

## Impurity Profiling of Street Methamphetamine Samples Seized in Kermanshah, Iran with Special Focus on Methamphetamine Impurities Health Hazards

Neda Amini<sup>1</sup>, Afshar Etemadi-Aleagha<sup>2</sup> and Maryam Akhgari<sup>3\*</sup>

<sup>1</sup>Department of Toxicology & Pharmacology, pharmacology & Toxicology Department, Faculty of pharmacy, Pharmaceutical Sciences Branch, Islamic Azad University (IAUPS), Iran

<sup>2</sup>Department of anesthesiology, Tehran University of Medical Sciences (TUMS), Amir Alam Hospital, Tehran, Iran

<sup>3</sup>Department Forensic Toxicology, Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran, \*Corresponding author: Maryam Akhgari, Assistant professor of Forensic Toxicology, Department of Forensic Toxicology, Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran, Tel: +98 2156524763; Fax: +98 2156524763; Email: akhgari1349@yahoo.com

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### Abstract

**Objective:** Methamphetamine abuse remains a significant public health concern since its ascent to peak popularity in Iran. Methamphetamine possesses one of the most domestic markets among other drugs of abuse in Kermanshah, Iran. Clandestine methamphetamine laboratories employ different methods and consequently a wide range of chemicals for the illicit production of methamphetamine. Yet there is limited information about active pharmaceutical ingredients in methamphetamine samples seized in Kermanshah, Iran. The current study aimed to identify active pharmaceutical ingredients and manufacturing by-products in methamphetamine samples seized in Kermanshah, Iran. As no organ in the body remains unscathed by methamphetamine and its impurities abuse, the other purpose of the present study was to discuss health effects associated with impure methamphetamine abuse in a brief review.

**Methods:** Analytical study was conducted on 53 methamphetamine samples using gas chromatography/mass spectrometry method. We reviewed the health outcomes of methamphetamine abuse and the evidences supporting pharmacological effects of methamphetamine impurities.

**Results:** Analysed methamphetamine samples contained methamphetamine, amphetamine, ecstasy, phenmetrazine, pseudoephedrine, tramadol, benzaldehyde, acetic acid and other chemicals. Information has been discussed for common harmful effects of methamphetamine and its impurities abuse.

**Conclusion:** Illicit methamphetamine crystals contained different chemical impurities originated from manufacturing processes and active pharmaceutical ingredients deliberately added to them. The main prominent synthetic routes for methamphetamine synthesis are Leuckart and Nagai methods in Kermanshah, Iran. In addition to the chemical hazards present in methamphetamine laboratories, there are many hazards posed to anyone involved in direct and indirect contact with these contaminants.

**Keywords:** Methamphetamine; Illicit production; Forensic analysis; Impurity profiling; Methamphetamine impurity; Health hazards

### Introduction

Methamphetamine (MA) was one of the most popular abused substances in the world during the past two decades. This highly addictive substance was introduced to Iranian drug black market in 2005 [1]. According to the United Nations Office on Drugs and Crime (UNODC) report, Iran ranked fifth behind Thailand in MA seizure between 2010-2012 [2]. Yearly increases in MA seizures reported by Iran's Drug Control Headquarters confirms that the availability of this substance is increasing [3]. Now, MA is the most common available amphetamine type stimulant (ATS) in Iran and its popularity is growing rapidly [4]. The growing demand for MA encourages drug makers to produce illicit forms of this substance in clandestine laboratories. These laboratories were discovered in Iran since 2008 [2]. Illegal manufacture of MA is an imperfect procedure resulting in the production of a chemical containing substantial amounts of impurities called Sheshesh/Shishe (glass), Shabu, Dar Va Panjereh, Gach, Lachaki,

Ice and Crystal in Iran [5]. There are many chemical procedures for MA synthesis including phosphorous-Iodine (Moscow, Nagai, Hypo), Birch, and metal hydrogenation (Emde), using ephedrine and pseudoephedrine as precursors, and Reductive Amination from phenyl-2-propanone (P2P) [6].

