

Volatile Substance Misuse: An Updated Review of Toxicity and Treatment

Jonathan B. Ford · Mark E. Sutter · Kelly P. Owen ·
Timothy E. Albertson

Published online: 7 May 2013
© Springer Science+Business Media New York 2013

Abstract Educational campaigns and legislative actions may have led to an overall decrease in the prevalence of volatile substance misuse (VSM) in many countries; however, it is still a common practice throughout the world. Studies currently suggest that girls are misusing volatile substances more than before and at a prevalence rate equal to or exceeding that of boys in several countries. Products that may be misused are ubiquitous and relatively easy to acquire. The most commonly misused substances in recent studies are fuels such as butane or petrol and compressed gas dusters and deodorants that may contain fluorocarbons and/or butane. Detection of VSM is challenging, therefore physicians must maintain a high level of suspicion based on history and clinical presentation. Clues to misuse are often subtle and may include the patient's proximity to a volatile substance or paraphernalia when found intoxicated, dermal burns, blisters, pigments, or rashes, and chemical odors. The primary targets of toxicity are the brain and the heart. The leading cause of death from VSM is from ventricular dysrhythmias. Treatment of toxicity begins with support of airway, breathing, and circulation. Exogenous catecholamines should be avoided if possible due to the theoretical "sensitized" and irritable myocardium. In the case of ventricular dysrhythmias, direct current defibrillation and/or

beta-adrenergic receptor antagonism should be used. New evidence demonstrates the addictive potential of VSM yet effective therapy remains uncertain. Further research is needed in developing methods for preventing, detecting, and treating the harmful effects of VSM.

Keywords Volatile substance misuse · Volatile substance abuse · Huffing · Sniffing · Sudden sniffing · Death syndrome

Introduction

Since the last publication on volatile substance abuse in Clinical Reviews in Allergy and Immunology [1], the practice of inhaling vapors from volatile chemicals in order to alter one's sensorium, is now commonly referred to as volatile substance misuse (VSM). While a few classic substances such as aerosol paints and adhesives are still misused, the once popular nitrates of the 1970s are rarely misused today [2]. Newer products such as computer dusters, containing 1,1-difluoroethane, air fresheners, containing butane or isobutene, and gas fuels, are now more commonly misused, and may have more fatal consequences. The epidemiology of VSM has also changed. Educational campaigns in the United States (US) and the United Kingdom (UK) that began in the mid 1990s have led to a decrease in VSM. Legislative action and other means to reduce VSM are now becoming commonplace in the US and other countries and may contribute to the decrease in prevalence of misuse. While the overall use has decreased in many countries, the demography, particularly between genders, has changed since previous reports [2–10].

Though the primary toxicity from VSM is on the brain and heart, several volatile chemicals can have a significant affects on the dermatologic, renal, hematological, digestive tract, and respiratory systems. Newer data implicates VSM

J. B. Ford · M. E. Sutter · K. P. Owen · T. E. Albertson
Department of Emergency Medicine, School of Medicine,
University of California, Davis, 4150 V Street, PSSB 2100,
Sacramento, CA 95817, USA

J. B. Ford (✉) · T. E. Albertson
Veterans Administration Northern California Healthcare System,
10535 Hospital Way,
Mather, CA 95655, USA
e-mail: jonathan.ford@ucdmc.ucdavis.edu

T. E. Albertson
Department of Internal Medicine, School of Medicine,
University of California, Davis, 4150 V Street, PSSB 3100,
Sacramento, CA 95817, USA

in both dependency and withdrawal. This review provides an update of VSM with new information regarding current epidemiology, mortality, substances misused, mechanism of action, and the toxicity of specific organ systems. While there is much information to be learned from studies on occupational exposure to these substances, more attention has been given to studies where the substances were misused for recreational purposes.

Epidemiology

VSM is a worldwide problem, second only to marijuana use in many countries, which tends to preferentially affect younger people. This is likely because the products are legal, inexpensive, and relatively easy to obtain. In the US, VSM peaked in the late 1990s and has been continually decreasing [2]. During this time, anti-drug campaigns began educating youth on the dangers of VSM. The University of Michigan's Monitoring The Future (MTF) survey is performed annually to determine drug use in US 8th, 10th and 12th grade students. In 2012, 6.2, 4.1, and 2.9 % of 8th, 10th, and 12th grade students, respectively, had used inhalants within the previous year compared to 12.8, 9.6, and 8 % in 1996 [2]. All grade levels had a decrease in use from 2011. The misuse of nitrates in 2012 was less than 1 % of 12th graders [2]. Furthermore, VSM has decreased significantly in those older than 23 years of age with less than 1 % reporting misuse within the previous year [2]. The UK initiated similar educational campaigns in 1992, which also resulted in significantly decreased misuse in schoolchildren aged 11–15, from 21 % in 1995 to 9 % in 2007 [3, 4]. However, despite the decrease in VSM in the US and UK, use seems to be increasing in other countries.

In the most recent report from the European School Survey Project on Alcohol and Other Drugs (ESPAD), a survey given to European teenagers aging 15–16 years old, use increased in 15 of 36 countries surveyed. In the UK, there was a slight increase in lifetime VSM to 10 % [5]. More concerning, the countries of Croatia and Latvia had an increase from 11 to 28 % and 13 to 23 %, respectively from 2007 to 2011 [5]. The latest school survey from Mexico found that 6.7 % of Mexican high school students had misused inhalants in the past year [6]. A similar survey from 2011 in Israel found that 17 % of respondents reported having ever used inhalants, with 18 % of those reporting frequent use (defined as greater than six times per month) [7]. Finally, a 2008 survey of school children aged 12 to 17 in Australia found that 13.5 % had used inhalants within the past year [8].

Previous reports showed that VSM was higher in boys than girls. However, recent reports have shown a reversal in this trend across many countries. For example, the 2008

Australian study showed that 14.1 % of females had misused in the past year, compared to 12.9 % of boys [8]. In Mexico, as of 2006, females had equal prevalence of misuse to males [6]. The 2011 MTF survey showed that girls in the US were more likely to use inhalants than boys in grades 8 and 10, however boys were still much more likely than girls to misuse volatile substances by grade 12 [9]. The 2011 ESPAD report showed that equal portions of girls and boys had used inhalants where as boys had previously been 1–2 % higher than girls [5]. Despite fewer boys reporting substance misuse, data from the St. George's National Programme on Substance Abuse Death found that boys in the UK were much more likely to die from a volatile substance than girls [10].

The misuse of volatile substances spans across all races, levels of education, and socioeconomic backgrounds. When comparing poison center data on VSM with US Department of Labor and US Census Bureau data from 2000 to 2005, there was not a trend between poverty, unemployment, or high school graduation rates [11]. They did find a trend toward increased misuse in rural settings. Additionally, reports in the US have consistently demonstrated that Hispanics and Caucasians are more likely to misuse substances than African-Americans [9]. In Canada, VSM may be more common in First Nations and Inuit communities [12] while in Mexico, it is more common in children that live and work in the street than in those that attend high school [6].

Methods of Misuse

Several methods exist to misuse volatile substances, which is often dependent on the specific product (Table 1). For instance, compressed gas dusters ("dusting") or nitrate canisters may be discharged directly into the mouth and inhaled. Other products, such as paints and adhesives, can be sprayed or placed into a bag, and then subsequently the air from the bag is inhaled. This is referred to as "bagging" [1]. Additionally, some fuels, solvents, and adhesives such as butane, acetone, and glue can be simply inhaled from their containers in a method referred to as "sniffing" [1]. Finally, the term "huffing" is when a substance is applied to a cloth and placed over the nose and mouth [1].

Substances Misused

There are many household products that can be misused (Table 2). Adhesives are a readily abused product because they often contain toluene, naphtha (a mixture of liquid hydrocarbons), xylene, hexane, and/or benzene. Spray paints can also contain similar compounds as adhesives, depending on the brand and color. Classic inhalant misuse agents such as amyl nitrite and butyl

Table 1 Methods of misuse

Term	Definition
Dusting	Direct inhalation of vapors specifically from compressed gas dusting products
Huffing	Direct inhalation of vapors from product container or from a cloth soaked with substance
Bagging	Inhalation of vapors from a plastic or paper bag after substance has been placed inside the bag
Sniffing	Smelling of vapors directly from product container or from a bag or on a cloth

nitrite are still available as solvents for video head cleaning or packaged in small capsules called “poppers”. Small cartridges

of nitrous oxide or “whippets” used mainly to dispense whipped cream can be easily obtained from internet retailers. Other easily obtainable substances include gasoline and butane lighter refills. Refrigerants, for example, Freon (DuPont; Wilmington, Delaware), are misused from sources such as refill canisters or directly from air conditioning units. Other commonly misused substances include solvents such as acetone, acrylic nail remover, nail polish remover, mothballs, and mineral spirits. Many products are mixtures of several solvents which can lead to unintended toxicity. For instance, carburetor cleaners may contain methanol. Methanol is easily absorbed via the lungs and can cause toxicity that includes metabolic acidosis and blindness [13, 14].

