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# **Methamphetamine: History, Pathophysiology, Adverse Health Effects, Current Trends, and Hazards Associated with the Clandestine Manufacture of Methamphetamine**

**David Vearrier, MD,  
Michael I. Greenberg, MD, MPH,  
Susan Ney Miller, MD, Jolene T. Okaneku, MD, and  
David A. Haggerty, MD**

## **Introduction**

Developed as an amphetamine derivative, methamphetamine quickly became a popular medication during the 1940s and 1950s, prescribed for a variety of indications. Extensive diversion of methamphetamine during the 1960s and an increasing awareness of the adverse health effects associated with methamphetamine led to the withdrawal of most of the indications for licit methamphetamine use and declines in legal production of the drug. However, the illicit manufacture of methamphetamine increased to meet the demand for methamphetamine, and methamphetamine abuse has increased with variable geographic penetrance over the last 30 years.

Methamphetamine is an indirect sympathomimetic agent that is distinguished from amphetamine by a more rapid distribution into the central nervous system (CNS), resulting in the rapid onset of euphoria that is the desired effect for those abusing the drug. Increases in monoamine neurotransmission are responsible for the desired effects—wakefulness, energy, sense of well-being, and euphoria—as well as the excess sympathetic tone that mediates many its adverse health effects.

Methamphetamine is associated with adverse effects to every organ system. Although the most significant morbidity and mortality occur because of cardiovascular effects, such as myocardial infarction and hypertensive crisis, no organ system remains unscathed by methamphet-

amine abuse. Methamphetamine abuse is a serious public health problem because of both costs associated with treatment of methamphetamine-associated adverse health effects and crime and violence perpetrated to obtain methamphetamine or because of methamphetamine-related aggressive behavior.

Of further concern are the hazards and environmental effects of “meth labs,” frequently small operations housed in residential buildings, where methamphetamine is manufactured from precursor chemicals. Hazards associated with methamphetamine laboratories include blast injuries, thermal burns, chemical injury, and toxic exposures. Unfortunately, a significant percentage of methamphetamine laboratories are housed in residential buildings where children are present, potentially resulting in pediatric exposures to methamphetamine, precursor chemicals, and drug use paraphernalia.

This article reviews the history of methamphetamine use and abuse, describes its mechanism of action and pathophysiology, delineates adverse health effects, and describes current epidemiologic trends. It also discusses the process and precursor chemicals involved in the manufacture of methamphetamine and hazards associated with clandestine methamphetamine laboratories.

## The History of Methamphetamine

### Discovery and Early Methamphetamine Use

Amphetamine-type stimulants, which include methamphetamine and amphetamine, were developed as synthetic alternatives to ephedra. Ephedra is a botanic extract of *Ephedra sinica* and has been used in traditional Chinese medicine as ma huang for over 5000 years. In 1885, ephedrine, the active alkaloid present in ephedra, was extracted and studied. Ephedrine was recognized to be similar to epinephrine, which was also isolated around the turn of the 20th century, but could be taken orally, had a longer duration of action, produced more pronounced and dependable CNS stimulation, and had a larger therapeutic index. The search for a synthetic ephedrine substitute resulted in the development of amphetamine-type stimulants, produced via modification of the ephedrine skeleton with the pharmaceutical goals of CNS stimulation, bronchodilation, or nasal vasoconstriction.<sup>1-3</sup> Japanese chemist Akira Ogata first synthesized methamphetamine in 1919 using ephedrine as a precursor.

Early amphetamine use was primarily via nasal insufflation. In 1932, Smith, Kline, and French began marketing the amphetamine inhaler Benzedrine for use in asthma and congestion. The insufflated amphet-

amine caused vasoconstriction of the nasal mucosa, decreasing mucosal swelling and edema, and the inhaler was initially available without a prescription. In 1959 the S. Pfeiffer Company began producing Valo inhalers that contained 150-200 mg of methamphetamine.<sup>4,5</sup>

## The Heyday of Licit Methamphetamine Use

Desirable “side effects” associated with amphetamine-type stimulant inhalers were noted, resulting in expanding indications for amphetamines and the introduction of oral amphetamine-type stimulant medications. For example, the side effect of wakefulness suggested its value in treating narcolepsy and conditions of drowsiness or exhaustion. Its appetite-depressant effects led to the use of amphetamines, including methamphetamine, for weight loss.<sup>4</sup> Other early indications and off-label uses for methamphetamine included schizophrenia, asthma, morphine addiction, barbiturate intoxication and narcosis, alcoholism, excessive anesthesia administration, migraine, heart block, myasthenia gravis, myotonia, enuresis, dysmenorrhea, Meniere’s disease, colic, head injuries, hypotension, seasickness, persistent hiccups, heart block, head injuries, infantile cerebral palsy, codeine addiction, tobacco smoking, pediatric behavior issues, Parkinson’s disease, and epilepsy.<sup>5</sup> Amphetamines and their analogs were being presumptively promoted as effective and safe without risk of addiction. In 1940, methamphetamine tablets under the commercial name Methedrine were introduced to the market by the Burroughs Wellcome Company.<sup>1,6</sup>

Methamphetamine was also used by the military. In World War II, methamphetamine was available to military personnel as Pervitin in Germany and Philopon in Japan. Temmler Pharmaceutical Company introduced Pervitin in 1938 to the European market. Pervitin was available as 3 mg tablets that physicians could provide for the German military units. Dainippon Pharmaceutical Company made Philopon available in Japan in 1941. Methamphetamine in Germany and Japan and amphetamine use in the USA were used to increase alertness, reduce fatigue, and suppress the appetite of soldiers.<sup>4,5</sup> Use of methamphetamine extended to include war-related industry workers to improve shift work abilities. Later, the USA military used amphetamines in the Korean War and the Vietnam War. Today, the use of stimulants, like amphetamines and methamphetamine, is permitted to treat combat fatigue and promote wakefulness in combat. A survey of Persian Gulf War pilots reported substantial use of stimulants to decrease fatigue during combat.<sup>1</sup>

During the 1940s and 1950s, methamphetamine was liberally prescribed for numerous indications and large quantities of it were licitly produced.

A broad segment of the population used methamphetamine for a variety of reasons. Housewives, truck drivers, students, and professionals used amphetamines and methamphetamine to promote wakefulness, improve mood or attention, and lose weight. Numerous users gradually increased the doses they used as they developed tolerance to the effects of the drugs.<sup>1,4,5</sup>

The ways in which the medications could be misused spread quickly. Inhalers could be broken open and the contents ingested directly or filters could be soaked in alcohol or coffee to reduce irritation of the mouth. Extracting drugs from inhalers for intravenous injection was another method of abuse, first being reported in 1959. Reports of robberies, murder, and other violent acts were linked to inhaler misuse.<sup>4,5</sup> Prison populations also abused these inhalers, which could be smuggled within containers or letters. Methamphetamine abusers would combine the drug with illicit substances, such as heroin or barbiturates. Use in conjunction with a barbiturate produced what was referred to as “bolt and jolt,” a street term for the increased pleasure associated with this combination of drugs.<sup>1,4,5</sup>

In response to a Food and Drug Administration warning of misapplication of the inhalers, some pharmaceutical companies responded by adding a denaturant to deter ingestion. Abusers adapted by injecting the product after boiling off the denaturant. In 1959, the Food and Drug Administration restricted amphetamine and dextroamphetamine inhalers to prescription-only distribution. Methamphetamine inhalers, such as Valo, continued to be marketed until 1965. Starting with Benzedrine in 1949, most of these nasal inhalers were removed from the market by 1971.<sup>4</sup>

## The Gradual Recognition of Adverse Health Effects

Reports of serious adverse health effects of amphetamines began appearing as early as 1935. One early study reported that even at the recommended therapeutic dose of an amphetamine inhaler, most subjects experienced pallor, flushing, palpitations, and increases in pulse rate and blood pressure. Six of the 20 subjects in that study developed multiple extrasystoles and chest pain. Other studies reported convulsions, coma, loss of consciousness, nausea, vomiting, difficulty breathing, tremor, tetany, tachycardia, pallor, psychosis, and cyanosis.<sup>4,5</sup>

As an early response to recognition of potential dangers associated with amphetamine use and misuse, state and federal restrictions were enacted, halting the over-the-counter sale of oral amphetamine preparations. These restrictions required that amphetamines be marketed under a label

**TABLE 1.** Street names for methamphetamine

Meth	Dimethylphenethylamine
Speed	Methedrine
Crystal meth	Desoxyn
Ice	Chalk
Batu	Poor man's cocaine
Shabu	Tweak
Glass	Uppers
Tina	Biker's coffee
Crank	Trash
Go-fast	Black beauties
Stove top	Methlies quick
Yaba	Yellow barn

warning against use except under medical supervision. However, inhalers containing amphetamines or methamphetamine were not covered under this regulation.<sup>4</sup>

As the abuse of methamphetamine increased, so did the number of monikers associated with the drug (Table 1). During the 1960s, the term “speed freaks” became popular to describe high-dose, compulsive users of amphetamine and methamphetamine.<sup>1,5</sup> Demographically, amphetamine-type stimulant abuse at that time was most common among Caucasians with a middle-class socioeconomic status. The prevention slogan “speed kills” was introduced by antidrug activists during the 1960s, prompted by the serious medical and psychiatric consequences of abuse, although some argue that the slogan may have done as much to popularize the abuse of amphetamines as to prevent it.

In response to the burgeoning diversion of legally produced amphetamine-type stimulants to the criminal underworld, the USA federal government passed the Drug Abuse Control Amendments of 1965, which required record keeping throughout the manufacture, distribution, prescription, and sale of these medications. Ultimately, this bill was ineffective in preventing diversion of amphetamine-type stimulants to the black market. Subsequently, the Comprehensive Drug Abuse Prevention and Control Act of 1970 limited the accepted medical uses for prescribed amphetamines and classified amphetamines as Schedule II medications. Over the course of the 1970s, there was a gradual decrease in the number of amphetamines prescribed and decreasing legal production of the drugs was resulting in less diversion to the street. A 90% decrease from prelegislation level was accomplished by the mid-1980s; the rate at which amphetamines was being prescribed had decreased by 90% from the

heyday of the 1960s and continued to decrease by another one-third by 1990.<sup>1</sup>

## Diversion of Pharmaceutical Products and Illicit Manufacture

It has been estimated that legal pharmaceutical production of amphetamine was 3.5 billion tablets in 1958, enough to supply every person in the USA at the time with 20 standard doses.<sup>4</sup> Prescriptions peaked in 1967 at 31 million, whereas amphetamine production increased to 10 billion tablets by 1970.<sup>7</sup> A consequence of the overproduction of amphetamines was diversion to illegal traffic. Supplies of amphetamine and methamphetamine from legal production found their way to the black market via pharmaceutical companies, wholesalers, pharmacists, and physicians.<sup>4,6</sup>

