

Toward a Comparative Overview of Dependence Potential and Acute Toxicity of Psychoactive Substances Used Nonmedically

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ABSTRACT

A procedure is outlined for comparing dependence potential and acute toxicity across a broad range of abused psychoactive substances. Tentative results, based on an extensive literature review of 20 substances, suggested that the margin of safety ("therapeutic index") varied dramatically between substances. Intravenous heroin appeared to have the greatest risk of dependence and acute lethality; oral psilocybin appeared to have the least. Hazards due to behavioral deficits, perceptual distortion, or chronic illness were not factored into the assessments.

INTRODUCTION

Drugs differ in their potential adverse health effects. Although individual health impairment is only one aspect of widespread drug abuse costs (e.g., accidents involving others, family dysfunction, lost productivity), it is probably the most direct and prominent indicator of risk. This paper will present a preliminary comparative overview of the dependence potential and the acute physical toxicity of 20 psychoactive substances used nonmedically in North America.

Despite the fact that researchers are characteristically cautious and skeptical about the validity of broad-based comparisons, legislators and administrators are often forced—in the light of publicized abuses of some substances—to take decisive

action regardless of the amount or quality of scientific information available. In order to provide empirical data for policy decisions, the Committee on Problems of Drug Dependence and the National Institute of Mental Health initiated in 1948 an on-going series of research studies on the abuse liability of psychoactive substances (1). In the last decade the scope of work has broadened from the original focus on narcotic analgesics to an extensive range of stimulants and sedative-hypnotic compounds (2).

When comparisons are made among substances, they typically include only substances that fall within a similar chemical structures or action prototype category [e.g., stimulants (3, 4), sedative-hypnotics (5–7)]. Studies that attempt to rank-order or make numerical comparisons *across* pharmacological categories are much less common, although a respectable number of such studies have been published (e.g., Refs. 8–17). One obvious reason for the relative infrequency of such broad comparative studies is the formidable complexity of controlling for the host of biological, biochemical, learning, and environmental factors that influence the subjective and behavioral effects of even a single substance.

MEASUREMENT OF DEPENDENCE

A comparison of dependence potentials cannot be estimated without first establishing an effective dose. Operational definitions of an effective dose typically employ drug self-administration or drug discrimination paradigms (18). A variety of sophisticated laboratory procedures with both human and nonhuman animals has been developed in recent years (cf. Refs. 2, 19–23). In self-administration studies, the effective dose may be determined by observing the amount of drug required to maintain stable responding by the animal under different experimental conditions (e.g., continuous free access to the substance, substitution of the substance for a placebo or a standard reinforcing substance). By permitting an organism to choose one of two drugs or allowing it to substitute a particular substance for a range of other substances, the *relative* reinforcing strength of the experimental drug can be measured. Human verbal reports of subjective effects (13, 24) and of drug-seeking behavior in natural settings (25, 26) have been used to supplement laboratory observations.

Physical dependence is often (but not always) characterized by development of physiological tolerance to the drug and by withdrawal symptoms upon removal of the drug. A measurable abstinence syndrome has been the traditional *sine qua non* for “addiction” (27). When withdrawal symptoms appear minimal or nonexistent, *psychological* dependence has been employed as a theoretical construct

to explain drug-seeking behavior. Cocaine, for example, can act as strong positive reinforcer by producing self-reported positive mood states (4, 10), but its absence has less potential to serve as a negative reinforcing situation because the drug produces comparatively modest physical withdrawal symptoms (28–30). Conversely, nicotine has weak positive consequences (e.g., increased alertness or improved motor skills) compared to more salient negative consequences (e.g., withdrawal symptoms of drowsiness and headaches) (31). Thus, if dependence is measured by a desire to repeat a positive experience, cocaine and methaqualone would likely be reported as most addictive (7, 32, 33). If dependence is measured by relief of physical craving or by unsuccessful attempts to stop use, nicotine and opioids probably would be ranked as most addictive (8, 11, 14).

An individual user's withdrawal symptoms have social or public significance primarily to the extent that they act as negative reinforcers for drug-seeking behavior already in the person's repertoire. And because the avoidance of such withdrawal symptoms cannot explain the initial drug-taking episode, the combining of physical and psychological factors into a single "dependence potential" category would seem to be a tolerable loss of information. This is a tentative and debatable decision, but it appears consonant with the rationale of DSM-III-R that shifted the focus of definitions of drug dependence *away from* aversive experiences in the absence of substances *to* behaviors exhibited in relation to the presence or potential presence of substances (34).

MEASUREMENT OF TOXICITY

"Toxicity" customarily refers to the extent to which a chemical has adverse effects on a living organism. The most traditional laboratory measure of physiological risk has been the "therapeutic index" (35), although the term may be inappropriate when referring to substances that have no established medicinal value. The number of animals that show a specified reaction, and the number of animals that die, can be plotted at various dosage levels and time intervals in order to generate dose-response curves characterizing the substance of interest. The ratio of the median lethal dose (LD_{50}) to the median effective dose (ED_{50}) provides a one-point estimate of how selective or nontoxic a substance is in producing the specified reaction.

A general functional similarity between animal species has been well-documented for some substances (18, 36), but other substances show considerable interspecies and interstrain variability. For example, the LD_{50} of parenterally administered MDMA in mice is apparently twice the LD_{50} in rats (37, 38); the

LD₅₀ of intravenous mescaline is about twice as much for mice as for dogs, but less than for monkeys (39). The desire to use less invasive laboratory procedures (40, 41), and to verify the applicability of nonhuman animal studies to humans, has focused attention on data sources that come "naturally." Unfortunately, information received from sources such as hospital emergency rooms and coroner offices is problematic at best and misleading at worst. For an illustration of potential misinterpretation, consider the raw numbers of a 4-year study (42) of toxic accidents in one county in Arizona. Coroner records showed that carbon monoxide deaths outnumbered cocaine deaths, and that caffeine was more often involved in fatalities than amphetamines. These seemingly anomalous statistics are easily explained: the number of people exposed to a substance, as well as its inherent toxicity, influences the number of deaths. Yet exposure is seldom factored into the drug fatality statistics cited in the popular media or in U.S. Government publications (e.g., *Drug Enforcement Statistical Report*, *National Intelligence Consumers Report*).

Nonetheless, even death *rates* among users prove difficult to interpret. Fatalities from intentional suicide (43–45) and from misadventures with law enforcement (46, 47) should probably be discounted when using morbidity rates to compare pharmacological toxicity. Furthermore, the initial health status of the deceased is often unknown, and when the purported cause of death or illness is an illicit substance, the trauma may not be due to the putative substance at all, but rather, extenders or contaminants which often go undetected in postmortem examinations (48–50). Most decedents ingest more than one psychoactive substance (typically alcohol).

The most comprehensive epidemiological data collection system relevant to drug abuse is the Drug Abuse Warning Network (DAWN). It collects information from approximately 740 emergency rooms and 90 medical examiner's offices in 27 metropolitan areas of the United States (51). The problematic nature of using DAWN data to estimate toxicity has been illustrated by Anthony and Trinkoff (52). They computed the number of emergency room episodes and deaths per one million prescriptions for 10 different benzodiazepines. Because benzodiazepines compose a relatively narrow subclass of sedative/hypnotic drugs, we might reasonably expect a positive correlation between the number of prescriptions written, emergency room episodes, and deaths. Surprisingly, there was no correlation between these three variables for any of the drugs except diazepam (Valium). Even then, we cannot justifiably conclude that diazepam is the most toxic of the 10 benzodiazepines until we control for possible confounding variables (e.g., diazepam users may use the drug for a longer period of time or may be heavier users of alcohol). DAWN reports do not include such information.

