P2P Specific toxicity data lacking. Similar compounds used in fragrances and pharmaceuticals.	Liquid	Skin, eyes
Methylamine Ammonia odor present at very low levels. See also irritants, corrosives.	Gas Liquid Solid	Skin, eyes, inhalation Skin, eyes, inhalation Skin, eyes

SOURCE: Oregon Department of Human Resources 1988

Heavy Metal and Organic Contaminants Associated With Illicit Methamphetamine Production

Brent T. Burton

INTRODUCTION

Methamphetamine is a powerful stimulant drug commonly known on the street as "crank" or "speed." It is currently the most popular and widespread amphetamine that is illegally manufactured, distributed, and abused.

Illicit methamphetamine is produced in clandestine laboratories that are widespread in the United States. The profit motive for the clandestine chemist is enormous, with some laboratories producing in excess of $300,000 per week in street value. Although several other illicit drugs of abuse are occasionally manufactured in clandestine laboratories, methamphetamine accounts for almost 95 percent of all clandestine laboratory seizures. The frequency of laboratory seizures has been increasing nationwide over the past decade (Anon 1988). The States of California, Texas, Oregon, and Washington have shown the greatest increase in clandestine laboratory activity.

Adverse health effects to the abuser are not limited to toxic effects of the drug. Illicit drugs produced in clandestine laboratories by unskilled chemists are likely to contain potentially toxic contaminants due to unintended reaction by-products and reagent residuals. Process errors in the production of clandestine drugs previously have resulted in severe health effects, including acute Parkinson's disease from attempted production of 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP) and acute lead poisoning from injection of methamphetamine (Allcott et al. 1987; Ballard et al. 1985; Norton et al. 1989).

The average concentration of methamphetamine street samples is approximately 40 to 50 percent (Hall et al. 1988). Most contaminants found in illicit drugs are intentionally added by the distributor to dilute or "cut" the product to increase profits. Such substances include lactose, mannitol, lidocaine, procaine, caffeine, quinine, and sodium bicarbonate and may account for as

much as 94 percent of the finished product (Grinspoon and Bakalar 1985). In the case of drugs produced by the clandestine chemist, additional contaminants may be introduced by the production process. One can predict such potential contaminants due to unreacted substances or unintended reaction products from known production methods available to the clandestine chemist. Though unintended contaminants may be introduced into the finished drug by the clandestine chemist, the extent and types of substances as a result of the production process have not yet been adequately studied.

HISTORY

Methamphetamine was developed in 1919 as an amphetamine derivative by A. Ogata, a Japanese pharmacologist. However, it was not until the 1930s that the pharmacologic properties of amphetamines became known. The sympathomimetic properties of amphetamines initially made them useful as vasoconstrictor agents, and they were first introduced into the marketplace in 1932 as Benzedrine, an inhaler designed for relief of nasal congestion. Users of these nonprescription inhalers soon noted that the amphetamine contents were powerful central nervous system stimulants. This property subsequently made amphetamines useful drugs in the treatment of narcolepsy and some forms of depression but also made them desirable as drugs of abuse.

The abuse of amphetamine began almost as soon as it was available as an over-the-counter medication. Shortly after the Benzedrine nasal inhaler became available in 1931, abusers were taking apart the spray bottle to retrieve the paper inside containing 250 mg of amphetamine. These strips of paper then were consumed in chewing gum or stirred into a beverage for its stimulating and euphoric effect (Grinspoon and Hedblom 1975).

By 1962 the legal production of amphetamines was estimated by the Food and Drug Administration to be more than 8 billion tablets per year, with output increasing every year. Much of the amphetamine abuse of the 1950s and 1960s occurred as a result of prescription abuse by individual patients obtaining drugs from their private physician, many of whom knowingly were writing prescriptions for profit.

