# INVESTIGATION OF CUTTING AGENT TOWARDS THE DETECTION OF METHAMPHETAMINE BY MARQUIS AND SIMON'S TESTS


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# INVESTIGATION OF CUTTING AGENT TOWARDS THE DETECTION OF METHAMPHETAMINE BY MARQUIS AND SIMON'S TESTS

**by**


## SAMANTHA ROSE STEWART


**Thesis submitted in partial fulfilment of the requirements for the degree of Bachelor of Science in Forensic Science with Honours**

## FEBRUARY 2025

# CERTIFICATE

This is to certify that the dissertation entitled **"INVESTIGATION OF CUTTING AGENT TOWARDS THE DETECTION OF METHAMPHETAMINE BY MARQUIS AND SIMON'S TESTS"** is the bona fide record of research work done by **SAMANTHA ROSE STEWART** during the period of October 2024 to February 2025 under my supervision. I have read this dissertation and that is my opinion in it conforms to acceptable standards of scholarly presentation and is gully adequate, in scope and quality, as a dissertation to be submitted in partial fulfilment for the degree of Bachelor of Science in Forensic Science with Honours.

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## DECLARATION

I hereby declare that this dissertation is my original work, with the exception of citations that are properly acknowledged. I also declare that it has not previously been or simultaneously submitted, in this entirety, for any degrees at Universiti Sains Malaysia or any other institution. I grant Universiti Sains Malaysia permission to use this dissertation for teaching, research or promotional purposes.

Samantha Rose Stewart

Date: 27 Feb 2025

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| CNS | Central Nervous System |
| EWS | European Early-Warning Systems |
| FTIR | Fourier Transform Infrared Spectroscopy |
| GC-MS | Gas Chromatography-Mass Spectrometry |
| HIV | Human immunodeficiency virus |
| HPLC | High Performance Liquid Chromatography |
| LED | Light-emitting diode |
| LSD | Lysergic acid diethylamide |
| MDMA | Methylenedioxymethamphetamine |
| MOE | Ministry of Education |
| PCM | Paracetamol |
| PDMS | Polydimethylsiloxane |
| UNODC | United Nations Office on Drug and Crime |

# SIASATAN AGEN PEMOTONG KE ARAH PENGESANAN METHAMPHETAMINE OLEH UJIAN MARQUIS DAN SIMON

## ABSTRAK

Methamphetamine ialah perangsang kuat yang sering ditemui dalam pasaran dadah haram dan sentiasa dicampur dengan agen adukan untuk menambah kuantiti atau meniru kesannya. Saringan seperti ujian Marquis dan Simon’s banyak digunakan untuk pengenalpastian awal methamphetamine.  Walau bagaimanapun, kehadiran agen adukan berkemungkinan mempengaruhi keputusan ujian, yang berpotensi menyebabkan salah tafsir dalam analisis forensik. Kajian ini bertujuan untuk menyiasat pengaruh agen adukan terhadap pengesanan methamphetamine menggunakan ujian kolorimetri. Dalam kajian ini, sampel methamphetamine kehadiran atau ketidakhadiran pelbagai agen adukan seperti kafein, kanji, fruktosa, mannitol, paracetamol (PCM), dan laktosa disediakan dan diuji menggunakan reagen Marquis dan reagen Simon dalam keadaan terkawal. Hasil kajian menunjukkan bahawa agen adukan seperti gula dan paracetamol memberi kesan ketara terhadap keamatan dan rona warna yang terbentuk selepas tindak balas kimia, antaranya ialah tindak balas antara kumpulan hisroksil dari gula dengan reagen dan keterlarutan paracetamol. Tindak balas kimia ini boleh membawa kepada keputusan positif atau negatif palsu dalam penyiasatan forensik. Kesimpulannya, kajian ini menekankan batasan ujian warna presumptif apabila terdapatnya agen adukan dan menegaskan keperluan untuk protokol ujian yang piawai serta kaedah analisis pengesahan bagi meningkatkan ketepatan analisis dadah forensik.

**INVESTIGATION OF CUTTING AGENT TOWARDS THE DETECTION OF METHAMPHETAMINE BY MARQUIS AND SIMON'S TESTS**

## ABSTRACT


Methamphetamine is a potent stimulant frequently encountered in illicit drug markets, often adulterated with cutting agents to enhance volume or mimic its effects. Presumptive colorimetric tests, such as the Marquis and Simon's tests, are widely used for preliminary methamphetamine identification. However, the presence of cutting agents may influence test outcomes, leading to potential misinterpretations in forensic analysis. This study aims to investigate the influence of cutting agents on methamphetamine detection using colorimetric tests. In this study, methamphetamine samples with and without various cutting agents including caffeine, starch, fructose, mannitol, PCM, and lactose, were prepared and tested using the Marquis and Simon's reagents under controlled conditions. The findings revealed that cutting agents such as sugars and paracetamol significantly alter the colour intensity and hue of the colour formed upon the chemical reactions, among are the reaction between hydroxyl groups of the sugars react and the reagents, and the solubility of paracetamol. These chemical reactions could lead to false positives or negatives in forensic investigations. In conclusion, this study highlighted the limitations of presumptive colour tests in the presence of cutting agent and emphasised the need for standardised testing protocols and confirmatory analytical methods to enhance forensic drug analysis accuracy.

