# Inhalation Studies With Drugs of Abuse

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## INTRODUCTION

In recent years, smoking or inhalation of drugs has become a popular route of administration among drug users. Various drugs of different classes have been abused by inhalation or smoking, including phencyclidine (PCP), cocaine, heroin, methamphetamine, and marijuana. This increased popu-larity of smoking drugs has resulted from the fast onset of drug action and fears related to contracting acquired immunodeficiency syndrome (AIDS) or other infectious diseases from intravenous (IV) injections. In particular, heroin smoking has increased dramatically; approximately 74 percent of the heroin addicts in India use this method of administration, and it is also popular in the United States (Griffiths et al. 1994). The shift toward smoking heroin has also been associated with an increased availability of illicit heroin on the streets, which has declined in price and increased in purity (Huizer 1987). Consequently, there is an increased risk of overdose.

Inhalation is a very potent route of drug administration, and is characterized by fast absorption from the nasal mucosa and the extensive lung capillaries. Inhalation results in an immediate elevation of arterial blood drug con-centration and a higher bioavailability due to avoiding drug metabolism by the liver. The fact that smoking or inhalation provides rapid delivery of drugs to the brain may result in an immediate reinforcing effect of the drug and further contribute to its abuse liability or risk of dependency. Smoking or inhalation of drugs may also lead to other adverse effects, such as pulmonary diseases or deleterious cardiovascular consequences. Moreover, the parent drugs may be degraded, leading to inhalation of toxic pyrolytic products (Benowitz 1990; Wesson and Washburn 1990). For example, there have been reports of heroin leucoencephalopathy, a life-threatening condition that has occurred in some individuals after smoking heroin (Wolters et al. 1982). This condition was not associated with IV administration and no impurities present in the drug were identified as the cause, but may have been caused by pyrolytic products of either heroin or impurities present in the samples (Wolters et al. 1982).

The rapid increase in smoking drugs of abuse raised concerns about drugs that are currently abused using other routes of administration: Can they also be

smoked? Furthermore, it is unknown whether their abuse liability, side effects, and toxicity would be increased by smoking. Thus the major goal of this research has been to develop guidelines for predicting which drugs can potentially be abused by smoking or inhalation.

To reach this goal, the first step was to establish a predictive parameter for the volatility of drugs. Underscoring the importance of volatility is the practice of smoking various drugs of abuse in combination or with other agents in an effort to enhance their volatility and thereby increase their pharmacological effects. For example, the addition of either caffeine or barbiturates has been shown to improve the volatilization of heroin (Huzier 1987).

One physiochemical parameter that might play a critical role in the volatility of a compound is vapor pressure. Accordingly, the authors hypothesized that vapor pressure could be positively correlated with both volatility and pharmacological potency after smoking. Thus, the vapor pressures of a variety of drugs were determined, and then the volatili-zation of selected compounds was studied.

A second goal of this work was to investigate the volatilization of these drugs and identify their major pyrolysis products. Analytical methods employing gas chromatography/mass spectrometry (GC/MS) and high performance liquid chromatography (HPLC) were developed to identify and quantify drugs and their pyrolytic products after volatilization.

Despite the increase in smoking and inhalation of drugs of abuse, relatively little is known about the consequences of this route of administration. Therefore, the third research goal has been to develop a reliable animal model to evaluate the pharmacology and biodisposition of drugs after inhalation. In these studies, the pharmacological effects of volatilized drugs were assessed in mice. In addition, the brain, plasma, and whole-body levels of drugs occurring after inhalation were quantified in order to obtain biodisposition information. These studies provided the strategy and the tools for prediction of drugs that can be abused by smoking or inhalation.

## VAPOR PRESSURE AND VOLATILITY

In general, absorption of inhaled drug is dependent upon the physical characteristics of the drug, including particle size, lipid solubility, and volatility. Clearly, a drug's volatility would play an important role in determining its inhalation potential. Drug volatility is determined by many factors, including boiling point, melting point, and vapor pressure. Since many abused substances are less volatile than organic solvents and are smoked

at very high temperatures, effects of melting and boiling points on the volatilization would be negligible. On the other hand, vapor pressure may serve as a good indication of volatility.

$$pV = nRT$$

Based on the ideal gas law,

equation 1

where p is the partial pressure of the gas, R is the gas constant, n is the number of molecules, V is the volume of the gas phase of the compound, and T is the temperature in kelvin, the partial pressure of the gas becomes the vapor pressure ($P_v$) when the gas and liquid phases of the compound reach equilibrium at a particular temperature. Then, equation 1 can be expressed as

equation 2

where C = n/V and is the concentration of the compound in the gas phase and is directly proportional to the vapor pressure. This relationship suggests that the vapor pressure of a compound is positively correlated with volatility; the higher concentration of the gas, the more volatile it is. Therefore, the volatility of a drug at a certain temperature is determined by its vapor pressure and the volatilization temperature.

$$P_v = CRT$$

Due to a lack of information on vapor pressure for a variety of drugs of abuse and related compounds, the authors determined this parameter by an indirect method based on a system using gas chromatography and relative retention times. This approach is a modification those described by others (Hamilton 1980; Westcott and Bidleman 1981; Bidleman 1984). The original method is based on in the relationship between solid vapor pressure and GC column retention time (or volume retention time, $V_R$), and has been used in determination of vapor pressures for herbicides, pesticides, and a variety of nonpolar organic compounds. The vapor pressure ($P_v$) of two substances at the same temperature (as well as their latencies of vaporization, $L_V$) are related by

equation 3 $\ln P_1 = (L_1/L_2) \ln P_2 - C$

$\ln [(V_R)_1/(V_R)_2] = [1-(L_1/L_2)] \ln P_2 - C$

and the fact that vapor pressure has been shown to be related to column retention volumes by equation 4