Illegal manufacture of methamphetamine emerged as a new source of the drug and became increasingly important as a diversion of licitly produced methamphetamine became more difficult. The first known illicit production of methamphetamine occurred in 1962 in San Francisco, CA. During the late 1960s, the Haight-Ashbury neighborhood of San Francisco became a center of methamphetamine abuse, particularly among young adults and college students. Illegal manufacture was imperfect and the methamphetamine contained substantial amounts of impurities. However, by the mid-1980s, virtually all street methamphetamine was manufactured in clandestine laboratories rather than diverted from legally produced pharmaceutical products.<sup>5,7,8</sup>

Association with motorcycle gangs led to the early reputation of methamphetamine as a “biker drug” in the 1960s and 1970s. The nickname “crank” originated from the bikers’ tendency to transport the methamphetamine in the crankcases of their motorcycles. Motorcycle gangs, including Hell’s Angels, were responsible for manufacturing and distributing methamphetamine along the Pacific Coast and have been associated with distribution networks that contributed to a rise in methamphetamine use in the 1960s. These motorcycle gangs contributed up to 90% of methamphetamine produced in the USA in the 1970s and 1980s. Their customer base was primarily in Southern California and Oregon and much of the distribution involved the intravenous or crushable tablet form.<sup>1</sup> Eventually, as illicit production of methamphetamine shifted to Mexico, the motorcycle gangs transitioned to purchasing methamphetamine from Mexican manufacturers and focused their profit-making on the distribution of the drug.<sup>1,7</sup>

Following a lull in amphetamine and methamphetamine use during the 1970s and early 1980s because of declining prescriptions and licit

**TABLE 2.** Selected methods of self-administration of methamphetamine

<b>Method of Administration</b>	<b>Slang Terms Associated with Technique</b>
Anal suppository	Butt rocket, plugging
Ingestion	None
Inhalation	Chasing the white dragon
Insufflation	Snorting
Intravenous injection	Banging, mainlining, slamming
Vaginal suppository	None

production, methamphetamine use in the West Coast began to increase again in the mid-1980s and steadily spread into the Midwest through the 1990s. The Northeast and Mid Atlantic were relatively spared up until just this past decade.<sup>1</sup> Epidemiologically, methamphetamine abuse in the 1980s occurred predominantly among Caucasian males, many of whom were truck drivers, construction workers, and other blue-collar workers.

During this period, a new form of methamphetamine, methamphetamine hydrochloride, was popularized. “Ice” or “crystal meth,” as methamphetamine hydrochloride was called, could be smoked, resulting in an almost immediate onset of euphoria and contributing to its increasing popularity among amphetamine abusers. The epidemic started in West Honolulu and included those from the working class, public housing projects, and Filipino community, but over time expanded to Hawaii and the West Coast and then throughout the USA.<sup>7,8</sup> Table 2 describes some of the more popular methods of methamphetamine self-administration. More legislation was passed during this period, which included the Federal Controlled Substance Analogue Enforcement Act of 1986 and Chemical Diversion and Trafficking Act of 1988, with the latter act regulating precursor chemicals in an attempt to stem the illicit production of methamphetamine.<sup>2</sup>

The 1990s experienced an expansion of local manufacture and regional distribution of methamphetamine. Manufacturing in both “mom-and-pop labs” and large-scale “super labs” became widespread throughout the West Coast and Midwest states. In areas with adequate illicit drug infrastructure and high methamphetamine demand, like the Central Valley of California, organized networks of producers and distributors predominate. In areas with less established infrastructure, the methamphetamine supply is produced by local “cooks” and distributed by a relational network of people. Clandestine laboratories are often, although not exclusively, set up in rural areas because of the strong odors associated with methamphetamine production and are moved frequently to prevent detection.

In response to an epidemic of methamphetamine abuse, the federal government has passed measures designed to stem rising methamphetamine manufacture and abuse. The Methamphetamine Control Act of 1996 was passed to strengthen penalties and tighten controls on precursors.<sup>7,8</sup> The most recent federal law is the Combat Methamphetamine Epidemic Act of 2005, which regulates the purchase of products containing pseudoephedrine, ephedrine, and phenylpropanolamine, all of which can be used in the manufacture of methamphetamine. Specifically, drugs containing these precursors must be stored behind a pharmacy counter; purchase requires proof of identification, and purchases are limited to a maximum of 3.6 g of pseudoephedrine per day.<sup>1</sup> Despite this recent law, methamphetamine manufacturers circumvent these restrictions by “smurfing” or sending multiple people to make several pseudoephedrine purchases at different retail centers.

Currently, most of the methamphetamine available in the USA is produced domestically or in Mexico. Since the early 1980s, Mexican drug cartels have trafficked both methamphetamine and its precursors into the USA. Cartels in Mexico purchase bulk ephedrine or pseudoephedrine from countries with less strict oversight of methamphetamine precursor chemicals, such as India, Germany, and China. Despite efforts by both the USA and the Mexican governments to prohibit the import of precursor chemicals, methamphetamine production continues to increase.<sup>1,8</sup>

## Pathophysiology

Methamphetamine is a member of the phenylethylamine class of psychostimulants. Similar in structure to amphetamine, an added N-methyl group confers added lipid solubility, allowing for more rapid crossing of the blood–brain barrier (Fig 1). This property of methamphetamine causes a higher ratio of central to peripheral action and a more rapid onset of central effects.<sup>9</sup> The pathophysiology of methamphetamine primarily relates to its effects on multiple neurotransmitter systems. Dopamine (DA), a catecholamine, is the major neurotransmitter impacted by methamphetamine use. However, methamphetamine also affects serotonergic, noradrenergic, and glutamatergic systems as well.<sup>10</sup> The acute adverse effects of such neurotransmitter dysregulation are predominantly because of catecholamine excess. Specifically, this involves cardiovascular activation via norepinephrine release from sympathetic nerve endings as well as psychoactive stimulation from large quantities of DA release into brain synapses, including the caudate, putamen, and ventral striatal regions.<sup>11,12</sup> In contrast, chronic methamphetamine use has been shown to cause persistent dopaminergic deficits.



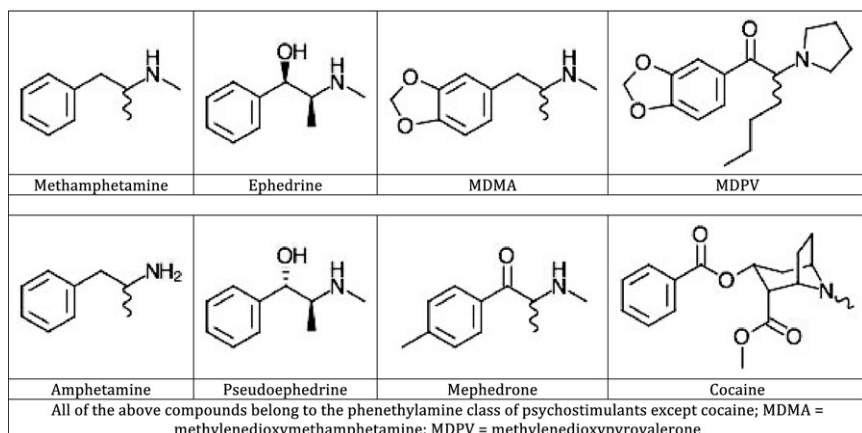
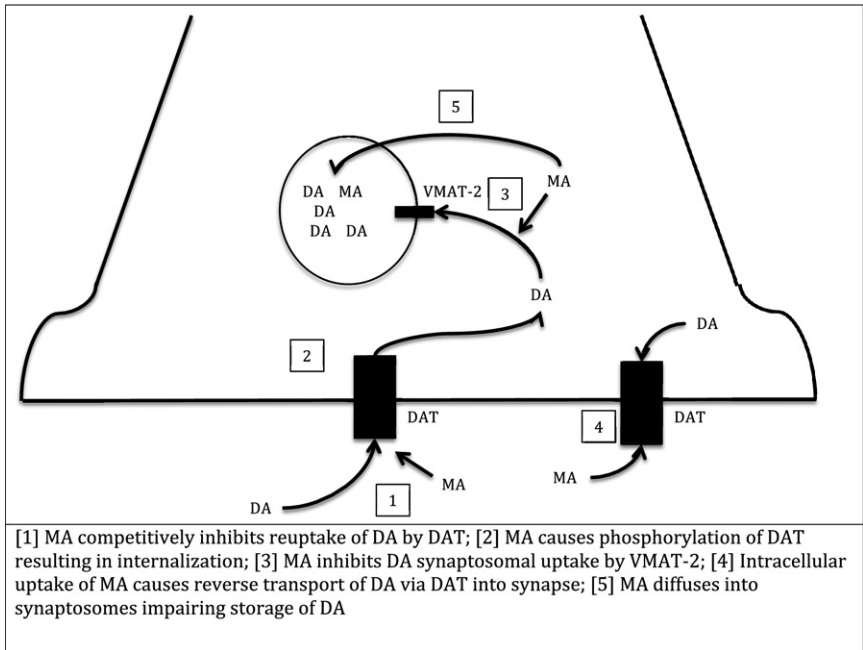


FIG 1. Structures of methamphetamine and selected other psychostimulants.

Methamphetamine's main mechanism of action is its ability to increase neuronal release of monoamines, particularly DA (Fig 2). Much of this release is mediated via alterations in both the plasmalemmal dopamine transporter (DAT) and the vesicular monoamine transporter-2 (VMAT-2). The function of VMAT-2 in normal cells is to sequester cytoplasmic DA into vesicles for storage and subsequent release. As such, it is an important regulator of cytoplasmic DA levels.<sup>13</sup> Methamphetamine interferes with the function of VMAT-2, impairing its ability to store DA into vesicles. This effect has been shown to occur in rats as early as 1 hour post-administration using repeated, high doses of methamphetamine.<sup>14</sup> This mechanism is in contrast to other sympathomimetics that act as synaptic reuptake inhibitors, such as cocaine or methylphenidate, where DA uptake into vesicles is increased.<sup>15,16</sup> Both decreased vesicular binding and decreased vesicular uptake of DA have been demonstrated in the presence of methamphetamine.<sup>17,18</sup> These actions are believed to occur via a subcellular redistribution of vesicles containing VMAT-2. In the presence of methamphetamine, VMAT-2 relocates from a synaptosomal to a nonsynaptosomal location within the neuron.<sup>19</sup> This relocation impairs the neuron's ability to sequester DA within vesicles for storage and later deposition into the synapse.

In addition to VMAT-2, cytoplasmic DA levels are also highly regulated by DAT. Under normal conditions, DAT clears extracellular DA from the synaptic cleft back into the nerve terminal. This reuptake of DA is then stored into synaptic vesicles via VMAT-2 for later release. Evidence suggests that several factors impair the normal function of DAT



**FIG 2.** Mechanism of action of methamphetamine on dopamine neurotransmission.

in the presence of methamphetamine. Phosphorylation of DAT via protein kinase C occurs in response to methamphetamine, leading to internalization of DAT.<sup>20</sup> Once internalized, DAT oligomers and higher molecular weight DAT-associated protein complexes form, impairing the normal function of DAT.<sup>21,22</sup> In a phosphorylation-independent mechanism, methamphetamine also interferes with DAT reuptake of DA through competitive inhibition.<sup>23</sup> Methamphetamine exists as an enantiomeric mixture of d- and l-stereoisomers, with d-methamphetamine 3- to 10-fold more potent at inhibiting DA reuptake via DAT than l-methamphetamine.<sup>13</sup> Correspondingly, l-methamphetamine has minimal CNS effects, whereas d-methamphetamine is the rotamer responsible for the euphoria associated with methamphetamine abuse.

