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REVIEW

# Inhalant abuse among adolescents: neurobiological considerations

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Experimentation with volatile substances (inhalants) is common during early adolescence, yet limited work has been conducted examining the neurobiological impact of regular binge use during this key stage of development. Human studies consistently demonstrate that chronic use is associated with significant toxic effects, including neurological and neuropsychological impairment, as well as diffuse and subtle changes in white matter. However, most preclinical research has tended to focus on acute exposure, with limited work examining the neuropharmacological or toxicological mechanisms underpinning these changes or their potential reversibility with abstinence. Nevertheless, there is growing evidence that commonly abused inhalants share common cellular mechanisms, and have similar actions to other drugs of abuse. Indeed, the majority of acute behavioural effects appear to be underpinned by changes in receptor and/or ion channel activity (for example, $GABA_A$, glycine and $5HT_3$ receptor activation, NMDA receptor inhibition), although nonspecific interactions can also arise at high concentrations. Recent studies examining the effects of toluene exposure during the early postnatal period are suggestive of long-term alterations in the function of NMDA and $GABA_A$ receptors, although limited work has been conducted investigating exposure during adolescence. Given the critical role of neurotransmitter systems in cognitive, emotional and brain development, future studies will need to take account of the substantial neuromaturational changes that are known to occur in the brain during childhood and adolescence, and to specifically investigate the neuropharmacological and toxicological profile of inhalant exposure during this period of development.
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**Abbreviations:** MRI, magnetic resonance imaging; PN, postnatal day; VTA, ventral tegmental area

## Introduction

The deliberate inhalation of volatile substances ('inhalants') can cause serious harm to the integrity of the CNS and disrupt normal trajectories of psychological, emotional and neurobiological development (Balster, 1998; Kurtzman *et al*., 2001; Bowen *et al*., 2006; Lubman *et al*., 2006). Historically, volatile substances (for example, nitrous oxide, chloroform and ether) were popularly inhaled by adult populations for intoxication in the late nineteenth and early twentieth centuries. However in recent times, inhalant use has emerged as a relatively common problem among children and adolescents. Adolescent glue sniffing was first noted in the United States during the 1940s, with reports of petrol sniffing subsequently appearing during the following decade. Today, the inhalation of volatile substances by adolescents is practiced worldwide, although there is marked variability in the type and pattern of substances abused.

Sniffing the fumes of aerosol spray paint or 'chroming' is the most popular form of inhalant abuse within Australia, whereas petrol sniffing remains a significant problem for indigenous communities, especially within remote settings (Cairney *et al*., 2002; Lubman *et al*., 2006). In Britain, inhalant abuse frequently involves butane gas from lighter refills, and has been associated with numerous deaths (Field-Smith *et al*., 2001). However, preventing and treating affected youth is difficult due to the complex psychosocial issues that these individuals typically face (for example, unstable and dysfunctional families, state-based care, school absenteeism, forensic issues, comorbid drug use and mental health problems) (Lubman *et al*., 2006). Despite long-standing awareness of the significant morbidity and mortality associated with inhalant abuse, neuropharmacological research has been comparatively sparse until recently, with limited data available on neurobiological sequelae or effective treatment approaches. For these reasons, inhalant

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abuse is increasingly gaining the attention of researchers, health providers, politicians and the public.

## Epidemiology

Although both Australian and American population and school-based surveys consistently document high rates of experimental inhalant use during early adolescence (up to 26% of 12-year-old students), fortunately only a minority of teenagers report inhaling on a regular basis (up to 4%), (Johnston *et al*., 2003; White and Hayman, 2004). Nevertheless, the actual rate of inhalant abuse among young people is likely to be somewhat higher as young people at high risk of becoming regular users (for example, the homeless and non-school attendees) are unlikely to be included within such surveys. Epidemiological figures are also likely to be affected by the episodic and cyclical nature of inhalant abuse among youth populations, such that brief periods of intensive use within distinct locations may not be accurately captured.

Studies in the United States and Australia report few overall significant differences in lifetime inhalant use by gender among adolescents (White, 2001), although in the lower grades girls tend to report higher rates of lifetime use than boys, whereas use is more prevalent among boys in the upper grades (Johnston *et al*., 2003). In terms of regular use, rates among older students tend to be about twice as high among male subjects as female subjects (weekly use among 17-year olds: male subjects 2.2%; female subjects 1.1%) (White, 2001), and this continues into adulthood (0.4% cf. 0.1% in adults aged 26 or older) (SAMHSA, 2001). This is also the pattern seen in clinical populations, where there is a preponderance of male inhalant users accessing treatment (Morton, 1987; Sakai *et al*., 2004).