Table 2 Commonly misused substances

Substance	Source
Volatile solvents	
Acetone	Adhesives, nail polish remover, paint thinner
<i>n</i> -Hexane	Adhesives, degreasers
Methanol	Paint remover, degreasers
Methylene chloride	Paint remover
Methyl butyl ketone	Denaturant, adhesive thinner, degreasers
Naptha	Spray paint, adhesives, marker pens, lighter fluid
Naphthalene	Moth balls, toilet fresheners
Paradichlorobenzene	Moth balls, toilet fresheners
Toluene	Spray paint, adhesives, paint remover
Xylene	Spray paints and adhesives
Fuels	
Butane	Cigarette lighter refill, propellant
Gasoline (Petrol)	Portable containers
Kerosene	Lighter fluid, lamp oil
Naphtha	Lighter fluid, propellant
Propane	Portable heating appliances
Halogenated hydrocarbons	
1,1-Difluoroethane (R-152a)	Compressed gas computer duster, propellant
Tetrachloroethane (R-130 and R-130a)	Refrigerant
Tetrafluoroethane (R-134a)	Refrigerant, computer duster
Tetrachloromethane (CCl ₄)	Solvent, refrigerant
Trichloromethane	Adhesives, degreaser, spot remover
Trichloroethane	Adhesives, degreaser, spot remover, typewriter or ink correction fluid
Tetrachloroethylene (“PERC”)	Dry cleaning solvent
Trichloroethylene	Degreaser
Anesthetics	
Chloroform	Laboratory anesthetic
Ether	Laboratory anesthetic
Nitrous oxide	Dentist’s office, whipped cream dispensers
Nitrites	
Amyl nitrite	Poppers
Butyl nitrite	Video head cleaner, poppers

Mortality

In 2011, there were 35 cases reported to the National Poison Data System (NPDS) involving an inhalational exposure to a volatile substance that resulted in a fatality [15]. One of the cases involved an unintentional occupational exposure to a nitrate. Additionally, there were 27 cases cited intentional misuse of volatile substances. Of the 27 cases, 24 cases involved “freon”. Freon is probably a general term used for halogenated hydrocarbons such as 1,1-difluoroethane. Five cases involved children or adolescents under the age of 18 (four freon and one paint and lighter fluid). An additional case of an 8-year-old female most likely involved the intentional inhalational abuse of freon but the route of exposure was listed as unknown as she was found deceased by pre-hospital personnel. Other substances listed in fatal exposures were: paint, lighter fluid, hair spray, propane, methane, air freshener, toluene, and “other propellant with hydrofluorocarbons” [15]. A review of NPDS from 1993 to 2008 found 167 fatalities [16]. Butane, propane, and air fresheners had the highest fatality rates of 58.1, 25.0, and 21.8 % respectively [16]. In the UK, 211 fatalities were reported from 2003–2007. Most of the deaths were associated with misuse of gas fuels such as butane [10].

Absorption, Metabolism, and Elimination

Volatile substances are well absorbed via the lungs, transferring rapidly and efficiently across the alveoli-capillary membrane. Once absorbed, they readily dissolve in blood and are transported to tissues. Given their highly lipophilic properties, they are distributed primarily to tissues with high lipid content such as the nervous system, liver, kidneys, and adipose tissue. The toxicokinetics of 1,1-difluoroethane, was recently studied using a murine model. Following inhalation for 30 s, peak levels in the brain occurred within seconds [17]. In this model, intoxication was evident at 20 s post inhalation, peak effect was at 4 min, and rats were back to baseline at 8 min [17].

The metabolism and elimination of several other substances has also been studied. Few are exhaled unchanged from the lungs. In rats, 70–90 % of tetrachloroethylene was recovered from expired air with a half-life of 7 h [18]. However, most chemicals undergo substantial biotransformation in the liver and are excreted by the kidneys. Carbon tetrachloride (CCl_4 or tetrachloromethane) is metabolized primarily by cytochrome (CYP) 2E1 in the liver [19]. As much as 78 % of inhaled toluene is excreted as hippuric acid in the urine within 12 h of exposure [20]. Volatile hydrocarbons such as butane and propane are primarily metabolized by (ω -1)-oxidation [21]. Organic nitrates and nitrites are degraded through enzymatic denitration by hepatic glutathione-organic nitrate reductase [22]. Inhaled nitrous

oxide is metabolized rapidly to nitrates and with the creation of methemoglobin [23]. Substances that have toxic metabolites will be discussed later.

Detection of Abuse

Few clinical laboratories will have the ability to analyze for a specific volatile substance. In acute toxicity, a high-degree of suspicion is required to quickly diagnose and stabilize patients. History and physical exam can lead to clues for VSM (Table 3). First, pre-hospital personnel may find containers of the product near the patient. Next, clinical exam findings such as paint pigment may be found on the face or hands. Hydrofluorocarbons, such as dusters, may cause frostbite on the mouth or hands. Finally, the distinct odor of fuel or solvents can be recognized on the clothes or body. In the outpatient setting, when VSM is suspected, samples of urine and blood may be sent to reference laboratories where gas chromatography, headspace gas chromatography, or ion chromatography can be used to detect volatile substances and their metabolites. Care must be taken when collecting and transporting the samples given the volatile nature of the substances. Additional ancillary findings that may aid in diagnosis will be discussed in regards to that particular substance.

Legislation

Many states in the US, and several countries, have enacted laws in an attempt to reduce VSM, particularly in young people. For example, a Connecticut law defines certain volatile chemicals including toluene and nitrous oxide as a “restricted substance”, and makes it unlawful for a vender to willingly sell such a substance to a person for illicit purposes [24]. The law also presumes that anyone who misuses a substance, is psychologically dependent on it, which allows

Table 3 Signs and symptoms of volatile substance misuse

Organ System	Examples
Central Nervous System	Altered sensorium, confusion, headache, memory impairment, incoordination, ataxia
Nose	Sneezing, congestion, recurrent epistaxis
Skin	Perioral dermatitis, blisters, burns, paint pigment, chemical odor
Peripheral Nervous Symptoms	Sensory and motor polyneuropathy
Hematologic	Megaloblastic anemia, methemoglobinemia, carboxyhemoglobinemia
Musculoskeletal	Muscle wasting
Renal	Renal tubular acidosis

them to obtain medical treatment [24]. As of 2009, 25 other states also had laws that pertained to the misuse of volatile substances. Many make it unlawful to knowingly sell products to persons for illicit purposes or to use products for their mind-altering effects, and have penalties ranging from fines to imprisonment [24]. In 1999, the UK introduced Cigarette Lighter Refill (Safety) Regulations that prohibited the sale of butane gas lighter refills to persons under the age of 18 years [10]. This led to a reduction in gas fuel deaths by 80 % from 1983–1987 compared to 2003–2007 [10]. Between 1987 and 2003, the UK also initiated the Department of Health Advertising Campaign that may also have contributed to a reduction in deaths related to VSM. Australian legislation also makes it illegal for retailers to sell volatile substances to people who they reasonably suspect may misuse them. These laws give police authority to search anyone suspected of possessing substances for the purpose of misuse and to seize the products. Additionally police are allowed to temporarily detain people misusing substances in order to take them to a “safe place” [25]. Australia also uses a less volatile fuel called “Opal” in remote areas, in place of traditional petrol, in effort to reduce petrol sniffing [26].

Clinical Toxicity of VSM

Central Nervous System

Volatile substances are misused for their CNS effects in part due to the rapidity for which they occur. While their exact mechanisms of action are unknown, several *in vitro* studies have provided insight into potential receptor mediated mechanisms. Specific targets thought to be responsible for clinical effects include augmentation of *N*-methyl-D-aspartic acid (NMDA), gamma-aminobutyric acid A (GABA_A), glycine, nicotine, dopamine, and serotonin receptors as well as nerve membrane ion channels [27]. Similar to ethanol, in a murine model, toluene inhibits NMDA receptor-mediated currents in a concentration-dependent manner [28]. Toluene, 1,1,1-trichloroethane, and trichloroethylene enhance GABA_A and serotonin-3 (5-HT_{3A}) receptor mediated currents in dose-dependent manner [29] while toluene and trichloroethylene, but not trichloroethane, enhance glycine receptor function [30]. Toluene increases dopamine levels in several areas of the brain including the striatum, prefrontal cortex, and ventral tegmental area [31–33]. Increased dopamine released from the mesolimbic dopamine neurons is important for the psychological dependence of toluene [34]. Although controversial at this time, there is evidence of physical dependence after chronic inhalant use leading to a withdrawal syndrome upon abstinence [35]. A case of severe withdrawal characterized by tremor, hypertonia, ataxia, irritability, and altered mental state was reported in a patient who misused toluene for many years [36]. This

patient was shown to have depletion of dopamine from presynaptic neurons by DaTscan, a single-photon emission computed topography procedure that uses ioflupane iodine-123 to detect dopamine transporters [37]. Dramatic tolerance to propane with repeated misuse has also been reported [38]. The areas of the brain affected appear to be dependent on dose and duration of exposure. Thus, multiple receptors and neurotransmitters are involved in producing the clinical effects seen with volatile substance misuse.

Acute CNS intoxication occurs rapidly after inhalation giving users a feeling of euphoria, excitement, and disinhibition. A survey given to teenagers in Mexico found that visual, auditory, somatic, and tactile hallucinations were common [39]. Dizziness, ataxia, slurred speech, tinnitus, blurred vision, and confusion may occur. Significant CNS impairment has resulted in fatal motor vehicle collisions that occurred while the drivers were misusing inhalants [40, 41]. Following the initial excitatory phase, CNS depression usually occurs, but is rarely severe. Few cases of respiratory arrest have been reported [42]. Electroencephalogram (EEG) studies performed during acute toluene intoxication, demonstrated low amplitude slow wave activity in the bilateral parieto-occipital regions, which resolved several days later [43]. Recovery may be rapid depending on dose.

Acute CNS adverse effects can be severe. A prolonged state of delirium lasting 3 weeks was reported in patient who abused nitrous oxide [44]. Butane encephalopathy has been reported in several cases [45–47]. Abnormal EEG findings, consistent with drug-induced encephalopathy, were found in a 13-year-old female 4 days after she last used butane from an aerosolized deodorant [45]. There is an additional report of a 16-year-old male who suffered bilateral thalamic injuries, resulting in persistent akinetic mutism and apathy after butane inhalation [46]. Encephalopathy is also frequently reported with mothball abuse, particularly those that contain paradichlorobenzene (PDB) [48–51]. Leukoencephalopathy may be seen on MRI in people who misuse PDB [49, 51]. Acute cerebral edema associated with VSM may be fatal. After inhaling butane from a lighter refill, a 16-year-old male died from severe intracranial hypertension that was refractory to bilateral decompression craniotomy [52]. Fatal cerebral edema with tonsillar herniation has been reported in a 15-year-old boy who inhaled typewriter correction fluid containing trichloroethane [53]. Rarely, patients may present with seizures. Temporal lobe seizures have been reported due to acute trichloroethylene intoxication [54]. These complications are unpredictable, and in general do not appear dependent on solvent, duration of misuse, or dose.

