocarbon solvents, acts acutely as a narcotic. The degree of central nervous system (CNS) depression produced by toluene inhalation is, of course, both time- and concentration-dependent. The onset of toluene-induced narcosis is quite rapid upon inhalation of high vapor concentrations. CNS depression in mice, as evidenced by loss of coordination, is manifest within 5 minutes of inhalation of 10,600 ppm toluene (Peterson and Bruckner, 1976b). Kojima and Kobayashi (1973) report that rats exposed to 20,000 ppm of toluene die within 30-50 minutes. The average toluene level in the brain of the animals at death is 0.89 mg/g of tissue.

Inhalation of toluene by humans is reported to elicit a variety of manifestations of narcosis, ranging from diminished psychomotor performance and fatigue upon low-level exposure (Von Oettingen et al., 1942; Gamberale and Hultengren, 1972) to intoxication and unconsciousness upon high-level exposure (Lurie, 1949; Longley et al., 1967). Although it was felt that the current threshold limit value of 100 ppm for toluene (Criteria Document, 1973) would protect workers from any depressant effects, studies by Astrand (1975) have demonstrated that exercise may enhance total uptake of a variety of solvents sufficiently to impair certain mental functions in human subjects (Soderlund, 1975).

Organ Toxicity

Animal. Toxicity studies of animals subjected to prolonged toluene inhalation have revealed little evidence that toluene exerts a biologically significant toxic action on any organ system. Early reports of toluene-induced myelotoxicity have been discounted in that toluene was then likely contaminated by benzene. High concentrations of toluene have been reported to have a limited irritant effect on the lungs, liver, and kidneys in several species of animals (Svirbely et al., 1943; Fabre et al., 1955). This histopathologic manifestation was apparently of minor consequence, in that no evidence of cumulative injury on repeated toluene exposure was noted. In a later study of several species of animals, 30 daily sessions of exposure to 1,085 ppm toluene over a 6-week period failed to alter body weight gain, hematologic parameters, or organ histopathology (Jenkins et al., 1970). Bruckner and Peterson (1976), utilizing the mouse as an animal model of human solvent abuse, failed to detect lung, liver, or kidney injury in animals subjected for 3 hours for 5 of 7 days at 4,000 ppm of toluene vapor for up to 8 weeks.

Inhalant abuse subjects. Liver and kidney injury have occasionally been noted in persons who have abused toluene (Grabski, 1961; Massengale et al., 1963; Sokol and Robison, 1963; Barman et al., 1964; Press and Done, 1967; O'Brien et al., 1971; Pinkhas et al., 1972; Taher et al., 1974). Those investigators who did see evidence of hepatorenal injury in certain patients generally found the damage to be mild and transitory. The more severe cases of injury commonly involved exposure to mixed solvents, or both solvents and drugs.

There have been widely scattered reports of other forms of toxicity in persons who intentionally inhale vapors of products containing toluene. Grabski (1961) and Knox and Nelson (1966) reported brain damage in an individual who regularly abused toluene Cerebellar dysfunction was more recently reported in another patient who had repeatedly sniffed toluene-based spray paint (Kelly, 1975). Blood dyscrasias have been seen following abuse of products containing toluene in combination with other solvents (Powars, 1965; Pinkhas et al., 1972). A variety of hydrocarbon solvents, including toluene, have been implicated in "sudden sniffing death" (Winek et al., 1968; Bass, 1970; Winek and Collom, 1971). Taylor and Harris (1970) found that toluene produced electrocardiographic abnormalities and sensitized the heart to asphyxia-induced atrioventricular block, thereby predisposing to ventricular fibrillation or arrest.

Potential Health Risks

Toluene has been shown to alter the metabolism of a number of other solvents. The biotransformation of benzene and styrene (Ikeda et al., 1972) and of trichloroethylene (Ikeda, 1974) are

inhibited upon coadministration of toluene. Ikeda and Ohtsuji (1971) also observed that phenobarbital-pretreated rats were tolerant to toluene narcosis, apparently as a result of an increased ability to metabolize toluene. Toluene, in combination with certain chemicals, has been shown to the more actuely toxic than would be predicted on the basis of simple additive toxicity (Smyth et al., 1969).

With the exception of cardiac sensitization, there is little firm evidence that toluene exerts a specific toxic effect on any organ system in experimental animals or in man. Even repeated inhalation exposures to high levels of the solvent do not appear to result in significant injury. There is firm evidence, however, that toluene may markedly alter the metabolism of other solvents. Since abused commercial products commonly contain mixtures of solvents including substantial amounts of toluene, the role of toluene in potentiation of toxicity of the other solvent. components deserves thorough investigation.

Xylene

Xylene ($C_6H_4(CH_3)_2$; xylol, dimethyl benzene) is a volatile, flammable liquid at room temperature. It is practically insoluble in water, but freely miscible with most organic liquids. Xylene exists in three dimethyl isomeric forms: 1,2 (ortho); 1,3 (meta); 1,4 (para). Xylene is produced from both petroleum and coal tar, and is used as a solvent or filler in a myriad of commercial products including paints, lacquers, varnishes, dyes, inks, cements, cleaning fluids, gums and resins, oils, rubber, and gasoline. Xylene is also used in the chemical industry as a synthetic intermediate. Because of such widespread use and availability, there is a potential for abuse of xylene.

Acute Toxicity

Like other organic solvents, xylene has both direct irritant and CNS depressant actions upon inhalation. Based on subjective responses of humans, 200 ppm of xylene was reported to be slightly irritating to the eyes, nose, and throat, but to have little recognizable depressant effect (Nelson et. al. , 1943; Carpenter et al., 1975). Eye irritation was seen in the latter study in rats exposed to levels of mixed xylenes as low as 1,300 ppm. Mild, reversible corneal damage was reported in German industrial workers (Schmid, 1956; Matthaus, 1964) and in rabbits (Wolf et al., 1956) exposed to xylene. Respiratory irritation occurred in some rats subjected acutely to levels exceeding 1,000 ppm (Carpenter et al., 1975). Pulmonary edema and hemorrhage were seen at autopsy in one of three painters who died after being overcome by vapors of a solvent containing 90% xylene (Morley et al., 1970). Subjective symptoms of narcosis such as "lightheadedness" and "giddiness" have been reported in other industrial exposure cases involving xylene (Goldie, 1960; Glass,

1961). The threshold limit value for industrial exposures in the United States was set at 100 ppm (Criteria Document, 1975). It was felt that this standard would protect against minimal irritation or depressant effects which might impair attention, judgment, or perception.

Results of inhalation studies of the relative acute toxicity of the isomers of xylene and related solvents, such as toluene and benzene) are conflicting. Consideration of the reports leads one to conclude, however, that each is of the same order of acute toxicity. Individual isomers (Cameron et al., 1938) are seemingly equivalent in narcotic potency/acute toxicity with mixed xylene vapors (Carpenter et al., 1975). Carpenter and coworkers report the 4-hour LC_{50} for rats to be 6,700 ppm, and the LT_{50} at 11,000 ppm to he 92 minutes. Prostration of the animals was Seen within 20 minutes at the 11,000 ppm level.

Metabolism

Upon systemic absorption, xylene is metabolized primarily to toluic acid. Bray et al. (1949) demonstrated in rabbits that from 60 to 88 percent of the three isomers were oxidized to their corresponding toluic acids, with formation of xylenols a relatively minor pathway. These findings are confirmed in later studies in rabbits, rats, and guinea pigs (Fabre et al., 1960; Bakke and Scheline, 1970) and in humans (Ogata et al., 1970). Ogata and coworkers state that m- and p-xylene are metabolized in man principally to m- and p-hippuric. acid, which can be readily quantitated in the urine. The rapidity of formation and excretion of these relatively nontoxic metabolites, coupled with the small amounts of phenolics produced, is believed responsible for the low degree of systemic toxicity usually seen upon xylene exposure.

Organ Toxicity

Systemic toxicity has been attributed on occasion to xylene inhalation Although early investigators believed that xylene shared myelotoxic properties with benzene, more recent studies (Speck and Moeschlin, 1968; Jenkins et al., 1970; Carpenter et al., 1975) indicate that xylene uncontaminated with benzene does not exert myelotoxicity Toxicity to the cardiovascular (Hirsch, 1932; Sikora and Gala, 1957), female reproductive (Michon, 1965), and skeletal (Kucera, 1968) systems has been reported in humans, but not substantiated. Liver and/or kidney damage was diagnosed in workers exposed to xylene (Ghislandi and Fabiani, 1957; Joyner and Pegues, 1961; Morley et al., 1970). Fabre et al. (1960) saw histopathologic evidence of renal injury in rats and rabbits subjected to mixed xylene vapors for up to 130 days, though Jenkins et al. (1970) and Carpenter et al. (1975) could not detect hepatorenal damage in several species of animals tested comparably. The absence of toxicity in these latter two studies may be attributahle to an insufficient xylene exposure level. DiVincenzo

and Krasavage (1974) confirmed that xylene can cause liver injury, as demonstrated in guinea pigs by elevation of serum ornithine-carbamyl transferase activity and liver lipids following intraperitoneal injection of xylene. Whether xylene-induced hepatorenal injury may occur under circumstances of solvent abuse remains to be determined. As it has been proposed that phenolic metabolites of xylene may be potent toxicants, concomitant exposure to agents which enhance xylenol formation may potentiate xylene toxicity. Potential interactions of xylene with drugs and with other solvents would therefore be worthy of investigation.

Styrene

Styrene ($C_6H_5CHCH_2$; vinylbenzene, phenylethylene) is a colorless, oily liquid with a penetrating, pungent odor. It is only sparingly soluble in water, but quite soluble in organic solvents. Styrene is used primarily as a solvent and substrate for synthetic rubber and plastics.

Absorption and Acute Toxicity

Systemic absorption occurs readily upon inhalation of styrene (Astrand, 1975), with systemic distribution largely dependent upon lipid content of tissues. As with other organic solvents, the highest styrene levels following inhalation are seen in adipose tissue (Shugaev, 1969). Acute vapor exposure is characterized by narcosis and by irritation of the nose, eyes, and throat. Carpenter et al. (1944) report that humans exposed to 800 ppm of styrene experience immediate irritation of mucous membranes, followed by signs of significant CNS depression. Stewart et al. (1968), in testing human subjects exposed to styrene vapor concentrations of approximately 50, 100, 200, and 375 ppm, report both objective and subjective signs of irritation and narcosis only at the highest solvent level. This finding is confirmed by recent studies of Gamberale and Hultengren (1974). The current threshold limit value of 100 ppm is thus felt to protect the worker from any distress. Shugaev (1969) observes a positive correlation between concentration of styrene in the rat brain and degree of styrene-induced narcosis. The 4-hour LC_{50} for styrene in the rat is reported by Shugaev to be approximately 3,000 ppm, while the 2-hour LC_{50} in the mouse is about 5,000 ppm.

Metabolism

Although a portion of systemically absorbed styrene is eliminated via the lungs, the majority is apparently metabolized. Stewart et al. (1968) estimate in humans that from 0.7 to 1.2 percent of the total quantity of styrene absorbed upon inhalation is exhaled in the first several hours postexposure. Danishefsky and Willhite (1954) find that the rat rapidly metabolizes styrene, eliminating over 85 percent of a subcutaneous dose within 24 hours. Approx-

imately 3 percent of the styrene is exhaled unchanged, 12 percent exhaled as CO_2, 71 percent excreted in the urine, and 3 percent excreted in the feces. The pathways of metabolism of sytrene are reviewed by Leibman (1975). The majority of styrene is believed to undergo microsomal oxidation to styrene oxide, which is in turn hydrated to form phenylethylene glycol. This intermediate may be decarboxylated to produce benzoic acid and ultimately hippuric acid, or oxidized to mandelic acid and phenylglyoxylic acid. Although hippuric acid is a major metabolite in rodents (Ohtsuji and Ikeda, 1971), styrene exposure does not lead to a significant elevation of urinary hippuric acid in man (Stewart et al., 1958; Ikeda et al., 1974). Rather, mandelic and phenylglyoxylic acids predominate and are used as indices of human exposure to styrene. Pretreatment of rats with phenobarbital is known to enhance formation of styrene metabolites, while coadministration of toluene or SKF 525-A inhibits styrene metabolism (Ohtsuji and Ikeda, 1971; Ikeda et al., 1972).

Organ Toxicity

The acute toxic effects of styrene would appear to be due to the parent compound, although metabolites may play a role in subsequent manifestations of injury. Ohtsuji and Ikeda (1971) find styrene oxide to be four times as acutely toxic as styrene, although styrene glycol, mandelic acid, and phenylglyoxylic acid are reported to be equally or less toxic than styrene (Vera and Madlo, 1966). Reports of styrene-induced organ toxicity are quite rare. Although two accounts of hepatotoxicity in workers exposed to styrene appear in the Russian literature (Kats, 1962; Orlova and Solovera, 1962), the etiology of these injuries remains unproven. Histopathological and hematological studies of several species of laboratory animals, exposed to 1,300 ppm and 2,000 ppm of styrene daily for 6 months, fail to reveal significant toxic effects (Spencer et al., 1942; Wolf et al. (1956).

Potential Health Risks

Epoxides have been implicated in hepatotoxicity and carcinogenicity. Any circumstance which would enhance epoxide formation or longevity might increase covalent binding and tissue injury due to styrene oxide (Leibman, 1975). Also, it appears likely that styrene may significantly alter the metabolism and bioactivity of other organic chemicals.

Naphthalene

Naphthalene ($C_{10}H_8$; naphthalin, tar camphor) is a white, crystalline solid which volatilizes appreciably at room temperature. It is obtained primarily from coal tar and petroleum. Naphthalene is insoluble in water, but quite soluble in organic solvents. It is used commercially as a substrate for synthesis of a number of chemicals, as a moth repellent, as a toilet bowl deodorant, and as

a veterinary antiseptic and vermicide. Naphthalene is also a common constituent of such hydrocarbon mixtures as gasolines, thinners, and assorted organic solvents.

Acute Toxicity

Naphthalene is absorbed systemically upon inhalation of its vapors, as indicated by toxic manifestations in exposed subjects. A paucity of information exists, however, concerning most aspects of the pharmacokinetics and acute toxicity of naphthalene. Gerarde (1960) relates that time- and concentration-dependent eye irritation, headache, nausea, vomiting, and perspiration may occur upon vapor inhalation. The two principal dangers of naphthalene exposure are possible cataract formation and hemolytic anemia.

Organ Toxicity

Hemolytic action. The literature contains numerous accounts of acute hemolysis following oral ingestion of naphthalene, but relatively few reports of the malady in persons exposed by inhalation (Gleason et al., 1976). The classic findings in those afflicted include: marked decreases in hematocrit, hemoglobin, and erythracyte count; leukocytosis; erythrocytic fragmentation, Heinz body formation, and anisocytosis; hyperbilirubinemia; hemoglobinuria and dysuria. Persons with a hereditary deficiency of erythrocytic glucose-6-phosphate dehydrogenase activity appear particularly susceptible to the hemolytic effects of not only naphthalene, but a variety of other chemicals. The severity of hemolysis is apparently dependent upon the degree of enzyme deficiency and upon the extent of naphthalene exposure, with heavy exposures presumably capable of causing hemolysis in normal individuals, In a study by Valaes et al. (1963) of 21 infants with hemolytic anemia caused by naphthalene inhalation, glucose-6-phosphate dehydrogenase activity was normal in 9 of the 21. It is speculated here that a limited capability of the infants to conjugate and excrete naphthalene metabolites may have also been a causative factor, in that naphthalene itself is not believed to cause hemolysis. Mackell et al. (1951) report that naphthalene acutely produces no hemolysis when incubated in vitro with suspensions of human erythrocytes, or when injected intravenously (i.v.) into rabbits. α-]Naphthol is a relatively potent hemolytic agent under these experimental conditions, while ß-naphthol and α- and ß-naphthoquinone are less active in vitro and inactive in vivo.

Cataract induction. The ability of naphthalene to induce cataract formation is reviewed in detail by Grant (1974). This toxic effect, like the hemolytic action, appears to be dependent upon biotransformation of naphthalene to specific metabolites. Studies of the metabolism of naphthalene are well summarized in a recent paper by Rock et. al. (1976). Naphthalene may be converted via

several intermediates to 1,2-dihydroxynaphthalene, which in turn is autoxidizable to 1,2-naphthoquinone. Van Heyningen and Pirie (1967) present evidence that 1,2-naphthoquinone may indeed be formed in the eye, where it may exert its toxic effects by reacting with a variety of intracellular cofactors, as well as with structural and enzymatic proteins (Rees and Pirie, 1967). The progression of lesions, as seen microscopically, is described by Pirie (1968) in rabbits fed 1 gram of naphthalene daily. Principal changes in the lens, in order of appearance, include: vacuolation between epithelial cells; disarrangement of cells; inhibition of mitosis; cellular destruction with inadequate cell reduplication. Injury of retinal cells and deposition of oxalate crystals within the retina and vitreous body are also described by Pirie (1968). Accounts of ocular injury upon naphthalene inhalation in humans are rare. Ghetti and Mariani (1956) described lens opacities in 8 of 21 workers exposed to naphthalene fumes.

Potential Health Risks

Very little toxicological information has been derived from studies involving inhalation of naphthalene vapors. The current threshold limit value for occupational exposure has been set at 10 ppm, in that eye irritation was said to occur at 15 ppm (Hygienic Guide Series, 1967). Nau et al. (1966) reported cataracts in rats subjected repeatedly by inhalation to mixtures of C_9 - C_{12} hydrocarbons containing naphthalene. It would appear that certain individuals who abuse solvents 'containing large quantities of naphthalene might predispose themselves to hemolytic anemia and/or cataract formation. Properly designed investigations of this phenomenon should be conducted.

ALIPHATIC HYDROCARBONS

General Properties

The aliphatic hydrocarbons (paraffins) are a series of straight- and branched-chain hydrocarbons, including: alkanes (saturated); alkenes (one double bond); alkadienes (two double bonds); alkatrienes (three double bonds). Those aliphatics with at least one double bond are also known as olefins. These hydrocarbons occur naturally as mixtures in petroleum, from which they may be separated by cracking processes and fractional distillation. For purposes of the present paper, discussion will be limited largely to the straight-chain alkanes of intermediate length. Alkanes containing fewer than five carbon atoms are gases at room temperature, while pentane and the higher alkanes are volatile, flammable liquids. All are insoluble in water, but miscible in other organic solvents. These aliphatics are used individually as solvents and are major constituents of such mixtures as petroleum ether, gasoline, kerosene, and assorted thinners and solvents.

Acute Toxicity

Relatively little 'emphasis has been placed on the toxicological evaluation of the aliphatic hydrocarbons. Each may produce narcosis and loss of consciousness if breathed in sufficiently high concentrations. Narcotic potency has been demonstrated to vary directly with the lipophilicity, or number of carbon atoms in the molecule. Swann et al. (1974), upon cxposing mice for 5 minutes to a series of vapor concentrations of n-pentane, n-hexane, and iso-octane, noted increasing mucous -membrane irritation and narcotic potency with increasing carbon chain length. According to Spector (1956), lethal levels for mice were found to be as follows: n-pentane--128,200 ppm; n-hexane--40,000 ppm; n-heptane--15,900 ppm. Shugaev (1969) noted an apparent increase in the acute toxicity of 4-carbon aliphatics in mice with increasing unsaturation and/or branching of molecular structure. He also noted a positive correlation between hydrocarbon level in the brain and depth of narcosis, ranging from deep anesthesia to minimal disturbance in locomotion.

Cardiotoxicity

With the exception of respiratory irritation and CNS depression manifest acutely upon exposure to high vapor concentrations, the aliphatic hydrocarbons were regarded until recently as relatively innocuous. A number of these solvents have been shown, however, to have the potential to induce ventricular fibrillation. In an early study, Chenoweth (1946) found heptane to be quite potent in eliciting arrhythmia in dogs challenged with epinephrine. Much higher levels of methane and butane, in conjunction with increased doses of epinephrine, were required to produce ventricular fibrillation. Other aliphatic hydrocarbons which have more recently been shown to sensitize the heart included ethane, acetylene, propane, propylene, isobutane , butene , and isopentane (Krantz et al., 1948; Reinhardt et al., 1971).

Neurotoxicity

Another significant toxic effect ascribed to certain of the aliphatic hydrocarbons has been induction of peripheral neuropathy. The ability of n-hexane to produce nerve damage will be discussed here under a separate heading. A report by Prockop et al. (1974), of neuropathy in seven men who abused a lacquer thinner, suggested that n-heptane in combination with other solvents might also be neurotoxic. The lacquer thinner was found to consist of at least 11 components, including 0.5% n-hexane and 15.5% 2-heptanone (Prockop, 1976). n-Heptane is metabolized primarily to 2-heptanol (Frommer et al., 1972), with subsequent hydroxylation and/or oxidation likely. Since this metabolic sequence closely resembles that of n-hexane, an established neurotoxin, n-heptane may be neurotoxic as well. Studies are needed to investigate this phenomenon.

n-Hexante

n-Hexane ($CH_3(CH_2)_4CH_3$) is a colorless, volatile liquid at room temperature. It is insoluble in water, but miscible with organic solvents. n-Hexane is used as a solvent, often in combination with other aliphatic and aromatic hydrocarbons. Since n-hexane is currently a principal component of many "over-the-counter" glues and cements, individuals who abuse these products may subject themselves to quite high vapor concentrations of n-hexane (Korobkin et al.. 1975),

Absorption and Acute Toxicity

n-Hexane is readily absorbed via the lungs. Bohlen et al. (1973) relate that the uptake of n-hexane, into the blood and tissues of rats follows an exponential function, with tissue concentrations at saturation directly proportional to lipid content of each tissue. Swann et. al. (1974) report on the acute depressant effects of 5 minutes inhalation of a series concentrations of n-hexane in mice, noting at: 8,000 ppm--no anesthesia; 16,000 ppm--light anesthesia: 32,000 ppm- deep anesthesia; 64,000 ppm--respiratory arrest within 4.5 minutes of exposure. In an acute toxicity study, Kimura et al. (1971) found n-hexane, with an oral LD_{50} of 49.0 ml/kg, to be the least toxic of a number of organic solvents tested in young rats. The occupational threshold limit value of 500 ppm for n-hexane is based on data derived from human studies in which giddiness and dizziness are experienced at 5,000 pmm. while eye and throat discomfort headache, and nausea are claimed by some subjects at about 1.500 ppm.

