Inhalant Use and Inhalant Use Disorders in the United States

More than 22 million Americans age 12 and older have used inhalants, and every year more than 750,000 use inhalants for the first time. Despite the substantial prevalence and serious toxicities of inhalant use, it has been termed "the forgotten epidemic." Inhalant abuse remains the least-studied form of substance abuse, although research on its epidemiology, neurobiology, treatment, and prevention has accelerated in recent years. This review examines current findings in these areas, identifies gaps in the research and clinical literatures pertaining to inhalant use, and discusses future directions for inhalant-related research and practice efforts.

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Inhalant abuse refers to the intentional inhalation of vapors from commercial products or specific chemical agents to achieve intoxication. Abusers may inhale vapors directly from a container, from a bag into which a substance has been placed, or from a rag soaked with a substance and then placed over the mouth or nose (American Psychiatric Association [APA], 2000). Intoxication occurs rapidly and is short-lived, although some abusers repeatedly or continuously self-administer inhalants to maintain a preferred level of intoxication.

Inhalant abuse and dependence criteria parallel the generic substance abuse and dependence diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; APA, 2000). The criteria do not include withdrawal symptoms, although some evidence suggests a characteristic withdrawal syndrome (Perron et al., 2009a). Amyl nitrate, other nitrite vasodilators, and nitrous oxide are sometimes abused by inhalation, but the criteria specifically exclude them from the list of substances considered.

Glue, shoe polish, toluene, spray paints, gasoline, and lighter fluid are among the inhalants most commonly abused by young people (Substance Abuse and Mental Health Services Administration [SAMHSA], 2008b). However, hundreds of products containing single substances or mixtures that can produce intoxication if inhaled are commercially available (Table 1). The huge variety of products that emit psychoactive vapors poses difficulties for classification. The current approach of grouping inhalants by form, product type, or intended use has conceptual and heuristic limitations. Classification into groups that share pharmacological properties and distinctive patterns of abuse may be more useful, but is unavailable at present because little is known about the pharmacologic effects of many abused vapors.

TABLE 1. Commonly Abused Inhalant Products and Their Constituents

GLUES AND ADHESIVES	
Airplane glue	Toluene, ethyl acetate
Other glues and cements	Hexane, toluene, methyl chloride, acetone, methyl ethyl ketone, methyl butyl ketone, benzene, xylene, trichloroethylene, tetrachloroethylene, chloroform
AEROSOLS	
Spray paint	Butane, propane (U.S.), fluorocarbons, toluene, hydrocarbons, xylene
Hair spray	Butane, propane (U.S.), chlorofluorocarbons
Deodorant; air freshener	Butane, propane (U.S.), chlorofluorocarbons
Analgesic spray	Chlorofluorocarbons
Asthma spray	Chlorofluorocarbons
Fabric spray	Butane, trichloroethane
PC cleaner	Dimethyl ether, hydrofluorocarbons
Video head cleaner	Ethyl chloride
ANESTHETICS	
Gaseous	Nitrous oxide
Liquid	Halothane, enflurane, desflurane, isoflurane
Local	Ethyl chloride
CLEANING AGENTS	
Dry cleaning	Tetrachloroethylene, trichloroethane
Spot remover	Xylene, petroleum distillates, chlorohydrocarbons
Degreaser	Tetrachloroethylene, trichloroethane, trichloroethylene
Lacquer; thinners	Acetone, methanol, ethyl acetate, methyl chloride, toluene
SOLVENTS AND GASES	
Nail polish remover	Acetone, ethyl acetate, toluene (rarely)
Paint remover	Toluene, methylene chloride, methanol, acetone, ethyl acetate
Paint thinner	Petroleum distillates, esters, acetone
Correction fluid and thinner	Trichloroethylene, trichloroethane, isoparaffins
Fuel gas	Butane, isopropane
Lighter fluid	Butane, isopropane
Fire extinguisher	Bromochlorodifluoromethane
Gasoline	Benzene, n-hexane, toluene, xylene

Modified from Sharp and Rosenberg (2005).

Inhalant use disproportionately afflicts the poor, mentally ill, and juvenile- and criminal-justice involved.

Although inhalant abuse is common and associated with harmful outcomes that may rival or exceed those of other psychoactive drugs (Dinwiddie, 1994; 1998; Sharp and Rosenberg, 2005), inhalants remain the least-studied class of psychoactive agents (Balster, 1996). There are no clearly effective treatment interventions reported in the clinical research literature. Here we discuss the consequences of inhalant abuse and review potential treatments under investigation and harm reduction measures that appear to be effective.

EPIDEMIOLOGY OF INHALANT USE

The most informative surveys of inhalant use are the Monitoring the Future (MTF) survey, the Youth Risk

Behavior Survey (YRBS), and the National Survey on Drug Use and Health (NSDUH) (Table 2). They reveal:

- An estimated 9 percent of the U.S. population age 12 and older—22.5 million people—has used an inhalant for its psychoactive properties at least once (NSDUH);
- Inhalant use tends to start early, with 58 percent of users reporting first use by the end of ninth grade (MTF);
- Thirteen percent of students in grades 9 through 12 reported having ever used an inhalant on the 2007 YRBS;
- Fewer students in older grades than in younger grades (15.7 percent in 9th grade, 9.9 percent in 12th grade) reported having ever used an inhalant on the 2008 MTF, suggesting that many who start using inhalants early drop out of school;
- Most inhalant users initiate the behavior quite young, and most discontinue it quickly (Crocetti, 2008; d'Abbs and MacLean, 2008; SAMHSA, 2008b; Siqueira and Crandall, 2006). For example, the 2006 MTF indicated that on average, half of 8th, 10th, and 12th graders who had ever used inhalants had not done so during the past year (Johnston et al., 2007). However, as noted above, young people who drop out of school appear to continue using inhalants at higher rates than those who stay;
- White and Hispanic students reported lifetime use rates (14.4 percent) that were about twice those of African Americans (8.5 percent; YRBS);
- Important risk factors for inhalant use among middle and high school students include low levels of parental education and a lack of intention to complete 4 years of college (MTF);
- More than half of eighth graders saw the regular use of inhalants as a "great risk," but only a third attributed the same amount of danger to using an inhalant once or twice (MTF).

Studies have produced a range of estimates of inhalant users' risk of developing an inhalant use disorder.

The MTF and NSDUH have produced conflicting findings regarding whether gender influences adolescent inhalant use. The 2006 MTF indicated that more 8th- and 10th-grade girls than boys, and more 12th-grade boys than girls, had used an inhalant (Johnston et al., 2007). In contrast, the NSDUH and its predecessor, the National Household Survey on Drug Abuse (NHSDA), have consistently shown equal use rates among boys and girls (Neumark, Delva, and Anthony, 1998; SAMHSA, 2006; Wu, Pilowsky, and Schlenger, 2004).

Inhalant, use disproportionately afflicts subpopulations including the poor, mentally ill, and juvenile- and criminal-justice involved (Howard et al., 1999). For example, studies have documented inhalant use rates of:

- 34.3 percent among 475 juvenile probationers surveyed in Utah (Howard and Jenson, 1999). The earlier that individuals had initiated use and the more frequently they used, the higher the likelihood that use was associated with significant psychosocial dysfunction;
- 36.9 percent of 723 Missouri youth surveyed in a residential treatment center for antisocial behavior (Howard et al., 2008);
- approximately 18 percent of 847 adolescents referred to a treatment program for substance abuse or behavioral problems (Sakai et al., 2004). In addition, 10 percent of adult substance abusers surveyed in a treatment center had used inhalants more than five times (Compton et al., 1994).

Efforts have been made to identify subtypes of inhalant users, which could facilitate the identification of at-risk individuals, assessment, and treatment planning (Perron, Vaughn, and Howard, 2007; Vaughn, Perron, and Howard, 2007). These studies have found elevated inhalant use rates among youths who experienced a recent major depressive episode (SAMHSA, 2008a) and a subgroup of adolescents who used inhalants to "self-medicate" for unhappiness and anxiety (Perron, Vaughn, and Howard, 2007). These latter youths exhibited significantly more polydrug use, psychiatric comorbidity, and antisocial behavior than did two other classes of adolescent inhalant users.

Low monetary cost and ease of access probably contribute to the concentration of inhalant use among younger children and adolescents; low-income and unemployed adults; people living in isolated rural or reservation settings; and people housed in institutions such as psychiatric hospitals, prisons, and residential treatment centers. Inhalants can also be purchased and used without arousing the suspicion of parents, salespeople, school or law enforcement professionals, social service workers, or health care providers (Anderson and Loomis, 2003). Few people, for example, think of butane cigarette lighters, computer air dusters, nail polish, nail polish remover, or paint thinner as items that can be abused for their psychoactive effects; if challenged, young people can often offer plausible benign explanations for having these items.