The relationship between vapor pressure and column retention times can be determined from the combination of equations 3 and 4:
equation 5

Therefore, a plot of ln $[(V_R)_1/(V_R)_2]$ versus ln $P_2$ should yield a straight line with either a positive or negative correlation coefficient depending on the ratio of $(V_R)_1/(V_R)_2$ . The value of $(L_1/L_2)$ can be calculated from the slope and thus $P_1$ determined from equation 3. If substances 1 and 2 are the unknown and standard compounds, respectively, then the vapor pressure of the unknown at a given temperature can be determined. The relationship between vapor pressure and temperature can be simply described by the Clausius-Clapeyron equation:
equation 6

Therefore, the vapor pressure at any temperature can be extrapolated by the linear regression between ln P and 1/T.

Since this technique has primarily been used for estimating vapor pressures of pesticides, these chemicals were utilized to establish a working model to determine the vapor pressures of drugs of abuse. The authors' strategy was to determine the vapor pressure of drugs of abuse by employing a pesticide with known $P_v$ values as a standard. A GC/MS was equipped with a 4-meter capillary column. The helium carrier gas was adjusted to a 1.11 milliliter per minute (mL/min) flow rate and a 78.26 mL/min split for a split ratio of 79:1. The injector port was kept at 200%C, detector port at 225%C, and the source of the MS at 200%C. The oven temperature was kept constant during any given analysis. All test compounds were dissolved in hexane or

chloroform at 0.5 to 4.0 milligrams per mL (mg/mL) in order to obtain a substantial peak from a 1 microliter (L) injection. Since eicosane and octadecane are commonly used as standard compounds in determining the vapor pressure of other pesticides, both compounds were used to standardize the GC column. Various pesticides (nonpolar organic compounds), such as naphthalene, phenanthrene, pyrene, and benzo[a]pyrene were then injected and retention times obtained for 5 to 8 temperatures at 10%C increments, ranging from 40%C to 190%C. The natural logs of the ratios of the retention times of the standard and test compounds were then plotted against the natural log of the vapor pressure of the standard at each temperature.

Both octadecane and eicosane standardization yielded vapor pressures of the pesticides very close to published values. Of these two compounds, the values obtained with eicosane exhibited a higher correlation coefficient. Thus, eicosane appeared to be the better standard for approximating the values of various drugs of abuse. However, the plot of relative retention time ratios of several of the drugs of abuse to the published vapor pressure of eicosane (equation 5) correlated poorly (table 1). This result eliminated eicosane as a standard for measuring the vapor pressures of drugs of abuse. In the search for another standard, dibutyl phthalate proved to be a good candidate. Using eicosane as a standard, the vapor pressure of dibutyl phthalate, at 25%C, was determined as $6.89 \times 10^{-5}$ torr, which fell within the published vapor pressure range of $1.2 \times 10^{-6}$ to $4.4 \times 10^{-5}$ torr (Small et al. 1948). By the same method, the vapor pressures of dibutyl phthalate at different temperatures were then determined against eicosane. Equation 6 was then solved for dibutyl phthalate: $\ln P = A + B/T$ where $A = 25.179$, $B = -10{,}364$, P is in torr and T is in kelvins. Using dibutyl phthalate as a standard, the natural log of the relative retention time ratios plotted against the natural log of its vapor pressures at the respective temperatures yielded a high correlation for various drugs of abuse (figure 1). Thus, vapor pressures at 25%C could be approximated for drugs representing a variety of classes (table 1).

Vapor pressures of selected compounds are listed in table 1. In comparing different classes of drugs, the opioids appear to have relatively low vapor pressure, suggesting that they are less volatile than other drugs. As can also be seen in table 1, nicotine exhibited relatively high volatility, which is consistent with the fact that cigarette smoking is the most popular method of nicotine administration. Vapor pressures for methamphetamine and amphetamine appeared to be higher than that of nicotine at 25%C, but their vapor pressures could not be determined by the present method since their volatility exceeded the range of the standard at the temperatures that were

**TABLE 1.** *Determining the vapor pressures of drugs of abuse using dibutyl phthalate as the standard.*

| Drugs (Free base) | Correlation coefficient of In $(VR)_1/(VR)_2$ to In P: Eicosane | Correlation coefficient of In $(VR)_1/(VR)_2$ to In P: Dibutyl phthalate | Vapor pressures (Torr, at 25%C) |
|---|---|---|---|
| Nicotine | A | 0.871 | $2.61 \times 10^{-2}$ |
| MDMA | — | 0.997 | $4.47 \times 10^{-3}$ |
| Caffeine | — | 0.997 | $8.56 \times 10^{-4}$ |
| PCP | — | 0.984 | $1.49 \times 10^{-4}$ |
| Secobarbital | — | 0.996 | $5.72 \times 10^{-5}$ |
| Pentalbarbital | — | 0.948 | $4.16 \times 10^{-5}$ |
| Methaqualone | 0.751 | 0.896 | $1.60 \times 10^{-5}$ |
| Cocaine | 0.748 | 0.996 | $9.79 \times 10^{-6}$ |
| Morphine | — | 0.943 | $9.49 \times 10^{-7}$ |
| 9-THC | — | 0.986 | $1.01 \times 10^{-7}$ |
| Heroin | 0.981 | 0.983 | $5.71 \times 10^{-8}$ |
| Fentanyl | — | 0.982 | $2.41 \times 10^{-8}$ |

KEY: A = Values were not determined.

studied. Compounds with high vapor pressures are predicted to be much more volatile and consequently more likely to be smoked than those possessing low vapor pressures.