Chronic VSM can have devastating consequences. Chronic headaches, sleep disturbances, and mood changes are associated with chronic exposure of solvents [55]. There is convincing evidence that demonstrates neuropsychiatric impairments in chronic inhalant abusers. In one study

comparing the neuropsychiatric performance of chronic solvent misusers with abusers of other drugs such as ethanol or cocaine, solvent users had more significant impairment in working memory and executive functioning [56, 57]. Magnetic resonance imaging (MRI) of these patients demonstrated an increased number of abnormalities in the thalamus, basal ganglia, pons, and cerebellum than the comparison group [56].

There is some evidence of neuroanatomical recovery with abstinence of VSM that appears dependent on duration and severity of misuse and duration of abstinence [58, 59]. The CNS effects of chronic toluene abuse are well described. Characteristic symptoms include dementia, cerebellar ataxia, tremor, oculomotor abnormalities, deafness, hyposmia, and corticospinal tract dysfunction [60]. Toluene misuse may lead to optic neuropathy [61, 62]. Cerebellar and cerebral atrophy can be seen on MRI and computed topography, while demyelination and gliosis can be seen on MRI of chronic toluene users [63, 64]. CNS lesions were also demonstrated by MRI in a 51-year-old woman who misused a solvent containing *n*-hexane [65]. The patient's MRI lesions improved after abstinence from the solvent. Methanol toxicity can develop from misuse of products such as carburetor cleaners and carries the risk of retinal injury and loss of vision through, as well as an anion-gap metabolic acidosis through formic acid which is a metabolite [13, 14].

Leaded gasoline was a cause of encephalopathy in gasoline sniffers prior to the removal of tetraethyl lead (TEL) [66–69]. Generalized tonic-clonic seizures and status epilepticus have been reported in chronic petrol sniffers, perhaps due to lead content [68]. Leaded gasoline is still present in significant amounts in Bangladesh and Senegal [70] and may be present in rural communities of Canada and Australia [69, 71].

Cardiac

Acute cardiac toxicity is the most common cause of mortality with VSM. The term “sudden sniffing death syndrome” has been used for decades to describe lethal ventricular dysrhythmias and sudden cardiac death associated with VSM. Many patients do not survive to be treated at a health-care facility and those that do are significantly unstable. While halogenated hydrocarbons were once thought to have the highest risk of causing sudden cardiac death, other volatile substances have been found to have a similar effect [72–74]. There are many case reports of ventricular fibrillation (VF) occurring in patients misusing butane [75–84]. The mechanism by which these volatile substances cause ventricular dysrhythmias is not fully understood. Previous understanding of the pathophysiology was that certain volatile substances “sensitize” the myocardium to catecholamines [85]. Surges of endogenous catecholamines, from

hallucinations, fright, or exertion for example, provide a catalyst for generating a dysrhythmia [86]. Recent studies provide further insight into the pathophysiology. Patients who misused toluene had statistically significant longer QT dispersion intervals on electrocardiogram (ECG) than did non-users. Those that were symptomatic (defined as recent syncope in chronic users) had longer intervals than their asymptomatic counterparts [87]. QT dispersion is a measure of the heterogeneity of repolarization time in the ventricular myocardium. The concept recognizes that regions of the myocardium may repolarize at different rates depending on action potential duration and activation time [88]. Increased QT dispersion may occur in acute myocardial infarction (AMI), and other disease states, and has been used to predict risk of ventricular dysrhythmias in AMI [88]. In the previous mentioned study, patients who misused toluene also had significantly prolonged corrected QT (QTc) intervals on ECG [87]. Patients with increased QTc duration are at greater risk for torsades de pointe [89]. Inhibition of the human ether-a-go-go related gene (hERG) otherwise known as the delayed rectifier potassium channel (I_{Kr}) is most likely the mechanism of increased QTc duration and dispersion. Additionally, toluene is known to cause hypokalemia which can further exacerbate the QTc duration. Chloroform has also been shown to inhibit the I_{Kr} and other volatile substances likely share this capability [90]. Inhibition of cardiac sodium channels is another important mechanism of generating dysrhythmias. In a study using rat myocytes, toluene completely inhibited the fast inward sodium channel in a voltage-independent and slowly reversible manner [91]. There is also evidence for inhibition of cardiac calcium channels by halogenated hydrocarbons [90]. Thus, all aspects of the cardiac action potential appear to be affected by halogenated hydrocarbons. Other misused volatile substances probably cause cardiac toxicity by these mechanisms, but research is lacking.

In addition to conduction abnormalities, volatile substances may have direct myocardial toxicity. There are case reports of young healthy adolescents with acute myocardial infarction diagnosed by electrocardiogram and elevated cardiac muscle enzymes. Substances cited in these reports include butane [81, 82, 92] and difluoroethane [93], which were used just prior to presentation. The mechanism of toxicity appears to be coronary vasospasm, as two of these patients underwent emergent coronary angiography that demonstrated no significant coronary atherosclerosis [81, 92]. The chronic misuse of inhalants such as toluene [94, 95], butane [96], difluoroethane [93], and 1,1,1-trichloroethane [97] has been implicated in causing dilated cardiomyopathy with significantly depressed ejection fraction. The pathophysiology may be chronic ischemia from repeated exposure, direct myocardial damage, or a chronic inflammatory process. Diffuse myocardial interstitial fibrosis was

found on autopsy of two patients who died suddenly after misusing butane [98] and in one patient who misused difluorochloromethane from an air conditioner [99]. This evidence may support the possible mechanism of a chronic inflammatory process as a toxic mechanism as a result of VSM.

Peripheral Nervous System

Several misused volatile substances are known to cause significant peripheral nervous system disease. Chronic misuse of nitrous oxide is known to cause a multifocal progressive sensorimotor polymyeloneuropathy [100, 101]. Patients may present with numbness, ataxia, limb weakness, impotence, or incontinence. Axonal degeneration and demyelination were observed using electron microscopy on a sural nerve biopsy of one patient exposed to nitrous oxide daily for 1 year [102]. These findings can be observed on electromyogram (EMG) [101, 103]. The pathophysiology is due to irreversible inactivation of cyanocobalamin (B12) through oxidation of cobalt [104]. Inactivated B12 inhibits methionine synthase which impairs formation of tetrahydrofolate. Tetrahydrofolate is required for DNA synthesis and myelin production. Patients may present with near normal levels of B12 despite clinical B12 deficiency [105–107]. An elevated total homocysteine may aid in making the diagnosis of clinical B12 deficiency from nitrous oxide exposure [107]. Symptoms, neuroimaging, and EMG studies may completely normalize with abstinence and supplementation of B12 [108–110].

The solvents *n*-hexane and methyl *n*-butyl ketone (MBK) cause multifocal progressive sensorimotor polyneuropathy with prolonged exposure. *n*-Hexane is present in some petrols while MBK is used to denature alcohols and to thin adhesives. They share a common metabolite, 2,5-hexanedione, which is neurotoxic [111]. One report of 4 patients addicted to inhaling *n*-hexane demonstrated axonal loss, swelling, and degeneration, with thinning of the myelin on sural nerve biopsies [111]. Muscle wasting, particularly in the distal limbs can be observed [112]. EMG studies are significant for nerve conduction blocks [111, 112]. A 4-year-old boy developed a severe peripheral neuropathy from repeated deliberate inhalation of petroleum (naphtha) that contained *n*-hexane [113]. These findings have been demonstrated in multiple other case reports of patients misusing products containing *n*-hexane or MBK [112, 114–117]. The clinical course of patients who develop neuropathy is described as biphasic with a period of “coasting” for 2–3 months in which symptoms persist after abstinence followed by a slow and variable recovery for about 1–2 years [118]. A patient who inhaled both naphthalene and PDB mothballs daily for years

developed peripheral neuropathy, however it is unclear which type of mothball caused this finding [119].

There are a few misused inhalants that may cause cranial nerve toxicity. Trichloroethylene is the most frequently cited volatile substance to affect the cranial nerves. A patient who misused trichloroethylene presented with palsies of the third, fifth, and sixth cranial nerves [120]. The trigeminal nerve is thought to be the most frequent cranial nerve affected by trichloroethylene [121, 122]. Toluene has also been implicated in causing sensorineural hearing loss in a 27-year-old male who sniffed “model airplane glue” frequently over a period of 5 years [123] and a 27-year-old woman who also was addicted to sniffing glue [124].

Respiratory Tract

The respiratory tract is the site of entry for volatile substances and is perhaps most vulnerable to volatile substance toxicity. Despite this, little is written about the specific toxicity incurred by the respiratory tract with VSM. Select methods of misuse may lead to higher pulmonary complications. For instance, “bagging” may lead to hypercapnia, hypoxia, and asphyxia [1]. Long-term VSM does appear to cause chronic respiratory tract symptoms. In a recent study of 31 adults who chronically misused volatile substances, 45 % reported nasal congestion, 38 % reported increased sputum production, 32 % reported exercise intolerance, and 22 % reported cough [125]. Additional observed sequelae of chronic VSM includes chronic rhinitis, recurrent epistaxis, and sneezing [126]. VSM may exacerbate reactive airway disease in certain individuals [96].