EPIDEMIOLOGY OF INHALANT USE DISORDERS

Inhalant use disorders are among the least prevalent substance use disorders. In nationally representative

TABLE 2. Nationally Representative Surveys of Inhalant Use

Survey Name	Design, Target Population, and Frequency of Administration	Inhalant Question	Estimates of Lifetime Prevalence of Inhalant Use	Limitations and Strengths of the Surveys
Monitoring the Future	Annual cross-sectional survey since 1975 for 12th-graders and since 1991 for 8th- and 10th-graders	"On how many occasions (if any) have you sniffed glue, or breathed the contents of aerosol spray cans, or inhaled any other gases or sprays in order to get high in your lifetime?" "During the past 12 months?" "During the past 30 days?"	2010, by grade: 8th: 14.5 % 10th: 12.0% 12th: 9.0%	School-based survey misses dropouts and truants. Uses single omnibus item for inhalant use assessment. Provides data on perceived danger and disapproval of inhalants.
Youth Risk Behavior Survey	Semi-annual cross-sectional survey conducted since 1991 for grades 9 through 12	Middle school version: "Have you ever sniffed glue, or breathed the contents of spray cans, or inhaled any paints or sprays to get high?" Response options: Yes/No. High school version: "During your life, how many times have you sniffed glue, breathed the contents of aerosol spray cans, or inhaled any paints or sprays to get high?" Response options: 0 times; 1 or 2 times; 3 to 9 times; 10 to 19 times; 20 to 30 times; 40 or more times.	2009, by grade: 9–12: 11.7% 10th: 12.5% 12th: 9.1%	School-based survey misses dropouts and truants. Provides data on comorbid risk behavior and state-specific findings.
National Survey on Drug Use and Health	Annual cross-sectional survey of U.S. residents 12 and older conducted since 1971	"These next questions are about liquids, sprays, and gases that people sniff or inhale to get high or to make them feel good. Have you ever, even once, inhaled [INHALANT NAME] for kicks or to get high? Response options: Yes/No for the following inhalants: a) amyl nitrite "poppers," locker room odorizers or "rush;" b) correction fluid, degreaser, or cleaning fluid; c) gasoline or lighter fluid; d) glue, shoe polish, or toluene; e) halothane, ether, or other anesthetics; f) lacquer thinner or other paint solvents; g) lighter gases, such as butane or propane; h) nitrous oxide or "whippets; " i) spray paints; j) some other aerosol spray; and k) any other inhalants besides the ones that have been listed.	2007 by grade: 8th: 12.0% 10th: 10.7% 12th: 8.2% 9–12: 10.8% 12 years or older: 9.1% or 22,470,000 U.S. residents.	Household survey that captures dropouts and truants, but misses institutionalized populations and respondents younger than 12. Provides state-specific estimates.

surveys, youths reporting symptoms that would permit a diagnosis of inhalant abuse or dependence have included 0.6 percent of the 15- to 24-year-old participants in the 1992 National Comorbidity Survey (NCS) (Anthony, Warner, and Kessler, 1994), and 0.2 percent of the 12- to 17-year-olds who responded to the 2002–2003 NHSDA (Wu, Pilowsky, and Schlenger, 2004). The past-year prevalence of inhalant use disorder among adult participants in the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions was 0.02 percent (Grant et al., 2004).

Motor deficits observed in mice exposed to toluene imply long-lasting brain damage.

Studies have produced a range of estimates of inhalant users' risk of developing an inhalant use disorder. At the lower end, an analysis of NCS data yielded an estimate that 7.9 percent of 15- to 24-year-olds with a history of inhalant use were dependent (Anthony, Warner, and Kessler, 1994). Similarly, Wu, Pilowsky, and Schlenger (2004) found that 6 percent of 12- to 17-year-olds who reported past-year use on the 2000 and 2001 NHSDA surveys met criteria for past-year inhalant abuse, and 4 percent met criteria for past-year dependence. Higher estimates for rates of inhalant use disorders among individuals with histories of inhalant use include:

- 18 percent among adults who participated in the nationally representative National Epidemiologic Survey on Alcohol and Related Conditions (Wu and Howard, 2007b);
- 47 percent among a community sample of 162 young adults in St. Louis, Missouri (Ridenour, Bray, and Cottler, 2007).

The wide divergence in prevalence estimates may reflect the presence of elevated-risk groups in some samples. For example, Howard and Perron (2009) found a 47 percent prevalence of inhalant use disorders among 279 juvenile justice-involved inhalant users in Missouri. In the Wu, Pilowsky, and Schlenger NHSDA-based study (2004), adolescents who had initiated inhalant use before age 15 were five to six times as likely as those who had started later to be diagnosed with inhalant dependence in the year prior to the survey.

CONSEQUENCES OF INHALANT USE

Inhalant use is associated with a large number of adverse effects and psychosocial outcomes.

Acute Effects

Inhalant intoxication produces a syndrome similar to alcohol intoxication, consisting of dizziness, incoordination, slurred speech, euphoria, lethargy, slowed reflexes, slowed thinking and movement, tremor, blurred vision, stupor or coma, generalized muscle weakness, and involuntary eye movement (APA, 2000). Inhalant use can result in chemical and thermal burns (Moreno and Beierle, 2007), withdrawal symptoms (Keriotis and Upadhyaya, 2000), persistent mental illness (Jung, Lee, and Cho, 2004), and catastrophic medical emergencies such as ventricular arrhythmias leading to "sudden sniffing death" (Avella, Wilson, and Lehrer, 2006; Bowen, Daniel, and Balster, 1999). Inhalant intoxication also increases the risk for fatal injuries from motor vehicle or other accidents (Bowen, Daniel, and Balster, 1999).

Neurological and Cognitive Effects

Studies of occupationally exposed workers laid the foundation for much of what we know about inhalant-related cognitive deficits. Morrow and colleagues (1997) found significant learning and memory impairments in journeyman painters relative to controls and evidence that many patients' inhalant-related cognitive problems were slow to resolve (Morrow, Steinhauer, and Condray, 1996; 1998).

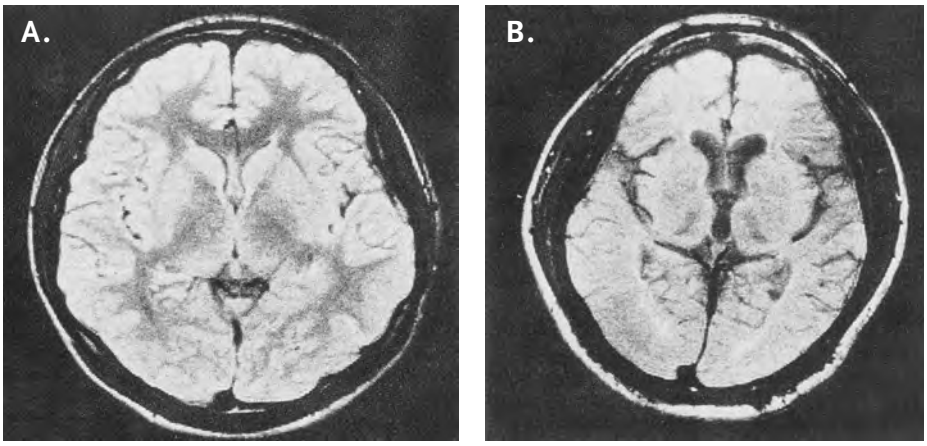
Even a single occupational exposure leading to inhalant intoxication can produce long-term memory problems and processing speed impairments (Stollery, 1996), an ominous finding given that inhalant abuse is characterized by exposures to neurotoxins at much higher levels than those typically incurred in occupational exposures (Bowen, Wiley, and Balster, 1996).

Early research with recreational inhalant users noted that, similar to the findings with occupational exposures, these individuals have memory, attention, and judgment deficits compared with controls and polydrug users (Hormes, Filley, and Rosenberg, 1986; Korman, Trimboli, and Semler, 1980). Maruff and colleagues (1998) found that current inhalant users performed worse than former users and controls in a test of visual-spatial memory that challenges the test taker to remember the location in which a symbol briefly flashed on a computer screen. Tenebein and Pillay (1993) found diminished brain activity in response to visual and auditory events, a possible marker for neurological dysfunction, in 8 of 15 inhalant users 9 to 17 years of age, even though the youths had no clinical evidence of neurological abnormalities.