# CHAPTER 1

# INTRODUCTION

## 1.1 Introduction

Methamphetamine is one of the most potent and highly addictive stimulants affecting the central nervous system. As a synthetic substance, it is classified within the amphetamine-type stimulants, known for their stimulant effects and potential for abuse. Methamphetamine is illicitly manufactured in clandestine laboratories and is closely related to amphetamine, another stimulant in the phenethylamine family [Shafi et al., 2020].

Previous studies have mentioned that illicit methamphetamine is rarely encountered in its pure form, as it is frequently adulterated with cutting agents to increase bulk or mimic the drug’s effects, thereby maximising profits for manufacturers (Cole et al., 2010). Commonly used cutting agents include caffeine, starch, paracetamol, and sugars (e.g., fructose, lactose, and mannitol). These substances are often inert but may sometimes influence the analytical methods used to detect methamphetamine in forensic testing.

Presumptive colorimetric tests, such as the Marquis and Simon's tests, are widely used for detecting methamphetamine and related compounds in seized drug samples. These tests rely on chemical reactions with the target analyte to produce distinct colour changes, offering a quick and cost-effective method for preliminary identification. However, these tests may also be impacted by the presence of cutting agents, which may alter the observed results leading to false results (Knutson et al., 2021).

## 1.2 Problem Statement

While colorimetric tests such as Marquis and Simon's are commonly used for detecting methamphetamine, their outcomes could be influenced by the presence of cutting agents. Cutting agents such as sugars (fructose, lactose, mannitol) and paracetamol (PCM) might affect the intensity and accuracy of colour changes, creating challenges in distinguishing pure methamphetamine from cut samples. Such interference might lead to misinterpretation of drug purity and composition, complicating forensic drug analysis and producing wrong results.

Despite the widespread use of these tests, limited research has been conducted on how presence of cutting agents affect the test results of both Marquis and Simon's test. This knowledge gap highlights the need to systematically investigate the impact of adulterants on presumptive colorimetric tests.

## 1.3 General and Specific Objectives

The general objective for this study is to investigate the relationship between the composition of methamphetamine and its resultant colour change based on the types of cutting agents added to the drug. To achieve the general objective, specific objectives of the study were set as follows:

i. To compare the outcome of the colour change based on the amount of methamphetamine.
ii. To compare the outcome of the colour change based on the type of adulterant added to the methamphetamine samples.

## 1.4 Significance of Study

The findings of this study are expected to enhance the understanding of how methamphetamine adulteration affects the outcomes of presumptive colorimetric tests, particularly the Marquis and Simon’s tests. By systematically analysing the effects of various cutting agents, this research addresses a critical gap in forensic drug analysis especially for the screening procedure.

The study’s results could contribute to improved accuracy and reliability in preliminary drug identification, enabling forensic professionals to better interpret colorimetric test outcomes in cases involving adulterated methamphetamine samples. Furthermore, the insights gained from the current study could inform the development of updated testing protocols or guidelines that account for the influence of cutting agents, thereby reducing the likelihood of false positives, false negatives, or misinterpretations. Ultimately, this research could support the broader goal of enhancing the integrity of forensic investigations, ensuring that the chemical composition of seized drug samples is accurately identified, and aiding the judicial process.

## 1.5 Scope of the Study

This study focuses on investigating the effects of various cutting agents namely caffeine, starch, fructose, mannitol, paracetamol (PCM), and lactose on the outcomes of Marquis and Simon’s tests when mixed with methamphetamine. The research was limited to analysing methamphetamine-to-cutting agent ratios of 1:1 to evaluate the influence of adulteration on the intensity and reliability of colorimetric reactions.

The study did not address other colorimetric tests beyond Marquis and Simon’s, nor did it include other cutting agents or alternative ratios of methamphetamine-to-adulterant mixtures. Additionally, while the study examined the chemical interactions and visual colour changes, it did not delve into the physiological or pharmacological effects of adulterated methamphetamine on users.

The experimental design involved only the screening testing under controlled conditions to ensure consistent and reliable results. The findings were intended to provide insights for forensic practitioners and researchers but are not meant to replace advanced confirmatory methods such as chromatography or spectroscopy.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Methamphetamine

Methamphetamine is a synthetic stimulant that has been utilized as the primary ingredient in numerous illegal substances (Choodum & Nicdaeid, 2016). Methamphetamine is one of the most potent and addictive stimulants of the central nervous system. It is a synthetic substance classified as an amphetamine-type stimulant; however, it is more potent than amphetamines. It is produced illegally in clandestine laboratories. It is a potent and extremely addictive central nervous system (CNS) stimulant that belongs to the phenethylamine family, which is closely related to amphetamine, another stimulant (Munawar et al., 2024). Methamphetamine stimulates excessive dopamine secretion in the central nervous system, making it one of the most misused stimulants worldwide, as indicated by a sevenfold increase in global seizures over the last two decades (Awang et al., 2022). Figure 2.1 shows the chemical compound of methamphetamine.