Concurrent with reuptake inhibition, methamphetamine also causes efflux of DA into the synapse. Although the exact mechanism of this has been debated, recent evidence suggests 2 distinct processes are involved. Studies using amphetamine demonstrate a slow process in which amphetamine is transported intracellularly down its concentration gradient via DAT in exchange for cytoplasmic DA. This transports DA out of the cell and into the synapse in a reverse fashion through DAT compared with its

normal physiological role of DA reuptake. A second proposed mechanism involves amphetamine inducing rapid millisecond bursts of release of intracellular DA through DAT via a channel-like mechanism. Such a process releases quantities of DA analogous to calcium-dependent exocytosis of synaptic vesicles, and this may play a role in the psychostimulant properties of amphetamines.<sup>24</sup> Presumably, similar mechanisms of action occur with methamphetamine.

Synaptic DA release by methamphetamine is dependent on both depletion of DA from vesicles and reversal of the physiological role of DAT, with vesicular DA release being the rate-limiting step.<sup>18,25</sup> Impairment of VMAT-2 causes relative elevations in cytoplasmic DA levels, thus allowing transport of DA down its concentration gradient into the synaptic cleft in the presence of methamphetamine. The chemical properties of methamphetamine also contribute to such cytoplasmic DA elevations. As a highly lipophilic molecule, methamphetamine freely diffuses into nerve terminals and across vesicular membranes at high concentrations to accumulate in synaptic vesicles. Further, as a weak base, the accumulation of methamphetamine within these vesicles leads to a disruption of the electrochemical gradient necessary for DA storage. This consequently leads to elevated cytoplasmic DA concentrations and eventual reverse transport through DAT into the synapse.<sup>18,26</sup>

In contrast to the acute effects of increased synaptic DA efflux, repeated high-dose administration of methamphetamine has been demonstrated to cause persistent dopaminergic deficits in both animals and humans. Through methamphetamine-induced aberrant cytosolic DA accumulation, DA-associated reactive oxygen species are formed and believed to contribute to this depletion.<sup>18</sup> Methamphetamine-associated reactive oxygen species cause eventual activation of the Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) pathway, leading to neuronal apoptosis.<sup>27</sup> Deficits in DA nerve terminal markers (including decreases in DA, DAT, and tyrosine hydroxylase) have been demonstrated in postmortem studies of human striatum.<sup>28,29</sup> PET studies have also shown significant loss of striatal DAT in chronic methamphetamine users. Although abstinence has been reported to lead to some recovery in DAT, particularly in the caudate and putamen regions, this has not been reported to correlate with functional cognitive recovery on neuropsychological testing.<sup>30,31</sup> These fundamental changes underlie the neurotoxic effects believed to cause persistent dopaminergic deficits in chronic abusers.

Chronic methamphetamine abuse has been reported to result in histopathological changes in the brain. Chronic methamphetamine abuse leads to gray- and white-matter density changes and altered concentrations of

metabolites in the frontal gray and white matter and anterior cingulate gray matter that are dose-dependent and that may only be partially reversible with abstinence.<sup>32-36</sup> Damage to striatal dopamine and fore-brain serotonin terminals and degeneration of somatosensory cortical neurons have been demonstrated in rats.<sup>37</sup> One of the mechanisms thought to be responsible is methamphetamine-induced dopamine release, resulting in reactive oxygen species, causing striatal neurotoxicity, caspase-dependent apoptosis, and glial activation.<sup>38-44</sup> Advanced age and male gender may be risk factors for more pronounced neuronal damage, perhaps because of increased susceptibility to damage from reactive oxygen species and the lack of protective effects of estrogen, respectively.<sup>45-47</sup> The degree of degeneration of frontal gray- and white-matter integrity and frontal white-matter hypometabolism has been reported to correlate with poor performance on some neuropsychological tests.<sup>33,47,48</sup>

Chronic methamphetamine abuse causes histopathological changes to cardiac myocytes. Treatment of rats with methamphetamine over a period of weeks has been reported to cause subendocardial myocytic degeneration and necrosis followed by extensive myocytic degeneration, necrosis, and fibrosis.<sup>49</sup> Electron microscopy of these lesions shows degeneration of the mitochondria.<sup>50,51</sup> Other histopathological lesions associated with methamphetamine abuse include myocyte hypertrophy with disorganization of myofibrils, microtubules, and actin structures.<sup>52</sup> Histopathological cardiomyocyte changes are associated with release of lactate dehydrogenase and creatine phosphokinase, 2 markers of cardiomyocyte damage. Additionally, this damage may occur in the presence or absence of beta-blockade, suggesting that methamphetamine is directly myotoxic in addition to the toxicity that may result from sympathetic overstimulation.<sup>53-55</sup> Some of these histopathological changes may be gradually or partially reversible following discontinuation of the drug.<sup>56</sup> The histopathological lesions seen with chronic methamphetamine abuse are consistent with lesions seen in cardiomyopathy and may explain the development of cardiomyopathy in chronic methamphetamine abusers.<sup>57</sup>

## **Adverse Health Effects of Methamphetamine Abuse**

### **Cardiovascular**

Chest pain is a common complaint associated with methamphetamine administration. Chest pain accounts for 38% of emergency department visits and 28% of admissions in methamphetamine-intoxicated patients.<sup>58</sup> Tachycardia and hypertension are common clinical findings in metham-

phetamine intoxication.<sup>59</sup> Although in some patients, chest pain is due solely to methamphetamine-induced hypertension and tachycardia or anxiety, acute coronary syndrome (ACS) is common among methamphetamine users and patients with chest pain in the context of methamphetamine abuse should be evaluated for ACS.<sup>60</sup>

In 1 small series of patients presenting to an emergency department with chest pain after methamphetamine use, 25% were found to have ACS and 8% suffered a cardiac complication, including ventricular fibrillation, ventricular tachycardia, and supraventricular tachycardia.<sup>61</sup> Putative mechanisms for myocardial infarction in the setting of methamphetamine abuse include accelerated atherosclerosis, rupture of preexisting atherosclerotic plaques, hypercoagulability, and epicardial coronary artery spasm.<sup>62,63</sup> Methamphetamine abusers have significantly higher rates of coronary artery disease than the public.<sup>64</sup> Even patients with normal coronary arteries are at risk for methamphetamine-induced myocardial infarction because of coronary spasm, which may be refractory to intracoronary vasodilator therapy.<sup>63</sup> Acute myocardial infarction following methamphetamine use may be severe, resulting in cardiogenic shock and death.<sup>65</sup>

Methamphetamine is also associated with cardiac dysrhythmias. In 1 case series of methamphetamine-intoxicated patients, a prolonged corrected QT interval (QTc >440 ms) was found in 27.2% of participants, suggesting that methamphetamine-induced alterations in cardiac conduction may be partly responsible for its dysrhythmogenic effects.<sup>66</sup> Premature ventricular contractions, premature supraventricular contractions, accelerated atrioventricular conduction, atrioventricular block, intraventricular conduction delay, bundle branch block, ventricular tachycardia, ventricular fibrillation, and supraventricular tachycardia all have been reported in the setting of methamphetamine intoxication.<sup>55,61,66</sup> Methamphetamine-induced dysrhythmias may also occur because of myocardial ischemia or infarction.

Methamphetamine abuse is associated with an acute dilated cardiomyopathy with global ventricular dysfunction. This cardiomyopathy occurs in the absence of cardiac ischemia or infarct as measured by nuclear myocardial perfusion study and in the absence of coronary stenosis as measured by cardiac catheterization.<sup>67</sup> Methamphetamine-associated cardiomyopathy may result in acute cardiogenic pulmonary edema and may be reversible.<sup>65,68,69</sup> Several putative mechanisms by which methamphetamine may induce cardiomyopathy include recurrent coronary artery spasm, small vessel disease, or diffuse myocardial toxicity because of overstimulation of cardiac adrenergic receptors.<sup>67</sup> Methamphetamine-

induced cardiomyopathy has been reported to resemble transient apical ballooning syndrome (previously known as Takotsubo cardiomyopathy), a specific cardiomyopathy caused by transient left ventricular dysfunction thought to be linked to excessive catecholamines.<sup>70</sup>

Methamphetamine use may be associated with aortic dissection, likely because of its hypertensive effects resulting in increased wall shear stress.<sup>71</sup> Methamphetamine appears to carry a greater risk for aortic dissection than cocaine and may be second only to hypertension in its importance as a risk factor for aortic dissection.<sup>72</sup> Aortic dissection associated with methamphetamine abuse is also associated with cardiac tamponade and sudden death.<sup>73</sup>

Intravenous methamphetamine abuse has been associated with endocarditis. As with other intravenous drugs of abuse, methamphetamine-associated infective endocarditis is frequently right-sided and may result in death.<sup>74,75</sup>

## Dermatologic

Methamphetamine abuse predisposes to repetitive, stereotypical skin-picking, resulting in excoriations on the face and extremities.<sup>76</sup> In some cases, skin picking may be related to methamphetamine-induced formication or delusions of parasitosis.<sup>77</sup> Both skin-picking and the use of nonsterile needles in intravenous methamphetamine abusers may result in skin and soft-tissue infections. In 1 series of methamphetamine abusers presenting to an emergency department, skin infection accounted for 6% of emergency department visits and 54% of subsequent admissions to the hospital. Methamphetamine-related skin infections may take the form of cellulitis or cutaneous abscess.<sup>58</sup>

## Hematological

Methamphetamine users may have a higher risk of contracting human immunodeficiency virus (HIV) because of unsafe sex practices or use of contaminated needles during methamphetamine administration. Methamphetamine users have been reported to be more likely to engage in risky sexual behaviors than nonusers. Men who have sex with men (MSM), heterosexual men, and heterosexual women who use methamphetamine report more sexual partners than nonusers and more casual or anonymous sex partners.<sup>78</sup> Methamphetamine users are more likely to participate in sexual activities that confer a higher risk of HIV transmission, such as anal sex and sex with known injection drug users, and are less likely to use condoms during vaginal and anal intercourse.<sup>79</sup> Additionally, methamphetamine use is associated with paying for or being paid for sex.<sup>79</sup>

Methamphetamine use is associated with a higher risk of sexual HIV infection.<sup>79</sup> The use of contaminated needles is another source of HIV infection in methamphetamine users. As with other intravenous drugs of abuse, the sharing of needles and the corresponding risk of contracting a blood-borne disease, including HIV, is not uncommon.<sup>80</sup>

Methamphetamine abuse is associated with necrotizing angitis. Histologic features include fibrinoid necrosis of the intima and media of blood vessels with destruction of vascular smooth muscle.<sup>81,82</sup> Macroscopically, affected arteries display segmental narrowing with aneurysm formation, resulting in a “beaded” appearance.<sup>81</sup> Drug-induced necrotizing angitis may result in target organ damage to the heart, brain, liver, kidney, bowel, and pancreas with clinical manifestations of myocardial infarction, ischemic or hemorrhagic stroke, renal failure, hepatic necrosis, bowel infarction, and pancreatitis, among others.<sup>83,84</sup>

