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Review

Pharmacokinetics, pharmacodynamics and toxicology of new psychoactive substances (NPS): 2C-B, 4-fluoroamphetamine and benzofurans

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ABSTRACT

Background: Recently, the number of new psychoactive substances (NPS) appearing on the illicit drug market has shown a marked increase. Although many users perceive the risk of using NPS as medium or low, these substances can pose a serious health risk and several NPS have been implicated in drug-related deaths. In Europe, frequently detected NPS are 4-bromo-2,5-dimethoxyphenethylamine (2C-B), 4-fluoroamphetamine (4-FA) and benzofurans (5-(2-aminopropyl)benzofuran (5-APB) or 6-(2-aminopropyl)benzofuran (6-APB)). However, little is known about the health risks of these specific NPS.

Methods: In this paper, existing literature on the pharmacokinetics and pharmacodynamics of 2C-B, 4-FA and benzofurans (5-APB/6-APB) was reviewed.

Results: Our review showed that the clinical effects of 2C-B, 4-FA and benzofurans (5-APB/6-APB) are comparable with common illicit drugs like amphetamine and 3,4-methylenedioxymethamphetamine (MDMA). Therefore, NPS toxicity can be handled by existing treatment guidelines that are based on clinical effects instead of the specific drug involved. Even so, information on the health risks of these substances is limited to a number of case reports that are complicated by confounders such as analytical difficulties, mislabelling of drugs, concomitant exposures and interindividual differences.

Conclusion: To aid in early legislation, data on clinical effects from poisons centres and user fora should be combined with (*in vitro*) screening methods and collaboration on an (inter)national level is essential. As a result, potentially hazardous NPS could be detected more quickly, thereby protecting public health.

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1. Introduction

Over the past years, an increasing number of new psychoactive substances (NPS) has become available on the worldwide illicit drug market. The presence of NPS on the European drug market is monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) which has reported an ongoing increase of newly detected NPS every year. The number of first time notified NPS reported to the EMCDDA increased from 15 in 2007 to 101 in 2014 (EMCDDA, 2007, 2015a), bringing the total number of presently monitored NPS to more than 450.

1.1. What are NPS? Definition and classification

NPS are defined as new narcotic or psychotropic drugs, in pure form or preparation, that are not controlled by the 1961 United Nations Single Convention on Narcotic Drugs or the 1971 United Nations Convention on Psychotropic Substances, but which may pose a public health threat comparable to substances that are listed in these two conventions (EMCDDA, 2006). Many NPS were developed years ago and are therefore not newly designed but are in fact, newly introduced on the user's market. NPS can be divided in several groups based on their chemical structure or mechanism of action. These groups include: piperazines, benzodiazepines, arylamines, tryptamines, opioids, phenethylamines, synthetic cannabinoids, synthetic cathinons and other substances (EMCDDA, 2015a).

1.2. Prevalence

One of the main groups of NPS that are notified to the EMCDDA by European member states are synthetic phenethylamines (EMCDDA, 2014). The interest in these substances increased with the publication of the book 'Phenethylamines I Have Known and Loved (PIHKAL)' in 1991 (Shulgin and Shulgin, 1991). From that time onwards, mainly ring-substituted phenethylamines like 4-bromo-2,5-dimethoxyphenethylamine (2C-B) were encountered on the international drug market. However, in recent years, other phenethylamines have started to appear. Since 2005, the most commonly encountered phenethylamines in the EU include 4-fluoroamphetamine (4-FA) and 2C-related substances like 2,5-dimethoxy-4-iodophenethylamine (2C-I) and

2,5-dimethoxy-4-ethylphenethylamine (2C-E). Because 2C-B was added to Schedule II of the 1971 Convention on Psychotropic Substances, it is by definition not an NPS. Nevertheless, 2C-B is still the most frequently reported "new" phenethylamine to the EMCDDA (King, 2014).

Like in the EU, 2C-B and 4-FA were the most frequently detected NPS in the Netherlands in 2013. In addition, benzofurans (5-(2-aminopropyl)benzofuran (5-APB) or 6-(2-aminopropyl)benzofuran (6-APB)) were also frequently detected (Hondebrink et al., 2015). 5-APB and 6-APB were first reported to the EMCDDA in 2010 (5-APB, United Kingdom) and 2011 (6-APB, Hungary) (EMCDDA, 2010a, 2011). Since then, their presence on the illicit drug market has rapidly increased. For instance, 6-APB was amongst the most frequently offered NPS in online shops in 2012, indicating widespread (online) availability (EMCDDA, 2012).