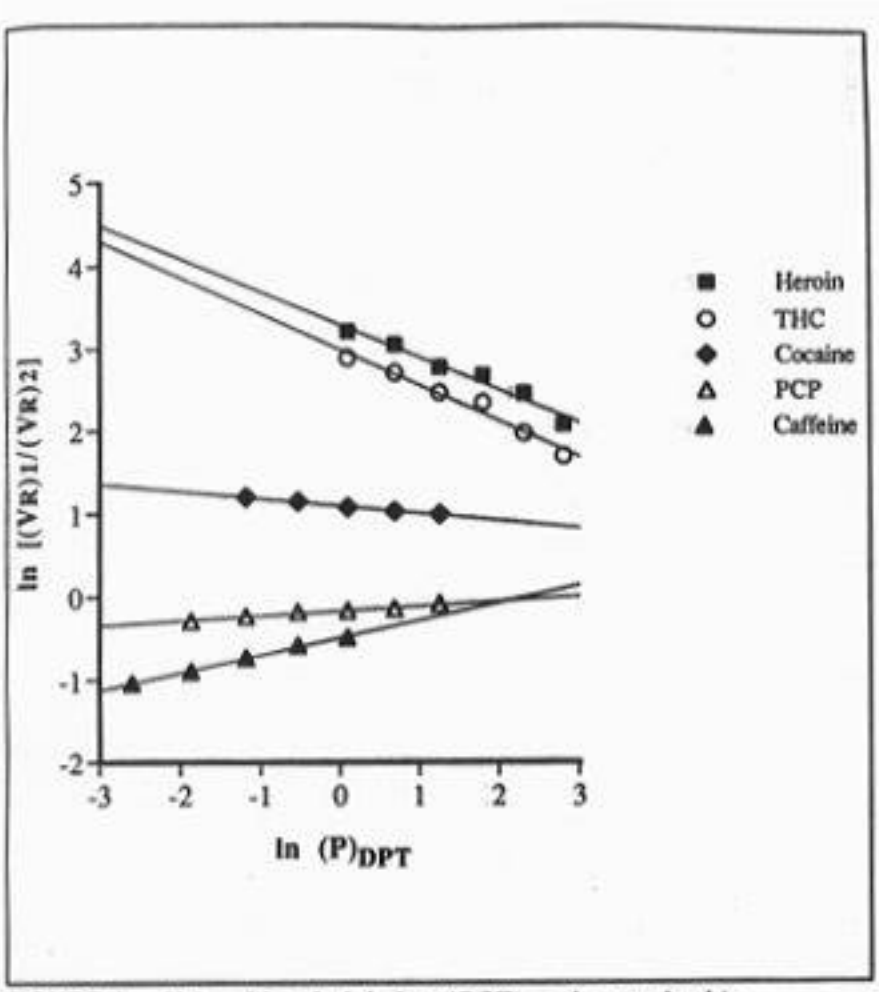


**FIGURE 1.** *Using dibutyl phthalate (DPT) as the standard in determining vapor pressures of drugs of abuse. Plots represent the linear correlation between the natural log of the vapor pressure of DPT and the natural log of ratios of retention times at different temperatures. Positive correlations indicate that the test compounds have higher vapor pressures than the standard, while negative correlations indicate that the test compounds have lower vapor pressures than the standard.*

## INHALATION EXPOSURE OF DRUGS OF ABUSE IN THE MOUSE INHALATION MODEL: PHARMACOLOGICAL ASSESSMENT

Although drug volatility can provide fundamental information about the inhalation potential for drugs of abuse, it is only one of many factors necessary for producing a pharmacological effect. Pharmacokinetic and pharmacodynamic considerations have considerable bearing on a drug's ability to produce an effect. Presently, relatively little is known about the potency of drugs of abuse after inhalation or smoking. In order to deter-mine the relationship between volatility and pharmacological potency by the inhalation route, the authors developed an animal model to approx-imate the conditions of human inhalation. The approach involved a volatilization-inhalation drug delivery system developed over the past 10 years in this laboratory. The design of this inhalation apparatus is illustrated in figure 2.