Subsequent studies have disclosed that recurrent inhalant intoxication can lead to neurological disorders, including Parkinsonism, impaired cognition due to degradation of brain cells (encephalopathy) or loss of brain cells (cerebral atrophy), and loss of muscle strength and

coordination due to damage to the cerebellum (cerebellar ataxia) (e.g., Finch and Lobo, 2005; Gautschi, Cadosch, and Zellweger, 2007). Imaging studies of inhalant abusers have documented thinning of the corpus callosum (the band of nerve fibers joining the cerebral hemispheres) and lesions of the white matter that facilitates communication between brain cells (Finch and Lobo, 2005; Gautschi, Cadosch, and Zellweger, 2007). Regional reductions in cerebral blood flow are observable with functional magnetic resonance imaging (fMRI) after 1 year of inhalant use (Okada et al., 1999; Yamanouchi et al., 1998). Other radiologic abnormalities found in inhalant users include areas of reduced MRI signal strength (hypointensities) in the thalamus and basal ganglia (Lubman, Yücel, and Lawrence, 2008) and irregular uptake of radiolabeled pharmaceuticals in single-photon emission computed tomography (SPECT) studies (Küçük et al., 2000). Lubman and colleagues (2008) reviewed recent clinical and neuroimaging studies of chronic inhalant abusers, documenting significant cognitive deficits, structural abnormalities in specific brain areas (e.g., periventricular, subcortical, and white matter), and reduced brain perfusion and blood flow.

FIGURE 1. Brain Atrophy in a Toulene Abuser



Compared with the brain of an individual with no history of inhalant abuse (A), that of a chronic toluene abuser (B) is smaller and fills less of the space inside the skull (the white outer circle in each image). Courtesy of Neil Rosenberg, M.D., *NIDA Research Report* (NIH 05-3818).

Animal models have been helpful for studying acute and chronic biobehavioral effects of inhalants. They have shown that toluene and other inhalants can have reversible disruptive effects on response rates in behavior modification protocols; most of these effects appear to be greater after binge patterns of exposure than after lower levels of exposure (see Bowen et al., 2006, for review). In one of the few animal studies to examine the impact of binge-pattern exposures on higher cognitive processes, Bowen and McDonald (2009) reported that mice exposed to high concentrations of toluene (3,600 and 6,000 parts per million) for 30 minutes per day for 40 days (similar to the amounts chronic abusers inhale) demonstrated long-lasting motor deficits on a waiting-for-reward task. This result implies the presence of long-term brain damage, possibly resulting from cerebellar insult or cortical cell loss. Further animal trials are needed to identify toluene's impact on cognition so that these toluene-related impairments can be recognized early and measures can be initiated to prevent potentially extensive neurological damage. Additional preclinical studies suggest that toluene and 1,1,1-trichloroethane (TCE) impair learning, memory, and attention (e.g., von Euler et al., 2000).

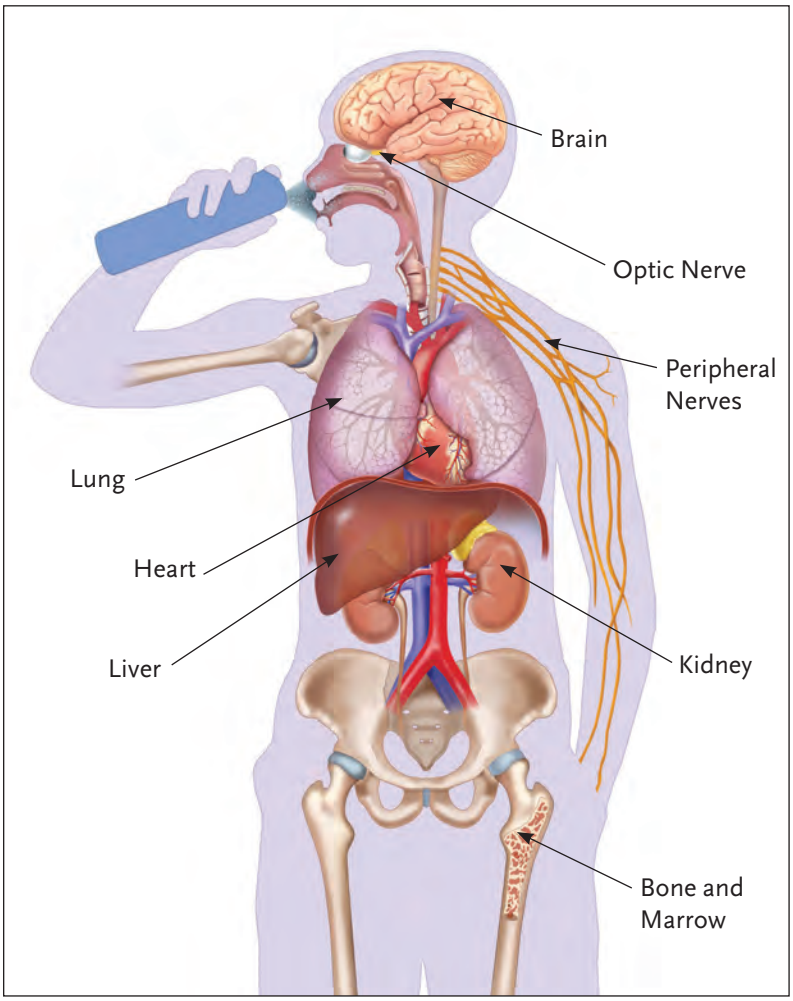
Effects on Organs Other Than the Brain

Evidence is mounting that inhalants can cause chronic medical problems affecting multiple organ systems (Figure 2). Animal studies, case reports, and small clinical investigations have implicated inhalant use in liver, heart, and kidney toxicity; bone demineralization; bone marrow suppression; and reduced immunity (T-cell responsivity) (e.g., Karmakar and Roxburgh, 2008; Takaki et al., 2008). Diminished plasma and red blood cell levels of selenium and zinc have also been noted, potentially impairing immune function and increasing the risk for infectious disease (Zaidi et al., 2007). O'Brien, Yeoman, and Hobby (1971) reported a case of liver and kidney failure in a 19-year-old who had sniffed glue for 3 years, and Wiseman and Banim (1987) diagnosed irreversible congestive heart failure in a 15-year-old patient who had sniffed glue for 2 years. Inhalants can also cause peripheral neuropathy leading to chronic pain and vision-impairing optic nerve damage (e.g., Twardowschy et al., 2008).

Adult inhalant abusers have higher rates of major depression, suicidal ideation and attempts, and anxiety and substance use disorders.

Several recent studies suggest that inhalant abuse is associated with serious pulmonary dysfunction and disease. An epidemiological study of 29,195 adults aged 35 to 49 participating in the NSDUH found that duration of inhalant abuse was significantly positively associated with likelihood of having experienced tuberculosis, bronchitis, asthma, and sinusitis (Han, Gfroerer, and Colliver, 2010). Cayir and colleagues (2011) compared

FIGURE 2. Organs Damaged by Inhalant Exposure



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18 volatile solvent abusers with 18 control subjects (all of whom were tobacco smokers), noting that radioisotope pulmonary clearance was significantly accelerated in the solvent abuser group. The authors concluded that alveolo-capillary membrane dysfunction may follow inhalant abuse. A recent death of an 18-year-old man due to bilateral pneumonia following inhalation of a computer keyboard cleaner has also raised concerns about potential pulmonary consequences of inhalant abuse (Schloneger, Stull, and Singer, 2009).

Psychosocial Effects

Workers occupationally exposed to inhalants experience relatively high post-exposure levels of depression and anxiety (Morrow et al., 2000). Condray and colleagues (2000) found that journeyman painters were significantly more likely than controls (41 percent versus 16 percent) to meet lifetime criteria for a mood disorder and that virtually all painters who met criteria for a mood disorder experienced their first episode after starting their painting careers.

Relatively little is known about the natural history of inhalant use, inhalant use disorders, and associated psychiatric and psychosocial comorbidities in the general population. Clinical, criminological, and general population studies have identified robust associations between lifetime inhalant use, other drug use, and mental health disorders or symptoms. For example, SAMHSA (2005) estimated that youths who had used inhalants by ages 12 or 13 were nearly five times as likely than nonusing peers to have used another psychoactive drug. Associations between early-onset inhalant use and risk for later heroin and intravenous drug use (Storr, Westergaard, and Anthony, 2005; Wu and Howard, 2007a), antisocial behavior, and polydrug abuse have also been identified (SAMHSA, 2005).

