Life Sciences 97 (2014) 2–8

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Minireview

# Bath salts and synthetic cathinones: An emerging designer drug phenomenon

Christopher L. German *, Annette E. Fleckenstein, Glen R. Hanson

*Department of Pharmacology & Toxicology, University of Utah, Salt Lake City, UT 84112, USA*

ARTICLE INFO

*Article history:*
Received 3 May 2013
Accepted 19 July 2013

*Keywords:*
Synthetic cathinone
Bath salts
Mephedrone
Methylone
MDPV
Stimulants
Designer drugs

ABSTRACT

Synthetic cathinones are an emerging class of designer drugs abused for psychostimulant and hallucinogenic effects similar to cocaine, methylenedioxymethamphetamine (MDMA), or other amphetamines. Abuse of synthetic cathinones, frequently included in products sold as 'bath salts', became prevalent in early 2009, leading to legislative classification throughout Europe in 2010 and schedule I classification within the United States in 2011. Recent pre-clinical and clinical studies indicate that dysregulation of central monoamine systems is a principal mechanism of synthetic cathinone action and presumably underlie the behavioral effects and abuse liability associated with these drugs. This review provides insight into the development of synthetic cathinones as substances of abuse, current patterns of their abuse, known mechanisms of their action and toxicology, and the benefits and drawbacks of their classification.



**Contents**



## Introduction

Designer drugs are synthetic compounds developed to provide rewarding effects similar to illicit drugs of abuse (*e.g.* opioids, amphetamines, and marijuana) while circumventing existing legislative classification and penalty. Recently, designer drug mixtures have been marketed and sold as 'legal highs' over the internet and in head shops worldwide. The synthetic cathinones are one of the most prevalent classes of compounds found in these products, frequently sold as 'bath salts' or 'fertilizer' despite having no such purposes and are insufflated (snorted), ingested, or injected by users seeking psychostimulant effects similar to cocaine, methylenedioxymethamphetamine (MDMA) or other amphetamines. Possession, use, and synthesis of the synthetic cathinones was legal until their emergency schedule I classification in 2011 followed by permanent schedule I classification in the Synthetic

*Abbreviations:* Meth, methamphetamine; MDMA, methylenedioxymethamphetamine; MDPV, methylenedioxypyrovalerone; Mephedrone, 4-methylmethcathinone; Methylone, 3,4,-methylenedioxymethcathinone; DA, dopamine; 5-HT, serotonin; DAT, dopamine transporter; SERT, serotonin transporter; TH, tyrosine hydroxylase.

* Corresponding author at: University of Utah, Department of Pharmacology & Toxicology, 30 South 2000 East, Room 201, Salt Lake City, UT 84112. Tel.: +1 801 587 9203.
*E-mail address:* christopher.german@utah.edu (C.L. German).

0024-3205/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.lfs.2013.07.023

Drug Abuse Prevention Act of 2012 (Drug Enforcement Administration, 2011). Schedule I classification will undoubtedly reduce access to and consumption of synthetic cathinones, but will also limit research on these relatively unstudied compounds to a very small number of laboratories and institutions that have been licensed to work with schedule I drugs.

This review aims to provide insight into the development of synthetic cathinones as substances of abuse, current patterns of their abuse, known mechanisms of their action and toxicology, and the benefits and drawbacks of their classification. A brief history of designer drugs will be followed by a description of the manner and prevalence of current synthetic cathinones abuse. This review will then focus on emerging research describing the mechanisms of action, toxicology, and abuse liability of synthetic cathinone compounds, and discuss why categorizing the chemical basis for these substances is important and necessary. Finally, the impact of scheduling upon the ability to research and understand the pharmacology of these drugs will be described.

## A brief history of designer drugs

The Controlled Substances Act of 1970 established a framework for regulating substances of abuse within the United States (US) by scheduling them based upon medical use, abuse liability, and risk of developing physical or psychological dependence. Compounds are classified on a scale from schedule I to V, with schedule I drugs considered to have the greatest risk and abuse liability without significant medical application and schedule V drugs having accepted medical use with minimal liability or risk. Following passage of the Controlled Substances Act of 1970, a number of compounds were abused to mimic the effects of popular illicit drugs while avoiding regulation. The term 'designer drug' was coined in the early 1980s to describe such compounds, which were often synthesized in small home laboratories from widely available over-the-counter drugs or chemical precursors and not illegal provided they were structurally different from scheduled drugs (Ziporyn, 1986). Synthetic opioids were the first compounds termed designer drugs, appearing in California as 'China White' in 1979 and produced by fentanyl modification to mimic the effects of heroin and morphine (Henderson, 1988; Kram et al., 1981; Ziporyn, 1986).

