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# Multi-drug cocktails: Impurities in commonly used illicit drugs seized by police in Queensland, Australia

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ABSTRACT

*Background:* Impurities in commonly used illicit drugs raise concerns for unwitting consumers when pharmacologically active adulterants, especially new psychoactive substances (NPS), are used. This study examines impurities detected in illicit drugs seized in one Australian jurisdiction.

*Methods:* Queensland Health Forensic and Scientific Services provided analytical data. Data described the chemical composition of 9346 samples of 11 illicit drugs seized by police during 2015-2016. Impurities present in primary drugs were summarized and tabulated. A systematic search for published evidence reporting similar analyses was conducted.

*Results:* Methamphetamine was the primary drug in 6608 samples, followed by MDMA (1232 samples) and cocaine (516 samples). Purity of primary drugs ranged from ~30% for cocaine, 2-CB and GHB to > 90% for THC, methamphetamine, heroin and MDMA. Methamphetamine and MDMA contained the largest *variety* of impurities: 22 and 18 variants, respectively. Drug adulteration patterns were broadly similar to those found elsewhere, including NPS, but in some primary drugs impurities were found which had not been reported elsewhere. Psychostimulants were adulterated with each other. Levamisole was a common impurity in cocaine. Psychedelics were adulterated with methamphetamine and NPS. Opioids were quite pure, but some samples contained methamphetamine and synthetic opioids.

*Conclusions:* Impurities detected were mostly pharmacologically active adulterants probably added to enhance desired effects or for active bulking. Given the designer nature of these drug cocktails, the effects of the adulterated drugs on users from possible complex multi-drug interactions is unpredictable. Awareness-raising among users, research into complex multi-drug effects and ongoing monitoring is required.

## 1. Introduction

There is evidence that illicit drugs, synthesized in clandestine laboratories and compounded in tabletting presses, contain a wide range of contaminating substances including other drugs (Cole et al., 2011; Giné et al., 2014; Qi et al., 2007). We refer to these adulterants, additives or other ingredients as 'impurities' in this study. Whether intentionally added or not, the effects on humans of mind-altering substances contaminated with impurities will be unpredictable and may be potentially fatal (Cole et al., 2011; Knuth et al., 2018; Kudlacek et al., 2017). The unpredictability arises as complex pharmacological interactions are possible between illicit drugs, the impurities they contain, and their molecular targets, as the few available studies suggest (Barbera et al., 2013; Jones et al., 2012; Oesterheld et al., 2004).

Impurities in commonly used illicit drugs raise several concerns. Firstly, consumers will generally not be aware they are taking a cocktail of drugs rather than just the primary recreational drug alone. Secondly, the strength of the cocktail is likely to be inconsistent. Finally, the consumer will have little understanding of the possible outcomes resulting from taking a primary drug contaminated with active impurities. Thus, beyond simply enhancing the desired effects, there may be serious clinical consequences for consumers when pharmacologically active constituents, especially new or novel psychoactive substances (NPS), are mixed with the more commonly used recreational drugs (Brunt et al., 2017; Giné et al., 2014).

Little is known about adverse health outcomes in users of illicit drugs contaminated with impurities, their compound modes of action or possible pharmacological interactions (Brunt et al., 2009; Giné et al., 2014). Better understandings of clinical outcomes, especially any severe consequences, is required to assist with prompt diagnosis and decisions

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on management and treatment options for drug users and to help raise awareness of these risks for potential new users and for the general public.

For this study, data were available describing the chemical composition of 9346 samples of 11 illicit drugs seized by police in the Australian State of Queensland in twelve months (2015–2016). Types of impurities found in each primary drug tested are first summarized and compared to the impurities found in similar analyses of drugs seized by enforcement agencies or provided by drug testing programs elsewhere in the world and reported primarily in peer-reviewed published literature. The possible pharmacological interactions and net physiological effects on humans are discussed and gaps in our current knowledge highlighted.

## 2. Methods

### 2.1. Data

Queensland Police Service (QPS) is required to provide analytical data as evidence in every illicit drug prosecution in Queensland. The Queensland Forensic and Scientific Services (QFSS) laboratory is a NATA (National Analytical Testing Authority) accredited laboratory. QFSS provided the analytical data used in this study. No person or prosecution matter was identifiable. Analytical protocols used for the various primary drugs are based on those developed by the United States Drug Enforcement Administration Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) (U.S. Department of Justice Drug Enforcement Administration, 2016). All laboratories providing analyses for police purposes across Australia adhere to these guidelines. Specific methods used are based on Gas Chromatography Mass Spectrometry (GC—MS), reported in detail elsewhere (Cheng et al., 2006; Qi et al., 2006). It is important to stress that these analytical methods are designed to quantitate only for the primary drug(s) to meet police prosecution requirements. In this study, impurities detected in the primary drugs were detected in the chromatograms in searching of SWGDRUG, in-house developed libraries and commercial libraries. We report results only in a qualitative manner, i.e., presence or absence. Seized drugs were imported from overseas, synthesized locally or compounded in tabletting presses.

The source of THC (delta-9-tetrahydrocannabinol) analyzed is mainly hashish block or oil, dried chopped leaves or residues from smoking implements. Fresh cannabis plant materials are determined botanically in Queensland; hence, they are not included in our data. Cannabinol is a natural cannabis component which reduces THC's negative effects (Grotenhermen, 2003; Swift et al., 2013) and was detected in most THC samples but was not classified as impurities given this well-known co-occurrence.

### 2.2. Types of primary drugs and impurities found

Table 1 reports information for 9264 samples with 52 impurities found in nine of the 11 primary drugs. For the purposes of Table 1, each impurity was counted as one 'case', and as individual samples had up to four impurities, there were 9321 cases. Information for PMA (para-methoxyamphetamine) and LSD (lysergic acid diethylamide) was not included in Table 1. Although both were detected as primary drugs, only one of the two PMA samples contained an impurity, viz. ethylone, and no impurities were detected in the 80 LSD samples.

Table 1 groups the remaining nine primary drugs in columns. The 52 impurities listed in the rows were grouped according to the main known physiological effect or function of each (Baumeister et al., 2015; Hill and Thomas, 2011; Liechti, 2015; Nichols, 2004, 1986; Rolland et al., 2014; Schifano et al., 2016; Vollenweider, 2001) as 'psychostimulants', 'psychedelics', 'opioids' and 'CNS (central nervous system) depressants and antipsychotics' and 'pharmacologically active bulking agents'. The 'psychedelics' were further divided into four sub-groups of impurities, and these were labelled: 'classic hallucinogens' (e.g., DMT), 'dissociative anesthetics' (e.g., Ketamine), 'empathogens' (e.g., MDMA) and 'cannabinoids' (e.g., THC) according to the impurity's primary molecular target (i.e., serotonin receptor, NMDA receptor, serotonin transporter and cannabinoid receptor, respectively) (Baumeister et al., 2014; Liechti, 2015).

Samples with 'no impurity' found are listed in the first row of Table 1. Pharmacologically active bulking agents in Table 1 were grouped as: 'local anesthetics', 'antihelminthics', 'analgesics' and 'N-isopropylbenzylamine'. Common inert bulking agents (e.g., sugar in cocaine) (Shannon, 1988) were not found in this study because analytical protocols precluded their detection. Abbreviations used for the pharmacologically active drugs are provided as footnotes in Table 1.

### 2.3. Literature search

Table 1 also contains citations to relevant literature. Peer-reviewed published journal articles reporting impurity profiling of seized drugs or impurity profiling of drug testing in similar forensic laboratories worldwide were retrieved in a search using PubMed, ProQuest, Scopus and EBSCO databases. Initial searches used the terms 'police', 'seized drugs', and 'impurity profiling', with separate searches conducted for each primary drug. Descriptions of impurities detected in the seized drugs in reported studies were compared with the impurities found in the Queensland samples with relevant citations incorporated into Table 1.

Potential toxicity of impurities was examined using information available in the general pharmacology and toxicology literature. Authors YP, AC and ML discussed and synthesized this information.