The drug culture of the 1960s brought a dangerous new route of administration for amphetamines. An injectable form of pharmaceutical methamphetamine rapidly became responsible for the amphetamine abuse lifestyle known as the "speed freak." The dangerously addictive nature of injectable amphetamines became obvious with the advent of the amphetamine-tolerant freak who would inject as much as 15 g of amphetamine during a single day (Grinspoon and Hedblom 1975).

Until the 1970s most amphetamines were obtained from pharmaceutical sources that were diverted into the black market. It has been estimated that as much as 50 percent of legitimate amphetamine production was diverted by shipments to unauthorized persons, thefts, or prescription forgeries (Morgan 1981).

Due to the abuse of amphetamines and other drugs in the United States, the Controlled Substance Act (CSA) was passed in 1970, which designated control schedules for drugs according to their abuse potential. This act dramatically changed the availability of pharmaceutical amphetamines by requiring special procedures for manufacturers to register shipments and provide detailed accounting of transactions involving controlled substances. Predictions that strict controls would result in a shift to clandestine production of methamphetamine did not materialize at that time. However, the increased availability and use of cocaine in the 1970s may have temporarily reduced market demand for methamphetamine.

As amphetamines became more difficult to obtain, purity of street samples began to decline. During the mid-1970s many street samples sold as amphetamine contained little or none of it, and a variety of drugs began to show up that were being sold as amphetamine. Samples of street amphetamines in 1973, after the effect of the CSA was apparent, contained only about 10 percent amphetamine on average (Morgan 1981). Most often, over-the-counter drugs with stimulant properties such as caffeine, ephedrine, and phenylpropanolamine were substituted and sold as amphetamine. This practice eventually led to the drug "look-alike" business, a thriving mail-order enterprise offering these legal over-the-counter drugs packaged and promoted with names, tablet shapes, and colors designed to mimic amphetamines.

Since the mid-1980s there has been a reemergence of the illicit use of methamphetamine. One such indicator is the rapid increases that have been documented in numbers of clandestine laboratories seized by law enforcement agencies. Most recently, media reports have focused on the increasing popularity of "ice," a smokable form of methamphetamine (Lerner 1989). The use of this crystalline form of methamphetamine has been prevalent especially in Hawaii, where it is imported from Pacific rim countries. As this form of methamphetamine becomes more widely available in the United States, it is possible that stimulant users once again will shift to methamphetamine.

CLANDESTINE SYNTHESIS OF METHAMPHETAMINE

Illicit manufacture of methamphetamine is a simple process that does not require special knowledge or expertise in chemistry. Most methamphetamine is

produced by relatively uneducated persons who synthesize the drug from published or handwritten recipes. The drug subculture provides abundant opportunities for the potential clandestine chemist to obtain recipes, or even attend cooking classes, for methamphetamine. Many recipes in circulation are handwritten instructions that describe how to procure the needed chemicals, glassware, and supplies. These instructions often include detailed sketches and descriptions of the procedure so the novice can produce methamphetamine without prior training. Some underground recipes even describe the legal status of various chemicals and methods to avoid detection by law enforcement officials.

Several publications, available in bookstores or by mail order, describe the methods of drug manufacture. One such publication, *Psychedelic Chemistry*, describes detailed recipes for the production of several drugs. In addition, information is provided about how to obtain chemicals and laboratory equipment without prompting the attention of law enforcement officials (Smith 1981).

The clandestine chemist need not resort to handwritten underground recipes or try to locate the proper reference text in a bookstore. Numerous scientific journals provide a wealth of information regarding drug synthesis, including alternate procedures for a variety of processes, that the chemist may select depending on chemical availability. The educational level of persons utilizing such references must be more sophisticated than that of the typical clandestine chemist due to the highly technical nature of the journals. An example of such an article is a description of a currently unused but proposed method of production, authored by chemists of the U.S. Drug Enforcement Administration (DEA) (Cason et al. 1984). These references usually are torn or cut out of library journals, presumably to reduce competition from other would-be clandestine chemists.