Studies of adults in substance abuse treatment and in the general population indicate that inhalant users have higher rates of major depression, suicidal ideation and attempts, anxiety disorders, and other substance use disorders than nonusers of inhalants (Howard et al., 2010a; 2010b). Wu and Howard (2007b) and Wu, Howard, and Pilowsky (2008) documented dramatically elevated rates of mood and anxiety disorders, personality disorders, and substance use disorders in a nationally representative sample of U.S. inhalant users. Inhalant use and inhalant use disorders also appear to raise the odds for stressful life events such as having troubles at school or with a boss or co-worker, being fired, or being arrested or sent to jail (Dinwiddie, 1994; 1998).

Some researchers have questioned whether inhalant use contributes directly to subsequent drug use and adverse psychosocial outcomes, arguing instead that it may be a general indicator of a deviant disposition (Howard and Jenson, 1999; 2010a; 2010b). Published reports suggest that childhood and adolescent inhalant use may be a "red flag" signaling membership in a subgroup of antisocial youths that is marked by high levels of psychiatric symptoms, polydrug use, and psychosocial impairment, as well as earlier onset of behavior problems and a wider range of antisocial conduct than are typical of nonusers of inhalants (Howard and Jenson, 1999; Howard et al., 1999; 2008; Freedenthal et al., 2007; Jacobs and Ghodse, 1988; McGarvey, Canterbury, and Waite, 1996). Additional studies are needed to evaluate how inhalant abuse contributes to the etiology of psychiatric disorders and related mental, emotional, and physical disabilities.

Effects on the Fetus

Maternal inhalant use during pregnancy may produce effects in offspring similar to those seen in fetal alcohol syndrome (Jones and Balster, 1998; Bowen and Hannigan, 2006; Hannigan and Bowen, 2010). One study, for example, reported high rates of head and facial deformities, smaller-than-normal head and brain development, low birth weight, developmental delays, and other pregnancy and birth complications in infants born to women who inhaled solvents recreationally (Pearson et al., 1994). Tenebein (1993) described a neonatal withdrawal syndrome potentially attributable to maternal inhalant use. Recent laboratory studies also have demonstrated evidence of growth and developmental aberrations, physical deformities, and other adverse outcomes (e.g., Bowen et al., 2005; 2007; 2009; Bowen, Hannigan, and Cooper, 2009).While discussion of these findings is beyond the scope of this paper, they have been capably reviewed by Bowen and colleagues (2006), Lubman and colleagues (2008), and Hannigan and Bowen (2010).

NEUROBIOLOGY OF INHALANT USE

Much has been learned during the past decade about inhalants' pharmacological properties and effects (Bowen et al., 2006; Lubman, Yücel, and Lawrence, 2008). Although there has been limited research on the reinforcing properties of inhalants, animal studies suggest that several abused inhalants function as reinforcers (see Bowen et al., 2006, p. 643, for a review of findings). For example, in the conditioned place preference reward paradigm, toluene increases rats' tendency to gravitate to a chamber in which they formerly received the drug over one in which they did not (Lee, Schiffer, and Dewey, 2004). Of the few studies that have examined self-administration of inhaled compounds in nonhuman species, one demonstrated that mice will self-administer intravenous toluene and TCE (Blokhina et al., 2004), and another has shown that rats will self-administer ether vapor (Pogorelov and Kovalev, 1999). Other investigations have demonstrated that nonhuman primates will self-administer chloroform, ether, nitrous oxide, and toluene (see Evans and Balster, 1991).

Toluene and TCE appear to produce motor excitation at low concentrations and sedation, anesthesia, coma, and death at higher concentrations (Bowen and Balster, 1998). Benzene and diethyl ether also produce tranquilizing effects (Bowen, Wiley, and Balster, 1996; Paéz-Martinez, Cruz, and López-Rubalcava, 2003). Bowen and colleagues (2006) concluded that "the anxiolytic [anxiety reducing] effects of solvents are not an unexpected finding since these compounds, like other [central nervous system] depressants, act as positive modulators of $GABA_A$ receptors… [W]hat remains unclear is whether other solvents share these anxiolytic properties, the relative potencies to produce these effects, and whether tolerance (or sensitization) develops after chronic binge exposure."

The neuropharmacological effects of these solvents do not appear to be limited to modulation of the GABA receptor. Drug-discrimination studies using laboratory animals (Bowen et al., 1999) have shown that toluene can induce subjective effects similar to those of the psychedelic anesthetic phencyclidine (PCP), suggesting that toluene, like PCP, may block the NMDA receptor. It should be noted, however, that toluene failed to induce subjective effects similar to those of dizocilpine, another selective NMDA receptor blocker, in a similar drug-discrimination study (Shelton and Balster, 2004).

In support of these behavioral results, recent *in vitro* studies have demonstrated that several abused inhal-

Toluene can induce subjective effects similar to those of phencyclidine (PCP).

FUTURE RESEARCH

Inhalant abuse is one of few types of substance abuse for which demonstrably effective treatment interventions are largely absent from the clinical research literature. Specific areas for future research include:

- Ethnographic studies of cross-national patterns of inhalant use, including products (agents) used and consequences of use;
- Longitudinal studies of the trajectory of inhalant use and inhalant use disorders, including factors that predict initiation, escalation, maintenance, and cessation of use (e.g., Perron et al., 2009b);
- Investigations of the clinical manifestations of inhalant use disorders, including the nature and characteristics of tolerance and withdrawal symptoms across a wide range of abused inhalants;
- Studies of acute and long-term consequences of inhalant use;
- Psychometric evaluations of the reliability, validity, and latent structure of DSM-IV inhalant abuse and dependence diagnoses (e.g., Howard et al., 2001; Howard and Perron, 2009);
- Efficacy trials of combined pharmacological and psychosocial interventions for adolescents and adults with inhalant use disorders;
- Taxonomic efforts to identify subtypes of inhalant users and abusers;
- Evaluations of promising inhalant use prevention interventions; and
- Evaluations of product modification, law enforcement, and other supply-side approaches to reducing the availability of abused inhalants in the social and physical environments.

ants act with varying affinity and efficacy at a number of molecular sites. Toluene appears to cause its central nervous system depressant effects in large part by noncompetitively preventing glutamate stimulation of NMDA NR1 and NR2B receptor subtypes (Bale et al., 2005; Cruz et al., 1998), and prolonged exposure to toluene increases levels of brain NMDA receptors (Williams, Stafford, and Steketee, 2005). Other solvents, including benzene, ethylbenzene, propylbenzene, TCE, and xylene, also antagonize the NMDA receptor (Cruz, Balster, and Woodward, 2000; Raines et al., 2004).

A recent study showed that toluene and alcohol exert opposite effects on two channels that mediate the passage of potassium into and out of brain cells (the large-conductance calcium-activated potassium channel and G protein–coupled inwardly rectifying potassium channel). Alcohol excites these channels, but toluene inhibits them, a finding that eliminates them as likely candidates to underlie effects that toluene and alcohol produce in common (Del Re, Dopico, and Woodward, 2006). Exposure to toluene increases dopamine levels in the rat prefrontal cortex and striatum and increases neuronal firing in the ventral tegmental area in a manner similar to other drugs of abuse, effects that could be integral to the rewarding effects of toluene (Riegel and French, 1999; 2002; Riegel et al., 2004; 2007). Gerasimov and colleagues (2002; 2005) demonstrated that radioactively labeled toluene, butane, and acetone were rapidly taken up and cleared from areas such as the striatal and frontal brain regions of nonhuman primates.

An instrument for assessing abuse of 55 products is available without cost.

SCREENING AND ASSESSMENT

Systematic screening and assessment of inhalant use would facilitate earlier and more effective prevention and treatment, but clinicians appear to have a low index of suspicion for inhalant use and related problems (Anderson and Loomis, 2003). A few attempts have been made internationally to develop paper-and-pencil screening assessments of inhalant use, but these instruments are of limited utility for U.S. practitioners (e.g., Ogel et al., 2005). Howard and colleagues (2008) prepared the Volatile Solvent Screening Inventory (VSSI) and Comprehensive Solvent Assessment Interview (CSAI). The VSSI is freely available, requires approximately 20 minutes to complete, and assesses past-year and lifetime frequency of use of 55 inhalant chemicals and products, medical history, demographic characteristics, current psychiatric symptoms, suicidal thoughts and attempts, trauma history, temperamental traits such as impulsivity, and the frequency and nature of antisocial behavior in the prior year. The CSAI is also free, requires 20 to 90 minutes to complete (depending on the extent of the reported history of inhalant use), and assesses reasons for starting and stopping inhalant use; typical modes, locations, contexts and subjective effects of use; adverse acute consequences of inhalant intoxication; perceived risks of inhalant use; estimated likelihood of future use; sibling and friends' inhalant use; and DSM-IV inhalant abuse and dependence criteria. The reader can access these instruments on the Internet: *dx.doi.org/10.1016/j.drugalcdep.2007.08.023* (Howard et al., 2008).