## 3. Results

### 3.1. Overview

Amongst the primary drugs, methamphetamine was the most frequently detected drug (6608 samples), followed by MDMA (3,4-methylenedioxymethamphetamine, 'ecstasy') (1232 samples), cocaine (516 samples), and THC (368 samples). In Australia, cannabis (10.4%) was the most commonly used illicit drug followed by cocaine (2.5%), ecstasy (2.2%) and meth/amphetamines (1.4%) in 2016 (Australian Institute of Health and Welfare, 2017). Not surprisingly, these use patterns are generally reflected in the drugs seized by police in this Queensland sample.

Samples were generally found to be quite pure: 100% of LSD samples, 98% of THC, 97% of methamphetamine, 96% of heroin and 91% of MDMA had no reported impurities. Although the methamphetamine and MDMA samples were typically of high purity, they nonetheless contained the largest *variety* of impurities: 22 in methamphetamine and 18 in MDMA. Methamphetamine and MDMA were also most frequently found as impurities in other primary drugs. Cocaine, 2C-B (2,5-dimethoxy-4-bromophenethylamine) and GHB (gamma-hydroxybutyric acid, 'liquid ecstasy' or 'fantasy') were less pure compared with the other drugs.

In the following, taking each broad group listed in Table 1 in turn, we discuss impurities detected in the primary drug and summarise alongside this what is known from the literature reporting impurities in primary drugs seized and tested elsewhere.

### 3.2. Psychostimulants and their impurities

#### 3.2.1. Methamphetamine

Almost all (97%) of methamphetamine samples were free of impurities (Table 1). The most frequently found impurity in methamphetamine was *N*-isopropylbenzylamine (37 cases). *N*-isopropylbenzylamine is known to be used to mimic or adulterate crystal methamphetamine ('ice') because of its ready availability and similar

**Table 1**
Nine primary drugs and associated impurities found in illegal substances seized by Queensland Police Service, July 2015-June 2016.

| Impurities | Primary drugs | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cocaine [516]* No impurity: 32% < 165 > ** | Amphetamine [85] No impurity: 67% < 57 > | Methamphetamine (Meth) [6608] No impurity: 97% < 6427 > | 2C-B [67] No impurity: 31% < 21 > | MDMA [1232] No impurity: 91% < 1120 > | THC [368] No impurity: 98% < 359 > | Heroin [312] No impurity: 96% < 301 > | Morphine [49] No impurity: 88% < 43 > | GHB [27] No impurity: 30% < 8 > |
| **Psychostimulants** | Meth (13)*** Amphetamine(1) | Meth (25) DMA (14) Cocaine (1) Methylphenidate (1) | DMA (30) Amphetamine (24) Cocaine (15) *α-PHP (1)**** *N-Methyl-2-AI (1)* Ethylphenidate (1) Phenethylamine (1) DMMA (1) | _ | Meth (34) Cocaine (10) Phenethylamine (7) DMAA (5) Amphetamine (2) | Cocaine (4) Meth (1) | Meth (7) Cocaine (2) | _ | _ |
| **Psychedelics** Classic Hallucinogens | _ | _ | *25C-NBOME (1)* *25I-NBOME (1)* | *5-MeO-DALT (46)* | *5-MeO-DALT (8)* *2C-T-2 (6)* DMT (2) *2C-B (1)* | _ | _ | _ | _ |
| Dissociative anaesthetics | _ | _ | Ketamine (1) *Methoxetamine (1)* | _ | *Methoxetamine(1)* | _ | _ | _ | _ |
| Empathogens | MDMA (10) | MDMA (2) | MDMA (36) | MDMA (1) | *Ethylone (18)* MDA (16) *Dibutylone (3)* *Methylone (2)* MDDM (1) | MDMA (1) | _ | _ | _ |
| Cannabinoids | THC (4) | _ | THC (13) | _ | THC (1) | *4-Fluoro-AMB (3)* *5-Fluoro-UR-144 (1)* *5-Fluoro-AKB48 (1)* | _ | _ | _ |
| **Opioids** | Heroin (2) | _ | Heroin (3) | _ | _ | _ | DXM (3) | Codeine(4) Thebaine (2) Paraverine (2) Noscapine (2) MA-morphine (1) Heroin (1) Acetylcodeine (1) Oxycodone (1) Fentanyl (1) | _ |
| **CNS depressants and Antipsychotics** | _ | _ | Diazepam (3) Alprazolam (1) 1,4-butandiol (2) Quetiapine (5) | _ | 1,4-butandiol (1) | _ | Diazepam (1) | Alprazolam (1) | GBL (19) 1,4-butandiol (2) |
| **Pharmacologically active bulking agents** Local anaesthetics | Lignocaine (103) Benzocaine (6) | Lignocaine (1) | Lignocaine (7) | _ | _ | _ | _ | _ | _ |
| Anti-helminthic | Levamisole (214) | _ | Praziquantel (1) | _ | _ | _ | _ | _ | _ |
| Analgesics | Phenacetine (7) | _ | _ | _ | _ | _ | _ | _ | _ |
| *N*-isopropyl benzylamine | _ | _ | *N*-isopropyl benzylamine (37) | _ | _ | _ | _ | _ | _ |
| **Others** | _ | _ | _ | _ | Sildenafil (2) | Desvenlafaxine (1) | _ | _ | _ |

(*continued on next page*)

**Table 1** (*continued*)

| Impurities | Primary drugs | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cocaine [516]* No impurity: 32% < 165 > ** | Amphetamine [85] No impurity: 67% < 57 > | Methamphetamine (Meth) [6608] No impurity: 97% < 6427 > | 2C-B [67] No impurity: 31% < 21 > | MDMA [1232] No impurity: 91% < 1120 > | THC [368] No impurity: 98% < 359 > | Heroin [312] No impurity: 96% < 301 > | Morphine [49] No impurity: 88% < 43 > | GHB [27] No impurity: 30% < 8 > |
| **Literature reporting impurities in each primary drug** | Bernardo et al. (2003); Broséus et al.(2015); Brunt et al. (2009); Evrard et al. (2010); Giné et al.(2014); Lapachinske et al. (2015); Schneider and Meys (2011); Vinkovic et al. (2018) | Giné et al.(2014); Vlatka et al. (2008) | Amini et al. (2015); Baldwin et al. (2018); Camilleri and Caldicott (2005); Dayrit and Dumlao (2004); Qi et al. (2006, 2007); Shekari et al. (2016); U.S. Department of Justice Drug Enforcement Administration (2008); Zhang et al. (2008); | | Brunt et al. (2012, 2017); Cheng et al.(2006); Giné et al. (2014); Neeltje et al. (2009); Palhol et al. (2002); Tanner-Smith (2006); Togni et al. (2015) | | Chan et al. (2012); Schneider and Meys (2011) | Baldwin et al. (2018) | |

Impurities are named and reported in descending order of frequency of occurrence.

Abbreviations: 2C-B = 2,5-dimethoxy-4-bromophenethylamine; 2C-T-2 = 2,5-dimethoxy-4-ethylthiophenethylamine; 5-MeO-DALT = 5-methoxy-*N,N*-diallyltryptamine; 25I-NBOMe = 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine; 25C-NBOMe = 4-chloro-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine; 4-Fluoro-AMB = Methyl(1-4-fluoropentyl)-1-indazole-3-carbonyl)-valinate; 5-FluoroUR-144 = (1-(5-fluoropentyl)-1-indol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methnone; 5-FluoroAKB48 = N-(1-adamantanyl)-1-(5-fluoropentyl)-indazole-3-carboxamine; α-PHP = alpha-pyrrolidinohexiophenone; DMA = N,*N*-dimethylamphetamine; DMMA = 1,2-dimethylamylamine; DMT = N,*N*-dimethyltryptamine; DXM = Dextromethorphan; Ethylone = (3,4-methylenedioxy)ethylcathine; GBL = Gamma-butyrolactone; GHB = Gamma-hydroxybutyric acid; MA-morphine = Monoacetylmorphine; MDA = 3,4-methylenedioxyamphetamine; MDDM = 3,4-methylenedioxy-*N,N*-dimethylamphetamine; MDMA = 3,4-methlylenedioxymethamphetamine; MDPV = 3,4-methlyenedioxypyrovalerone; Meth = Methamphetamine; Methylone = (3,4-methylenedioxy)methylcathine; N-Methyl-2-AI = N-Methyl-2-aminoindane; THC = delta9-tetrahydrocannabinol.