Some evidence exists regarding direct toxicity imposed by volatile substances on the respiratory tract. A study of 18 chronic volatile substance misusers demonstrated alveolo-capillary membrane dysfunction using technetium-99m (Tc-99m) diethylenetriaminepentaacetic acid scintigraphy when compared to non-misusers [127]. All patients in both groups were smokers. The substances involved were thinners and adhesives. This finding was also observed on an early study in “hard-core glue-sniffers” using the same technique [128]. Acute pneumonitis and bronchodilator responsive airway obstruction was demonstrated in several patients after unintentional inhalation of a leather protector containing isobutane, ethyl acetate, *n*-heptane, and fluoroaliphatic hydrocarbons [1, 129]. Despite this, a recent small study failed to show differences in pulmonary functions tests in volatile substance misusers compared to controls [125]. A relationship between Goodpasture’s syndrome and hydrocarbon exposure has been hypothesized based on 43 case reports, however given the small numbers of cases, a definitive link has not been determined [130]. Recently, fatal diffuse alveolar hemorrhage was reported in one 18-year-old male who inhaled tetrafluoroethane from a computer

cleaner [131]. This patient had an exhaustive evaluation to rule-out other known causes of alveolar hemorrhage and had only minimal elevated of glomerular basement membrane antibodies.

Digestive Tract

VSM may cause toxicity to areas of the digestive tract. Computer dusters that contain difluoroethane or tetrafluoroethane may be directly discharged into the mouth and therefore cause injury. Severe angioedema has been reported in cases of computer duster misuse [132]. The significant amount of edema present may be a manifestation of frostbite caused by exposure to compressed fluorocarbons. Partial and full thickness burns of the lips, oropharynx, esophagus, and large airways have been reported from misusing these products [133–135]. Frostbite of the mouth has also been seen with inhalation of propane [136].

Given that the liver metabolizes many substances that are misused, it seems fitting that certain substances have been reported to cause direct liver toxicity. Carbon tetrachloride is a classic volatile substance known to cause centrilobular necrosis due to the formation of a reactive metabolite by CYP2E1 [137]. Other substances reported to cause hepatotoxicity from misuse include butane [137], mothballs of unknown type [119], and trichloroethylene, including a case of fatal hepatic failure [138–141]. A mouse model demonstrated that hepatotoxicity of trichloroethylene is probably mediated by CYP2E1 metabolism to a toxic metabolite [142].

Renal

Perhaps the most studied substance in terms of its effect on the kidney is toluene. With chronic misuse, toluene causes renal tubular acidosis (RTA). While the exact mechanism is unknown, Batlle et al. found that chronic toluene use impaired urinary acidification by decreasing the rate of proton secretion in the collecting tubule with normal renal bicarbonate reabsorption [143]. Clinically, patients may present with diffuse weakness or paralysis from severe hypokalemia. Retention of toluene's metabolites, particularly hippuric acid, may generate a profound anion-gap metabolic acidosis [144]. An infant was found to have RTA at birth attributed to maternal toluene misuse during pregnancy [145]. Trichloroethylene has been shown to have a consistent but low incidence of renal cell carcinoma (RCC) in rats and has a weak association of RCC in epidemiologic studies of workers exposed to trichloroethylene [146]. There is one case report of a 51-year-old male with long-term trichloroethylene misuse that developed RCC [147].

Hematological

Several misused volatile substances may cause hematological toxicity. Nitrous oxide classically causes a megaloblastic anemia that may mimic pernicious anemia. The mechanism for this toxicity is oxidation of cobalt in B12 and relative B12 deficiency. The condition is typically reversible with abstinence of nitrous oxide. Methemoglobinemia is frequently reported with amyl nitrite misuse [148–151]. Nitrites are strong oxidizing agents that can oxidize ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) in hemoglobin, myoglobin, and cytochrome molecules [148, 149]. Severe anemia has also been reported with long-term misuse of naphthalene containing mothballs [152]. The mechanism of toxicity is unknown. Both inhalation and ingestion of naphthalene may cause acute hemolytic anemia [153]. Vulnerable persons are typically very young, and glucose-6-phosphate dehydrogenase (G6PD)-deficient, but may also occur in the setting of normal G6PD activity [153, 154]. An infant born to a mother who inhaled naphthalene developed hemolytic anemia in utero [155]. The infant, as well as both parents, were G6PD-deficient [155]. Methylene chloride is found in some carburetor cleaners and solvents and may cause significant carboxyhemoglobinemia [156, 157]. Methylene chloride is metabolized by CYP2E1 to carbon monoxide (CO) in a manner that may have delayed peak toxicity, and has a longer apparent half-life than exogenous CO [158]. Finally, benzene may be a contaminant in toluene containing products and may increase the risk of acute myeloid leukemia [159].

Dermatologic

Certain products and chemicals have been associated with abnormal dermatologic findings. As previously mentioned, compressed fluorocarbons may cause frost bite and burns. Significant burns of the face and hands may occur [160–162]. Perioral and perinasal dry erythematous papules or sores may be observed and are referred to a “huffer’s rash” [163]. “Degreaser’s flush” is a disulfiram-like reaction in patients exposed to trichlorethylene who then consume ethanol [164].

Reproductive

The previously mentioned effects on the infants of mothers who misuse volatile substances are proof that many of these chemicals cross the placenta and are toxic to the developing fetus. The fact that more girls of reproductive age are misusing volatile substances may lead to more infants being born with congenital abnormalities. The term “fetal solvent syndrome” describes a constellation of physical and behavioral effects, which resembles fetal alcohol syndrome, in

infants born to mothers that misused volatile substances during pregnancy [165]. In the 1980s, the effect of toluene misuse on the embryo was termed “toluene embryopathy” [166]. Characteristic features of toluene embryopathy include microcephaly, central nervous system dysfunction, minor craniofacial and limb anomalies, developmental delay, and variable growth deficiencies [166–169]. Other effects on the fetus have been reported. Methemoglobinemia causing hydrops fetalis was reported after an 18-year-old female unintentionally received a large single acute exposure to a butane/propane mixture [170]. Infants born to mothers who sniffed petrol during pregnancy were more likely to have lower birth weight, lower levels of hemoglobin, and lower appearance, pulse rate, grimace, activity, and respiratory effort (APGAR) scores [171]. Neonatal withdrawal symptoms such as excessive high pitched crying, sleepiness, tremor, hyperactive Moro reflex, hypotonia, and poor feeding were described in one cohort study of infants born to mothers who misused solvents during their pregnancy [172]. In this study, 32/48 infants included met criteria for treatment of withdrawal, based on the Finnegan Neonatal Abstinence Scoring System, and 28/32 were treated with phenobarbital [172]. The authors also claim that several infants had a “chemical odour” at birth that persisted for several days indicating recent misuse.

Treatment

There are no specific antidotes to treat the adverse effects of VSM. Initial treatment includes removal from the exposure and an immediate assessment of the patient’s airway, breathing, and circulation. Placement of an endotracheal tube is prudent in patients who present with angioedema or burns to the mouth and/or nose as well as those that are obtunded or otherwise unable to maintain their airway. While respiratory depression or arrest is rare, patients may require support

with supplemental oxygen due to acute lung injury from aspiration or direct chemical effects. The use of beta-2-agonist bronchodilators should be avoided if possible given the extreme risk of cardiac dysrhythmias. Maintaining adequate circulation is perhaps the most challenging aspect of VSM toxicity as cardiac arrest is the most likely cause of sudden death. Successful resuscitation has been reported after defibrillation with direct current [76, 79, 80, 84, 173, 174]. Several of these patients subsequently received an antidysrhythmic such as amiodarone [82], lidocaine [79, 173], and bretylium [74]. Caution is advised in the use of antidysrhythmics in VSM toxic patients. Amiodarone and bretylium have a theoretical risk of worsening dysrhythmias given the complex pathophysiology of volatile substances involving multiple ion channel inhibition as discussed before. Given the theory of myocardial sensitization and initiation of dysrhythmias by catecholamines, exogenous epinephrine should be avoided if possible and efforts to calm the patient made. It seems reasonable then that, in patients presenting with ventricular dysrhythmias, a beta-adrenergic antagonist may be beneficial. The use of beta-blockers in cardiac arrest due to VF or pulseless ventricular tachycardia (VT) is dates back to the early 1980s. Stimulation of beta-adrenergic receptors during VF or VT increases myocardial oxygen consumption, reduces subendocardial perfusion, and worsens intrapulmonary shunting caused by hypoxic pulmonary vasoconstriction leading to increased myocardial dysfunction [175, 176]. In animal models of induced VF arrest, beta-blockade reduced myocardial oxygen demand, improved post-resuscitation myocardial function, decreased the number of defibrillation attempts, and prolonged survival [176]. There are two prospective human trials that assessed the use of beta-blockade in shock refractory VF [177, 178]. While they are small studies, they did demonstrate safety and efficacy of the therapy. Though propranolol, esmolol, landiolol, carvedilol, and atenolol

Table 4 Potential therapeutic interventions for complications of VSM

Condition	Potential therapy
Ventricular fibrillation	Direct current defibrillation, beta-adrenergic-receptor blockade, avoidance of catecholamines
Seizures	Benzodiazepines, barbiturates, propofol
Hepatitis	n-acetylcysteine (especially if carbon tetrachloride)
Renal tubular acidosis	Potassium replacement, hemodialysis
Skin burns and blisters	Local wound care and management
Methemoglobinemia	Methylene blue (for moderate to severe symptoms)
Carboxyhemoglobinemia	Supplement oxygen
Megaloblastic anemia	Folinic acid (if from nitrous oxide)
Methanol toxicity	Fomepizole or ethanol if fomepizole is unavailable, hemodialysis
Peripheral neuropathy	Cyanocobalamin (vitamin B12) (if from nitrous oxide)
Neonatal abstinence	Phenobarbital
Chemical dependence	Family therapy, activity base therapy

have been studied, there is currently no consensus on which agent is superior [176]. Recently, direct current defibrillation followed by esmolol was used in the successful resuscitation of a 25-year-old woman who sustained VF arrest following an exposure to isobutane from an air freshener [174]. Esmolol has the advantage of beta-1 selectivity, a rapid onset, easy titratability, and ultrashort half-life. [179].