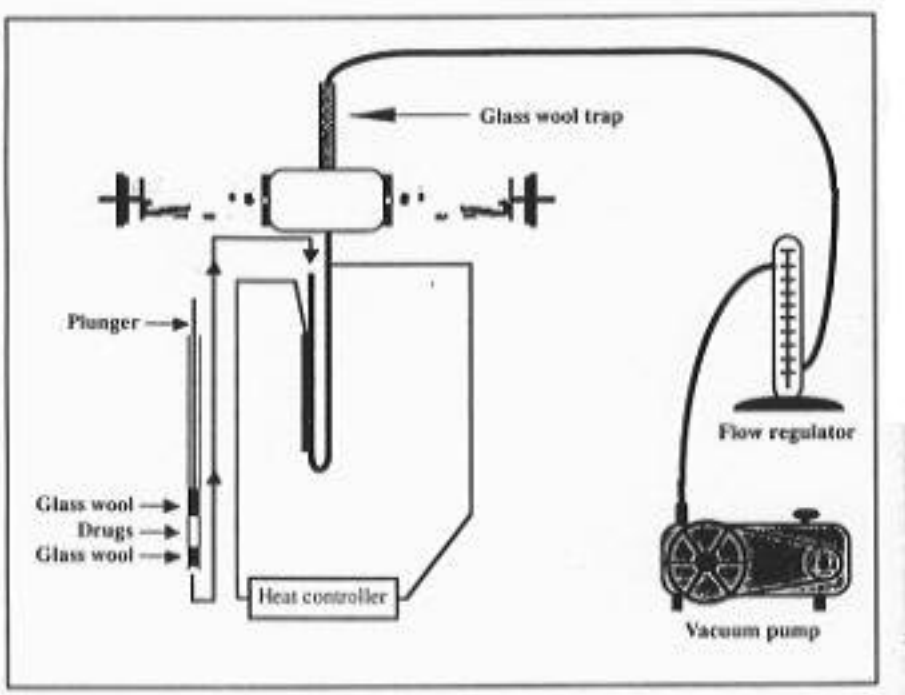


**FIGURE 2.** *Mouse inhalation apparatus.*

The apparatus consisted of a U-shape glass volatilization pipe preheated to a designed temperature, a nose-only exposure unit containing six mice, a glass wool trap (packed with 0.5 g of glass wool fiber) that sequestered the vaporized test compound, and a vacuum system that created negative pressure and pulled the air through the

entire apparatus. The airflow was regulated at a rate of 400 mL/min by a flow meter placed after the glass wool trap. The entire system was contained within a hood. A known amount of test compound (either in dry powder or liquid form), packed in between two pieces of glass wool in a glass plunger, was injected into the preheated pipe and volatilized. Animals were exposed to the vapor for 5 minutes, and then the appropriate pharmacological effects for each respective drug were measured.

These studies allowed the authors to optimize the volatilization conditions by using a pharmacological endpoint. Once conditions for volatilizing a drug had been established, then pharmacological potency was determined by exposing mice to different quantities of volatilized drug. This strategy represents a deviation from traditional inhalation approaches involving optimization of volatilization using analytical methods. The rationale for using a pharmacological endpoint is that failure of an agent to produce behavioral effects via inhalation renders the analytical considerations moot.

To determine the feasibility of evaluating the volatilization of drugs with different pharmacological properties, several compounds that are abused by smoking or inhalation were selected. It is well known that changing the route of administration has important effects on the development of drug dependency (Griffiths 1994); thus the authors elected to compare pharma- cological effects after inhalation and IV administration. Heroin was chosen because of the shift toward smoking among heroin users and the lack of systematic studies on the pharmacological potency, onset, and duration of action of smoked heroin. Other drugs of abuse such as PCP and meth-amphetamine are also commonly smoked (Wesson and Washburn 1990). PCP was initially abused by oral and IV administration routes associated with many adverse effects.

The discovery that smoking PCP-laced cigarettes allowed for a better titration of doses and fewer side effects propelled it to the forefront of drug abuse. Previously, the authors studied the pyrolysis of PCP in parsley cigarettes, which employed a much higher temperature than the currently used system (Freeman and Martin 1981; Lue et al. 1986, 1988; Martin and Boni 1990). Those studies demonstrated that more than 50 percent of the drug was delivered intact. The pharmacology of smoked PCP-laced cigarettes in mice and rats has also been characterized (Freeman and Martin 1982; Martin and Freeman 1983; Wessinger et al. 1985).

The incidence of inhalation or smoking of methamphetamine has risen very recently in the United States. Several investigators have examined the volatilization and pyrolysis of this compound (Cook et al. 1991, 1993; Miller and Kozel 1991). Sekine and Nahahara (1987) studied the volatilization of methamphetamine applied to tobacco cigarettes and found that about 15 percent of the drug was delivered in the main stream of the smoke and several pyrolysis products were formed. Studies of the volatilization, biodisposition, and pharmacokinetics of smoked metham-phetamine hydrocloride (Cook et al. 1991, 1993; Perez-Reyes et al. 1991) demonstrated that this compound can be easily volatilized in the temperature range of 200 to 400%C, while 90 percent of the parent drug is delivered intact. The pharmacological effects of methamphetamine administered by inhalation or IV injection appeared to be similar.

Using the rodent inhalation model depicted in figure 2, mice were assessed for locomotor activity after exposure to methamphetamine vapor, antinociception after exposure to heroin, and motor coordination after exposure to PCP. Temperatures used for volatilization of these drugs are listed in table 2. These temperatures were empirically derived

TABLE 2. *Relative potencies of drugs by inhalation exposure and IV administration.*

| Drugs | Inhalation $ED_{50}$ (mg)[A] | IV $ED_{50}$ (mg/kg) |
|---|---|---|
| Heroin [B] | 1.1 [B] | 0.28 |
| PCP HCl [C] | 2.8 [C] | 0.1 |
| Methamphetamine-HCl [D] | 3.9 [D] | 0.9 |

KEY: A = Based upon the amount of drug added to the volatilization chamber. B = Free base volatilized at 250%C. C = Volatilized at 275%C. D = Volatilized at 200 %C. $ED_{50}$ = Median effective dose.