## Gastrointestinal

Methamphetamine users are at higher risk for contracting viral hepatitis than nonusers because of risky sexual behavior and the use of contaminated needles. Methamphetamine users are more likely to be infected with hepatitis A and B than nonusers and, among methamphetamine users, injection users have a higher prevalence of both diseases than noninjection users.<sup>85</sup> Use of contaminated needles puts methamphetamine users at particular risk for hepatitis C infection, although hepatitis C infection is also more common among methamphetamine users who smoke or insufflate the drug than it is in the general population.<sup>86,87</sup>

Even in the absence of viral hepatitis, methamphetamine abuse has been reported to cause acute liver injury with hepatic necrosis and centrilobular degeneration.<sup>88</sup> Additionally, methamphetamine enhances the hepatic toxicity of other agents, such as carbon tetrachloride. Although the cause of the hepatic injury is unclear, it has been proposed that an adrenoreceptor-related mechanism or stimulation of Kupffer cells may be responsible.<sup>89,90</sup>

Mesenteric infarction requiring total proctocolectomy and resection of the ileum and jejunum has been reported following methamphetamine use with microscopic examination showing changes consistent with acute vasculitis.<sup>91</sup> Segmental ischemic colitis in the absence of thrombosis, vasculitis, or vasospasm with spontaneous resolution has also been reported.<sup>92</sup> Methamphetamine may cause mesenteric ischemia or infarction by several mechanisms, including necrotizing vasculitis, cardiovascular shock, sympathomimetic vasospasm, or splanchnic vasoconstriction.

tion.<sup>93-95</sup> It remains unclear how important each of these mechanisms is to methamphetamine-induced mesenteric infarction.

Severe acute necrotic hemorrhagic pancreatitis has been reported in cases of sudden death in chronic methamphetamine abusers. Histopathology studies of the effect of chronic methamphetamine abuse on pancreatic tissues suggest that methamphetamine may cause regional hemorrhage, acinar cell death, and fibrosis possibly because of tissue hypoxia or necrotizing angiitis.<sup>96,97</sup>

## Genitourinary

Methamphetamine users are more likely to be diagnosed with a sexually transmitted disease (STD) than nonusers because of an increased likelihood of engaging in risky sexual behaviors.<sup>78,79</sup> Prolonged sex while on methamphetamine can lead to chafing or soft-tissue injury to the genitals with correspondingly higher risk of transmission of an STD or blood-borne infection.<sup>98</sup> Injection methamphetamine abusers have a higher prevalence of STD infections than noninjection methamphetamine abusers.<sup>99</sup> Among methamphetamine-dependent gay men, an elevated prevalence of chlamydia, syphilis, and genital and oral gonorrhea has been reported with a lifetime prevalence of genital gonorrhea of 40%. Psychiatric comorbidity may be associated with a higher prevalence of STD infection in methamphetamine-dependent individuals.<sup>100</sup> In 1 study in Thailand, methamphetamine users were reported to have higher rates of chlamydial infection than opiate users.<sup>101</sup>

## Musculoskeletal

Perhaps the most publicized adverse health effect of methamphetamine abuse, by both governmental agencies and the lay media, is “meth mouth” (Fig 3).<sup>102,103</sup> Methamphetamine induces dental decay through multiple mechanisms, including xerostomia from sympathetic overstimulation and bruxism, resulting in multiple dental caries.<sup>104,105</sup> Also of concern is the consumption of large quantities of sugared soft drinks in an attempt by the user to resolve the xerostomia and lack of oral hygiene during extended periods of drug abuse.<sup>106,107</sup> Although dental decay because of methamphetamine abuse is well documented, 1 study found that the degree of dental decay in methamphetamine users as compared to other substance users in an inpatient chemical dependency treatment unit was similar, suggesting that at least some of the dental decay associated with methamphetamine abuse is due to factors common to substance abuse in general, such as poor personal hygiene and malnutrition.<sup>108</sup>





**FIG 3.** "Meth mouth." Severe dental caries because of methamphetamine abuse. (Reprinted with permission from Hamamoto DT, Rhodus NL. Methamphetamine abuse and dentistry. *Oral Dis* 2009;15:27-37.) (Color version of figure is available online.)

Methamphetamine abuse is also associated with rhabdomyolysis. In 1 series of patients presenting to an emergency department with rhabdomyolysis, 43% had urine drug immunoassays positive for methamphetamine. Methamphetamine-induced rhabdomyolysis may be due to psychomotor agitation or seizures.<sup>109</sup>

Methamphetamine-intoxicated patients are at increased risk for traumatic injury. In 1 case series of methamphetamine-positive patients presenting to an emergency department, the most common chief complaint was blunt trauma, accounting for 33% of emergency department visits and 74% of subsequent admissions.<sup>58</sup> Among a case series of consecutive trauma patients, methamphetamine was the most commonly used illicit drug. Trauma patients with positive urine drug immunoassays for methamphetamine are more likely to suffer from violent mechanisms of injury, including assault, gunshot wound, and stabbing than trauma patients testing negative for methamphetamine. They are also more likely to have attempted suicide, be a victim of domestic violence, or have an altercation with law enforcement.<sup>110,111</sup> Methamphetamine users have also been reported to be more likely to have severe injuries, to leave against medical advice, and to die from their injuries.<sup>110,112</sup>

Pott's puffy tumor (osteomyelitis of the frontal bone) has been associated with intranasal methamphetamine use. Local methamphetamine-induced ischemic injury to the sinus mucosa is thought to produce an

environment conducive to the development of frontal bone osteomyelitis and subperiosteal abscess.<sup>113</sup>

## Neurological

Methamphetamine is associated with many neurological adverse health effects, although the most devastating is intracranial hemorrhage. Methamphetamine-induced hypertension and tachycardia may lead to intracranial hemorrhage, in patients with or without preexisting cerebrovascular disease.<sup>114</sup> Methamphetamine may be more toxic than cocaine in inducing intracranial hemorrhage, possibly because of its more prolonged cardiovascular effects.<sup>115</sup> Methamphetamine-induced necrotizing angiitis may also play a role in methamphetamine-associated intracranial hemorrhage with fibrinoid necrosis of the intima and media of vessels predisposing to vessel rupture.<sup>81,116,117</sup> Intraparenchymal bleeds in the cerebrum, cerebellum, corpus callosum, basal ganglia, and brainstem have been reported and may result in death.<sup>81,114,116-119</sup> Fatal intraventricular hemorrhages have also been reported.<sup>120</sup> A number of intracranial berry aneurysm ruptures related to methamphetamine intoxication have been reported, frequently with fatal results.<sup>73,115</sup> Subarachnoid hemorrhage in the absence of berry aneurysm or arteriovenous malformation has also been reported.<sup>117</sup>

Methamphetamine abuse is also associated with ischemic stroke.<sup>119,121-123</sup> As with intracranial hemorrhage, methamphetamine-induced hypertension, tachycardia, and necrotizing angiitis may contribute to the development of ischemic stroke.<sup>121</sup> For intravenous methamphetamine use, fillers, such as talc, may also contribute to ischemic or hemorrhagic stroke.<sup>94</sup> Methamphetamine-induced ischemic stroke may occur in the absence of evidence of chronic hypertension or cerebral vasculopathy.<sup>117,119</sup>

Methamphetamine intoxication also causes seizure. Methamphetamine-induced seizures may occur in persons with or without any past medical history of seizure disorder. In 1 series of methamphetamine-intoxicated patients presenting to an emergency department, 7% of patients with altered level of consciousness had tonic-clonic seizure and, of those patients, 75% had no previous history of seizure.<sup>58</sup> Limited evidence suggests that chronic methamphetamine exposure may lower the seizure threshold more than a single acute exposure.<sup>124</sup>

Methamphetamine abuse also results in cognitive impairment, which may be persistent. Current methamphetamine users have impaired performance on tests of memory, the ability to manipulate information, attention, and abstract thinking as compared to matched controls, al-

though they showed no impairment in psychomotor speed, intelligence, or verbal fluency. Heavier methamphetamine users have greater cognitive impairment than less frequent users.<sup>125</sup> Methamphetamine may selectively impair visual memory more than verbal memory, perhaps because of executive function damage.<sup>126</sup> Conversely, at low administered doses, some studies have reported that single doses of methamphetamine may improve reaction times, cognitive performance, and verbal memory.<sup>10,127</sup>

Following methamphetamine abstinence of 1-2 weeks, chronic methamphetamine abusers show persistent impairment on neurocognitive measures of attention, psychomotor speed, verbal learning and memory, and executive system measures.<sup>128</sup> Following prolonged methamphetamine abstinence (mean abstinence of 20 months), chronic methamphetamine abusers still display impaired attentional control that may be related to changes in neurochemicals in frontostriatal brain regions and to microstructural changes in the white matter of the corpus callosum.<sup>129,130</sup>

Patients with HIV or hepatitis C may be particularly at risk for developing cognitive impairment because of methamphetamine abuse. Hepatitis C infection augments methamphetamine-induced cognitive deficits in the areas of learning, abstraction, and motor skills as well as global neuropsychological impairment.<sup>131</sup> HIV similarly interacts with methamphetamine to produce cognitive deficits.<sup>132</sup> HIV-positive chronic methamphetamine users display additional neuronal injury and glial activation in the frontal cortex and basal ganglia as compared to HIV-negative methamphetamine users.<sup>133</sup> This effect is amplified in patients with high HIV viral loads.<sup>134</sup> A combination of methamphetamine and HIV proteins has been implicated in causing significant neuronal toxicity, possibly by activating caspase-dependent cell death pathways leading to neuronal apoptosis.<sup>135-137</sup>

Rarely, methamphetamine abuse has been associated with choreoathetosis. This may be due to central dopaminergic effects of methamphetamine and has been reported only in the setting of acute methamphetamine intoxication.<sup>138,139</sup> Other reported neurological sequelae of methamphetamine intoxication include photophobia and ataxia.<sup>140</sup>

## Ophthalmologic

Acute unilateral vision loss has been reported following intranasal methamphetamine abuse. The vision loss is believed to be due to ischemic optic neuropathy secondary to methamphetamine-induced vasospasm and methamphetamine-associated vasculitis.<sup>141,142</sup>

## Psychiatric

Methamphetamine abuse is associated with psychiatric disease. Methamphetamine intoxication is associated with restlessness, insomnia, hallucinations, paranoia, and disturbance of consciousness.<sup>143</sup> Abstinence following methamphetamine intoxication is associated with depression, anhedonia, irritability, and poor concentration, although these symptoms are frequently mild and transient.<sup>144</sup> Methamphetamine users are more likely to carry a psychiatric diagnosis and be prescribed psychiatric medications than cocaine users.<sup>80</sup>