The preparation of prescribed drugs is well controlled and should have the minimum impurities, however the goal of illegal preparation of substances is to make money with the minimum cost. Use of illicit methods for production and lack of quality control can contribute to the low quality of street drugs [7].

Illicit manufacturing of MA produces a large amount of waste materials including heavy metals, volatile, flammable and corrosive chemicals. Furthermore many drugs are used to "cut" or adulterate MA samples. Impurities in MA samples may have pharmacological and toxicological properties similar or different from proposed synthesized substance [8,9]. The presence of other active pharmaceutical ingredients in illegal street substances in Iran is

worrying since they can modify or intensify the signs and symptoms of intoxication and fatal drug overdose [10].

Street MA is an impure cocktail that contains synthetic intermediates, byproducts and active pharmaceutical ingredients deliberately added to it depending on the synthetic procedures used and the capabilities of procedures to purify the end product.

It is believed that MA abuse has many negative health consequences. First reports of serious adverse health effects of amphetamines began in 1935. Low dose administration of amphetamine inhaler caused flushing, palpitation and high blood pressure [11]. The world medical literature reported 43 methamphetamine-associated deaths in a 35-year interval before controlled substances act in 1970 [12].

There are some studies concerning impurity profiling of MA samples in Iran. Also MA is among the most abused substances in many provinces in Iran such as Kermanshah [13]. According to a report, Iran's anti-narcotic police forces had seized 800 kg of illicit drugs in a two week period in Kermanshah in 2014 [14]. Thus MA abuse is one of the most social problems in Kermanshah, Iran. Authorities' attention is focusing more and more on the growing issue of MA abuse-associated health hazards in Iran, however information concerning the pharmacology of the MA impurities is very limited.

The main goal of the present study was to characterize impurities in MA samples seized in Kermanshah, Iran and also to discuss MA impurities health hazards in more details.

## Materials and Methods

All chemicals and solvents were of analytical reagent grade obtained from Merck (Darmstadt, Germany). Standards for drugs were obtained from pharmaceutical companies, Tehran, Iran. Methamphetamine (MA) hydrochloride, amphetamine hydrochloride (AM), Methylenedioxyamphetamine (MDMA) hydrochloride and pseudoephedrine hydrochloride were obtained from Lipomed Pharmaceutical (Arllesheim, Switzerland).

Qualitative and quantitative analyses were conducted on street MA samples. Included in the present study were 53 MA samples collected from anti-narcotic police seizures in Kermanshah, Iran during 30 December 2013 to 1 January 2015. Samples were referred to forensic toxicology laboratory, Kermanshah, Iran for systematic toxicological analysis using gas chromatography/mass spectrometry (GC/MS) method.

Laboratory analyses of samples were as follows:

### Sample preparation

Five grams of MA samples were weighed out from each seizure. Samples were crushed well to a fine powder. Fifty milligrams of each sample was mixed in 1 mL of phosphate buffer solution (pH=10 and 0.1 M) and vortexed for 5 min. Each sample was mixed with 500  $\mu$ L of ethyl acetate and vortexed for 10 min. The mixture was centrifuged for 5 min at 3000 rpm. Aqueous phase was frozen in a cooling bath and the organic phase (ethyl acetate) was separated for subsequent analysis. Inert substances, bulking agents and herbal constituents were not tested due to little interest in this study context.

Methanol (100  $\mu$ L) was added to residues, and after mixing, 0.2  $\mu$ L of sample was injected into GC/MS. All of the samples were analysed qualitatively, except for methamphetamine, amphetamine and

methylenedioxyamphetamine. These three ingredients were analysed quantitatively. The linearity of the method was evaluated at five concentration levels ranging from 30-1500 ng/mL ( $y=5.54 \times 10^{-2} X + 1.8 \times 10^{-1}$ ) with  $r^2=0.9910$  for MA, concentration levels ranging from 30-1500 ng/mL ( $y=3.171 \times 10^{-4} X + 2.33 \times 10^{-3}$ ) with  $r^2=0.9954$  for AM and concentration levels ranging from 40-1500 ng/mL ( $y=1.09 \times 10^{-2} \chi + 1.574 \times 10^{-1}$ ) with  $r^2=0.9999$  for MDMA. Limit of detection (LOD) was 10 ng/mL for all three analytes. Limit of quantitation (LOQ) was 30 ng/mL for MA and AM and 40 ng/mL for MDMA.