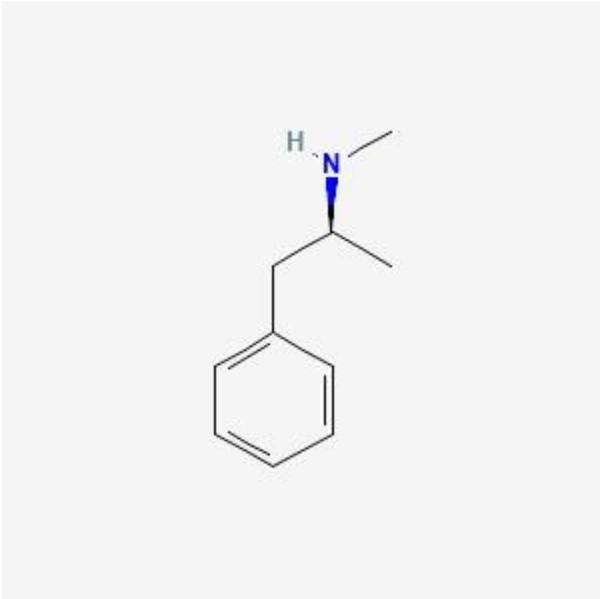


Figure 2.1 Chemical compound of methamphetamine. Adapted from National Center for Biotechnology Information [Online image].

N-benzylmethylamine can be used to reductively alkylate and hydrogenolyses phenyl-2-propane to create methamphetamine. After forming, the anticipated product

N-benzylmethylamine is hydrogenolysed to produce toluene and methamphetamine. Gas chromatography and mass spectrometry can be used to assess the reaction's progress, the intermediates that were created during the reaction, and the final products (Skinner, 1993). The United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988, and the Single Convention on Narcotic Drugs both classify methamphetamine as a schedule II restricted substance. It is a highly addictive substance that has strong stimulant effects on the central nervous system (CNS) (Usman et al., 2024).

During the 1990s, illicit methamphetamine was discovered in Sabah, Malaysia, as the dissemination of methamphetamine continues to spread in East and Southeast Asia, as a trade manufacturing increases, according to a UNODC research titled "Synthetic Drugs in East and Southeast Asia: Recent Developments and Challenges" in

2022. The number of methamphetamine seizures throughout East and Southeast Asia in 2021 was expected to be seven times more than a decade ago, totalling 172 tonnes (Audi et al., 2023). Although possession, trafficking, and manufacture of methamphetamine are forbidden and heavily punished by international law, abuse of methamphetamine is increasing in places like the United States, Europe, Australia, and New Zealand (Awang et al., 2022).

### 2.1.1 The Effects of Methamphetamine on User's Health

Recent studies have mentioned that methamphetamine induces multiple symptoms and side effects such as cardiopulmonary symptoms, which include chest pain, palpitations and shortness of breath [18]. To add, methamphetamine use causes an increase in blood pressure, increasing the risk of stroke and ocular abnormalities due to the enhanced release of catecholamines like norepinephrine and dopamine from the synaptic cleft. Haemorrhagic strokes are the most prevalent kind of methamphetamine-related strokes. Vasoconstriction, pulmonary hypertension, atherosclerotic plaque development, cardiac arrhythmias, myocardial infarction, and cardiomyopathy are more conditions linked to meth. Multiple ion channels' expression and activity can be impacted by cocaine and meth amphetamines. One of the organs most frequently impacted by methamphetamine use is the kidney, and its effects are widely known.

When consumed in high enough doses, methamphetamine overdose frequently results in renal dysfunction, multisystem organ failure, and death. According to (Edinoff et al. 2022), deaths related to methamphetamine use has multiplied into quadruple from 3616 to 16127, between the 2013 and 2019 in the United States. These deaths are usually associated with medical complications as methamphetamine induces multiple symptoms and side effects.

### 2.1.2 The Psychiatric Effects of Methamphetamine

A study found that methamphetamine use is also frequently associated with psychiatric symptoms. These symptoms might include psychosis, delusions, anxiety, and agitation. To add, methamphetamine usage is also associated with increased use of health services and underlying psychological illnesses (Edinoff et al., 2022). According to (Hypse, 2019), all addictive substances, particularly methamphetamine, have been shown to have harmful effects on the midbrain's personality regions. These personality regions involved the cognitive structures which are the self-control tract, the pleasure centre, motivational and motor centres, centres for emotional control, appetite and sleep cycle, judgement and cognitive processes, and memory.

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## 2.2 Cutting Agents

Cutting agents are substances that are classified as diluents, which are pharmacologically inactive and readily available substances, and adulterants which are pharmacologically active which are usually more expensive and less available than diluents (Fioretin et al., 2018). There are reasons to add theses cutting agents into these illicit drugs, one of it is to add bulk of these drugs. According to (Skinner, 1993), adulterants are usually cheap, easily available, and legal as evidence presented indicates that caffeine, paracetamol, and sugars are common bulking agents. Another reason is that the adulterants may have been added to improve or replicate the effects of illegal drugs, either to conceal a subpar product or to create the appearance of a higher-quality substance (Cole et al., 2010). Furthermore, some cutting agents make it easier to administer illegal drugs, particularly to make smoking them more effective as studies have shown that procaine and caffeine may evaporate heroin at a lower temperature, making smoking heroin easier (Cole et al., 2010).