In summary, neither nonhuman experimental studies nor clinical statistics yield unambiguous results with respect to acute lethal dosages. The "best guess lethal dose" for an average adult human who has not developed tolerance to the substance is probably the LD_{50} extrapolated from a broad range of laboratory animal studies that falls within the range of lethality cited in clinical or forensic reports.

RATING PROCEDURE

As a means of exploring the feasibility of broad-based comparative rating, a literature review was conducted that focused on 20 psychoactive substances. Six major drug classes were represented: anesthetics (ketamine, PCP, nitrous oxide), cannabis (marijuana), depressants/sedative-hypnotics (diazepam, ethanol, methaqualone, secobarbital), hallucinogens/psychedelics (LSD, MDMA, mescaline, psilocybin), opiates (heroin, morphine, opium), and stimulants (amphetamine, caffeine, cocaine carbonate, cocaine hydrochloride, nicotine).

In contrast to conventional deductive inquiries (e.g., meta-analyses) in which a sampling frame and statistical parameters are specified in advance, this preliminary investigation used an inductive procedure (53). No hypotheses were proposed in advance regarding the relative dependence potential or acute lethality/toxicity of the substances.

The initial step of the review process was simply to compile literature references cited in standard psychopharmacology texts (54–57) and published bibliographies (58–61) that appeared likely to give a quantitative estimate of dependence potential or toxicity. Sources cited in these materials were scanned for additional relevant books, book chapters, and articles. Next, seven on-line computer databases were interrogated: Biosis Previews (1969–1992), Current Contents (1989–1992), Embase (1982–1992), Health Periodicals Database (1976–1992), Medline (1986–1992), PsychInfo (1966–1992), and Toxline (1965–1992). The database descriptors included each of the 20 target substances, cross-indexed with the terms "toxicity," "dependence," "dependency," "dose," "dosage," "reinforcement," and "therapeutic index." This procedure yielded approximately 12,800 English language citations. Many of these citations were redundant because the same serial publication was indexed in more than one database. Research reports which appeared, on the basis of their title or abstract, to focus primarily on pharmacokinetics, medicinal biochemistry, drug design, anatomy, therapy, or legislation were excluded from the domain of eligible citations. These restrictions limited the review to about 950 potentially relevant articles. Approximately 70% of these articles were accessed and read. Of these, about 350 articles were found to give

a quantitative estimate of lethality or an empirically derived comparison of dependence potential, and were not obviously duplicative of a similar study published by the same authors in a different book or journal. These 350 articles constitute the database of findings reported here. This procedure undoubtedly missed some relevant studies both in books and journals, as well as in sources not searched (e.g., technical reports, conference presentations, and dissertations).

Simply in terms of the quantity of published research, there was a substantial difference between substances. The one substance that far exceeded all others as a topic of investigation was ethyl alcohol. Caffeine ran a distant second; nicotine came in third, followed by benzodiazepines and amphetamine derivatives. These five substances are not the most consciousness-altering or habit-forming, but their legitimate legal status and widespread use make them the most accessible to researchers. Of the 20 target substances, opium had the fewest published reports, followed by mescaline. "Crack" cocaine also had very few reports of experimental studies, reportedly due, in part, to technical problems caused by cocaine smoke particles being too large to pass beyond the upper respiratory tract of small laboratory animals (62, 63).

In an effort to mitigate gross interpretative errors and personal bias, drafts of several versions of a summary data table were sent, over a 2-year period, to an ad hoc panel of 35 toxicologists and psychopharmacologists, selected on the basis of their having published significant research in the area of abusable substances. These researchers were asked to correct and comment on the findings. Twenty-four written or telephone replies were received. Most of the comments were brief and related only to the particular substance or class of substances about which the researcher had published. Where an apparent error occurred in the data table or where an apparent discrepancy existed between reviewers, a second request for comment was made. Four such requests were mailed, two replies were received.

RESULTS

A summary of acute lethality and dependence potential estimates is presented in Table 1.

The acute lethal dose is the presumed LD₅₀ for a 70-kg nontolerant adult human. Both the lethal doses and the effective doses listed in Table 1 are point estimates of the median of an *unspecified range* of values. The effective dose of a drug was defined as the median amount of the substance capable of serving as a reinforcer for self-administration or of eliciting a verbal self-report of a

generally desired subjective state (e.g., alertness, sociability, visionary dreaming, euphoria) in a 70-kg nontolerant adult human. Because the route of administration is such a critical factor in bioavailability [e.g., oral morphine sulfate being about 1/6 as potent as subcutaneous morphine sulfate (56)], the data in Table 1 are specifically limited to the route indicated for each substance. It should be noted that a substance may be used for several different therapeutic or recreational purposes, and therefore may have several ED curves. A 200–400-mg dose of meprobamate would probably be effective in producing euphoria or relief from anxiety, but a higher dose would be needed to produce sleep. Therefore the margin of safety changes as the purpose changes. The ED level for recreational or psychotherapeutic uses tends to be lower than for generally accepted medical uses (cf. Refs. 109, 116).

Dose response curves could not be generated, and no confidence intervals for the medians can be specified. Therefore, rather than present the resultant LD/ED ratio ("safety margin") in numeric terms in Table 1, a qualitative scale was used (ranging from "very large" to "very small") in order to emphasize the uncertain nature of the median estimates.

The number of literature references was limited to five reports or articles for any one substance. Citation preference was given to review articles, with second preference for original experimental studies. Therefore, in some cases the size of an effective or lethal dose appears in a study referenced in the review article rather than in the review itself; also, numerous relevant clinical or forensic case reports are not cited.

As a means of facilitating comparison of the substances, the information in Table 1 is presented in matrix form in Fig. 1. Opiates, as a group, have the most narrow margin of safety and the greatest dependence potential. Conversely, cannabis and hallucinogens/psychedelics have the widest margins of safety and the lowest dependence potential. The extreme positions are occupied by oral psilocybin and by intravenous heroin. The apparent safety margin of psilocybin appears to be several hundred times greater than that of heroin.

Despite troublesome limitations of the data sources, the magnitude of the difference between many of the substances suggests that they can be reliably and meaningfully ordered with respect to their dependence potential and acute lethality.