Chronic methamphetamine abuse is associated with depressive symptoms and suicidal ideation.<sup>145,146</sup> Among adolescent methamphetamine users, 16% reported suicidal ideation.<sup>147</sup> Suicide attempts during methamphetamine intoxication are common and may involve overdose, slash wounds to the extremities, and jumps from heights.<sup>58,148</sup> In methamphetamine-dependent gay men, 25% report a history of at least 1 suicide attempt.<sup>100</sup> In 1 series of completed youth suicides, alcohol and methamphetamine were the most common substances found in the blood.<sup>149</sup> Risk factors for methamphetamine-related suicide attempt include female gender, intravenous methamphetamine use, history of methamphetamine-induced psychosis, methamphetamine-induced depressive disorder, and family history of psychotic disorders.<sup>150,151</sup>

Methamphetamine abuse may be associated with self-injurious behavior and self-mutilation. Methamphetamine-intoxicated individuals may be motivated by bizarre religious, sexual, or neurotic thoughts and self-mutilation may take a variety of forms, such as eye enucleation or genital self-mutilation.<sup>152</sup> In some chronic methamphetamine abusers, self-mutilation may be recurrent or severe.<sup>153</sup>

Chronic methamphetamine abuse may result in psychosis with predominant auditory hallucinations, persecutory delusions, delusions of reference, and pathologic hostility.<sup>154-157</sup> Methamphetamine-induced psychosis mimics paranoid schizophrenia and patients with either disease have been found to have similar deficits in neurocognitive functioning.<sup>158</sup> In 1 sample of methamphetamine abusers, 13% screened positive for psychosis, whereas another 23% had at least 1 psychotic symptom (eg, unusual thought content). Dependent methamphetamine abusers were 3 times more likely to have psychotic symptoms than nondependent abusers, and the prevalence of psychosis in methamphetamine abusers was reported to be 11 times higher than in the general population.<sup>159</sup> In Thailand, 10% of psychiatric hospital admissions are for methamphetamine-related psychosis.<sup>160</sup>

Chronic methamphetamine abuse results in behavioral sensitization to the drug where even small doses may then trigger a relapse of the psychosis and the duration of vulnerability to relapse progressively becomes longer.<sup>161,162</sup> Although in some patients methamphetamine psychosis may be transient, in others psychosis may persist despite months of abstinence and be resistant to antipsychotic medications.<sup>163</sup> Young age at onset of methamphetamine abuse, heaviness of methamphetamine abuse, schizoid or schizotypal personality disorder, and history of preexisting neurological disorder (eg, learning disorder or attention-deficit/hyperactivity disorder) are risk factors for the development of persistent methamphetamine-induced psychosis.<sup>155,164</sup> In addition, the extent of neuronal damage in the basal ganglia correlates with severity of psychiatric symptoms.<sup>165</sup>

## Pulmonary

Acute noncardiogenic pulmonary edema may occur after smoking methamphetamine despite normal pulmonary artery and pulmonary wedge pressures. Respiratory failure and hypotension requiring mechanical ventilation and vasopressor support have been reported and have been reported to be reversible.<sup>68</sup>

Methamphetamine is strongly associated with idiopathic pulmonary arterial hypertension (PAH).<sup>166</sup> Methamphetamine intoxication has been shown to cause an acute rise in pulmonary arterial pressures.<sup>167</sup> Although the role methamphetamine plays in inducing PAH remains unclear, proposed mechanisms include toxic endothelial injury, hypoxic insult, direct spasm, vasculitis, and dysregulation of vascular tone.<sup>168</sup> One favored hypothesis is that methamphetamine induces PAH by the same mechanism as fenfluramine, through interaction with serotonin transporters resulting in serotonin release.<sup>169</sup>

An additional concern in methamphetamine-induced PAH is the use of outpatient intravenous therapy. In severe cases of PAH, continuous epoprostenol or treprostinil infusions may be indicated and infused in the outpatient setting through an indwelling central intravenous catheter. Use of such indwelling catheters in methamphetamine users may be complicated by homelessness, inability to properly care for the catheter, or infection because of the patient accessing the catheter to administer illicit drugs.<sup>170</sup>

## Renal

Acute renal failure may be reported following methamphetamine abuse and may be due to myoglobinuria, hypotension, or necrotizing angitis.<sup>91</sup>

Myoglobinuric renal failure because of methamphetamine-associated rhabdomyolysis is frequently self-limited, although hemodialysis may be temporarily necessary. Rarely, methamphetamine-associated myoglobinuric renal failure may be persistent, resulting in end-stage renal disease.<sup>109</sup> Methamphetamine-associated necrotizing angitis has also been associated with renal insufficiency culminating in end-stage renal disease requiring hemodialysis.<sup>84</sup>

## Obstetrical

Methamphetamine is increasingly a drug of choice among substance-dependent pregnant women.<sup>171</sup> Methamphetamine abuse during pregnancy is concerning both for the risk of adverse pregnancy outcome and for possible damage to the developing fetus. Methamphetamine abuse is also associated with perinatal maternal death and has been implicated as a possible contributing factor to amniotic fluid embolism.

Several adverse pregnancy outcomes have been associated with prenatal maternal methamphetamine use. Methamphetamine use is associated with fetal growth restriction and premature delivery.<sup>172-175</sup> Placental insufficiency, hemorrhage, and abruption have also been associated with maternal methamphetamine abuse.<sup>175,176</sup> Prenatal methamphetamine exposure is thought to put a fetus at higher risk for intraventricular hemorrhage and cavitory lesions in the brain.<sup>175</sup> Additionally, maternal methamphetamine abuse is associated with inadequate prenatal care.<sup>177</sup>

Prenatal exposure to methamphetamine has been suggested to increase the risk for adverse postnatal outcomes. Prenatal methamphetamine exposure has been linked to neonatal neurobehavioral outcomes of decreased arousal, increased physiological stress, and poor quality of movement in a dose–response relationship.<sup>178,179</sup> Prenatal methamphetamine exposure has been reported to cause neonatal toxic hepatitis with cholestasis.<sup>180</sup> Children with prenatal methamphetamine exposure have been noted to have structural and chemical brain differences as compared to healthy controls and structural differences correlate with poorer performance on attention and verbal memory tests.<sup>181,182</sup> Animal studies have also suggested that prenatal methamphetamine exposure may adversely affect the myelination process.<sup>183</sup> Rats exposed prenatally to methamphetamine are reported to have lower seizure threshold, lower birth weights, and impaired sensory-motor coordination.<sup>184,185</sup> Rat studies have also suggested that some methamphetamine-related deficits, such as sensory-motor correlation, may affect 2 generations of offspring.<sup>186</sup> Although methamphetamine has been reported to be teratogenic in animal studies, no human studies have confirmed this effect.<sup>187,188</sup>

## Exploratory Methamphetamine Exposure in Children

Inadvertent pediatric exposure to methamphetamine may be increasing. In 1 series of methamphetamine-dependent patients presenting for drug rehabilitation, 44% had children in their home. Of children found in methamphetamine laboratories by police or child protective services, 45% have a positive hair specimen for 1 or more illicit drugs with the most common positive result being methamphetamine.<sup>189</sup> Common signs and symptoms of methamphetamine poisoning in the pediatric population include tachycardia, agitation, inconsolable crying, irritability, and vomiting. Rhabdomyolysis is a common complication.<sup>190,191</sup> Seizure is a less common symptom of pediatric methamphetamine poisoning.<sup>191</sup> Transient cortical blindness secondary to methamphetamine poisoning has been reported in an infant.<sup>192</sup> Pediatric methamphetamine poisoning may be difficult to distinguish from scorpion envenomation, resulting in unnecessary exposure to antivenom.<sup>190,193</sup>

Children may also be at risk of traumatic injury or abuse because of parental behaviors while using methamphetamine. Parental supervision while on a methamphetamine binge may be lax and caregivers may sedate their children with benzodiazepines or diphenhydramine while engaging in methamphetamine abuse. In addition, children in homes where methamphetamine is abused are reported to be at higher risk for exposure to age-inappropriate material, such as pornography.<sup>189</sup>

## Methamphetamine-Associated Death

Methamphetamine abuse may be directly or indirectly fatal. Direct methamphetamine-related mortality is frequently due to catastrophic neurological or cardiac complications, while indirect methamphetamine-related deaths are frequently traumatic in nature. In 1 series of methamphetamine-related fatalities, the cause of death was categorized as natural, accidental, suicidal, homicidal, or uncertain in 13%, 59%, 11%, 14%, and 3% of cases, respectively. In another series, homicide and suicide accounted for 27% and 15% of methamphetamine-related fatalities, respectively.<sup>194</sup> In a series of autopsies in methamphetamine-positive patients, the most common cause of death was multiorgan system dysfunction, followed by cardiovascular or cerebrovascular disease, traumatic shock, asphyxiation, and exsanguination.<sup>195</sup>

Methamphetamine-related fatalities constitute a significant public health problem in areas where methamphetamine abuse is prominent: in Taiwan, 12.1% of all autopsy cases in 1 year were related to metham-

phetamine. Males may be more likely to suffer methamphetamine-related death than females.<sup>195,196</sup>

Concomitant abuse of another drug, eg, cocaine or ethanol, has been identified as a factor in some methamphetamine-related fatalities and varies in frequency depending on cultural norms.<sup>197</sup> Although animal studies have suggested that concomitant ethanol ingestion is protective against some of the toxic effects of methamphetamine, ethanol intoxication may simultaneously increase the risk of accidental or traumatic death.<sup>198</sup>

A frequently reported cause of direct methamphetamine-related fatality is multisystem organ failure secondary to methamphetamine toxicity, which is characterized by hyperthermia, pulmonary congestion, coma, shock, hyperthermia, acute renal failure, metabolic acidosis, and hyperkalemia.<sup>195,198-200</sup> As with other illicit drugs, body packers and body stuffers are at risk for death in the event of package rupture.<sup>201-203</sup> Methamphetamine-induced agitation and hyperactivity can cause death secondary to metabolic acidosis and hyperthermia.<sup>204</sup>

Intracranial hemorrhage is a commonly reported neurological complication of methamphetamine abuse resulting in death.<sup>118</sup> Methamphetamine-related status epilepticus may also contribute to death.<sup>202</sup> Cardiac complications of methamphetamine abuse that are frequently reported to result in death include arrhythmia and acute myocardial infarction.<sup>65,66</sup> Methamphetamine-related hypertension and tachycardia may cause sudden death because of berry aneurysm rupture or aortic dissection with cardiac tamponade.<sup>73</sup>

Indirect methamphetamine-related fatalities are frequently traumatic and may be due to accident, assault, or suicide.<sup>205</sup> Methamphetamine-related traffic deaths could result from riskier driving behavior while intoxicated, and blood amphetamine concentration is positively correlated to traffic-related impairment.<sup>194,206,207</sup> In 1 study of traffic-related fatalities, methamphetamine was found in the blood of 5% of fatally injured drivers.<sup>208</sup>