* [] Total number of seized samples of each primary drug are in [] brackets.

** < > Total number of seized samples with no impurity are in < > brackets.

*** () The number of cases, where each impurity was detected, are in round brackets ().

**** NPS or 'designer drugs' are in italics.

physical properties (U.S. Department of Justice Drug Enforcement Administration, 2008; Weston, 2010). Our methamphetamine samples were also adulterated with common recreational drugs including MDMA, cocaine and heroin as found elsewhere (Amini et al., 2015; Baldwin et al., 2018; Dayrit and Dumlao, 2004; Giné et al., 2014; Qi et al., 2007, 2006; Shekari et al., 2016; Zhang et al., 2008). Several different NPS were found including: 25C-NBOMe (4-chloro-2,5-dimethoxy-*N*-(2-methoxybenzyl)phenethylamine) and α-PHP (alpha-pyrrolidinohexiophenone). *N,N*-dimethylamphetamine (DMA) appears to be a bulking agent or a by-product of methamphetamine synthesis. One methamphetamine sample contained praziquantel, an anti-helminthic drug for parasitic worm infection. Five of the Queensland samples contained quetiapine, an antipsychotic drug. This is a novel finding, as quetiapine has not been reported as an impurity in methamphetamine elsewhere.

#### 3.2.2. Amphetamine

The majority of impurities detected in amphetamine were methamphetamine and DMA (Table 1), which were also found in seized amphetamine in Eastern Europe as by-products of amphetamine synthesis (Vlatka et al., 2008). The presence of a characteristic mixture of methamphetamine, amphetamine and DMA in several samples suggested ephedra was used as a starting material (Andrews, 1995; Qi et al., 2006). Furthermore, given the relative intensities of methamphetamine and DMA relative to amphetamine in the GC–MS traces it would appear that the manufacturers originally aimed to produce methamphetamine but obtained a larger proportion of amphetamine with smaller proportions of DMA and methamphetamine instead (Qi et al., 2006). Amphetamine samples were not adulterated with any NPS. This contrasts with the situation in Europe where 4-FA (4-fluoroamphetamine) is a commonly found NPS adulterant in amphetamine (Brunt et al., 2017; Giné et al., 2014; Lonkhuyzen et al., 2015)

#### 3.2.3. Cocaine

Cocaine was one of the least pure substances amongst the 11 primary drugs. Approximately two-thirds (68%) of cocaine samples were adulterated with a range of other substances (Table 1). The most abundant impurity in cocaine samples (ahead of local anesthetics and phenacetine) was levamisole, an antihelminthic drug. These bulking agents have been found as impurities in cocaine in several reports (Bernardo et al., 2003; Broséus et al., 2015; Brunt et al., 2009; Evrard et al., 2010; Giné et al., 2014; Lapachinske et al., 2015; Vinkovic et al., 2018; Schneider and Meys, 2011). THC, MDMA and heroin were also found in our cocaine samples; these are not commonly found as adulterants in cocaine elsewhere. Cocaine samples were not adulterated with any NPS.

### 3.3. Psychedelics and their impurities

#### 3.3.1. MDMA

Although 19 different substances were detected as impurities in MDMA, 91% of the samples tested showed no impurities (Table 1). Psychostimulants (e.g., methamphetamine), psychedelics (e.g., MDA) and several NPS (e.g., ethylone) were major impurities found in our MDMA samples, and were also found in studies elsewhere, while the common impurities such as ketamine or PMA were not detected (Brunt et al., 2012, 2017; Camilleri and Caldicott, 2005; Cheng et al., 2006; Giné et al., 2014; Neeltje et al., 2009; Palhol et al., 2002; Tanner-Smith, 2006; Togni et al., 2015). Two samples of sildenafil (a drug prescribed for erectile dysfunction in Australia) were found in MDMA samples; sildenafil has not been reported as an impurity elsewhere.

#### 3.3.2. 2C-B

2C-B is a hallucinogenic NPS. It shows stimulant effects at lower doses, but as dose increases it can bring agitation, hyperthermia, hypertension, seizure and psychosis (Dean et al., 2013; Lonkhuyzen et al., 2015; Schifano et al., 2016). Only 31% of 2C-B samples were free of impurities (Table 1); the rest were mostly adulterated with 5-MeO-DALT (5-methoxy-*N,N*-diallyltryptamine), which is a designer tryptamine derivative (Corkery et al., 2012). 2C-B has been reported in the literature as an impurity in seized MDMA or LSD (Giné et al., 2014; Togni et al., 2015).

#### 3.3.3. THC

Most of the THC samples (98%) contained no impurity (Table 1). Impurities found in Queensland THC samples included cocaine, methamphetamine, MDMA, three types of synthetic cannabinoids (NPS) and desvenlafaxine, an antidepressant drug. There are no previous reports of seized THC samples adulterated with these organic impurities (Cole et al., 2011; Swift et al., 2013).

### 3.4. Impurities in opioids and CNS depressants

#### 3.4.1. Opioids

Morphine and heroin samples were generally of high purity; 88% and 96% were pure, respectively (Table 1). The reduced purity of some morphine samples is likely due to alkaloid impurities from the synthesis process, including codeine, monoacetylmorphine or noscapine (Chan et al., 2012; Farhoudian et al., 2014).

Heroin and morphine samples were found adulterated with psychostimulants, CNS depressants and synthetic opioids such as oxycodone, fentanyl or dextromethorphan (Table 1). Similar impurity profiles have been reported in Europe, North America and/or Asia, (Baldwin et al., 2018; Chan et al., 2012; Pichini et al., 2018; Schneider and Meys, 2011). A previous Australian study found fentanyl-laced heroin (Rodda et al., 2017), while this study found a fentanyl-laced morphine.

#### 3.4.2. CNS depressants

Less than 30% of GHB samples were pure (Table 1). GBL (gamma-butyrolactone) or 1,4-butanediol were the main impurities. These substances are easily accessible industrial solvents (Schifano et al., 2015). Since GBL is an immediate precursor of GHB (and they are able to interconvert), GBL in our samples could be either a synthesis or degradation product of clandestinely synthesized GHB rather than intentionally added (Busardò et al., 2017).

## 4. Discussion

Impurities found in the samples of seized drugs in Queensland are mostly pharmacologically active substances which seem to have been strategically added to the primary drug to enhance or mimic its desired effects and/or to bulk up the primary drug with a cheaper active component to reduce the cost to the supplier and thereby maximize profits (Cole et al., 2011; Kudlacek et al., 2017). Some of the more unusual impurities may derive from cross-contamination of packaging or tabletting presses (Power et al., 2017; Qi et al., 2006; Shekari et al., 2016). Few by-products of synthesis were reported.

NPS as impurities in common illicit drugs were observed, including: synthetic cathinones ‘bath salts’ (methylone, ethylone, α-PHP), psychedelic phenethylamine (2C-B ‘Nexus’, 25I-NBOMe ‘N-bomb’), a ketamine derivative (methoxetamine ‘special M’), a tryptamine derivative (5-MeO-DALT) and synthetic cannabinoids. Although the frequency of NPS occurrence is currently much lower than that of other impurities, we suspect that it will rise as the use of NPS in designer cocktails becomes more prevalent in the Australian drug market, as has been already observed in Europe (Brunt et al., 2017; Giné et al., 2014). Seemingly relentless innovation to develop NPS by minor changes of chemical structure brings significant challenges for legislators, enforcement, clinicians and forensic laboratories (Rosenauer et al., 2013; Wright and Harris, 2016).

The wide variety of impurities detected overall, including NPS and other drugs of high potency, has substantial public health implications.