based upon their pharmacological effectiveness in mice in inhalation studies. In order to measure the antinociceptive effects of heroin, the tail-flick apparatus described by Dewey and colleagues (1970) was used. Fifteen minutes after the inhalation exposure or IV administration of heroin, the mouse's tail was placed under a radiant heat lamp and the amount of time required for the animal to flick its tail from under the heat source was recorded. Baseline reaction latencies ranged from 2 to 4 seconds, and the maximal allowable reaction time was 10 seconds. The percent of maximal percent effect (percent MPE) was calculated for each animal. Volatilization of heroin free base resulted in a dose-related antinociception with maximal effects occurring in mice exposed to the vapor from 3 mg of heroin free base. Dose-response curves generated for heroin are illustrated in figure 3 and the $ED_{50}$ values are listed in table 2. These data clearly show that heroin-induced antinociception is qualitatively similar after inhalation and IV administration. Similar to the results in the present study, smoking heroin has been reported to be as potent as IV heroin in humans (Jenkings et al. 1994). In a controlled clinical study, the pharmacokinetic and pharmacodynamic profile of smoked heroin was evaluated in human subjects. It was demonstrated that the behavioral effects of smoked heroin were as potent and rapid in onset as IV administration.

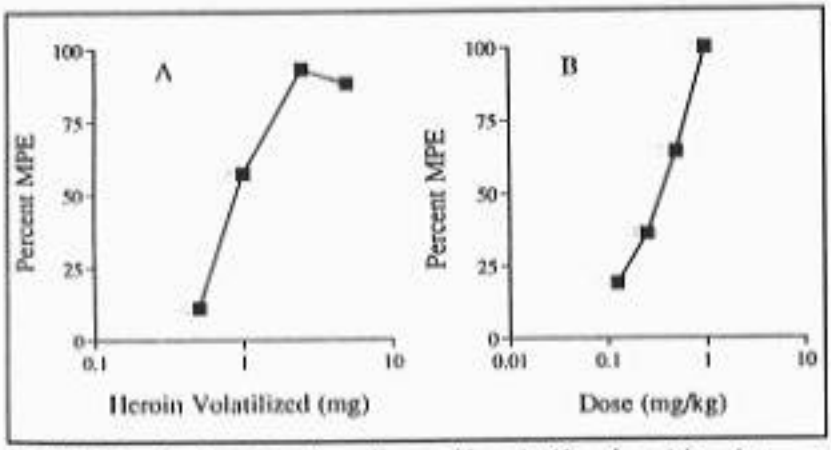


**FIGURE 3.** *Antinociceptive effects of heroin (free base) in mice after inhalation exposure (panel A) or IV administration of heroin HCl (panel B). All subjects were assessed in the tail-flick test 15 min after drug administration. The results are the means of at least six mice/group.*

Stimulant effects are readily quantified by measuring spontaneous activity. For these studies mice were placed in individual photocell activity cages (6.5 x 11 in) with 16 photocell beams per chamber. Individual mice were placed into one of six chambers and allowed to acclimate for 10 minutes. They were removed from the activity chambers and either injected IV with saline or drug or exposed to volatilized methamphetamine. Immediately after the injection or inhalation exposure, the mice were returned to the chambers, and interruptions of the photocell beams were recorded for the next 40 minutes using an animal activity monitor. Activity in the chamber was then expressed as the total number of beam interruptions for the total 40 minutes. Maximal possible stimulation was determined from double reciprocal plots of photocell interruptions versus dose so that the data could be expressed as percentage of maximal stimulation. Methamphetamine produced a dose-related stimulation of spontaneous activity with maximal stimulation occurring with volatilization of 25 mg of drug. This stimulation was comparable to that produced by IV administration of methamphetamine in the dose range of 0.5 to 4.0 mg/kg (figure 4). The $ED_{50}$ of metham-phetamine by both routes of administration are summarized in table 2.

The final drug to be evaluated for pharmacological effects following inhalation was PCP hydrochloride (HCl). Motor incoordination produced by PCP HCl was evaluated by the inverted-screen test (Coughenour et al. 1977). Fifteen minutes after drug exposure, the mice were placed on a wire screen that was immediately inverted. The percentage of animals that climbed onto the top within 60 seconds was recorded. Only mice successfully completing the task in a pre-experimental test were used. Mice (in groups of six) exposed to the volatilization of PCP HCl in the range of 2 to 6 mg exhibited a dose-related inhibition of motor function as depicted in figure 5. Mice exposed to the volatilization of 1 mg of PCP displayed altered behavior to a greater degree than those exposed to 2 mg; this most likely represents an aberration. The disruption of motor function following inhalation is comparable to that produced by IV administration of PCP in the dose range of 0.03 to 1.0 mg/kg.