In addition to national and international monitoring systems that detect the presence of NPS on the illicit drug market, data on actual NPS use can be obtained from survey studies, mainly on sub-population level. For example, a recent European survey amongst ~13,000 young adults reported a lifetime and last year's prevalence of NPS use of 8% and 3%, respectively. Although NPS are not the most frequently used drugs of abuse, their use is increasing with a lifetime prevalence of 5% in 2011 to 8% in 2014 (Flash Eurobarometer 330, 2011; Flash Eurobarometer 401, 2014). In addition, a study amongst Spanish students reported an overall lifetime use of 'legal highs' of 0.7%, with the use of 'research chemicals', 'Spice' products and mephedrone, being 0.4%, 1.1% and 0.4%, respectively (Clinical Committee, 2011). Furthermore, the lifetime and last year's prevalence of use of 'benzofury' was reported to be 2.7% and 2.3% in nightlife visitors, mainly from the United Kingdom (EMCDDA, 2013). In the Netherlands, last year's prevalence of use of 2C-B and 4-FA was comparable to that of established drugs in 2013, like psychedelic mushrooms, GHB and ketamine (~10%, Goossens et al., 2014). Recently, a novel method to investigate trends in drug use was applied, in which pooled urine samples collected from stand-alone urinals in central London were analysed. During a 6-month period, this resulted in the detection of 13 NPS, including mephedrone and 5-APB (Archer et al., 2012, 2014).

1.3. User characteristics

A recent US study combining several databases to provide insight in the characteristics of NPS users, showed that NPS users

are primarily young male adults (Maxwell, 2014). Although this is consistent with other studies (Helander et al., 2013, 2014; Winstock et al., 2014; Vazirian et al., 2015; Hondebrink et al., 2015), NPS use has also been reported in teens and adults up to 73 years of age (Carhart-Harris et al., 2011). NPS use often takes place at a party or event (65%) and with friends (60%) (Flash Eurobarometer 401, 2014).

According to the Flash Eurobarometer survey, most users obtain NPS via a friend (70%), whereas a minority (30%) buy them from a drug dealer. Although NPS can readily be purchased on the Internet and in specialized smart- or headshops (EMCDDA, 2012), these sources of drug purchase were reported by only 13% of the respondents in this survey (Flash Eurobarometer 401, 2014). In contrast, a different study reported 'purchased over the Internet' (71%) followed by 'received from a friend' (10%) as the most common sources of NPS (Helander et al., 2013). These differences might be explained by the connectivity (rural or urban area) of NPS users to multiple sources of drug purchase (Bilinski et al., 2012; Flash Eurobarometer 330, 2011).

1.4. Public health concerns

There is a perception that NPS are relatively safe; only 60% of young adults perceive the health risk of using NPS as high, whereas 40% perceive it as medium to low (Flash Eurobarometer 401, 2014). In addition, not all NPS dealers provide information on ingredients, advised dosage and negative side effects and many market their products as 'herbal' or 'natural drugs', implying there are no health risks (Hillebrand et al., 2010). Even so, NPS use can pose serious health threats resulting in hospitalization and deaths. The European Union Early Warning System for NPS has issued ~80 public health alerts during the last five years to alert the network on serious and urgent issues regarding NPS use (EMCDDA, 2015a). In addition, approximately 10% of all drug-related emergency department visits in Europe involved NPS. Although systematic data on NPS-related deaths is difficult to find, some data is available. In Hungary, NPS were involved in roughly half of the reported drug-induced deaths in 2013. In addition, the Early Warning System indicated that methylenedioxypyrovalerone (MDPV, first detected in 2008) was involved in 99 deaths at the time of its risk assessment in 2014 (EMCDDA, 2015b). Also, forensic casework has recently shown an increased presence of benzofurans (5-APB/6-APB) (Elliott and Evans, 2014), indicating potential toxicity and mortality. Notably, benzofurans have been implicated in several deaths in recent years (Clemente et al., 2012), although analytical confirmation is often lacking. Furthermore, the Dutch Poisons Information Centre (DPIC) was consulted about 35 NPS exposures in 2013 and 77 in 2014, mostly involving 4-FA, mephedrone, methoxetamine, 2C-B and benzofurans (5-APB/6-APB) (Hondebrink et al., 2015; Mulder-Spijkerboer et al., 2015).