Though cardiac dysrhythmias are often the cause of fatalities, nervous system effects may also require treatment. Benzodiazepines are typically first line agents for toxin-induced seizures. Mannitol, elevation of the head to 30°, and decompression craniotomy may be required to control volatile substance associated cerebral edema [53, 76, 84]. The use of B12 supplementation has been helpful in treating nitrous oxide induced peripheral neuropathy. Lead encephalopathy is usually treated with chelation. However, as TEL is an organic form of lead, chelation may not be effective [42, 71, 180]. In one study of 20 chronic petrol sniffers in Australia, 18 received a chelator that decreased blood lead levels but did not significantly improve symptoms [42].

Other treatments are based on the specific toxicity of the inhalant. Methemoglobinemia, from nitrous oxide, may be treated with methylene blue, if indicated based on percentage, symptomatology, and comorbidities. Symptomatic anemia and hemolytic anemia may require blood transfusions [154]. Nitrous oxide induced megaloblastic anemia may be treated with administration of B12 but there is little data on efficacy. Folinic acid was successful at preventing bone marrow toxicity in a rat model, but has not been definitively proven to be effective in humans [181–184]. It should be noted that the negative human studies were performed in patients undergoing general anesthesia with nitrous oxide, and several studies involved pre-treatment with folinic acid [182, 184]. Thus, caution should be used when extrapolating this information to frequent nitrous oxide misuse.

Methanol toxicity should be treated with alcohol dehydrogenase (ADH) inhibition, preferably with fomepizole, but ethanol may be used if fomepizole is unavailable [185]. Intravenous folinic acid should be given to limit the formation of toxic metabolites, but is not an alternative to ADH inhibition [185]. Hemodialysis is often needed due to severe acidosis and very long elimination half-life of methanol [13, 185]. When dealing with methylene chloride, physicians must account for the delayed peak of the development of carboxyhemoglobinemia (COHb) from methylene chloride. It is safest to observe patients for 24 h and measure serial COHb levels. Supplemental oxygen, as close to 100 % FiO₂ as possible, should be used to decrease the half-life [186]. Hyperbaric oxygen therapy has been used but did not prevent the rise of COHb in two methylene chloride exposed patients [187, 188]. Carbon tetrachloride hepatotoxicity may be treated with *N*-acetylcysteine [189]. Severe hypokalemia from toluene should be treated with

supplemental potassium. Rapid reversal of life-threatening hypokalemia, acidemia, and acute renal failure with hemodialysis was reported in one patient following toluene misuse [190] (Table 4).

Recovery from Volatile Substance Misuse

There have been several studies evaluating the treatment of the psychological dependence of VSM through case management, counseling, activity and engagement programs, and residential programs. Unfortunately, a recent systematic review of all studies involving psychotherapy for VSM was not able to draw any conclusions on an evidence-based therapeutic approach [191]. There is some evidence to support family therapy as a way to stop VSM. In one study, 78 % of participants had abstained from VSM at 6-months, after undergoing family therapy [191]. There may be at least a short reduction in VSM when intensive activity based therapy is used. Better randomized controlled trials are needed to further investigate methods of VSM interventions.

Conclusion

Many factors, including educational campaigns and legislation, have made it increasingly more difficult to procure volatile substances. While the prevalence of VSM in youths has decreased overall, it has increased in young females compared to previous decades, and remains a worldwide problem particularly in rural communities. Fluorocarbons such as 1,1-difluoroethane found in computer dusters, butane or propane fuels, and butane/isobutane mixtures used as propellants in air fresheners are ubiquitous and cause considerable morbidity and mortality when misused. Beyond sudden sniffing death syndrome, long-term VSM leads to cognitive impairment for the misuser and for infants born to mothers who misuse during pregnancy. While more information is known about their mechanisms of toxicity, little is known about effective treatments for volatile substances. In order for physicians to make a difference, they must have a high index of suspicion as well as respect for the toxicity of these substances and their addictive potential.

References

1. Marelich GP (1997) Volatile substance abuse. *Clin Rev Allergy Immunol* 15:271–289
2. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE (2012) Table 2 Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12. The Monitoring the Future study, the University of Michigan. Retrieved February 12, 2013 from <http://www.monitoringthefuture.org>

3. Hibell B, Andersson B, Bjarnason T, Kokkevi A, Morgan M, Narusk A (1995) The 1995 ESPAD Report Alcohol and Other Drug Use Among Student in 26 European Countries. Retrieved February 12, 2013 from <http://www.espad.org/en/Reports-Documents/ESPAD-Reports/>
4. Hibell B, Guttormsson U, Ahlström S et al. (2007) The 2007 ESPAD Report Substance Use Among Students in 35 European Countries. Retrieved February 12, 2013 from <http://www.espad.org/en/Reports-Documents/ESPAD-Reports>
5. Hibell B, Guttormsson U, Ahlström S et al. (2011) The 2011 ESPAD Report Substance Use Among Students in 36 European Countries. Retrieved February 12, 2013 from <http://www.espad.org/en/Reports-Documents/ESPAD-Reports>
6. Villatoro JA, Cruz SL, Ortiz A, Medina-Mora ME (2011) Volatile substance misuse in Mexico: correlates and trends. *Subst Use Misuse* 46(Suppl 1):40–45
7. Neumark Y, Bar-Hamburger R (2011) Volatile substance misuse among youth in Israel: results of a national school survey. *Subst Use Misuse* 46(Suppl 1):21–26
8. White V, Smith G (2009) Tobacco, alcohol, over-the-counter and illicit substance use among Australian secondary school students 2008, Report prepared for: Drug Strategy Branch Australian Government Department of Health and Ageing. Retrieved February 12, 2013 from http://www.decd.sa.gov.au/drugstrategy/files/links/ASSADS_Aust_sec_schools_re.pdf
9. Johnston L, O'Malley PM, Bachman JG, Schulenberg JE (2012) Monitoring the Future national survey results on drug use, 1975–2011. Volume I: Secondary school students. Ann Arbor: Institute for Social Research, The University of Michigan. Retrieved February 12, 2013 from <http://www.monitoringthefuture.org/pubs.html>
10. Butland BK, Field-Smith ME, Ramsey JD, Anderson HR (2012) Twenty-five years of volatile substance abuse mortality: a national mortality surveillance programme. *Addiction* 108:385–393
11. Spiller H, Lorenz DJ (2009) Trends in volatile substance abuse. *J Addict Dis* 28:164–170
12. Dell D, Hopkins C (2011) Residential volatile substance misuse treatment for indigenous youth in Canada. *Substance Use & Misuse* 46:107–113
13. Wallace EA, Green AS (2009) Methanol toxicity secondary to inhalant abuse in adult men. *Clin Toxicol* 47:239–242
14. LoVecchio F, Sawyers B, Thole D, Beuler MC, Winchell J, Curry SC (2004) Outcomes following abuse of methanol-containing carburetor cleaners. *Hum Exp Toxicol* 23:473–475
15. Bronstein AC, Spyker DA, Cantilena LR Jr, Rumack BH, Dart RC (2012) 2011 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report. *Clin Toxicol* 50:911–1164
16. Marsolek MR, White NC, Litovitz TL (2010) Inhalant abuse: monitoring trends by using poison control data, 1993–2008. *Pediatrics* 125:906–913
17. Avella J, Kunaparaju N, Kumar S, Lehrer M, Zito SW, Barletta M (2010) Uptake and distribution of the abused inhalant 1,1-difluoroethane in the rat. *J Anal Toxicol* 34:381–388
18. Pegg DG, Zempel JA, Braun WH, Watanabe PG (1979) Disposition of tetrachloro(14C)ethylene following oral and inhalation exposure in rats. *Toxicol Appl Pharmacol* 51:465–474
19. Omar SA, Artime E, Webb AJ (2012) A comparison of organic and inorganic nitrates/nitrites. *Nitric Oxide: Biol Chem* 26:229–240
20. Löf A, Wigaeus Hjelm E, Colmsjö A, Lundmark BO, Norström A, Sato A (1993) Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to 2H8-toluene. *Br J Ind Med* 50:55–59
21. Tsukamoto S, Chiba S, Muto T, Ishikawa T, Shimamura M (1985) Study on the metabolism of volatile hydrocarbons in mice—propane, *n*-butane, and iso-butane. *J Toxicol Sci* 10:323–332
22. Needleman P (1976) Organic nitrate metabolism. *Annu Rev Pharmacol Toxicol* 16:81–93
23. Wennmalm A, Benthin G, Edlund A et al (1993) Metabolism and excretion of nitric oxide in humans. An experimental and clinical study. *Circ Res* 73:1121–1127
24. Spiegel S (2009) State Laws on Inhalant use, Office of Legislation Research Report. Retrieved February 12, 2013 from <http://www.cga.ct.gov/2009/rpt/2009-R-0251.htm>
25. Drug & Alcohol Information Centre (2007) Volatile Substance Misuse Drug and Alcohol Information Centre. Retrieved February 7, 2013 from <http://www.drugarm.com.au/files/pdf/VSM.PDF>
26. MacLean SJ, D'abbs PH (2011) Five challenges for volatile substance misuse policy and intervention in Australia. *Drug Alcohol Rev* 30:223–227
27. Bowen SE, Batis JC, Paez-Martinez N, Cruz SL (2006) The last decade of solvent research in animal models of abuse: mechanistic and behavioral studies. *Neurotoxicol Teratol* 28:636–647
28. Cruz SL, Gauthereau MY, Camacho-Munoz C, Lopez-Rubalcava C, Balster RL (2003) Effects of inhaled toluene and 1,1,1-trichloroethane on seizures and death produced by *N*-methyl-D-aspartic acid in mice. *Behav Brain Res* 140:195–202
29. Lopreato GF, Phelan R, Borghese CM, Beckstead MJ, Mihic SJ (2003) Inhaled drugs of abuse enhance serotonin-3 receptor function. *Drug Alcohol Depend* 70:11–15
30. Beckstead MJ, Weiner JL, Eger EI 2nd, Gong DH, Mihic SJ (2000) Glycine and gamma-aminobutyric acid(A) receptor function is enhanced by inhaled drugs of abuse. *Mol Pharmacol* 57:1199–1205
31. Stengard K, Hoglund G, Ungerstedt U (1994) Extracellular dopamine levels within the striatum increase during inhalation exposure to toluene: a microdialysis study in awake, freely moving rats. *Toxicol Lett* 71:245–255
32. Gerasimov MR, Schiffer WK, Marsteller D, Ferrieri R, Alexoff D, Dewey SL (2002) Toluene inhalation produces regionally specific changes in extracellular dopamine. *Drug Alcohol Depend* 65:243–251
33. Riegel AC, Zapata A, Shippenberg TS, French ED (2007) The abused inhalant toluene increases dopamine release in the nucleus accumbens by directly stimulating ventral tegmental area neurons. *Neuropsychopharmacology* 32:1558–1569
34. Funada M, Sato M, Zhou X, Kanai H, Wada K (2005) Neuroadaptive mechanisms form development of psychological dependence on volatile organic solvents. *Japan J Psychopharm* 25:1–9
35. Perron BE, Howard MO, Vaughn MG, Jarman CN (2009) Inhalant withdrawal as a clinically significant feature of inhalant dependence disorder. *Med Hypotheses* 73:935–937
36. Kouzoupis AV, Konstantakopoulos G, Oulis P, Kalfakis N, Papageorgiou SG (2010) A case of severe toluene withdrawal syndrome treated with clonazepam. *J Neuropsychiatr Clin Neurosci* 22:E16–E17
37. Papageorgiou SG, Karantoni E, Pandis D, Kouzoupis AV, Kalfakis N, Limouris GS (2009) Severe dopaminergic pathways damage in a case of chronic toluene abuse. *Clin Neurol Neurosurg* 11:864–867
38. Grosse K, Grosse J (2000) Propane abuse. Extreme dose increase due to development of tolerance. *Der Nervenarzt* 71:50–53
39. Cruz SL, Dominguez M (2011) Misusing volatile substances for their hallucinatory effects: a qualitative pilot study with Mexican teenagers and a pharmacological discussion of their hallucinations. *Subst Use Misuse* 46(Suppl 1):84–94
40. Broussard LA, Brustowicz T, Pittman T, Atkins KD, Presley L (1997) Two traffic fatalities related to the use of difluoroethane. *J Forensic Sci* 42:1186–1187