Cutting agents can constantly change over time (Fioretin et al., 2018), due to the result of manufacturing, production or storage techniques, for example alkaloids. The variety of substances used to adulterate illicit drugs adds to the unpredictable nature of the drug's effects, including the potential for unknown or unexpected synergistic reactions, and negative health effects (Cole et al., 2010). Not only that, but these substances are also intentionally added to illicit drugs, mainly to increase profits at various stages in the lifespan of the illicit drug (Fioretin et al., 2018). To boost their profit, they tend to 'skim' the drugs as they divide them into smaller amounts, for example by selling them slightly underweight amounts or add substances which complement or enhance the effects of the drug for the users. For example, caffeine is added into methamphetamine as it has stimulant properties that can create similar although usually milder, effects to the primary drug (Cole et al., 2010).

## 2.3 Colorimetric Tests

Presumptive tests are widely employed to rapidly screen for the presence or absence of drugs, enabling analysis to quickly rule out negative samples. These tests, particularly colorimetric methods, are favoured for their simplicity and speed in detecting drugs such as methamphetamine in samples. Recommended by the United Nations International Drug Control Programme (1994), colorimetric tests rely on chemical reactions between the substance of interest, which is the analyte, and specific reagents. These reactions produce visible colour changes that can be observed without specialised equipment, making them accessible and practical for initial screening. The colour produced serves as an indicator of the analyte's presence, allowing analysts to make a preliminary assessment. Because of their efficiency and ease of use, colorimetric tests are often the first technique applied in forensic drug analysis (Choodum & Nicdaeid, 2016). There are two well-known colorimetric tests specifically used for methamphetamine detection are the Marquis and Simon's test.

Colorimetric tests are considered presumptive, in that they can only identify presence or non-presence of a particular substance based on the test administered Colorimetric tests can be quite sensitive, with limits of detection in the microgram range depending on the spot test utilized and the analyte. Multiple tests with multiple reagents can be used if a mixture of drugs is suspected, though each test requires in the low milligram range of substance and destroys the substance in testing. With the proper standards, these tests can be quite specific, although multiple analyses may be required for high specificity. Some knowledge about what the substance is supposed to be, and about general appearance of certain substances can increase specificity (Peacock et al., 2021).

Colorimetric tests exist for most drugs of abuse, including cocaine, various pharmaceutical opioids, amphetamines, LSD (lysergic acid diethylamide), cathinones (bath salts), heroin, and fentanyl. There may be other novel psychoactive substances that do not (yet) have any associated colorimetric tests. Each specific named test will have information on what analytes it can be used with (Peacock et al., 2021). colour tests are advantageous for the field detection of illicit drugs because of their simplicity, low cost, and rapidity (Sobue et al., 2024).

### 2.3.1 Marquis Test

The Marquis test is one of the most versatile and widely used colorimetric assays in drug analysis. It has been adopted by forensic laboratories and law enforcement agencies globally as a presumptive test for substances such as amphetamine, morphine, and heroin (Choodum & Nicdaeid, 2016). The test utilises the Marquis reagent, which consists of concentrated sulfuric acid and 40% formaldehyde. when the reagent reacts with alkaloids, it facilitates a process known as complexation, where the alkaloids form larger molecular structures. This reaction produces a distinct colour change that serves as a visual cue indicating the presence of the target substance. For example, amphetamines typically produce an orange to brown colour, while other substances may result in different hues, aiding in the differentiation of various drugs (Knutson et al., 2021). Figure 2.2 shows the mechanism of the Marquis test for methamphetamine.

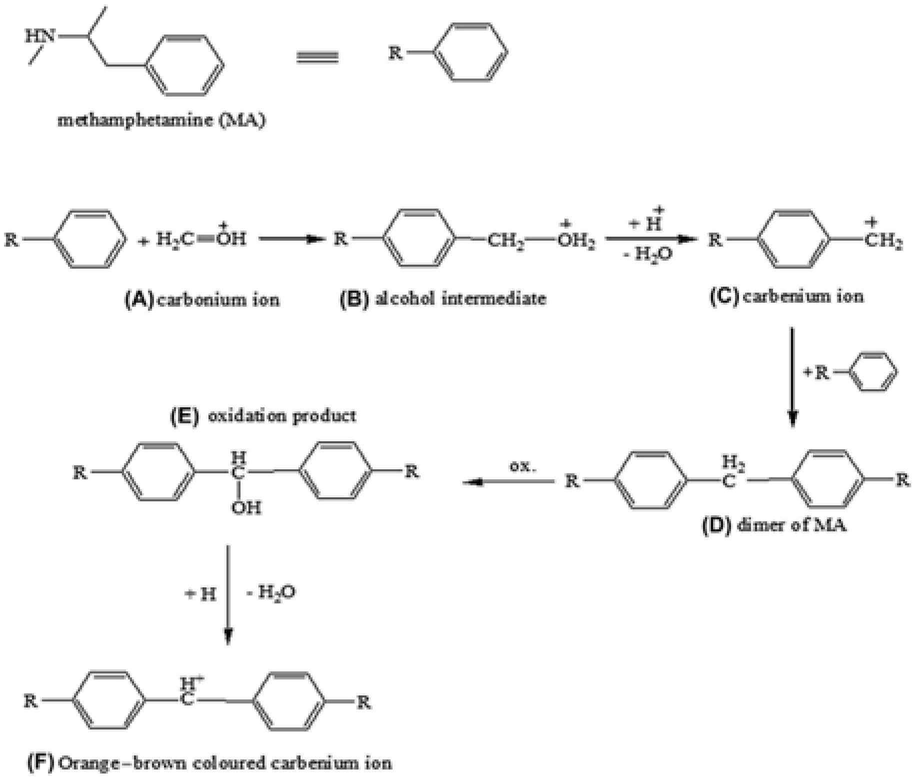


Figure 2.2 Mechanism of the Marquis test for methamphetamine. Adapted from Choodum and Nicdaeid (2016).