1.5. Health risks of specific NPS: review of the literature

Despite the increasing use and presence of NPS on the illicit drug market, the health risks associated with the use of many frequently detected NPS are not well known. This information is not only of importance for healthcare professionals to provide appropriate treatment in case of an overdose, but is also crucial in the process of legislation, prevention and control (Wood and Dargan, 2012). Due to their structural resemblance, it is likely that clinical effects following NPS exposure partly overlap those following exposure to more common illicit drugs, like amphetamine or 3,4-methylenedioxy-methamphetamine (MDMA, the main active ingredient in ecstasy) (Table 1). Nevertheless, the need for peer-reviewed data is high. To investigate the clinical effects following NPS use, we performed a literature review for two of the

most frequently detected new phenethylamines in the EU, 2C-B and 4-FA. In addition, we reviewed the literature on benzofurans, because of their increasing popularity and potential for serious health effects. Mephedrone and methoxetamine were excluded from this review, as their pharmacokinetics and pharmacodynamics have been recently reviewed elsewhere (Dybdal-Hargreaves et al., 2013; Miotto et al., 2013; Zawilska, 2014).

2. Methods

We conducted a literature search on 2C-B, 4-FA and benzofurans (5-APB/6-APB) using PubMed. Articles up to July 2015 were reviewed. Our review was limited to literature published in English and Dutch. Relevant articles were selected on available information about the pharmacokinetics and pharmacodynamics (including information on clinical effects and toxicology) of the NPS involved. For 2C-B the search entry was ("4-bromo-2,5-dimethoxyphenethylamine" Supplementary Concept)) OR (2CB[Title/Abstract]) OR (2-CB[Title/Abstract]) OR (2C-B[Title/Abstract]). For 4-FA this was (p-fluoroamphetamine[Title/Abstract]) OR (para-fluoroamphetamine[Title/Abstract]) OR (4-fluoroamphetamine[Title/Abstract]) OR (4-FA[Title/Abstract]) OR (4FA [Title/Abstract]) OR (1-(4-fluorophenyl)propan-2-amine[Title/Abstract]) OR ("4-fluoroamphetamine" [Supplementary Concept]). For 5-APB and 6-APB the search entry was ("6-(2-aminopropyl)benzofuran" [Supplementary Concept]) OR (6-(2-aminopropyl)benzofuran[Title/Abstract]) OR (benzofury[Title/Abstract]) OR (6-APB[Title/Abstract]) OR (6APB[Title/Abstract]) OR (1-benzofuran-6-ylpropan-2-amine[Title/Abstract]) OR (5-(2-aminopropyl)benzofuran[Title/Abstract]) OR (5-APB[Title/Abstract]) OR (5APB[Title/Abstract]) OR (1-benzofuran-5-ylpropan-2-amine[Title/Abstract]). Bibliographies of relevant articles were reviewed for additional literature. Due to the scarcity of peer-reviewed information, we also included data from the popular drug users' website Erowid.

3. Results

3.1. 2C-B

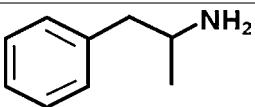
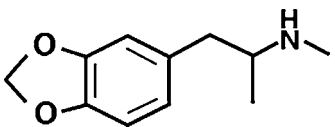
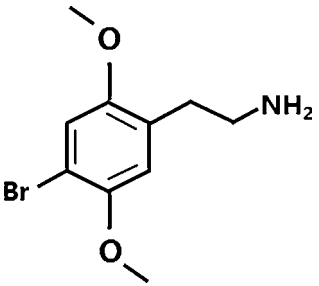
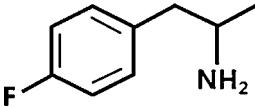
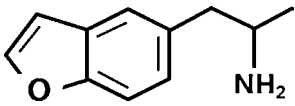
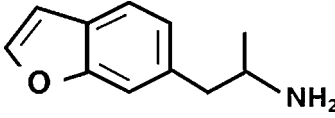
3.1.1. Class. 2C-B (4-bromo-2,5-dimethoxyphenethylamine), also known as Nexus, Venus, Bromo, Bees, EroX, Synergy, Performax or Toonies (Dean et al., 2013; Cole et al., 2002; Rohanová et al., 2008; Giroud et al., 1998), is a NPS belonging to the 2C-type of phenethylamine drugs that all have a 2,5-dimethoxyphenethylamine backbone in common (de Boer and Bosman, 2004) (Table 1). 2C-B was first synthesized in the 1970s for psychotherapeutic use (Shulgin and Carter, 1975; Shulgin and Shulgin, 1991), but was abandoned due to significant gastrointestinal effects and the lack of empathogenic effects (Dean et al., 2013). Later, it was used as a (legal) substitute for MDMA in the club scene (NDIC, 2001). 2C-B was added to Schedule II of the 1971 United Nations Convention on Psychotropic Substances in 2001 (King, 2014) and is currently controlled in most countries.