Efforts are under way to improve laboratory diagnosis of inhalant use and abuse (e.g., Chakroun et al., 2008; Thiesen, Noto, and Barros, 2007), but such tests are not yet widely available, nor have they been implemented in routine clinical practice. Findings from the occupational toxicology and inhalant abuse literature suggest that bioassays for hippuric acid, o-cresol levels, and benzylmercapturic acid may eventually be useful urinary markers of toluene abuse (Broussard, 2000; Chakroun et al., 2008; Çök, Dagdelen, and Gökçe, 2003; Inoue et al., 2004; Ukai et al., 2007).

TREATMENT AND PREVENTION

Few studies have examined pharmacological or psychosocial interventions for those who use inhalants or who have inhalant-induced disorders. Reasons for the lack of studies are unclear. Drug abuse researchers may have been slow to recognize the importance of inhalant use disorders, perhaps because of the stigmatized nature of the behavior. Studies may be difficult to execute because of the social disenfranchisement of inhalant users and their frequent residence in locations that are geographically isolated (e.g., rural settings or reservations) or inhospitable to clinical research (e.g., juvenile or criminal justice facilities or psychiatric hospitals). In addition, people who have inhalant use disorders may be difficult to recruit, assess, and follow because they are typically dependent on multiple drugs and afflicted with comorbid mood, anxiety, and personality disorders.

Treatment programs that specialize in inhalant dependence are almost nonexistent in the United States; only one, the Tundra Swan Inhalant Treatment Program of the McCann Treatment Center in Bethel, Alaska, is currently operating. This center is administered by the Yukon-Kuskokwim Health Corporation and serves 15 to 19 youths at a time, who range in age from 10 to 18 years and reside mostly in nearby rural Alaskan

areas. Treatment services include traditional indigenous cultural practices, such as native dancing, crafts, and sweat lodges, and intensive family involvement. No formal evaluations of the Tundra Swan program have been published.

Nevertheless, substance abuse treatment practitioners express a desire for specialized training in inhalant-related assessment and treatment. Beauvais and colleagues (2002) surveyed 550 program directors in the United States: nearly three-quarters (73.9 percent) responded that inhalant abusers were somewhat-to-substantially more difficult to treat compared with abusers of other drugs, and only 15.1 percent thought current training resources were sufficient. A large survey of agencies serving young people in Wisconsin reported similar findings: 40.6 percent of respondents indicated that inhalant abusers exhibit brain impairments and medical, family, and developmental concerns that are more severe than those of other drug abusers (Malesevich and Jadin, 1995). Survey respondents tended to believe that detoxification and treatment stays should be longer for inhalant abusers than for abusers of other psychoactive drugs. Given the substantial prevalence and serious consequences of inhalant abuse and the virtual absence of specialty inhalant treatment programs in the United States, it is important that practitioners become aware of current inhalant screening and treatment approaches.

Pharmacological Interventions

Pharmacologic treatments for inhalant use disorders have rarely been evaluated. A few studies have documented reductions in psychotic symptoms in inhalant abusers, although it is not clear whether the psychoses were due to or simply comorbid with the inhalant abuse:

- Misra, Kofoed, and Fuller (1999) reported successful use of risperidone to treat paranoid psychosis in a 25-year-old Caucasian man who had been inhaling gasoline and carburetor cleaner almost daily for 5 years and who had failed to fully respond to prior trials with thioridazine and divalproex. Risperidone given at a dosage of 0.5 mg twice daily for 4 weeks reduced auditory and visual hallucinations, paranoia, and aggressive behavior. When the dose of risperidone was increased to 1 mg twice daily, craving for inhalants was significantly reduced, paranoid ideation ceased, and continuous abstinence from inhalants was maintained for 12 weeks. The researchers recommended that risperidone be studied further as a treatment for craving in inhalant-dependent people.
- Hernandez-Avila and colleagues (1998) conducted a randomized trial with 40 psychotic men with histories of inhalant abuse who were treated with either haloperidol or carbamazepine. After 5 weeks of treatment, the men in both the carbamazepine and haloperidol groups showed reductions in symptom severity of 48.3 percent and 52.7 percent, respectively, on the Brief Psychiatric Rating Scale. The investigators concluded that approximately half of the patients in each arm of the study responded to treatment, but that carbamazepine caused fewer side effects.

One case report and one preclinical study have reported positive but very preliminary evidence of potentially effective pharmacotherapies for inhalant dependence. Shen (2007) described the successful treatment of a 21-year-old man who had been using inhalants for 4 years but had no history of other substance abuse problems. When treated with 100 mg of lamotrigine daily, the subject reported fewer cravings for inhalants and achieved 6 months of continuous abstinence without significant side effects from the medication. Lee, Schiffer, and Dewey (2004) reported preclinical evidence suggesting that vigabatrin, a selective GABA transaminase inhibitor, could be an effective treatment for inhalant dependence.

Lamotrigine and vigabatrin have shown potential effectiveness for treating inhalant dependence.

Psychosocial Interventions

Few psychosocial interventions have been tested with inhalant users in the United States. Holistic approaches incorporating elements of traditional indigenous cultures have reportedly been used successfully in Canada (Dell, Dell, and Hopkins, 2005; YSAC Annual Report, 2007) and with aboriginal populations in Australia (Preuss and Brown, 2006). Demand-reduction interventions—including community-based approaches, education, youth and recreation programs, clinical management and counseling, and residential programs—were comprehensively evaluated in a recent Australian report (d'Abbs and MacLean, 2008). The relevance of these findings to an American context is uncertain. The recommendation that treatment be broadly focused on the diverse problems of inhalant users is certainly sensible, as are the notions that aftercare and family involvement are crucial.

D'Abbs and MacLean (2008) addressed the highly controversial topic of harm reduction interventions. These interventions have, for example, encouraged inhalant users to avoid covering their heads with plastic bags to prevent accidental asphyxiation; sniff from containers with small surface areas; avoid inhalation in

enclosed places or in hazardous places such as next to busy roadways; inhale under supervision; take precautions to avoid burns, overdose, and aspiration of vomitus; and avoid inhalants such as butane and propane that pose heightened risk for sudden death. Ethnographic studies indicate that some inhalant users take the initiative to minimize risks associated with their inhalant use (Sandover, Houghton, and O'Donoghue, 1997).

Broadly focused biopsychosocial treatment interventions may well be critically important given the manifold problems of inhalant abusers. Outreach to homeless young people and adults, youths who have dropped out of school or who are frequently truant, people in juvenile or adult correctional facilities or psychiatric hospitals, and inhalant abusers who are not actively seeking treatment is critical.

Several promising prevention strategies have been identified in recent years.

Additional treatment research is also critical, because current findings suggest that inhalant abusers may have comparatively poor treatment outcomes (e.g., Sakai, Mikulich-Gilbertson, and Crowley, 2006).

Prevention

Prevention approaches targeted to inhalant use are uncommon and have not always been successful (e.g., Brown et al., 2007; Collins, Johnson, and Becker, 2007; Furr-Holden et al., 2004). However, several promising prevention strategies have been identified in recent years. Schinke and colleagues evaluated correlates of inhalant use among adolescent girls and subsequently reported significantly reduced inhalant use at a 2-year followup in a randomized controlled trial of a gender-specific, computer-delivered prevention intervention for adolescent girls and their mothers (Schinke, Fang, and Cole, 2008; 2009).

An innovative, integrated approach to inhalant use prevention involving community mobilization efforts, environmental strategies, and school-based activities was described by Johnson and colleagues at the Pacific Institute for Research and Evaluation. They describe results of a related feasibility evaluation (Johnson et al., 2007), explain how the environmental component—designed to reduce retailers' sales of inhalants—can be implemented and evaluated (Courser et al., 2007), and present positive findings from a randomized controlled evaluation of the intervention, which was implemented in frontier Alaskan communities (Johnson et al., 2009). These reports and others that present positive findings regarding inhalant prevention (e.g., Spoth et al., 2007) suggest that comprehensive, theory-informed, and gender-specific prevention approaches may be effective methods for inhalant use prevention.

Supply-side interventions have not been widely applied in the United States, but in Australia they have included adding "bittering" agents to frequently abused inhalant products, selling gasoline substitutes such as aviation fuel or Opal gas that are not readily abused, and modifying products so that they are no longer sought out by abusers of inhalants.

CONCLUSIONS

More than 22 million Americans age 12 and older have used inhalants, and more than three-quarters of a million become new users annually. Inhalant use may lead to inhalant abuse or dependence in less than 10 percent to nearly 50 percent of cases, depending on the characteristics of the population studied. There are many acute and long-term consequences of inhalant use and these can be catastrophic, but far more needs to be learned about the full range of maladies associated with use of specific inhalant products and factors that increase vulnerability for these disorders.