FUTURE HEALTH RISK ASSESSMENTS

The study reported here is merely a prototype of a more in-depth review that would be needed for a policy-relevant comparison of health risks. First, with

Table 1. Acute Toxicity and Dependence Potential of Psychoactive Substances^a

Substance	Effective dose ^b	Lethal dose	Safety margin	Dependence potential	References ^c
Narcotics (opiates):					
Heroin (intravenous)	4 mg	30 mg	Very small	Very high	64-68
Morphine (intramuscular)	10 mg	90 mg	Very small	High	55, 64, 69-71
Opium (smoked)	100 mg	800 mg	Very small	High	72-76
Sedative-hypnotics (depressants):					
Barbiturates:					
Secobarbital (oral)	100 mg	2500 mg	Small	Moderate/high	56, 77-79
Benzodiazepines:					
Diazepam (oral)	2 mg	2000 + mg	Very large	Moderate	5, 80-83
Ethanol:					
Alcohol (oral)	27 g (2 beers) ^d	270 g	Very small	Moderate	84-88
Methaqualone (oral)	75 mg	10,000 mg	Moderate	High	55, 64, 89-91
Stimulants:					
Amphetamines (oral)	10 mg	200 mg	Small	Moderate	3, 4, 28, 92, 93
Caffeine:					
Coffee (oral)	100 mg (1.5 cup) ^e	10,000 mg	Moderate	Low/moderate	94-98
Cocaine (intranasal):					
Hydrochloride powder	100 mg (5 lines or 1/4th g) ^f	2500 mg	Moderate	High/moderate ^g	8, 29, 99-101
Cocaine (smoked):					
Carbonate precipitate ("crack")	15 mg (1 rock) ^h	375 mg	Moderate	Very high	25, 102-105
Nicotine (smoked):					
Tobacco	1 mg (1 cigarette) ⁱ	60 mg	Moderate	High/moderate	14, 31, 106-108
Anesthetics					
Ketamine (intramuscular)	50 mg ^j	1300 mg	Moderate	Low	69, 109-113
Nitrous oxide (inhaled)	1 L ^k	24 L	Moderate	Low/moderate	114-118
Phencyclidine (smoked) (PCP)	5 mg (1 "Sherman") ^l	200 mg	Moderate	Moderate/high	119-123
Hallucinogens:					
LSD-25 (oral)	50 mcg	14,000 mcg ^m	Large	Very low	124-128

MDMA (oral) ("Ecstasy")	125 mg	1875 mg	Small	Moderate/low	129-133
Mescaline (oral)	350 mg	6000 mg	Small	Very low	37, 134-137
Psilocybin (oral)	4 mg (4 'shrooms') ^b	14,000 mg	Very large	Very low	138-142
Cannabis:					
Marijuana (smoked)	1.5 mg (1/2 joint) ^c	4000 mg	Very large	Low/moderate	143-147

^aThe information presented here should not be used as a dosage guide. Wide individual differences exist with respect to a person's metabolism, sensitivities, and psychological vulnerability.

^bDosage amounts refer to the quantity of active substance administered; it does not include the amount of the inactive material used as a filler, medium, or "cut." The dosage indicated is the estimated median amount for an "average" 70 kg adult human. Substances are presumed to be administered within approximately 5 minutes.

^cReaders who wish citations relevant to a dosage for a specific substance, which do not appear in references cited, should contact the present writer.

^dAssumes 13,500 mg alcohol per 12 fluid ounces container of beer having 5% alcohol by volume, resulting in 25.7 mg/100 mL of blood alcohol per beer (adjusted for 75% absorption on an empty stomach of a 70 kg human with 52,500 mL of body fluid) (cf. Ref. 148).

^eAssumes ground coffee at 65-120 mg caffeine, instant coffee at 50-100 mg, per 148 mL (5 ounce) cup.

^fBased on a "line" of approximately 50 mg, or "1/4th gram" total, containing 40% cocaine, with 60% adulterants.

^gIntranasal cocaine powder usually shows mild-to-moderate physical withdrawal symptoms, but compulsive drug-seeking (i.e., psychological dependence) is sometimes vigorous and sustained.

^h100 mg street "rock" of free-base cocaine with 15% inactive residues (e.g., baking soda), smoked in pipe with approximately 20% cocaine intake.

ⁱCigarette type (e.g., standard, low tar, filter) have nicotine content ranging from 0.2% to almost 5% (31), but smokers tend to titrate to approximately 1 mg per cigarette by varying number and duration of puffs (106, 149).

^jNonmedical self-administration is often *oral* with an effective dose of approximately 200 mg; median lethal oral dose yet to be determined.

^kED₅₀ is roughly equivalent to street use of two balloons, one-half of 3.5 L "whippet" cartridge, or one 1.5 L whipped cream can of approximately 100% N₂O with 70% of the contents inhaled. N₂O cartridges have been found to contain three contaminants; whipped cream dispenser cans 26 contaminants [150]. The LD₅₀ estimate would constitute six normal breaths of 100% N₂O, based on average respiratory gas exchange capacity of an adult human of 4 L.

^lOne PCP cigarette ("Sherman") sprinkled with, or soaked in, 15 mg phenacyclidine with only 33% inhaled and absorbed via pulmonary route due to pyrolytic destruction.

^mLD₅₀ not established. Present estimate speculatively assumes 0.2 mg/kg for a 70-kg human, based on reported LD of 0.3 mg/kg in rabbits and 0.1 mg/kg in an elephant.

ⁿAssumes 1 mg of indole alkaloids per mushroom. (One gram of dry weight mushrooms contains approximately 2 mg psilocybin; however, the potency varies greatly between specimens, and "street 'shrooms" may be contaminated with LSD or PCP.)

^oThere are great variations in the efficiency of the smoking process. This calculation is based on a medium street-grade 700 mg cigarette containing 1.5% delta-9-THC with 30% intake (151, 152).