Organ Toxicity

Occupational toxicity. Neuropathy has been attributed to n-hexane inhalation in both occupational settings and in solvent-abuse cases. The earliest reference to hexane as a possible cause of neuropathy appeared in the 1960's in Japanese journals (Oishi et al., 1964: Wada et al., 1965. Yamada, 1967; Sobue et al., 1968; Yamamura, 1969). Each of the cases described in these publications was related to industrial exposure. In the comprehensive clinical study of Yamamura (1969), 93 of 1,662 workers with potential exposure to n-hexane were found to exhibit nerve damage. It was estimated that these individuals were exposed during working hours to 500-2,500 ppm of n-hexane. The neuropathy associated with these cases involved both the sensory and motor systems, with sensory loss predominant. Histologic, electromyographic, and nerve conduction velocity studies revealed degenerative changes consistent with denervation including axonal swelling and loss of myelin. More recently, industrial cases of n-hexane-induced neuropathy have been observed in the United States (Herskowitz et al., 1971; Paulson and Waylonis, 1976).

Inhalant abuse neuropathy. Neuropathy has been linked in numerous instances with n-hexane in solvent abuse cases (Gonzalez and Downey, 1972, Goto et al., 1974; Shirabe et al., 1974; Korobkin et al., 1975; Towfighi et al., 1976). In some instances the patients had intentionally inhaled volatiles without n-hexane for years without apparent detrimental effect, but developed crippling peripheral neuropathy within a matter of months after switching to products containing n-hexane. In each circumstance, however, n-hexane was only one component of a solvent mixture. Clinical findings in these cases were analogous to the industrial cases. Microscopic examinations revealed axonal swelling, accumulation of neurofilaments in axons, myelin thinning and denudation, and skeletal muscle changes characteristic of neurogenic atrophy. Most patients in these studies exhibited gradual functional improvement upon discontinuation of solvent abuse.

Animal neuropathy. A limited number of studies utilizing experimental animals have been conducted to determine whether n-hexane is actually a neurotoxin. In an early study, Miyagaki (1967) exposed mice 24 hours daily for 1 year to n-hexane at levels of approximately 100, 250, 500, 1,000, and 2,000 ppm. Miyagaki saw electrophysiological and histological evidence of nerve damage only at the three highest concentrations, leading him to conclude that the mouse was much less sensitive than man to neurotoxic effects of n-hexane. The rat has been demonstrated to be more susceptible than the mouse (Kurita, 1967; Ishii et al., 1972), with Schaumburg and Spencer (1976) seeing evidence of neuropathy after 1 to 2 months in rats exposed continuously to air containing 400-600 ppm of n-hexane. Schaumburg and Spencer, on the basis of their findings of both peripheral and central axonal degeneration, suggested that permanent CNS damage as well as peripheral degeneration may also occur in humans.

n-Hexane and related compounds are metabolized by the microsomal enzyme system, possibly to metabolite(s) which actually are neurotoxic. Frommer et al. (1974) observed with rat liver microsomes the formation of three isomeric alcohols from n-hexane, with 2-hexanol the predominant metabolite. Secondary hydroxylation and alcoholic oxidation to form the corresponding ketones likely occur to some degree, in that DiVincenzo et al. (1976) have recently detected 5-hydroxy-2-hexanone and 2,5-hexanedione in the serum of guinea pigs dosed with n-hexane. As discussed elsewhere in this monograph, 2,5-hexanedione may well be the metabolite responsible for apparent n-hexane-induced neuropathy

Since each of the aforementioned industrial and solvent abuse cases involved exposure to mixed solvents, it is possible that certain of the extraneous solvents may have modified the neurotoxicity of n-hexane. If 2,5-hexanedione is principally responsible for n-hexane neuropathy, chemicals which would enhance the metabolism of n-hexane logically might increase its apparent neuro-

toxicity. Frommer et al. (1974) noted that phenobarbital pretreatment elicited a several-fold increase in 2-hexanol formation in rat microsomes, while Abdel-Rahman and coworkers (1976) found that phenobarbital hastened the elimination of 2-hexanone (methyl n-butyl ketone) from the bloodstream of rats. Abdel-Rahman and his colleagues observed that chronic phenobarbital treatment seemed to protect rats dosed with 2-hexanone, but 2-butanone (methyl ethyl ketone) potentiated neurotoxicity in such animals. Since Traiger et al. (1975) have shown 2-butanone to be an inducer of microsomal enzyme activity, it is possible that 2-butanone may enhance 2,5-hexanedione production from 2-hexanone, or conversely may competitively inhibit glucuronidation and excretion of 2,5-hexanedione. Suzuki et al. (1974) found that coadministration of toluene did not seemingly alter elimination of n-hexane from the bloodstream, although levels of n-hexane metabolites were not measured. The influence of other solvents, drugs, and alcohol on n-hexane metabolism and neurotoxicity remains subject to speculation.

Other organ pathology A paucity of information, other than that relating to neurotoxicity, is available concerning the potential of n-hexane to produce organ damage. Although hepatorenal injury is usually not manifest in patients treated for n-hexane-induced neuropathy, Paulson and Waylonis (1976) did see elevation of certain serum enzymes indicative of liver injury in one such patient. Nix et al. (1976) report morphologic evidence of injury in mice exposed continually to 6,000 and 12,000 ppm of mixed hexanes for 2 to 49 days. The severity of histopathologic change in these mice varies directly with duration of exposure and solvent level. Bohlen et al. (1973) relate that n-hexane inhalation may elicit hepatic lipid accumulation. This is confirmed in guinea pigs by DiVincenzo and Krasavage (1974), who also find that n-hexane produces an increase in serum ornithine-carbamyl transferase activity. Studies conducted under conditions approximating solvent abuse should be performed to assess the hepatorenal toxicity of n-hexane.

MIXED ALIPHATIC/AROMATIC HYDROCARBONS

Gasoline

Gasoline (petrol) is a mixture of C_4 to C_{12} hydrocarbons, including paraffins, olefins, naphthenes, and aromatics. The relative amounts of various constituents depend upon the origin of the petroleum and the method of preparation. Gasoline is normally obtained from crude petroleum by thermal or catalytic cracking and by fractional distillation. Leaded gasolines contain approximately 3 ml of tetraethyl lead per gallon to prevent engine "knocking" (Lane, 1966). Gasoline is used primarily as a fuel, but enjoys some industrial applications as a solvent or thinner.

Acute Toxicity

Inhalation of gasoline vapors may result in both mucous membrane irritation and narcosis. In an early study of human subjects by Drinker et al. (1943), exposure to approximately 1,000 ppm of gasoline for 1 hour produced slight eye, nose, and throat irritation, but little evidence of narcosis. When Drinker et al. (1943) exposed subjects to 2,600 ppm, slight dizziness accompanied the eye irritation, while at 10,000 ppm marked intoxication was experienced after 4 to 5 minutes. A more recent study by Davis et al. (1960) of three different unleaded gasolines revealed no manifestations of intoxication in humans subjected for 30 minutes to any of the gasolines at concentrations of 200, 500, and 1,000 ppm. The only significant effect noted was eye irritation at the 1,000 ppm level. Little definitive animal experimentation has been reported to date which has assessed the acute toxicity of commonly used gasolines.

Deaths have been reported in persons who have inhaled concentrated gasoline vapors. Aidin (1958) measured gasoline levels varying from 8,000 to 35,000 ppm under conditions approximating those which resulted in a fatal intoxication. Wang and Irons (1961) related circumstances surrounding the death of a man who was overcome within 5 minutes after entering a tank estimated to contain 5,000 to 16,000 ppm of gasoline vapor. More recently, two fatal cases were reported in which the gasoline concentration measured in the brain of one victim 30 hours after death was 0.3 to 0.4 mg/g of tissue, while that in the liver of the second victim was 0.7 mg/g (Nelms et al., 1970). Gasoline was detected by gas chromatography in the liver of an adolescent who died suddenly upon deliberately sniffing gasoline fumes, although no attempt was made at quantitation (Poklis, 1976).

It is difficult to establish, with any degree of certainty, vapor and tissue concentrations of gasoline required to produce intoxication and death. The time elapsed between subject death and analysis, as well as problems with analytical sensitivity and specificity in published reports, leave room for a good deal of conjecture. Quantitation is complicated by the large number of aliphatic and aromatic hydrocarbons present in all gasolines. Should the major components of a particular gasoline be ascertained, one is faced with the problem of attributing narcosis to individual hydrocarbons or to combinations of hydrocarbons which may interact with one another in vivo. The researcher is also faced with great variability in gasoline composition.

Death upon acute exposure to gasoline fumes is generally attributed to severe CNS depression terminating in respiratory paralysis (Machle, 1941). Autopsy reports in humans commonly include the finding of pulmonary irritation, although the edema seen in the respiratory tract does not appear severe enough to be fatal (Wang and Irons, 1961; Nelms et al., 1970; Poklis, 1976), Poklis sug-

gests that death may result in some cases from sensitization of the myocardium, since both gasoline (Chenoweth, 1946) and numerous constituents of gasoline are known to predispose to cardiac arrhythmias (see discussion of individual solvents).

Inhalation Abuse

Intentional inhalation of gasoline fumes is widely reported in the medical literature. One of the first reports is by Clinger and Johnson in 1951, with subsequent accounts by Faucett and Jensen (1952), Edwards (1960), Lawton and Malmquist (1961), Oldham (1961), Easson (1962), Gold (1963), Bethell (1965), Durden and Chipman (1967), Law and Nelson (1968), Carroll and Abel (1973), and Poklis (1976). In most instances the subjects in these cases relate that gasoline sniffing produces pleasant sensations, although frightening hallucinations are experienced by some individuals The subjects commonly sniff gasoline vapors from an opened container for 2 to 5 minutes to attain a "high," although they may sniff for too long and lose consciousness. An abuse episode may last for several hours, during which the person must repeatedly inhale gasoline in order to maintain the high.

Organ Toxicity

Physical and neurological examinations of patients who abused gasoline for as long as 11 years generally have failed to reveal evidence of residual injury. The patients characteristically have exhibited serious emotional problems which often improved upon abstention from solvent inhalation. At least four cases involving abnormal electroencephalograms have been reported in persons who abused gasoline (Faucett and Jensen, 1952; Lawton and Malmquist, 1961; Law and Nelson, 1968; Carroll and Abel, 1973). In the latter two reports, elevated lead levels were measured in the urine or blood, suggesting tetraethyl lead as the causative agent . Chelation therapy resulted in a significant reduction in blood lead levels and a marked symptomatic improvement in the patient described by Law and Nelson (1968). Durden and Chipman (1967) related the history of a man who had inhaled gasoline fumes for 7 years without apparent harm. but developed severe hepatorenal injury upon drinking beer and inhaling vapor of a solvent containing 60% carbon tetrachloride. Anemia has on occasion been described in industrial workers exposed to benzene-contaminated gasoline (Machle, 1941; Amorati et al., 1952: McLean, 1960; Verwilghen et al. , 1975). Salamone (1961) observed aplastic anemia in rabbits subjected 8 hours daily for 80 days to 60 mg/l of gasoline vapors. The presence of benzene in varying amounts in gasolines (Parkinson, 1971; Runion, 1975) raises the possibility that myelotoxicity may be an unrecognized hazard of gasoline abuse.

Miscellaneous Hydrocarbon Solvents

Vast quantities of hydrocarbon solvents are used annually in the United States. The majority of these are not single chemicals, but complex mixtures having boiling ranges varying from less than 10° F to more than 100° F. These hydrocarbon solvents are comprised of varying proportions of aliphatics (paraffins), benzene, alkylbenzenes, and mono- and dicycloparaffins. Solvent mixtures are commonly used in paints and surface coatings as thinners and fillers. Large volumes are also used in the dry cleaning industry, for extraction of edible oils, as lighter fluid and fuel, and as solvents for pesticides, inks, and rubber cement. Because of such widespread use and access, the potential exists not only for occupational exposure during legitimate solvent use, but for intentional inhalation for purposes of self-intoxication.

Acute Toxicity

Despite the common use of hydrocarbon solvent mixtures, there is Little published information pertaining to their toxicity. Knowledge up to 1940 is compiled by Von Oettingen (1940), while information through the 1960's is summarized by Gerarde (1960, 1963) and by Browning (1965). The majority of reports suffer from inadequate identification of physical properties and composition of the solvent mixtures tested. Thus, comparison of results from one study to another and application of a study's findings to an immediate solvent exposure situation are difficult.

With the advent of more definitive analytical techniques, better characterization has been possible for hydrocarbon mixtures being tested for their toxicity. Rector et al. (1966) found that samples of mineral spirits contained a complex mixture of saturated and unsaturated aliphatics (80-87 percent) and aromatics (13-19 percent), with a boiling range of 140°-190° C. Upon continuous exposure of dogs, monkeys, rabbits, rats, and guinea pigs for as long as 90 days to a range of concentrations of mineral spirits, fatalities/toxicity were seen only in the guinea pig (Rector et al., 1966). No biochemical or histopathologic explanation could be found for the selective toxicity of mineral spirits in the guinea pig. Nau et al. (1966), in an evaluation of the subacute inhalation toxicity of C_9 - C_{12} fractions of petroleum distillates in rats and monkeys, observed certain hematologic abnormalities, depression of body weight gain, and mucous membrane irritation in each species. The C_{11} - C_{12} fraction was found to be more toxic than the C_9 - C_{10} fraction, leading Nau and his coworkers to recommend threshold limit concentrations of 50 and 25 ppm, respectively, for the C_9 - C_{10} and C_{11} - C_{12} fractions. Hine and Zuidema (1970) reported toxicological studies in rats of a number of hydrocarbon mixtures having relatively narrow boiling ranges (i.e., consisting of a limited number of components). Upon inhalation of high vapor concentrations of these mixtures, the rats exhibited

incoordination, prostration, and convulsions before dying. Scrutiny of the data of Hine and Zuidema revealed: (1) aromatic fractions were more acutely lethal than were corresponding aliphatics; (2) acute lethality was directly proportional to the number of carbon atoms or average molecular weight of components of each hydrocarbon fraction.

To date, the most definitive reports on inhalation toxicology of hydrocarbon mixtures have been published as a series of articles by Carpenter et al. (1975-1976). A standard protocol was followed for 12 different solvent mixtures in evaluation of their "no-ill-effect" level in rats and dogs, LT_{50} and LC_{50} in rats, central nervous system effects in cats, subacute toxicity in rats and dogs, respiratory irritation in mice, and odor and irritation thresholds in humans. The LC_{50} values commonly ranged from 5,000 to 9,000 ppm, although values as low as 1,400 ppm and as high as 15,000 ppm were measured, Some solvent mixtures such as kerosene were so poorly volatile that lethal vapor levels could not be achieved. Signs of narcosis preceding death on acute exposure commonly included loss of coordination, ataxia, loss of proprioception, salivation, unconsciousness, tremors, and convulsions Narcotic and irritant potency varied directly with the carbon content and boiling range. Solvent concentrations, which acutely elicited "no ill effect," were used for subacute exposures lasting up to 14 weeks. Toxicological parameters including hematology, serum enzyme measurements, urinalyses, histopathology, body weight and organ weight monitoring, and electrocardiogram recordings revealed little or no evidence of solvent-induced injury within the 14-week study periods. These studies lend additional support to the concept that the majority of aliphatic and aromatic hydrocarbons appear to be relatively nontoxic, even when encountered as mixtures.

Potential Health Risks

A variety of maladies have been tentatively attributed to inhalation of hydrocarbon solvents, Beirne and Brennan (1972) and Zimmerman et al. (1975) reported a number of cases of autoimmune glomerulonephritis which appeared to be associated with prior exposure to individual solvents or solvent mixtures. These investigators advanced the theory that antibody production ensued following solvent-induced injury of lung or kidney membranes. Capurro (1976) suggested that hydrocarbon solvents might , via a similar mechanism, alter the immune status of subjects and predispose them to certain forms of cancer. Finally, recent studies have demonstrated inferior psychological performance (Lindstrom, 1973) and an increased incidence of nonspecific neuropsychiatric disorders (Axelson et al. , 1976) in workers including painters, varnishers, dry cleaning employees, and printers. These findings may be important in light of psychological problems commonly manifested in individuals who abuse solvents.

The occasional variances from normal seen by Carpenter et al. (1975-1976) for certain subacute toxicity parameters, coupled with aforementioned finding of Nau et al. (1966), and others illustrate the harmful nature of repeated high-level inhalation of mixed solvent vapors. Few investigations have yet been conducted to assess the toxicity of such solvent mixtures under conditions approximating human solvent abuse.

ALIPHATIC NITRITES

The relatively low molecular weight aliphatic nitrites are very volatile, highly flammable liquids. The most commonly used and abused of these is amyl nitrite ($C_5H_{11}NO_2$). Synonyms for this compound are isoamyl nitrite and isopentyl nitrite. Aliphatic nitrites have several medical applications. Among these are treatment of angina pectoris (Aviado, 1972; Dewey et al., 1973), cyanide poisoning (Aviado, 1972; Stine et al., 1976), and hydrogen sulfide poisoning (Stine et al., 1976). Amyl nitrite is also occasionally used in the diagnosis of ventricular septal defects (Aviado , 1972).

Abuse

Amyl nitrite NF (Vaparole) is supplied in crushable glass ampules which contain 0.3 ml of the compound. In the drug culture these are known as "poppers" or "snappers." This drug has been popular in the male homosexual population for a number of years (Everett, 1972, 1975b; Gay et al., 1975; Gay and Sheppard, 1972, 1973; Hollister, 1975a, 1975b). More recently it has become popular in the heterosexual community (Everett, 1972; Everett, 1975b; Gay and Sheppard, 1972 and 1973). Apparently, the most effective time to inhale the drug is just before orgasmic climax (Everett, 1972 and 1975b; Gay et al., 1975; Gay and Sheppard, 1972, 1973; Hollister, 1975a; Pearlman and Adams, 1970). The apparent effect is lengthening the time and intensity of the pleasurable feeling associated with climax (Everett, 1972 and 1975b; Gay and Sheppard, 1972, 1973; Hollister, 1975a, 1975b; Knoepfler, 1977; Louria, 1970; Pearlman and Adams, 1970). Although this drug has been used in intercourse by both sexes, it is much more popular in the homo- and heterosexual male population (Everett, 1972, 1975b). Some questionable increases in sexual aggressiveness have also been associated with the use of this drug (Everett, 1975a; Gay et al., 1975). These compounds are apparently becoming increasingly popular in drug-oriented populations .

Toxicity

The use of amyl nitrite may be accompanied by medical complications . Limited toxicological data have been available. When given to mice by i.p. injection, the LD_{50} was 130 mg/kg. When given

i.v. the LD_{50} was 51 mg/kg Dewey et. al., 1973). When dogs were administered amyl nitrite i.v., low doses elicited tremors and ataxia, while higher doses produced convulsions and death (Dewey et al., 1973). When these same investigators exposed the dogs to the drug by inhalation, one dog became quiet and another ataxic for a short period. When they were subjected to repeated inhalation doses of amyl nitrite at 20- to 90-second intervals for up to 7 minutes. varying degrees of pharmacologic effects were noted, ranging from no effect to ataxia, gagging, vomiting, urination, defecation, and even brief convulsions. These effects seemed to be somewhat related to the frequency of dose and the number of doses. Other side effects have been noted in people who have used or abused this drug, including dizziness, headache, tachycardia, hypotension, syncope, and increased intraocular pressure (Everett, 1972, 1975b); Gay and Sheppard, 1973; Hollister, 1975a, 1975b; Louria, 1970; Pearlman and Adams, 1970). Nitrites in general have also been associated with methemoglobinemia and rare sudden deaths (Louria, 1970). Amyl nitrite is contraindicated in certain persons who have cardiovascular problems (Everett, 1975b; Hollister, 1975a, 1975b). If abuse of such drugs continues to escalate medical complications may be seen more frequently. Few if any investigations have been conducted on the effects of butyl nitrites and related components contained in over-the-counter products such as Locker Room or Rush.

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Chapter 10

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY OF HALOGENATED SOLVENTS AND PROPELLANTS

Domingo M. Aviado

INTRODUCTION

In recent years, there has been a considerable amount of investigation into the pharmacology and toxicology of halogenated solvents and propellants as they relate to the abuse of aerosol products. The prevalent opinion is that the major hazard from their abuse is death from cardiac arrest, However, since the solvents and propellants contained in aerosol products are potentially toxic to the lungs, liver, and kidney, it will be necessary to review briefly the extracardiac actions of the halogenated inhalants. There is no reported case indicating that their abuse exerts a permanent, irreversible damage to organs other than the heart.

The pharmacologic features and toxicity of the halogenated solvents and propellants are presented by grouping them according to the nature and the number of halogen in the chemical structure. Since there are review articles on the toxicity of the halogenated compounds (Von Oettingen, 1955; Browning, 1965), this chapter will emphasize the relative toxicities of the halogenated inhalants. The rating of toxicity is based on animal experiments performed by the author and his collaborators, as well as information reported by other investigators.

FLUORINATED HYDROCARBONS

At the time of writing this chapter several government agencies were in the process of banning fluorinated propellants used in aerosol products, The compelling reason is the suspected depletion of the ozone layer in the ionosphere, rather than to toxicities identified through animal studies. In any event, it is important to review the inhalational toxicity of fluorinated propellants to provide a basis for any propellants now under consideration to replace the fluorinated ones in current issue.

Cardiotoxicity of Fluorinated Propellants

The most harmful effects so far demonstrated during brief inhalation of fluorocarbons relate to the heart: cardiac arrhythmia, depression of myocardial contractility, and reduction in cardiac output. The lowest. concentration that influences the heart is 0.3% of trichlorofluoromethane (FC 11) which sensitizes the heart to epinephrine-induced arrhythmia. It is the opinion of the author that this concentration is reached when aerosols are abused and that fatalities are caused by this mechanism. Comparative experiments indicate that FC 11 is more toxic than the other two fluorocarbons (FC 12 and FC 114). For each of the three propellants, the dog heart is more sensitive than the monkey heart (see Table 1).