The carbenium ion is the orange-brown product in which it is formed due to the reaction of aromatic compound and formaldehyde in acidic medium. This mechanism is complex and not fully understood. The carbenium ion (A) is formed from the formaldehyde reacting with the aromatic ring of methamphetamine to produce (B) the alcohol intermediate. Under strong acidic conditions, the carbenium ion (C) is produced, and then it is further reacted with a second molecule of methamphetamine to produce a dimer (D). Oxidation of the dimer is assisted by trace metal impurities in the sulfuric acid producing the product (E) as a coloured carbenium ion (F).

### 2.3.2 Simon's Test

Simon's test is another important colorimetric assay, primarily designed to detect secondary amines, including methamphetamine. This test has been extensively utilised in forensic research and field investigations for methamphetamine identification. Simon's test involves the use of two reagents which are, a solution of 10% acetaldehyde in aqueous sodium nitroprusside solution. Simon's test involves the use of two reagents which are, a solution of 10% acetaldehyde in aqueous sodium nitroprusside which is 1 % w/v, referred to as reagent S1, and a 2% solution of sodium carbonate in water which is denoted as reagent S2. Occasionally a third reagent which is 50 % acetaldehyde solution in 50% ethanol solution, is prepared separately (Knutson et al., 2021).

To perform the test, one drop of reagent S1 is added to the suspect material, followed by two drops of reagent S2. If reagent S3 is used, the protocol involves adding one drop of reagent S2 to the sample, stirring, and then sequentially adding one drop each of reagents S1/1 and S3. A positive result for methamphetamine is indicated by the formation of a blue product, which is distinct and easily recognizable. The precision of Simon's test in detecting secondary amines makes it an invaluable tool for confirming methamphetamine in complex mixtures (Knutson et al., 2021). Figure 2.3 shows the mechanism of Simon's test for methamphetamine.

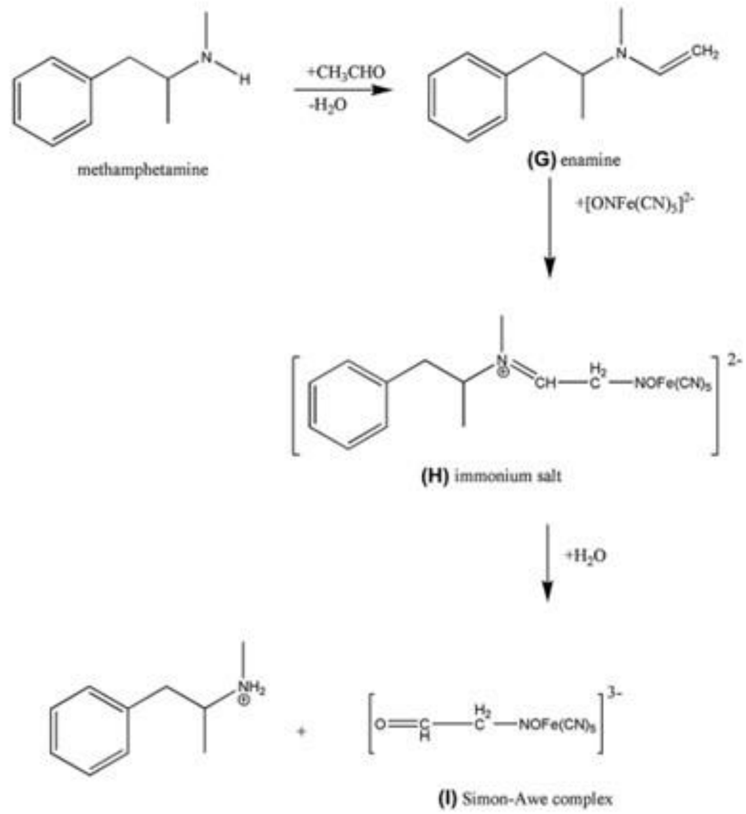


Figure 2.3 Mechanism of Simon's test for methamphetamine. Adapted from Choodum and Nicdaeid (2016).

The blue product is formed from the Simon's test as this is commonly referred to as a Simon-Awe complex. Through an addition-condensation process, methamphetamine reacts with acetaldehyde and then produces an anamine (G) which then subsequently combines with sodium nitroprusside to form an immonium salt intermediate (H). The intermediate then reacts with water to form the blue Simon-Awe complex (I) (Knutson et al., 2021).

### 2.3.3 Previous Studies about Colour Testing

Spot and colorimetric tests provide presumptive identification based on the chemical reactions that occur between analytes and specific indicators. These tests employ a variety of indicator reagents such as cobalt thiocyanate, Dille-Koppanyi, Duquenois-Levine, Mandelin, Marquis, nitric acid, para-dimethylaminobenzaldehyde, ferric chloride, Froehde, Mecke, Zwikker, and Simon's (nitroprusside). When these indicators react with the analyte, a chemical reaction takes place that produces a colour change, which is characteristic of the specific substance being tested (Peacock et al., 2021). The resulting colour staining depends on the chemical nature of the analyte under examination.