These inhalation studies demonstrate the feasibility of evaluating the potency of drugs with different pharmacological actions following inhalation exposure. The comparison of pharmacological effects after both inhalation and IV administration revealed very similar dose-response relationships for each of these three drugs. However, valid potency comparisons can be made between inhalation and IV administration only

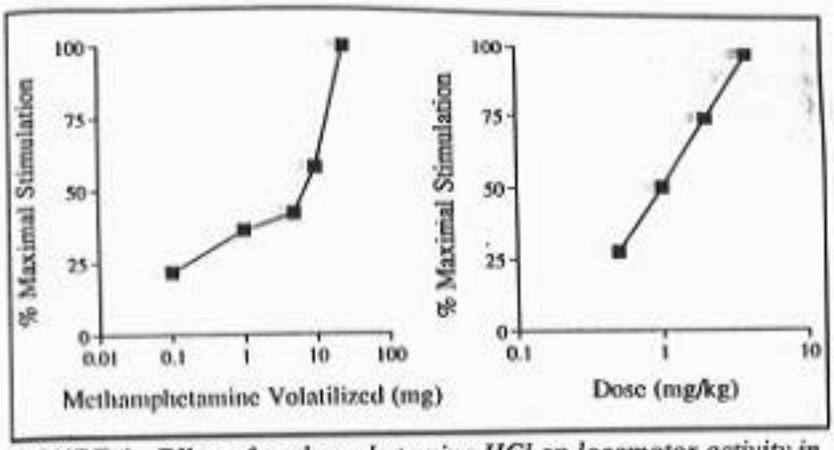


**FIGURE 4.** *Effect of methamphetamine HCl on locomotor activity in mice after inhalation exposure (panel A) or IV administration (panel B). Control mice produced 2,892±265 interruptions of the photocell beams whereas exposure to the vapors from 30 mg of methamphetamine produced 13,503±652. IV administration of 4.0 mg/kg of methamphetamine HCl resulted in 13,224±1420 interruptions of the photocell beams. The effects produced by the other doses of drugs are expressed as percentage of this maximal stimulation produced by methamphetamine. The results are the means of at least six mice/group.*

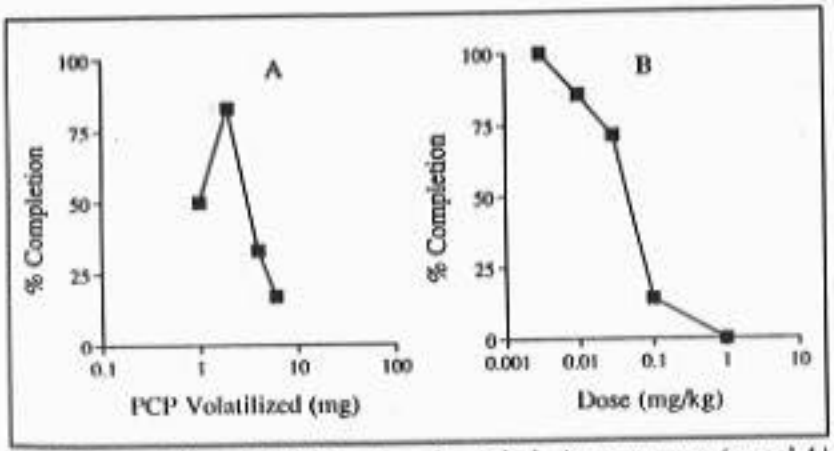


**FIGURE 5.** *Effect of PCP in mice after inhalation exposure (panel A) or IV administration (panel B) in the inverted-screen test. The results are the means of at least six mice/group.*

if the biological concentrations of the parent drug are known. In addition to differences in the pharmacokinetics of drugs administered by these two routes, the dose of the drug administered by inhalation must be deter- mined. In the studies described above, the potencies are expressed in terms of amount of drug added to the volatilization apparatus. In order to establish dosimetry, the animals are exposed to the volatilization of the radiolabeled drug under the same conditions used for the potency measurement. Whole-body determination of total radioactivity provides the dose of the volatilized drug.

An additional possible confound is the formation of pyrolysis products during volatilization, which could contribute pharmacological effects. The authors' strategy is to utilize volatilization conditions in such a way that minimal pyrolysis occurs, thus eliminating the possible contribution of pharmacological effects and simplifying determination of dosimetry.

To demonstrate the feasibility of this approach, the authors have chosen to determine the volatilization and dosimetry of heroin for the purpose of making valid potency comparisons between IV and inhalation exposure.

## VOLATILIZATION OF HEROIN

Heroin represents a logical choice for establishing inhalation procedures. Smoking and inhalation of heroin, known as "chasing the dragon," have largely replaced opium smoking for almost a century. It has become the most popular method of heroin use in recent years due to searches for alternatives to IV injections and the drug's increased availability. The most common method of smoking heroin involves heating the drug on a piece of aluminum foil and inhaling the vapor. An often reported obser-vation is that the aluminum foil contains black residues of decomposed heroin after smoking. In pyrolysis studies, Huzier (1987) and Cook and Jeffcoat (1990) reported that heroin undergoes extensive decomposition at temperatures that are presumably required for volatilization.

Studies of the volatilization of the drugs of abuse together with the assessment of pharmacological effects in laboratory animals after inhalation exposure can provide important information for drug inhalation potential in humans. Using the same volatilization-inhalation apparatus as shown in figure 2, the volatilization of heroin was investigated. Heroin free base, 1 and 5 mg doses, was heated for 5

minutes at 250%C. The glass wool trap and the pipe were then flushed with ethanol. Concentrations of the heroin and its pyrolytic products were analyzed by GC/MS and HPLC.