## Gas chromatography/mass spectrometry (GC/MS) technique

GC/MS had been used as the mainstay of pharmaceutical analysis. An Agilent model 7890A gas chromatograph (Agilent Technologies, Sdn Bhd, Selangor, Malaysia) fitted with split/splitless injector and a HP5-MS capillary column (cross-linked 5% methyl phenyl silicone, 30 m length  $\times$  0.25 mm ID  $\times$  0.25  $\mu$ m film thickness) was used. The capillary column was connected to a mass analyzer (MS 5975C) (Agilent Technologies) operated by electron impact (70 eV) in full scan mode (50-550 m/z). NIST, Wiley and MPW 2011 libraries were used for identification of precursors, intermediates, final products and active pharmaceutical ingredients.

## Results

To detect pharmaceutical and non-pharmaceutical ingredients, precursors, intermediates and synthetic by-products in methamphetamine samples in Kermanshah, Iran, we analysed 53 MA samples using GC/MS technique. All of the samples were white crystals with different crystal shapes and sizes. GC/MS analysis showed that all of the samples contained MA and five of them contained amphetamine. The most frequent impurity in MA samples was phenyl-2-propanone followed by phenmetrazine and pseudoephedrine. Figure 1 shows the GC/MS chromatogram of one impure methamphetamine sample. Other impurities, frequency of their occurrence in seized samples and the reason for their presence are shown in Table 1. Quantitative analysis of samples showed that the range of MA, AM and MDMA contents in street MA samples was 15-33%, 9-11% and 2-4% respectively. It is important to say that not all impurities were present in all samples.

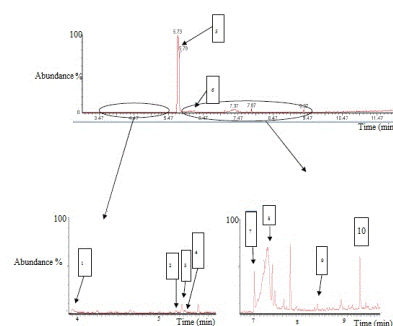


Figure 1: Chromatogram of impure methamphetamine.

## Discussion

The purpose of the present study was to characterize the impurities in MA samples seized in Kermanshah, Iran. Furthermore this study

discusses health consequences associated with direct and indirect contact with MA and its impurities.

According to the results of the study, all of the samples were in white crystalline form. This result was in agreement with those of Khajeamiri et al. [15]. Our study demonstrated that MA samples contained various types of precursors, intermediates, active pharmaceutical ingredients and other illicit drugs in combination with

MA and AM. A wide variety of reagents and precursors are used in the production of ATS [6].

Acetic acid was detected in about 90% of samples. Acetic acid is used in the manufacture of MA using P2P as starting reagent [16]. Also acetates, such as acetic acid or lead acetate are used in cooking processes to precipitate MA as final product [17,18].

Potential reason for presence as impurity or additive	Frequency occurrence No (%)	of Impurity found
Used in the production of MA using P2P	50 (94.34)	Acetic acid
Intermediate reagent in the production of MA by the Leuckart or reductive amination methods	25 (47.17)	Phenyl-2-propanone
Conversion of ephedrine to phenmetrazine at GC high temperature	11 (20.75)	Phenmetrazine
Cutting agent in the production of ATS	10 (18.87)	N,N-Dimethylamphetamine
Indicative of Leuckart route used for MA production		
Used as precursor in MA synthesis	10 (18.87)	Pseudoephedrine
An intermediate in MA synthesis procedure from ephedrine and pseudoephedrine by Emde and Nagai methods	9 (16.98)	1,2-dimethyl-3-phenylaziridine
Starting material in the synthesis of P2P	5 (9.43)	Benzaldehyde
Deliberately added active pharmaceutical ingredient	5 (9.43)	Tramadol
Product of Nagai method, product of MA precipitation using acetic moiety	3 (5.67)	N-acetylmethamphetamine
Overlapping with areas of MA synthesis	2 (3.77)	Ecstasy
Produced as incomplete hydrolysis of MA in Leuckart reaction	1 (1.89)	N-Formylmethamphetamine
An intermediate in MA synthesis procedure from ephedrine and pseudoephedrine by Emde and Nagai methods	1 (1.89)	N-Benzyl 2-methylaziridine