Drugs with added impurities will have inconsistent relative concentrations of each constituent due to the typically poorly-controlled, clandestine drug synthesis processes (Parrott, 2004; Rose et al., 2013). Consumers of common illicit drugs are now often unintentionally taking cocktails of drugs (Cole et al., 2011; Parrott, 2004; Tanner-Smith, 2006) with unknown physiological effects. These unknown effects will be further amplified when the drug cocktail is taken alongside other drugs such as marijuana and alcohol (Calle et al., 2018; Parrott, 2004). Adverse reactions along with unexpected and distressing drug experiences may include overdoses, serious behavioral disturbances and disrupted cognitive capacities (Baldwin et al., 2018; Barbera et al., 2013; Cole et al., 2011; Diestelmann et al., 2018; Kudlacek et al., 2017; Tanner-Smith, 2006; Wright and Harris, 2016; Zawilska and Wojcieszak, 2017).

### 4.1. Potential toxic effects of impurities found in Queensland drug seizures

It is well-known that intentional poly-drug use increases risks for overdose, impaired driving and violence (Caldicott et al., 2003; Diestelmann et al., 2018; Knoy et al., 2014; Wright and Harris, 2016). However, there are few studies of the toxicological effects of unintentionally administering illicit drugs that contain pharmacologically active impurities (Brunt et al., 2009; Giné et al., 2014).

#### 4.1.1. Combinations of popular illicit drugs

The combinations of common primary drugs and impurities, found in the Queensland samples, have considerable potential to cause drug interactions leading to adverse clinical outcomes (Cole et al., 2011; Tanner-Smith, 2006).

For instance, the co-administration of cocaine and MDMA may acutely increase plasma MDMA concentration since one of the main metabolic pathways of MDMA involves hepatic CYP450 isoenzyme CYP2D6, which is inhibited by cocaine (Shen et al., 2007). Thus, cocaine may slow down MDMA elimination, resulting in plasma accumulation leading to MDMA toxicity (Greene et al., 2008; Oesterheld et al., 2004; Pilgrim et al., 2011; Shen et al., 2007). Additionally, cocaine, as a serotonin re-uptake inhibitor, may enhance the serotonergic effects already induced by MDMA, possibly causing serotonin toxicities (Oesterheld et al., 2004). Other pharmaceutical or recreational drugs with pro-serotonergic effects and/or CYP2D6 inhibitors may cause similar drug interactions, with effects that are probably dose-dependent (Gillman, 2005; Oesterheld et al., 2004; Shen et al., 2007; Silins et al., 2007).

The risk of cardiac toxicity may be greatly increased by co-ingestion of cocaine with methamphetamine (Paratz et al., 2016) since sympathomimetic properties of cocaine and methamphetamine may induce cardiovascular complications (Fleury et al., 2008; Paratz et al., 2016; Rezkalla and Kloner, 2007).

The combination of psychostimulants and opioids, generally cocaine and heroin, is popularly known as 'speedball' (Cunha-Oliveira et al., 2010; Leri et al., 2003; Park et al., 2018; Trujillo et al., 2011). Such co-use of cocaine with heroin or synthetic opioids has been linked with an increase in cocaine-related fatal overdose in the US (Jones et al., 2017; Pichini et al., 2018) and with an increased risk of neurotoxicity and behavioral change in some animal studies (Cunha-Oliveira et al., 2010; Trujillo et al., 2011). Furthermore, the symptoms of cocaine-induced myocardial infarction (e.g., chest pain) may be masked by co-administration of heroin. This may confound a diagnosis of myocardial infarction and result in fatality (Attaran et al., 2005).

Fatal cases are reportedly more likely when multiple opioids are co-ingested, for example when morphine or heroin are adulterated with synthetic opioids (e.g., dextromethorphan or fentanyl) (Baldwin et al., 2018; Barbera et al., 2013; Pichini et al., 2018). Respiratory depression induced by heroin or morphine is reinforced by co-administration of the synthetic opioids (Barbera et al., 2013; Behrman, 2008). Similar synergistic adverse effects may be created by diazepam-adulterated heroin because both CNS depressants and opioids suppress the activity of the respiratory center in the brain (Horsfall and Sprague, 2017; Jones et al., 2012).

The combination of methamphetamine and MDMA, often seen in ecstasy tablets (Tanner-Smith, 2006), has been related to mood disorder, violent behavior, sleep problems, serotonin syndromes, and drug overdoses (Brecht and von Mayrhauser, 2002; Pilgrim et al., 2011; Tanner-Smith, 2006).

#### 4.1.2. High potency drugs in drug cocktails

Drugs with high potency can cause serious adverse effects at low dosages. For example, fentanyl is reportedly 50–100 times more potent than morphine (Pichini et al., 2018). In Canada, fentanyl is added to heroin, morphine, cocaine and methamphetamine (Baldwin et al., 2018). Increased use of fentanyl-laced drugs has been associated with increased incidence of fatal overdoses in North America, Australia and Japan (Pichini et al., 2018).

The NPS found in the Queensland samples, such as 2C-B, 25I-NBOMe, α-PHP ethylone, methylone, 5-MeO-DALT, methoxetamine or synthetic cannabinoids are particularly problematic, as the potency of these new NPS is generally high and poorly described. Fatalities and severe toxicities possibly caused by NPS have been reported, including: cardiac toxicity, serotonin toxicity, hyperthermia, seizures, psychosis, agitation, aggression, excited delirium, and violent/bizarre behavior (Bersani et al., 2014; Castaneto et al., 2014; Corazza et al., 2012; Hill et al., 2013; Hoyte et al., 2012; Jovel et al., 2014; Khullar et al., 2014; Liechti, 2015; Monte et al., 2014; Rose et al., 2013; Schifano et al., 2016, 2015; Zawilska and Wojcieszak, 2017). Moreover, the presence of plasma α-PVP (alpha-pyrrolidinovalerophenone, a precursor of α-PHP), methylone or ethylone are related to cases of impaired driving, possibly bringing further drug-related harm (Knoy et al., 2014; Wright and Harris, 2016; Zawilska and Wojcieszak, 2017).

PMA, a NPS with high potency but slow onset of action, is often marketed as MDMA and is allegedly responsible for overdoses in Australia and elsewhere (Caldicott et al., 2003; Dams et al., 2003; Johansen et al., 2003). When drug users unknowingly consume MDMA contaminated (or substituted) with PMA, the onset of the effect is delayed by the PMA. Unaware of this, users tend to re-dose bringing increased risk of overdose (Caldicott et al., 2003; Johansen et al., 2003; Kudlacek et al., 2017; Sherlock et al., 1999). A similar explanation may apply to methoxetamine-laced drugs (Corazza et al., 2012) or GHB with impurities (Silvester, 2017).

#### 4.1.3. Active bulking agents as impurities

Bulking agents found were all pharmacologically active with the potential to cause serious harm and even death. For example, pulmonary lymphocytic vasculitis-related fatality (Karch et al., 2016) is reportedly associated with levamisole-adulterated cocaine which also reportedly causes agranulocytosis and skin necrosis, described as "flesh eating Cocaine" in the UK (Daly, 2015; Lusher, 2016) following case reports (Massera et al., 2012; van der Veer et al., 2015v). Levamisole and its metabolite, aminorex, at high doses may also be psychoactive and extend the duration of euphoria and enhance hallucinogenic effects (Kudlacek et al., 2017; Lee et al., 2012). Local anesthetics are reported to enhance the toxic effects of cocaine synergistically, including hallucination, seizure, respiratory depression or cardiovascular collapse when taken in large doses (Derlet et al., 1991; Knuth et al., 2018; Shannon, 1988). Analgesic phenacetin present in cocaine reinforces hallucination and is linked with adverse cardiac effects (Brunt et al., 2009).