3.1.2. Pharmacokinetics. 2C-type drugs are usually consumed orally in a dose of 4–30 mg (Shulgin and Carter, 1975; Shulgin and Shulgin, 1991; Giroud et al., 1998). On average, effects last for 4–8 h depending on the dose and the user's susceptibility (Shulgin and Shulgin, 1991; Karch, 2002). Nasal insufflation is rarely practiced, but it produces more rapid and intense effects than oral exposure (Caudevilla-Gállico et al., 2012; Dean et al., 2013). Although limited pharmacokinetic data is available, experimental studies have shown that 2C-B metabolism involves monoamine oxidase (MAO-A and B) enzymes (Kanamori et al., 2013; Theobald and Maurer, 2007) and probably cytochrome P450 enzymes (Carmo et al., 2005). *In vitro* studies using human hepatocytes detected six metabolites following 2C-B exposure (Carmo et al., 2005). Many of these metabolites were also found in urine of humans exposed to 2C-B (de Boer et al., 1999b; Kanamori et al., 2013). One study reported 2C-B concentrations in urine, which amounted up to 0.3–0.7 mg/L and could only be detected during the first 3 h after exposure (de Boer et al., 1999b).

Other basic kinetic parameters are only available from animal studies. In rats, the elimination half-life of 2C-B was approximately

Table 1

Chemical name, abbreviation and chemical structure of several common drugs and NPS.

Chemical name	Abbreviation	Chemical structure
Amphetamine	–	
3,4-methylenedioxymethamphetamine	MDMA	
4-bromo-2,5-dimethoxyphenethylamine	2C-B	
1-(4-fluorophenyl)propan-2-amine (4-fluoroamphetamine)	4-FA	
5-(2-aminopropyl)benzofuran	5-APB	
6-(2-aminopropyl)benzofuran	6-APB	

1 h, the volume of distribution 16 L/kg and the clearance 9.8 L/h. Maximal serum concentrations (~ 2 mg/L, $8 \mu\text{M}$) were attained within 30 min after administration of a very high 2C-B dose (50 mg/kg, s.c., comparable to 8 mg/kg for a human adult (using the body surface area (BSA) normalization method; Reagan-Shaw et al., 2008)). 2C-B was detected in several tissues, of which the lungs and brain contained the highest 2C-B concentrations (Rohanová et al., 2008).

3.1.3. Pharmacodynamics: mechanism of action. Exposure to 2C-B increases neurotransmitter levels in the brain, primarily dopamine (DA) (Pálénček et al., 2013), and likely also serotonin (5-HT) and norepinephrine (NE) (Montgomery et al., 2007). In animals, increased DA release has been shown following exposure to 25 mg/kg 2C-B. In addition, DA levels can increase further due to a decreased breakdown of DA, indicating inhibition of MAO enzymes (Pálénček et al., 2013). Furthermore, at high concentrations, 2C-B inhibits the reuptake of 5-HT and NE by inhibiting the 5-HT reuptake transporter (SERT) and the NE reuptake transporter (NET) ($\text{IC}_{50} \sim 300$ and $\sim 70 \mu\text{M}$ respectively, Montgomery et al., 2007), which likely increases 5-HT and NE brain levels (see Table 2 for overview). However, during recreational use, low serum concentrations of $\sim 1 \mu\text{M}$ were reached (see Section 3.1.4). It is therefore unknown, whether these mechanisms also occur in humans.