ATS= Amphetamine-Type Stimulants; MA= Methamphetamine; P2P= Phenyl-2-Propanone

**Table 1:** Impurities, frequency of their occurrence and the reason for their presence in seized methamphetamine samples, Kermanshah, Iran.

More than 20% of samples showed positive results for phenmetrazine. Ephedrine may be converted to phenmetrazine in the presence of formaldehyde contaminated solvents. According to the United Nations (UN) Convention of Psychotropic Substances, 1971 phenmetrazine is a controlled substance and can be abused for its mood elevating property [19]. This can be one of the reasons for adding this substance to MA samples.

Pseudoephedrine or ephedrine is used as precursors for illicit MA production. It can be used in its pure form or extracted from medicines called sympathomimetic decongestants used as cold or flu drugs [20].

The presence of N-formylmethamphetamine, P2P and benzaldehyde in seized MA samples supports more evidence for the use of Leuckart method as one of the most routine ways for the production of MA in Kermanshah, Iran.

About 18% of studied samples contained N,N-dimethylamphetamine (DMA). DMA is a cutting agent or adulterant added to MA or other ATS [11]. Li et al., 2006 reported that DMA is

the products of pyrolysis at high temperatures using GC/MS analysis method [21].

The presence of benzaldehyde in about 10% of samples suggests that it was used as starting material for the production of P2P, which is converted to MA in Leuckart method [15].

Aziridine derivatives were detected in 17% of analysed samples. This is possibly due to the involvement of Nagai method for the production of MA [22].

N-acetyl methamphetamine was found in about 6% of samples. This substance is the product of the reaction of MA with ethylacetate. Precipitating of MA in acidic condition in the presence of acetates as solvent yields N-acetylmethamphetamine [14]. It can be produced from thermal decomposition of an unknown compound in the injection port of gas chromatography instrumentation too [23].

The origin of some of the impurities in MA samples in the present study is obscure. Tramadol was detected in about 10% of samples. To our knowledge this is the first report indicating the presence of tramadol in illicit MA samples. Tramadol has different chemical

structure in comparison to ATSS and cannot be categorized as synthetic by-products. One possible explanation for the detection of other illicit drugs in MA samples is the common preparation places for these substances or adding them to MA samples deliberately.

There are reports from clinical toxicology and poison centers in Iran indicating increasing in the frequency of MA abuse [24]. Addiction to ATS is a serious public health problem with many negative consequences and complications [25]. Methamphetamine abuse can result in many direct and indirect health effects. They can be categorized as follows:

### **Adverse health consequences related to direct exposure to methamphetamine and its impurities**

**Neurologic side effects:** Methamphetamine has lipophilic structure and can distribute in CNS following different routes of administration [26]. Methamphetamine abuse has terrible neurologic consequences. Chronic use of MA causes elevations of dopamine, serotonin and other monoamines. Mounting in dopamine level can change the function of central nervous system (CNS) which manifests as a range of neurologic disorders [27]. Intracranial hemorrhage is associated with methamphetamine-induced hypertension and tachycardia [28]. Basal ganglia and brainstem bleeding as well as ischemic stroke were reported in MA abusers [29,30]. Seizure, memory loss, aggression and impairment in attention, cognition, decision making and psychosis are other neurologic effects of MA abuse [31,32]. Chronic MA abuse causes toxic psychosis characterized by visual, auditory and tactile sensory hallucinations [33]. Methamphetamine toxicity has neuroimmune basis. Exposure to MA can affect adaptive and innate immunity; it can inhibit cascades of events which can alter cellular or behavior functions. High dose or repeated MA exposure alters the function of glial cells causing neuroinflammation, neural damage and behavioral impairments [34].