One of the commonly used colorimetric tests for detecting the presence of cocaine is the Scott test. This test is valued for its simplicity, speed, and cost-effectiveness as a preliminary screening method, frequently used to suggest the presence of cocaine in drug seizures based on the development of a blue colour. However, the presence of cutting agents can interfere with the test's accuracy, potentially leading to false positives that suggest cocaine is present even when it is not.

Another example of a colorimetric method is the use of the Fast Blue B (FBB) reagent for estimating the total cannabinoid content in cannabis samples. This reagent has been immobilized on polydimethylsiloxane (PDMS) (Journet-Martinez et al., 2023), which enhances its ability to effectively with the cannabinoids and produce a measurable colour change for analysis.

## 2.4 Impacts of Methamphetamine Purity and Cutting Agents

Methamphetamine's toxicity and effects have been extensively studied, with numerous research efforts dedicated to understanding both its short- and long-term impacts. Among these studies, it has been estimated that methamphetamine's effects can last approximately 8 to 10 times longer than an equivalent dose of cocaine, which contributes to the drug's potential for addiction and prolonged physiological strain on users (Hypse, 2018). The extended duration of methamphetamine's effects poses serious challenges for habitual users, as it increases their exposure to the drug's harmful consequences, particularly its impact on various organ systems.

One of the most concerning effects of methamphetamine use is its link to severe cardiovascular complications, including myocardial infarction (heart attack) and haemorrhagic stroke. Chronic use of methamphetamine places significant stress on the heart, leading to elevated blood pressure, vasoconstriction, and increased cardiac workload, all of which heighten the risk of catastrophic cardiovascular events. Additionally, methamphetamine use is associated with a range of psychiatric symptoms, including agitation, anxiety, paranoia, hallucinations, delusions, and full-blown psychosis (Edinoff et al., 2022).

These psychiatric manifestations often persist even after cessation of drug use, contributing to long-term mental health deterioration. Adulterants present in illicitly manufactured methamphetamine compounds further exacerbate health risks. Because methamphetamine is often synthesised in uncontrolled settings, various cutting agents or contaminants are introduced into the drug. These adulterants can be pharmacologically active substances or inert fillers that negatively impact users' health (Cole et al., 2010). The combination of methamphetamine and these adulterants creates unpredictable toxicological interactions that can significantly increase the dangers associated with methamphetamine consumption.

From a physiological perspective, methamphetamine affects multiple organ systems, leading to a broad spectrum of complications. Cardiopulmonary symptoms such as chest pain, palpitations, and shortness of breath are common, while methamphetamine-related myocardial infarctions have been documented in both acute and chronic users. In the central nervous system, methamphetamine use is linked to neuropsychiatric symptoms such as agitation, paranoia, hallucinations, seizures, and drug-induced psychosis. In some cases, methamphetamine-induced psychosis may uncover underlying psychiatric disorders, exacerbating pre-existing conditions. The drug has also been implicated in cerebral vasculitis, a condition that can lead to cortical blindness and ischemic strokes, further demonstrating the extent of neurological harm caused by methamphetamine (Edinoff et al., 2022).

Infectious diseases such as endocarditis, HIV, and viral hepatitis are frequently observed in methamphetamine users, particularly among individuals who administer the drug intravenously. The practice of needle-sharing significantly increases the risk of bloodborne infections, while the drug's impact on decision-making and impulse control often leads to high-risk behaviours, including unprotected sex and needle reuse. Methamphetamine use has also been linked to pulmonary hypertension, a lifethreatening condition resulting from chronic cardiovascular stress. In addition to these systemic complications, methamphetamine users may experience hyperthermia, rhabdomyolysis, and acute liver and kidney failure, further underscoring the widespread physiological damage caused by the drug (Hypse, 2018).

When methamphetamine is ingested, inhaled, or injected, it rapidly enters the bloodstream and crosses the blood-brain barrier due to its lipophilic nature. The half-life of methamphetamine varies depending on the route of administration but typically ranges from five to thirty hours. Once in the brain, methamphetamine exerts its effects by promoting the excessive release of dopamine, serotonin, epinephrine, and norepinephrine. This results in heightened energy levels, euphoria, and increased confidence, which contribute to the drug's high addiction potential. Methamphetamine achieves this by depleting synaptic vesicles, inhibiting neurotransmitter reuptake, and reducing the expression of transporters on neuronal cell surfaces, leading to a prolonged and intensified neurochemical response (Hypse, 2018; Edinoff et al., 2022).

The toxic effects of methamphetamine are particularly pronounced in the midbrain, which houses critical neural structures responsible for personality, emotion, judgment, and motivation. These include the ventral tegmental area (self-control tract), nucleus accumbens (pleasure centre), striatum (motor and motivational centres), amygdala (emotional regulation), hippocampus (memory formation), and the frontal lobes (cognitive and executive function). Methamphetamine's prolonged neurochemical influence disrupts the function of these brain regions, leading to behavioural dysregulation, cognitive impairments, and emotional instability. The chronic overstimulation of dopamine receptors results in a phenomenon known as anhedonia, where individuals struggle to experience pleasure in the absence of methamphetamine use. This state of dopamine deficiency often drives compulsive drug-seeking behaviour, contributing to the cycle of addiction (Edinoff et al., 2022).