Young people from low-income, chaotic, fractured or abusive households appear to have the highest rates of use (see Oetting *et al*., 1988 for a review), but high rates have also been reported across disparate indigenous communities (Beauvais and Oetting, 1988; Chalmers, 1991). In these communities, both in Australia and North America, lifetime prevalence rates of petrol sniffing among adolescents are reported to be as high as 50–60%, and appear to be associated with the isolation (both geographical and social), poverty and unemployment prominent among these marginalized groups, rather than cultural issues (Cairney *et al*., 2002). High rates of inhalant abuse have also been documented among street children living in South America, Eastern Europe and Asia (Forster *et al*., 1996; Pagare *et al*., 2004). Neumark *et al*. (1998) reported that 77% of inhalant-using adolescents in the United States used for more than 1 year, 47% for more than 2 years, with 10% using for more than 6 years. However, petrol sniffing in indigenous communities, especially in rural and remote settings, may continue in combination with alcohol and other drug abuse for time periods in excess of 10 years (Oetting *et al*., 1988; Brady and Torzillo, 1994; Burns *et al*., 1995). Chronic users typically have histories of numerous social difficulties, disadvantaged backgrounds and high levels of psychological problems (Oetting *et al*., 1988; Lubman *et al*., 2006), suggesting that these young people may abuse inhalants to help cope with underlying emotional and social distress.

## Compounds abused

Inhalants encompass a broad range of volatile compounds (see Box 1), such as nitrites, anaesthetic gases and organic solvents. This review particularly focuses on the latter category, as these compounds are most commonly misused by adolescents. However, a number of excellent early reviews discussing the neuropharmacology of nitrites and anaesthetic gases are available for the interested reader (Evans and Balster, 1991; Dinwiddie, 1994; Balster, 1998).

Organic solvents are easily accessible to young people, as they are found in numerous readily available household and commercial products (for example, paint products, glues, petrol, correction fluid, lighter fuel and aerosols), and are cheap and legal. Such products typically contain a mixture of solvents, including aliphatic hydrocarbons (for example, isobutane, *n*-butane, *n*-hexane and propane), aromatic hydrocarbons (for example, toluene and xylene), chlorinated hydrocarbons (for example, tetrachloroethylene, 1,1,1-trichloroethane and trichloroethylene) and ketones (for example, acetone, butanone and methyl iso-butyl ketone) (Ramsey *et al*., 1989). However, it is toluene (also known as methylbenzene or phenylmethane), a clear and colourless flammable liquid commonly used as an industrial solvent in the manufacturing of paints, chemicals, pharmaceuticals and rubber, that appears to have the highest potential for abuse.

**Box 1** Inhalants and their common chemical constituents

*Volatile solvents*
- Correction fluids (1,1,1-trichloroethane)
- Dry-cleaning fluids (trichloroethylene, 1,1,1-trichloroethane)
- Glues (*n*-hexane, toluene, xylene)
- Nail polish remover (acetone, esters)
- Paint thinners and removers (dichloromethane, toluene, xylene)
- Petrol (benzene, *n*-hexane, toluene, xylene)

*Aerosols (may contain chlorofluorocarbons and fluorocarbon propellants)*
- Deodorants and hairsprays
- Fabric protector sprays
- Spray paints (toluene, methyl isobutyl ketone)
- Vegetable oil sprays

*Gases*
- Bottled gas (propane)
- Cigarette lighter fluid (butane)
- Medical anaesthetics (ether, chloroform, nitrous oxide)
- Whipped cream (nitrous oxide)

*Nitrites*[a]
- Amyl nitrites

[a]Nitrites are often not considered under the umbrella of inhalant abuse due to differences in epidemiology, neurochemistry, direct effects and reasons for use (primarily used as sexual enhancers).

Given their highly lipophilic nature, organic solvents have rapid access to the brain (peaking within 1–3 min in primates and rodents), although the brain/blood ratio remains high for an extended period (Gerasimov, 2004; Gerasimov *et al*., 2005). Animal imaging studies also report high uptake and slower clearance in white matter compared with other brain regions (Gerasimov, 2004), indicating higher levels of exposure. Aliphatic hydrocarbons are generally eliminated unchanged via respiration, whereas aromatic hydrocarbons tend to be converted to hydrophilic metabolites, via the hepatic microsomal system, before being excreted in the urine. However, the psychopharmacology of inhalants has been largely characterized in workers following occupational exposure, and it is unclear whether the pharmacokinetics are similar in young users simultaneously exposed to high concentrations of multiple solvents (Dinwiddie, 1994).

Young people typically abuse volatile substances by deliberately inhaling available vapours 15–20 times over a relatively brief period (for example, 10–15 min). This results in very high concentrations being inhaled (>6000 p.p.m.), although the exact concentration typically varies by compound (Bowen *et al*., 2006). 'Sniffing' involves direct inhalation from a container or a piece of clothing sprayed with the substance. Some users attempt to increase the amount of available vapours by heating the substance first, or by holding a soaked cloth over the nose or mouth (that is, 'huffing'). 'Bagging' further increases the concentration of inhaled vapours, and involves breathing from a paper or plastic bag containing the volatile substance. Typically, experimental use begins with the sniffing of inhalants, gradually progressing through huffing and bagging as their misuse escalates (Henretig, 1996).

## Neuropharmacological effects of inhalants: cellular level

Compared with other drugs of abuse, relatively little work has been undertaken exploring the neurobiology of inhalant misuse. Nevertheless, over the past decade, considerable preclinical research has been conducted investigating the effects of acute inhalant exposure in adult animals (see Bowen *et al*., 2006 for a comprehensive review). Although the psychopharmacological profile of commonly abused inhalants differ, there is increasing evidence that they act upon common molecular targets. The majority of behavioural effects occur at micromolar inhalant concentrations, and appear to be underpinned by changes in receptor activity and/or membrane ion channels (Bowen *et al*., 2006). Nonspecific interactions, via altered membrane permeability, can also arise at high concentrations (Bowen *et al*., 2006).