Extracardiac Organs

There is no indication that fluorocarbons affect the liver and kidneys (Jenkins et al., 1970). The effect on the airways varies from species to species: Fluorocarbon 11 produces bronchospasm in the rat and mouse but not in the dog and monkey, fluorocarbon 12 only in the mouse and monkey, and fluorocarbon 114 in all four animal species, There is no comparative information in man although aerosol hair-sprays produce temporary bronchospasm. It has also been suspected that deaths of asthmatic patients who misuse aerosol bronchodilators are the result of bronchospasm and cardiac arrhythmia caused by the fluorocarbons (Aviado, 1975a).*

DICHLORINATED HYDROCARBONS

Although there are no reports in the literature of abuse with dichlorinated solvents, it. is necessary to review their pharmacologic and toxicologic actions because they are likely to replace the fluorinated propellants in aerosol products. At the time of this writing, methylene chloride in combination with hydrocarbons has been adopted by some manufacturers of aerosol products (Aviado et al., 1977). Since other dichlorinated solvents have similar

*Editor's Note: Isoproterenol was also present in high concentrations in these British preparations.

TABLE 1

INHALATIONAL TOXICITY OF FLUORINATED HYDROCARBONS*

	Minimal Effective Concentration		
	Trichloro-fluoro-methane (CCl_3F) FC 11	Dichloro-difluoro-methane (CCl_2F_2) FC 12	Dichloro-tetrafluoro-ethane ($CClF_2CClF_2$) FC 14
Cardiac Arrhythmia			
Dog heart sensitized to epinephrine	0.3%	5.0%	5.0%
Monkey heart spontaneous arrhythmia	2.5%	10.0%	10.0%
Monkey heart tachycardia	2.5%	10.0%	10.0%
Myocardial Contractility			
Monkey heart depression	2.5%	10.0%	10.0%
Dog heart depression	0.5%	10.0%	2.5%
Hemodynamic parameters			
Dog cardiac output reduced	1.0%	10.0%	10.0%
Dog total systemic vascular resistance increased	2.5%	20.0%	5.0%
Airway resistance			
Dog bronchospasm	(absent)	(absent)	10.0%
Monkey bronchospasm	(absent)	10.0%	20.0%
Rat bronchospasm	2.5%	(absent)	15.0%
Mouse bronchospasm	1.0%	2.0%	2.0%

*Adapted from Aviado 1975b.

effects on the central nervous system as the other abused solvents, three other dichlorinated hydrocarbons are included in the following discussion.

At the outset, it should be stated that there is no published comparison of the solvents under consideration. The author and his colleagues have some unpublished results on the cardiotoxicity of dichlorinated solvents when administered as a vapor by inhalation to anesthetized dogs. The minimal concentrations that depress myocardial contractility are as follows:

methylene chloride 2.5%
acetylene dichloride 1.5%
ethylene dichloride 0.5%
propylene dichloride 0.25%.

There is a ten-fold difference between the most toxic and the least toxic of the group. Compared to other chlorinated solvents, such as methyl chloroform (0.25%) and trichloroethylene (0.05%), methylene chloride stands out as the least cardiotoxic among the di- and trichlorinated hydrocarbons.

Methylene Chloride

Methylene chloride (CH_2Cl_2)is one of the most widely used solvents for paint stripping. It is also used as a carrier in rapid-dry paints and spray paints. A combination of methylene chloride and hydrocarbons is under consideration as a replacement for the fluorocarbons currently in use in aerosol products.

So far, there are no reports in the literature of the abuse of methylene chloride. However, its introduction as a substitute for fluorocarbons in aerosol products will raise questions of its toxicity in the event that aerosol products, in general, continue to be abused. The few cases of occupational poisoning from methylene chloride do not show pathologic lesions in the liver and kidneys. However, sublethal amounts of methylene chloride produce hepatic necrosis in animals (Criteria Document, 1976a). Additional investigation is needed to determine the potential effect of methylene chloride on the liver, kidneys, and lungs following brief daily exposure in animals.

The major concern regarding the safety of methylene chloride is that it is metabolized to carbon monoxide in the liver. Stewart and Hake (1976) have cautioned users of paint removers containing methylene chloride that the formation of carbon monoxide can produce cardiovascular stress and even death. However, there are no other known paint removers safer than methylene chloride, so its benefit-to-risk ratio justifies its continued use provided proper precautions (such as ventilation) are taken to minimize the amount inhaled by the individual in the course of paint stripping.

The amount of methylene chloride contained in aerosol products is limited in quantity compared to that needed for paint stripping. Nevertheless, the cardiac effects of methylene chloride should be analyzed, particularly because of its formation to carbon monoxide . The fundamental questions that need to be answered are as follows: Does the formation of carbon monoxide increase the cardiotoxicity of methylene chloride? Are the cardiac effects exaggerated in the ischemic heart? Does methylene chloride interfere with normalization of an elevated carboxyhemoglobin? The following discussion reviews the effects of carbon monoxide, methylene chloride, and interaction between both.

There is no question that methylene chloride, per se, influences the heart because experiments reported by Kiessling in 1921 and by Joachimoglu in 1925 showed depression of the perfused heart and excised vessel using artificial perfusates without hemoglobin. In 1935 Hermann and Vial reported that the injection of epinephrine caused ventricular fibrillation in a dog that had been inhaling methylene chloride vapor. The concentration of methylene chloride was not mentioned. However, the list of volatile solvents that sensitized the heart to cardiac arrhythmia induced by epinephrine included the following: carbon tetrachloride, chloroform, and methyl chloride.

Cardiac Arrhythmia in Mice

The electrocardiogram was used to detect arrhythmia and conduction defect of the heart (Aviado and Belej, 1974). The minimum concentrations of methylene chloride that produced abnormalities in the electrocardiogram were as follows: 20% methylene chloride in air with intravenous injection of 6 μg/kg of epinephrine and 40% without injection of epinephrine. The concentrations of trichlorofluoromethane (FC 11) that produced arrhythmias were 5% and 10%, respectively, indicating that methylene chloride is less cardiotoxic than the fluorocarbon.

Cardiac Arrhythmia in Dogs

Reinhardt et al. (1971, 1973) and Clark and Tinston (1973) used conscious dogs and recorded the electrocardiogram. The concentrations of methylene chloride and related compounds that sensitize the heart to epinephrine-induced arrhythmias were as follows:

	Reinhardt et al.	Clark and Tinston
methylene chloride	2.0%	2.4%
trichlorofluoromethane (FC 11)	0.5%-1.2%	1.25%
carbon tetrachloride	----	0.5%

Reinhardt et al. could not test greater than 2.0%, concentrations of methylene chloride because the dog could not tolerate the mixture. Clark and Tinston succeeded in administering up to 3.4% and reported a mean concentration of 2.4% to sensitize the heart, which is two times that for trichlorofluoromethane (FC 11) and almost five times higher than carbon tetrachloride.

Cardiac Arrhythmia in Carbon Monoxide Poisoning

In cases of human carbon monoxide poisoning, there are abnormalities in the electrocardiogram indicating myocardial ischemia. These appear when carboxyhemoglobin levels exceed 50%, which is high enough to produce loss of consciousness.

In dogs, the threshold saturations that produce cardiac changes were determined by Ehrich et al. (1944). There was depression of the R-T segment and degenerative changes for a few hours at 40% carboxyhemoglobin. Heart block and myocardial hemorrhages and necroses were observed only when the carboxyhemoglobin level exceeded 75% for 1 hour or longer. In rats poisoned with 10,000 parts per million (ppm) carbon monoxide inhalation for 10 minutes, high enough to elevate carboxyhemoglobin to 65%, ultrastructural changes in the heart, consisting of intracellular edema, swelling of mitochondria, and disruption of lysosomes, were reported. Suzuki (1969) concluded that the effects of carbon monoxide on the heart result not only from hypoxemia but also from the direct toxic effects on the specific respiratory enzymes. Twenty-four hours after the inhalation, the hearts of most rats appeared essentially normal so that the toxic effect was reversible. From the foregoing experiments, cardiac arrhythmias appear only if carboxyhemoglobinemia exceeds 40 percent, which is not attained during ordinary use of methylene chloride.

Interaction Between Carboxyhemoglobin and Solvents on the Heart

For completeness, it is necessary to discuss the question of interaction between the direct cardiac effects of methylene chloride and the indirect cardiac consequence of carboxyhemoglobinemia resulting from metabolism of methylene chloride. Does carboxyhemoglobinemia increase the vulnerability of the heart to epinephrine-induced arrhythmia? The answer was supplied in 1974 by Kaul et al. In dogs with elevated levels of carboxyhemoglobin (to 35%) by inhalation of carbon monoxide, there was no increase in vulnerability of the ventricles to arrhythmias provoked by epinephrine and petroleum ether. There are no experiments reported involving methylene chloride. However, it is safe to conclude that carboxyhemoglobin, per se, does not increase the sensitivity of the heart to hydrocarbon-epinephrine arrhythmias and that although methylene chloride is converted to carbon monoxide, this does not increase the vulnerability of the heart. In other words, the arrhythmogenicity of methylene chloride is not enhanced by the small amount of carbon monoxide produced by its metabolism.

Myocardial Contractility

It was stated earlier that the threshold concentration that would depress significantly myocardial contractility of the canine heart is 2.5% methylene chloride. Since this was performed in an intact animal, it was not possible to differentiate the effects of carbon monoxide formation separately from the nonmetabolized solvent. Experiments recently completed have succeeded in the identification of cardiac effects related and unrelated to carbon monoxide (Juhasz-Nagy et al., 1977; Zakhari et al., 1977).

In the canine heart-lung preparation, the inhalation of methylene chloride was not accompanied by a rise in carboxyhemoglobin. Thus, it was possible to identify the myocardial depressant action of methylene chloride alone without formation of carbon monoxide.

In the dog with intact heart, the hemodynamic effects of methylene chloride alone were not exaggerated by the combined administration of carbon monoxide. This ischemic heart was no more reactive to methylene chloride and to carbon monoxide compared to the nonischemic heart. Furthermore, the initial elevation of carboxyhemoglobin following the inhalation of carbon monoxide was not influenced in its normalization pattern by the inhalation of methylene chloride. These results indicate that the metabolic conversion of methylene chloride to carbon monoxide does not occur in the heart, does not influence the normalization of carboxyhemoglobinemia even in the presence of methylene chloride, and that carboxyhemoglobinemia does not exaggerate the cardiac effects of methylene chloride. As a matter of fact, the author believes that conversion to carbon monoxide reduces the cardiac depressant action of methylene chloride in as much as the same concentration is more depressant in the heart-lung preparation where there is no formation of carbon monoxide, compared to the heart of an intact animal where metabolism is possible.

Acetylene Dichloride

Acetylene dichloride (CHClCHCl) is used as a solvent for waxes, resins, acetyl cellulose, and rubber. It is contained in some antiknock gasolines, fumigant mixtures, and in cleansing products. There is one reported fatality after inhalation of the acetylene dichloride vapor in a small enclosure (Hamilton, 1933). Menshick (1957) reported four others and collected 27 instances of occupational poisoning from the literature. There were pathological lesions in the liver and kidneys.

Ethylene Dichloride

Ethylene dichloride (CH_2ClCH_2Cl) is a constituent of rubber cement , degreasing solvent mixtures, and leaded fuels. The Criteria Document (1976b) reviews almost a hundred cases of accidental poisoning and occupational inhalation of ethylene dichloride. Hepatic and renal lesions are the major lesions seen at postmortem examination.

Propylene Dichloride

This solvent is a component of furniture finisher, paint remover, and soil fumigants. A case of acute poisoning from oral ingestion of propylene dichloride ($CH_2ClCHClCH_2$) was reported by Chiappino and Secchi (1968). Histologic studies of the liver biopsy showed diffuse phenomena of turbid degeneration of the liver cells and ultrastructural changes in Golgi apparatus, mitochondria, and

endoplasmic reticulum. Secchi et al. (1968) reported on seven cases of acute poisoning from commercial solvents sold as trichloroethylene. Chemical analysis of solvents responsible for poisoning revealed that severe liver toxicity occurred only in patients poisoned by mixtures rich in propylene dichloride and 1,2-dichloroethane. In these patients, cytoplasmic and mitochondrial enzymes appeared in the serum, which indicates severe lesions in the cytoplasmic and mitochondrial membranes.

Propylene dichloride brought about an increase in serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase activities in mice. The extent of hepatic damage is less than that produced by chloroform (Osanai, 1967). Heppel et al. (1946) found that weanling rats fed for several weeks with low-protein choline-deficient diets were more susceptible to the toxic effects of inhalation of propylene dichloride vapors (1,000 ppm for '7 hours) than the control group. Secchi and Alessio (1971) found that humans poisoned with a mixture of commercial chlorinated organic solvents containing propylene dichloride showed an increase in the activity of the following serum enzymes: sorbitol dehydrogenase glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, lactic dehydrogenase, glutamate dehydrogenase, RNase, ß-glucuronidase, and acid phosphatase.

The pathological changes resulting from daily exposures to propylene dichloride were described in detail by Highman and Heppel (1946). In their study, guinea pigs and rats were exposed to 2,200 ppm of propylene dichloride for various intervals of time. The most conspicuous changes were noticed in the adrenal glands of guinea pigs which showed extensive coagulation and focal hemorrhagic necrosis of the cortex, and congestion with hemorrhagic necrosis of the adrenal medulla. Both guinea pigs and rats showed fatty degeneration of the liver and kidneys. Except for the adrenal glands of guinea pigs, lesions and marked necrosis noticed after the first few exposures to propylene dichloride underwent rapid resolution 3 or 4 days after the end of the first exposure despite continuation of daily exposures.

TRICHLORINATED SOLVENTS

There was a time when methyl chloroform, trichloroethylene, and chloroform were used as general inhalational anesthetics, but the introduction of new anesthetics has made the trichlorinated solvents obsolete. However, all three trichlorinated hydrocarbons are widely used as commercial solvents and have been abused by inhalation. This section will not discuss chloroform because its cardiotoxicity, hepatotoxicity, and nephrotoxicity are generally known.

Methyl Chloroform

Methyl chloroform (CH_3CCl_3)is used as a solvent primarily for vapor degreasing and cold cleaning of metals and machinery. It

is used as a solvent in cosmetic and household aerosol products. There are four reported cases in the literature of the abuse of a cleanser containing methyl chloroform: One case of chemical pneumonia and another of respiratory arrest were reported by Hall and Nine (1966). The respective blood levels of methyl chloroform were 13.0 and 72 mg/100 ml. The third case of non-industrial poisoning was dcscribed by Stewart and Andrews (1966) and consisted of accidental ingestion of 0.6 g/kg of methyl chloroform. There were signs of depression of the central nervous system. The patient recovered after supportive treatment.

The fourth and most recent fatality from methyl chloroform was reported in 1974 by Travers. An 18-year-old apprentice seaman collapsed on the deck of his ship A bottle of methyl chloroform was found in his bunk along with a rag soaked with the solvent. After different supportive measures were taken, progressive hypotension and bradycardia, unresponsive to isoproterenol and norepinephrine infusions, and several episodes of cardiac arrest eventuated in his death 24 hours after collapse. Autopsy showed right atrial and ventricular dilation and circumferential left ventricular subendocardial hemorrhage. Microscopically, widespread recent infarction was observed. Mild congestion of viscera, cerebral edema, and Purkinje cell chromatolysis were also noted. Postmortem analysis failed to detect methyl chloroform in the liver, kidney, blood, or brain.

Absorption Metabolism, and Disposition

Morgan et al. (1970, 1972) used radioactive chlorine-38 labeled methyl chloroform in human volunteers to study its absorption and excretion in the lungs. The solvent was absorbed and excreted more rapidly than the fluorocarbons described in the preceding section. The urinary excretion of nonlabeled methyl chloroform was examined by Tada et al. (1968). who exposed two male volunteers to methyl chloroform and reported an increase in urinary excretion of trichloroacetic acid. as determined by the alkaline pyridine method. However, the increase was not in proportion to the concentration of the vapor and the duration of exposure, as far as the exposures to 1.16 and 2.26 mg/l were concerned. Monzani et al. (1969) reported that among 18 workers exposed to 1.0 mg/l, only one showed a detectable amount of trichloroacetic acid (9.72 mg/l urine). Seki et al. (1975) examined the urine samples collected from seven workers, and on the basis of excretion of trichloromethanol, estimated the biological half-life to be 8.7 hours for methyl chloroform

Cardiotoxicity

The proarrhythmic activity of methyl chloroform has been investigated in the dog. Rennick et al (1949) demonstrated sensitization of the heart to epinephrine induced arrhythmias after the inhalation of 0.33 to 0.53 g/kg (of methyl chloroform in dogs under

barbital anesthesia. They also concluded that ventricular arrhythimas could be more regularly induced with methyl chloroform than with chloroform, but less than with cyclopropane. Reinhardt et al. (1973) found the minimal concentration that causes sensitization in the dog to be 27.8 mg/l. The effective concentration$_{50}$ (EC_{50}) was 40.7 mg/l in another group of dogs examined by Clark and Tinston (1973).

Somani and Lum (1965) and Lucchesi (1965) instilled 133.6 mg/kg of methyl chloroform intratracheally and injected epinephrine (10 µg/kg) intravenously. This combination caused ventricular fibrillation except in dogs that were pretreated with beta-adrenergic blocking agents.

In the absence of injection of epinephrine, the administration of methyl chloroform produces alterations in the electrocardiographic pattern as follows:

Humans (Dornette and Jones, 1960)	nodal rhythm premature ventricular contractions depression S-T segment
Monkeys (Krantz et al., 1959)	flattened or inverted T wave
Dogs (Krantz et al. , 1959)	flattened or inverted T wave
Mice (Aviado and Belej, 1974)	2nd degree block and ventricular fibrillation

There is also a depression in contractility of the perfused frog heart (Lazarew, 1929), the canine heart-lung preparation (Aviado and Belej, 1975), and the primate heart in situ (Belej et al, 1974). A depression of oxygen consumption also occurs in heart slices obtained from rats anesthetized with methyl chloroform but not in those from unanesthetized rats (Krantz et al, 1959). As a result of myocardial depression, a fall in systemic blood pressure is detected in the dog and the monkey when anesthetized with methyl chloroform.

Herd et al. (1974) found that the peripheral vasodilation due to methyl chloroform could be reversed by phenylephrine hydrochloride. Furthermore, injection of calcium ion ameliorated the depression of myocardial contractility and hypotension induced by methyl chloroform.

The hemodynamic effects of various inhaled concentrations of methyl chloroform were investigated in the anesthetized intact dog preparation (Aviado et al., 1976). A minimal effective concentration of 0.1% (5.42 mg/l) decreased peak left ventricular pressure,

mean aortic pressure, and mean pulmonary arterial flow by 3%, 3%, and 4%, respectively. A concentration of 0.25% (13.9 mg/l) decreased peak left ventricular pressure, maximal rate of rise of left ventricular pressure, dp/dt, mean aortic pressure, and mean pulmonary arterial flow by 7%, 13%, 6%, and 6%, respectively. A concentration of 0.5% (27.1 mg/l) exaggerated all previous responses. A concentration of 1% (54.2 mg/l) decreased peak left ventricular pressure, dp/dt, mean aortic pressure, mean pulmonary arterial flow, and systemic vascular resistance by 22%, 33%, 24%, 15%, and 11%, respectively, while it increased pulmonary vascular resistance by 17%. It may be concluded from this study that methyl chloroform is a general depressant of cardiovascular function, effective in a minimal inhaled concentration of 0.1%. At this concentration, the most sensitive indices of its cardiovascular depressant effects are peak systolic pressure, mean aortic pressure, and cardiac output. With progressively increasing concentrations, the decrease in the maximal rate of rise of left ventricular pressure, dp/dt, occurs to the greatest extent, while the decrease in mean aortic pressure and in peak left ventricular pressure occupying an intermediate position. A mixture of 0.5% FC 11 and 0.05% methyl chloroform exhibits no potentiative or additive effects, probably implying differences in basic mechanisms by which each agent brings about its cardiovascular depressant action. The effects demonstrated in these experiments serve to explain death from poisoning with methyl chloroform.

Pneumotoxicity

In the monkey, inhalation of 138.8 to 277.5 mg/l of methyl chloroform causes depression of respiratory minute volume accompanied by a decrease in airway resistance and an increase in pulmonary compliance (Aviado and Smith, 1975). The pulmonary toxicity of eight chlorinated solvents was studied in rabbits by the physiogram method. The overall toxicity of methyl chloroform was less than the corresponding unsaturated compound trichloroethylene. The presence of a double bond provoked a central depression greater than that observed with the corresponding saturated compounds (Truhaut et al. , 1972). No information is available on pneumotoxicity in other animal species.

Hepatotoxicity

The effects of methyl chloroform were investigated in several animal species. The mouse has been studied most extensively. The intraperitoneal (i.p.) injection of 5.3 to 16.0 g/kg prolonged the sleeping time induced by pentobarbital, an effect brought about by interference with metabolizing enzymes in the liver; the hepatotoxic effective $dose_{50}$ (ED_{50}) was found to be 11.2 g/kg (Plaa et al. , 1958). However, it is difficult to exclude the possibility that the prolongation of sleeping time is caused by the addition of the hypnotic effects of pentobarbital and methyl chloroform, instead of the latter producing hepatic lesions.

Additional signs of hepatic dysfunction include retention of sulfobromophthalein and change in serum glutamic-pyruvic transaminase (SGPT) activity following injection (Klaassen and Plaa, 1966) or inhalation of methyl chloroform (Gehring, 1968). The doses of methyl chloroform required to cause death and a significant SGPT elevation in 50 percent of mice within 24 hours are as follows:

Route of administration	24-hr LD_{50}	SGPT activity ED_{50}	SGPT activity potency ratio LD_{50}/ED_{so}
Intraperitoneal	4.70 g/kg	2.91 g/kg	1.62
Intraperitoneal	4.94 g/kg	3.34 g/kg	1.50
Inhalation	74.25 mg/l for 595 min	74.25 mg/l for ≤ 595 min	<1.00 -

MacEwen et al. (1974) exposed mice continuously for 100 days. The concentration of 1.34 mg/l had no effect on the liver whereas 5.42 mg/l caused an increase in liver weight and elevation of liver triglycerides. The minimal concentration tolerated continuously is between the two levels tested.