#### 4.1.4. Mixtures of drugs causing neurochemical imbalance

Unravelling the effects of adulterated drugs on physiological change, especially in the brain, is a complex task, as co-dosing may cause synergistic change (Barbera et al., 2013; Clemens et al., 2007, 2006, 2005, 2004; Cunha-Oliveira et al., 2010; Horsfall and Sprague, 2017; Jones et al., 2012; Trujillo et al., 2011) and/or imbalance of

neurochemicals in multiple neurotransmitter systems (Haile et al., 2012; Schifano et al., 2016). For example, methamphetamine, amphetamine, MDMA, THC and heroin found in the Queensland samples, in combination with alcohol and nicotine, have the ability to directly or indirectly enhance the dopaminergic system in the mesocorticolimbic pathway, despite differences in the initial molecular target (Koob and Volkow, 2010; Korpi et al., 2015; Nestler, 2005). Furthermore, cocaine acts on multiple neurotransmitter systems in addition to the dopaminergic system (Haile et al., 2012). With cocaine as the primary drug inducing neurochemical changes in multiple neurotransmitter systems, the presence of additional psychoactive impurities may significantly reinforce system imbalance and neuroadaptation (Koob and Volkow, 2010; Schifano et al., 2016). This change is believed to be involved in the pathophysiology of developing addiction, psychosis and impulsive or violent behavior (Haile et al., 2012; Koob and Volkow, 2010; Korpi et al., 2015; McKetin et al., 2014, 2006; Schifano et al., 2016; Seo et al., 2008; Siever, 2008). In turn, this will likely reinforce drug associated harm to others through domestic violence, dangerous driving, or violent crime (Diestelmann et al., 2018; Knoy et al., 2014; Topp et al., 2002; Wright and Harris, 2016). How acutely drugs with impurities induce these behavioral effects and how these behavioral effects change with long-term use warrants future thorough research, as this is now clearly a persistent public health problem.

### 4.2. The role of the drug testing programs in the identification of impure and laced drugs

Pill-testing has been used in harm reduction programs in a number of countries (Barratt et al., 2018) including: Netherlands (Spruit, 2001), Austria (Kriener et al., 2001), Switzerland (Hungerbuehler et al., 2011), Spain (Gine et al., 2016), Portugal (Martins et al., 2015), Wales (WEDINOS, 2018), Colombia (Acción Técnica Social, 2016), Canada (Sage, 2015) and the USA (Dundes, 2003). In these programs, drugs are handed in by users at festivals or clubs, then the content of the drug is analyzed on site and the results are given to the users along with harm reduction advice (Groves, 2018). In Australia, a trial of pill-testing was conducted at a music festival in April 2018 in which two samples contained dangerous substances out of 85 samples tested (Makkai et al., 2018). Later, in the Australian summer of 2018/2019, drug overdoses at music festivals caused much policy debate about pill testing programs (McGowan, 2019). The contribution of these pill testing programs to public health has been significant. They provide great opportunities to raise awareness of the presence of impurities in primary drugs and to regularly update information for the community about new designer drugs entering the market (Giné et al., 2014). Running in parallel, there are ongoing advances in laboratory testing to ensure that up-to-date toxicological information, that includes these newer drugs, is provided to clinicians (Brunt et al., 2017).

### 4.3. Limitations

The study lacked information on concentrations and quantities of impurities found alongside the primary drugs. This is not surprising, as there is no legislative requirement for this level of reporting, and as a result very few previous studies have reported such information (Dayrit and Dumlao, 2004). Data for one year provides a limited view of longer-term patterns. Quantitative impurity profiling of multiple types of seized drugs over several years would improve our understanding of trends and consequences of adulteration in Queensland's drug market, particularly with any rise in the use of NPS.

## 5. Conclusions

A broad sweep of analyses from samples of illicit drugs seized in Queensland during 2015–2016 revealed drug adulteration patterns found for the common illicit drugs that were both similar and different to patterns found elsewhere. A wide range of adulterants were found, and this included NPS. Given the designer nature of these drug cocktails, the physiological consequences may be unexpected by users, with both possible and likely increased incidences of overdose and other undesirable clinical outcomes. At the moment, there is very little empirical data on the pharmacological interactions between drugs and the impurities they may contain and the clinical outcomes and behavioral changes that may result. Filling these major gaps in knowledge would enhance our understanding of the unpredictable impulsive and/or bizarre behaviors increasingly being dealt with by frontline health care and law enforcement workers (McKetin et al., 2006). There is an urgent need to increase public awareness of adulterants in commonly used illicit drugs and the potential risks for users of these drug cocktails. In particular there needs to be a focus on MDMA, methamphetamine and opioids, where several varieties of NPS and other high potency additives were found as impurities, and on cocaine, GHB, and 2C-B, where nearly 70% of all seized samples were highly adulterated drug cocktails.

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## Contributors

YP conducted the literature searching and review. AC, ML, and YP analysed the information and drafted the paper. AC and ML commented on drafts of the paper and assisted YP in its writing and preparation and approved the final version for submission. PC furnished the data for the study, interpretation of the information and its significance, contributed to near-final drafts of the paper and approved the final version for publication. All authors contributed to and approved of the final version of the manuscript.

## Conflict of interest

Nothing declared.

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## References

Acción Técnica Social, 2016. Balance échela cabeza 2016. Acción Técnica Social, Colombia.
Amini, N., Etemadi-Aleagha, A., Akhgari, M., 2015. Impurity profiling of street methamphetamine samples seized in Kermanshah, Iran with special focus on methamphetamine impurities health hazards. J. Clin. Toxicol. 5, 4.
Andrews, K.M., 1995. Ephedra's role as a precursor in the clandestine manufacture of methamphetamine. J. Forensic Sci. 40, 551–560.
Attaran, R., Ragavan, D., Probst, A., 2005. Cocaine-related myocardial infarction: Concomitant heroin use can cloud the picture. Eur. J. Emerg. Med. 12, 199–201.
Australian Institute of Health and Welfare, 2017. National Drug Strategy Household Survey 2016: Detailed Findings, Drug Statistic Series. Australian Institute of Health and Welfare, Canberra.
Baldwin, N., Gray, R., Goel, A., Wood, E., Buxton, J.A., Rieb, L.M., 2018. Fentanyl and heroin contained in seized illicit drugs and overdose-related deaths in British Columbia, canada: an observational analysis. Drug Alcohol Depend. 185, 322–327.
Barbera, N., Busardò, F.P., Indorato, F., Romano, G., 2013. The pathogenetic role of adulterants in 5 cases of drug addicts with a fatal outcome. Forensic Sci. Int. 227, 74–76.
Barratt, M.J., Bruno, R., Ezard, N., Ritter, A., 2018. Pill testing or drug checking in Australia: acceptability of service design features. Drug Alcohol Rev. 37, 226–236.
Baumeister, D., Barnes, G., Giaroli, G., Tracy, D., 2014. Classical hallucinogens as antidepressants? A review of pharmacodynamics and putative clinical roles. Ther. Adv. Psychopharmacol. 4, 156–169.
Baumeister, D., Tojo, L.M., Tracy, D.K., 2015. Legal highs: staying on top of the flood of novel psychoactive substances. Ther. Adv. Psychopharmacol. 5, 97–132.
Behrman, A.D., 2008. Luck of the draw: common adulterants found in illicit drugs. J. Emerg. Nurs. 34, 80–82.
Bernardo, N.P., Siqueira, M.E.P.B., de Paiva, M.J.N., Maia, P.P., 2003. Caffeine and other