41. Hahn T, Avella J, Lehrer M (2006) A motor vehicle accident fatality involving the inhalation of 1,1-difluoroethane. *J Anal Toxicol* 30:638–642
42. Fitzgerald RL, Fishel CE, Bush LL (1993) Fatality due to recreational use of chlorodifluoromethane and chloropentafluoroethane. *J Forensic Sci* 38:477–483
43. Turkoglu C, Aliyev F, Celiker C, Uzunhasan I, Kocas C (2010) Slow heart-slow brain: consequence of short-term occupational exposure to toluene in a young woman: what is the real mechanism? *Clin Cardiol* 33:E68–E71
44. Serman AB, Coyle PK (1983) Subacute toxic delirium following nitrous oxide abuse. *Arch Neurol* 40:446–447
45. Harris D, Mirza Z (2005) Butane encephalopathy. *Emerg Med J* 22:676–677
46. Kile SJ, Camilleri CC, Latchaw RE, Tharp BR (2006) Bithalamic lesions of butane encephalopathy. *Pediatr Neurol* 35:439–441
47. Doring G, Baumeister FA, Peters J, von der Beek J (2002) Butane abuse associated encephalopathy. *Klinische Padiatr* 214:295–298
48. Feuillet L, Mallet S, Spadari M (2006) Twin girls with neurocutaneous symptoms caused by mothball intoxication. *N Engl J Med* 355:423–424
49. Kumar N, Dale LC, Wijdicks EF (2009) Mothball mayhem: relapsing toxic leukoencephalopathy due to *p*-dichlorobenzene neurotoxicity. *Ann Intern Med* 150:362–363
50. Reygagne A, Garnier R, Chataigner D, Echenne B, Efthymiou ML (1992) Encephalopathy due to repeated voluntary inhalation of paradichlorobenzene. *Journal De Toxicologie Clinique Et Experimentale* 12:247–250
51. Hernandez SH, Wiener SW, Smith SW (2010) Case files of the New York City poison control center: paradichlorobenzene-induced leukoencephalopathy. *J Med Toxicol* 6:217–229
52. Peyravi M, Mirzayan MJ, Krauss JK (2012) Fatal outcome despite bilateral decompressive craniectomy for refractory intracranial pressure increase in butane intoxication. *Clin Neurol Neurosurg* 114:392–393
53. D'Costa DF, Gunasekera NP (1990) Fatal cerebral oedema following trichloroethane abuse. *J Royal Soc Med* 83:533–534
54. Mutez E, Le Rhun E, Perriol MP et al (2006) Trichloroethylene intoxication presenting with temporal seizures. *Rev Neurol* 162:1248–1251
55. Rutchik JS, Wittman RI (2004) Neurologic issues with solvents. *Clinics in occupational and environmental medicine* 4:621–56
56. Rosenberg NL, Grigsby J, Dreisbach J, Busenbark D, Grigsby P (2002) Neuropsychologic impairment and MRI abnormalities associated with chronic solvent abuse. *J Toxicol Clin Toxicol* 40:21–34
57. Takagi M, Yucel M, Cotton SM et al (2011) Verbal memory, learning, and executive functioning among adolescent inhalant and cannabis users. *J Stud Alcohol Drugs* 72:96–105
58. Dingwall KM, Cairney S (2011) Recovery from central nervous system changes following volatile substance misuse. *Subst Use Misuse* 46:73–83
59. Cairney S, Maruff P, Burns CB, Currie J, Currie BJ (2005) Neurological and cognitive recovery following abstinence from petrol sniffing. *Neuropsychopharmacology* 30:1019–1027
60. Holmes JT, Filley CM, Rosenberg NL (1986) Neurologic sequelae of chronic solvent vapor abuse. *Neurology* 36:698–702
61. Lloyd MJ, Fraunfelder FW (2007) Drug-induced optic neuropathies. *Drugs Today* 43:827–836
62. Twardowsky CA, Teive HA, Siquineli F et al (2008) Optic neuritis due to solvent abuse. *Arquivos de neuro-psiquiatria* 66:108–110
63. Tamrazi B, Almast J (2012) Your brain on drugs: imaging of drug-related changes in the central nervous system. *Radiographics* 32:701–719
64. Borne J, Riascos R, Cuellar H, Vargas D, Rojas R (2005) Neuroimaging in drug and substance abuse part II: opioids and solvents. *Top Magn Reson Imaging* 16:239–245
65. Hashizume A, Koike H, Kawagashira Y et al (2011) Central nervous system involvement in n-hexane polyneuropathy demonstrated by MRI and proton MR spectroscopy. *Clin Neurol Neurosurg* 113:493–495
66. Robinson RO (1978) Tetraethyl lead poisoning from gasoline sniffing. *JAMA* 240:1373–1374
67. Boeckx RL, Postl B, Coodin FJ (1978) Gasoline sniffing and tetraethyl lead poisoning in children. *Pediatrics* 60:140–145
68. Goodheart RS, Dunne JW (1994) Petrol sniffer's encephalopathy. A study of 25 patients. *Med J Aust* 160:178–181
69. Ross CA (1982) Gasoline sniffing and lead encephalopathy. *Can Med Assoc J* 127:1195–1197
70. Clune AL, Falk H, Riederer AM (2011) Mapping Global Environmental Lead Poisoning in Children. *Journal of Health and Pollution*. 1. Retrieved on February 13, 2013 from <http://www.journalhealthpollution.org/ojs/ojs2.2.4/index.php/journalhealthpollution/article/view/43/64>.
71. Tenenbein M (1997) Leaded gasoline abuse: the role of tetraethyl lead. *Hum Exp Toxicol* 16:217–222
72. King GS, Smialek JE, Troutman WG (1985) Sudden death in adolescents resulting from the inhalation of typewriter correction fluid. *JAMA* 253:1604–1606
73. Smeeton WM, Clark MS (1985) Sudden death resulting from inhalation of fire extinguishers containing bromochlorodifluoromethane. *Med Sci Law* 25:258–262
74. Brady WJ Jr, Stremski E, Eljaiek L, Aufderheide TP (1994) Freon inhalational abuse presenting with ventricular fibrillation. *Am J Emerg Med* 12:533–536
75. Rohrig TP (1997) Sudden death due to butane inhalation. *The Am J Forensic Med Pathol* 18:299–302
76. Williams DR, Cole SJ (1998) Ventricular fibrillation following butane gas inhalation. *Resuscitation* 37:43–45
77. Sugie H, Sasaki C, Hashimoto C et al (2004) Three cases of sudden death due to butane or propane gas inhalation: analysis of tissues for gas components. *Forensic Sci Int* 143:211–214
78. Rieder-Scharinger J, Peer R, Rabl W, Hasibeder W, Schobersberger W (2000) Multiple organ failure following inhalation of butane gas: a case report. *Wien Klin Wochenschr* 112:1049–1052
79. LoVecchio F, Fulton SE (2001) Ventricular fibrillation following inhalation of Glade Air Freshener. *Eur J Emerg Med* 8:153–154
80. Girard F, Le Tacon S, Maria M, Pierrard O, Monin P (2008) Ventricular fibrillation following deodorant spray inhalation. *Annales francaises d'anesthesie et de reanimation* 27:83–85
81. Godlewski K, Werner B, Sterlinski M et al (2006) Myocardial infarction after butane inhalation in a 14-year-old boy. *Kardiologia polska* 64:305–308
82. De Naeyer AH, de Kort SW, Portegies MC, Deraedt DJ, Buysse CM (2011) Myocardial infarction in a 16-year old following inhalation of butane gas. *Ned Tijdschr Geneeskde* 155:A3443
83. Edwards KE, Wenstone R (2000) Successful resuscitation from recurrent ventricular fibrillation secondary to butane inhalation. *Br J Anaesth* 84:803–805
84. Woods DT, Perry AW, Solomou S (2012) The neuropsychological sequelae of a 14-year-old girl following successful resuscitation from ventricular fibrillation and collapse secondary to butane gas inhalation. *Resuscitation* 83:e214–e215
85. Dodd DE, Vinegar A (1998) Cardiac sensitization testing of the halon replacement candidates trifluoriodomethane (CF3I) and 1,1,2,2,3,3,3-heptafluoro-1-iodopropane (C3F7I). *Drug Chem Toxicol* 21:137–149
86. Reinhardt CF, Mullin LS, Maxfield ME (1973) Epinephrine-induced cardiac arrhythmia potential of some common industrial solvents. *J Occup Med* 15:953–955