MA increases metabolism in the CNS and skeletal muscles resulting in an elevation in the brain and body temperature. This substance dysregulates body temperature and promotes heat generation and retention in the body by suppressing the mechanisms which facilitate temperature reduction, hence producing hyperthermia which can be fatal in untreated cases [35].

Phenmetrazine causes CNS stimulation, cardiotoxicity causing tachycardia, arrhythmias, hypertension and cardiovascular collapse. Myocardial ischemia, ventricular dysfunction and infarction can occur in severe poisoning [36].

N,N-dimethylamphetamine induces degeneration of nerve terminals in the mouse striatum. It has dopamine depleting effects [37].

Pseudoephedrine has CNS stimulant properties and can produce agitation, anxiety, restlessness, weakness and irritability. High doses cause severe sweating, fever, heart failure and asphyxiation leading to death [38].

When pseudoephedrine is used as precursors in MA synthesis, chloroephedrine is formed as an intermediate. This intermediate has sympathomimetic property and induces heart rate and mean arterial pressure increase in rats [39].

Ecstasy acts as a hallucinogenic amphetamine. It shows sympathomimetic responses like amphetamine. At high doses ecstasy induces severe hyperthermia. Fatal dysrhythmias, ventricular

fibrillation, asystole, rhabdomyolysis, hepatotoxicity, acute renal failure, subarachnoid hemorrhage, cerebral infarction and intracranial bleeding have been reported following ecstasy use. Chronic use of ecstasy may cause prominent damage to the serotonergic axons and nerve terminals [40].

Combination of different types of drugs as drug cocktails may be prepared to get an enhanced effect. Combination of MA and opioid drugs such as tramadol can be dangerous. Coadministration of tramadol and CNS stimulants such as MA increases the risk of seizure [41]. Tramadol inhibits the reuptake of serotonin in nerve terminals [42]. A build up of serotonin content can occur as a result of combined action tramadol and other serotonin reuptake inhibitors such as MA [43]. Serotonin toxicity has many health effects including hyperthermia, hypertension, tremor, diarrhea and confusion [44,45].

MA and ecstasy combination may have greater acute effects such as rhabdomyolysis and cardiac disease in comparison to the equivalent doses of each substance alone [46]. Detection of tramadol and ecstasy in MA samples seized in Kermanshah is an important issue to take into consideration that this cocktail can have negative health consequences for abusers. Diluents and adulterants such as talc can cause ischemia or hemorrhagic stroke after intravenous administration [30].

Acute lead poisoning was reported as a result of lead-contaminated MA abuse [32]. Abdominal pain, muscle weakness, seizure, coma and CNS damage are common side effects of lead poisoning [17].

$\alpha$ -Benzyl-N-methylphenethylamine (BNMPA) is an impurity of illicit MA with convulsant activity in experimental studies. This impurity exerts its convulsant activity through similar mechanism with MA and is a toxic substance for CNS [12].

**Cardiovascular side effects:** Chest pain, acute coronary syndrome, hypertension, tachycardia, cardiac dysrhythmia, cardiomyopathy, aortic dissection and myocardial toxicity due to the overstimulation of cardiac adrenergic receptors, endocarditis, myocardial ischemia and damage to the blood vessels of the brain were reported in MA abusers [11,47,48].

**Cutaneous and soft tissue effects:** Skin and soft tissue infections are common dermatologic effects of MA abuse. Formication is an abnormal skin sensation known as delusional paresthesias, similar to that of crawling of insects on or under the skin. Dehydration, sweating and escape of toxic wastes create a sensation on the nerve endings called formication. This phenomenon causes MA user to pick his/her skin obsessively with fingernails making open red sores (crank bug), most commonly on the face and arms. Skin sores may be infected by staph bacteria and if left untreated can cause dangerous sepsis or deeper abscess [49].