Results from volatilization of heroin free base indicated high efficiency at the employed temperature. The extent of volatilization after 5 minutes of heating appeared to be independent of the drug quantity. At 250%C, heroin was found to be volatilized over 75 percent. More than 90 percent of the initial amount was recovered as unchanged heroin after volatilization. Monoacetylmorphine, the only degradation product that resulted from the volatilization of heroin, accounted for less than 5 percent of the total drug. In contrast to the authors' results, Cook (1991) found that heroin was extensively degradated to a variety of products, including 6-acetyl morphine, N,6-diacetylnormorphine, and N-acetylnormorphine, after heating in a quartz furnace tube at 250%C. On the other hand, Huizer (1987) studied the pyrolysis of both heroin free base and its hydrochloride salt by using a TAS oven (a thermomicro separation, transfer, and application procedure) or heating on a piece of aluminum foil. They found that heroin HCl required a higher volatilizing temperature than the free base to completely

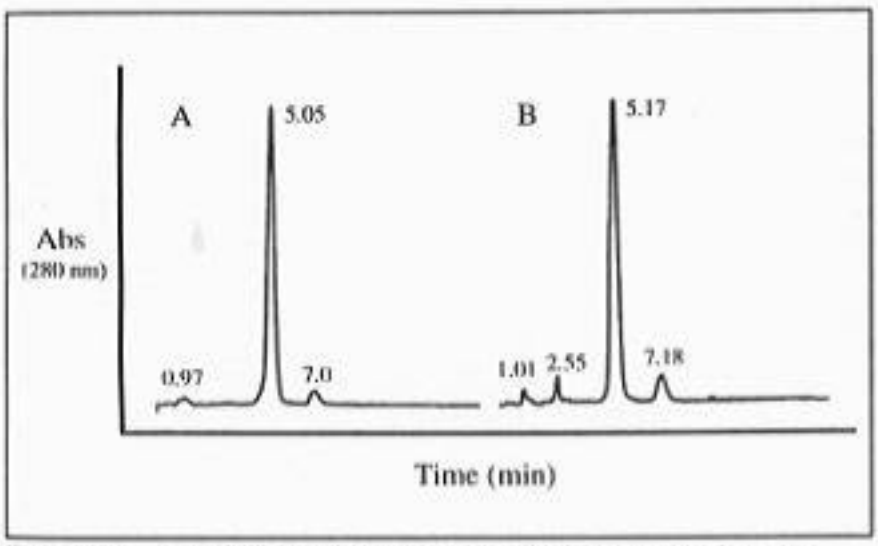


**FIGURE 6.** *HPLC chromatograms of standard heroin free base in ethanol solution (panel A.) and ethanol extract of glass wool from volatalization of heroin free base (panel B.). Retention times: heroin free base, 5 min; monoaceto-morphine, 2.5 min; and monoacetocodine, 7 min. Mono-acetocodeine is an impurity present in the heroin free base.*

volatilized (275 versus 225%C for the salt and free base, respectively). Heating heroin HCl resulted in the parent compound and 6-monoacetyl-morphine, along with small amounts of N,6-diacetylnormorphine and N,3,6-triacetylnormorphine; the amounts of the later two pyrolysis products increased when the temperature was increased from 275 to 325%C. Pyrolysis of heroin free base produced mainly heroin and 6-monoacetyl-morphine; as the temperature was increased from 225 to 325%C, trace amounts of morphine were detected. Analyses of the results from heating heroin on aluminum foil indicated that 17 and 62 percent of the heroin salt and free base, respectively, were recovered in the condensate. This later value is similar to the percentage of heroin recovered in the present study. Huizer's method was similar to the system described in this chapter in terms of employing a steady airflow through the system. Variations in the composition and nature of the heroin samples being smoked by users may be expected to influence volatilization efficiency. Huzier (1987) also demonstrated that the presence of caffeine and barbiturate increased the volatilization of heroin free base and the hydrochloride salt, respectively. Taken together, these results demonstrate that, in addition to volatility, temperature and airflow are important determinants of the volatilizing efficiency of a drug.

## BIODISPOSITION OF HEROIN AFTER INHALATION EXPOSURE

The $ED_{50}$ values obtained from inhalation studies (table 2) were based on the amounts of drug that were added into the pipe prior to volatilization, which precluded direct comparison of potencies to those obtained by IV administration. To evaluate the relative pharmacological potency of the inhaled drugs, the actual tissue concentrations of the drugs resulting from inhalation are required. Therefore, the biodisposition of heroin was investigated by exposing mice to volatilized [$^3$H.]-heroin.

Results of the biodisposition analysis of [$^3$H]-heroin are summarized in table 3. The whole-body concentrations of heroin equivalents that produced a 50 percent MPE for inhalation exposure and IV injection were 0.60 and 0.28 mg/kg, respectively. The concentrations of heroin equivalents in brain and plasma resulting from inhalation and IV administration were also very close. Doses of heroin that produced 100 percent MPE through inhalation exposure or IV injection showed a similar pattern of results. These data suggest that heroin is

equipotent when administered by inhalation exposure or IV injection. It is known that the acetyl groups on the heroin molecule enable it to enter the brain easily, suggesting that the equilibrium of heroin between the brain and plasma can be reached rather quickly regardless of the route of administration. Furthermore, since heroin is extensively metabolized by the liver and other tissues, the immediate metabolite of heroin, 6-monoacetylmorphine, has been reported to be both as potent and lipophilic as heroin (Way et al. 1959). Thus, the concentrations of drug equivalents found in brain in the present study undoubtedly reflect heroin and its metabolites.

It has also been demonstrated that, in humans, the time course of heroin in plasma and the appearance and disappearance of heroin metabolites after inhalation and IV administration are similar (Jenkings et al. 1994). The half-lives of heroin after smoking and IV administration were 3.3 and 3.6 minutes, respectively.