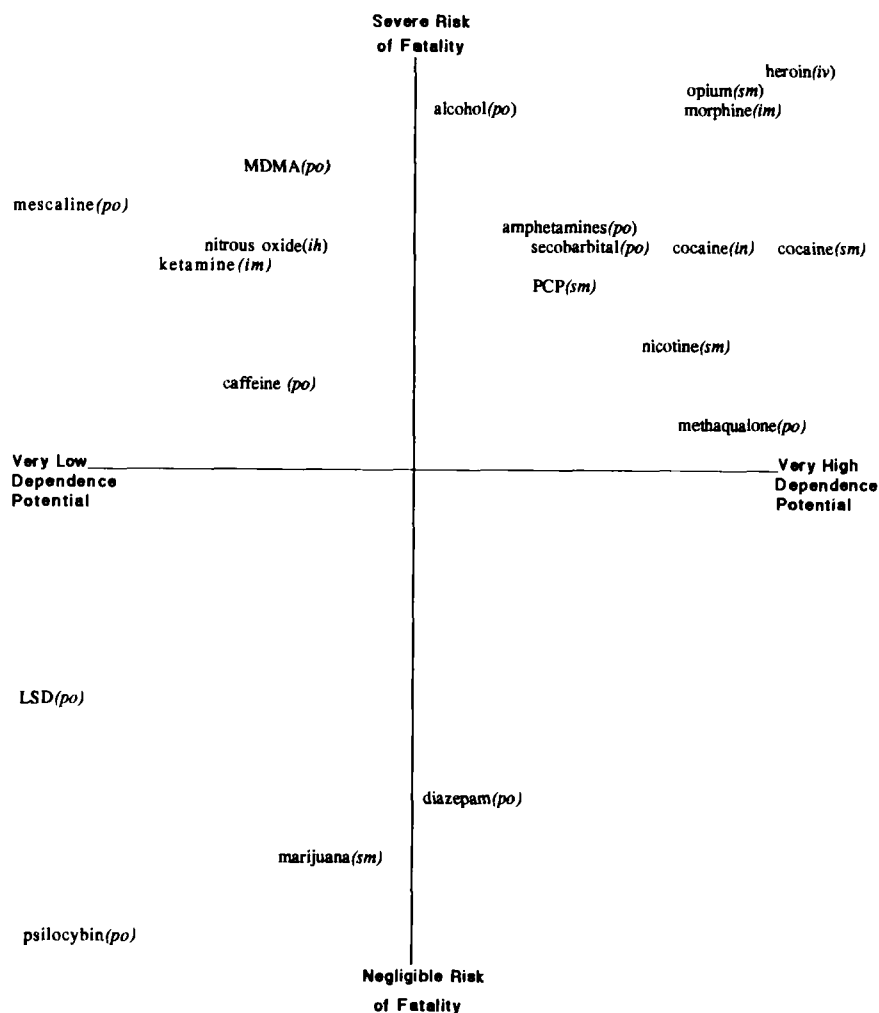


Fig. 1. Acute toxicity and dependence potential of psychoactive substances. Routes of administration are: *iv* = intravenous, *im* = intramuscular, *sm* = smoked, *po* = oral (swallowed), *ih* = inhaled, *in* = intranasal.

respect to acute health hazards, an index of "general toxicity" should be devised that would include nonfatal trauma and behavior/perceptual decrements. Death is a very gross indicator of adverse health impact, and indeed, acute lethality may be almost irrelevant for a few substances that have a relatively large therapeutic index or safety margin (e.g., LSD, psilocybin). Several researchers

(153, 154) have proposed a “reinforcement/toxicity” ratio as a metric, similar to the therapeutic index, that would permit a rank-ordering of psychophysiological toxicity of psychoactive substances. Reaction time, sensory thresholds, and anorectic effects were used by these researchers as criteria of acute toxicity. Potentially traumatic psychological disturbances are not limited to hallucinogens, but include all opiates, many depressants, and some stimulants at high doses (42, 123). Safety margins should also be adjusted to reflect the probability of chronic disease and long-term complications from particular types of substance use (e.g., emphysema, needle-transmitted hepatitis).

Second, estimates of dependence potential need to be better documented with respect to their ecological validity. Generalizing the results of an experiment *across* a given population (e.g., alcoholics in treatment) must be distinguished from generalizing results *to* a larger population (e.g., to all young people who have used an alcoholic beverage). Reportedly, one-half to two-thirds of adults in the United States use alcohol, yet only 8 to 10% are believed to be dependent on alcohol (155). Similarly, several longitudinal studies of young adult drug users (e.g., Refs. 156, 157) have claimed that as many as 75% of these people had experimented with cocaine, but 9 to 20% reported subsequent daily or compulsive cocaine use. We would be very hesitant to predict the potential negative impact of a state lottery on the average citizen if we studied only compulsive gamblers. Addicts or postaddicts may be unusually sensitive (or insensitive) to certain compounds. Oversampling these individuals increases the probability of observing false positives (84). Yet virtually no published studies have randomly selected human participants from a nonaddict population in order to compare self-administration rates across different classes of psychoactive substances as these are used in normal social settings. There are obvious ethical reasons for not exposing naive volunteers—even if informed and willing—to some substances. Nonetheless, this legitimate reason does not diminish the fact that most experimental studies of dependence potential lack demographic representativeness.

Estimating the magnitude of dependence and the incidence of severe toxicity in exposed populations would require consideration of variables such as age, gender, life-style, and patterns of exposure, as well as dosage levels. How such projected health hazards should be managed (in contrast to how they are assessed) involves political, social, and economic factors well beyond the scope of scientific risk assessment (cf. Ref. 158). Indeed, the priority ratings made for purposes of public health promotion or law enforcement—now often based on a “worst case” or “media visibility” approach—would not necessarily coincide with the ratings of dependence potential and toxicity.

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REFERENCES

1. Eddy, N. B., *The National Research Council Involvement in the Opiate Problem: 1928-1971*, National Academy of Sciences, Washington, D.C., 1973.
2. Fischman, M. W., and Mello, N. K. (Eds.), *Testing for Abuse Liability of Drugs in Humans* (NIDA Research Monograph 92), U.S. Government Printing Office, Washington, D.C., 1989.
3. Davis, W. M., Bedford, J. A., Buelke, J. L., et al., Acute toxicity and gross behavioral effects of amphetamines, four methoxyamphetamines, and mescaline in rodents, dogs, and monkeys, *Toxicol. Appl. Pharmacol.* **45**:49-62 (1978).
4. Foltin, R. W., and Fischman, M. W., Assessment of abuse liability of stimulant drugs in humans: A methodological survey, *Drug Alcohol Depend.* **28**:3-48 (1991).
5. Griffiths, R. R., and Wolf, B., Relative abuse liability of different benzodiazepines in drug abusers, *J. Clin. Psychopharmacol.* **10**:237-243 (1990).
6. Guarino, J. J., Roacher, J. D., Kirk, W. T., et al., Comparison of the behavioral effects and abuse liability of ethanol and pentobarital in recreational sedative users, in *Problems of Drug Dependence 1989* (NIDA Research Monograph 95), (L. S. Harris, Ed.), U.S. Government Printing Office, Washington, D.C., 1990, pp. 453-454.
7. Orzack, M. H., Friedman, L., Dessain, E., et al., Comparative study of the abuse liability of Alprazolam, Lorazepam, Diazepam, Methaqualone and placebo, *Int. J. Addict.* **23**:449-467 (1988).
8. Anthony, J. C., and Petronis, K. R., Cocaine and heroin dependence compared: Evidence from an epidemiological field survey, *Am. J. Public Health* **79**:1409-1410 (1989).
9. Goldstein, A., and Kalant, H., Drug policy: Striking the right balance, *Science* **249**:1513-1521 (September 28, 1990).
10. Haertzen, C. A., Kocher, T. R., and Miyasato, K., Reinforcements for the first drug experience can predict later drug habits and/or addiction: Results with coffee, cigarettes, alcohol, barbiturate, minor and major tranquilizers, stimulants, marijuana, hallucinogens, heroin, opiates and cocaine, *Drug Alcohol Depend.* **11**:147-165 (1983).
11. Hammersley, R., Forsyth, A., and Morrison, V., Objective and subjective aspects of addiction: Cigarettes, alcohol, cannabis and heroin compared. *Br. J. Addict.* **83**:1472(abstr.) (1988).
12. Iwamoto, E., and Martin, W., A critique of drug self-administration as a method for predicting abuse potential of drugs, in *Problems of Drug Dependence* (NIDA Research Monograph 81), (L. S. Harris, ed.), U.S. Government Printing Office, Washington, D.C., 1988, pp. 457-465.
13. Jasinski, D. R., and Henningfield, J. E., Human abuse liability assessment by measurement of subjective and physiological effects, in *Testing for Abuse Liability of Drugs in Humans* (NIDA Research Monograph 92), (M. W. Fischman and N. K. Mello, Eds.), U.S. Government Printing Office, Washington, D.C., 1989, pp. 73-100.