## **Methamphetamine Abuse-Associated Toxicologic Exposures**

Most reported toxicologic exposures because of methamphetamine are in the context of production of methamphetamine, discussed below. However, methamphetamine abuse has been linked to acute lead poisoning. Depending on the method of synthesis used, methamphetamine manufacture may involve lead acetate. Lead poisoning due to methamphetamine abuse may be due to a high lead content in the drug because



of inadequate processing during manufacture or deliberate contamination.<sup>209</sup> In 1 outbreak of methamphetamine-associated lead poisoning, 14 confirmed cases occurred in 1 year because of intravenous use of a batch of methamphetamine that was 60% lead by weight.<sup>210</sup> However, lead poisoning is not thought to be widespread among methamphetamine users and may occur only episodically with batches of contaminated drug.<sup>211</sup>

## Current Trends

### Domestic Trends

Several agencies collect data useful in identifying trends in methamphetamine use. A frequent limitation in these data sets is the inclusion of methamphetamine in a general category labeled “non-cocaine stimulants,” making it difficult to track trends in methamphetamine as opposed to trends in stimulant abuse in general. Examples of national data sources include the National Survey on Drug Use and Health, Monitoring the Future, Youth Behavior Risk Surveillance System, Treatment Episode Data Set, Drug Abuse Warning Network, Substance Abuse and Mental Health Services Administration, and Arrestee Drug Abuse Monitoring system.<sup>1</sup>

A 2004 report issued by Substance Abuse and Mental Health Services Administration estimates that, in 2004, 12 million or 2.9% of the US population aged 12 years or older have tried methamphetamine in their lifetime; 1.4 million used it in the past year, and 600,000 used it in the past month. The highest rates of past year methamphetamine use were found among Native Hawaiians or Pacific Islanders (2.2%) and American Indians or Alaska Natives (1.7%), whereas lower rates of past year use were found among whites (0.7%), Hispanics (0.5%), blacks (0.1%), and Asians (0.2%).<sup>1</sup> Another survey estimates rates of past year methamphetamine use among persons aged 12 or older were highest in Nevada (2.0%), Montana (1.5%), and Wyoming (1.5%), while the lowest rates were in Connecticut, Maryland, Massachusetts, New Jersey, and New York.<sup>212-214</sup> The highest rates of amphetamine- or methamphetamine-related emergency department visits are reported in San Francisco, Seattle, San Diego, and Los Angeles. In the 2002 Drug Abuse Warning Network database, white patients were responsible for 65% of amphetamine- or methamphetamine-related emergency department visits; 58% of visits were men, and most visits involved patients aged 18-34 years.<sup>215,216</sup>

Subpopulations at disproportionate risk for methamphetamine use reportedly include criminal offenders and MSM. Currently, men and

women abuse methamphetamine equally, unlike many other illegal drugs where there is a male predominance among abusers. Methamphetamine abusers frequently engage in criminal and/or violent behavior and many have been involved with the criminal justice system.

Among MSM, methamphetamine abuse is associated with high-risk sexual behaviors. Methamphetamine is increasingly abused by MSM while engaging in sexual activity, termed “party and play” or “PnP,” and abuse is common in sex clubs and “circuit parties.”<sup>1,8,217</sup> The number of methamphetamine laboratories seized by USA law enforcement agencies increased by 25% between 2001 and 2004.<sup>214</sup> Methamphetamine laboratory incidents, defined as discovery of laboratories, dumpsites, or methamphetamine manufacture equipment, also continue to increase. In March 2009, 966 methamphetamine laboratory incidents were reported nationally, an increase from 756 in March 2008 and 596 in March 2007. A total of 11,239 methamphetamine laboratory incidents were reported nationally in calendar year 2010, with the majority of incidents and the largest increases occurring in the Midwest and the South (Fig 4).<sup>218,219</sup>

## Global Trends

International trends show increasing amphetamine use. The 2011 United Nations Office of Drugs and Crime estimates annual prevalence of amphetamine-type stimulants as the second most widely used illicit drug in the world, following cannabis. Amphetamines, which include methamphetamine, amphetamine, and methcathinone, are used by 14-56 million people worldwide in 2009, with more specific estimates made difficult by uncertainty in abuse rates in China and India. Of the amphetamine-type stimulants, methamphetamine is estimated to be the most widely manufactured. Asia manufactures a substantial proportion of the worldwide production of methamphetamine, with methamphetamine manufacture being particularly prevalent in East and Southeast Asia, including the Philippines, China, Myanmar, and Malaysia. Global seizures of amphetamine-type stimulants have more than tripled between 1998 and 2009, a much faster rate of increase than has been seen with seizures of cocaine, heroin, morphine, and cannabis. Methamphetamine seizures were most common in Oceania, Africa, North America, and Asia. It is estimated that the majority of methamphetamine laboratories dismantled worldwide are located in North America.<sup>220</sup>

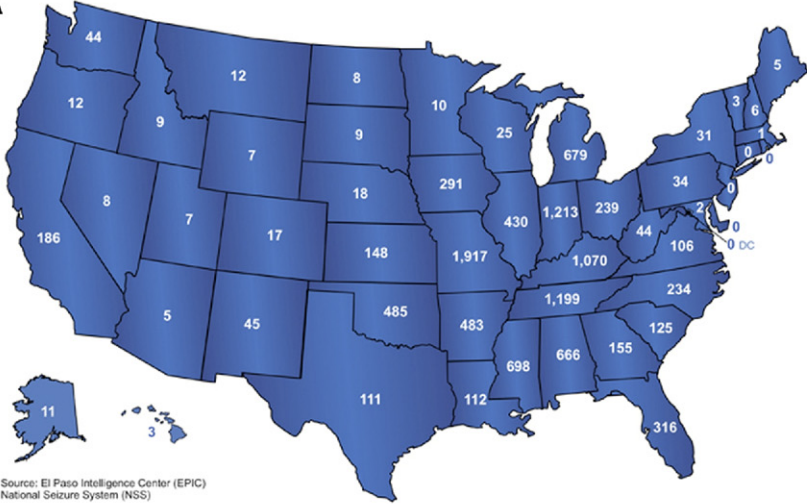
## Clandestine Methamphetamine Laboratories

Clandestine methamphetamine laboratories are operated throughout the USA and make up over 80% of clandestine drug laboratories.<sup>221</sup> In 2008,

Calendar Year 2010  
Total: 11,239

Total of All Meth Clandestine Laboratory Incidents  
Including Labs, Dumpsites, Chem/Glass/Equipment

A



Calendar Year 2005  
Total: 12,974

Total of All Meth Clandestine Laboratory Incidents  
Including Labs, Dumpsites, Chem/Glass/Equipment

B

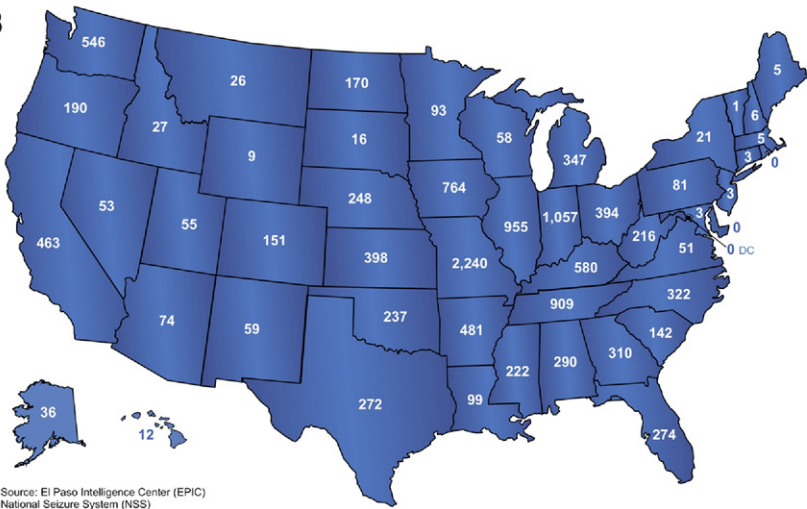
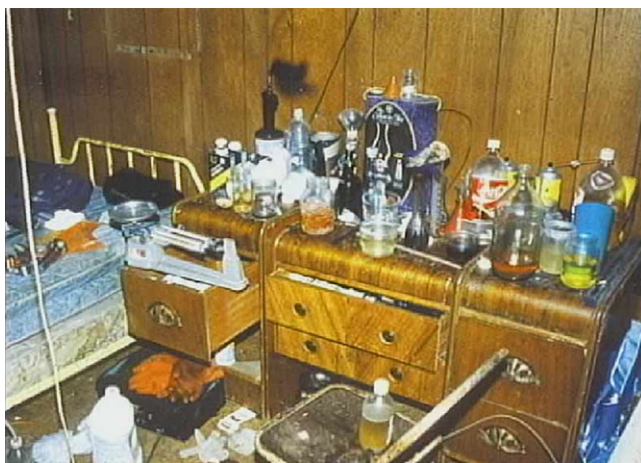


FIG 4. Trends in meth clandestine laboratory incidents in the USA in (A) 2010 and (B) 2005. (Source: [http://www.justice.gov/dea/concern/map\\_lab\\_seizures.html](http://www.justice.gov/dea/concern/map_lab_seizures.html).) (Color version of figure is available online.)



**FIG 5.** Illicit meth lab in a bedroom. (Reprinted with permission from Methamphetamine Awareness and Prevention Project of South Dakota [<http://www.mapps.org/>].) (Color version of figure is available online.)

6783 methamphetamine laboratories were found, predominantly in the Midwest.<sup>61</sup> Laboratories vary in size from “mom-and-pop” operations to large-scale “super labs” (Fig 5).<sup>222</sup>

Illicit drug manufacturers, also known as “cooks,” may obtain their “recipes” from other cooks, the chemistry literature, underground culture/resources, or the Internet.<sup>222</sup> Methamphetamine can be made using several different techniques, none of which are safe outside the clinical laboratory. The first method used in the manufacture of illicit methamphetamine was developed in the 1960s and involved the precursor chemical phenyl-2-propanone (P2P). P2P was combined with alcohol and an aluminum amalgam, usually aluminum foil or wire mixed with a small amount of mercuric chloride, and allowed to react overnight.<sup>223</sup> The methamphetamine is then isolated using hydrochloric acid, organic solvents, and filters.<sup>222</sup>

A second method using the precursor chemical P2P combined it with N-methylformamide and formic acid in the Leuckart reaction; the intermediate is then refluxed with hydrochloric acid to form methamphetamine.<sup>222-224</sup> In 1980, the Drug Enforcement Administration made P2P a Schedule II controlled substance, which led to the illicit manufacture of P2P.<sup>225</sup> Phenylacetic acid can be combined with acetic anhydride, lead acetate, or acetic acid with pyridine to form P2P.<sup>222-224</sup> Other methods of manufacturing P2P involve thorium oxide and pumice or benzaldehyde and nitroethane.<sup>222,223</sup> The Chemical Diversion and

Trafficking Act of 1987 placed restrictions on P2P precursors, forcing illicit methamphetamine producers to manufacture their own phenylacetic acid. This can be accomplished using benzyl cyanide or benzylchloride.<sup>222</sup>