Acute solvent exposure appears to produce NMDA receptor inhibition, with the NR1–NR2B subunit combination the most sensitive to inhibition (Bowen *et al*., 2006). Cruz *et al*. (1998) reported that toluene produces a rapid, non-competitive, almost complete and reversible inhibition of the cationic currents through NMDA receptors, using recombinant receptors expressed in *Xenopus* oocytes ($IC_{50} = 0.17$ mM). This effect was not due to nonspecific membrane changes as membrane integrity was only affected at high concentrations (>20 mM). Bale *et al*. (2005b) demonstrated similar acute inhibition of NMDA receptors in cultured rat hippocampal neurons ($IC_{50} = 1.5$ mM). Interestingly, however, this study also examined semi-chronic (4 days) exposure to toluene and noted an increase in NMDA-evoked responses with a decrease in GABA-evoked responses. In parallel, NMDA receptor subunits (NR2A and NR2B) were upregulated (Bale *et al*., 2005b). Collectively, these findings would be consistent with a hyperexcitability/hyper-glutamatergic state during withdrawal following chronic exposure, a situation that similarly occurs during withdrawal from alcohol (for example, Chen *et al*., 1999). Previous reports have found that inhalation of 575 p.p.m. toluene in rats achieves a brain concentration of 18 p.p.m. (Benignus *et al*., 1981), suggesting that approximately 3% of the inhaled dose accesses the brain within the conditions employed. Consequently, within *in vitro* preparations, an $IC_{50}$ of 1.5 mM (as described above) equates to an inhalation exposure of approximately 4600 p.p.m. (the molecular weight of toluene being 92.13 g mol$^{-1}$), which is consistent with binge concentrations inhaled by most human users.

Using expression of receptor subunits in *Xenopus* oocytes, acute solvent administration (0.3–2 mM) has been found to increase $\alpha1\beta1$ $GABA_A$, $\alpha1$ glycine and $5HT_3$ receptor activation (Beckstead *et al*., 2000; Lopreato *et al*., 2003). There is also evidence that toluene and perchloroethylene acutely inhibit nicotinic ACh receptors (particularly $\alpha4\beta2$, $\alpha3\beta2$ and $\alpha7$ subunits) (Bale *et al*., 2002, 2005a), whereas acute toluene exposure has been shown to regulate hippocampal muscarinic receptor binding (Tsuga and Honma, 2000). Interestingly, toluene (0.5 mM) inhibits calcium-dependent potassium channels and G-protein-coupled, inwardly rectifying potassium channel-mediated currents in oocytes, an effect that is opposite to ethanol within this system (Del Re *et al*., 2006). Although experiments in oocytes are difficult to compare with *in vivo* research, the effective concentrations of toluene concur with studies in both animals and humans (Benignus *et al*., 1981; Garriott *et al*., 1981). Recent preliminary work in cell expression systems suggests that toluene acutely disrupts the activity of numerous voltage-gated ion channels (Cruz *et al*., 1998; Beckstead *et al*., 2000; Bale *et al*., 2005b), calcium signalling (Westerink and Vijverberg, 2002), ATPases (Calderon-Guzman *et al*., 2005) and G proteins (Tsuga *et al*., 1999; Tsuga and Honma, 2000), although further research is needed to determine the behavioural implications of these findings.

## Neuropharmacological effects of inhalants: receptor expression/neurochemistry

Chronic toluene exposure has a myriad of effects on brain chemistry and receptor expression. For example, 80 p.p.m. toluene for 6 h a day, 5 days a week over 3 months resulted in reduced [$^3$H]neurotensin binding in the orbital cortex, but increased accumbal binding of [$^3$H]etorphine to opioid receptors (von Euler *et al*., 1988). More recently, acute toluene exposure was shown to increase μ-opioid receptor protein in brain stem nuclei, including the dorsal raphe and periaqueductal grey (Saracibar *et al*., 2001), whereas seven

daily injections of toluene (600 mg kg$^{-1}$ i.p.) increased dopamine and serotonin levels in rat basal ganglia (Riegel *et al*., 2004). In addition, complex, time-dependent changes in the levels of 3-nitrotyrosine in the caudate and accumbens were interpreted as a potential index of oxidative stress (Riegel *et al*., 2004).