In mice, the inhalation for 1 hour of 16.5 mg/l of methyl chloroform caused stimulation of the oxidative activity of microsomal enzymes in the liver, manifested by shortening of sleeping time induced by hexobarbital (Lal and Shah, 1970). These results following inhalation are opposite to those described above for i.p. injection and call into question the validity of using sleeping time to indicate hepatic enzyme activity.

The hepatotoxicity has been investigated in rats following inhalation of methyl chloroform (13.75 to 16.5 mg/l) for 24 hours (Fuller et al., 1970). It decreased the duration of action of hexobarbital, meprobamate, and zoxazolamine. There was an in vitro increase in the metabolism of these compounds by hepatic microsomal enzymes under the influence of methyl chloroform. The carbon monoxide-binding pigment (cytochrome p-450 reduced) and nicotinamide adenine dinucleotide phosphate cytochrome reductase activity of the hepatic microsomal fraction were increased. Pretreatment of rats with cycloheximide or actinomycin D prevented the decrease in the hexobarbital narcosis and the increase in hepatic drug metabolism induced by methyl chloroform. It is noteworthy that, after 24 hours of methyl chloroform inhalation, its concentration in the liver was markedly greater than that in the blood.

The inhalation of methyl chloroform in a concentration of 54.28 mg/l for 4 or 6 hours has no effect on liver function of rats fed with ethanol, although there was potentiation of hepatotoxicity of carbon tetrachloride by the alcohol (Cornish and Adefuin, 1966).

Pretreatment of rats with phenobarbital sensitized the liver to the hepatotoxicity of carbon tetrachloride but not to methyl chloroform injected i.p. (Cornish et al., 1973). The i.p injection of methyl chloroform (1 mg/kg) did not influence liver function in normal rats but was hepatotoxic in alloxan-induced diabetic animals (Hanasono et al., 1975). In the perfused rat liver, methyl chloroform did not influence hepatic blood flow or the morphology of the hepatic parenchymal cells to the same extent as carbon tetrachloride (Rice et al.. 1967). However. there was an inhibition of respiration of liver mitochondrial preparation following the addition of methyl chloroform (Herd and Martin, 1975).

Oral administration of 1.65 g/kg of methyl chloroform in liquid paraffin to rats for 7 days caused an increase in both microsomal and cell sap protein concentrations in the liver (Platt and Cockrill, 1969). Intraperitoneal injection of methyl chloroform (3.74 g/kg, i.e., 75% of the LD_{50}) in male rats produced no significant effect on the hepatic triglyceride level, nor was any decrease in hepatic glucose-G-phosphatase activity detected (Klaassen and Plaa, 1969). Disturbances in liver function have been reported in dogs (Klaassen and Plaa, 1967) and in rabbits (Truhaut et al., 1967). In all of these investigations, liver function was readily influenced by the administration of methyl chloroform.

Of the laboratory animals investigated, the guinea pig appears most prone to liver injury. While Adams et al. (1950) reported no organic injury after 3 months of repeated daily exposure to 8.20 mg/l for 7 hours per day, Torkelson et al. (1958) reported the presence of slight lung and liver pathology in guinea pigs exposed repeatedly to 5.5 mg/l for 1.2 hours per day or 11 mg/l for 0.5 hour per day for 3 months. Methyl chloroform produced in mice an enlargement of hepatocytes with cellular. infiltration and vacuolation and with slight necrosis only in the lethal range (Klaassen and Plaa, 1966).

Comparison of the hepatotoxic action of the different chlorinated hydrocarbons shows that this increases within each series with the number of chlorine atoms in each molecule. The assumption of some investigators such as Lucas (1928) that the hepatotoxic action is due to liberation of hydrobromic or hydrochloric acid, was not shared by Barrett et al. (1939). It appear's questionable whether the hepatotoxic action of chlorinated hydrocarbons should be affiliated with the liberation of hydrochloric acid or the formation of phosgene, but it is more likely that it is produced by the molecule in toto and it is probably linked to the fat solubility of the solvents (Van Oettingen, 1944).

Nephrotoxicity

The renal effects of methyl chloroform have been less extensively studied. This solvent produces definite disturbances of renal

function in mice (Klaassen and Plaa. 1966; Plaa and Larson, 1965) and in dogs (Klaassen and Plaa, 1967) as shown by phenolsulfonphthalein, glucose, and protein excretion data. The kidneys are less vulnerable than the liver to toxic properties of methyl chloroform. Little or no microscopic changes were observed (Klaassen and Plaa, 1966).

Trichloroethylene

The detailed description of the pharmacologic and toxicologic features of methyl chloroform is intended to serve as a comparison with other chlorinated solvents. A monograph describing the features of trichloroethylene ($CHClCHCl_2$) can be consulted for details. Briefly it can be stated that although methyl chloroform and trichloroethylene have many similar uses in industry and in consumer products. trichloroethylene contained in cleaning fluid, glue, and aerosol products is more widely abused by teenagers. The most frequent lesion encountered during postmortem examination of addicts who indulge in sniffing trichloroethylene is hepatic necrosis and nephropathy. There are also cases of unusual lesions in the brain including ecchymotic foci in the dentate nucleus and cerebral vascular accident. The reports of sudden death without pathological explanation indicate that cardiac arrest is the probable cause. In animal experiments, the threshold concentration that depresses the contractility of the canine heart is as follows: 0.05% trichloroethylene, a concentration which is five times more toxic than methyl chloroform. The hepatotoxicity of trichloroethylene is 1.3 times greater than for methyl chloroform (see references cited by Aviado et al., 1976).

Acute Inhalation Toxicity of Chlorinated Hydrocarbons

The organ toxicity and related toxicology has been discussed in the preceding paragraphs. Assembled in the table at the top of the next page are representative values of the lethal effects on small animals of several of the chlorinated hydrocarbons that have been reported. Principal sources of these data are reviews by Aviado and the Criteria Documents.

CONCLUDING REMARKS

The discussion on the pharmacologic. and toxicologic features of chlorinated propellants and solvents has one common theme: almost all of them are cardiotoxic, hepatotoxic, and nephrotoxic. This generalization is based on observations of animal experiments and human cases of accidental or occupational poisoning. There is no information derived directly from individuals who abuse the aerosols and consumer products containing halogenated hydrocarbons. However, it is safe to interpolate the pattern of toxicity in animals and humans from large doses of the halogenated compounds to anticipate the dangers to individuals who abuse the solvents and propellants.

ACUTE INHALATION TOXICITY OF CHLORINATED HYDROCARBONS

Compound	Dose ppm x Hours	Effect	Species
FC 11	100,000 x 0.5	LC_{50}	Rat
FC 12	800,000 x 4	LC_{LO}	Rat
Carbon tetrachloride	9,500 x 8	LC_{50}	Mouse
Methylene dichloride	26,700 x 0.33	LC_{50}	Mouse
	14,500 x 2	LC_{50}	Mouse
Trichloroethylene	12,566 x 4	LC_{50}	Rat
Methyl chloroform	16,400 x 4	LC_{50}	Rat
Tetrachloroethylene	10,000 - 19,000 x 2	LC_{50} (Approx.)	Rat

*LC50= Lethal concentration which kills 50 percent of the animals by a specified time.

Past experience with the fluorinated propellants indicates that when abused, the primary concern is death from cardiac arrest, cardiac arrhythmia, and depression of myocardial contractility. In the event that the fluorinated propellants are banned, the chlorinated compounds, together with the hydrocarbon gases, will probably be accepted as substitutes. This chapter has covered the potential cardiac effects in the event that chlorinated compounds replace the fluorinated compounds. From the standpoint of cardiotoxicity, methylene chloride is the least potent as far as animal studies are concerned. As soon as the new aerosol products containing methylene chloride become widely distributed, the questions as to its abuse potential and cardiotoxicity in man will undoubtedly be answered.

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Chapter 11

NERVOUS SYSTEM DAMAGE FROM MIXED ORGANIC SOLVENTS

Leon Prockop and Daniel Couri

INTRODUCTION

General Comments

Epidemic inhalation of the vapors of intoxicating hydrocarbons has been known only during the past quarter century. In a 1973 review, Cohen stated that the use of commercial solvents as a means of achieving an intoxicated state probably started in California during the late 1950's. Since then, inhalant abuse has been quite widespread. For example, in an upper middle class high school in California, 7 percent of the boys and 2.5 percent of the girls have sniffed intoxicants. Other data derived from high schools throughout the country are similar. A 1975 study (Abelson and Atkinson) reported data on inhalant abuse gathered by means of a nationwide probability sample designed to reach two parts of the United States population: adults over 18 and youths ages 12-17. Of the adults, 2.8 percent reported use of glue or other inhalants on one or more occasions. In the youth experience, 8.5 percent were involved.

A wide variety of products are employed, including glues and cements, gasoline, cleaning solutions, lighter fluid, and paint and lacquer thinner (Hofmann and Hofmann, 1975). All of the products contain one or more organic substances that have a generalized depressant effect on the central nervous system (CNS) similar to that of volatile general anesthetic agents. Other effects

include photophobia, irritation of the eyes, diplopia, tinnitus, sneezing,. rhinitis, coughing, vomiting, diarrhea, chest pain, and muscle-joint pains. As detailed in Chapter 4 of this monograph, inhalant abuse can cause alteration of nervous system function.

Pathophysiological Considerations

Little is known about the pharmacology of the volatile solvents. For example, relatively little is known about the biotransformation of n-hexane, known to produce peripheral neuropathy in humans, in mammalian systems. It is presumed that the lipid solubility of volatile solvents causes CNS depression by impairing membrane permeability and neural transmission. The exact mechanism(s) whereby volatile solvents, whether alone or in mixtures, causes permanent nervous damage, e.g., neuropathy, cerebellar dysfunction or encephalopathy, is not known. Pathological findings, to be discussed below, include neuropathy which is primarily axonal with subsequent demyelination. Perinodal axonal swellings with neurofibrillary tangles have been described (Schaumberg and Spencer, 1976), Experimentally, axoplasmic flow is impaired (Spencer and Schaumberg, 1975). Referring to damage outside the nervous system, Hofmann (1975) states that the toxic effects of individual volatile solvents are numerous and include bone marrow aplasia with benzene, hepatic cell dysfunction with trichloroethylene, and kidney damage with a variety of esters.

Information Derived From Accidental or Occupational Exposure

Over the last few decades, great advances have been made in establishing approximations of the safe or permissible limits of accidental or occupational exposure for the protection of workers engaged in processes involving exposure to these solvents. Such exposure may be to either a single solvent or to mixed solvents. In the case of single solvent exposure more than mixed solvent exposure, information gathered from experimental studies with laboratory animals along with the cumulative experiences of many industries provided the data base for the estimations of relative risk and potential health hazard associated with each of the most commonly used volatile solvents (and other chemical agents). In general, concern for occupational exposures restricted studies of these safety evaluations to those time intervals and concentrations of substances consistent with the usual working day conditions. As a consequence, animal studies became increasingly formalized to include exposure to a single agent for a duration of 5 to 7 hours/day, 5 days/week. Valuable information regarding lethality and tissue or organ damage was obtained at very high concentrations of exposure, while chronic low level exposures yielded subtle, less drastic alterations from normal. These kinds of studies continue to serve as indices for potential hazards associated with human exposures.

EFFECTS OF MIXED SOLVEN'I'S

For the specific hazard invoIved in the inhalational misuse, i.e., inhalant abuse, of these volatile solvents, the pattern and conditions of exposure are markedly different from those of the work environment. Literature reports of the intentional inhalation of solvents commonly describe a typical pattern of tolerance development. Beginners usually inhale one or more days per week, and quickly progress to a compulsive practice of multiple experiences daily (Bass, 1970; Cohen, 1975; Massengale et al., 1963; Press and Done, 1976). Those experiencted in volatile solvent inhalant usage express a preference for one or more of the commercially available solvents (or solvent mixtures) based upon the qualities of taste and odor. Often the user will detect changes in the quality of the product; in some cases these changes are accompanied by the appearance of clinical symptoms in the user. Estimations of inhaled solvent vapor concentrations are vague but are most likely extraordinarily high and extremely variable. The high concentrations of solvent vapors inhaled repetitively for years result in a chronic insult to the nervous system which cannot. readily be evaluated or understood from any of the available systematic studies in anesthesiology or from chronic low level safely evaluation studies. Fundamental studies directed towards understanding this usage pattern are not yet. available. However, it is important to describe some basic principles of solvent vapor exposure already gained from our experiences in: (A) general comments and principles; (B) the area of clinical and pathological features of nervous system damage secondary to inhalant abuse both in humans and experimentally in rats and; (C) the area of industrial exposure which is relevant to the inhalant abuse of volatile sol vents. In addition, three other items will be briefly discussed: (D) reports of increased toxicity from mixed solvent exposure (E) reports of increased toxicity attributable to the inhalant abuse of mixed solvents and (F) additional experimental data related to the biological effects of mixed solvents.

General Comments and Principles

Before discussing the five specific related subjects, a number of general statements are in order. Definition of the mechanism or mechanisms whereby a single solvent causes impairment of organs or organ systems is difficult. Little of a conclusive nature is known. Obviously, the situation of mixed solvents, as encountered commonly with the inhalant abuser, provides problems of even greater complexity. More than one toxic: substance may be in the mixture. Each toxin may act alone to produce an additive effect to that of another toxin(s) within the mixture. Alternatively, synergistic action may occur whereby the net toxic effect may be more than simply additive. Furthermore, one toxin may alter the metabolism so that another substance in the mixture. otherwise nontoxic, becomes toxic. A metabolite formed from one solvent within a mixture may extend the toxic effect of its parent

compound or of another compound within the mixture. A parent compound may be toxic in itself. Likewise , a metabolite of this parent compound may exert an equal toxic effect. One solvent within a mixture may enhance the toxic effect of another by facilitating its entry into an organ or into organ systems or by acting as a vehicle or carrier for its penetration into the extracellular or intracellular space, Thus, the carrier function served by one of the solvents within a mixture may allow the penetration of another solvent within the mixture (i.e., a more specific toxic agent) into a specific site. Finally, biotransformation may occur so that the toxicity of one solvent within the mixture may be enhanced in the presence of other solvents.

Given these general principles, more specific consideration will be given to the topics mentioned above.

Clinical and Pathological Features of "Huffer's" Neuropathy Secondary to Inhalant Abuse in Humans and Experimentally in Rats

Clinical Data

Seven young men developed severe, diffuse, progressive, predominantly motor polyneuropathy after inhalant abuse involving a commercially available lacquer thinner (Prockop et al., 1974). Neurogenic muscular at atrophy was prominent. Three were completely paralyzed, including bulbar involvement and required artificial respiration, and one died. Significant abnormal laboratory findings were: visual fields in two patients showed central and paracentral scotomas; nerve conduction rates ranged from 0 to 30 m/sec (normal, 42 to 55) with electromyographic evidence of acute denervation; electron microscopy of sural nerve in five patients documented segmental paranodal axonal distention by neurofilamentous masses; light microscopy of postmortem tissue showed chromatolysis of anterior horn cells and axonal swellings in the dorsal columns (Means et al., 1976). Examination of five patients 1-1/2 years later defined residual neurological deficit in all ranging from mild to severe (Prockop, unpublished data).

Toxicological Data

The seven men had been "huffing" the same brand of commercially available lacquer thinner without adverse effect from 6 months to 2 years, although other organic solvents had been used by several individuals for as long as 10 years. Several weeks before onset of symptoms, the patients noted a change in the odor of the lacquer thinner. This odor change correlated with a solvent formula change, apparently prompted by increased cost of previously used solvents. Gas chromatographic and mass spectrographic analysis of two different lacquer thinner mixtures both marketed under the same label was performed by the Physical and Chemical Analysis Branch of the National Institute of Occupational

Safety and Health. One mixture was identified by the patients as "the good stuff" and was, according to them, inhaled regularly for weeks or months without adverse effects. The second lacquer thinner mixture was identified by the patients as the "bad stuff." They noted the malodorous change at the onset of its use. Clinical symptoms and signs developcd shortly thereafter. Components of the commercial lacquer thinners samples #1 and #2) expressed as volume percent are as follows:

	#1	# 2
Toluene	47	3.9
Isobutyl acetate	12.2	12.6
Acetone	11.3	12.7
Methyl ethyl ketone		
Xylene	9.1	43.6
Isopropyl alcohol	6.8	0.5
Isobutyl isobutyrate	5.7	0.5
Isobutyl alcohol	4.7	3.5
2-Heptanone	3.2	15.5
2-Nitropropane	-	5.8
Isopropyl acetate	-	1.2
n-Hexane	-	0.5

Data From In Vivo Animal Studies

In studies performed by Tison and Prockop (1977), Sprague-Dawley rats weighing from 250-300 grams were exposed to various combinations of the organic solvents in the mixtures as identified above. Animals were maintained in air-tight chambers which allowed them to move about freely and to partake of food and water ad libitum. This system was so constructed that the "good" or "bad" solvents, whether used alone or in mixtures, were vaporized by a dripping technique so that the concentration of any solvent within the exposure chamber remained constant during the entire exposure period. Concentrations of the vapors to which the animals were exposed were analyzed daily by gas chromatography to assure a constant exposure. The results of these studies will be reported here in summary fashion and are still of a preliminary nature. Further studies are in progress and more conclusive presentation in print can be expected subsequent to their completion.

The mixture of chemicals comprising sample #1 was reconstituted from reagent grade chemicals available commercially. The mixture was vaporized in the manner described briefly above and vented through the exposure chamber. Eight rats were exposed to this vapor for 1,200 hours without clinical evidence of peripheral neuropathy nor other ailments. The animals were sacrificed and

portions of the sciatic nerve were prepared in standard techniques and analyzed by light and electron microscopy.* No abnormalities were noted. Another group of eight rats was exposed to the vapor of solvents reconstituted according to the percentages tabulated under sample #2 for a total of 975 hours. The average concentration of each solvent within the exposure and their respective threshold limit values will he presented later. The rats showed clinical signs of neurological damage characterized by difficulty in walking, inability to stand on their hind legs, and difficulty with turning movements after 900 hours of exposure. Two animals from this group were removed from the exposure after 400 hours of exposure. There were no clinical signs of neuropathy but light microscopy demonstrated the following (Means and Tison, unpublished data): (1) teased fiber preparations showed only "ruffled" myelin in a small percent of fibers, (2) light microscopy showed intra-axonal aggregates of Periodic Acid Schiff (PAS) positive material. In addition, rare degenerating fibers were identified in transverse sections of epon-embedded toluidine blue stained material; (3) electron microscopy demonstrated intra-axonal, membrane- bound aggregates of glycogen Redundant axonal membrane containing Schwann cell organelles were present in paranodal areas. Rare onion bulb formations and denuded axons were also identified. Similar analysis of animals exposed for 900 hours demonstrated more prominent pathological signs of neuropathy, predominantly of an axonal variety.

Subsequent studies, some of which are still in progress or remain to be done, were designed to determine which solvent or solvents within the neurotoxic mixture (i.e., sample #2) were responsible for the experimental findings and, therefore, for the toxicity in the humans. Although it is not appropriate to present details of the studies here, several of the findings can be reported. Ten rats exposed to methyl amyl ketone for 2300 hours at a concentration of 1,300 mg/m^3 (three times the TLV) showed no clinical signs of neurological impairment. No histological changes were found in peripheral nerves. Likewise, rats exposed for 975 hours to 400 mg/m^3 and 2-nitropropane at 350 mg/m^3 of methyl amyl ketone showed no clinical evidence of peripheral neuropathy. Rats exposed to 10 mg/m^3 of methyl ethyl ketone for 1,300 hours appeared normal clinically. Animals exposed to the constituents of sample #2, except for hexane, isopropyl alcohol, and isopropyl acetate, for 1,000 hours were clinically well.

These data indicate that sample #1 is not a neurotoxic mixture but sample #2 is a potent neurotoxin. The solvent or combination of solvents within this mixture which exerts this action requires further investigation, some of which is in progress. The remarks

*Light and electron microscopy analyses were performed and are described here by Eugene Means, M.D., Tampa VA Hospital Research Services, College of Medicine, University of South Florida.

made in the general section above with respect to potential synergistic action of two or more solvents and potentiation of toxic effects must be borne in mind in these and other studies investigating the effects of mixed solvents on the central and peripheral nervous system.

The epidemiological data gathered in the "epidemic" of "huffer's neuropathy" in Tampa indicate that a third lacquer thinner mixture was used by one group of inhalant abusers and that it was also responsible for neuropathy in the individuals involved. This third lacquer thinner has a formula different from either sample #1 or sample #2 above. Toxicological and experimental data are, as yet, too preliminary for discussion here.*

Industrial Exposure to Mixed Solvents Relevant to Mixed Inhalant Abuse

Toxicologic studies involving the industrial solvents methyl n-butyl ketone (2-hexanone, MBK) and methyl ethyl ketone (2-butanone, MEK) were initiated when 85 workers in a plastics coating and printing plant were afflicted with a toxic peripheral neuropathy of varying severity (Abdel-Rahman et al., 1976; Abdel-Rahman and Couri, 1977; Couri, 1974; Couri et al., 1977b). Investigations were directed towards isolating and identifying the neurotoxic agent(s) responsible for the occurrence of these peripheral neuropathies .

The first objective was to determine whether the suspected solvent, MBK, had any neurotoxic potential. For this purpose, several laboratory animal species were exposed to various vapor concentrations of MBK, MEK, and MEK/MBK combinations. The studies with MEK/MBK vapor mixtures involved those solvents in ratios which corresponded to that of the factory setting. The salient findings of these studies can be summarized as follows.