14. Kozlowski, T., Wilkinson, A., Skinner, W., et al., Comparing tobacco cigarette dependence with other drug dependencies, *J. Am. Med. Assoc.* **26**:898-901 (1989).
15. Lukas, S. E., Mendelson, J. H., Amass, L., et al., Behavioral and EEG studies of acute cocaine administration: Comparisons with morphine, amphetamine, pentobarbital, nicotine, ethanol and marijuana, in *Problems of Drug Dependence 1989* (NIDA Research Monograph 95), (L. S. Harris, Ed.), U.S. Government Printing Office, Washington, D.C., 1990, pp. 146-151.
16. Mello, N. K., and Mendelson, J. H., Operant analysis of human self-administration: Marijuana, alcohol, heroin, and polydrug use, in *Methods of Assessing the Reinforcing Properties of Abused Drugs* (M. A. Bozarth, Ed.), Springer-Verlag, New York, 1987, pp. 522-572.
17. Zablik, J. E., Roache, J. D., Johnson, W., et al., Dependence liability of caffeine, cocaine, nicotine and phencyclidine, *Res. Commun. Substances Abuse* **4**:93-95 (1983).
18. Brady, J. V., and Lukas, S. E., *Testing Drugs for Physical Dependence Potential and Abuse Liability* (NIDA Research Monograph 52), U.S. Government Printing Office, Washington, D.C., 1984.
19. Bozarth, M. A. (Ed.), *Methods of Assessing the Reinforcing Properties of Abused Drugs*, Springer-Verlag, New York, 1987.
20. Goldberg, S. R., and Stolerman, I. P., *Behavioral Analysis of Drug Dependence*, Academic Press, London, 1986.
21. Johanson, C. E., and Schuster, C. R., Animal models of self-administration, in *Advances in Substance Abuse: Behavioral and Biological Research* (N. K. Mello, Ed.), JAI Press, Greenwich, Connecticut, 1981, pp. 219-297.
22. Krasnegor, N. A. (Ed.), *Self-Administration of Abused Substances: Methods for Study* (NIDA Research Monograph 20), U.S. Government Printing Office, Washington, D.C., 1978.
23. Sanger, D. J., Screening for abuse and dependence liabilities, in *Behavioural Models in Psychopharmacology: Theoretical, Industrial, and Clinical Perspectives* (P. Willner, Ed.), Cambridge University Press, Cambridge, 1991, pp. 485-502.
24. Haertzen, C. A., and Hickey, J. E., Addiction Research Center Inventory (ARCI): Measurement of euphoria and other drug effects, in *Methods of Assessing the Reinforcing Properties of Abused Drugs* (M. A. Bozarth, Ed.), Springer-Verlag, New York, 1987, pp. 489-524.
25. Smart, R. G., Crack cocaine use: A review of prevalence and adverse effects, *Am. J. Drug Alcohol Abuse* **17**:13-26 (1991).
26. Feldman, H. W., Aga, M. H., and Beschner, G. M. (Eds.), *Angel Dust: An Ethnographic Study of PCP Users*, Lexington Books, Lexington, Massachusetts, 1979.
27. Jaffe, J. H., and Jaffe, F. K., Historical perspectives on the use of subjective effects measures in assessing the abuse potential of drugs, in *Testing for Abuse Liability of Drugs in Humans* (NIDA Research Monograph 92), (M. W. Fischman, and N. K. Mello, Eds.), U.S. Government Printing Office, Washington, D.C., 1989, pp. 43-72.
28. Fischman, M. W., Cocaine and the amphetamines, in *Psychopharmacology: The Third Generation of Progress* (H. Y. Meltzer, Ed.), Raven Press, New York, 1987, pp. 1543-1552.
29. Gawin, F. H., and Ellinwood, E. H., Cocaine dependence, *Ann. Rev. Med.* **40**:149-161 (1989).
30. Woolverton, W. L., and Kleven, M. S., Evidence for cocaine dependence in monkeys following a prolonged period of exposure, *Psychopharmacology* **94**:288-291 (1988).
31. Jones, R. T., Tobacco dependence, in *Psychopharmacology: The Third Generation of Progress* (H. Y. Meltzer, Ed.), Raven Press, New York, 1987, pp. 1589-1595.
32. Griffiths, R. R., and Sannerud, C. A., Abuse of and dependence on benzodiazepines and other anxiolytic/sedative drugs, in *Psychopharmacology: The Third Generation of Progress* (H. Y. Meltzer, Ed.), Raven Press, New York, 1987, pp. 1536-1542.
33. Bourgois, P., In search of Horatio Alger: Culture and ideology in the crack economy, *Contemp. Drug Probl.* **16**:619-650 (1989).

34. Rounsaville, B. J., Spitzer, R. L., and Williams, J. B. W., Proposed changes in DSM-III substance use disorders: Description and rationale, *Am. J. Psychiatry* **143**:463-468 (1986).
35. Nies, A. S., Principles of therapeutics, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (A. G. Gilman, T. W. Rall, A. S. Nies, and P. Taylor, Eds.), Pergamon Press, New York, 1990, pp. 618-630.
36. Johanson, C. E., Woolverton, W. L., and Schuster, C. R., Evaluating laboratory models of drug dependence, in *Psychopharmacology: The Third Generation of Progress* (H. Y. Meltzer, Ed.), Raven Press, New York, 1987, pp. 1617-1625.
37. Hardman, H. F., Haavik, C. O., and Seavers, M. H., Relationship of the structure of mescaline and seven analogs to toxicity and behavior in five species of laboratory animals, *Toxicity Appl. Pharmacol.* **25**:299 (1973).
38. Logan, B. J., Lavery, R., Sanderson, W. D., et al., Differences between rats and mice in MDMA (methylenedioxymethylamphetamine) neurotoxicity, *Eur. J. Pharmacol.* **152**:227-234 (1988).
39. Martin, W. R., The nature of opioid and LSD receptors: Structural activity relationship implications, in *QuaSAR: Quantitative Structure Activity Relationships of Analgesics, Narcotic Antagonists and Hallucinogens* (NIDA Research Monograph 22), (G. Barnett, M. Trsic, and R. Willette, Eds.), U.S. Government Printing Office, Washington, D.C., 1978, pp. 60-67.
40. Bruce, R. D., A confirmatory study of the up-and-down method for acute oral toxicity testing, *Fundam. Appl. Toxicol.* **8**:97-100 (1987).
41. Goldberg, A. M., and Frazier, J. M., Alternatives to animals in toxicity testing, *Sci. Am.* **261**:24-30 (1989).
42. Froede, S. W., Byers, J. M., Wolfgang, G. S., et al., An analysis of toxic deaths, 1982-1985, Pima County, Arizona, *J. Forensic Sci.* **32**:1676-1693 (1987).
43. Chadly, A., Marc, B., Barres, D., et al., Suicide by nitrous oxide poisoning, *Am. J. Forensic Med. Pathol.* **10**:330-331 (1989).
44. Fraser, A. D., Isner, A. F., and Moss, M. A., A fatality involving clomipramine, *J. Forensic Sci.* **31**:762-765 (1986).
45. Sperry, K., and Sweeney, E. S., Suicide by intravenous injection of cocaine: A report of three cases, *J. Forensic Sci.* **34**:244-248 (1989).
46. Introna, F., and Smialek, J. E., The "mini-packer" syndrome: Fatal ingestion of drug containers in Baltimore, Maryland, *Am. J. Forensic Med. Pathol.* **10**:21-24 (1989).
47. Kramer, L. D., Locke, G. E., Ogunyemi, A., et al., Cocaine-related seizures in adults, *Am. J. Drug Alcohol Abuse* **16**:309-317 (1990).
48. Allen, J. W., A private inquiry into the circumstances surrounding the 1972 death of John Gomill, Jr., who died after allegedly consuming ten hallucinogenic mushrooms while residing in Hawaii, *J. Psychoactive Drugs* **20**:451-454 (1988).
49. Bal, T. S., Gutteridge, D. R., Johnson, B., et al., Adverse effects of the use of unusual phenethylamine compounds sold as illicit amphetamine, *Med. Sci. Law* **29**:186-188 (1989).
50. Shannon, M., Clinical toxicity of cocaine adulterants, in *Ann. Emerg. Med.* **17**:1243-1247 (1988).
51. DAWN (Drug Abuse Warning Network), *Emergency Room Mentions*, National Institute on Drug Abuse, Rockville, Maryland, 1988.
52. Anthony, J. C., and Trinkoff, A. M., U.S. Epidemiologic data on drug use and abuse: How are they relevant to testing abuse liability of drug? in *Testing for Abuse Liability in Humans* (NIDA Research Monograph 92), (M. Fischman and N. K. Mello, Eds.), U.S. Government Printing Office, Washington, D.C., 1989, pp. 241-266.
53. Lincoln, Y. S., and Guba, E. G., *Naturalistic Inquiry*, Sage Publications, Beverly Hills, California, 1985.
54. Gilman, A. G., Rall, T. W., Nies, A. S., and Taylor, P. (Eds.), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed., Pergamon Press, New York, 1990.