Williams *et al*. (2005) exposed rats to toluene (8000 p.p.m.) for 10 days (30 min day$^{-1}$) and demonstrated increased NR1 and NR2B receptor subunits in the medial prefrontal cortex and NR2B subunits in the nucleus accumbens, suggesting an increase in neuronal excitability with prolonged exposure. Chronic exposure was also found to increase $GABA_A$ $\alpha$1 subunit levels in the medial prefrontal cortex, but decrease expression in the ventral mesencephalon (Williams *et al*., 2005). Although such findings highlight the potential for excitotoxic neuronal damage with chronic inhalant exposure, most human studies have reported relatively more damage to white matter structures and the lipid component of the myelin sheath (Rosenberg *et al*., 1988a; Filley *et al*., 2004). However, the cellular mechanisms underpinning this toxic damage remain undetermined. Animal studies that have attempted to elucidate the pathophysiological mechanisms of toluene encephalopathy tend to suggest that gliosis and activation of astrocytes in white matter, as opposed to neuronal death, is the main mechanism responsible (Huang *et al*., 1992, 1993; Gotohda *et al*., 2000). In line with this notion, Aydin *et al*. (2003) used magnetic resonance spectroscopy to demonstrate decreased levels of *N*-acetylaspartate (a metabolite produced within neuronal mitochondria that reflects neuronal density and functional viability) and increased myoinositol-containing compounds in a sample of chronic users. These findings suggest that inhalant abuse does not cause active demyelination or breakdown in the neuronal membrane, but rather, may lead to impaired functional viability as a result of diffuse axonal injury.

## Neuropharmacological effects of inhalants: behaviour

Like other drugs of abuse, inhalants appear to be reinforcing due to their ability to modulate mesolimbic dopaminergic activity. Toluene (300, 750 and 1000 mg kg$^{-1}$ i.p.) has been shown to induce c-fos activation in both the ventral tegmental area (VTA) and nucleus accumbens (Lo and Chen, 2005). Using *in vitro* electrophysiology, Riegel *et al*. (2007) have recently demonstrated that toluene (370 $\mu$M) stimulates mesoaccumbal neurotransmission in both adolescent postnatal day (PN) (19–40) and adult (PN 60) brain slices by selectively activating VTA dopaminergic neurons directly, and that this persisted when synaptic transmission was reduced. Perfusion of toluene ($\geqslant$3 mM) directly into the VTA increased dopamine concentrations within both the VTA and the nucleus accumbens, suggesting that there are increases in somatodendritic dopamine release within the VTA as a consequence of increased neuronal firing. Further, microdialysis revealed that toluene was more effective in increasing dopamine concentrations within the nucleus accumbens when infused directly into the posterior compared with the anterior VTA, and was completely ineffective when administered adjacent to the VTA. The authors have previously demonstrated the physiological relevance of their paradigms to typical human exposure levels (Riegel *et al*., 2003), and both findings are consistent with research examining the neuropharmacological effects of other psychoactive drugs within the mesolimbic system (Rodd-Henricks *et al*., 2000; Adell and Artigas, 2004; Zangen *et al*., 2006). Long-term exposure to toluene has been found to induce persistent dopaminergic dysfunction within the rat basal ganglia, which is associated with enduring behavioural and cognitive deficits (Hillefors-Berglund *et al*., 1995; Cintra *et al*., 1999; von Euler *et al*., 2000). Although such work suggests exposure to toluene may be neurotoxic in animals, much less is known about the neurobiological and associated behavioural consequences of long-term toluene exposure in humans.

Although studying the neural basis of inhalant self-administration has not been possible in animal models as yet (although a successful intravenous model has recently been reported in mice; Blokhina *et al*. (2004)), animals reliably demonstrate conditioned place preference to a range of commonly abused inhalants (Yavich *et al*., 1994; Funada *et al*., 2002; Lee *et al*., 2006). Inhaled toluene can act as a discriminative stimulus (>4000 p.p.m.), and mice can be trained to selectively discriminate inhaled toluene over isoflurane or ethylbenzene in a time-dependent manner (Shelton, 2007). Further drug discrimination studies have also demonstrated that toluene and other abused inhalants share discriminative stimulus effects with a variety of classic CNS depressants, such as ethanol (1–1.25 g kg$^{-1}$ i.p.), oxazepam (up to 20 mg kg$^{-1}$ i.p.) and pentobarbital (20 mg kg$^{-1}$ i.p.) (Evans and Balster, 1991). More recent studies have reported that inhalants may substitute for a wider range of drugs than previously thought, including partially with phencyclidine (Bowen *et al*., 1999) and amphetamine (Bowen, 2006), supporting the notion of cross-sensitization between inhalants and other drugs of abuse.

Similar to other CNS depressants, inhaled toluene tends to produce a dose-related continuum of effects that progress from motor excitation at low concentrations (that is, 500–4000 p.p.m.) to sedation, motor impairment and anaesthesia at higher concentrations (6000–15 000 p.p.m.) (Evans and Balster, 1991; Bowen *et al*., 2006). However, the locomotor stimulant properties of toluene in rodents can be markedly attenuated by lesioning accumbal dopaminergic terminals with 6-hydroxydopamine or by systemic treatment with the mGluR2/3 agonist LY379268 (Riegel *et al*., 2003). Prolonged exposure to high concentrations of toluene can result in coma and subsequent death (as a result of respiratory depression). In general, inhalant exposure results in biphasic changes in motor activity and operant behaviour (increasing activity at low doses and decreasing it at high doses), similar to other CNS depressants (Evans and Balster, 1991; Bowen *et al*., 2006). Although some inhalants have proconvulsant properties (for example, the $GABA_A$ antagonist flurothyl), most of the commonly abused solvents have anticonvulsant effects (Evans and Balster, 1991; Bowen *et al*., 2006), probably as a consequence of their activity on NMDA and $GABA_A$ receptors. Repeated toluene exposure produces sensitization

to its motor-increasing effects (Himnan, 1984), and has also been shown to enhance cocaine's motor-increasing effects (cross-sensitization), suggesting that they share a common neurochemical pathway (Beyer *et al*., 2001).