Because the clandestine chemist usually lacks skill and training in chemistry, there are multiple opportunities for errors or misunderstanding of proper procedure. Attempts at shortcuts, inadequate filtering, salt washing, or solvent extraction could result in serious contamination with reagents. At least one clandestine chemist apparently completely misunderstood the proper procedure and produced a finished product that contained 60 percent lead with phenyl-2-propanone (P2P) but no methamphetamine (Norton et al. 1989).

Numerous chemicals associated with the illicit production of methamphetamine are listed below. Although only a few chemicals may be required for production, there are multiple reagents and precursors that can be substituted for those that are difficult to obtain legally. Thus, there may be many chemicals that potentially can contaminate the finished product.

SOLVENTS

Acetone
Benzene
Chloroform
Ethyl ether
Ethanol
Freon
Hexane
Isopropanol
Methanol
Pyridine
Toluene

PRECURSORS

Acetaldehyde
Acetic anhydride
Allyl benzene
Benzyl cyanide
Benzylchloride
Diethylmalonate
Dimethylformamide
Ephedrine
Ethanol
Ethyl acetate
Formic acid
Hydrogen gas
Hydrogen peroxide
Methylamine
N-methylformamide
Nitroethane
Phenyl-2-propanone
Phenylacetic acid
Phenylacetylchloride

REAGENTS

Metals

Aluminum
Barium sulfate
Calcium chloride
Copper chloride
ron
Lead acetate
Lithium aluminum hydride
Magnesium
Magnesium sulfate
Manganese oxide
Mercuric oxide
Mercuric chloride
Palladium
Palladium chloride
Potassium cyanide
Sodium acetate
Sodium ethoxide
Sodium cyanide
Sodium
Cyanotrihydroborate
Sodium
Thorium oxide

Nonmetals

Butylamine
Iodine
Phosphorous
Phosphorouspentachoride
Thionyl chloride

Acids

Acetic acid
Hydrochloric acid
Hydroiodic acid
Perchloric acid
Phosphoric acid
Sulfuric acid

Bases

Ammonia
Sodium hydroxide
Sodium carbonate

PRODUCTION PROCESSES

P2P is the primary precursor most often used by the clandestine chemist. The amalgam and Leukart processes are the most popular (figure 1), accounting for about 90 percent of clandestine methamphetamine production (Frank 1983). Processes involving P2P as the precursor often utilize methylamine to provide the amine group and thus formulate methamphetamine in a simple single-step reaction procedure. The amalgam method utilizes a combination of mercuric chloride and aluminum foil as catalysts (figure 1). These and all reactions require a variety of acids and solvents for extraction and purification of the finished product.

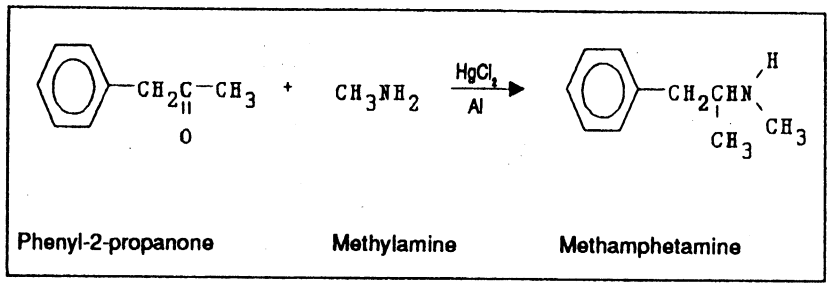

FIGURE 1. *Synthesis of methamphetamine utilizing the amalgam method catalyzed by mercuric chloride and aluminum foil*

The clandestine manufacturing and purification procedure is represented by the following instructions paraphrased from a recipe obtained from a clandestine chemist (Dallosta 1985): The process is initiated by adding mercuric chloride, aluminum foil, isopropanol, and sodium hydroxide to a reaction vessel and heating. When the solution comes to a boil, the P2P and methylamine are added to the mixture and heated for 4 hours. The reaction material then is passed through filter paper to remove contaminants. Excess methylamine is removed by the application of heat to the reaction product. The remaining mixture containing "freebase amine" is purified with a salt wash to "kill the poisonous mercuric chloride." The product then is acidified to adjust the pH, crystallized, purified with solvent in a separatory funnel, and then recrystallized and packaged for distribution.