55. Ellenhorn, M. J., and Barceloux, D. G., *Medical Toxicology: Diagnosis and Treatment of Human Poisoning*, Elsevier, New York, 1988.
56. Julian, R. M., *A Primer of Drug Action*, 5th ed., Freeman, New York, 1988.
57. Meltzer, H. Y., *Psychopharmacology: The Third Generation of Progress*, Raven Press, New York, 1987.
58. Abel, E. L., *A Comprehensive Guide to the Cannabis Literature*, Greenwood Press, Westport, Connecticut, 1979.
59. Andrews, T., *A Bibliography of Drug Abuse: Supplement 1977-1980*, Libraries Unlimited, Littleton, Colorado, 1981.
60. Snow, B., *Drug Information: A Guide to Current Resources*, Medical Library Association, Chicago, 1989.
61. Turner, C. E., Urbanek, B. S., Wall, G. M., et al., *Cocaine: An Annotated Bibliography*, University Press of Mississippi, Jackson, Mississippi, 1988.
62. Snyder, C. A., Wood, R. W., Graefe, J. F., et al., "Crack smoke" is a respirable aerosol of cocaine base, *Pharmacol. Biochem. Behav.* **29**:93-95 (1988).
63. Wood, R. W., Animal models of drug self-administration by smoking, in *Research Findings on Smoking Abused Substances* (NIDA Research Monograph 99), (C. N. Chiang and R. L. Hawks, Eds.), U.S. Government Printing Office, Washington, D.C., 1990, pp. 159-169.
64. Cox, C. T., Jacobs, M. R., Leblanc, A. E., et al., *Drugs and Drug Abuse: A Reference Text*, Addiction Research Foundation, Toronto, 1983.
65. Inturrisi, C. E., Max, M. B., Foley, K. M., et al., The pharmacokinetics of heroin in patients with chronic pain, *New Engl. J. Med.* **310**:1213 (1984).
66. Platt, J. J., *Heroin Addiction: Theory, Research, and Treatment*, 2nd ed., Krieger, Malabar, Florida, 1986.
67. Strang, J., Lessons from an English opium eater: Thomas de Quincey reconsidered, *Int. J. Addict.* **25**:1455-1465 (1990).
68. Way, E. L., Kemp, J. W., Young, J. M., et al., The pharmacologic effects of heroin in relationship to its rate of biotransformation, *J. Pharmacol. Exp. Ther.* **129**:144-154 (1960).
69. Preston, K. L., and Jasinski, D. R., Abuse liability studies of opioid agonist-antagonists in humans, *Drug Alcohol Depend.* **28**:49-82 (1991).
70. Jaffe, J. H., and Martin, W. R., Opioid analgesics and antagonists, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (A. G. Gilman, T. W. Rall, A. S. Nies, and P. Taylor, Eds.), Pergamon Press, New York, 1990, pp. 485-501.
71. Ray, O. R., and Ksir, C., *Drugs, Society, and Human Behavior*, 4th ed., Times Mirror/Mosby, St. Louis, Missouri, 1990.
72. Blackwell, J. S., Opiate dependence as a psychological event: Users' reports of subjective experience, *Contemp. Drug Probl.* **12**:331-350 (1985).
73. Brecher, E., and Editors of *Consumer Reports, Licit and Illicit Drugs*, Little, Brown & Co., Boston, Massachusetts, 1972.
74. Edwards, G., Opium and after, *Lancet* **351**:1 (February 16, 1980).
75. Isbell, H., Opium poisoning, in *Textbooks of Medicine*, 11th ed. (P. B. Beeson and W. McDermott, Eds.), Saunders, Philadelphia, 1963, pp. 1744-1749.
76. Westermeyer, J., *Poppies, Pipes, and People*, University of California Press, Berkeley, California, 1982.
77. Arena, J. M., and Drew, R. H., *Poisoning*, 5th ed., Thomas, Springfield, Illinois, 1986.
78. Sellers, E. M., Alcohol, barbiturate and benzodiazepine withdrawal syndromes: Clinical management, *Can. Med. Assoc. J.* **139**:113-120 (1988).
79. Tracqui, A., Kintz, P., Mangin, P., et al., A fatality involving secobarbital, nitrazepam, and codeine, *Forensic Toxicol.* **10**:130-133 (1989).