Consistent with the animal data, acute inhalant exposure in human subjects results in short-lived excitation, as well as subjective feelings of euphoria and light-headedness (Kurtzman *et al*., 2001). Intoxicated users feel less inhibited, making them more likely to act impulsively or take risks. Continued use leads to dizziness, sleepiness, slurred speech, blurred vision and headaches. At this stage, users may appear confused, ataxic or begin responding to hallucinations. With higher doses, further CNS depression occurs, which may result in seizures, coma and even cardiopulmonary arrest (Kurtzman *et al*., 2001).

Users are at risk of suffocation or burns from exploding solvents, although deaths among young people are largely associated with 'sudden sniffing death' or accidental injury as a result of impulsive risk taking and impaired motor skills while intoxicated. Between 1971 and 1999, 1857 deaths were attributed to inhalants in the UK (Field-Smith *et al*., 2001), the majority of whom were male subjects (87%) and under the age of 20 years (66%; mostly aged 14–18 years). There is no apparent safe level of use, with even first-time experimental users at risk of sudden sniffing death as a result of cardiac arrhythmias (particularly after abuse of toluene, chlorofluorocarbons and butane) (Bass, 1970). Indeed, of the 73 UK individuals who died in 1999, 43% had no previous evidence of inhalant use (Field-Smith *et al*., 2001). Inhalants appear to sensitize the myocardium to endogenous catecholamines, which may result in fatal ventricular arrhythmias if the user is startled or agitated (Kurtzman *et al*., 2001). Cruz *et al*. (2003) recently demonstrated that toluene reversibly inhibits cardiac voltage-activated sodium channels in a concentration-dependent manner, which may partially explain their arrhythmogenic effects. The practice of spraying inhalants directly into the mouth is also potentially fatal, as the cooling agents within aerosols can produce death by asphyxiation (via a frozen larynx) or pulmonary oedema (Chalmers, 1991).

## Chronic effects of inhalants

*Medical complications*

Chronic inhalant use is associated with significant toxic effects, including neurological, renal, hepatic and pulmonary damage (Marjot and McLeod, 1989; Dinwiddie, 1994; Kurtzman *et al*., 2001). Persistent neurological deficits have been associated with regular long-term exposure (Fornazzari *et al*., 1983; Hormes *et al*., 1986; Lolin, 1989), and include peripheral neuropathy, cerebellar dysfunction, cranial nerve damage, cortical atrophy, encephalopathy and dementia. However, these studies typically comprise small samples of adult users referred for treatment, and are confounded by other potential causes of neurological damage (for example, head injury and hypoxia), as well as other substance abuse. In fact, in a comprehensive review of this area, Lolin (1989) concluded that apart from peripheral neuropathy, clinical features of neurological toxicity are generally nonspecific, with no evidence of a clear dose–response relationship. However, there does appears to be a clearer relationship between the nature of neurological damage and the type of chemicals involved (Spencer and Schaumburg, 1985), especially in relation to toluene and *n*-hexane (Lolin, 1989). In fact, there is strong evidence that chronic abuse of both *n*-hexane (a constituent of petrol and many glues) and methyl *n*-butyl ketone (a constituent of many paints) is strongly associated with peripheral neuropathy, whereas chronic toluene abuse is associated with cerebellar disease, encephalopathy and dementia (Lolin, 1989). There is also increasing evidence that there is strong relationship between neurological abnormalities and frequency and duration of exposure (Maruff *et al*., 1998). Maruff *et al*. (1998) reported high rates of subtle neurological abnormalities in a group of non-encephalopathic chronic petrol abusers, with a strong correlation between length of use and the magnitude of neurological deficits. A follow-up study found that the severity of these abnormalities reduced with abstinence, and even normalized completely in some subjects (Cairney *et al*., 2005).

A number of renal disorders are associated with chronic inhalant abuse (especially toluene-containing compounds), including renal tubular acidosis, urinary calculi, glomerulonephritis and renal failure (O'Brien *et al*., 1971; Zimmerman *et al*., 1975; Streicher *et al*., 1981; Kaneko *et al*., 1992). Toxic hepatitis and hepatic failure have also been documented (O'Brien *et al*., 1971), whereas benzene is associated with bone marrow suppression, resulting in leukaemia, lymphoma and aplastic anaemia (Powars, 1965; Kurtzman *et al*., 2001). The most common pulmonary effects are due to direct damage to pulmonary tissue or are related to asphyxiation, although some hydrocarbon compounds may also cause chemical pneumonitis (Dinwiddie, 1994).