Many designer drugs were first synthesized for research or medicinal purposes by chemists in academia or the pharmaceutical industry. The means of synthesis and effects of these compounds were widely available in the research literature, only to be rediscovered at a later date (in some cases decades later) and repurposed as drugs of abuse. For example, MDMA was first synthesized, described and patented by Merck in 1912, but did not appear on the streets until 1970 and was not extensively abused until the mid-1980s (for a fascinating review on the history of MDMA, see (Freudenmann et al., 2006)). Following the widespread abuse of China White and other fentanyl analogues, psychostimulants developed decades earlier emerged and gained popularity as designer drugs, including the amphetamine analogues methylenedioxy-amphetamine (MDA), methamphetamine (Meth) and MDMA.

Under the Controlled Substances Act, the government had no authority to prosecute the possession, production, or consumption of illicit drug analogues – the designer drugs – until those specific compounds were scheduled. The growing abuse of designer drugs led to the Controlled Substance Analogue Enforcement Act of 1986, which dictated that any substance intended for human consumption with a chemical structure similar to a schedule I or II controlled substance that has a similar or greater stimulant, depressive, or hallucinogenic effect shall be treated as a schedule I substance (Anti-Drug Abuse Act of 1986). To sidestep prosecution under the Analogue Enforcement Act, two tactics have been employed by designer drug producers. First, designer drugs that achieve the stimulant, depressant or hallucinogenic effects of schedule I substances with little structural analogy have been pursued and developed. Second, designer drugs have been explicitly marketed as products 'not for human consumption'. Both strategies, in part, have led to the production and abuse of synthetic cathinones in the US without legal ramification until their recent scheduling.

## History and abuse prevalence

Synthetic cathinones are the most common group of psychoactive compounds, along with piperazines, found within 'bath salts' sold through the internet and in head shops worldwide (Davies et al., 2010). The most widely abused synthetic cathinones – 4-methylmethcathinone (mephedrone), 3,4-methylenedioxymethcathinone (methylone), and 3,4-methylenedioxyprovalerone (MDPV) – are all derivatives of cathinone, a naturally occurring stimulant found in the leaves of khat. Cathinone is an alkaloid, similar in structure and action to amphetamine, whose analogues have been used as stimulants for centuries (Kalix, 1981). Chewing khat dates back to at least the tenth century and continues today, with its origins and popularity associated with East Africa and the Arab Peninsula (Gebissa, 2010). The chemical structures and synthesis of some synthetic cathinones have long been known but only recently abused. Methcathinone, a methylated analogue of cathinone, was synthesized in 1928 (Sanchez, 1929) and was the first synthetic cathinone designer drug, with reports of abuse beginning in the early 1990s (Emerson & Cisek, 1993). Synthesis of mephedrone and MDPV were first described in 1929 (Sanchez, 1929) and 1967 (G.m.b.H. BI., 1967), respectively, but abuse was not reported until the early 2000s. Methylone is a more recent analogue, patented 1996 (Jacob Peyton III, 1996).

Following their discovery, the synthetic cathinones were ignored until their abuse as a legal alternative to MDMA was first reported on internet drug websites in 2003 (Morris, 2010) and became prevalent within the United Kingdom in 2009 (BBC, 2009). Mephedrone is the most widely abused synthetic cathinone within Europe, whereas MDPV and methylone are the most frequently abused synthetic cathinones within the US. Synthetic cathinones are most frequently consumed as white powder or crystalline 'bath salts' mixtures but are also taken orally in tablet and pill forms (Wood et al., 2012). Tablets or pills sold throughout Europe containing mephedrone are marketed as 'meow meow', 'bubbles', 'top cat', '4-MMC', and 'ecstasy'. Though ecstasy has long been synonymous for MDMA (Freudenmann et al., 2006), mephedrone appears to be replacing MDMA in many tablets marketed as ecstasy (Brunt et al., 2011). Indeed, recent seizures of ecstasy by law enforcement throughout Europe indicate that tablets often contain a mixture of mephedrone, MDMA and caffeine, with mephedrone as the primary constituent in the majority of tablets (Addiction, 2011; Brunt et al., 2011).

Bath salts are synthetic cathinone powders distributed under trade names such as 'Ivory Wave', 'White Lightning' and 'Vanilla Sky' and labeled as "not for human consumption" to avoid penalty under the Analogue Enforcement Act (Addiction, 2011; Davies et al., 2010; Kasick et al., 2012; Winstock et al., 2011). These compounds are most frequently insufflated (snorted), but nasal agitation leads many users to smoke bath salts, take them orally or rectally, or to inject them intravenously or intramuscularly (Addiction, 2011; Kavanagh et al., 2013). Since crystallized synthetic cathinones are water soluble, bath salts are readily dissolved in beverages and orally ingested (Addiction, 2011). As with tablets, mephedrone is more prominent in European bath salts whereas MDPV is more prominent in US bath salts.

Despite distribution through street-level dealers, head shops, smoke shops, adult book stores, gas stations and internet retailers within Europe, the US and worldwide, the overwhelming majority of synthetic cathinones are produced in China and its surrounding South East Asian countries. The synthetic cathinones are commonly transported in powder-form to distributors, where they are then tabletted, pilled or adulterated prior to sale (Addiction, 2011). Producers and sellers claim to provide synthetic cathinones with over 99% purity. However,