80. Ashton, H., Protracted withdrawal syndromes from benzodiazepines, *J. Substance Abuse Treatment* **8**:19-28 (1991).
81. deWit, H., and Griffiths, R. R., Testing the abuse liability of anxiolytic and hypnotic drugs in humans, *Drug Alcohol Depend.* **28**:81-111 (1991).
82. Miller, N. S., and Gold, M. S., Benzodiazepines: Tolerance, dependence, abuse, and addiction, *J. Psychoactive Drugs* **22**:23-33 (1990).
83. Rosenthal, S. A., Girgenti, A. J., and Brown, M. T., Apparent diazepam toxicity in a child due to accidental ingestion of misrepresented quaalude, *Vet. Human Toxicol.* **26**:320-321 (1984).
84. Heishman, S. J., Stitzer, M. L., and Bigelow, G. E., Alcohol and marijuana: Comparative dose effect profiles in humans, *Pharmacol. Biochem. Behav.* **31**:649-655 (1989).
85. Kaim, S. C., Klett, C. J., and Rothfeld, B., Treatment of the acute alcohol withdrawal state: A comparison of four drugs, *Am. J. Psychiatry* **125**:1640-1646 (1969).
86. Rall, T. W., Hypnotics and sedatives; ethanol, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (A. G. Gilman, T. W. Rall, A. P. Nies, and P. Taylor, Eds.), Pergamon Press, New York, 1990, pp. 360-383.
87. Wallgren, H., and Barry, H., *Actions of Alcohol*, Vol. 2, Elsevier, Amsterdam, 1970.
88. Wimer, W., Russlee, J. A., and Kaplan, H. L., *Alcohols Toxicology*, Noyes Data Corp., Park Ridge, New Jersey, 1983.
89. Ionescu-Pioggia, M., Bird, M., and Cole, J. O., Subjective effects of methaqualone, in *Problems of Drug Dependence 1989* (NIDA Research Monograph 95), (L. S. Harris, Ed.), U.S. Government Printing Office, Washington, D.C., 1990, pp. 454-455.
90. Litovitz, L. T., Methaqualone, in *Poisoning and Drug Overdose* (L. M. Haddad and F. J. Winchester, Eds.), Sanders, Philadelphia, 1973, pp. 466-467.
91. Reynolds, J. E. F. (Ed.), *Martindale: The Extra Pharmacopoeia*, 29th ed., The Pharmaceutical Press, London, 1989, pp. 751-752.
92. Huff, J. S., Amphetamines/stimulants, in *Manual of Toxicologic Emergencies* (E. K. Noji and G. D. Kelen, Eds.), Year Book Medical Publishers, Chicago, 1988, pp. 350-355.
93. Seiden, L. S., and Ricurte, G. S., Neurotoxicity of methamphetamine and related drugs, in *Psychopharmacology: The Third Generation of Progress* (H. Y. Meltzer, ed.), Raven Press, New York, 1988, pp. 360-371.
94. Abbott, P. J., Caffeine: A toxicological overview, *Med. J. Aust.* **145**:518-521 (1986).
95. Griffiths, R. R., and Woodson, P. P., Caffeine physical dependence: A review of human and laboratory animal studies, *Psychopharmacologia* **94**:437-451 (1988).
96. Rall, T. W., Drugs used in the treatment of asthma, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (A. G. Gilman, T. W. Rall, A. S. Nies, and Taylor, Eds.), Pergamon Press, New York, 1990, pp. 618-637.
97. Stavric, B., Methylxanthines: Toxicity to humans. 2. Caffeine, *Food Chem. Toxicol.* **26**:645-662 (1988).
98. Stern, K. N., Chait, L. D., and Johanson, C. E., Reinforcing and subjective effects of caffeine in normal human volunteers, *Psychopharmacology* **98**:81-88 (1989).
99. Johanson, C. E., and Fischman, M. W., The pharmacology of cocaine related to its abuse, *Pharmacol. Rev.* **41**:3-44 (1989).
100. Jones, R. T., The pharmacology of cocaine, in *Cocaine: Pharmacology, Effects, and Treatment of Abuse* (NIDA Research Monograph 50), (J. Grabowski, Ed.), U.S. Government Printing Office, Washington, D.C., 1984, pp. 34-49.
101. Smart, E. G., and Anglin, L., Do we know the lethal dose of cocaine? *J. Forensic Sci.* **32**:303-311 (1987).
102. Cheug, Y. W., Erickson, P. G., and Landau, T. C., Experience of crack use: Findings from a community-based sample in Toronto, *J. Drug Issues* **21**:121-140 (1991).

103. Ettinger, N. A., and Albin, R. J., A review of the respiratory effects of smoking cocaine, *Am. J. Med.* **87**:664-668 (1989).
104. Jones, R. T., The pharmacology of cocaine smoking in humans, in *Research Findings on Smoking of Abused Substances* (NIDA Research Monograph 99), (C. N. Chaing and R. L. Hawks, Eds.), U.S. Government Printing Office, Washington, D.C., 1990, pp. 30-41.
105. Perez-Reyes, M., DiGuiseppe, S., Ondrusek, G., et al., Free-base cocaine smoking, *Clin. Pharmacol. Ther.* **32**:459-467 (1982).
106. Henningfield, J. E., Pharmacologic basis and treatment of cigarette smoking, *Clin. Psychiatry* **45**:24-33 (1984).
107. Saxena, K., and Scheman, A., Suicide plan by nicotine poisoning: A review of nicotine toxicity, *Vet. Human Toxicol.* **27**:495-497 (1985).
108. Warburton, D. M., The puzzle of nicotine use, in *The Psychopharmacology of Addiction* (M. Lader, Ed.), Oxford University Press, Oxford, 1988, pp. 27-49.
109. Hansen, G., Jensen, S. B., Chandresh, L., et al., The psychotropic effect of ketamine, *J. Psychoactive Drugs* **20**:419-425 (1988).
110. Faithfull, N. S., Poelman, K. M., and Erdmann, W., Ketamine-induced dysrhythmia and its antagonism: A case report, *Eur. J. Anaesthesiol.* **4**:287-291 (1987).
111. Hodgson, E., Mailman, R. B., and Chambers, J. E., *Dictionary of Toxicology*, Van Nostrand Reinhold, New York, 1980.
112. Jansen, K. L. R., Ketamine—Can chronic use impair memory? *Int. J. Addict.* **25**:133-139 (1990).
113. Rogo, D. S., Ketamine and the near-death experience, *Anabiosis* **4**:87-96 (1984).
114. Danton, W. G., May, J. R., and Lynn, E. J., Psychological and physiological effects of relaxation and nitrous oxide training, *Psychol. Rep.* **55**:311-322 (1984).
115. Daynes, G., The initial management of alcoholism using oxygen and nitrous oxide: A transcultural study, *Int. J. Neurosci.* **49**:83-86 (1989).
116. Block, R. L., Ghoneim, M. W., Kumar, V., et al., Psychedelic effects of a subanesthetic concentration of nitrous oxide, *Anesth. Prog.* **37**:271-276 (1990).
117. Enticknap, J. B., A case of fatal accidental N₂O poisoning, *Med. Sci. Law* **1**:404-409 (1961).
118. Layzer, R. B., Nitrous oxide abuse, in *Nitrous Oxide* (E. I. Eger, Ed.), Elsevier, New York, 1985, pp. 251-257.
119. Aniline, O., and Pitts, F. N., Phencyclidines (PCP): A review and perspectives, *CRC Crit. Rev. Toxicol.* pp. 145-177 (April 1982).
120. Blaster, R., The behavioral pharmacology of phencyclidine, in *Psychopharmacology: The Third Generation of Progress* (H. Y. Meltzer, Ed.), Raven Press, New York, 1987, pp. 1573-1755.
121. Burns, R. S., and Lerner, S. E., Causes of phencyclidine-related deaths, *Clin. Toxicol.* **12**:463-481 (1978).
122. McCarron, M. M., Phencyclidine intoxication, in *Phencyclidine: An Update* (NIDA Research Monograph 64), (D. H. Clouet, Ed.), U.S. Government Printing Office, Washington, D.C., 1986, pp. 214-217.
123. Poklis, A., Graham, M., and Maginn, D., Phencyclidine and violent deaths in St. Louis, Missouri: A survey of medical examiners' cases from 1977 through 1986, *Am. J. Drug Alcohol Abuse* **16**:265-274 (1990).
124. Fysh, R. R., Oon, M. C. H., Robinson, K. N., et al., A fatal poisoning with LSD, *Forensic Sci. Int.* **28**:109-113 (1985).
125. Jaffe, J. H., Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. (A. G. Gilman, T. W. Rall, A. S. Nies, and P. Taylor, Eds.), Pergamon Press, New York, 1990, pp. 522-572.
126. Klock, J. C., Boerner, U., and Becker, C. E., Coma, hyperthermia, and bleeding associated with massive LSD overdose: A report of eight cases, *West. J. Med.* **120**:183-188 (1973).