Inhalant misuse during pregnancy is associated with significant risks, as inhalants readily cross the placenta (Jones and Balster, 1998). There is an increased risk of spontaneous abortion and premature labour (Jones and Balster, 1998), as well as withdrawal symptoms in the neonate (Tenenbein *et al*., 1996). Toluene abuse is consistently associated with infant malformation, including similar craniofacial deformities as those seen with fetal alcohol syndrome (Pearson *et al*., 1994; Jones and Balster, 1998). Animal studies also demonstrate that repeated high-dose maternal toluene exposure adversely affects prenatal development and early postnatal maturation of pups, producing significant developmental delays (Bowen *et al*., 2006). Bowen *et al*. (2007b) recently reported that prenatal exposure to high binge-like concentrations of toluene (8000 or 12 000 p.p.m. for 15 min twice daily from gestation day 8 through 20) significantly altered later spontaneous and amphetamine-induced locomotor behaviour. Such findings highlight the long-lasting deleterious impact of inhalant exposure during key developmental periods.

Although chronic inhalant exposure is associated with significant toxic effects, the mechanism by which different volatile substances damage tissues and organ systems remains unclear. This issue is further complicated by the fact that many products contain more than one type of inhalant. Furthermore, there are limited data addressing the

impact of volatile substances on developmental age or gender. As such, the incidence and nature of significant medical complications among this population are largely unknown, as is the extent to which these effects are reversible following abstinence.

*Neuropsychological and neurobiological complications*

Although severe neurological effects of chronic inhalant exposure have been documented in adults, very little is known about the neurobiological and neuropsychological effects of exposure to this class of drugs on the human brain, especially during the developmental period between childhood and adolescence. Clinical studies investigating this question are few and have been criticized on methodological grounds (see Chadwick and Anderson, 1989b; Yücel *et al*., 2008). Nevertheless, there is consistent evidence that chronic long-term use is likely to result in neurological deficits and cognitive impairment, including impaired attention, speed of information processing, psychomotor coordination, learning and memory, executive abilities (including working memory), as well as tests of verbal intelligence (Chadwick *et al*., 1989a; Maruff *et al*., 1998; Cairney *et al*., 2002; Rosenberg *et al*., 2002; Yücel *et al*., 2008). Interestingly, many of the commonly observed neuropsychological deficits (for example, impairments in processing speed, sustained attention, memory retrieval, executive function and language) are consistent with white matter pathology, further supporting the notion that toluene preferentially affects white matter (relative to grey matter) structures (see Yücel *et al*., 2008). Studies in animal models support the notion of cognitive impairment, although most studies have examined the impact of repeated exposure to solvents at low concentrations. For example, von Euler *et al*. (2000) reported that toluene inhalation (80 p.p.m. for 4 weeks, 6 h $day^{-1}$, 5 days $week^{-1}$) affected spatial memory on the Morris water maze (a hippocampal-dependent task) and reduced beam-walk performance 4 weeks post-exposure. Few animal studies have examined the impact of chronic high-dose exposure on learning and memory processes, particularly during adolescence, nor explored which molecular targets are involved, although NMDA antagonism is likely to be relevant (Bowen *et al*., 2006).

Neuroimaging studies consistently support the notion of long-term harms associated with chronic inhalant exposure, with evidence of diffuse atrophy of the cerebrum, cerebellum and brain stem, sulcal widening and ventricular dilation (Rosenberg *et al*., 1988a, b, 2002; Yamanouchi *et al*., 1995, 1997; Yücel *et al*., 2008). Observed abnormalities appear to be greater in periventricular, subcortical (for example, basal ganglia and thalamus) and white matter regions (relative to cortical and grey matter regions), and are characterized by demyelination, hyperintensities, callosal thinning and loss of grey–white matter boundaries (Yamanouchi *et al*., 1995, 1997; Okada *et al*., 1999; Aydin *et al*., 2003). Although neuroanatomical changes have also been reported in other drug-using samples, structural abnormalities appear to be more common among inhalant abusers (Rosenberg *et al*., 2002). For example, in a recent magnetic resonance imaging (MRI) study comparing 55 inhalant abusers (mean age 30 years) and 61 cocaine abusers (mean age 29 years), structural brain abnormalities were more common (almost 44% compared with 25%) and more extensive in the inhalant-using group, and this group performed significantly worse on tests of working memory and those requiring focused attention, planning and problem solving (Rosenberg *et al*., 2002). Interestingly, even within the inhalant-using group, solvent abusers had more extensive and severe abnormalities in brain white matter than other inhalant users, and these abnormalities were associated with greater cognitive impairment. These findings are in concordance with rodent models of solvent abuse, which also show long-term adverse effects of chronic exposure. For example, using MRI of living rats and autoradiograms of frozen brain sections, von Euler *et al*. (2000) demonstrated a 6–10% decrease in the area of the cerebral cortex (particularly the parietal cortex) in rats exposed to toluene (80 p.p.m. for 4 weeks, 6 h $day^{-1}$, 5 days $week^{-1}$) 4 weeks before. Taken together, these findings support the notion that chronic solvent abuse is associated with neurobiological and cognitive deficits, and that different types of inhalants may be associated with differing patterns of impairments.