Chronic exposure of cats, rats and chickens to MBK vapors or MEK/MBK combined vapors resulted in the development of peripheral neuropathies (Abdel-Rahman et al., 1976; Couri, 1974; Couri et al., 1977b). Furthermore, electrodiagnostic techniques revealed a slowing of nerve conduction velocity, positive waves, and fibrillations in cats at various times after solvent exposure. Also, animals with clinical neuropathies showed histopathological and ultrastructural changes in sciatic nerve preparations characterized by paranodal axonal swelling, denudation of myelin, increased number of neurofilaments, and a decrease in neurotubules. Animals exposed to MEK vapors did not exhibit any neurotoxicity; at very high levels slight to moderate narcosis occurred in

*Segments of the research work discussed in this section were performed at the Research Service, Tampa VA Hospital.

chicken, cat, rat, and mouse. The ketone vapors alone, or in combination, did not produce peripheral neuropathy in mice.

Significance of the MBK Study in Relationship to the Inhalation Abuse of 1ndustrial Solvents

It is important that these studies demonstrated that after chronic exposure to MBK vapors, chickens. cats, and rats (but not mice) developed peripheral neuropathy It is significant that a more severe toxicity was observed at a shortened time of exposure to MEK/MBK combined vapors when compared to MBK alone. This finding of increased toxicity with mixed solvent vapors may be of paramount importance to the problem of inhalant abuse of industrial solvents. Because many of the industrial solvents used are of technical grade quality or are used as mixtures of miscible solvents, the possibility of producing an exaggerated adverse effect is more likely if the MEK/MBK example can be generalized. Reports of other solvent mixtures supporting this generalization will be described below.

Enhanced Toxicity of MBK when Combined With MEK

In studies with three groups of six rats continuously exposed to vapors of MEK, 1,500 parts per million (ppm); MBK, 400 ppm; or MEK/MBK, 1,500/150 ppm, it was clear that MBK alone produced severe neuropathies at 12 weeks; and that the MBK/MEK group all developed severe neuropathies by the sixth week of exposure (Couri, 1974). Similar data demonstrating the marked increase in toxicity and a shortened time for onset were obtained with cats and chickens. Animals exposed to MEK alone did not develop neuropathy.

To investigate the possibility that the enhanced toxicity of the mixed solvent vapors may be attributed to an alteration in MBK or its metabolite(s), the kinetics of plasma MBK in rats exposed to MBK alone and combined MBK/MEK vapors were determined (Abdel-Rahman et al., 1976). The MBK content in tht: plasma of rats exposed to MBK/MEK was not measured after a single 8-hour exposure, but did increase with continuous vapor exposure reaching 24 mg% (mg per 100 ml of' blood) at 23 days. The plasma MEK content showed an inverse relationship to that of MBK. After 6 days of exposure, 2,5-hexanedione, an MBK metabolite, was detected in plasma. This metabolite is also capable of producing peripheral neuropathies in experimental animals (Abdel-Rahman and Couri, 1977; Abdel-Rahman et al., 1977, Couri et al., 1977a; Saida et al., 1976; Spencer and Schaumberg, 1976). In contrast to the MBK/MEK data, the plasma of animals exposed to MBK alone did not contain any measurable MBK (detection sensitivity 30 ng). It was observed that the MBK/MEK vapor exposure resulted in a prolonged and increased plasma titer of MBK and its metabolite compared to MBK alone. Toxicity and mortality occurred. The MBK/MEK exposure gropu all showed severe neu-

ropathies The experiment was limited to 23 days because of the severity of the neuropathy The animals were removed from the exposure chamber and held for recovery. One animal died on the 22nd day of exposure and the other five died within the next 10 days. In the MBK group two of six animals exhibited mild neuropathies and no fatalities occurred after 60 days of continuous exposure. It is clear from this study that the animals exposed to the combined MEK/MBK solvent vapors manifested markedly enhanced neurotoxicities with a shortened time to occurrence and a dramatic increase in mortality.

Kinetics of Plasma MBK and MEK After Exposure to Solvent Vapors

Animals exposed to MBK vapors always showed nondetectable levels (<30 ng) of MBK in the orbital sinus blood samples (Couri, 1976). This was difficult to reconcile with the observed neurotoxicity after MBK exposure. In order to examine this further, animals were prepared with jugular vein catheters exteriorized in such a way that jugular blood samples could be obtained throughout the period of exposure to either MBK or MBK/MEK vapors. There was a gradual increase in jugular blood MBK content throughout the 150-minute (MBK, 500 ppm exposure) period studied. The animal was removed from the exposure chamber and a retro-orbital blood sample was obtained as in the previous experiments. The data clearly indicate that in this 2-minute time interval 6.8 mg% MBK in blood rapidly diminished to a nondetectable level. After an hour of rest (in air) this same animal was then replaced in the exposure chamber containing MBK/MEK, 500/800 ppm. Throughout the 60-minute exposure to MBK/MEK, the MBK content in blood was about twice that observed after MBK (500 ppm) alone, MEK content increased with time and no solvent metabolites were detected. The presence of MEK vapors somehow allowed a greater accumulation and a persistence of MBK in blood. This was demonstrated in another set of two experiments where animals were exposed to MBK/MEK 400/1,200 ppm for 150 minutes; afterwards, postexposure blood samples were obtained simultaneously from the jugular and the orbital sinus. In both experiments, at 3 minutes postexposure the jugular vein and orbital sinus blood content of MBK agreed very well. However, there was a considerable loss of both MBK and MEK content in this time interval. The striking features of the postexposure period at 13 (and 15) minutes is the persistence of both MBK and MEK in blood which is about 90 percent of their concentrations seen 10 minutes earlier (in air). Again, inhalation of MBK/MEK vapors resulted in higher blood levels of each solvent for a longer period of time. This, in part, can account for the increased toxicity and mortality of these combined vapors described above.*

*Segments of the research work discussed in this section were performed at the College of Medicine, Division of Toxicology, Ohio State University.

The combined solvents encountered in the inhalational abuse of industrial solvents such as paint thinners., glues, adhesives, lacquers, and paint solvents should be critically examined for combinations which might produce much greater toxicity attributable to the presence of one or more of its components in the mixture.

Reports of Increased Toxicity From Mixed Solvent Vapor Exposures

There are several reports of industrial toxicities that involved the presence of MEK in a mixture with other solvents(s); for example, with 10% 2-nitropropane/MEK, 500 ppm; acetone/MEK, each 300-500 ppm (Elkins, 1959); MEK and an unsaturated ketone impurity (Smith and Mayers, 1944); in each of these cases workers presented symptoms which were of greater severity than could be accounted for by any of the individual components. Similarly, such events have been reported for ketones in combination with butyl, ethyl, and amyl acetates, and other solvents (Heim DeBalzac and Agasse-Lafone, 1922; Sessa and Troisi, 1947; both studies cited in Browning, 1965). However, studies of Llewellyn, 1963; Fasset, 1963; and Oglesby et al., 1949 (all cited in Browning, 1965) indicated that workers exposed to 1,000-2,000 ppm acetone for years exhibited no permanent deficits but only a dull headache with temporary anorexia. Bone marrow injury related to benzene exposure was considered to be a toxicity of toluene. Later, the presence of benzene contamination in toluene was established to be responsible for the myelotoxic events (Hamilton and Hardy, 1974). This example of marrow toxicity caused by very low levels of benzene in toluene can be looked upon as an enhanced toxicity of low concentrations of benzene when combined with toluene.

Reports of Increased Toxicity Attributable to the Inhalant Abuse of Mixed Solvents

There are many case reports of toluene inhalant abuse in the medical literature. Some of the histories indicate that toluene is often a favorite solvent for inhalation. The two cases of Shirabe, et al. (1974) illustrate this preference. These comrades inhaled a glue containing principally toluene (70-100%) for more than 2 years; just prior to the onset of their toxic polyneuropathies they switched to inhaling a glue composed of toluene 55% and n-hexane 45%. Evaluation of the clinical course by the authors led them to conclude that the polyneuropathies were due to n-hexane and possibly a contributory effect from toluene. Similarly, in the case reported by Korobkin et al. (1975) the patient had been inhaling contact cement vapors for about 5 years; when afflicted with a polyneuropathy he still continued his habit; however, he switched to a glue without n-hexane Three months later he was unable to walk; subsequent hospitalization for approximately 1 year resulted in some degree of recovery. The case reported by

Knox and Nelson, 1966, described a patient who purchased "certified pure" gallons of toluene for his inhalation habit of 14 years duration. He had permanent brain damage with diffuse cerebral atrophy. Another use of "pure" toluene reported by Grabski, 1961, had a degenerative lesion of the lateral cerebellar lobes as a result of years of inhalation of toluene vapors.

Spencer et al. (1975) reported minimal axonal degeneration with giant axonal swelling in rats exposed to methy n-butyl ketone (MBK), an isomer of methyl isobutyl ketone (MIBK). They stated that minimal axonal degeneration due to MIBK may be related to the presence of 3% MBK in the commercial grade of MIBK. Oh and Kim (1976) reported giant axonal swelling in a case of "huffer's" neuropathy in a man who had "huffed" two kinds of lacquer thinner--the first containing methyl ethyl ketone, methyl isobutyl ketone, acetone, and toluene; the second containing acetone, methanol, toluene, isopropyl alcohol, ethylene glycol, and monoethyl ether acetate. Prockop (1977) documented the case of a woman who developed peripheral neuropathy, bilateral optic neuropathy, as well as evidence of cerebral and cerebellar damage after chronic inhalation of volatile hydrocarbons in the course of her work as a commercial artist utilizing a silk-screen process.

Additional Experimental Data Related to the Biological Effects of Mixed Solvents

Couri and coworkers (1977c) have studied the influence of inhaled ketone solvent vapors on hepatic microsomal biotransformation. Young male Wistar rats were housed in environmental chambers and exposed to solvent vapors (methyl n-butyl ketone, MBK, 225 ppm; methyl ethyl ketone, MEK, 750 ppm; MBK, 225 ppm/MEK, 750 ppm) . Hexobarbital sleep times were significantly reduced following exposure to MBK/MEK or MEK, but MBK exposure did not alter sleep time measurements. Aniline hydroxylase, aminopyrine demethylase, neoprontosil reductase, and p-nitrobenzoate reductase activities were significantly enhanced two- to three-fold in MBK/MEK and MEK exposure groups compared to controls.

Peripheral neuropathies caused by exposure to hexane and 2-hexanone (MBK) exhibit similar clinical and pathological features. In both in vivo and in vitro studies Couri et al. (1977a) have determined that MBK and n-hexane undergo biotransformation to a common metabolite, 2,5-hexanedione. In the in vitro studies, hepatic reduction of MBK required the cytosolic enzyme to form 2-hexanol. The oxidation of MBK and hexane required microsomal enzymes to form 2,5-hexanedione and 2-hexanol, respectively.

Although the pathophysiological mechanism(s) by which these compounds, i.e., hexane and MBK and their metabolite 2,5-hexanedione, produce neuropathy is unknown, Abdel-Rahman and coworkers (1977) have demonstrated MBK and MBK metabolites markedly decrease pupillary response and locomotor activity in guinea pigs.

CONCLUDING REMARKS

Little is known about the mechanism(s) whereby single solvents produce nervous system and other organ system damage. Even less is known about the effects of mixed solvents. Unquestionably, further extensive laboratory investigation is urgently needed. This is especially true because further changes in the composition of organic solvents may produce human exposure, both accidental and in the inhalant abuse situation, to dangerous neurotoxins.

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PRECLINICAL BEHAVIORAL DYSFUNCTIONS

Chapter 12

PRECLINICAL BEHAVIORAL TOXICOLOGY OF INHALANT SOLVENTS

Robert E. Bowman

TWO PROBLEMS: DEPENDENCY AND BEHAVIORAL TOXICITY

There are two broad and basically different classes of behavioral questions which may be raised regarding inhalant solvents. The first class revolves around the topic of the reinforcing properties of inhalant substances and deals with the determinants of drug dependency and dependency potential of the inhalant solvents. The second class of questions relates to the alterations in nondrug behavior induced by the inhalation of volatile solvents, or what may broadly be termed the behavioral toxicity of the inhalant solvents. These two main topics, dependency and toxicity, will each be considered in turn in this chapter.

BEHAVIORAL ASPECTS OF DRUG DEPENDENCY AND DRUG DEPENDENCY POTENTIAL.

Definitions of Terms

The term "drug dependence" was recommended in 1964 by the World Health Organization (WHO) Expert Committee on Addiction-Producing Drugs (cited by Fraser, 1974). Drug dependence was operationally recognized as "...the repeated administration of a drug on a periodic or continuous basis." (Fraser, 1974). The term included either psychic or physical dependence or both. However, the term excluded any connotation regarding the degree of risk to the subject or to the public from the drug dependence. To fill this gap, Fraser (1974) proposed that the concept of risk

from drug dependence be embodied in the term "drug abuse," defined as follows: "abuse of a drug exists if its use so harmfully affects the individual and/or society as to require its control." Fraser's proposal has some merit, since the term "drug abuse" is not needed as a synonym for the more established term "drug dependence," and since the word "abuse" already stereotypically carries the connotation of harm in its common usage. However, in subsequently discussing "abuse potential" of drugs, Fraser (1974) was exclusively concerned with dependency mechanisms, and considered no factors relevant to assessing harm. Furthermore, the term "drug abuse" appears frequently to be utilized by most authors simply as a synonym for drug dependency.

The question of harm from drug use is a question of toxicity, in the broadest sense of both physiopathological and behavioral toxicity, and will be so treated here. In Fraser's sense, the term "drug abuse" is premature for many inhaled solvents, since the current data are often insufficient regarding toxicity under the conditions of human usage. Therefore, this chapter will in general avoid the terms "drug abuse" and "abuse potential" in favor of "drug dependency" and "dependency potential."

Preclinical Models of Drug Dependency

Drug dependency occurs by definition if one repeatedly self-administers the drug. The dependency may be maintained by either physical dependence or behavioral (psychic) dependence on the drug, or both. Physical dependence is recognized by the appearance of a physiological syndrome upon withdrawal of the drug, typically following high or prolonged dosage with the drug. Behavioral dependence can be recognized through verbal reports of subjective effects in humans, or by the appearance of drug dependence in the absence of a physiological withdrawal syndrome.

Behavioral Dependence

The study of the determinants of drug dependency, and especially of psychic dependency, is probably the central problem from the standpoint of control or treatment of inhalant solvent abuse. Such studies in the human must rely on clinical material and retrospective assessments and are reviewed elsewhere in this monograph. Experimental studies of solvent dependency can ethically only be done in the animal. To perform such studies requires the availability of animal models of inhalant dependency, and research on such models is at an early stage.

By analogy with learning paradigms, one may distinguish two stages in drug dependency, namely the acquisition of and then the maintenance of the self-administration responses. The factors determining acquisition and maintenance of drug dependency may differ somewhat, so that both of these stages probably require study.

The squirrel monkey has been shown to acquire self-administration of nitrous oxide (Wood et al., in press) delivered to a helmet encasing the head. The monkeys learned to press a lever to deliver selected concentrations of nitrous oxide for a 15-second interval. The lever rate declined when delivery of nitrous oxide was discontinued, and increased with increasing numbers of lever responses (a progressive fixed ratio schedule) required to deliver a single reinforcer. At a fixed ratio set at 20 responses to deliver nitrous oxide for each single reinforcement interval of 15-second duration, response rates increased with increasing concentrations of nitrous oxide. Nitrous oxide was clearly a reinforcer and controlled the response rates for its delivery, but appeared to be only a weak reinforcer.

Yanagita et al. (1970) had earlier reported toluene self-administration in the monkey. Thus, Wood (1976) switched one of the monkeys self-delivering nitrous oxide to toluene delivery. The monkey readily transferred its lever responses to the delivery of toluene, and indeed the data indicated toluene to be a more potent reinforcer than was nitrous oxide. From the data of response rates versus toluene concentrations, Wood proposed that one might be able to determine a "self-administration limit value" below which the solvent concentration would not act as a reinforcer. Wood's estimate of this parameter for toluene was 560 ppm. Wood suggested that this might be a useful parameter in regulating maximal permissible levels for occupational exposures, chosen to preclude the possibility of workers' adventitiously learning an inhalation dependency through solvent exposures at their job.

Aside from this, no other data could currently be found on the acquisition of solvent dependencies. It may be possible to train an acquisition of dependency by eliminating the lever and letting the monkey stick its head into a helmet with a solvent atmosphere (Ron Wood, personal communication), thereby more directly mimicking the response topology of the human with an inhalant dependency. Rodents could also be trained in a two-chambered apparatus, with free access to the solvent atmosphere maintained in one chamber. Frequency of entries and duration of time in the solvent chamber would reveal the development and maintenance of any solvent dependency.

The potential usefulness of animal acquisition models of solvent dependency is difficult to assess. With respect to alcohol dependency, Freund (1975) stated his doubts that "...animal experimentation can contribute significantly to the elucidation of the complex human psychological and sociological factors that interact to induce the initiation of excessive alcohol consumption." If this point is true for alcohol dependency, it will also be true for solvent dependency. It is perhaps premature to prejudge this issue. It may well be that solvent dependency and excessive consumption would be increased in animals which were socially separated or malnourished, or reared in impoverished environments or stressed with noxious stimuli. On the other hand, solvent dependency might

be decreased by the addition of aversive solvents to the solvent mixture. Such findings could offer valuable support to theoretical formulations regarding the determinants of drug dependency in the human. It is perhaps only the role of verbal or cultural factors in human dependency, if any, which could not be assessed in the animal model.

Physical Dependence

The determination of withdrawal syndromes (physical dependency) is best done by experimenter-controlled administration of drugs to the animal, and does not require self-administration by the animal. Freund (1975) has reviewed a number of methods related to rodent physical dependency syndromes following alcohol. Goldstein (1975) utilized inhalant exposure to alcohol to obtain the prolonged, continuous exposures necessary to produce physical dependency; she further used behavioral measures (convulsions on handling) to assess the severity of withdrawal symptoms over time following cessation of alcohol delivery. Withdrawal syndromes peaked about 10 hours after termination of alcohol exposure and disappeared at about 30 hours postexposure; physical dependence developed progressively to a maximum at about 2 weeks of exposure. Skoricová and Molcan (1972), among others, reported an abstinence syndrome in patients who had been inhaling about 30 ml daily of trichloroethylene for an average of a year prior to treatment. However, the question of withdrawal syndromes to volatile solvents appears generally undetermined.

Procedures similar to those reviewed by Freund (1975) could well be useful in assessing the ability of a variety of solvents to induce physical dependence. However, as Fraser (1974) points out with respect to opiates, the occurrence of physical dependency does not per se predict the dependency potential ("abuse potential") for a compound .

Aversive Properties of Solvents

One might suppose that aversive solvents would not sustain a dependency. This is the obvious rationale for the adulteration of glues with allyl-isothiocyanate. If so, then the measured aversiveness of various solvents could be useful in assessing their dependency potential. Unfortunately, it seems likely that "acquired tastes" may occur with inhaled solvents, and that aversiveness upon initial exposures might disappear later or be counteracted by factors of positive reinforcement given prolonged exposures. For example, thresholds for irritation of the eye or respiratory membranes have been reported for many of the volatilized solvents at levels well below the concentrations reported inhaled in solvent dependencies. Nevertheless, initial aversiveness, if sufficiently strong, should serve as a first line of defense against the development of dependency. Given a suitable animal model for the self-acquisition of solvent dependency, then it will be possible to study the role of volatile aversive additives on the acquisition of

dependency. It may be possihle to identify solvents which produce a "bad trip" (possibly through cholinergic effects) and which could be used as adulterants in solvent mixtures to obviate the attractive reinforcing properties of the mixture. Alternatively, adulteration with solvents having noxious odors (such as the mercaptans) or highly irritant properties might also prove beneficial in avoiding not only solvent dependencies but also excessive adventitious inhalation in the occupational use of solvents. Unfortunately, this latter probably would not be well tolerated by the occupational or legitimate users of solvent mixtures.

There are no systematic studies on the aversiveness of the inhalant solvents . In humans, verbal report can be employed to assess the pleasantness of solvents. For example, Rosenberg (1974) reported that 44 percent of 110 women and 18 percent of 259 men found the inhalation of nitrous oxide to be unpleasant. Aside from a few solvents (such as the anesthetics) which are widely utilized as safe with humans, work with humans would be limited for the most part to low concentrations or to brief exposures.

There are a variety of procedures possible in animals for assessing aversive properties. Vogel and Nathan (1975) utilized the taste aversion paradigm in rats to measure the aversive properties of certain barbiturates, nonbarbiturate hypnotics, and ethyl ether. They administered the chosen drug immediately after the consumption of 100 licks of sweetened condensed milk and then 7 days later they measured the time to complete 100 licks within a maximum time limit of 600 seconds. Anesthetic doses of all of the drugs tested induced subsequent aversion for the milk solution. This procedure shows promise for application to solvent inhalation in general, since ethyl ether in the above experiment exhibited effects similar to those of injected anesthetics. A somewhat simpler and perhaps more general procedure would be to measure the latency of animals to exit from chambers containing a graded concentration series of solvent vapors as the unconditioned stimulus. However, aversive paradigms for inhalant solvents remain to be established in detail, and with suitable controls.

Properties of the Dependency Potential

Human self-experimentation has already established a clinical literature indicative of the dependency potential for a number of volatile solvents. However, these data are in general not quantitative and do not provide parametric or comparative information about the potency of various volatiles for producing dependencies.

General aspects of determining the dependency potential of opiate-like drugs have been discussed by Fraser (1974), who concluded "...that a comprehensive pharmacological profile of a drug is essential in animals and man and that a battery of tests for dependence may be necessary before an unknown drug can be appropriately classified as to relative abuse." However, it would

appear that the main experimental technique for predicting the dependency potential of a drug in man is to observe that the drug will sustain self-administration in the monkey (and perhaps in other species),

Other techniques may also be possible. For example, Colpaert et al. (1976a, 1976b) have proposed a discriminative procedure which does not rely upon an animal model of dependency. They trained rats to select a particular one of two levers for food reward when injected with an opiate (fentanyl) and the other lever when injected with the carrier substance for their drugs. They then tested a series of opiate-related drugs for their ability to induce the rats, shortly after an injection, to select the drug lever over the carrier lever. This paradigm relied upon the ability of the rat to detect a distinctive perceptual internal state associated with the presence of the drug in the body, and to respond accordingly when that drug or similar drugs reproduced that state on successive occasions (test for generalization). Colpaert referred to this as producing the "narcotic cue," and argued that drugs which produced internal states discriminated as similar by the subject would be drugs which would be alike with regard to dependency potential. This is a reasonable position, and could be true for many, if not all, drugs, but it remains to be definitively established.