87. Alper AT, Akyol A, Hasdemir H et al (2008) Glue (toluene) abuse: increased QT dispersion and relation with unexplained syncope. *Inhal Toxicol* 20:37–41
88. Ueda H, Hayashi T, Tsumura K et al (2007) QT dispersion and prognosis after coronary stent placement in acute myocardial infarction. *Clin Cardiol* 30:229–233
89. Lin YL, Hsiao CL, Wu YC, Kung MF (2011) Electrophysiologic, pharmacokinetic, and pharmacodynamic values indicating a higher risk of torsades de pointes. *J Clin Pharmacol* 51:819–829
90. Himmel HM (2008) Mechanisms involved in cardiac sensitization by volatile anesthetics: general applicability to halogenated hydrocarbons? *Crit Rev Toxicol* 38:773–803
91. Cruz SL, Orta-Salazar G, Gauthereau MY, Millan-Perez Pena L, Salinas-Stefanon EM (2003) Inhibition of cardiac sodium currents by toluene exposure. *Br J Pharmacol* 140:653–660
92. El-Menyar AA, El-Tawil M, Al Suwaidi J (2005) A teenager with angiographically normal epicardial coronary arteries and acute myocardial infarction after butane inhalation. *Eur J Emerg Med* 12:137–141
93. Samson R, Kado H, Chapman D (2012) Huffing-induced cardiomyopathy: a case report. *Cardiovasc Toxicol* 12:90–92
94. Lisowska A, Skibinska E, Musial WJ (2004) Severe heart failure due to toxic cardiomyopathy in a young patient—a case report. *Kardiologia polska* 60:372–373
95. Vural M, Ogel K (2006) Dilated cardiomyopathy associated with toluene abuse. *Cardiology* 105:158–161
96. Steffee CH, Davis GJ, Nicol KK (1996) A whiff of death: fatal volatile solvent inhalation abuse. *Southern Med J* 89:879–884
97. McLeod AA, Marjot R, Monaghan MJ, Hugh-Jones P, Jackson G (1987) Chronic cardiac toxicity after inhalation of 1,1,1-trichloroethane. *Br Med J (Clin Res Ed)* 294:727–729
98. Pfeiffer H, Al Khaddam M, Brinkmann B, Kohler H, Beike J (2006) Sudden death after isobutane sniffing: a report of two forensic cases. *Int J Legal Med* 120:168–173
99. Phatak DR, Walterscheid J (2012) Huffing air conditioner fluid: a cool way to die? *The Am J Forensic Med Pathol* 33:64–67
100. Heyer EJ, Simpson DM, Bodis-Wollner I, Diamond SP (1986) Nitrous oxide: clinical and electrophysiologic investigation of neurologic complications. *Neurology* 36:1618–1622
101. Layzer RB (1978) Myeloneuropathy after prolonged exposure to nitrous oxide. *Lancet* 2:1227–1230
102. Shimizu T, Nishimura Y, Fujishima Y, Miyajima H, Honda N (1989) Subacute myeloneuropathy after abuse of nitrous oxide: an electron microscopic study on the peripheral nerve. *Clinical Neurol* 29:1129–1135
103. Blanco G, Peters HA (1983) Myeloneuropathy and macrocytosis associated with nitrous oxide abuse. *Arch Neurol* 40:416–418
104. Drummond JT, Matthews RG (1994) Nitrous oxide inactivation of cobalamin-dependent methionine synthase from *Escherichia coli*: characterization of the damage to the enzyme and prosthetic group. *Biochemistry* 33:3742–3750
105. Ghobrial GM, Dalyai R, Flanders AE, Harrop J (2012) Nitrous oxide myelopathy posing as spinal cord injury. *J Neurosurg Spine* 16:489–491
106. Butzkueven H, King JO (2000) Nitrous oxide myelopathy in an abuser of whipped cream bulbs. *J Clin Neurosci* 7:73–75
107. Krajewski W, Kucharska M, Pilacik B et al (2007) Impaired vitamin B12 metabolic status in healthcare workers occupationally exposed to nitrous oxide. *Br J Anaesth* 99:812–818
108. Lin RJ, Chen HF, Chang YC, Su JJ (2011) Subacute combined degeneration caused by nitrous oxide intoxication: case reports. *Acta Neurologica Taiwanica* 20:129–137
109. Senol MG, Sonmez G, Ozdag F, Saracoglu M (2008) Reversible myelopathy with vitamin B12 deficiency. *Singap Med J* 49:e330–e332
110. Srikanth SG, Jayakumar PN, Vasudev MK, Taly AB, Chandrashekar HS MRI in subacute combined degeneration of spinal cord: a case report and review of literature. *Neurology India* 50:310–2
111. Kuwabara S, Kai MR, Nagase H, Hattori T (1999) *n*-Hexane neuropathy caused by addictive inhalation: clinical and electrophysiological features. *Eur Neurol* 41:163–167
112. Smith AG, Albers JW (1997) *n*-Hexane neuropathy due to rubber cement sniffing. *Muscle Nerve* 20:1445–1450
113. Hall DM, Ramsey J, Schwartz MS, Dookun D (1986) Neuropathy in a petrol sniffer. *Arch Dis Child* 61:900–901
114. Tenenbein M, deGroot W, Rajani KR (1984) Peripheral neuropathy following intentional inhalation of naphtha fumes. *Can Med Assoc J* 131:1077–1079
115. Altenkirch H, Mager J, Stoltenburg G, Helmbrecht J (1997) Toxic polyneuropathies after sniffing a glue thinner. *J Neurol* 214:137–152
116. Korobkin R, Asbury AK, Sumner AJ, Nielsen SL (1975) Glue-sniffing neuropathy. *Arch Neurol* 32:158–162
117. Chang AP, England JD, Garcia CA, Sumner AJ (1998) Focal conduction block in *n*-hexane polyneuropathy. *Muscle Nerve* 21:964–969
118. Huang CC (2008) Polyneuropathy induced by *n*-hexane intoxication in Taiwan. *Acta Neurologica Taiwan* 17:3–10
119. Weintraub E, Gandhi D, Robinson C (2000) Medical complications due to mothball abuse. *South Med J* 93:427–429
120. Szlatenyi CS, Wang RY (1996) Encephalopathy and cranial nerve palsies caused by intentional trichloroethylene inhalation. *Am J Emerg Med* 14:464–466
121. Garrel S, Barret L (1986) Somatosensory evoked potentials of the trigeminal nerve in chronic trichloroethylene poisoning. *Revue D'electroencephalographie Et De Neurophysiologie Clinique* 16:133–139
122. Annau Z (1981) The neurobehavioral toxicity of trichloroethylene. *Neurobehav Toxicol Teratol* 3:417–424
123. Ehyai A, Freeman FR (1983) Progressive optic neuropathy and sensorineural hearing loss due to chronic glue sniffing. *J Neurol Neurosurg Psychiatry* 46:349–351
124. Williams DM (1988) Hearing loss in a glue sniffer. *J Otolaryngol* 17:321–324
125. Buker HS, Demir E, Yuncu Z, Gulen F, Midyat L, Tanac R (2011) Effects of volatile substance abuse on the respiratory system in adolescents. *Multidisciplinary Respiratory Medicine* 6:161–168
126. Flanagan RJ, Ives RJ (1994) Volatile Substance Abuse, United Nations Office on Drugs and Crime. Retrieved on January 28, 2013 from http://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1994-01-01_2_page007.html.
127. Cayir D, Demirel K, Korkmaz M, Koca G (2011) Evaluation of lung epithelial permeability in the volatile substance abuse using Tc-99m DTPA aerosol scintigraphy. *Ann Nucl Med* 25:554–559
128. Sundram FX (1995) Clinical studies of alveolar-capillary permeability using technetium-99m DTPA aerosol. *Ann Nucl Med* 9:171–178
129. Burkhart KK, Britt A, Petrini G, O'Donnell S, Donovan JW (1996) Pulmonary toxicity following exposure to an aerosolized leather protector. *J Toxicol Clin Toxicol* 34:21–24
130. Shah MK (2002) Outcomes in patients with Goodpasture's syndrome and hydrocarbon exposure. *Ren Fail* 24:545–555
131. Schloneger M, Stull A, Singer JI. Inhalant abuse: a case of hemoptysis associated with halogenated hydrocarbons abuse. *Pediatr Emerg Care* 25:754–7
132. Kurniali PC, Henry L, Kurl R, Meharg JV (2012) Inhalant abuse of computer cleaner manifested as angioedema. *Am J Emerg Med* 30(265):e3–e5
133. Kuspis DA, Krenzelok EP (1999) Oral frostbite injury from intentional abuse of a fluorinated hydrocarbon. *J Toxicol Clin Toxicol* 37:873–875