Although some inroads have been made in understanding the pharmacology and neurobiology of inhalant abuse during the past decade, more needs to be learned about similarities and differences of specific abused inhalants. Ethnographic reports suggest that many youths abuse inhalants in order to achieve a euphoric state (d'Abbs and MacLean, 2008); survey findings confirm that young people intentionally abuse inhalants to produce intoxication (Howard et al., 2008); and operant conditioning and other laboratory paradigms suggest that inhalants may act as reinforcers in much the same way as other drugs of abuse (Bowen et al., 2006).

Practitioners should maintain a high index of suspicion for inhalant use, screen for inhalant use and inhalant use disorders, and intervene early in the course of the disorder with educational interventions and approaches that have been used in the treatment of other substance use disorders (e.g., motivational enhancement and relapse prevention interventions). This approach seems reasonable until researchers develop and fully evaluate effective evidence-based interventions for inhalant abusers. Given the high prevalence of conduct, substance use, mood, anxiety, and personality disorders among inhalant abusers, it is important that practitioners also avail themselves of evidence-based interventions for these commonly co-occurring conditions (Hepner et al., 2007; Woolgar and Scott, 2005).

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REFERENCES

American Psychiatric Association, 2000. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.* Washington, D.C.: American Psychiatric Press.

Anderson, C.E., and Loomis, G.A., 2003. Recognition and prevention of inhalant use. *American Family Physician* 68(5):869–874, 876.

Anthony, J.C.; Warner, L.A.; and Kessler, R.C., 1994. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 2(3):244–268.

Avella, J.; Wilson, J.C.; and Lehrer, M., 2006. Fatal cardiac arrhythmia after repeated exposure to 1,1-difluoroethane (DFE). *American Journal of Forensic Medicine and Pathology* 27(1):58–60.

Bale, A.S., et al., 2005. Alterations in glutamatergic and gabaergic ion channel activity in hippocampal neurons following exposure to the abused inhalant toluene. *Neuroscience* 130:197–206.

Balster, R.L., 1996. *Inhalant abuse, a forgotten drug abuse problem.* College on Problems of Drug Dependence Presidential Address 1996, Conference Proceedings.

Beauvais, F., et al., 2002. A survey of attitudes among drug user treatment providers toward the treatment of inhalant users. *Substance Use & Misuse* 37(11):1391–1410.

Blokhina, E.A., et al., 2004. Intravenous self-administration of abused solvents and anesthetics in mice. *European Journal of Pharmacology* 485:211–218.

Bowen, S.E., et al., 1999. Phencyclidine- and diazepam-like discriminative stimulus effects of inhalants in mice. *Experimental and Clinical Psychopharmacology* 7(1):28–37.

Bowen, S.E., et al., 2005. Abuse pattern of gestational toluene exposure and early postnatal development in rats. *Neurotoxicology and Teratology* 27(1):105–116.

Bowen, S.E., et al., 2006. The last decade of solvent research in animal models of abuse: Mechanistic and behavioral studies. *Neurotoxicology and Teratology* 28:636–647.

Bowen, S.E., et al., 2007. Gestational toluene exposure effects on spontaneous and amphetamine-induced locomotor behavior in rats. *Neurotoxicology and Teratology* 29(2):236–246.

Bowen, S.E., et al., 2009. Alterations in fetal morphology following abuse patterns of toluene exposure. *Reproductive Toxicology* 27(2):161–169.

Bowen, S.E., and Balster, R.L., 1998. A direct comparison of inhalant effects on locomotor activity and schedule-controlled behavior in mice. *Experimental and Clinical Psychopharmacology* 6(3):235–247.

Bowen, S.E., and Hannigan, J.J., 2006. Developmental toxicity of prenatal exposure to toluene. *American Association of Pharmaceutical Scientists* 8:E419–E424.

Bowen, S.E., and McDonald, P., 2009. Abuse pattern of toluene exposure alters mouse behavior in a waiting-for-reward operant task. *Neurotoxicology and Teratology* 31(1):18–25.

Bowen, S.E.; Daniel, J.; and Balster, R.L., 1999. Deaths associated with inhalant abuse in Virginia from 1987 to 1996. *Drug and Alcohol Dependence* 53:239–245.

Bowen, S.E.; Hannigan, J.H.; and Cooper, P.B., 2009. Abuse pattern of gestational toluene exposure alters behavior in rats in a "waiting-for-reward" task. *Neurotoxicology and Teratology* 31(2):89–97.

Bowen, S.E.; Wiley, J.L.; and Balster, R.L., 1996. The effects of abused inhalants on mouse behavior in an elevated plus-maze. *European Journal of Pharmacology* 312(2):131–136.

Broussard, L.A., 2000. The role of the laboratory in detecting inhalant abuse. *Clinical Laboratory Science* 13(4):205–209.

Brown, C.H., et al., 2007. Examining the effects of school-based drug prevention programs on drug use in rural settings: Methodology and initial findings. *Journal of Rural Health* 23: 29–36.

Cayir, D., et al., 2011. Evaluation of lung epithelial permeability in the volatile substance abuse using Tc-99, DPTA aerosol scintigraphy. *Annals of Nuclear Medicine,* e-pub ahead of print.

Chakroun, R., et al., 2008. Inhalant abuse detection and evaluation in young Tunisians. *Journal of Forensic Sciences* 53(1):232–237.

Çok, I.; Dagdelen, A.; and Gökçe, E., 2003. Determination of urinary hippuric acid and o-cresol levels as biological indicators of toluene exposure in shoe-workers and glue sniffers. *Biomarkers* 8(2):119–127.

Collins, D.; Johnson, K.; and Becker, B.J., 2007. A meta-analysis of direct and mediating effects of community coalitions that implemented science-based substance abuse prevention interventions. *Substance Use & Misuse* 42(6):985–1007.

Compton, W.M., et al., 1994. Inhalant use: Characteristics and predictors. *American Journal on Addictions* 3(3):263–272.

Condray, R., et al., 2000. Mood and behavioral symptoms in individuals with chronic solvent exposure. *Psychiatry Research* 97:191–206.

Courser, M.W., et al., 2007. An evaluation of retail outlets as part of a community prevention trial to reduce sales of harmful legal products to youth. *Evaluation Review* 31(4):343–363.

Crocetti, M., 2008. Inhalants. *Pediatrics in Review* 29:33–34.

Cruz, S.L., et al., 1998. Effects of the abused solvent toluene on recombinant N-methyl-d-aspartate and non-N-methyl- d-aspartate receptors expressed in *Xenopus* oocytes. *Journal of Pharmacology and Experimental Therapeutics* 286(1):334–340.

Cruz, S.L.; Balster, R.L.; and Woodward, J.J., 2000. Effects of volatile solvents on recombinant N-methyl- d-aspartate receptors expressed in *Xenopus* oocytes. *British Journal of Pharmacology* 131:1303–1308.

d'Abbs, P., and MacLean, S., 2008. *Volatile substance misuse: A review of interventions.* National Drug Strategy, Monograph Series No. 65. Australian Government, Department of Health and Aging.

Del Re, A.M.; Dopico, A.M.; and Woodward, J.J., 2006. Effects of the abused inhalant toluene on ethanol-sensitive potassium channels expressed in oocytes. *Brain Research* 1087(1):75–82.

Dell, C.; Dell, D.E.; and Hopkins, C., 2005. Resiliency and holistic inhalant abuse treatment. *Journal of Aboriginal Health* March:1–13.

Dinwiddie, S.H., 1994. Abuse of inhalants: A review. *Addiction* 89(8):925–939.

Dinwiddie, S.H., 1998. Psychological and psychiatric consequences of inhalants. In: R. Tarter (ed.) *Handbook of Substance Abuse: Neurobehavioral Pharmacology.* New York: Plenum, pp. 269–278.

Evans, E.B., and Balster, R.L., 1991. CNS depressant effects of volatile organic solvents. *Neuroscience & Biobehavioral Reviews* 15(2):233–241.

Finch, C.K., and Lobo, B.L., 2005. Acute inhalant-induced neurotoxicity with delayed recovery. *Annals of Pharmacotherapy* 39:169–172.

Freedenthal, S., et al., 2007. Inhalant use and suicidality among incarcerated youth. *Drug and Alcohol Dependence* 90(1):81–88.

Furr-Holden, C.D.M., et al., 2004. Developmentally inspired drug prevention: Middle school outcomes in a school-based randomized prevention trial. *Drug and Alcohol Dependence* 73(2):149–158.