Examination of brain perfusion/blood flow is a useful approach for detecting abnormalities early, as they tend to be related to, but precede neuropsychological and structural abnormalities. A recent single photon emission computed tomography study by Okada *et al*. (1999) examined regional abnormalities of cerebral blood flow and their relation to an amotivational syndrome in 16 chronic solvent abusers along with 5 normal subjects (matched only on age; individuals with alcohol/drug dependencies or psychiatric disorders were excluded). This study showed that compared with controls, chronic solvent abusers had statistically significant reductions in regional cerebral blood flow in the prefrontal cortex, bilaterally. In addition, the severity of hypoperfusion in the prefrontal cortices was related to the degree of severity of the avolition-apathy, implying that this frontal hypoperfusion may be a biological substrate for the amotivational state. Another recent study of brain perfusion using single photon emission computed tomography in long-term inhalant abusers found that all 10 subjects had significant and diffuse perfusion abnormalities (Kucuk *et al*., 2000). Subjects in this group were aged between 16 and 18 years, and had been dependent for a mean of 4 years, although all had ceased use approximately 5 months previously. The mean IQ of this group was 84, but this was not different from the control sample of a similar background and socioeconomic status. Although these findings are consistent with the structural and neuropsychological literature and suggest consistent and profound abnormalities of brain perfusion, further studies incorporating larger samples and long-term follow-up are required to reach more specific and substantive conclusions.

Few studies have specifically investigated recovery of function after prolonged exposure to inhalants. Cairney *et al*. (2004, 2005) found significant improvements in previously identified neurobehavioural impairments (that is, palmomental reflexes, postural tremor, saccadic disinhibition, impaired associate learning and attentional dysfunction) following 2 years abstinence from petrol sniffing, and

in many cases, these deficits normalized. However, although those with the greatest levels of impairment showed the greatest degree of improvement with abstinence, they were less likely to recover completely. Several other studies have also reassessed their subjects with further neuropsychological and/or neuroimaging investigations and have reported either greater impairments with continued inhalant use (Ehyai and Freemon, 1983; Caldemeyer *et al*., 1993) or significant improvements following sustained abstinence (Ryu *et al*., 1998). Other studies have found associations between the duration and extent of inhalant use and MRI abnormalities (Unger *et al*., 1994; Aydin *et al*., 2002). Aydin *et al*. (2002) documented white matter lesions in 46% of homeless individuals ($n = 41$, mean age 17.5 years) who had been chronically abusing paint thinner for at least 1 year (mean 4.6 years). In total, 27% were noted to have atrophic dilation of the ventricles and sulci, whereas 20% had thalamic hypointensity. The development of white matter changes and thalamic hypointensity were significantly associated with duration of abuse longer than 4 years. Unger *et al*. (1994) assessed eight adults (aged 25–62 years) with histories of long-term toluene abuse and demonstrated varying degrees of cortical cerebral, cerebellar and brain stem atrophy, as well as periventricular hyperintensities and poor grey–white matter differentiation. The severity of these changes was associated with the duration and extent of toluene abuse.

Although several studies support the notion that recovery of function is possible with prolonged abstinence, one study (Deleu and Hanssens, 2000) failed to find any significant improvement in MRI or neuropsychological measures following 5 months of abstinence, whereas another group (Rosenberg *et al*., 1988a) reported no improvements in MRI measures of brain pathology after 18 months. The cognitive findings are in keeping with animal work demonstrating neural damage to the rat hippocampus (CA3 and CA2) following chronic exposure to toluene (1500 p.p.m. 6 h $day^{-1}$, 5 days $week^{-1}$ for 6 months), even though animals were killed 4 months after their last drug exposure (Korbo *et al*., 1996).

## Developmental issues

The typical onset of experimentation with inhalants occurs earlier than with most other drugs of abuse, in the preteen years, coinciding with the time of maturation of crucial cognitive and emotional brain structures (Spear, 2000). Indeed, adolescence encompasses an extensive period of neural maturation (for example, synaptic pruning and myelination), particularly in areas associated with core executive and self-regulatory skills, such as inhibitory control and affect-regulation (Giedd *et al*., 1999; Gogtay *et al*., 2004; Paus, 2005). There is now an emerging literature indicating that the adolescent brain may be more vulnerable to the effects of psychoactive substances as a result of the extensive neuromaturational processes that are occurring during this period (Lubman *et al*., 2007). Further, there is growing evidence that adolescent animals may respond differently to psychoactive substances compared with adult animals (White *et al*., 2002). Indeed, in one of the relatively few studies conducted to date, Bowen *et al*. (2007a) recently reported that adolescent rats exhibited less sensitivity to the initial effects of high-dose toluene (20 min of 4000 p.p.m.) compared with adults, and demonstrated less sensitization with repeated exposure. Such findings suggest that adolescents may be able to tolerate higher doses of psychoactive substances before experiencing similar behavioural effects, despite being more vulnerable to their neurotoxic properties (Lubman *et al*., 2007).

Taken together, these findings indicate that chronic inhalant exposure during early adolescence may result in greater structural and functional brain disturbances, as well as subsequent impaired cognitive development. This in turn may contribute to individuals experiencing difficulties in regulating or ceasing their use (due to problems with planning, attention and impulse control), particularly in individuals with premorbid vulnerabilities. Thus, in view of the potent toxicity of volatile substances, the projected impact of inhalant abuse during this key phase of brain development would be expected to be great, probably exceeding that of other drugs of abuse. However, the literature to date is deficient in this area, with few studies examining the effects of acute and chronic inhalant exposure both early and late in development.