The above papers dealt with the problem of opiate dependency, and their relevance to inhalant solvent dependencies is, of course, open to question. It now appears that the opiates may owe their dependency properties to their ability to stimulate the so-called opiate receptor in the brain. Endogenous small polypeptides with opioid properties have recently been discovered which are quite potent in reducing pain. The extent to which inhalant solvents might also affect the opiate receptor is unknown and probably deserves investigation. There is a question whether inhalant dependencies in man tend to lead to later dependencies on hard drugs. If certain solvents stimulated the opiate receptor, this would provide a common physiological basis for different dependencies, and would imply a possible link between dependencies on those inhalants in early life and other drug dependencies in later life.

For a variety of reasons, it seems likely that solvent dependencies will be based on diverse neural mechanisms. If so, then the classification of solvents with common mechanisms could be important. Such classification would have to rely on several lines of evidence, including behavioral evidence. It would be pertinent, for example, whether the use of a particular solvent was followed by a physical dependency (withdrawal syndrome) or whether there was a discriminative similarity between one solvent and another in a test situation similar to that of Colpaert et al. (1976) or whether one solvent might readily substitute for another in a self-administration paradigm. The question of an abstinence syndrome in particular is important for several reasons and should be assessed for a

spectrum of solvents, for example, by procedures similar to those discussed by Freund (1975) and demonstrated by Goldstein (1975) in the case of ethanol dependence.

BEHAVIORAL TOXICITY OF SOLVENTS

Definitions of Intoxication, Persisting Toxicity, Irreversible Toxicity, Remote Toxicity, Covert Toxicity, and Tolerance

Given that subjects are exposed to solvent vapors for whatever reason (self-administration, occupational exposure, or accident), the question of the toxic effects from the exposure becomes pertinent. In other words, the study of solvent toxicities does not require animal models of solvent self-administration and may be done during or after involuntary administration of the solvent vapors to the subjects. The chronological characteristics of the toxic manifestations lead to some important definitions with regard to toxicities. Acute, transient, or reversible toxicity (intoxication) occurs only when the solvent is present in the body and disappears when the solvent is cleared from the body. Chronic, enduring, or persisting toxicity represents damage to the subject which persists long after the solvent has been cleared from the body, and which results from long-lasting metabolic or morphological alterations that the solvent produced while present in the body. Some of these long-lasting alterations might be reversible, which would be evidenced by eventual recovery, and some might be irreversible within the life span of the animal. It is also possible to define a "remote toxicity, " referring to a delayed damage which would not be apparent during or soon after the solvent exposure, but which would only manifest itself at some long time after the cessation of exposure. Behaviorally, an example of remote toxicity would be a subject who tested normal after solvent exposure, but who eventually showed an earlier or more extensive failure of neurobehavioral processes with aging.

With regard to the degree of toxicity, it also appears useful to consider the concept of occult or covert toxicity, representing damage not sufficient to be observed by the tests used. Such damage might be unmasked by more sensitive tests, or by the eventual appearance of remote toxicity with aging, or would be implied for single solvent exposures if repeated solvent administrations eventually produced a total loss sufficient to be measurable.

Additionally, it is useful to define cumulative toxicity to refer to the appearance of toxic signs only after repetitive or continuous chronic exposure to toxins such as the inhalant solvents. The phenomenon is well documented, and emphasizes that the toxic profile for a drug cannot be established simply by a few exposures of the animal. It is necessary to keep in mind, of course, that chronic toxic exposure may produce symptoms secondary to the drug action (e.g., symptoms mediated by malnutrition, sleep disturbance, etc.)

Finally, a common phenomenon with chronic intake of drugs or toxins is the development of tolerance to the substance, so that increased amounts of the substance are required to elicit a given effect. It may be that the increased drug dosage which is self-administered consequent upon the development of tolerance for certain drug effects may eventuate in the appearance of new toxic signs and hence account for some of what is here termed cumulative toxicity. Whether indeed tolerance develops to the various inhaled solvents is still open to question. It seems almost certain that tolerance will be observed with at least some of the solvents, and the clinical literature on inhalant solvents is suggestive of the development of tolerance. However, experimental data on this point are lacking.

Dose Response Curve, Dose Effect Curves, and Threshold Limit Values

If one has chosen some biological (in this case, behavioral) endpoint for toxicity, for example, locomotor activity, then one can plot the proportion of subjects who show a stipulated degree of disturbance in this endpoint versus the dose of the volatilized drug producing this disturbance (a dose-response curve). Alternatively, one may quantify the degree of alteration in the endpoint, measured in individual subjects and averaged over the group, for groups of subjects at different doses of the drug (a dose-effect curve). This distinction between dose-response and dose-effect functions has been proposed by the Subcommittee on the Toxicology of Metals under the Permanent Commission and International Association of Occupational Health in 19'74 (Nordberg, 1976).

For most behaviors, the dose-response and dose-effect curves can be expected to exhibit no effects when assessed at sufficiently low concentrations and exposure durations of a toxic volatile. This could be because of a neural "reserve" in most neurobehavioral systems, or because of neurobehavioral abilities to compensate for a certain degree of neural damage, or because of compensation through neural reorganization following central nervous system (CNS) damage. It could also be that no organic neural damage is produced by the drug up to some dose level. At and above some concentration-duration, however, behavioral alterations will become apparent, and will increase in magnitude as the concentration-duration of exposure continues to increase. The intersection of the function of measurable behavioral effects versus drug dose with the mean behavioral response of nonexposed (control) subjects can be taken as a threshold limit value of the drug. This defines the upper drug dose which is just short of producing measurable toxicity.

Threshold Limit Values (TLV) as a term has been defined to refer to safe levels of airborne contaminants; i.e., levels under which "nearly all workers may be repeatedly exposed, 8 hours a day,

without adverse effects. Threshold limit values refer to time-weighted concentrations for a 7- or 8-hour workday and 40-hour workweeks" (Cornish, 1975). TLV's may be set on the basis of systemic toxicity, or on the basis of other factors such as irritation of eye or respiratory membranes, narcosis, nuisance, etc. The American Conference of Governmental Industrial Hygenists (ACGIH) has published a yearly guide entitled "Threshold Limit Values of Airborne Contaminants."

In quantifying the dosage of volatile solvents, both the concentration of the solvent and the duration of time for delivery must be taken into account. Elkins (1959) discusses the limitations of Habers' law, which states that the concentration of drug times the duration of the administration equals a constant in terms of the potency of various dose-duration combinations for producing any particular toxic endpoint. This law can only hold for time intervals short enough to avoid significant drug metabolism, etc. For repeated or chronic exposures over many days or weeks, it will generally be necessary to study several selected dose-duration combinations, rather than treating solvent concentration and duration of exposure as variables which can be traded off according to Habers' formulation.

It is important to estimate threshold limit values as a succinct statement of drug toxicity, permitting comparison of the toxicities of different inhalant solvents and also providing for comparison of the sensitivities of different behavioral endpoints for toxicity. It is vital to note, however, that a threshold limit value does not imply the absence of <u>any</u> toxicity, but only the absence of <u>measured</u> toxicity for a given biological endpoint. There could well be covert toxicity which would require particular conditions or procedures to unmask.

Anesthetic Properties of Volatile Solvents and Determination of Anesthetic Potency (MAC or AD_{50})

Most, if not all, of the inhalant solvents act as anesthetics. It is possible that the dependency potential of solvents may be related to their anesthetic properties. A characteristic of many anesthetics which is not emphasized enough is the production of an excitation stage that occurs at low doses of the anesthetic, or prior to the onset of depressant effects at higher doses of the anesthetic. It seems likely that neural inhibitory mechanisms are suppressed by low doses of the anesthetic, thereby releasing excitatory mechanisms normally held in check by the inhibitory systems. As the dose of the anesthetic increases, then additionally the excitatory systems themselves are suppressed and the depression stage of anesthesia then occurs (Bushnell et al., 1975). Various psychological effects of the volatile solvents reported in the human clinical literature imply an anesthetic spectrum which includes excitation, loss of inhibitory controls, and depressant actions.

It is not clear whether solvents are inhaled for their excitant effects or for their depressant effects, or both. Theories concerning the psychological determinants of inhalant solvent dependencies would obviously benefit from knowledge on this point. One attraction of the inhalants may well be that the same substance is both an "upper" and a "downer," and the user need only titrate his inhalation to obtain either excitation or depression, as his needs dictate. The rapidity of absorption of inhalants, and the consequent short latency for action on the CNS, indicates that such a behavioral titration might readily be feasible.

In delineating the acute behavioral toxicity of the volatile solvents, it therefore seems important to assess their anesthetic and analgesic properties. The currently accepted measure of anesthetic potency is the minimum alveolar anesthetic concentration, or MAC. The statistical definition of MAC was recently emphasized by De Jong and Eger (1975) as the dose which anesthetizes 50 percent of the population (AD_{50}). Other anesthetic doses can also be defined, such as the AD_{50} or AD_{95}, and De Jong and Eger (1975) described the use of probit or logit analysis to aid in the calculation of any of these parameters. Thus, MAC or anesthetic dose (AD) is simply a variant of the concepts of effective dose (ED) and lethal dose (LD), which are familiar parameters in pharmacology and toxicology (Casarett and Doull, 1975).

There is a conflict between the acronym MAC as used in anesthesiology and the same acronym as utilized earlier (Elkins, 1959) and as still utilized (Casarett, 1975) in industrial toxicology. In toxicology, MAC has variously been reported to mean "maximum allowable concentration," "maximum acceptable concentration," or "maximum atmospheric concentration" (Elkins, 1959; Casarett, 1975). Nuisance effects, as well as toxic effects, may be used in setting the MAC value. The MAC is set so that "deleterious effects are insignificant at exposure levels below the MAC for eight hours a day, five days a week over a working lifetime" (cited by Casarett, 1975). As can be seen, the MAC and the TLV refer conceptually to much the same value of the toxicant, namely, the highest continuous or frequent exposure level which can be tolerated without adverse or deleterious consequences. Guides on MAC values for many substances, including the volatile solvents, have been published as cited by Casarett (1975) and reprinted by Elkins (1959).

An important feature of anesthetic potency, as measured by MAC or by other response properties, was demonstrated by Shim and Andersen (1972). They pointed out that MAC was defined in terms of the loss of the motor response to a pinch or a cut. If other behavioral or biological endpoints were utilized to determine effective doses of the anesthetic, such as loss of the righting reflex, loss of respiratory activity, or loss of cardiac activity, then different AD_{50} values were generally obtained. Shim and Andersen tested eight anesthetics. The righting reflex was generally abolished at the lowest concentrations, MAC occurred next, then

respiratory arrest at higher concentrations. Each endpoint occurred at a very consistent value of a given anesthetic, but the potencies and interrelationships between biological endpoints differed for each anesthetic. For example, chloroform abolished the righting reflex at a dose of 1 MAC, whereas trichloroethylene abolished the righting reflex at a dose of 0.65 MAC. The six other anesthetics fell between these extremes.

Most studies of anesthetics have concentrated on measures of the depressant actions of the compound in question, using the above techniques. From the standpoint of inhalant dependencies, it will also be pertinent to determine effective doses or dose ranges for excitatory effects and for loss of inhibitory functions. This can readily be done within the framework of the above methodology simply by utilizing behavioral endpoints characteristic of excitation or loss of inhibitory function. For example, excitation can be assessed in terms of lever rate for appetitive reinforcement under the influence of the chosen anesthetic agents (Bushnell et al., 1975). There are numerous ways to measure losses of inhibition, as well as other approaches to the assessment of excitation, which will suggest themselves to those trained in behavioral methods.

Behavioral Data on Intoxication (Acute Toxicity) With Inhalant Solvents

The question of intoxication is almost exclusively a behavioral question. Volatilized solvents will only be repeatedly inhaled if they in fact produce an intoxication state which includes reinforcing kinds of events or perceptual change. Most intoxications, however, will not be specifically limited to reinforcing properties, but will also include other behavioral changes, some of which may constitute individual or social risks. Given the present frequency of inhalant intoxications, there is an increasing need to define and document any particular features of the acute toxicity which constitute risk. Such documentation will allow recognition and control of any unusually hazardous solvents, or will establish the basis for sociolegal definitions of solvent intoxication. For example, with specific reference to toluene and trichloroethylene, Bauer and Molcan (1974) have briefly discussed the problem of volatile solvent intoxication and traffic safety, and legal cases have already arisen in this general regard in the United States.

Factors involving risk would include a loss of alertness, a loss of reaction time, a loss of inhibitions, a loss of judgmental capacity, losses in sensory capacities, losses in motor control, and losses of reflexes. Especially pertinent to document would be solvents which may be deliberately inhaled to the loss of consciousness, since the user might be liable to serious risk (such as overdosage) in that event. Solvents which produce aversive reactions when inhaled at higher doses, such as amyl nitrite in the dog (Dewey et al., 1973) may be relatively safe from the dangers of voluntary inhalation either to unconsciousness or to death.

Data will be discussed immediately below on the acute behavioral toxicity of several of the volatile solvents which have been reported to sustain inhalant dependencies in man. There is only a small literature on a few pure solvents, and no systematic studies at all on solvent mixtures.

Nitrous Oxide

Nitrous oxide has probably been more studied for acute behavioral toxicity at subanesthetic concentrations than any other volatile solvent. A series of studies by Hannah Steinberg and collaborators appeared in the 1950's. Steinberg (1954) found that all of a series of verbal and motor tests were performed less well by subjects given 30% nitrous oxide in oxygen than by controls breathing air. The more "complex" the verbal task appeared, the more it tended to be affected. In confirmation, Parkhouse et al. (1960) found modest changes in analgesia and various verbal tests at 20% nitrous oxide in oxygen, and larger changes at 30% and 40% nitrous oxide in oxygen. This suggests a threshold for losses in verbal behavior in the vicinity of 20 vol.%, or of 200,000 ppm (parts per million) of nitrous oxide. The same workers (Henrie et al., 1961) could find no consistent changes in EEG (scalp electrodes) at 30% nitrous oxide, despite the behavioral effects noted.

Porter (1972) reviewed and ingeniously analyzed the data of some 14 studies on nitrous oxide, including the above, in addition to 45 studies on other anesthetics, and concluded that nitrous oxide was a weak amnestic agent, interfering either with registration or retrieval of memories for events just preceding or occurring during nitrous oxide inhalation.

Wallenstein and Rosner (19'76) found that 35% and 50% nitrous oxide in oxygen produced cortical and hippocampal EEG changes in rats in the direction of large, and very large irregular activity. The appearance of the very large irregular activity was said to be correlated with a reduced likelihood of performing a shuttle avoidance task, but no behavioral data were presented.

Other behavioral changes have been noted, generally nonquantitatively. Parkhouse et al. (1960) indicated that some subjects under 40% nitrous oxide "... showed a marked tendency to reveal inherent temperamental instabilities," and that some subjects become uncooperative and difficult to manage. The subjects used by Parkhouse et al. (1960) were all professional personnel who had volunteered for the experiment and could be considered probably above average in their motivations to cooperate. Hence, this description by Parkhouse et al. (1960), which is suggestive of losses of inhibitory control under these subanesthetic doses, is indicative of the potentialities for social dysfunction attendant upon inhalant dependencies.

A phenomenon of a different type, namely transient hearing loss, has also been reported with nitrous oxide in patients with certain

ear problems (Patterson and Bartlett, 1976). This resulted from high middle ear pressures produced by the nitrous oxide. The extent of transient or permanent acoustic trauma from this phenomenon if nitrous oxide were repeatedly inhaled is unknown,

A particularly pertinent study is that of Hahn and Rokitka (1976). They exposed colonies of deer mice to either nitrogen, argon, or nitrous oxide in mixtures containing normal amounts of oxygen under hyperbaric conditions continuously for 3 days. Motor capabilities were scored by observers on a 3-point scale, and running wheel activity was scored continuously. They subsequently evaluated the ED_{50} for narcotic potency of each of these gases using probit plots of running wheel scores (as percent of activity at sea level pressures) versus gas pressure. The ED_{50} of 1.1 atmospheres estimated for N_2O from these data is open to question as discussed by Rahn and Rokitka, but is close to MAC (1.05 atmospheres), and is smaller than the ED_{50} estimated by various authors for abolishing the righting reflex of mice. The ED_{50}s for nitrogen, argon, and nitrous oxide were exactly correlated with the lipid solubilities of these three gases (linear on a log-log plot). The lines identified in their Figure 4 as 95 percent confidence limits on the linear regression should have been curved to depict increasing error of regression as the line progresses away from the point $\bar{X}, \bar{Y}$ (Snedecor and Cochran. 1967). Nevertheless, the paper is instructive for the kinds of quantitative methodology needed in assessing acute toxicities, and also for the use of hyperbaric conditions to assess the anesthetic potencies of weak agents.

It can be seen that the literature offers a beginning to the quantitative behavioral toxicology of nitrous oxide. For example, no formal estimates of the TLV for different effects were found, although the data of Parkhouse et al. (1960) are suggestive of a TLV of perhaps 10-15 vol.% of nitrous oxide in oxygen for various behavioral effects, including analgesia, and an ED_{50} of about 37 vol.%. One MAC for nitrous oxide has been listed as 105 vol.% (Eger, 1974). ED_{50} values for other behavioral endpoints (righting reflex and wheel running) range from 160 vol.% down to 110 vol.%. Other behavioral tests (namely verbal tests) would appear to have TLV's in the vicinity of 10 vol.%.

No data were found on body burdens of nitrous oxide at various inhalant concentration, nor on rate of recovery from nitrous oxide anesthesia, From the data of Wood et al. (in press), monkeys self-administered nitrous oxide at a rate per hour which corresponded to a continuous average concentration of nitrous oxide of 5-20 vol.% over the hour. This dose likely was in the range of excitant effects, but not depressant effects. This would be an interesting point to confirm. Free response use of nitrous oxide in the dependent human is not known Wood noted that nitrous oxide appeared to be a weak reinforcer for sustaining self-administration. This is interesting since nitrous oxide is also only a weak anesthetic.

Chlorinated Hydrocarbons in Animals

The acute neurobehavioral toxicities of other inhalant solvents have been less investigated than has nitrous oxide. Horvath and Frantik (1973) reviewed data on nine inhalant solvents producing acute changes in five behavioral measures tested in rats. They listed "effective concentrations" of vapors and durations of exposure necessary to achieve various behavioral endpoints, but without stating whether or not these "effective concentrations" were ED_{50} values. The behavioral endpoints consisted of a 50 percent decline in spontaneous motor activity, a 100 percent increase in "inert. avoidance responses" (presumably referring to passive avoidance), a 50 percent decrease of total activity in avoidance conditioning, a 15 percent decrease in maximum running velocity, and a 25 percent decrease in running endurance. For a given solvent, all five of these behavioral changes were reported induced by about the same effective dose of the solvent. These behavioral effects were produced by 6 hours of inhalation of approximately the following doses and compounds: 6,400 ppm of dichloromethane, or 6,000 ppm of trichloroethane, or 3,440 ppm of trichloroethylene, or 1,820 ppm of tetrachloroethane, or 1,500 ppm of tetrachloromethane, or 1,000 ppm of trichloromethane, or 820 ppm of dichloroethane, or 730 ppm of carbon disulfide, or 450 ppm of tetrachloroethane.

Trichloroethylene in Humans

Behavioral endpoints have been employed in studies bearing on the TLV for the acute toxicity of trichloroethylene. Stopps and McLaughlin (1967) reported dose-effect curves for 2-3/4 hours of exposure to 100, 200, 300, and 500 ppm of trichloroethylene, measuring human manual dexterity, perceptual reversals of the Necker Cube, card sorting, and a modified reaction time task ("dial display"). Their data indicated a TLV in the vicinity of 100 ppm. Salvini et al. (1971) reported that human performance was significantly decreased by 110 ppm of trichloroethylene during two 4-hour exposures separated by 1-1/2 hours. Tasks included manual dexterity, complex reaction time, Wechsler memory scale, and the perception of a tachistiscopic presentation. Unfortunately, they only presented tables of their statistical analyses, and not of their data, so the magnitude of the effect was not. reported.

Toluene

Wilson (1943) and Von Oettingen et al. (1942) described intoxication of the CNS and impairment of coordination and reaction time from exposure to 200 ppm of toluene. Toluene first stimulates and later depresses the nervous system (Lewis and Patterson, 1974). Exposure for 3 hours at 600 ppm can produce a variety of symptoms, including mental confusion, exhilaration, and fatigue.

Gamberale and Hultengren (1972) reported human reaction time and perceptual speed to be impaired by 20-minute exposures to toluene at 100, 300, 500, and 700 ppm The TLV appeared to be in the vicinity of 100 ppm of toluene.

Ishikawa and Schmidt (1973) noted that about seven exposures to 30 minutes of toluene at 100 ppm daily produced a "forced turning" or circling locomotor movement in rats which was reversible if toluene exposure was discontinued. They reported loss of righting reflex at this dose, particularly on exposures subsequent to the first, as well as a characteristic hind leg scratching directed at the lower costal margin After two to three exposures, the rats "struggled vigorously" when being placed in the exposure chamber. If toluene was withdrawn for 14 days, the forced turning was reinstated after a mean of 1.5 daily reexposures. If toluene was withdrawn for 21 or 34 days, then the number of reexposures needed to reinstate the forced turning was not significantly different from the number needed to produce forced turning on the original exposure series.

Weiss et al. (in press) studied keypecking behavior on a "fixed consccutivc number" schedule in pigeons exposed to 0, 400, 800, 1,601). or 3,200 ppm of toluene in air. The pigeons had to give 20 or more consecutive responses on the left key before switching to respond to the right key in order to obtain a food reward. Latencies to recommence keypecking after reinforcement and to switch from the left to the right. key were suggestive of an excitatory effect of toluene at 800 ppm and a depressant effect at 3,200 ppm.