Unavailability of P2P and legal controls of other precursors have resulted in the increasingly popular use of ephedrine as a primary precursor. Ephedrine is a

common over-the-counter decongestant cold remedy that differs in molecular structure from methamphetamine only by the presence of a hydroxyl group at the β-carbon. A single-step hydrogenation reaction of ephedrine, which can be accomplished by several methods, will produce a high yield of methamphetamine. This reaction has the advantage of considerably less noticeable odor than reactions utilizing P2P (the unpleasant, lingering odor of P2P and another precursor, phenylacetic acid, has frequently been a clue to the operation of a clandestine laboratory). To escape detection and also utilize easily available chemicals, clandestine chemists may resort to using hydrogenation methods of ephedrine using red phosphorous as a catalyst with hydroiodic acid. In some cases clandestine chemists are fabricating high-pressure reaction vessels to react ephedrine with hydrogen gas. If ephedrine or P2P are not available, the chemist may resort to industrial chemicals, such as benzyl chloride, as the precursor.

PRECURSOR SYNTHESIS

Clandestine manufacture of methamphetamine became more complicated in 1980 when P2P was classified as a Schedule II controlled substance by DEA. In addition, States with clandestine drug laboratory problems, that is, California, Oregon, and Washington, have passed laws requiring that any person who purchases listed chemicals that may be used in methamphetamine production be reported to the State police. These legal restrictions on P2P, intended to curb the growth of clandestine methamphetamine, spurred the development of clandestine laboratories specializing in the production of P2P from phenylacetic acid. Legitimate P2P sells commercially for less than $100 per liter, but the same amount will net more than $4,000 for the clandestine chemist. Synthesis of P2P usually is accomplished by utilizing lead acetate as the primary reagent in a process that requires a distillation procedure (figure 2). In the hands of the unskilled or careless clandestine chemist, these processes may result in the introduction of contamination from lead and other reagents used in the production process.

In the absence of phenylacetic acid there are several alternative reactions the clandestine chemist may choose to produce methamphetamine, utilizing easily available chemicals but requiring more complex and often more dangerous reactions. For example, phenylacetic acid may be synthesized from industrial chemicals such as benzylchloride, toluene, or benzene. In a possible endless source of potential reaction pathways, the chemist may resort to manufacturing many precursors from uncontrolled chemicals. For example, ephedrine may be synthesized from propiophenone, or methylamine may be produced in a reaction with ammonia and methanol. The increasing complexity of the reaction sequence and the substantial numbers of chemicals required in the production

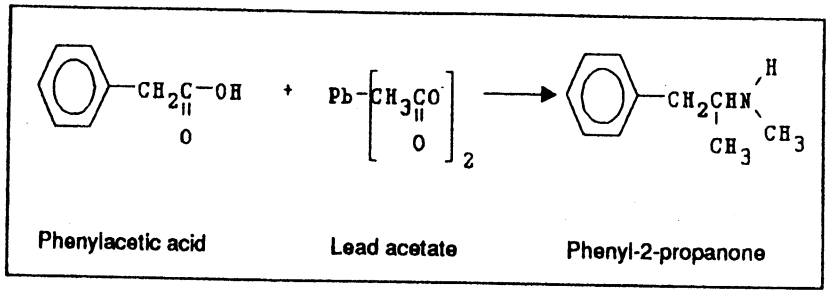

FIGURE 2. *Synthesis of the precursor P2P from phenylacetic acid and lead acetate*

process increase the risk of errors and the probability of toxic contamination in the final product.