Recently, a number of preclinical studies have specifically examined the effects of toluene exposure (500 mg $kg^{-1}$ i.p.) during the early postnatal period (postnatal day 4 (PN4) to PN9). These studies reported altered responses related to the glutamatergic system, with reduced hyperlocomotion induced by NMDA agonists (Chien *et al*., 2005), an increase in NR2A subunits in the hippocampus and cerebellum (Lee *et al*., 2005) and a decrease in NR2B levels (200–100 mg $kg^{-1}$ i.p. from PN4 to PN7; Chen *et al*., 2004). Toluene exposure (500 and 1000 mg $kg^{-1}$ i.p.) during this period (PN 4–9) has also been shown to increase seizure sensitivity to NMDA, picrotoxin and pentylenetetrazol, as well as bicuculline (a $GABA_A$ receptor antagonist) and methyl β-carboline-3-carboxylate (inverse agonists of the $GABA_A$/benzodiazepine receptor) in juvenile rats (Chen and Lee, 2002; Liu *et al*., 2007), suggesting that toluene may induce long-term alterations in the function of NMDA and $GABA_A$ receptors. Indeed, subunit- and brain area-selective alterations in $GABA_A$ receptors were also apparent in these animals when assessed with semi-quantitative reverse transcription-PCR (Liu *et al*., 2007). O'Leary-Moore *et al*. (2007), using high-resolution magnetic resonance spectroscopy to assess the effect of acute binge toluene inhalation (8000 or 12 000 p.p.m.) in juvenile rats, found significantly reduced levels of hippocampal GABA and glutamate. Of note, *N*-acetylaspartate, myoinositol, creatine and various choline-containing compounds were unchanged following acute exposure. Research specifically examining pharmacokinetic and pharmacodynamic responses to high-dose binge use during different stages of development is yet to be conducted.

It is important to note that there are high rates of mental health problems among inhalant abusers (Dinwiddie *et al*., 1990; Lubman *et al*., 2006), and many young users have experienced childhood mistreatment, which in itself has

been shown to affect neurogenesis, synaptic overproduction and pruning, and myelination in animal models of brain development (Teicher *et al*., 2003). Indeed, early severe stress results in a cascade of neurobiological changes (for example, persistent alterations within the hypothalamic–pituitary–adrenal axis and the catecholamine system) that affects a range of developmental processes within the brain (for example, delays in myelination and abnormalities in pruning). Taken together, these findings highlight the need to control for early childhood mistreatment or comorbid mental health issues when examining the effect of chronic inhalant exposure on neuropharmacological and neurobiological functioning. Preclinical research will be an important tool in this regard, particularly in determining the interaction between early life stress and subsequent inhalant exposure. Such work would clearly inform relevant public health responses.

## Concluding remarks

There has been a substantial increase in research examining the neurobiology of inhalants, although the bulk of preclinical work has largely focused on acute exposure to toluene, with limited emphasis on examining neuropharmacological differences across volatile substances. Many of these studies have utilized non-inhalation methods of administration (particularly neurochemical and electrophysiological research), and such approaches may produce distinct biobehavioural sequelae (Bowen *et al*., 2006). Further, the relevance of such findings to human abuse requires further delineation, and more animal studies that attempt to robustly model the human experience (brief, high concentrations of inhalation exposure) are clearly necessary. Nevertheless, there is growing evidence that commonly abused solvents share common cellular mechanisms, and appear to have similar actions to other drugs of abuse, particularly CNS depressants. Despite clear evidence of neuropsychological impairments in chronic users, as well as diffuse and subtle changes in white matter, limited animal work has been conducted examining the neuropharmacological or toxicological mechanisms underpinning these changes or their potential reversibility with abstinence.

Although there is often a marked variability in the type and pattern of inhalants used by adolescents, most epidemiological and clinical studies tend to describe inhalant users as a homogenous group, with little attention paid to differences in the chemical composition or toxic profile of substances inhaled. In addition, many of these studies include small samples of adult populations, with only limited neuropsychological and/or neuroimaging assessment. The lack of appropriately matched control groups and consideration of background educational, psychological, emotional and social factors further hinders the interpretation of the available data. Indeed, the failure to utilize longitudinal designs has meant that the natural course of inhalant abuse is largely uncharted, with limited data available on the correlates and consequences of use over the short- and long-term, including the nature of recovery with abstinence.

Future studies will need to take account of the substantial neuromaturational changes that are known to occur in the brain during childhood and adolescence, and to specifically investigate the neuropharmacological and toxicological profile of inhalant exposure during this developmental period. Prospective human studies will also be needed to determine to what extent the neuropsychological and neurobiological abnormalities found in chronic abusers are present premorbidly, and/or relate to previous trauma or mental disorder. Although the recent increase in inhalant-related neuroscience research is encouraging, more comprehensive programmes that examine the impact of chronic inhalant binges during adolescence are essential for addressing the dearth of effective prevention and treatment approaches.

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## Conflict of interest

The authors state no conflict of interest.

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