Repeated methamphetamine use has devastating consequences, not only for individual users but also for society. The drug is strongly associated with increased aggression, violent behaviour, and criminal activity. Physiological side effects such as severe weight loss, extreme tooth decay (commonly referred to as "meth mouth"), body sores, and accelerated aging are frequently observed among long-term users. The combination of poor hygiene, malnutrition, and drug-induced physiological stress contributes to a rapid decline in overall health.

Perhaps one of the most alarming aspects of methamphetamine use is its role in the spread of HIV and other sexually transmitted infections. Methamphetamine's impact on impulse control and risk-taking behaviour leads users to engage in unsafe sexual practices, particularly among populations where the drug is commonly injected. The correlation between use of methamphetamine and increased transmission rates of HIV has been widely documented, making it a significant public health concern (Hypse, 2018).

Methamphetamine has been labelled “America’s most dangerous drug” due to its widespread abuse and the severe medical and societal consequences associated with its use. The literature extensively documents the development of stimulant addiction and tolerance, demonstrating that methamphetamine users require increasingly larger doses to maintain the desired euphoria over time. This escalating pattern of use contributes to the drug’s destructive potential, as prolonged methamphetamine exposure leads to irreversible neurochemical and physiological changes (Edinoff et al., 2022).

The alarming rise in methamphetamine-related mortality rates underscores the urgency of addressing this public health crisis. Over the past decade, the mortality rate associated with methamphetamine use has doubled, reflecting the increasing prevalence and severity of methamphetamine-related medical complications. As research continues to uncover the far-reaching consequences of methamphetamine addiction, it becomes evident that urgent intervention strategies are necessary to mitigate its impact on individuals and communities alike. Without appropriate preventative measures and treatment options, the devastating effects of methamphetamine will continue to burden healthcare systems and society (Edinoff et al., 2022; Hypse et al., 2018).

### 2.4.1 The role of Cutting Agents in Methamphetamine-Related Health Risks

Methamphetamine is often adulterated with various cutting agents, significantly increasing the risk of adverse health effects. These cutting agents, which may include caffeine, sugars, or other stimulants, can exacerbate methamphetamine's harmful effects on the cardiovascular system, leading to heightened toxicity. The addition of these substances enhances the stimulant effects of methamphetamine, resulting in elevated heart rates and blood pressure, which can contribute to severe complications such as heart attacks and strokes (Edinoff et al. 2022; Harding et al. 2022).

Beyond cardiovascular risks, the presence of cutting agents alters the pharmacological profile of methamphetamine, creating unpredictable effects and increasing the likelihood of overdose. Many users remain unaware of the specific substances mixed with methamphetamine, which can lead to severe health complications. Since illicit drug manufacturers do not adhere to standardized formulations, the variability in the composition of methamphetamine presents a significant challenge in predicting its physiological effects. This lack of uniformity further complicates medical treatment, as healthcare providers may struggle to identify the precise cause of toxicity in affected individuals (Edinoff et al. 2022).

The unpredictability of methamphetamine's composition due to cutting agents poses a significant public health risk. Unintentional exposure to unknown adulterants can lead to unexpected and dangerous side effects. Some cutting agents, such as levamisole or phenacetin, have been linked to severe toxicities, including agranulocytosis (a dangerous drop in white blood cells) and kidney damage. In addition, certain cutting agents may enhance methamphetamine's neurotoxic effects, increasing the risk of cognitive impairment, mood disorders, and long-term psychiatric conditions such as paranoia and psychosis (Daniulaityte et al. 2023; Sheridan et al., 2006) Chronic exposure to these adulterated substances can complicate treatment and recovery efforts, making it more difficult for users to overcome addiction and mitigate its health consequences (Edinoff et al., 2022).

One of the most alarming concerns associated with cutting agents in methamphetamine is their role in increasing overdose risk. Because users are often unaware of the specific substances present in a batch of methamphetamine, they may misjudge the potency of the drug and consume higher doses than intended. This unpredictability can lead to dangerous physiological reactions, including hyperthermia, seizures, and organ failure. The increased risk of overdose underscores the need for greater awareness and harm reduction strategies, particularly among vulnerable populations who may lack access to reliable drug education and support services (Sheridan et al. 2006).

Furthermore, studies have highlighted that many users experience symptoms of 'overamping' rather than acute fatal overdoses (Daniulaityte et al., 2023). Overamping refers to an overwhelming stimulant effect characterized by extreme agitation, paranoia, increased heart rate, and severe dehydration. Despite experiencing these distressing symptoms, many individuals do not seek medical attention, often relying on self-care strategies such as hydration and rest to manage their condition. This behaviour reflects the stigma surrounding drug use, as well as the lack of accessible healthcare interventions tailored to methamphetamine users (Harding et al., 2022).

Addressing the risks associated with cutting agents in methamphetamine requires a multifaceted approach. Collaborative harm reduction strategies, such as drug-checking services and education campaigns, can empower users with knowledge about the substances they are consuming. By increasing awareness and providing access to safer consumption practices, public health initiatives can play a crucial role in mitigating the negative consequences of methamphetamine use. In addition, further research into the specific health effects of various adulterants will help inform treatment protocols and policy decisions aimed at reducing the burden of methamphetamine-related harm (Daniulaityte et al., 2023).