adulterants in seizures of street cocaine in Brazil. Int. J. Drug Policy 14, 331–334.
Bersani, F.S., Corazza, O., Albano, G., Valeriani, G., Santacroce, R., Mariotti, Bolzan, Posocco, F., Cinosi, E., Simonato, P., Martinotti, G., Bersani, G., Schifano, F., 2014. 25C-NBOMe: preliminary data on pharmacology, psychoactive effects, and toxicity of a new potent and dangerous hallucinogenic drug. Biomed Res. Int., 734749 2014.
Brecht, M.L., von Mayrhauser, C., 2002. Differences between ecstasy-using and nonusing methamphetamine users. J. Psychoactive Drugs 34, 215–223.
Broséus, J., Huhtala, S., Esseiva, P., 2015. First systematic chemical profiling of cocaine police seizures in Finland in the framework of an intelligence-led approach. Forensic Sci. Int. 251, 87–94.
Brunt, T.M., Koeter, M., Niesink, R., Brink, W., 2012. Linking the pharmacological content of ecstasy tablets to the subjective experiences of drug users. Psychopharmacology (Berl.) 220, 751–762.
Brunt, T.M., Constanze, N., Alexander, B., Daniel, M., Miren, U., Cécile, B., Mireia, V.V., 2017. Drug testing in Europe: monitoring results of the Trans European Drug Information (TEDI) project. Drug Test. Anal. 9, 188–198.
Brunt, T.M., Rigter, S., Hoek, J., Vogels, N., Van Dijk, P., Niesink, R.J.M., 2009. An analysis of cocaine powder in the Netherlands: content and health hazards due to adulterants. Addiction 104, 798–805.
Busardò, F.P., Kyriakou, C., Marchei, E., Pacifici, R., Pedersen, D.S., Pichini, S., 2017. Ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) for determination of GHB, precursors and metabolites in different specimens: application to clinical and forensic cases. J. Pharm. Biomed. Anal. 137, 123–131.
Caldicott, D.G.E., Edwards, N.A., Kruys, A., Kirkbride, K.P., Sims, D.N., Byard, R.W., Prior, M., Irvine, R.J., 2003. Dancing with "death": P-methoxyamphetamine overdose and its acute management. J. Toxicol. Clin. Toxicol. 41, 143–154.
Calle, P., Sundahl, N., Maudens, K., Wille, S.M., Van Sassenbroeck, D., De Graeve, K., Gogaert, S., De Paepe, P., Devriese, D., Arno, G., Blanckaert, P., 2018. Medical emergencies related to ethanol and illicit drugs at an annual, nocturnal, indoor, electronic dance music event. Prehosp. Disaster Med. 33, 71–76.
Camilleri, A.M., Caldicott, D., 2005. Underground pill testing, down under. Forensic Sci. Int. 151, 53–58.
Castaneto, M.S., Gorelick, D.A., Desrosiers, N.A., Hartman, R.L., Pirard, S., Huestis, M.A., 2014. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend. 144, 12–41.
Chan, K.-W., Tan, G.-H., Wong, R.C.S., 2012. Investigation of illicit heroin seized in Malaysia: physical characteristics and chemical profiling. Aust. J. Forensic Sci. 44, 353–369.
Cheng, J.Y.K., Chan, T.W., Chan, M.F., Hung, M.Y., 2006. Impurity profiling of ecstasy tablets seized in Hong Kong by gas chromatography–mass spectrometry. Forensic Sci. Int. 162, 87–94.
Clemens, K.J., Cornish, J.L., Hunt, G.E., McGregor, I.S., 2006. Intravenous methamphetamine self-administration in rats: effects of intravenous or intraperitoneal MDMA co-administration. Pharmacol. Biochem. Behav. 85, 454–463.
Clemens, K.J., Cornish, J.L., Li, K.M., Hunt, G.E., McGregor, I.S., 2005. MDMA ('ecstasy') and methamphetamine combined: Order of administration influences hyperthermic and long-term adverse effects in female rats. Neuropharmacology 49, 195–207.
Clemens, K.J., McGregor, I.S., Hunt, G.E., Cornish, J.L., 2007. MDMA, methamphetamine and their combination: possible lessons for party drug users from recent preclinical research. Drug Alcohol Rev. 26, 9–15.
Clemens, K.J., van Nieuwenhuyzen, P.S., Kong, M.L., Cornish, J.L., Hunt, G.E., McGregor, I.S., 2004. MDMA ("ecstasy"), methamphetamine and their combination: long-term changes in social interaction and neurochemistry in the rat. Psychopharmacology (Berl.) 173, 318–325.
Cole, C., Jones, L., McVeigh, J., Kicman, A., Syed, Q., Bellis, M., 2011. Adulterants in illicit drugs: a review of empirical evidence. Drug Test. Anal. 3, 89–96.
Corazza, O., Schifano, F., Simonato, P., Fergus, S., Assi, S., Stair, J., Corkery, J., Trincas, G., Deluca, P., Davey, Z., Blaszko, U., Demetrovics, Z., Moskalewicz, J., Enea, A., di Melchiorre, G., Mervo, B., di Furia, L., Farre, M., Flesland, L., Pasinetti, M., Pezzolesi, C., Pisarska, A., Shapiro, H., Siemann, H., Skutle, A., Enea, A., di Melchiorre, G., Sferrazza, E., Torrens, M., van der Kreeft, P., Zummo, D., Scherbaum, N., 2012. Phenomenon of new drugs on the Internet: the case of ketamine derivative methoxetamine. Hum. Psychopharmacol. 27, 145–149.
Corkery, J.M., Durkin, E., Elliott, S., Schifano, F., Ghodse, A.H., 2012. The recreational tryptamine 5-MeO-DALT (N,N-diallyl-5-methoxytryptamine): a brief review. Prog. Neuropsychopharmacol. Biol. Psychiatry 39, 259–262.
Cunha-Oliveira, T., Rego, A.C., Garrido, J., Borges, F., Macedo, T., Oliveira, C.R., 2010. Neurotoxicity of heroin–cocaine combinations in rat cortical neurons. Toxicology 276, 11–17.
Daly, M., 2015. The Truth About Britain's "flesh-eating" Cocaine. Vice, New York, NY.
Dams, R., De Letter, E.A., Mortier, K.A., Cordonnier, J.A., Lambert, W.E., Piette, M.H.A., Van Calenbergh, S., De Leenheer, A.P., 2003. Fatality due to combined use of the designer drugs MDMA and PMA: a distribution study. J. Anal. Toxicol. 27, 318–323.
Dayrit, F.M., Dumlao, M.C., 2004. Impurity profiling of methamphetamine hydrochloride drugs seized in the Philippines. Forensic Sci. Int. 144, 29–36.
Dean, B.V., Stellpflug, S., Burnett, A.M., Engebretsen, K.M., 2013. 2C or not 2C: phenethylamine designer drug review. J. Med. Toxicol. 9, 172–178.
Derlet, R.W., Albertson, T.E., Steven Tharratt, R., 1991. Lidocaine potentiation of cocaine toxicity. Ann. Emerg. Med. 20, 135–138.
Diestelmann, M., Zangl, A., Herrle, I., Koch, E., Graw, M., Paul, L.D., 2018. MDPV in forensic routine cases: psychotic and aggressive behavior in relation to plasma concentrations. Forensic Sci. Int. 283, 72–84.
Dundes, L., 2003. Dance safe and ecstasy. J. Health Soc. Policy 17, 19–37.