TOXICITY OF DRUG CONTAMINANTS

Although drug contamination may result in potentially serious adverse health effects for the drug user, the difficulty in studying such a group of subjects has made it problematic to document the extent of drug contaminant-induced illness from methamphetamine. For this reason most reports of drug contaminant illness have been anecdotal cases. Epidemiological investigation into this problem has not yet been accomplished.

There have been reports of contaminated drugs produced in clandestine laboratories that have resulted in disastrous health effects in the unsuspecting user. One such major outbreak of serious illness from contaminated drugs occurred in 1982 when an attempt was made by a clandestine chemist to produce the meperidine congener, MPPP. Instead, due to a relatively minor aberration in the reaction process, highly toxic 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) was synthesized and distributed on the street. Drug users unlucky enough to inject MPTP developed severe and permanent Parkinson's disease. Only by a series of coincidences was the cause of the Parkinson's disease traced to the contaminated drug (Ballard et al. 1985). It is not known how many other toxic substances may be created by the clandestine chemist attempting to make other illegal drugs, including methamphetamine.

Two case reports have documented human toxicity due to methamphetamine contamination. In both instances illness was caused by heavy contamination of lead. In 1987 two patients in Oregon were reported to have developed lead toxicity as a result of the injection of methamphetamine. Both patients

developed illnesses consistent with lead intoxication and presented with symptoms of nausea, vomiting, constipation, numbness and tingling, weakness, and headache. Laboratory data revealed elevation of liver enzymes, suggesting a diagnosis of infectious hepatitis. However, in view of the nonspecific clinical presentation, the possibility of lead poisoning apparently was not considered until basophilic stippling was found on the blood smear, which prompted an investigation for lead toxicity. A blood lead level of 204 μg/dL was measured in one of the patients (<40 μg/dL is normal). A blood lead level was not reported for the second patient, although a free erythrocyte protoporphyrin was elevated at 68 μg/L (<50 μg/L is normal). Both patients required chelation therapy with disodium calcium edetate. A sample of methamphetamine obtained later from one of the victims was shown to contain 899 ppm of lead. This would result in the injection of approximately 0.1 mg of lead per dose of drug (Allcott et al. 1987).

The second outbreak of lead poisoning was reported in 1988 and involved 12 methamphetamine abusers in a three-county area in Oregon. All cases came to medical attention between April 18 and September 15, 1988. The mean age of these patients was 27 years (range 24 to 36 years), nine males and three females. The most common complaints were gastrointestinal, that is, nausea, vomiting, abdominal pain, and constipation. Although lead poisoning typically is associated with neurological findings, only one patient complained of paresthesias. The physical examinations were remarkable for abdominal tenderness, but evidence of encephalopathy or neuropathy was not present. Anemia was common with a mean hematocrit of 29.8 percent (range 20 to 44 percent). Basophilic stippling was present in 10 cases. Elevation of liver enzymes was consistent with chemical hepatitis. The most severely poisoned patient also developed a clinical pancreatitis. The mean blood lead level was 146 μg/dL, with a range from 49 μg/dL to 513 μg/dL, the latter being the highest level yet reported in a living person. Seven patients underwent chelation treatment. Although followup was not possible for all patients, it appeared that all improved with treatment. It was presumed that this outbreak resulted from perhaps a single source because of the close proximity of the cases. Although the source or the responsible clandestine chemist could not be identified, one of the victims supplied a sample of the drug he had allegedly injected. Analysis of this drug revealed that the sample contained 60 percent lead (Norton et al. 1989). This concentration of lead would result in a dose of more than 50 mg of lead per injection.

The cases described above involved relatively large doses of lead that resulted in severe acute poisoning. Although smaller doses of lead in methamphetamine may result in illness, the effects may not be readily apparent to the clinician, particularly in view of the nonspecific symptoms frequently seen in lead poisoning. It is not known if methamphetamine abusers, as a group,

may be at risk of unrecognized chronic lead toxicity due to chronic low-level exposure to lead; chronic accumulation may not result in illness until large body burdens of lead have been attained.