On a receptor level, 2C-B activates the serotonergic 5-HT_{2C} receptor ($\text{EC}_{50} \sim 0.5 \mu\text{M}$; Acuña-Castillo et al., 2002) and likely the $\alpha 1$ adrenoreceptor (Lobos et al., 1992). In addition, 2C-B binds to 5HT_{1A}, 5HT_{1B} and 5HT_{1C} receptors (K_i 320, 25, 36 nM; Glennon

et al., 1988). Remarkably, 2C-B does not activate the 5-HT_{2A} receptor (Acuña-Castillo et al., 2002; Moya et al., 2007), although 2C-B has a hallucinogenic potency that is 15 times stronger than mescaline (Jacob and Shulgin, 1994). Hallucinogenic effects in general are usually attributed to the activation of the 5-HT_{2A} receptor (Nichols, 2004). In fact, activation of the 5-HT_{2A} receptor is strongly inhibited by 2C-B, already at nanomolar concentrations (Villalobos et al., 2004).

3.1.4. Pharmacodynamics: clinical effects and toxicology. Exposure to 2C-B results in amphetamine-like stimulating effects as well as mescaline-like hallucinogenic effects. At low doses (<10 mg) euphoria, increased tactile, visual, auditory and olfactory sensations and amphetamine-like stimulating effects are reported. Moderate doses (10–20 mg) may produce marked visual hallucinations with intense colour play and distortion of objects. Higher doses (>20 mg) may cause anxious hallucinations and sympathomimetic effects such as tachycardia, hypertension and hyperthermia (Huang and Bai, 2011; de Boer et al., 1999a; Giroud et al., 1998; Shulgin and Carter, 1975; Shulgin and Shulgin, 1991). Psychedelic effects following 2C-B use are milder compared to classical hallucinogenic drugs such as LSD (Caudevilla-Gállico et al., 2012; Shulgin and Carter, 1975). According to users, some unpleasant effects elicited by 2C-B include difficulty in focussing, trembling and sweating. Residual effects can last up to 48 h after intake and include insomnia and the involuntary reoccurrence of the experience ('flashbacks') (Caudevilla-Gállico et al., 2012).

Table 2
Monoamine transporter inhibition of several common drugs and NPS.

Substance	IC ₅₀ NET	IC ₅₀ DAT	IC ₅₀ SERT	Blood concentration (in life)	Lethal blood concentration
Amphetamine	0.1 ⁽¹⁾ ; 0.1 ⁽²⁾ ; 0.2 ⁽³⁾	1.3 ⁽¹⁾ ; 1.3 ⁽²⁾ ; 0.2 ⁽³⁾	>10.0 ⁽¹⁾ ; 45.0 ⁽²⁾ ; 3.8 ⁽³⁾	2 ⁽¹⁵⁾	13 (2–84) ⁽¹⁸⁾
MDMA	0.5 ⁽¹⁾ ; 0.4 ⁽²⁾ ; 0.7 ⁽⁴⁾ ; 6.6 ⁽⁵⁾	17.0 ⁽¹⁾ ; 31.0 ⁽²⁾ ; 1.4 ⁽⁴⁾	1.4 ⁽¹⁾ ; 2.0 ⁽²⁾ ; 0.7 ⁽⁴⁾ ; 34.8 ⁽⁵⁾	2–3 ⁽¹⁵⁾	19 (2–435) ⁽¹⁸⁾
2C-B	67.1 ⁽⁵⁾	–	312.9 ⁽⁵⁾	1 ⁽⁸⁾	–
4-FA	0.4 ⁽⁴⁾ ; 0.2 ⁽²⁾ ; 0.4 ⁽³⁾	0.8 ⁽⁴⁾ ; 3.7 ⁽²⁾ ; 0.3 ⁽³⁾	6.8 ⁽⁴⁾ ; 19.0 ⁽²⁾ ; 2.4 ⁽³⁾	2–3 [†] (9); 0.6 [†] *(10); 0.1 (0.04–3) [†] *(16); 0.8 ⁽¹¹⁾	4 ^{*(17)}
5-APB	3.2 ⁽⁶⁾ ; 0.2 ⁽⁷⁾	7.1 ⁽⁶⁾ ; 6.1 ⁽⁷⁾	0.1 ⁽⁶⁾ ; 0.3 ⁽⁷⁾	0.6–0.8 [†] (12); 2 ^{*(17)}	8 (0.6–24) ^{*(12)} ; 14 ⁽¹³⁾ ; 32 ^{*(14)}
6-APB	1.0 ⁽⁶⁾ ; 0.2 ⁽⁷⁾	2.0 ⁽⁶⁾ ; 3.3 ⁽⁷⁾	0.3 ⁽⁶⁾ ; 0.9 ⁽⁷⁾	0.6–0.8 [†] (12); 2 ^{*(17)}	8 (0.6–24) ^{*(12)}