The Drug Enforcement Administration classification of P2P as a Schedule II controlled substance also led methamphetamine manufacturers to seek out new methods by which to produce the drug.<sup>225</sup> In the early 1980s, methamphetamine manufacturers found that reacting ephedrine and pyridine with hydrogen iodide and red phosphorus in carbon disulfide was effective in producing methamphetamine.<sup>223</sup> Ephedrine and pseudoephedrine remain the most popular precursor chemicals today, because of ease of procurement in common over-the-counter cold medicines.<sup>222</sup> *E sinica* can also be used as a source for ephedrine and pseudoephedrine.<sup>226</sup>

Currently, there are 2 methamphetamine-manufacture methods using ephedrine or pseudoephedrine as a precursor chemical, both with the common goal of removing a hydroxyl group from the precursor: the cold or red phosphorus method and the Nazi or Birch method. The ephedrine or pseudoephedrine is extracted from over-the-counter medications using water or alcohol and heat.<sup>222</sup> The cold method uses red phosphorous and hydriodic acid to convert ephedrine/pseudoephedrine to methamphetamine.<sup>227</sup> Historically, Freon was used to extract the finished product, but other organic solvents may be used as well.<sup>222</sup> Hydriodic acid frequently must be illicitly manufactured because of restrictions placed on it as well.<sup>222</sup> In the Nazi/Birch method, an alkali metal (typically sodium or lithium) is combined with anhydrous ammonia and the ephedrine or pseudoephedrine and then subsequently with water or alcohol and hydrogen chloride gas to form methamphetamine.<sup>222-224</sup> This method is called the Nazi method because of the widespread belief that it was invented by the Nazis during World War II.<sup>228</sup>

The most recently reported method for making methamphetamine is called “shake and bake.” The “shake and bake” method requires less pseudoephedrine, a 2-L soda bottle, and no heat source. The pseudoephedrine is crushed and ammonium nitrate is added. This method can be done anywhere, including in a moving vehicle. A small amount of methamphetamine is produced using this method, making it useful for individuals attempting to manufacture their own methamphetamine but not for larger scale laboratories.<sup>229,230</sup> Tables 3 and 4 list common chemicals and equipment used in the manufacture of methamphetamine.

**TABLE 3.** Chemicals used in illicit methamphetamine manufacture<sup>222,228,230</sup>

<b>Chemical</b>	<b>Where It Is Used</b>	<b>Common Sources</b>
Acetic acid	P2P synthesis	Vinegar
Acetic anhydride	P2P synthesis	
Acetone	Solvent	Paint thinner, nail polish remover
Acetylene gas	Gas purge	Welding gas
Aluminum	P2P synthesis	Aluminum foil/wires
Anhydrous ammonia	Methamphetamine synthesis	Farm fertilizer
Ammonium nitrate	Methamphetamine synthesis	Fertilizer, cold compress packs
Benzaldehyde	P2P synthesis	
Benzene	Solvent	
Benzylchloride	Phenylacetic acid synthesis	
Benzyl cyanide	Phenylacetic acid synthesis	
Ephedrine	Methamphetamine precursor	Cold preparations
Ethanol	Solvent	Alcohol
Ethyl ether	Solvent	Engine starting fluid
Formic acid	Solvent	
Freon	Solvent	Refrigeration systems
Hydriodic acid	Methamphetamine synthesis	
Hydrochloric acid/gas (muriatic acid)	Solvent (acid), methamphetamine synthesis (gas)	Swimming pool supplies
Hydrogen gas	Gas purge, methamphetamine synthesis byproduct (lithium reacting with water)	
Hydrogen sulfide	Hydriodic acid synthesis	
Hypophosphorous acid	Methamphetamine synthesis	
Iodine	Hydriodic acid synthesis	Farming and health care supplies
Isopropanol	Solvent	Rubbing alcohol
Lead acetate	P2P synthesis	
Lithium	Methamphetamine synthesis	Photo batteries
Magnesium sulfate	Methamphetamine synthesis	Epsom salts
Mercuric chloride	Methamphetamine synthesis	
Methanol	Solvent	Heet®, gasoline additives
Methylamine	Methamphetamine precursor	
N-methylformamide	Methamphetamine precursor	
Nitroethane	P2P precursor	
Petroleum distillates	Solvent	Coleman fuel, kerosene, lacquer thinner, mineral spirits, naphtha, lighter fluid
Phenyl-2-propanone (P2P)	Methamphetamine precursor	
Phenylacetic acid	P2P precursor	
Phosphine gas	Methamphetamine synthesis byproduct	
Phosphoric acid	Methamphetamine precursor	Rust remover, colas
Pseudoephedrine	Methamphetamine precursor	Cold preparations
Pyridine	P2P synthesis	

**TABLE 3.** Continued

Chemical	Where It Is Used	Common Sources
Red phosphorous	Methamphetamine synthesis	Road flares, matchbook strikers
Sodium	Methamphetamine synthesis	
Sodium acetate	P2P synthesis	
Sodium chloride	Methamphetamine synthesis	Table salt
Sodium hydroxide	Methamphetamine synthesis and byproduct	Red devil lye
Sulfuric acid	Methamphetamine and P2P synthesis	Battery acid, drain cleaners
Thorium oxide	P2P synthesis	
Toluene	Synthesis/solvent	Brake cleaner
Trichloroethane	Methamphetamine synthesis	Gun scrubber/cleaner

**TABLE 4.** Equipment frequently used in illicit methamphetamine manufacture<sup>253,258</sup>

Aluminum foil	Blenders	Cheesecloth	Clamps
Coffee filters	Funnels	Gas cans	Hot plates
Ice chests	Jugs and bottles	Kitty litter	Laboratory beakers/glasses
Measuring cups	Pails/buckets	Paper towels	Plastic storage containers
Propane cylinders	Rubber gloves	Rubber tubing	Strainers
Tempered glassware	Thermometers	Towels/sheets/ pillowcases	

## Hazards Associated with Methamphetamine Laboratories

### Explosions/Burns

An estimated 30% of clandestine laboratories are found after an explosion or fire.<sup>231</sup> Patients injured in these incidents reportedly have more severe inhalational injury, are more likely to require endotracheal intubation, and spend a longer period on mechanical ventilation than case controls.<sup>230,232-234</sup> It has also been reported that these patients require more fluid resuscitation than other burn patients, with estimates between 2 and 3 times the Parkland formula.<sup>233,235</sup> These patients also had higher rates of pneumonia, respiratory failure, and sepsis when adjusted for percentage involvement of total body surface area (TBSA), age, and inhalational injury.<sup>234</sup> Agitation was also more common in the clandestine-laboratory-related thermal burn patient than in case controls, requiring higher doses of sedation and/or psychiatric evaluation.<sup>233</sup> Burns to the face and eyes are common.<sup>236</sup>

One study reported a 100% mortality rate for clandestine-laboratory-related thermal burn patients with TBSA of 40% or more. Comparatively,

non-methamphetamine-related burn patients with TBSA of 60% or greater are uniformly fatal. It has been theorized that the lower fatal TBSA in clandestine-laboratory-related thermal burn patients may be due to chemical injuries as well as toxicity from the methamphetamine itself.<sup>235</sup>

Other characteristics of clandestine-laboratory-related thermal burn patients are that they are more likely to be unemployed, uninsured, on Medicare/Medicaid, or receiving some type of government assistance.<sup>232,233,237</sup> Treatment of these patients costs more than treatment of other thermal burn patients, even after controlling for TBSA.<sup>232,233</sup>

## Chemical Injuries

Persons involved in clandestine methamphetamine manufacture may also be injured by exposure to the chemicals used to manufacture methamphetamine.<sup>232</sup> The type and severity of chemical injury vary with the substance and the route of exposure (eg, dermal absorption, inhalation, ingestion). Table 5 lists selected chemicals and their potential hazards. Two substances that are commonly implicated in clandestine-laboratory-related chemical injury are anhydrous ammonia and phosphine gas.

The primary use of anhydrous ammonia is as a farm fertilizer. It is also used in the Nazi/Birch method with an alkali metal to convert ephedrine or pseudoephedrine into methamphetamine.<sup>223,224</sup> To obtain anhydrous ammonia, methamphetamine manufacturers may steal it from storage containers at farms and subsequently store it in propane tanks.<sup>238</sup> Clandestine-laboratory-related anhydrous ammonia injuries are reported to involve higher TBSA, longer length of mechanical ventilation, and longer inpatient stays and have a higher overall complication rate than other anhydrous ammonia chemical injuries.<sup>239</sup> Injuries may be sustained, not just by the manufacturers themselves, but also by others living in the same household. Simulations of functional clandestine laboratories have reported ammonia vapor concentrations that approached or exceeded those deemed immediately dangerous to life and health, even at remote sites within the home.<sup>240,241</sup>

Anhydrous ammonia causes severe chemical injury to the skin, lungs, and eyes.<sup>242</sup> Anhydrous ammonia is an alkali that quickly penetrates the skin, causing liquefaction necrosis. Decontamination should be accomplished by copious irrigation. Dermal injury may require mechanical debridement and skin grafting.

Pulmonary injury due to ammonia may be classified as acute or chronic, depending on the nature of exposure. Acute pulmonary exposure occurs



**TABLE 5.** Hazards of selected chemicals found in clandestine laboratories<sup>222,228,230</sup>

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Acetic acid	Acute—eye irritation, airway inflammation, pulmonary edema, severe burns, corneal ulcers, permanent eye damage; chronic—upper airway irritation, eye irritation; flammable when heated
Acetic anhydride	Vapors—eye, mucus membrane, and skin irritation; high concentrations of vapors can lead to mucosal ulceration and bronchospasm; liquid—immediate burning, corneal/conjunctival edema, corneal opacification, vision loss, red to white/wrinkled skin; skin burns may be delayed
Acetone	Eye, skin, and upper airway irritation; prolonged exposure—coughing, blurry vision, tremors, seizures, stupor, bizarre behavior, coma, death; flammable/explosive mixed with air at room temperature; explosive when heated
Anhydrous ammonia	Burns to eyes, upper airway, and skin; conjunctivitis, lacrimation, corneal irritation, blindness (temporary and permanent); bronchospasm, wheezing, dyspnea, chest pain, pulmonary edema, chemical pneumonitis
Benzaldehyde	Narcotic at moderate doses; induces seizure at higher doses; eye and airway irritation; contact dermatitis; may be absorbed through skin
Benzene	Acute—headache, dizziness, breathing difficulties, coughing, pulmonary edema, coma, lung/liver/kidney damage, death; chronic—irritation of eyes and airway, allergies, confusion, short-term memory loss, bone marrow suppression, coma death; flammable, may cause flash fires
Benzylchloride	Eye, mucus membrane, skin irritation; headache, lacrimation, pulmonary edema, corneal injury, contact dermatitis
Ephedrine	Headache, hypertension, tachycardia, stroke; eye, lung, and skin irritation
Ethanol	Inhalation—irritation or upper airway, headache nausea/vomiting, drowsiness, confusion; ingestion—confusion, dizziness, seizures, blurry vision, blindness, coma, death; chronic—headache, decreased coordination, nervous system/liver/stomach/heart damage
Ethyl ether	Headache, “drunkenness” vomiting; spontaneously explosive in sunlight or oxygen or heat
Formic acid	Absorption through skin can cause systemic effects; severe, painful burns, bloody diarrhea, pulmonary edema, shock, death; explosive with contact of oxidizing agents
Freon	Eye irritation; vomiting, slurred speech, drunkenness, coma, death; inhalation can cause sudden cardiac death
Hydriodic acid	Irritation of upper airways at low concentrations and dyspnea, chest pain, bronchospasm, pneumonitis, pulmonary edema at high concentrations; eye and skin irritation and burns
Hydrochloric acid/gas (muriatic acid)	Skin burns and allergies; inhalation may lead to pulmonary edema and permanent lung damage
Hypophosphorous acid	Burns especially to mucus membranes
Iodine	Vomiting, delirium, headache, hypotension, shock; mucus membrane irritation, can lead to pulmonary edema; skin irritation