134. Albright JT, Lebovitz BL, Lipson R, Luft J (1999) Upper aerodigestive tract frostbite complicating volatile substance abuse. *Int J Pediatr Otorhinolaryngol* 49:63–67
135. Kurbat RS, Pollack CV Jr (1998) Facial injury and airway threat from inhalant abuse: a case report. *J Emerg Med* 16:167–169
136. Elliott DC (1991) Frostbite of the mouth: a case report. *Military Medicine* 156:18–19
137. Weber LW, Boll M, Stampfl A (2003) Hepatotoxicity and mechanism of action of haloalkanes: carbon tetrachloride as a toxicological model. *Crit Rev Toxicol* 33:105–136
138. McIntyre AS, Long RG (1992) Fatal fulminant hepatic failure in a “solvent abuser”. *Postgrad Med J* 68:29–30
139. Beisland HO, Wannag SA (1970) Trichloroethylene sniffing. Acute liver and kidney damage. *Tidsskrift for den Norske lægeforening* 90:285–288
140. Clearfield HR (1970) Hepatorenal toxicity from sniffing spot-remover (trichloroethylene). Report of 2 cases. *Am J Dig Dis* 15:851–856
141. Takaki A, Suzuki H, Iwasaki Y et al (2008) A 27-year-old man who died of acute liver failure probably due to trichloroethylene abuse. *J Gastroenterol* 43:239–242
142. Ramdhan DH, Kamijima M, Yamada N et al (2008) Molecular mechanism of trichloroethylene-induced hepatotoxicity mediated by CYP2E1. *Toxicol Appl Pharmacol* 231:300–307
143. Battle DC, Sabatini S, Kurtzman NA (1988) On the mechanism of toluene-induced renal tubular acidosis. *Nephron* 49:210–218
144. Dickson RP, Luks AM (2009) Toluene toxicity as a cause of elevated anion gap metabolic acidosis. *Respir Care* 54:1115–1117
145. Erramouspe J, Galvez R, Fischel DR (1996) Newborn renal tubular acidosis associated with prenatal maternal toluene sniffing. *J Psychoactive Drugs* 28:201–204
146. Lock EA, Reed CJ (2006) Trichloroethylene: mechanisms of renal toxicity and renal cancer and relevance to risk assessment. *Toxicol Sci* 91:313–331
147. Dubosq F, Linke C, Cardot V, Meria P, Desgrandchamps F, Teillac P (2005) Renal cell carcinoma and trichloroethylene. *Progres en urologie* 15:525–528
148. Wilkerson RG (2010) Getting the blues at a rock concert: a case of severe methaemoglobinaemia. *Emerg Med Australas* 22:466–469
149. Modarai B, Kapadia YK, Kerins M, Terris J (2002) Methylene blue: a treatment for severe methaemoglobinaemia secondary to misuse of amyl nitrite. *Emerg Med J* 19:270–271
150. Edwards RJ, Ujma J (1995) Extreme methaemoglobinaemia secondary to recreational use of amyl nitrite. *J Accid Emerg Med* 12:138–142
151. Stambach T, Haire K, Soni N, Booth J (1997) Saturday night blue—a case of near fatal poisoning from the abuse of amyl nitrite. *J Accid Emerg Med* 14:339–340
152. Praharaj SK, Kongasseri S (2012) Naphthalene Addict Subst Abus 33:189–190
153. Valaes T, Doxiadis SA, Fessas P (1963) Acute hemolysis due to naphthalene inhalation. *J Pediatr* 63:904–915
154. Santucci K, Shah B (2000) Association of naphthalene with acute hemolytic anemia. *Acad Emerg Med* 7:42–47
155. Athanasiou M, Tsantali C, Trachana M, Hatzioannides C (1997) Hemolytic anemia in a female newborn infant whose mother inhaled naphthalene before delivery. *J Pediatr* 130:680–681
156. Raphael M, Nadiras P, Flacke-Vordos N (2002) Acute methylene chloride intoxication—a case report on domestic poisoning. *Eur J Emerg Med* 9:57–59
157. Horowitz BZ (1986) Carboxyhemoglobinemia caused by inhalation of methylene chloride. *Am J Emerg Med* 4:48–51
158. Rioux JP, Myers RAM (1998) Methylene chloride poisoning: a paradigmatic review. *J Emerg Med* 6:227–238
159. Peckham T, Kopstein M, Klein J, Dahlgren J (2012), Benzene-contaminated toluene and acute myeloid leukemia: a case series and review of literature. *Toxicology and industrial health*. Epub ahead of print Jun 27, 2012
160. Lasala BJ, Zaenglein AL (2012) Cutaneous and mucosal blistering secondary to “Huffing”. *Pediatr Dermatol*. Epub September 4, 2012
161. Janezic TF (1997) Burns following petrol sniffing. *Burns* 23:78–80
162. Ho WS, To EW, Chan ES, King WW (1998) Burn injuries during paint thinner sniffing. *Burns* 24:757–759
163. Levine B (2003) Principles of forensic toxicology, 2nd edn. AACCC, Washington, DC
164. Wang RS, Nakajima T, Honma T (1999) Trichloroethylene inhibits aldehyde dehydrogenase only for aliphatic aldehydes of short chains in rats. *Toxicology* 132:9–18
165. Bowen SE (2011) Two serious and challenging medical complications associated with volatile substance misuse: sudden sniffing death and fetal solvent syndrome. *Subst Use Misuse* 46(Suppl 1):68–72
166. Hersh JH, Podruch PE, Rogers G, Weisskopf B (1985) Toluene embryopathy. *J Pediatr* 106:922–927
167. Hersh JH (1989) Toluene embryopathy: two new cases. *J Med Genet* 26:333–337
168. Arai H, Yamada M, Miyake S et al (1997) Two cases of toluene embryopathy with severe motor and intellectual disabilities syndrome. *Brain Dev* 29:361–366
169. Pearson MA, Hoyme HE, Seaver LH, Rimsza ME (1994) Toluene embryopathy: delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 93:211–215
170. Ozmen S, Seckin N, Turhan NO, Dilmenc G, Dilmenc U (1995) Fetal methemoglobinemia: a cause of nonimmune hydrops fetalis. *Am J Obstet Gynecol* 173:232–233
171. Dodd J (2001) Petrol sniffing in a pregnant Aboriginal population: a review of maternal and neonatal outcomes. *Aust N Z J Obstet Gynaecol* 41:420–423
172. Tenenbein M, Casiro OG, Seshia MM, Debooy VD. Neonatal withdrawal from maternal volatile substance abuse. *Archives of disease in childhood Fetal and neonatal edition*. 74, F204-7
173. Nee PA, Llewellyn T, Pritty PE (1990) Successful out-of-hospital defibrillation for ventricular fibrillation complicating solvent abuse. *Arch Emerg Med* 7:220–223
174. Senthilkumaran S, Meenakshisundaram R, Michaels AD, Balamurgan N, Thirumalaikolundusubramanian P (2012) Ventricular fibrillation after exposure to air freshener-death just a breath away. *J Electrocardiol* 45:164–166
175. Tang W, Weil MH, Sun S, Noc M, Yang L, Gazmuri RJ (1995) Epinephrine increases the severity of postresuscitation myocardial dysfunction. *Circulation* 92:3089–3093
176. de Oliveira FC, Feitosa-Filho GS, Ritt LE (2012) Use of beta-blockers for the treatment of cardiac arrest due to ventricular fibrillation/pulseless ventricular tachycardia: a systematic review. *Resuscitation* 83:674–683
177. Nademane K, Taylor R, Bailey WE, Rieders DE, Kosar EM (2000) Treating electrical storm : sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation* 102:742–747
178. Miwa Y, Ikeda T, Mera H et al (2010) Effects of landiolol, an ultra-short-acting beta1-selective blocker, on electrical storm refractory to class III antiarrhythmic drugs. *Circ J* 74:856–863
179. Wiest DB, Haney JS (2012) Clinical pharmacokinetics and therapeutic efficacy of esmolol. *Clin Pharmacokinet* 51:347–356
180. Burns CB, Currie B The efficacy of chelation therapy and factors influencing mortality in lead intoxicated petrol sniffers. *Aust N Z J Med*. 25:197–203

181. Skacel PO, Chanarin I, Hewlett A, Nunn JF (1982) Failure to correct nitrous oxide toxicity with folinic acid. *Anesthesiology* 57:557–558
182. Amos RJ, Amess JA, Nancekivell DG, Rees GM (1984) Prevention of nitrous oxide-induced megaloblastic changes in bone marrow using folinic acid. *Br J Anaesth* 56:103–107
183. Nunn JF, Chanarin I, Tanner AG, Owen ER (1986) Megaloblastic bone marrow changes after repeated nitrous oxide anaesthesia. Reversal with folinic acid. *Br J Anaesth* 58:1469–1470
184. Lee JH, Sung CH, Moon SH, Kim SN, Chung WH (1993) Folinic acid protection against hematopoietic depression induced by nitrous oxide in rats. *Anesth Analg* 77:356–361
185. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA (2002) American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol* 40:415–446
186. Rioux JP, Myers RA (1988) Methylene chloride poisoning: a paradigmatic review. *J Emerg Med* 6:227–238
187. Rioux JP, Myers RA (1989) Hyperbaric oxygen for methylene chloride poisoning: report on two cases. *Ann Emerg Med* 18:691–695
188. Rudge FW (1990) Treatment of methylene chloride induced carbon monoxide poisoning with hyperbaric oxygenation. *Military Med* 155:570–572
189. Galicia-Moreno M, Rodriguez-Rivera A, Reyes-Gordillo K et al (2009) N-acetylcysteine prevents carbon tetrachloride-induced liver cirrhosis: role of liver transforming growth factor-beta and oxidative stress. *Eur J Gastroenterol Hepatol* 21:908–914
190. Gerkin RD Jr, LoVecchio F (1998) Rapid reversal of life-threatening toluene-induced hypokalemia with hemodialysis. *J Emergency Med* 16:723–725
191. MacLean S, Cameron J, Harney A, Lee NK (2012) Psychosocial therapeutic interventions for volatile substance use: a systematic review. *Addiction* 107:278–288