Evrard, I., Legleye, S., Cadet-Taïrou, A., 2010. Composition, purity and perceived quality of street cocaine in France. Int. J. Drug Policy 21, 399–406.
Farhoudian, A., Sadeghi, M., Khoddami Vishteh, H.R., Moazen, B., Fekri, M., Rahimi Movaghar, A., 2014. Component analysis of Iranian crack; a newly abused narcotic substance in Iran. Iran. J. Pharm. Res. 13, 337–344.
Fleury, G., De La Garza II, R., Mahoney III, J.J., Evans, S.E., Newton, T.F., 2008. Predictors of cardiovascular response to methamphetamine administration in methamphetamine-dependent individuals. Am. J. Addict. 17, 103–110.
Gillman, P.K., 2005. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br. J. Anaesth. 95, 434–441.
Giné, C.V., Espinosa, I.F., Vilamala, M.V., 2014. New psychoactive substances as adulterants of controlled drugs. A worrying phenomenon? Drug Test. Anal. 6, 819–824.
Gine, C.V., Ventura Vilamala, M., Fornis Espinosa, I., Gil Lladanosa, C., Calzada Alvarez, N., Fito Fruitos, A., Rodriguez Rodriguez, J., Domingo Salvany, A., de la Torre Fornell, R., 2016. Crystals and tablets in the Spanish ecstasy market 2000-2014: are they the same or different in terms of purity and adulteration? Forensic Sci. Int. 263, 164–168.
Greene, S.L., Kerr, F., Braitberg, G., 2008. Review article: amphetamines and related drugs of abuse. Emerg. Med. Australas. 20, 391–402.
Grotenhermen, F., 2003. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin. Pharm. 42, 327–360.
Groves, A., 2018. "Worth the test?" Pragmatism, pill testing and drug policy in Australia. Harm Reduct. J. 15, 12–13.
Haile, C.N., Mahoney, J.J., Newton, T.F., De La Garza, R., 2012. Pharmacotherapeutics directed at deficiencies associated with cocaine dependence: focus on dopamine, norepinephrine and glutamate. Pharmacol. Ther. 134, 260–277.
Hill, S.L., Doris, T., Gurung, S., Katebe, S., Lomas, A., Dunn, M., Blain, P., Thomas, S.H.L., 2013. Severe clinical toxicity associated with analytically confirmed recreational use of 25I–NBOMe: case series. Clin. Toxicol. 51, 487–492.
Hill, S.L., Thomas, S.H., 2011. Clinical toxicology of newer recreational drugs. Clin. Toxicol. 49, 705–719.
Horsfall, J.T., Sprague, J.E., 2017. The pharmacology and toxicology of the "holy trinity". Basic Clin. Pharmacol. Toxicol. 120, 115–119.
Hoyte, C.O., Jacob, J., Monte, A.A., Al-Jumaan, M., Bronstein, A.C., Heard, K.J., 2012. A characterization of synthetic cannabinoid exposures reported to the national poison data system in 2010. Ann. Emerg. Med. 60, 435–438.
Hungerbuehler, I., Buecheli, A., Schaub, M., 2011. Drug checking: a prevention measure for a heterogeneous group with high consumption frequency and polydrug use—evaluation of Zurich's drug checking services. Harm Reduct. J. 8, 16.
Johansen, S.S., Hansen, A.C., Muller, I.B., Lundemose, J.B., Franzmann, M.B., 2003. Three fatal cases of PMA and PMMA poisoning in Denmark. J. Anal. Toxicol. 27, 253–256.
Jones, C.M., Baldwin, G.T., Compton, W.M., 2017. Recent increases in cocaine-related overdose deaths and the role of opioids. Am. J. Public Heal. 107, 430–432.
Jones, J.D., Mogali, S., Comer, S.D., 2012. Polydrug abuse: a review of opioid and benzodiazepine combination use. Drug Alcohol Depend. 125, 8–18.
Jovel, A., Felthous, A., Bhattacharyya, A., 2014. Delirium due to intoxication from the novel synthetic tryptamine 5-MeO-DALT. J. Forensic Sci. 59, 844–846.
Karch, S.B., Busardò, F.P., Vaiano, F., Portelli, F., Zaami, S., Bertol, E., 2016. Levamisole adulterated cocaine and pulmonary vasculitis: presentation of two lethal cases and brief literature review. Forensic Sci. Int. 265, 96–102.
Khullar, V., Jain, A., Sattari, M., 2014. Emergence of new classes of recreational drugs—synthetic cannabinoids and cathinones. J. Gen. Intern. Med. 29, 1200–1204.
Knoy, J.L., Peterson, B.L., Couper, F.J., 2014. Suspected impaired driving case involving α-pyrrolidinovalerophenone, methylone and ethylone. J. Anal. Toxicol. 38, 615–617.
Knuth, M., Temme, O., Daldrup, T., Pawlik, E., 2018. Analysis of cocaine adulterants in human brain in cases of drug-related death. Forensic Sci. Int. 285, 86–92.
Koob, G.F., Volkow, N.D., 2010. Neurocircuitry of addiction. Neuropsychopharmacology 35, 217–238.
Korpi, E.R., den Hollander, B., Farooq, U., Vashchinkina, E., Rajkumar, R., Nutt, D.J., Hyytia, P., Dawe, G.S., 2015. Mechanisms of action and persistent neuroplasticity by drugs of abuse. Pharmacol. Rev. 67, 872–1004.
Kriener, H., Billeth, R., Gollner, C., Lachout, S., Neubauer, P., Schmid, R., 2001. An inventory of on-site pill-testing interventions in the European Union. Vienna Social Projects. EMCDDA, Vienna.
Kudlacek, O., Hofmaier, T., Luf, A., Mayer, F.P., Stockner, T., Nagy, C., Holy, M., Freissmuth, M., Schmid, R., Sitte, H.H., 2017. Cocaine adulteration. J. Chem. Neuroanat. 83–84, 75–81.
Lapachinske, S.F., Okai, G.G., dos Santos, A., de Bairros, A.V., Yonamine, M., 2015. Analysis of cocaine and its adulterants in drugs for international trafficking seized by the Brazilian Federal Police. Forensic Sci. Int. 247, 48–53.
Lee, K.C., Ladizinski, B., Federman, D.G., 2012. Complications associated with use of levamisole-contaminated cocaine: an emerging public health challenge. Mayo Clin. Proc. 87, 581–586.
Leri, F., Bruneau, J., Stewart, J., 2003. Understanding polydrug use: review of heroin and cocaine co-use. Addiction 98, 7–22.
Liechti, M., 2015. Novel psychoactive substances (designer drugs): overview and pharmacology of modulators of monoamine signaling. Swiss Med. 145, w14043.
Lonkhuyzen, J.J.N., van Riel, A.J.H.P., Brunt, T.M., Hondebrink, L., 2015. Pharmacokinetics, pharmacodynamics and toxicology of new psychoactive substances (NPS): 2C-B, 4-fluoroamphetamine and benzofurans. Drug Alcohol Depend. 157, 18–27.
Lusher, A., 2016. The Flesh-eating, Bladder-wrecking Chemicals Hidden in Street Cocaine. The Independent, London.
Makkai, T., Macleod, M., Vumbaca, G., Hill, P., Caldicott, D., Noffs, M., Tzanetis, S., Hansen, F., 2018. Report on ACT GTM Pill Testing Pilot: Harm Reduction Service. Harm Reduction Australia, Leura.
Martins, D., Valente, H., Pires, C., 2015. CHECK!NG: the last frontier for harm reduction