127. Litovitz, L. T., Hallucinogens, in *Poisoning and Drug Overdose* (L. M. Haddad and J. F. Winchester, Eds.), Sanders, Philadelphia, 1983, p. 459.
128. Strassman, R. J., Adverse reactions to psychedelic drugs: A review of the literature, *J. Nerv. Ment. Disorders* **172**:577-593 (1984).
129. Bost, R. O., 3,4-Methylenedioxymethamphetamine (MDMA) and other amphetamine derivatives, *J. Forensic Sci.* **33**:576-587 (1988).
130. Glennon, R. S., Psychoactive phenylisopropylamines, in *Psychopharmacology: The Third Generation of Progress* (H. Y. Meltzer, Ed.), Raven Press, New York, 1987, pp. 1627-1634.
131. McKenna, D. J., and Peroutka, S. J., Neurochemistry and neurotoxicity of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"), *J. Neurochem.* **54**:14-22 (1990).
132. Ricaurte, G. A., Studies of MDMA-induced neurotoxicity in nonhuman primates: A basis for evaluating long-term effects in humans, in *Pharmacology and Toxicology of Amphetamine and Related Designer Drugs* (NIDA Research Monograph 94), (K. Asghar and E. DeSouza, Eds.), U.S. Government Printing Office, Washington, D.C., 1989, pp. 306-322.
133. Schmidt, C. J., Neurotoxicity of psychedelic amphetamine, methylenedioxymethamphetamine, *J. Pharmacol. Exp. Ther.* **240**:1-6 (1987).
134. Bergman, R. L., Navajo peyote use: Its apparent safety, *Am. J. Psychiatry* **128**:695-699 (1971).
135. Hoffer, A., and Osmond, H., *The Hallucinogens*, Academic Press, New York, 1967.
136. Hollister, L. E., Effects of hallucinogens in humans, in *Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives* (B. L. Jacobs, Ed.), Raven Press, New York, 1984, pp. 19-27.
137. Mack, R. B., Marching to a different cactus: Peyote (mescaline) intoxication, *N. C. Med. J.* **47**:137-138 (1986).
138. Lincoff, G., and Mitchel, D. H., *Toxic and Hallucinogenic Mushroom Poisoning: A Handbook for Physicians and Mushroom Hunters*, Van Nostrand Reinhold Co., New York, 1977.
139. Parashos, A. J., The psilocybin-induced "state of drunkenness" in normal volunteers and schizophrenics, *Behav. Neuropsychiatry* **8**:83-86 (1977).
140. Penden, N. R., Pringle, S. D., and Crooks, J., The problem of psilocybin mushroom abuse, *Human Toxicol.* **1**:417-424 (1982).
141. Singer, R., Hallucinogenic mushrooms, in *Mushroom Poisoning: Diagnosis and Treatment* (B. H. Rumack and E. Salzman, Eds.), CRC Press, West Palm Beach, Florida, 1978, pp. 201-208.
142. Spoerke, D. G., and Hall, A. H., Plants and mushrooms of abuse, *Emergency Med. Clin. North Am.* **8**:579-593 (1990).
143. Braude, M. C., Toxicology of cannabinoids, in *Cannabis and Its Derivatives* (W. D. M. Paton and J. Crown, Eds.), Oxford University Press., London, 1972, p. 90.
144. Bro, P., and Schou, J., Cannabis poisoning with analytical verification, *New Engl. J. Med.* **293**:1049-1050 (1975).
145. Mendelson, J. H., Marijuana, in *Psychopharmacology: The Third Generation of Progress* (H. Y. Meltzer, Ed.), Raven Press, New York, 1987, pp. 1563-1571.
146. Rohr, J. M., Skowlund, S. W., and Martin, T. E., Withdrawal sequelae to cannabis use, *Int. J. Addict.* **24**:627-631 (1989).
147. Selden, B. S., Clark, R. F., and Curry, S. C., Marijuana, *Emergency Med. Clin. North Am.* **8**:527-539 (1990).
148. McKim, W. A., *Drugs and Behavior: An Introduction to Behavioral Pharmacology*, 2nd ed., Prentice-Hall, Englewood Cliffs, New Jersey, 1991.
149. Revell, A. D., Smoking and performance—A puff-by-puff analysis, *Psychopharmacology* **96**:563-565 (1988).
150. Sahenk, Z., Mendell, J. R., Couri, D., et al., Polyneuropathy from inhalation of N₂O cartridges through a whipped-cream dispenser, *Neurology* **28**:485-487 (1978).

151. Chait, L. D., Delta-9-tetrahydrocannabinol content and human marijuana self-administration, *Psychopharmacology* **98**:51-55 (1989).
152. Perez-Reyes, M., Marijuana smoking: Factors that influence the bioavailability of tetrahydrocannabinol, in *Research Finding on Smoking of Abused Substances* (NIDA Research Monograph 99), (C. N. Chiang and R. L. Hawks, Eds.), U.S. Government Printing Office, Washington, D.C., 1990, pp. 42-61.
153. Brady, J. V., Lukas, S. E., and Hienz, R. D., Relationship between reinforcing properties and sensory/motor toxicity of CNS depressants; Implications for the assessment of abuse liability, in *Problems of Drug Dependence, 1982* (NIDA Research Monograph 43), (L. S. Harris, ed.), U.S. Government Printing Office, Washington, D.C., 1983, pp. 196-202.
154. Brady, J. V., Griffiths, R. R., Hienz, R. D., et al., Assessing drugs for abuse liability and dependence potential in laboratory primates, in *Methods of Assessing the Reinforcing Properties of Abused Drugs* (M. A. Bozarth, Ed.), Springer-Verlag, New York, 1987, pp. 45-84.
155. National Institute on Alcohol Abuse and Alcoholism, Announcement: Research on the recognition, management, and prevention of alcohol problems in a primary health care setting, *Cat. Fed. Domest. Assist.* No. 13.273 (1990).
156. Erickson, P. G., and Alexander, B. K., Cocaine and addictive liability, *Soc. Pharmacol.* **3**:249-270 (1989).
157. Siegel, R. K., Changing patterns of cocaine use: Longitudinal observations, consequences, and treatment, in *Cocaine: Pharmacology, Effects, and Treatment of Abuse* (NIDA Research Monograph 50), (J. Grabowski, Ed.), U.S. Government Printing Office, Washington, D.C., 1984, pp. 93-109.
158. National Research Council, Commission on Life Sciences, Committee on the Institutional Means for Assessment of Risks to Public Health, *Risk Assessment in the Federal Government: Managing the Process*, National Academy Press, Washington, D.C., 1983.