Wood (1976) studied toluene self-administration in a squirrel monkey. For concentrations of 1,000, 2,000, 3,000, and 10,000 ppm of toluene, delivered for 15 seconds per reinforcement, the monkey self-delivered 130, 130, 100, and 35 reinforcements per hour respectively. These reinforcement rates amounted to an average concentration of toluene over the hour of 540, 1,080, 1,300, and 1.460 ppm. These doses are in the range of excitatory effects (as measured in the pigeon), and not of depressant effects.

Halothane

The behavioral TLV for halothane may be quite low. Bruce et al. (1974) tested 40 male humans immediately after 4 hours of inhalation of either air or air plus 500 ppm of nitrous oxide or air plus 500 ppm of nitrous oxide plus 15 ppm of halothane (these mixtures mimic the atmospheres to which a surgical team might be exposed). Subjects exposed to nitrous oxide and air had a decrement on a digit span test. Those exposed to halothane plus nitrous oxide in air exhibited deficits on digit span, on word recall, on a visual tachistoscopic test, and on a complex, compound reaction time test. This complex reaction time test appears to be an exquisitely sensitive measure of intoxication, since Winter et al. (1975) reported a 9 percent decrement in this task in humans breathing oxygen-nitrogen compared to humans breathing oxygen-helium. Since hyperbaric nitrogen is narcotic (anesthetic), whereas hyperbaric helium is either nonnarcotic or only weakly narcotic, Winter et al. (1975) proposed that this test could detect a narcotic effect of nitrogen at atmospheric pressure.

Davison et al. (1975) assessed behavior in men anesthetized for 7.2 (mean) hours with halothane (1-2%) or halothane (.35-1.5%) plus nitrous oxide. Behavioral measurements were taken before anesthesia, and at 2, 3, 4, 6, 9, and 30 days after anesthesia. Somatic symptoms and mood changes were highest at 2 days postanesthesia, and were still significantly elevated at 4 days. Similarly, various "intellectual functions" (reading comprehension and reading speed, verbal reasoning, arithmetic) showed decrements at 2 and 4 days postanesthesia. All subjects had essentially recovered to control capabilities by 30 days.

Adam (1973) found that general anesthetics (cyclopropane, enflurane, and ether) at low doses impaired verbal memory processes but spared nonverbal, acoustic memory. At higher doses, a strong amnestic effect was obtained. Subsequently and in confirmation, Adam (1976) found that halothane or fluroxene produced a decrement in verbal memory search, but not in visual memory search, only within 24 hours of recovery from anesthesia. These reports imply that verbal behavior is particularly sensitive to anesthetic toxicity, compared to other types of sensory processing.

Porter (1972) reviewed five studies on halothane, which indicated an amnestic effect of halothane for events just preceding or concurrent with halothane exposure.

These data offer no quantitative estimate of the TLV for halothane, but do suggest that intoxication can occur at very low concentrations of solvent, particularly if the solvent is well retained in body lipids. In such cases, recovery to normal function can take several days.

Cumulative Behavioral Toxicity

Behavioral signs of toxicity may occur after repeated exposures to solvents that do not occur after one or a few exposures. This cumulative toxicity should not be confused with enduring toxicity, since many of the examples of cumulative toxicity appear to reverse within a few days or weeks after termination of solvent inhalations. The human clinical literature provides numerous examples of cumulative toxicity for drugs in general (i.e., the well-known amphetamine psychosis), and also a number of examples in the case of solvents. To illustrate, daily repetitions of solvent exposures for months have eventually produced delusions and hallucinations in the case of gasoline inhalation (Bethell, 1965) or of nitrous oxide inhalation (Brodsky and Zuniga, 1975). Therefore, experiments employing only short-term exposures in animals will not be sufficient to determine the toxicity of inhalant solvents.

Most of the literature on cumulative toxicity of solvents comes from research on occupational exposure. Knave et al. (1976) reported increased symptoms of neurasthenia, psychasthenia, and polyneuropathy in aircraft workers exposed daily for at least 5 years to jet fuel vapors. Since only one of these differences was

statistically significant, it is difficult to conclude in favor of cumulative toxicity on the basis of this study. Nevertheless, numerous earlier studies of gasoline exposures, cited by Knave et al. (1976), indicated findings of neurasthenia, psychasthenia, and polyneuropathy. Knave et al. (1976) had no data available on the exposure concentrations of the jet fuel vapors, except for one assay of 3,000 ppm in one workplace and 500 ppm in each of two other workplaces. Knave et al. (1976) cite Drinker et al. (1943) that exposure to 1,000 ppm of gasoline caused mild nausea, headache, and dizziness, and that 2,600 ppm caused intoxication and some anesthesia; eye and throat irritation was noted at 160 and 270 ppm. Kerosene does not cause eye irritation (Grant, 1974), and no eye irritation was noted by Knave et al. (1976) in the workers exposed to jet fuel. Felix (1872, as cited by Knave et al.) reported anesthesia and sleep following the inhalation of 20-40 gm of gasoline for 8-12 minutes, and nausea, eye and chest. irritation, and drowsiness after inhalation of 5-15 gm of gasoline for 7-12 minutes.

Workers exposed to various industrial solvents (tri-and tetrachloroethylene, toluene, xylene and their mixtures) were compared to workers evidencing carbon disulfide (CS_2) poisoning and to unexposed controls (Lindstrom, 1973). Decrements in sensorimotor and psychomotor performance and visual accuracy were observed in the solvent-exposed group. and generally worse deficits were seen in the CS_2-exposed group. No estimates of the degree of solvent exposure were reported, although tables were given of the occupations responsible for the exposures, and the particular major solvents which the workers were exposed to.

House painters were compared to a group of industrial workers of comparable age, and reported to be worse on reasoning capacity and psychomotor coordination (Sundell et al., 1975). This was suggested to be primarily an effect of exposure to the paint solvents.

Prendergast et al. (1967) reported physiological effects in animals of long-term inhalation of trichloroethylene, carbon tetrachloride, trichloroethane, dichlorodifluoromethane and dichloroethylene. Exposure periods were either continuous for 90 days, or 8 hours/day, 5 days/week for 6 weeks.

These behavioral toxicological data are extremely sketchy and offer no assessment of the relationship between behavioral measures and dose-duration parameters of exposure. It must be concluded that very little is known in the preclinical literature about the cumulative behavioral toxicity of inhalant solvents. This represents a serious gap in the toxicological knowledge concerning these compounds. since the hallmark of solvent dependencies in the human is long-term, repetitious self-exposure to the solvents. Many of the behavioral toxicological signs that are most disturbing in the habitual inhaler of solvents are likely to be the result of cumulative toxicity.

Enduring Behavioral Toxicity of Inhalant Solvents

Probably the most serious toxicological concern attendant upon solvent dependencies is the possibility of enduring or permanent damage consequent to the repeated inhalations. The clinical literature offers a spectrum of testimony on enduring damage. Wyse (1973), in reviewing inhalation dependencies, noted that the majority of "...residual effects.. sometimes seen between periods of inebriation in chronic users. are readily reversible, not life-threatening, and disappear when the practice is discontinued." Yet the exceptions to this generalization, as reported by Wyse (1973) or as occurring more recently in the literature, can be quite serious and tragic. Futhermore, clinical studies generally have not used sufficiently sensitive tests to rule out the possibility of subtle or covert damage from long-term inhalation dependencies.

Virtually all reports of enduring damage from solvent inhalation deal with relatively gross or striking physiopathology such as peripheral neuropathies, ocular nerve damage, and a variety of occasional CNS lesions. Lehnert et al. (1974), who reported the conclusions and recommendations of an international conference on long-term effects of halogenated hydrocarbon solvents, noted the narcotic properties of these solvents as a reason for investigating their effects on the CNS, and stated that ". . . insufficient information is available adequately to assess the effects of exposure on psychomotor performance and investigations in this field should be promoted." Such studies can only rigorously be conducted in animals.

There are three main paradigms of solvent exposure and behavioral testing which merit study for the occurrence of long-term toxicity. These paradigms will be considered briefly. Given that examples of enduring toxicity are discovered, then dose-response or dose-effect. relationships should be established, and TLV and ED_{50} parameters estimated. Despite the serious health consequences of enduring or permanent toxicity of chronically inhaled solvents, there is almost no preclinical literature directed to this issue. This may be related to the major investment in time and resources needed for such long-term studies.

Solvent Exposures During Neural Development

The teratological vulnerability of the fetus has been pointed out by Wilson (1965), with special reference to the intrauterine period of organogenesis, as being the most vulnerable for toxic-induced malformations. On the other hand, Dobbing (1968) promulgated the hypothesis that neural tissue is most vulnerable to toxic damage, not only during its initial period of differentiation, but during its period of most rapid rate of development. The latter variously occurs in late gestation or early postnatal life in mammals. Given that the CNS is limited in its recuperative powers, it is clear that damage to the CNS is quite apt to be persistent or permanent. Hence, solvent exposure of the young and developing animal is a paradigm most likely to yield long-lasting neurobehavioral damage.

The very early age at which solvent inhalation dependencies can develop in the human (as young as 5 years old or less) further offers strong reason to investigate early postnatal exposures in the animal.

One halogenated hydrocarbon, halothane, has been studied within the framework of developmental vulnerability (Quimby et al. , 1974, 1975). Rats were exposed to 10 ppm of halothane in air for 8 hours/day, 5 days/week. Groups exposed from conception to Day 60 of life postpartum were tested at 135-150 days of age, and had deficits in both aversive and appetitive maze learning tasks. They were also hyperalgesic to electric footshock at 11 months of age, compared to controls never exposed to halothane (Quimby et al., 1975). Rats first exposed to 10 ppm of halothane starting at Day 60 of age, and exposed for 8 hours/day, 5 days/week thereafter, did not suffer from unexposed controls on any of the above tests. Rats exposed in utero for a single Z-hour duration to 12,500 ppm of halothane (1 MAC) on either Day 3 or Day 10 of gestation exhibited hyperalgesia and a deficit in aversive learning similar to the above when tested starting at 75 days postpartum, while rats exposed on Day 17 of gestation did not differ from unexposed controls (Bowman, 1976). These data are suggestive of a neurobehavioral teratological effect of halothane possibly related to halothane toxicity on developing serotonergic neurons on Days 11-15 of gestation (Bowman and Smith, 1977). Whatever the mechanism, these data are indicative that exposure to neuroactive solvents early in life can have behavioral effects lasting for months to years beyond the termination of the exposure.

Postnatal exposure alone to neurotoxic agents can also have long-lasting behavioral effects, as suggested by a study by Sobotka and Cook (1974) involving exposure of rat pups lo lead. No similar studies involving solvent exposures were found.

Adult Solvent Exposure Followed by Conception and Testing of Their Offspring

Toxic agents which are mutagenic might alter the germ plasm of an adult, so that subsequent offspring conceived by that adult would exhibit neurobehavioral changes. This possibility is exemplified for lead toxicity by a study of Bradyd et al. (1975), who found that either adult male or adult female rats exposed to lead had offspring which exhibited altered behavior. This exposure-test paradigm has not been utilized in studies of solvent toxicity Presumably the mutagenicity of solvents would be crucial to such effects, such as the report by Forni et al. (1971) of chromosomal damage produced by benzene.

Adult Solvent Exposure With Subsequent Testing or the Same Adults

The most common paradigm in studies of toxicity has been to expose adult animals to the toxicant and then to test the same animals

subsequently. The adult should generaloy be less susceptible to toxic damage than the young or even the adolescent animal, anti chronic, high dose exposures may generally be the only conditions producing measurable persisting toxicity.

Aside from the clinical literature on neuropathology, virtually no data exist regarding the persistence of solvent toxicities in general, nor of behavioral toxicity in particular. In the literature on human occupational hazards, Axelson et al. (1976) reported increased neuropsychiatric incidences with increasing number of years spent working as a house painter, varnisher, etc. This may represent either cumulative toxicity or the gradual accretion of enduring deficits; the data are insufficient to decide this. In the preclinical literature, Contreras et al. (1976) exposed cats to benzene, toluene, or "thinner" and observed long term effects (up to 60 days postexposure) on EEG.

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SUMMARY

Chapter 13

APPROACHES TO THE PROBLEM

Charles W. Sharp

INTRODUCTION

This review has defined the nature of the inhalant abuse problem. Although the use of volatile substances may not be increasing to any great extent, it is a serious problem that needs attention. That the effects on the population are subtle should not be taken lightly . The consequences of such neurological deficits early in life may lead to markedly dysfunctional adults because of learning deficits during their maturation, or even residual neurological deficits when they reach maturity. Future use of the mixtures could cause even more serious and numerous incidents. It may be premature to approach any resolution of inhalant abuse without a thorough understanding and critical evaluation of the problem. However, certain steps can and should be taken to reduce its incidence and seriousness. Meanwhile, more definitive studies should be conducted to further define the extent and nature of the various types of inhalant abuse. The following is an attempt to assemble the thoughts and suggestions discussed by the many contributors to this monograph. It is intended to be provocative, if not controversial in order to enlist those with the expertise and interest to provide a defined course of action. This discussion will include the futuristic and ultimate goal of prevention, highlights of treatment approaches, as well as some specific guidelines for future research.

PREVENTION

Abuse prevention is interpreted in a number of ways. While the simplistic goal of total prevention is seldom achieved, modest progress can be made. No approach can be successful without recognizing the parties who must be active in any solution. As the problem has many facets, it will take a concerted effort by government, industry, and the general public to make progress. Not only are the capabilities and responsibilities widely dispersed in government, no one segment of commerce has the opportunity to oversee and control the abuse potential of the retail products. Industry is wary of more and more regulations, but it is also aware of the need to approach and resolve problems before they get out of hand. This has been brought out by recent court decisions in Minnesota and Florida related to protecting children from the dangers of solvent abuse. Those in positions of control inside and outside the government (administrators, law enforcement people, businessmen, and consumers) should make their interests known, contribute to discussions of the problem, and pool their knowledge about how products are formulated, distributed, and misused. Solutions similar to that of the addition of allyl-isothiocyanate (a noxious substance) to glue may then become obvious. Many other benefits could come about by this mutual participation and interaction on a problem particularly associated with our children.

Some of the potential approaches are discussed below, several of them emerging from discussion in the previous sections.

Addition of Obnoxious Materials to Solvents

The addition of oil of mustard (allyl-isothiocyanate) to glue was a response by the Testor Corporation when the widespread fad of glue sniffing occurred in the sixties. Also, thiols have been added to cooking gas to warn people of its dangers. Similar remedies might be utilized for other commercial products that are inhaled excessively. However, the introduction of these or similar additives to all volatile materials which might be sniffed may not be desirable. That is, the titrating level of additive necessary to prevent excessive inhalation may leave an undesirable or toxic odor on the person (e.g., hair sprays, deodorants), on the wall or in the room (e.g., paint sprays or air odorizers), or in the food (e.g., pan sprays). In addition, interactions of many of these compounds with the product may produce toxic compounds either in the product or in the human body. Under ideal conditions, irritants in products might be useful to alert the individual that he has titrated his system with enough of the product to be dangerous.

There are, however, serious questions about such an approach. How would one measure what is the unsafe amount of a mixture? What about the dangers of repeated or prolonged exposure to

these additive substances? Would the buildup of this substance produce unwarranted side effects? These are major concerns to those using these substances frequently in their occupations or around the home. For example, some of these substances could well become identified in the future as carcinogenic, as have some of the food additives.

Product Composition Changes to Lessen Euphoric Effects

There appears to have been an attempt to remove toluene (and hexane) from various products, especially glues, and to replace it with substances which may or may not be pleasant to inhale. As there is at present no known criterion for the identification of which compounds are likely to be sniffed, changing components on hunches is risky. The toxicity of the new compounds that are introduced may well exceed the toxicity of the substance (e.g. , toluene) being replaced. Therefore, the "improvement" of the product may be more wishful thinking than practical action. There seem to be no good data on what effects this, or any other action, has had on decreasing the inhalant use of glue. If, indeed, its use is less now than in the sixties, it may be due more to fads or a self-preferred switch to other mixtures. We know little about those elements that are important in the choice of a substance.

Not only is the approach of substitution carried out somewhat blindly, but also the measure of the toxicity of any product inhaled producing a euphoric state can only be tentatively extrapolated from knowledge related to other types of exposure. We know a good deal about the acute toxicities of these substances. However, when the subject recovers from a "snort," as most inhalant users do, we know very little about the after effects or how rapidly certain toxic symptoms are likely to occur after many repeated administrations. Therefore, making mixtures which would be nontoxic and/or aphoric for a child who might desire to inhale this material is difficult indeed.

Product Formulation Changes to Reduce Toxicity

Since it is known that the young will experiment, perhaps the mixture can be made "safer" so that there is an opportunity for the child to be dissuaded by other methods and approaches before any major damage has been done. The knowledge about toxicities of certain compounds alone or in mixtures after prolonged exposure is slowly coming in. For example, methyl butyl ketone and hexane have recently been implicated as causative agents of certain resulting neuropathies from exposure in a work environment. Also, potentiation of these toxicities may occur due to the presence of other volatile materials. These are only the more prominent examples of what may be occurring after the inhalation of these mixtures. The identification of these toxicities will lead,

generally, to not using those substances in many products. However, a more defined and systematic approach to choosing which compounds should be excluded from common household mixtures is needed. The distribution of knowledge of certain toxicities is very haphazard and may reach many of the formulators very slowly. It would be better if there were a simple system for identifying the more toxic mixtures prior to formulation and distribution. It may be even more important now that some changes in formulation are being sought to preserve the ozone layer. For example, freons may be removed for the purpose of preserving the ozone, but some substitutes may be utilized which could be even worse for children.

These replacement substances may in themselves be more toxic following repeated administration, may be more readily metabolized (often thought to be a desirable characteristic) to a more toxic compound, and may cause other undesirable interactions. It should be possible among various organizations and government agencies to establish more concrete guidelines for certain products. For instance, at least methyl butyl ketone, hexane, and benzene should not be included in any generally used consumer product--especially those which might be inhaled excessively.

Rather than add some different type of substance to mixtures, maybe one of the solvents or "active ingredients" could be utilized for this purpose. It should be highly volatile, nonreactive, and irritating so as to make the mixture undesirable for inhalation This would also be suitable as a warning of poor ventilation in everyday usage. Small amounts of compounds like methylene chloride might approach those desired properties for some mixtures .

Limitations of Sales and/or Use to Adults

This is a suggestion offered by leading manufacturers, especially as to the sale of airplane glues. In some areas these sales are restricted by law. In other situations the limitation may be de facto; e.g., amyl nitrite substitutes are sold mostly in "adult" shops in various regions of the country. However, there is no Federal restriction on who can purchase most volatile solvents, nor are they regulated now by the Drug Enforcement Agency (DEA). The Congressional Subcommittee on Alcohol and Drug Abuse has been examining the information on hand to see what, if any, action might be appropriate.

With the passage of the Toxic Substances Act (1976), there is an opportunity for this question to be considered on a broader basis. It remains to be seen, however, whether this aspect of solvent toxicity will "fall through the cracks" due to a lack of interest, awareness, etc. Only if those charged to implement these regulations consider this problem in their approaches and regulations will there be any possibility that national uniform action will be taken to solve this problem.

Another form of restriction is in usage. In some school districts there is a limit to the type of glues that children may use (e.g.) paste or Elmer's) and only teachers have acces to the containing volatile solvents. Also, marking perns are restricted to teachers' use. Since these early encounters with sweet smelling objects could assist in acquiring a liking for volatiles, restricted access may be desirable.

Modify Labels

A skull and cross bones label or a symbol of a child reaching for a spray can with a bold "X" through the symbol could be used on household solvents, but may be undesirable for a food or cosmetic spray. There are other possible modifications such as a "sniffing skull" on the label to make parents and children aware of the dangers. However, it would be necessary to establish by defined criteria which items need to be so labeled. This may not be an easy task, as we do not yet know how to determine those products most likely to be abused.

Community Action

This will take an unusual effort since most inhalant abusers interrelate very poorly with community action groups. However, it may be possible for certain social activists to identify and interact with gang leaders or other inhalant abusers and provide opportunities for these groups to come together and communicate on the inhalant situation. Any local (or national) approach to the problem should benefit from more discussions among the various active principles in the chain of events, that is, manufacturers, formulators, social scientists, anthropologists, Federal regulators, basic and clinical scientists and their supporting agencies, forensic toxicologists, legal and law enforcement officials, and others in the community, including chronic inhalant users.

One of the best communications networks is TV. Although there is danger of introducing inhalants lo children who might otherwise not think lo inhale solvents, certain approaches may be worthwhile. For example, while eliciting concern about the ingestion of certain undesired solvcnts, one could at the same time caution against prolonged inhalation (whether accidentally or on purpose) so that young children would grow up viewing this as a danger. Some of this information could also be included in general health pamphlets lo alert and warn parents and other adults of these additional potential dangers of normal household items. The dangerous products should be identified, at least by categories and with examples given

One approach to prevention in school would be to teach general pharmacology to elementary students. They appear to be attentive and receptive to knowledge of drugs during this period and seem eager to know the proper, as well as improper, use of

drugs. Typical situations of "misuse" of some drugs can be introduced along with the consequences of this misuse without directly associating these acts with certain abused drugs. A good general drug "usage" course could be interesting and yet not appear to be a "put down" on certain drugs (e.g., marihuana) as may be the case where only drugs of abuse are discussed. This would resolve the problem of identifying specific classes of drugs of abuse and putting them in the spotlight.

The predominant way of handling solvent abusers is by treating them in the same manner as those intoxicated with alcoholic beverages as the state of behavior produced by most volatile substances (especially solvents and anesthetics) is very similar to that of alcohol. The condition is briefer both in onset and duration. The extent of "drunkenness" is related to the type of substance and the duration of inhalation. There is little doubt that the behavior of these individuals is seriously impaired and that they should not be driving or working during or soon after the inhalation episode. As with the prohibition of alcohol, punishment probably is not a major deterrent. However, limitation of sales by Federal, State, or local governments, limitation of the production of certain mixtures, and the regulation of other related aspects of the problem may not only be useful but may be necessary to protect the health of our youth.