in party settings. Saúde e Soc. 24, 646–660.
Massera, D., Bachhuber, M., Shen, L., Karambelkar, A., 2012. Vasculitis in a cocaine user. BMJ Case Rep 2012.
McGowan, M., 2019. Parents of Drug-overdose Victims at Odds Over Benefits of Pill Testing: Doctors and Former Federal Police Commissioner Call for the Practice to Be Allowed at Music Festivals. Guardian Australia, Surry Hills.
McKetin, R., Lubman, D.I., Najman, J.M., Dawe, S., Butterworth, P., Baker, A.L., 2014. Does methamphetamine use increase violent behavior? Evidence from a prospective longitudinal study. Addiction 109, 798–806.
McKetin, R., McLaren, J., Riddell, S., Robins, L., 2006. The relationship between methamphetamine use and violent behavior. Crime Justice Bull. 97, 1–15.
Monte, A.A., Bronstein, A.C., Cao, D.J., Heard, K.J., Hoppe, J.A., Hoyte, C.O., Iwanicki, J.L., Lavonas, E.J., 2014. An outbreak of exposure to a novel synthetic cannabinoid. N. Engl. J. Med. 370, 389–390.
Neeltje, V., Tibor, M.B., Sander, R., Peter, V.D., Hylke, V., Raymond, J.M.N., 2009. Content of ecstasy in the Netherlands: 1993–2008. Addiction 104, 2057–2066.
Nestler, E.J., 2005. Is there a common molecular pathway for addiction? Nat. Neurosci. 8, 1445–1449.
Nichols, D.E., 2004. Hallucinogens. Pharmacol. Ther. 101, 131–181.
Nichols, D.E., 1986. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. J. Psychoact. Drugs. 18, 305–313.
Oesterheld, J.R., Armstrong, S.C., Cozza, K.L., 2004. Ecstasy: pharmacodynamic and pharmacokinetic interactions. Psychosomatics 45, 84–87.
Palhol, F., Boyer, S., Naulet, N., Chabrillat, M., 2002. Impurity profiling of seized MDMA tablets by capillary gas chromatography. Anal. Bioanal. Chem. 374, 274–281.
Paratz, E.D., Cunningham, N.J., MacIsaac, A.I., 2016. The cardiac complications of methamphetamines. Hear. Lung Circ. 25, 325–332.
Park, J.N., Weir, B.W., Allen, S.T., Chaulk, P., Sherman, S.G., 2018. Fentanyl-contaminated drugs and non-fatal overdose among people who inject drugs in Baltimore, MD. Harm Reduct. J. 15, 34.
Parrott, A.C., 2004. Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. Psychopharmacology 173, 234–241.
Pichini, S., Solimini, R., Berretta, P., Pacifici, R., Busard, F., 2018. Acute intoxications and fatalities from illicit fentanyl and analogues: an update. Ther. Drug Monit. 40, 38.
Pilgrim, J.L., Gerostamoulos, D., Drummer, O.H., 2011. Deaths involving MDMA and the concomitant use of pharmaceutical drugs. J. Anal. Toxicol. 35, 219–226.
Power, J.D., Kavanagh, P., McLaughlin, G., Barry, M., Dowling, G., Brandt, S.D., 2017. 'APAAN in the neck' – a reflection on some novel impurities found in seized materials containing amphetamine in Ireland during routine forensic analysis. Drug Test. Anal. 9, 966–976.
Qi, Y., Evans, I., McCluskey, A., 2007. New impurity profiles of recent Australian imported "ice": methamphetamine impurity profiling and the identification of (pseudo) ephedrine and Leuckart specific marker compounds. Forensic Sci. Int. 169, 173–180.
Qi, Y., Evans, I.D., McCluskey, A., 2006. Australian federal police seizures of illicit crystalline methamphetamine ('ice') 1998-2002: impurity analysis. Forensic Sci. Int. 164, 201–210.
Rezkalla, S.H., Kloner, R.A., 2007. Cocaine-induced acute myocardial infarction. Clin. Med. Res. 5, 172–176.
Rodda, L.N., Pilgrim, J.L., Di Rago, M., Crump, K., Gerostamoulos, D., Drummer, O.H., 2017. A cluster of fentanyl-laced heroin deaths in 2015 in Melbourne, Australia. J. Anal. Toxicol. 41, 318–324.
Rolland, B., Jardri, R., Amad, A., Thomas, P., Cottencin, O., Bordet, R., 2014. Pharmacology of hallucinations: several mechanisms for one single symptom? Biomed Res. Int., 307106 2014.
Rose, S.R., Poklis, J.L., Poklis, A., 2013. A case of 25I-NBOMe (25-I) intoxication: a new potent 5-HT2A agonist designer drug. Clin. Toxicol. 51, 174–177.
Rosenauer, R., Luf, A., Holy, M., Freissmuth, M., Schmid, R., Sitte, H.H., 2013. A combined approach using transporter-flux assays and mass spectrometry to examine psychostimulant street drugs of unknown content. ACS Chem. Neurosci. 4, 182–190.
Sage, C., 2015. Harm reduction and drug checking: a wrap-around service for festivals. Case Study: Shambhala Music Festival /ANKORS Drug Checking Harm Reduction Service Data 2015. ANKORS, Nelson, BC.
Schifano, F., Orsolini, L., Duccio Papanti, G., Corkery, J.M., 2015. Novel psychoactive substances of interest for psychiatry. World Psychiatry 14, 15–26.
Schifano, F., Papanti, G.D., Orsolini, L., Corkery, J.M., 2016. Novel psychoactive substances: the pharmacology of stimulants and hallucinogens. Expert Rev. Clin. Pharmacol. 9, 943–954.
Schneider, S., Meys, F., 2011. Analysis of illicit cocaine and heroin samples seized in Luxembourg from 2005-2010. Forensic Sci. Int. 212, 242–246.
Seo, D., Patrick, C.J., Kennealy, P.J., 2008. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. Aggress. Violent Behav. 13, 383–395.
Shannon, M., 1988. Clinical toxicity of cocaine adulterants. Ann. Emerg. Med. 17, 1243–1247.
Shekari, A., Akhgari, M., Jokar, F., Mousavi, Z., 2016. Impurity characteristics of street methamphetamine crystals seized in Tehran, Iran. J. Subst. Use 21, 501–505.
Shen, H., He, M.M., Liu, H., Wrighton, S.A., Wang, L., Guo, B., Li, C., 2007. Comparative metabolic capabilities and inhibitory profiles of CYP2D6.1, CYP2D6.10, and CYP2D6.17. Drug Metab. Dispos. 35, 1292–1300.
Sherlock, K., Wolff, K., Hay, A.W., Conner, M., 1999. Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. J. Accid. Emerg. Med. 16, 194–197.
Siever, L.J., 2008. Neurobiology of aggression and violence. Am. J. Psychiatry 165, 429–442.
Silins, E., Copeland, J., Dillon, P., 2007. Qualitative review of serotonin syndrome, ecstasy (MDMA) and the use of other serotonergic substances: hierarchy of risk. Aust. N.Z. J. Psychiatry 41, 649–655.
Silvester, J., 2017. The "bute" Loophole That Is Making Organised Crime Millions. The Sydney Morning Herald, Sydney.
Swift, W., Wong, A., Li, K.M., Arnold, J.C., McGregor, I.S., 2013. Analysis of cannabis seizures in NSW, Australia: cannabis potency and cannabinoid profile. PLoS One 8, e70052.
Spruit, I.P., 2001. Monitoring synthetic drug markets, trends, and public health. Subst. Use Misuse 36, 23–47.
Tanner-Smith, E.E., 2006. Pharmacological content of tablets sold as "ecstasy": results from an online testing service. Drug Alcohol Depend. 83, 247–254.
Togni, L.R., Lanaro, R., Resende, R.R., Costa, J.L., 2015. The variability of ecstasy tablets composition in Brazil. J. Forensic Sci. 60, 147–151.
Topp, L., Degenhardt, L., Kaye, S., Darke, S., 2002. The emergence of potent forms of methamphetamine in Sydney, Australia: a case study of the IDRS as a strategic early warning system. Drug Alcohol Rev. 21, 341–348.
Trujillo, K.A., Smith, M.L., Guaderrama, M.M., 2011. Powerful behavioral interactions between methamphetamine and morphine. Pharmacol. Biochem. Behav. 99, 451–458.
U.S. Department of Justice Drug Enforcement Administration, 2016. Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) Recommendation. Scientific Working Group for the Analysis of Seized Drugs, Washington, D.C.
U.S. Department of Justice Drug Enforcement Administration, 2008. N-Isopropylbenzylamine hydrochloride (as "ICE" methamphetamine mimics) on the West Coast. MICROGRAM Bull. 41, 31–32.
van der Veer, T., Pennings, E., Tervaert, J.W., Korswagen, L.A., 2015v. Levamisole-contaminated cocaine: a hairy affair. BMJ Case Rep pii, bcr2015210970.
Vinkovic, K., Galic, N., Schmid, G., 2018. Micro-HPLC-UV analysis of cocaine and its adulterants in illicit cocaine samples seized by Australian police fom 2012 to 2017. J. Liq. Chromatogr. Relat. Techno. 41, 6–13.
Vlatka, V., Slobodan, P., Sonja Banovic, S., Marina, N., 2008. Analysis of amphetamines illegally produced in Serbia. J. Serb. Chem. Soc. 73, 691–701.
Vollenweider, F.X., 2001. Brain mechanisms of hallucinogens and entactogens. Dialogues Clin. Neurosci. 3, 265–279.
WEDINOS, 2018. PHILTRE Annual Report 1st April 2017— 31st March 2018. Public Health Wales, Cardiff, UK.
Weston, R.G., 2010. Quick screening of crystal methamphetamine/methyl sulfone exhibits by raman spectroscopy. J. Forensic Sci. 55, 1068–1075.
Wright, T.H., Harris, C., 2016. Twenty-one cases involving alpha-pyrrolidinovalerophenone (α-PVP). J. Anal. Toxicol. 40, 396–402.
Zawilska, J., Wojcieszak, J., 2017. α-Pyrrolidinophenones: a new wave of designer cathinones. Forensic Toxicol. 35, 201–216.
Zhang, J.X., Zhang, D.M., Han, X.G., 2008. Identification of impurities and statistical classification of methamphetamine hydrochloride drugs seized in China. Forensic Sci. Int. 182, 13–19.