It has been suspected, but not yet documented, that drug abusers may be at risk of developing poisoning from other reagents used in the manufacturing process. Although mercury has been considered as a possible contaminant with significant health impact, there have not yet been any confirmed cases of mercury poisoning. However, it must be recognized that this may be due to the lack of case recognition in patients that have complications that are consistent with drug abuse such as hepatitis and nephritis. In an attempt to document excessive mercury exposure, hair samples of 12 methamphetamine abusers were measured for mercury. None of the samples showed a significant increase in mercury concentrations compared with nonuser controls (French 1985). However, this exploratory study could not overcome the difficulty of self-selection of patients and the inherent technical problems associated with collection and interpretation of hair sampling for mercury. Blood or urine levels were not measured, and drug samples were not assayed to determine if the drug users had been exposed to methamphetamine contaminated with mercury. Injection of mercuric chloride probably would produce severe burning pain at the injection site and the development of thrombophlebitis. Hepatitis and nephritis likely would occur following systemic absorption.

In addition to heavy metal contamination from reagents, the clandestine production process also may result in the formation of a variety of possible organic contaminants. One study revealed that contamination by organic products to be as high as 10 to 39 percent of the sample (LeBelle et al. 1973). Of the few studies that have attempted to characterize the contamination of illicit methamphetamine, most have attempted to identify drug contaminants as intermediates or markers of a particular process for evidentiary purposes (Kram et al. 1976; Sottolano 1988). It has been noted by forensic chemists that gas chromatographic analysis of illicit methamphetamine has demonstrated a variety of substances, including several contaminants that, thus far, have not been identified and have unknown toxicity. These contaminants are most often due to incomplete reactions, inadequate purification procedures, or unintended reactions. Attempts to identify some of these substances have required synthesis of expected contaminants to use as standards for confirmation of chemical structure. Noggle and colleagues (1985), utilizing liquid chromatographic procedure, noted that α-benzylphenethylamine derivatives were the most common contaminants. These derivatives were shown to have greater potency to induce seizures in mice than methamphetamine. Organic contaminants found in illicit methamphetamine are summarized in table 1.

TABLE 1. *Organic contaminants of illicit methamphetamine*

Substance	Reference
N,N-dimethylamphetamine	Kram et al. 1976
N-formylamphetamine	Kram et al. 1976
N-formylmethamphetamine	LeBelle et al. 1973
Dibenzylketone	Kram et al. 1976
a-benzylphenethylamine	Noggle et al. 1985
a-benzyl-N-methylphenethylamine	Barron et al. 1974
a,a'-dimethyldiphenethylamine	Kram et al. 1976
N-methyldiphenylethylamine	Kram et al. 1976
N,a,a'-trimethyldiphenethylamine	Barron et al. 1974

CONCLUSION

The clandestine production of methamphetamine is performed by unskilled chemists utilizing an array of potentially toxic chemicals. Residual reagents, solvents, and unintended reaction by-products may remain as contaminants in the finished product. Fourteen cases of acute lead poisoning have been reported in the medical literature as result of methamphetamine contamination. It is unknown if lead poisoning from methamphetamine is episodic, due to poor technique, or is more widespread but at a lower level of toxicity. Further investigation into the prevalence of lead toxicity is currently under way.

Toxicity due to other reagents and organic by-products remains a distinct possibility, although known cases have not been reported. Further research is needed to examine the extent of contaminants in illicit methamphetamine and to determine their adverse health implications.

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AUTHOR

Brent T. Burton, M.D.
Medical Director
Oregon Poison Center
Associate Professor of Emergency Medicine
Oregon Health Sciences University
3181 Southwest Sam Jackson Park Road
Portland, OR 97201