Early Warning System

Although an early warning system does not prevent inhalant abuse certain information obtained therefrom could be utilized in a preventive manner. It should alert agencies to the introduction of new substances and major increases (or decreases) in the use of familiar substances. However, there are important features of this type of system which should not be confused with a valid epidemiological study. Although DAWN (Drug Abuse Warning Network) may be an appropriate mechanism, this system does not pick up many trends on inhalant use partly because of the areas (cities) included in the survey and because the incidences reported by emergency rooms, medical officers, or crisis centers represent only a small percentage of the inhalant population. Since most inhalant users do not need general medical treatment, CODAP (CIient Oriented Data Acquisition Process) reports have also not been too successful in measuring inhalant use. The Poison Control Center, likewise, receives incomplete reports from similar sources. The Center for Disease Control might provide information on this. However, no such approach has been utilized to date. Also reports on arrests for drunkenness may assist in identifying inhalant drug users. Since a main source of information about the inhalant abusing population has been in-depth surveys of communities, it may be that as national and State mental health and other clinics reach out to resolve other health problems of the youth, they will also be in a position to obtain more information on the inhalant problem. Our best information

to date comes from psychiatric: emergency and rehabilitation clinics. For those still in the system, more effective use of the school survey system is also an 'important source of this information

TREATMENT

General

Outlining appropriate treatments is difficult. for a problem which has received little attention in most communities. A recent NIDA survey of CODAP-associated facilities in seven communities identified very few solvent abuse cases receiving any form of treatment either of a medical or psychiatric nature. Neither were any unique or unusual treatments for solvent albuse identified.

Generally, the average solvent abuser rarely utilizes any medical facility or personnel. The acute state of intoxication ends abruptly, usually in complete recovery of physiological state or occasionally in death. Nothing can be clone for these latter cases, and seldom are specific drugs useful in any case. Inhalant abuse subjects are treated similarly to other nonopiate drug abusers and are lumped into what is described as polydrug abuse treatment. For most, tranquilizing agents or various psychiatric assistance is given those showing signs of organic brain syndrome and they are then released. Some may be admitted through psychiatric emergency or related clinics into some type of remedial program. Only a small minority are hospitalized with severe complications needing extensive care and treatment.

For the majority, any impairments are not readily identifiable and may not be apparent to the subject, his family, or a doctor unless specifically examined for and diagnosed. Many of the symptoms that may need treatment are not picked up by the casual medical checkup. However, serious physiological disorders may occur and care should be taken to carefully evaluate basic sight, hearing, cognitive ability, pulmonary involvement, or liver and kidney damage prior to dismissing the patient's need for medical assistance. For example, a case of scotoma was not picked up early in the treatment of a silk screen operator. Therefore, she was not removed from the toxic environment as early as she should have been. Similar problems also occur with solvent abusers. This points out the need for more critical screening procedures and cxamination of inhalant abuse subjects to identify those physiological impairments associated with sniffing and other overexposures.

In light of these deficiencies, appropriate diagnoses and treatments should be established for inhalant abusers. In order to develop satisfactory treatments for inhalant abusers, it will be necessary to rigorously evaluate the immediate or long-term outcomes of some types of treatment It will be necessary not only

to use appropriate controls or comparative groups whose characteristics of treatment and outcome are thoroughly described, but to systematically follow up studies of treated subjects, utilize "blind" methodologies, and adequately analyze data. It may be desirable to validate outcome measures by use of informants, breath or urine analysis, as well as dependent measures included in the primary study. One should carefully define the variables of the treatment approach, including the failures, so that improved methodologies and protocols can be adopted for succeeding treatments. Any treatment should take into consideration that more than one type of "inhalant" subject may exist, e.g., the escapist or the euphoria-seeker, and that what started them sniffing may not be what maintains this condition.

A few of the treatments previously used for inhalant abusers will be briefly discussed in the following paragraphs. Although there is as yet no specific treatment identified with this group, one or more of the following might, with modification, provide a useful therapy. Hopefully, newer and more effective treatments will result from this and other discussions of the problem.

Psychotherapies

Although few therapies exist for solvent abuse subjects, several efforts have been invoked to alter their behavior. However, it has been noted that solvent abusers do not respond as well to therapeutic intervention, and longer treatments are necessary for this type of drug-dependent subject. Some aversive techniques have been used for a limited number of inhalant abusers. Although in one study as many as 50 percent were reported not to resume sniffing, a validation of this "clean" state is necessary. Also, the outcome for these subjects should be compared with other types of drug use, and any potential substitution of other drugs or other undesired habits needs to be determined. Also, the use of more extreme types of conditioned aversion such as use of foul odors or apomorphine injections needs to be critically approached and undertaken only in competent medical surroundings. Foul odors may not be so innocuous, and adverse reactions to other drugs may occur more in this population because of nutritional deficiencies or other associated problems.

The simplest approach of removing the substance has not been sufficient to deter the abuser. Arrests have been used in many communities to control this problem. Although no critical analysis of the outcome exists, it is not likely that this approach will succeed, just as prohibition of alcohol failed. The inverse approach has even been tried. Subjects were offered money not to sniff but chose not to accept.

Though not precisely a therapeutic intervention, other negative reinforcements occur. These include religious sanctions as well as tribal customs and authority. For example, there are fewer

inhalant users among those Indian youth who belong to the Native American Church than those who belong to Protestant or Catholic Churches. However, it may not necessarily have been the Indian culture and tradition that limited the number of solvent abusers. Different types of personalities may have skewed the subject populations by a preselection process such that fewer of those who joined the Native American Church would have inhaled under any circumstances. The influence of cultures or religions on solvent abuse has not yet been adequately assessed.

Some characteristic needs of solvent abusers which should be considered uppermost in any treatment paradigm include the following: improvement of peer relationships, development of suitable alternative activities, improvement of family interaction, development of self-esteem, reinforcement of appropriate behavior, ability to overcome moods of helplessness, increased verbal ability (intellectual capacity appears comparable to their peers), as well as improvement of interrelationships within the basic family and educational systems.

Maintenance

This method is utilized primarily in the treatment of opiate addiction by substituting one drug for another (usually both have opiate-like effects). However, in the broader concept, one can visualize the need for maintaining the patient's physiological and psychological equilibrium. This may be necessary for some subjects. Types of drug which have been used with inhalant abusers have included the psychotropics and tranquilizers. A word of caution in the use of depressants is apropos. Any patient who is taking such medication and then inhales a solvent would be enhancing those depressant effects since these solvents belong to the general class of depressants (along with alcohol). They also may be deposited in lipids and residual amounts may exert additive effects when other sedatives are subsequently administered. A typical example of this is "degreaser's flush." That is, people who work around degreasing vats using trichloroethylene all day become flushed after a few drinks after work.

Any state of drug maintenance should not be a major focus or long-term step in the rehabilitation effort but should probably be only supportive until more suitable approaches can be deployed. Also, it does not presently seem necessary or rational to substitute one solvent for another (e.g. , such as when ether use was substituted for alcohol in Ireland) even though the patient may so desire.

Other Approaches

Numerous communities have made efforts to resolve the problem of inhalant drug abuse. For example, efforts in Mexican-American communities (barrios) where concilios were formed involved par-

ents and neighbors in recreational and art form activities with the abuser and his peers. The success of this approach and its impact on the community is presently unknown. Other forms of vocational, physical, or occupational therapies should also be considered.

In all of the approaches, the individual variations of different cultures, races, sexes, ages, types of inhalant, stages of use, environment, health, and family structures are important considerations. This may well signify the number of different treatments, or variations thereof, necessary to treat these subjects. Treatment approaches should also take into account that the treatment may be worse than the habit. and/or that it may lead to a greater use of inhalants through anti-establishment or anti-family orientations

AREAS OF FOCUS FOR RESEARCH

This section is divided into three major areas for convenience of discussion but not with the intent of limiting one's approach to those problems which cover more than any one or parts of all of these areas. As an orientation, it should be emphasized here that future studies should be focused on testing and assessing a rigorously defined problem area rather than on accumulating yet more descriptive data on a limited number of subjects or compounds. Any studies should, therefore, thoroughly define a premise to be evaluated or established, substantiate this with findings using selective and appropriate measures, and should omit excessive tests that are redundant or irrelevant to that premise.

Epidemiological Studies

This is one of the most difficult areas to approach. Several salient points were discussed in a previous chapter and include problems of appropriate sample size, cost, choice of study of any one inhalant from amongst all the varieties used, identifying and reaching the inhalant population, the time required for Iongitudinal studies, the need for multidisciplinary teams to study the problem, establishment of standardized survey instruments, the use of appropriate community ethnographers, poor or incorrect recording of information at hospitals, clinics, courts, or even in interviews, and the problems related to clearance for these projects through government agencies. Many of these points need to be considered in studies in any of the following areas.

Deaths and Other Hazards

Although there has been considerable input into this area, very little of it is substantive enough to evaluate the problem. Many coroners and forensic toxicologists do not believe that there is a major physiological hazard related to inhalant use, yet many admit

that they do not carefully evaluate whether inhalants may be the potential cause in some deaths. For example, unless a can, rag, or some other evidence is found nearby, the examiner may not suspect solvent overdose. It has also been observed that unless alveolar air is appropriately sampled. the level of the more insoluble substances (e.g., freons) may be undetected. Appropriate evaluation of the incidence of this hazard, especially in several communities where the prevalence of use is high, would assist greatly in defining the extent of deaths related to inhalant use. Records would need to be thoroughly examined to evaluate whether some deaths listed as "cause unknown" might be due to inhalants. Even then it might be very difficult to get this information, even if the examiners are aware of the difficulties and are prepared ahead of time to obtain the needed data because, for different reasons, some people do not want to identify the deceased as an inhalant abuser.

Similarly, hospital and clinic information is often incomplete so that it is difficult to evaluate health hazards associated with inhalant use. Seldom is a good historical or clinical evaluation made of the admitted patient. This became clear during a recent NIDA study which utilized CODAP records in seven communities to examine the treatment of inhalant abusers. The information on inhalant users admitted appeared to be small. An illness may not be associated with inhalant use (purposely or unknowingly) as the acute problems associated with inhalant use arc brief and the chronic impairments are even difficult for a physician to relate to any particular agent or mixture, especially since the initiation of use is so remote from the onset of the disability.

Similar difficulties prevent the use of another system, DAWN, of the Drug Enforcement Agency. Mentions which are accumulated therein do not indicate how recent the event is, the amount used, or how long the person has been using. Also, two or more mentions may come from one person Therefore DAWN may pick up different types of drug use, but the system doesn't provide a good indication of the seriousness of the incident. It may also miss many hot spots of activity since only limited major metropolitan areas are surveyed. It might be possible that more State health centers would increase their vigilance on inhalant abuse especially through use of the primary school systems visiting health teams. School absentees would need to be included in any such analysis.

Although many clinics are set up to analyze for many drugs of abuse, few are equipped to measure solvents, especially mixtures. Therefore, validation by the type of inhalant used is unlikely and the data must come from in-depth personal interviews. This latter method is much less reliable when the subject knows that the data will be made available to authorities. Also, even when the interviewer has the confidence of the subject. the inhalant user usually has poor recall, especially of the substance used,

beyond a week or two. This may be due to brain damage resulting from inhalation or to a general lack of desire to know exactly what was used. Multiple drug use also complicates the approach to the problem.

In-Depth Surveys

It is difficult and expensive to obtain information on inhalant abuse at the national level. As we do know of some areas of high prevalence, it would be most appropriate to focus on some of these communities. In setting up these studies, one should consider some of the following aspects: use among different ethnic and social groups and different economic levels, with different age groups such as pre- and postadolescent inhalant users, and among different siblings (why does one sibling "sniff" and not the other); predisposing factors such as outlook, personality, family relationships and stability, community, tension release, machoism, aggression, health, achievement or accomplishment of important tasks, etc.; the conditions of inhalation, including different methods, individual or group settings, associated activities such as sex, gang activities, etc.; the inducements or causes associated with the use or with the reinforcement of use; the identification of types of sustances used (e.g. , brand names, etc.); the rationale for the choice of products and why they change; the relative weight of cost, availability, irritant or other disagreeable properties, nice odor or other agreeable properties, peer suggestion, etc.; the influences of teachers, friends, or officials on subjects before they become involved and in their future orientation; the progression from drug use to a drug-free state, heroin use, or to a more entrenched state of inhalant use, and the prominent factors associated with each. These investigations could utilize special schools, retraining centers, and various health clinics, especially psychiatric emergency rooms, where more of the nonschool subjects (dropouts) may be contacted. It is known that these subjects are not only hard to find, but are also difficult to get and keep in rehabilitative programs without small remunerations. This latter incentive may skew the sample populations obtained through these facilities and therefore usage patterns should be carefully scrutinized to determine the actual amount and type of use.

Clinical Studies

The need for clinical studies in the area of inhalant abuse is particularly pressing and at the same time very difficult to meet. One of the most important issues to resolve is the nature and extent of the physiological impairment that results from use of inhalants.

Impairments

First, the type, onset, and extent of tolerance or dependence produced by these substances should be determined. For example, is there a behavioral adaptation to the effects, as acquisition of different effects. or is some physiological tolerance involved? Similarly, is there any dependence and in which population(s) does it occur? If so, what are the withdrawal effects observed for subjects after they have been isolated from the inhalant scene?

The toxicity of most of these agents is established. However, it has been difficult to measure any symptoms of toxicity in the "average" user, There are numerous reports of defined impairments in certain individuals, yet it is unknown if these resulted from inhalant use or were pre-existing conditions in these subjects. An identified neurological impairment may be correlated more with one class of solvents than with others; yet there are almost as many different kinds of "solvents" as there are other drugs of abuse. The sorting problem may be endless. Recent evidence indicates that prolonged exposure to low levels of some of these solvents may be carcinogenic (e.g., benzene and tri- and perchloroethylene). Findings such as these result in limiting their use in many household products but may open the way to the use of other compounds with other toxicities. It would be especially unfortunate if substances were incorporated that produced irreversible neurological damage not easily detectable by present testing mechanisms. Also, although toxicities are associated with certain chemicals, it is not yet possible to extrapolate how much sooner these effects would occur at the repeated high dose levels of inhalant users. Nor are onsets of the dramatic (e.g., cognitive) impairments known nor how they differ among the various solvents.

Specific Symptoms of Inhalant Toxicity

As discussed in the clinical section, it would be important to characterize specifically the early manifestations of inhalation toxicity in clinical cases. Then one could possibly devise animal tests which would identify solvent mixtures that cause these problems. The cooperation of manufacturers and formulators in providing detailed information on the constituents of the products used could greatly facilitate determination of the etiological factors associated with certain compounds as well as assist in the development of rational approaches to animal studies.

One could possibly measure inhalant effects through a mapping of the visual field, especially through use of prospective or other longitudinal studies. More detailed acuity and visual field tests could then be pursued for those subjects with abnormalities using techniques such as computerized axial tomography (see neurology section). Presently electroencephalogram (EEG) measures would

not appear to be too useful as a test for inhalant effects due to the complexity and cost of exams. Also, electromyography is mostly used to validate an already noted muscle weakness and is not appropriate to measure early neuromuscular involvement. However, it would be important and useful to determine whether vision or any other easily measured neurological function is an early indication of a progressive impairment resulting from the use of many different inhalants.

Performance Impairments

The rate of progression and quality of performance decrement in inhalant abusers would be another area of investigation. How would an evening of intoxication affect an individual's performance at school, work, or "behind the wheel"? Also, what are the residual impairments that persist days, weeks, and months later and how do these progress with the development of inhalant use? Some of these impairments have been discussed in these pages. Although humans must be utilized for most of these studies for cognitive deficits to be properly evaluated, studies at present are generally limited to retrospective analysis. In the area of noncognitive deficits, it would help animal investigators if the intoxicated state of the individual could be more critically characterized in terms of animal behavior and functioning.

Preclinical Studies

Animals must be used for in-depth studies of toxicity and mechanisms. Although the acute toxicity of most solvent compounds has been determined, few have been studied under chronic exposure conditions and even fewer at the multiple high dose levels of exposure which snorters resort to. Also, the toxicity of mixtures has seldom been evaluated. This has led toxicologists and physicians to an overextrapolation of the data in trying to decide when and whether impairments may have resulted from overexposure to different substances. Although some studies are now underway to explore this area, many questions remain to be answered.

Development of Model Toxicity Systems

Determining impairment potential of substances. One goal would be the development of an inexpensive and simple animal model which would mimic the exposure situation of the inhalant user and measure the degree of toxicity produced by different substances. This model would subsume certain assessments of chronic toxicity and carcinogenic tests, both of which are very costly and time consuming. Also, it might be possible to devise a method whereby the exposure period for the effects that occur at the much higher doses could be extrapolated from chronic low dose studies. Any model should consider the unusual types of solvent administration and the fact that inhalation abusers do not usually dose themselves continuously at one defined level.

Evaluation of mixtures. Another type of study would be establishment of a suitable setup for the comparison of the toxicities of different mixtures over short periods. This screening method should be used to identify mixtures with toxicities greater or less than that of known individual components as determined by other standard tests. This rapid screening test could be used to prevent the misuse of what might otherwise appear to be a safe product. The test system might employ measures of optic nerve or retinal damage such as measured through use of dynamic pupillometry. Also, measurement of sciatic nerve damage may be appropriate (for details refer to the chapter on mixtures).

Behavioral toxicities. Numerous behavioral tests are now being developed to measure toxicity of industrial and environmental agents and some may be useful here. More emphasis should be placed on determining persistent or slowly reversible effects that would indicate possible disabilities which might result from these substances. The degree of altered state produced with different substances or classes of solvents should be compared and/or classified.

Classification of solvents for abuse liability. A basic problem, yet, is how to define the human emotional states in terms applicable to an animal model. More thought and new approaches may be called for to carefully and critically define this state of intoxication . Self-administration has been used to classify many drugs of abuse. In addition to the problem of a lack of correlation between discrimination on the part of animals and the use of various euphoric drugs by humans, there are the problems of volatility (administration) and disruption of the olfactory system. Also, food deprivation may result from either association with the bad odor or with the disruption of other senses as well as with a direct action of the solvent on behavior. Therefore, other behavioral paradigms must be utilized alone or in combination with the self-administration approaches to establish liability of any compound. One hypothesis may be worth exploring. Is there an association between a child's self-induced dizziness from "going round and round till he falls down" to the circling behavior of a rat under similar influences such as solvent intoxication? These states of dizziness may or may not be an altered state not unlike "euphoria."

Other tests that measure pulmonary, cardiac, liver, and kidney dysfunctions that are associated with inhalant abuse should be included in the screening program as many of the substances are known to affect these organs after either acute or chronic exposure.

Mixture-Related Toxicities

Problems associated with physical properties of volatiles. Volatility is an important property to be carefully considered in the

protocol for exposing an animal to mixtures. Are the effects following exposure related more to the highly volatile element or do the other components of the mixture contribute significantly? Other factors related to human exposure should also be considered in designing animal studies including: the style of administration (breathing from a bag or through a rag in the mouth), the frequency of replenishment of the volatile material, the clearance of air and fumes in the surrounding environment, and the length of titration period to produce the altered state.

As with other drugs, the period in between inhalation episodes is critical for the development of tolerance, toxicity, and dependence. Once these limits are established, it would be important to define the rate of onset of certain impairments following different exposure paradigms. Another related aspect would be a measure of how poor health (e.g., malnutrition or asthma) or other modified physiological states alter the onset of these conditions.

Problems associated with biochemical properties of volatiles. One of the reasons given for "snorting" is the fast action one gets. However, these more rapid acting components are also more lipid soluble. Therefore, one must be concerned with the lipid depot of these materials, especially since inhalation is often continued for several hours. Also, over the long term, some chemicals will be absorbed at a level below that of producing an altered state but yet could well be contributing to a toxic reaction because of their water solubility, metabolism, and/or other properties. With all the possibilities of different chemical, physiological, and physical interactions, it is difficult to summarize the potential toxicities even when the retention, metabolism, and excretion of each of the individual components are known, Therefore, it may be better to determine the potential toxicity through an evaluation of the whole mixture. This, of course, leads to the question of how one chooses the mixtures. With all the regional and yearly variations in the different types of mixtures, it is not a simple task. However, this should not deter industry and government from enthusiastically working on this formidable task.

Problems associated with impurities. Another type of interaction involves the active ingredients, solvents, and container impurities or break-down products. Although few of these are probably worth considering in any detail, any screening method for the evaluation of the "safety" of various mixtures should also consider this aspect. This could be accomplished through testing of the available products which are known to be abused. As previously learned from studies of pesticides and other chemicals, a minor component (even at 1 percent) may be important if it is highly volatile, toxic, stored, etc.

Establishing guidelines. Although the use of threshold limit values (TLV) or mininum allowable concentrations (MAC) are not appropriate here, it might be well to grade different types of

mixtures and relate their toxicity (time of onset, type of impairment, etc.) to a readily identifiable single chemical substance and/or gasoline(s).

FINAL COMMENT

Although this discussion has highlighted only a number of the problems associated with inhalant abuse, the reader is encouraged to read the preceding chapters and from studies included in the large bibliography for more pertinent thought and background related to many of the above discussions. If this discussion has given investigators in related subject areas a new perspective or insight into the problem of inhalant abuse, it has been worth the effort. Also, it is hoped that some of the hurdles have been visualized so that future efforts can proceed more systematically and smoothly.

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The search was conducted on the MEDLINE and TOXLINE data bases as well as the file of Psychological Abstracts and the NTIS data base.* Overall, the search strategy consisted of retrieval of references on the toxic effects--physical and behavioral--of solvents in general, or of specific chemicals when used as solvents, propellants, or in gaseous states. (A detailed description of the search strategy for each file has been prepared for NIDA for use in future updating of the bibliography.) The MEDLINE and TOXLINE searches cover material indexed from 1971 through July 1977; Psychological Abstracts coverage begins in 1967 and is current through June 1977; NTIS covers 1964 to June 1977. Some earlier reference texts are also included.

Though the bibliography was available to the authors of the present monograph, it was not possible nor was it the intention that they would review all of this material in their chapters. Indeed, the references at the end of each of the chapters of the monograph are unique to that particular subject matter and may or may not be referenced here. This bibliography is intended for the reader's use as a general reference list to the topic as a whole.

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