Gautschi, O.P.; Cadosch, D.; and Zellweger, R., 2007. Postural tremor induced by paint sniffing. *Neurology India* 55(4):393–395.

Gerasimov, M.R., et al., 2002. Study of brain uptake and biodistribution of [^{11}C]toluene in non-human primates and mice. *Life Sciences* 70(23):2811–2828.

Gerasimov, M.R., et al., 2005. Synthesis and evaluation of inhaled [^{11}C]butane and intravenously injected [^{11}C]acetone as potential radiotracers for studying inhalant abuse. *Nuclear Medicine and Biology* 32(2):201–208.

Grant, B.F., et al., 2004. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry* 61:807–816.

Han, B.; Gfroerer, J.C.; and Colliver, J. D., 2010. Associations between duration of illicit drug use and health conditions: Results from the 2005-2007 national surveys on drug use and health. *Annals of Epidemiology* 20(4):289–297.

Hannigan, J.H., and Bowen, S.E., 2010. Reproductive toxicology and teratology of abused toluene. *Systems Biology in Reproductive Medicine* 56(2):184–200.

Hepner, K.A., et al., 2007. The effect of adherence to practice guidelines on depression outcomes. *Annals of Internal Medicine* 147(5):320–329.

Hernandez-Avila, C.A., et al., 1998. Treatment of inhalant-induced psychotic disorder with carbamazepine versus haloperidol. *Psychiatric Services* 49(6):812–815.

Hormes, J.T.; Filley, C.M.; and Rosenberg, N.L., 1986. Neurologic sequelae of chronic solvent vapor abuse. *Neurology* 36(5):698–702.

Howard, M.O., et al., 1999. Inhalant use among urban American Indian youth. *Addiction* 94(1):83–95.

Howard, M.O., et al., 2001. Diagnostic concordance of DSM-III-R, DSM-IV, and ICD-10 inhalant use disorders. *Drug and Alcohol Dependence* 61(3):223–228.

Howard, M.O., et al., 2008. Inhalant use among incarcerated adolescents in the United States: Prevalence, characteristics, and correlates of use. *Drug and Alcohol Dependence* 93(3):197–209.

Howard, M.O., et al., 2010a. Inhalant use, inhalant-use disorders, and antisocial behavior: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Journal of Studies on Alcohol and Drugs* 71(2):201–209

Howard, M.O., et al., 2010b. Suicide ideation and attempts among inhalant users: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Suicide and Life-Threatening Behaviors* 40(3):276–286.

Howard, M.O., and Jenson, J.M., 1999. Inhalant use among antisocial youth: Prevalence and correlates. *Addictive Behaviors* 24(1):59–74.

Howard, M.O., and Perron, B.E., 2009. A survey of inhalant use disorders among delinquent youth: Prevalence, clinical features, and latent structure of DSM-IV diagnostic criteria. *BMC Psychiatry* 9:8. doi:10.1186/1471-244x-9-8.

Inoue, O., et al., 2004. Benzylmercapturic acid is superior to hippuric acid and o-cresol as a urinary marker of occupational exposure to toluene. *Toxicology Letters* 147(2):177–186.

Jacobs, A.M., and Ghodse, A.H., 1988. Delinquency and regular solvent abuse: An unfavourable combination? *British Journal of Addiction* 83(8):965–968.

Johnson, K., et al., 2007. A community prevention intervention to reduce youth from inhaling and ingesting harmful legal products. *Journal of Drug Education* 37(3):227–247.

Johnson, K.W., et al., 2009. Preventing youths' use of inhalants and other harmful legal products in frontier Alaskan communities: A randomized trial. *Prevention Science* 10(4):298–312.

Johnston, L.D., et al., 2007. *Monitoring the Future National Survey Results on Drug Use, 1975-2006.* Vol. I: Secondary school students. NIH Publication Number 07-6205. Bethesda, MD: National Institute on Drug Abuse.

Jones, H.E., and Balster, R.L., 1998. Inhalant abuse in pregnancy. *Obstetrics and Gynecology Clinics of North America* 25(1):153–167.

Jung, I.-K.; Lee, H.-J.; and Cho, B.-H., 2004. Persistent psychotic disorder in an adolescent with a past history of butane gas dependence. *European Psychiatry* 19:519–520.

Karmarker, G.C., and Roxburgh, R., 2008. Rhabdomyolysis in a glue sniffer. *The New Zealand Medical Journal* 121(1271):70–71.

Keriotis, A.A., and Upadhyaya, H.P., 2000. Inhalant dependence and withdrawal symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry* 39(6):679–680.

Korman, M.; Trimboli, F.; and Semler, I., 1980. A comparative evaluation of 162 inhalant users. *Addictive Behaviors* 5:143–152.

Küçük, N.Ö., et al., 2000. Brain SPECT findings in long-term inhalant abuse. *Nuclear Medicine Communications* 21(8):769–773.

Lee, D.E.; Schiffer, W.K.; and Dewey, S.L., 2004. Gamma-vinyl GABA (vigabatrin) blocks the expression of toluene-induced conditioned place preference (CPP). *Synapse* 54(3):183–185.

Lubman, D.I.; Yücel, M.; and Lawrence, A.J., 2008. Inhalant abuse among adolescents: Neurobiological considerations. *British Journal of Pharmacology* 154:316–326.

Malesevich, D., and Jadin, T., 1995. Of huffers and huffing: A survey of adolescent inhalant abuse. In: Center for Substance Abuse Treatment. *Treating Alcohol and Other Drug Abusers in Rural and Frontier Areas: 1994 Award for Excellence Papers*. Technical Assistance Publication Series 17. DHHS Publication Number (SMA) 95-3054. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Maruff, P., et al., 1998. Neurological and cognitive abnormalities associated with chronic petrol sniffing. *Brain* 121:1903–1917.

McGarvey, E.L.; Canterbury, R.J.; and Waite, D., 1996. Delinquency and family problems in incarcerated adolescents with and without a history of inhalant use. *Addictive Behaviors* 21(4):537–542.

Misra, L.K.; Kofoed, L.; and Fuller,W., 1999. Treatment of inhalant abuse with risperidone. *Journal of Clinical Psychiatry* 60(9):620.

Moreno, C., and Beierle, E.A., 2007. Hydrofluoric acid burn in a child from a compressed air duster. *Journal of Burn Care and Research* 28(6):909–912.

Morrow, L.A., et al., 1997. Neuropsychological performance of journeyman painters under acute solvent exposure and exposure-free conditions. *Journal of the International Neuropsychological Society* 3:269–275.

Morrow, L.A., et al., 2000. Increased incidence of anxiety and depressive disorders in persons with organic solvent exposure. *Psychosomatic Medicine* 62:746–750.

Morrow, L.A.; Steinhauer, S.R.; and Condray, R., 1996. Differential associations of P300 amplitude and latency with cognitive and psychiatric function in solvent-exposed adults. *Journal of Neuropsychiatry and Clinical Neurosciences* 8:446–449.

Morrow, L.A.; Steinhauer, S.R.; and Condray, R., 1998. Predictors of involvement in P300 latency in solvent-exposed adults. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 11(3):146–150.

Neumark, Y.D.; Delva, J.; and Anthony, J.C., 1998. The epidemiology of adolescent inhalant involvement. *Archives of Pediatric and Adolescent Medicine* 152:781–786.

O'Brien, E.T.; Yeoman, W.B.; and Hobby, J.A.E., 1971. Hepatorenal damage from toluene in a "glue sniffer." *British Medical Journal* 2:29–30.

Ogel, K., et al., 2005. Development and reliability study of the adolescent inhalant use severity scale. *Turkish Journal of Psychiatry* 16(4):1–7.

Okada, S.-I., et al., 1999. Regional cerebral blood flow abnormalities in chronic solvent abusers. *Psychiatric and Clinical Neurosciences* 53:351–356.

Páez-Martinez, N.; Cruz, S.L.; and López-Rubalcava, C., 2003. Comparative study of the effects of toluene, benezene, 1,1,1-trichloroethane, diethyl ether, and flurothyl on anxiety and nociception in mice. *Toxicology and Applied Pharmacology* 193(1):9–16.

Pearson, M.A., et al., 1994. Toluene embryopathy: Delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 93:211–215.

Perron, B.E., et al., 2009a. Inhalant withdrawal as a clinically significant feature of inhalant dependence disorder. *Medical Hypotheses* 73(6):935–937.

Perron, B.E., et al., 2009b. Prevalence, timing, and predictors of transitions from inhalant use to inhalant use disorders. *Drug and Alcohol Dependence* 100(3):277–284.