TABLE 3. *Recovery of heroin free base after volatilization.* [A]

| | Heroin recovered after volatilization (mg) | | |
|---|---|---|---|
| Amount (mg) | Glass wool | Pipe | Total |
| 1.10 Å 0.01 | 0.77 Å 0.03 | 0.16 Å 0.03 | 0.92 Å 0.06 |
| 5.11 Å 0.03 | 3.36 Å 0.22 | 1.42 Å 0.13 | 4.73 Å 0.18 |

KEY: A = Volatilization was carried out at 250%C. Values represent means Å SE.

This rodent inhalation model has proven to be reliable in studying the pharmacological effects of a variety of opioids, stimulants, and other drugs of abuse. In addition to predicting the inhalation potential of drugs of abuse by the comparison of inhalation and IV routes of administration, actual tissue concentrations of drug can be approximated with the use of radiolabeled compounds.

## CONCLUSION

Inhalation has become known to drug abusers as a rapid and potent route of administration. This route has also increased in popularity because of

**TABLE 4.** *Biodisposition of [H]- heroin free base.*

| | | | Drug equivalents[A] | | | Drug equivalents ratio[A] | |
|---|---|---|---|---|---|---|---|
| Route | Dose | % MPE | Brain (&g/g) | Plasma (&g/ml) | Body (&g/g) | Brain/body | Brain/plasma |
| IV N = 6 | 0.28 mg/kg | 50 | 0.04Å0.01 | 0.20Å0.05 | 0.19Å0.01 | 0.20Å0.02 | 0.15Å0.03 |
| | 1.0 mg/kg | 100 | 0.24Å0.02 | 0.82Å0.14 | 0.82Å0.04 | 0.30Å0.01 | 0.34Å0.07 |
| Inhalation N = 3 | 1.0 mg | 50 | 0.11Å0.02 | 0.38Å0.08 | 0.06Å0.14 | 0.31Å0.01 | 0.18Å0.01 |
| | 3.0 mg | 100 | 0.24Å0.01 | 0.86Å0.10 | 1.20Å0.25 | 0.29Å0.04 | 0.22Å0.05 |

KEY: A = Values represent means Å SE.

fears of contracting diseases such as AIDS from IV injection. However, smoking may increase the risk of other hazardous effects caused by pyrolytic products that are not associated with other modes of administration. Studies of the volatility and inhalation of drugs of abuse can provide important information for developing guidelines to predict their abuse potential upon inhalation.

One of the goals of this investigation was to use vapor pressure to predict drug volatility and thus the abuse potential through inhalation. Preliminary evidence from studies on the vapor pressure and pharmacology of the drugs of abuse is consistent with this notion. In table 5, the estimated vapor pressures of several drugs were compared with the temperature required to produce optimum pharmacological effects following inhalation. These results suggest that as vapor pressure increases (i.e., a more volatile drug), lower volatilization temperatures are required to produce a pharmacological effects.

Drugs in the salt form are much less volatile than their free bases and would be expected to require high temperatures for volatilization. It should be noted that vapor pressure information on the salts not currently available; however, the relative order of their vapor pressures is assumed to be the same as their free bases (table 5). In addition, the present results suggest that methamphetamine and amphetamine are more volatile than most of the other drugs tested. This is consistent with the popularity of methamphetamine smoking among drug users. Conversely, a drug that has extremely low vapor pressure would not be expected to be readily used by inhalation.

In order to study the pharmacological effects of a drug when smoked, and presumably its potential for abuse by inhalation, efforts were made to examine the relationship between a drug's volatility and its pharmacological potency upon inhalation. A rodent inhalation model was developed that enabled systematic investigation of the inhalation route of drug admini-stration. Using this model of inhalation, the pharmacological effects of a variety of drugs, including opioids, stimulants, and PCP, were evaluated in mice. It was demonstrated that inhalation produced pharmacological effects similar to those obtained from IV administration of heroin, PCP, and methamphetamine. Biodisposition studies with radiolabeled heroin enabled the authors to evaluate the relative potency of a drug following inhalation and IV injection. The tissue concentrations of heroin equivalents obtained after these two routes of administration revealed that smoking is equipotent to IV injection.

**TABLE 5.** *Comparison of vapor pressures and volatilizing temperatures.*

| | Vapor pressures at | Volatilizing temperature (%C) | |
|---|---|---|---|
| Drug | 25%C (Torr) | Free base | Salt |
| Methamphetamine | $> 10^{-2}$ | | 200 |
| Amphetamine | $> 10^{-2}$ | | 200 |
| PCP | $8.56 \times 10^{-4}$ | | 275 |
| Cocaine | $9.79 \times 10^{-6}$ | 220 | |
| Morphine | $9.49 \times 10^{-7}$ | 250 | |
| Heroin | $5.71 \times 10^{-8}$ | 250 | |
| Fentanyl | $2.41 \times 10^{-8}$ | 300 | |

Although the authors propose that vapor pressure can be used to predict whether a drug of abuse may be smoked, other physiochemical parameters, including particle size (Snyder et al. 1988) and lipid solubility (McQuay et al. 1989), also influence drug potency. The determination of these physiochemical parameters used concurrently with a reliable inhalation animal model will serve as useful tools for identifying which drugs may potentially be abused by inhalation.

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## ACKNOWLEDGMENTS

The author would like to thank Ms. Carlota Jackson and Ms. Yulin Chen for their technical assistance and Dr. William Glassco for advice and assistance in purifying free bases and chemical preparations. This research was supported by National Institute on Drug Abuse grant DA 082396.

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