In conclusion, the presence of cutting agents in methamphetamine significantly exacerbates health risks, contributing to cardiovascular complications, neurotoxicity, and unpredictable overdose potential. The variability in methamphetamine purity and composition underscores the importance of harm reduction efforts, increased medical awareness, and continued research into the impact of adulterants. By addressing these challenges, public health professionals and policymakers can work towards minimizing the adverse effects associated with methamphetamine use and improving treatment outcomes for affected individuals (Edinoff et al., 2022; Daniulaityte et al., 2023; Sheridan et al., 2006).

## 2.5 Statistics of Methamphetamine Abuse worldwide and Malaysia

The United Nations World Drug Report (2020) (Moszczynska, 2021) estimated that approximately 27 million people worldwide, or 0.5% of the global adult population, had used amphetamines, which include methamphetamine, amphetamine, and pharmaceutical stimulants, in the past year. Methamphetamine usage in the United States saw a nearly 40% increase between 2016 and 2018, followed by continued growth between 2018 and 2019. Similarly, in East and Southeast Asia, methamphetamine consumption has risen over the past decade. According to UNODC (2023), ten countries which are Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, the Philippines, the Republic of Korea, Singapore, and Thailand, have reported significant trends in crystal methamphetamine use.

In Thailand, most registered drug users in 2023 were methamphetamine tablet users, accounting for 84% of the total, while only 3% of users reported consuming crystal methamphetamine (UNODC, 2023). In Malaysia, methamphetamine use has continued to rise between 2016 and 2020 (NADA, 2021), with crystal methamphetamine being the most abused form of the drug (Statista Research Department, 2022; NADA).

According to statistics from the Malaysian Ministry of Education (MOE), methamphetamine is the most frequently abused drug among youths (Mallo, 2020). This is likely due to its affordability and accessibility (Abdul Ghani et al., 2021). NADA (2023) reported that between January and March 2023, 103,760 drug abusers were registered in Malaysia. Among them, youths with the age range of 19 to 39 are accounted for the highest proportion of with 59.6%, followed by adults with the age range of 40 years and older, at 39.9%; and teenagers with the age range of 13 to 18, with 0.4%.

Several factors contribute to youth drug abuse, including curiosity, thrill-seeking behaviour, and peer pressure (Ismail et al., 2023). Additionally, engagement in antisocial behaviours such as drug trafficking, gang involvement, and theft; may increase their likelihood of substance use. Other contributing factors include academic stress and strained relationships with parents (Alhammad et al., 2023).

Adults, on the other hand, may resort to drug use as a coping mechanism for life challenges and workplace stress. High-stress occupations, such as those in the healthcare and military sectors, may increase the risk of drug dependence (Li et al., 2021). Teenagers, however, are more likely to engage in substance abuse due to past traumas such as childhood domestic violence, the desire to experiment, and social pressure (Alhammad et al., 2022).

Between 2017 and 2020, methamphetamine use surpassed opioid use, highlighting its growing prevalence as a substance of abuse (Du et al., 2020; Mallo, 2020; NADA, 2021).

## 2.6 Statistics of Methamphetamine Seizures

According to Trana et al., 2022, drug seizures in Europe experienced a dramatic surge between 2010 and 2020, with methamphetamine seizures increasing by an astonishing 477%. While seizure data do not provide a complete picture of the drug supply chain, they serve as an indicator of evolving drug market dynamics. Previous studies have emphasized the necessity of an early-warning system (EWS) to detect the emergence of new drugs, including precursors and adulterants. The European Early-Warning System (EWS) was established to monitor these developments, facilitating the identification of synthetic substances, tracking shifts in drug trends, and detecting counterfeit drugs (UNODC, 2009).

In East and Southeast Asia, the methamphetamine market continued to expand in 2022, showing no signs of declining supply from Shan state, Myanmar, while new trafficking routes emerged [27]. In July 2021, Lao authorities discovered and dismantled several methamphetamine tablet production sites in the Udoxmai province. Law enforcement officials raided seven suspected facilities, arresting seven individuals and seizing a variety of illicit substances, precursor chemicals, and drug manufacturing equipment. Among the confiscated items were nearly 1.5 million methamphetamine tablets 846.5 kg or red-coloured methamphetamine tablet powder, multiple tablet rods, and 17 kg of plastic packaging materials. A month earlier, in June 2021, authorities in Udoxmai had conducted a similar operation, seized additional methamphetamine tablet production equipment and arrested another seven suspects. Additionally, in May 2021, police in Xay district seized 1.1 million methamphetamine tablets and 1,200 kg of bulking agents, further highlighting the region’s expanding drug production activities.

In contrast, Malaysia has witnessed a notable decline in the number of methamphetamine laboratories over the past five years. In 2018, authorities dismantled ten small-scale laboratories. However, this number significantly dropped to three in 2021 and two in 2022, with the remaining sites located in Perak and Negeri Sembilan. Between 2021 and 2022, Malaysian law enforcement agencies seized only 30 kg of ephedrine, with no reports of major precursor chemicals or designer precursors.