Perron, B.E.; Vaughn, M.G.; and Howard, M.O., 2007. Reasons for using inhalants: Evidence for discrete classes in a sample of incarcerated adolescents. *Journal of Substance Abuse Treatment* 34(4):450–455.

Pogorelov, V.M., and Kovalev, G.I., 1999. Dopaminergic involvement in the process of reinforcement from diethyl ether vapor in rats. *Progress in Neuropsychopharmacology & Biological Psychiatry* 23(6):1135–1156.

Preuss, K., and Brown, J.N., 2006. Stopping petrol sniffing in remote aboriginal Australia: Key elements of the Mt. Theo program. *Drug and Alcohol Review* 25:189–193.

Raines, D.E., et al., 2004. The N-methyl-d-aspartate receptor inhibitory potencies of aromatic inhaled drugs of abuse: Evidence for modulation by cation-π interactions. *Journal of Pharmacology and Experimental Therapeutics* 311:14–21.

Ridenour, T.A.; Bray, B.C.; and Cottler, L.B., 2007. Reliability of use, abuse, and dependence on four types of inhalants in adolescents and young adults. *Drug and Alcohol Dependence* 91(1):40–49.

Riegel, A.C., et al., 2004. Repeated exposure to the abused inhalant toluene alters levels of neurotransmitters and generates peroxynitrite in nigrostriatal and mesolimbic nuclei in rat. *Annals of the New York Academy of Sciences* 1025:543–551.

Riegel, A.C., et al., 2007. The abused inhalant toluene increases dopamine release in the nucleus accumbens by directly stimulating ventral tegmental area neurons. *Neuropsychopharmacology* 32:1558–1569.

Riegel, A.C., and French, E.D., 1999. An electrophysiological analysis of rat ventral tegmental dopamine neuronal activity during acute toluene exposure. *Pharmacology and Toxicology* 85:37–43.

Riegel, A.C., and French, E.D., 2002. Abused inhalants and central reward pathways: Electrophysiological and behavioral studies in the rat. *Annals of the New York Academy of Sciences* 965:281–291.

Sakai, J.T., et al., 2004. Inhalant use, abuse, and dependence among adolescent patients: Commonly comorbid problems. *Journal of the American Academy of Child & Adolescent Psychiatry* 43(9):1080–1088.

Sakai, J.T.; Mikulich-Gilbertson, S.K.; and Crowley, T.J., 2006. Adolescent inhalant use among male patients in treatment for substance and behavior problems: Two-year outcome. *American Journal of Drug and Alcohol Abuse* 32(1):29–40.

Sandover, R.; Houghton, S.; and O'Donoghue, T., 1997. Harm minimization strategies utilized by incarcerated aboriginal volatile substance users. *Addiction Research* 5(2):113–136.

Schinke, S.P.; Fang, L.; and Cole, K.C.A., 2008. Substance use among early adolescent girls: Risk and protective factors. *Journal of Adolescent Health* 43(2):191–194.

Schinke, S.P.; Fang, L.; and Cole, K.C.A., 2009. Computer-delivered, parent-involvement intervention to prevent substance use among adolescent girls. *Preventive Medicine* 49(5):429–435.

Schloneger, M.M.; Stull, A.; and Singer, J.I., 2009. Inhalant abuse: A case of hemoptysis associated with halogenated hydrocarbons. *Pediatric and Emergency Care* 25(11):754–757.

Sharp, C.W., and Rosenberg, N.L., 2005. Inhalants. In: J.H. Lowinson, P. Ruiz, R.B. Millman, and J.G. Langrod (eds.), *Substance Abuse: A Comprehensive Textbook.* Philadelphia: Lippincott Williams and Wilkins.

Shelton, K.L., and Balster, R.L. (2004). Effects of abused inhalants and GABA-positive modulators in dizocilpine discriminating inbred mice. *Pharmacology Biochemistry and Behavior* 79:219–228.

Shen, Y.-C., 2007. Treatment of inhalant dependence with lamotrigine. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 31(3):769–771.

Siqueira, L.M., and Crandall, L.A., 2006. Inhalant use in Florida youth. *Substance Abuse* 27(4): 27–35.

Spoth, R., et al., 2007. Substance-use outcomes at 18 months past baseline: The PROSPER Community-University Partnership Trial. *American Journal of Preventive Medicine* 32(5):395–402.

Stollery, B.T., 1996. Long-term cognitive sequelae of solvent intoxication. *Neurotoxicology and Tetratology* 18(4):471–476.

Storr, C.L.; Westergaard, R.; and Anthony, J.C., 2005. Early onset inhalant use and risk for opiate addiction by young adulthood. *Drug and Alcohol Dependence* 78:253–261.

Substance Abuse and Mental Health Services Administration (SAMHSA), Office of Applied Studies, 2005. *Inhalant Use and Delinquent Behaviors among Young Adolescents.* National Survey on Drug Use and Health, The NSDUH Report, March 17.

SAMHSA, Office of Applied Studies, 2006. *Characteristics of Recent Adolescent Inhalant Initiates.* The NSDUH Report, Issue 11.

SAMHSA, Office of Applied Studies, 2008a. *Inhalant Use and Major Depressive Episode among Youths Aged 12 to 17: 2004 to 2006.* The NSDUH Report, August 21.

SAMHSA, Office of Applied Studies, 2008b. *Inhalant Use Across the Adolescent Years.* The NSDUH Report, March 13.

Takaki, A., et al., 2008. A 27-year-old man who died of acute liver failure probably due to trichloroethylene abuse. *Journal of Gastroenterology* 43(3):239–242.

Tenebein, M., 1993. Neonatal abstinence syndrome due to maternal inhalant abuse. *Clinical Research* 41:298.

Tenebein, M., and Pillay, N., 1993. Sensory evoked potential in inhalant (volatile solvent) abuse. *Journal of Pediatrics and Child Health* 29(3):206–208.

Thiesen, F.V.; Noto, A.R.; and Barros, H.M.T., 2007. Laboratory diagnosis of toluene-based inhalants abuse. *Clinical Toxicology* 45(5):557–562.

Twardowschy, C.A., et al., 2008. Optic neuritis due to solvent abuse. *Arquivos de Neuro-Psiquiatria* 66(1):108–110.

Ukai, H., et al., 2007. Comparative evaluation of biomarkers of occupational exposure to toluene. *International Archives of Occupational and Environmental Health* 81(1):81–93.

Vaughn, M.G.; Perron, B.E.; and Howard, M.O., 2007. Variations in social contexts and their effect on adolescent inhalant use: A latent profile investigation. *Drug and Alcohol Dependence* 91(2-3):129–133.

von Euler, M., et al., 2000. Inhalation of low concentrations of toluene induces persistent effects on a learning retention task, beam-walk performance, and cerebrocortical size in the rat. *Experimental Neurology* 163:1–8.

Williams, J.M.; Stafford, D.; and Steketee, J.D., 2005. Effects of repeated inhalation of toluene on ionotropic $GABA_A$ and glutamate receptor subunit levels in rat brain. *Neurochemistry International* 46:1–10.

Wiseman, M.N., and Banim, S., 1987. "Glue-sniffer's heart?" *British Medical Journal* 294:739.

Woolgar, M., and Scott, S., 2005. Evidence-based management of conduct disorders. *Current Opinion in Psychiatry* 18(4):392–396.

Wu, L.T., and Howard, M.O., 2007a. Is inhalant use a risk factor for heroin and injection drug use among adolescents in the United States? *Addictive Behaviors* 32(2):265–281.

Wu, L.T., and Howard, M.O., 2007b. Psychiatric disorders in inhalant users: Results from The National Epidemiologic Survey on Alcohol and Related Conditions. *Drug and Alcohol Dependence* 88:146–155.

Wu, T.; Howard, M.O.; and Pilowsky, D.J., 2008. Substance use disorders among inhalant users: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addictive Behaviors* 33:968–973.

Wu, L.T.; Pilowsky, D.J.; and Schlenger, W.E., 2004. Inhalant abuse and dependence among adolescents in the United States. *Journal of the American Academy of Child and Adolescent Psychiatry* 43(10):1206–1214.

Yamanouchi, N., et al., 1998. Central nervous system impairment caused by chronic solvent abuse—A review of Japanese studies on the clinical and neuroimaging aspects. *Addiction Biology* 3(1):15–27.

Youth Risk Behavior Surveillance–United States, 2007. *Morbidity and Mortality Weekly Report,* 57:1–134.

Youth Solvent Addiction Committee Annual Report, 2007.

Zaidi, S.A., et al., 2007. Multi-organ toxicity and death following acute unintentional inhalation of paint thinner fumes. *Clinical Toxicology* 45(2):287–289.