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**TABLE 5.** Continued

Lead acetate	Mostly a chronic exposure concern; abdominal pain, nausea/vomiting, difficulty concentrating; increased exposure risk to children due to developing nervous system
Lithium	Eye, skin, upper airway, and lung irritation; water-reactive, generates hydrogen gas, explosive
Mercuric chloride	Acute—abdominal pain, vomiting, hematemesis, renal failure; bizarre behavior, lung damage; chronic—builds-up in brain/liver/kidneys; harmful fumes when heated
Methanol	Eye and airway irritation; headache, nausea/vomiting, abdominal pain, blindness, loss of consciousness, damage to brain/pancreas/kidneys
Methylamine	Eye, mucus membrane, skin irritation; allergic or chemical bronchitis; conjunctival hemorrhage, superficial corneal opacities, corneal edema
Nitroethane	Eye, mucus membrane, skin irritation; nausea/vomiting/diarrhea, mental status depression, ataxia, seizures
Petroleum distillates	Eye and skin irritation; delayed lung injury, depressed mental status, seizures, loss of consciousness; flammable mixed with air at room temperature
Phenyl-2-propanone (P2P)	Eye and skin irritation; nausea, headache, dizziness
Phenylacetic acid	Eye and skin irritation; nausea, headache, dizziness
Phosphine gas	Delayed pulmonary edema; dizziness, tremors, vomiting, seizures; flammable, explosively reacts with air
Phosphoric acid	Eye, skin, and upper airway irritation; chronic—allergies, lung/liver/bone marrow damage; releases phosphine gas when contacts metal
Pseudoephedrine	Headache, hypertension, tachycardia, stroke; eye, lung, and skin irritation
Pyridine	CNS depressant, liver/kidney damage, low back pain without kidney damage, headache, nausea/vomiting, vertigo
Red phosphorous	If heated, produces yellow phosphorous (skin burns); if heated with acid, produces phosphine gas
Sodium	Thermal and chemical skin burns; eye, mucus membrane, lung, and skin irritation; water-reactive, produces hydrogen gas and sodium hydroxide
Sodium hydroxide	Severe burns to eyes and skin; inhalation can lead to burns in air passages; carcinogen; metal or fire contact produces hydrogen gas
Sulfuric acid	Severe burns to eyes and skin; inhalation can lead to lung damage, respiratory failure; chronic—lung/liver/kidney damage, skin allergies; carcinogen; water-reactive, produces harmful and corrosive fumes
Thorium oxide	Radioactive alpha emitter; carcinogen
Toluene	Inhalation—irritation or upper airway, headache nausea/vomiting, drowsiness, confusion; ingestion—confusion, dizziness, seizures, blurry vision, blindness, coma, death
Trichloroethane	Eye, skin, upper airway, and lung irritation; pulmonary edema, pneumonia, death; corneal damage

with the inhalation of high concentrations of ammonia vapor over a short period (eg, ammonia discharge from a storage container) and is associated with facial and upper airway injury.<sup>243</sup> Early intubation should be undertaken because of the risk for glottis and supraglottic swelling resulting in compromise of the airway.

Conversely, chronic pulmonary exposure because of exposure to lower concentrations over a prolonged period (eg, ammonia fumes during methamphetamine manufacture) is associated with injury throughout the pulmonary tree. Chronic ammonia inhalational injury can be divided into 2 phases. The early phase is hallmarked by sloughing of pulmonary epithelium resulting in hypoxia, edema, and airway obstruction. Aggressive pulmonary toilet is necessary. The later phase presents with an initial improvement in ventilation, followed by the gradual onset of fixed obstruction that may be prolonged in nature. Bronchodilator and corticosteroid therapy may be of benefit, with antibiotics reserved for bacterial superinfections.<sup>242</sup>

Ocular exposure may result in severe corneal injury. Immediate copious irrigation should be instituted and the effectiveness of irrigation can be monitored by serial measurements of the pH of ocular secretions. Permanent vision loss from cataracts, atrophy of the iris, and acute angle closure glaucoma are potential adverse effects associated with ammonia-induced corneal injury. Corneal transplantation may be attempted; however, failure of transplantation secondary to scarring during the original injury has been reported.<sup>242</sup>

Phosphine gas is used as a grain fumigant, a precursor chemical, and a chemical warfare agent.<sup>244-246</sup> Phosphine gas is a byproduct of illicit methamphetamine manufacturing via the cold or red phosphorus method.<sup>227</sup> Phosphorous acid is formed when iodine and red phosphorus are combined to form hydriodic acid and readily decomposes into phosphine gas and phosphoric acid.<sup>244</sup> Heating of solutions containing red phosphorus also produces phosphine gas.<sup>240</sup> During simulations of functional clandestine laboratories, phosphine gas concentrations were reported to exceed recommended upper limits of exposure.<sup>247</sup>

Inhalational phosphine exposure causes irritant effects with dyspnea, cough, delayed noncardiogenic pulmonary edema, ventilator-dependent respiratory failure, and, in severe cases, death.<sup>244-246</sup> Exposure to phosphine gas may also result in ocular and dermal irritation.<sup>245</sup> A particularly insidious aspect of phosphine gas exposure in clandestine laboratories are case reports of law enforcement personnel being injured because of phosphine gas exposure during raids.<sup>248</sup> Patients with suspected phosphine exposure should be observed for a 24-hour period to monitor for

delayed-onset pulmonary edema. Supplemental oxygen and mechanical ventilation with positive end expiratory pressure may be necessary and corticosteroids have been reported to be of benefit in animal models.<sup>245</sup> Phosphine exposure in workers exposed to phosphine in industrial applications has been reported to result in prolonged pulmonary complaints, including exertional dyspnea, decreased exercise tolerance, and abnormal pulmonary function testing for years after exposure; these symptoms were seen in patients with a history of tobacco use or preexisting lung diseases.<sup>245</sup>

Methamphetamine manufacturers are not the only persons who could be harmed by the hazards present in clandestine laboratories. Other persons living or working in the same building may be exposed to chemicals involved in the manufacturing process.<sup>240,241,247,249,250</sup> First-responders and law enforcement personnel are also at risk for harm. First-responders (eg, police or firefighters) may be particularly at risk if there is no advance warning that caustic chemicals are present at a site.<sup>251</sup> The appropriate use of personal protective equipment and training in the recognition of clandestine laboratories is important in reducing risk for these civil servants.<sup>251</sup> Clandestine laboratory investigators are at risk of injury during the processing phase of a laboratory, where samples are taken and chemicals are removed.<sup>221</sup> Hospital personnel are also at risk if patients from clandestine laboratories are not appropriately identified and decontaminated before entry into the hospital.<sup>251</sup> Symptoms reported by first responders and law enforcement personnel include respiratory irritation, dyspnea, headache, skin irritation/burns, mucous membrane irritation, nausea/vomiting, and dizziness.<sup>221,251</sup>

## Pediatric Issues

In 17%-44% of discovered clandestine laboratories, children are living in the same building.<sup>252-255</sup> Children may be exposed to chemicals used in the manufacture of methamphetamine even if they are not in the area where the methamphetamine is being produced, because of either airborne exposure or environmental persistence of the substances.<sup>240,241,247,249,250</sup> Exposure can be to the methamphetamine itself or to precursor chemicals or solvents.<sup>256,257</sup> Preschool children are particularly at risk for exploratory ingestions due to hand-to-mouth behavior and the significant portion of the day they spend in the home.<sup>254,255</sup> Improper storage of chemicals near food items or in refrigerators increases the likelihood of pediatric exposures.<sup>258</sup> Environmental persistence of chemicals following the manufacture of methamphetamine in kitchens or food preparation areas also puts children at risk

for toxicity.<sup>259</sup> Children living in buildings containing clandestine laboratories are at risk for injury or death due to other nontoxicologic hazards: lack of running water, improper maintenance of the building or building contents, insect infestation, poor sanitation, booby-traps, loaded firearms, and drug paraphernalia (eg, butane lighters, used hypodermic needles); all may be present in buildings housing clandestine laboratories.<sup>255,259,260</sup> Parents or other adults may be more focused on manufacturing or using methamphetamine than in child care, resulting in neglect, while chronic abuse of methamphetamine may impair their judgment or hinder their ability to care for children.<sup>259,261</sup> Protocols are useful in directing health care providers in the assessment and treatment of these children. A multidisciplinary approach involving health care providers, emergency departments, social workers, law enforcement, and governmental children services departments is likely to yield the best results, with the health and physical safety of affected children being the utmost concern.<sup>255,260-262</sup>

## Environmental Contamination

For every pound of methamphetamine produced, it has been estimated that up to 6 pounds of hazardous waste are generated.<sup>258</sup> Following the seizure of a clandestine laboratory, extensive environmental remediation may be necessary. Currently, extensive debate still exists regarding the extent of remediation necessary and who is responsible for funding it.<sup>222,231,263-265</sup> Reported costs for environmental remediation vary from \$2000 to \$100,000, depending on the size of the laboratory and the practices of the manufacturers.<sup>266</sup> More research is necessary to determine the extent of remediation that must be performed and if there are any long-term health or environmental effects related to former clandestine methamphetamine laboratories and how these effects are moderated by environmental remediation.

## Conclusions

Methamphetamine abuse results in numerous adverse health effects, including myocardial infarction, aortic dissection, pulmonary edema, intracranial hemorrhage, ischemic stroke, mesenteric infarction, rhabdomyolysis with renal injury, necrotizing gingivostomatitis, psychiatric disease, persistent cognitive impairment, sexually transmitted disease, and transmission of blood-borne disease. Use in pregnant women has been associated with fetal loss and perinatal maternal death. Methamphetamine increases the risk of traumatic death, which may be a result of accident, suicide, or homicide.

Increases in methamphetamine abuse make methamphetamine a significant public health problem. Population morbidity and mortality, health care costs, and law enforcement costs associated with methamphetamine abuse are significant. Children living in clandestine laboratories or simply in homes where methamphetamine is abused are at risk for abuse, neglect, and toxicologic exposures.

The manufacture of methamphetamine also results in significant morbidity and mortality because of thermal and blast injuries, caustic injury, and other toxicologic exposures. Of additional concern is the risk posed by these laboratories to first responders and law enforcement personnel. Environmental persistence of hazardous waste generated by methamphetamine manufacture and the extent of necessary remediation efforts are further important issues that continue to generate debate.

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