Acetic acid is very hazardous in case of skin, eye contact or inhalation and ingestion. It may be toxic (irritant and corrosive) to kidneys, mucous membranes and teeth. Respiratory tract irritation and bronchial infection are other health consequences of acetic acid inhalation [50]. P2P may be toxic to mucous membranes and upper respiratory tract and can cause eye, skin or respiratory system irritation [51].

**Dental and oral cavity side effects:** Teeth damage is caused by MA and its impurities due to their acidic or basic pH [7]. Many factors contribute to the production of "meth-mouth" including reduction of salivary flow as a result of indirect sympathomimetic activity of MA, xerostomia, bruxism, consumption of soft drinks instead of water and

poor oral hygiene. Also MA abusers suffer from broken or loose, blackened or stained teeth and gingival inflammation [52,53].

**Musculoskeletal side effects:** Bone remodeling is under the control of the central nervous system. Also bone metabolism may alter as a result of CNS and hypothalamus stimulation by MA [54].

Bone mineral loss, bone fracture and osteoporosis due to MA abuse were reported in previous studies [55,56]. Kim et al. (2009) in a study conducted on 46 hospitalized male MA abusers found that the mean bone marrow density value was lower in MA abusers in comparison to control group [56]. Katsuragawa (1999) studied the effect of MA on the quality of calcaneus bone. Results showed that MA causes chronic effects on the metabolism of human skeletal system [55]. Luo et al. (2015) indicated that some essential elements such as magnesium and calcium deficiency can be connected with osteoporosis in persons who abuse MA [57].

**Other side effects:** Phosphine is a respiratory poison. It inhibits cellular respiration and results in multi-organ damage and death [58]. Phosphine gas is produced as a potentially toxic by-product during the production of MA by the hydroiodic acid/red phosphorous method [59]. There are case reports of accidental inhalation of phosphine in illicit MA production processes [60]. Chemicals and reagents such as phosphine in clandestine MA laboratories may be hazardous for law enforcement personnel during investigation of these MA cooking places [61].

Benzaldehyde is used as starting material in the production of P2P which is converted to MA in Leuckart method [16]. Chronic exposure to benzaldehyde may cause mutation [62].

Aziridine derivatives (1,2-dimethyl-3-phenylaziridine and N-Benzyl 2-methylaziridine) are produced as by-product in the manufacturing process of MA. Aziridines show their mutagenicity by electrophilic attack on DNA [63].

### **Adverse health consequences related to indirect exposure to methamphetamine and its impurities**

Production of illicit drugs is associated with acute and chronic health consequences not only for persons with direct contact but also for those who live near secret laboratories. [17,60]. Hazardous chemicals enter the environment and surface waters as contaminants and can be harmful to ecosystem by producing adverse physiological and toxic effects [64,65].

MA surface residues may have potential health effects. MA has low vapor pressure and remains on surfaces for a long time. Exposure to these contaminants through oral or dermal contact is of great importance to the environment contamination especially for young children exposed to re-emitted MA from surfaces [66]. "Drug endangered children" are described as children who are exposed to MA manufacturing environmental contaminants as well as parental abuse [31].

In fact the following points should be emphasized; chronic abusers in whom tolerance to the drug has developed may use as much as 5000-15000 mg of methamphetamine per day [67] and consequently may consume MA impurities in relatively high quantities.

We recommend further studies on samples obtained from other provinces or different geographic areas in Iran to detect impurities of illicit MA. As illicit drug manufacturers use different methods and precursors for MA synthesis, it is important to perform continuous

analysis of illicit drugs and study the pharmacologic effects of their impurities. In addition, other added drugs and adulterants may change at different time intervals.

We should say that we have encountered some limitations to perform the present study. Sample collection from anti-narcotic police was very difficult due to the illegality of abused substances. One limitation to this study was that it was not possible to analyse all active pharmaceutical ingredients quantitatively. However, this limitation did not overshadow our main purpose.

Although substance abuse effects on the body vary depending on the composition and active pharmaceutical ingredients in addition to proposed drug, all poly substance abuse negatively impacts abusers' health. Also MA crystals profiling can give valuable information to develop proper detoxification therapeutic regimen in addiction treatment centers.

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