2C-B, 4-bromo-2,5-dimethoxyphenethylamine; 4-FA, 4-fluoroamphetamine; 5-APB, (5-(2-aminopropyl)benzofuran; 6-APB, 2-aminopropylbenzofuran; DAT, dopamine reuptake transporter; MDMA, 3,4-methylenedioxymethamphetamine; NET, norepinephrine reuptake transporter; SERT, serotonin reuptake transporter. IC₅₀ values reflect the concentration (in μ M) required to inhibit the transporter by 50%. Blood concentrations are given in μ M. The blood concentration (in life) reflects the concentration described in subjects driving under the influence of drugs (DUID, marked with [†]) or case reports of non-lethal intoxications. *Co-ingestion of other psychoactive substances or alcohol. Details on *in vitro* studies and case reports can be found in Section 3.

References: (1) Simmler et al. (2013); (2) Rickli et al. (2015a); (3) Marona-Lewicka et al. (1995); (4) Nagai et al. (2007); (5) Montgomery et al. (2007); (6) Monte et al. (1993); (7) Rickli et al. (2015b); (8) Ho et al. (2013); (9) Röhrich et al. (2012); (10) Maas et al. (2015); (11) Al-Abri et al. (2014); (12) Elliott and Evans (2014); (13) McIntyre et al. (2014); (14) Adamowicz et al. (2014); (15) Uges et al. (2004); (16) Johansen and Hansen (2012); (17) Locatelli et al. (2013); (18) Verschraagen et al. (2007).

Intoxications with 2C-related substances have been linked to the development of an excited delirium syndrome. This syndrome consists of delirium with agitation, aggression and in many cases hyperthermia. Eventually, patients may die as a result of a sudden and unexpected cardiopulmonary arrest (Dean et al., 2013). Despite this, 2C-B attributed cases of excited delirium syndrome have not been analytically confirmed to date. In addition, no reported fatalities with 2C-B have been reported. In fact, limited data on human toxicity following 2C-B exposure is available, probably due to analytical limitations in detecting 2C-type drugs (Kerrigan et al., 2011a, 2011b, 2014). To date, only three case reports of 2C-B intoxicated patients are available in the literature. The first case report of 2C-B toxicity involved a 43-year-old woman who developed cerebral vasculopathy with persistent neurological deficits after ingestion of liquid 2C-B (Ambrose et al., 2010). The second case involved a young man who developed a persistent psychosis (2 months follow-up) after ingestion of a single 2C-B tablet (Huang and Bai, 2011). In both cases, the contribution of 2C-B was questionable, since urine samples were 2C-B negative and no drug samples were available for analysis. The third case involved a 19-year-old male who became unresponsive and developed several generalized tonic-clonic seizures following exposure to 2C-B. Other symptoms were lactic acidosis, rhabdomyolysis, sinus tachycardia, flushed skin, diaphoresis, clenched jaw, rigid extremities and mydriasis. The presence of 2C-B was confirmed in serum (0.34 mg/L, $\sim$ 1 μ M) (Table 2). No other drugs were detected (Ho et al., 2013). In addition to these case reports, several symptoms were reported to the DPIC after 2C-B exposure. These included mild effects like gastrointestinal symptoms, but also apathy, bradyphrenia, aggression, anxiety, hallucinations, drowsiness, reduced consciousness, mydriasis, hyperventilation, hypertension and tachycardia (Hondebrink et al., 2015).

3.2. 4-Fluoroamphetamine (4-FA)

3.2.1. Class. 4-FA (1-(4-fluorophenyl)propan-2-amine), also known as PFA, 4-FMP, flava, 4floor, 4-fluor or Flux CD cleaner, was first detected in Germany during a forensic seizure in 2003 (Rösner et al., 2005). By 2010, 4-FA was detected in 12 other European countries in both forensic seizures and samples offered to consumer testing facilities (Röhrich et al., 2012; Johansen and Hansen, 2012; Giné et al., 2014; Hondebrink et al., 2015; EMCDDA, 2010b). Notably, the current chemical structure of 4-FA is different from the chemical structure which was referred to in earlier studies in the 1980s. Because pharmacokinetics and -dynamics may differ between these different structures, our literature review focussed on the current 4-FA structure (Table 1).

3.2.2. Pharmacokinetics. Limited literature is available on the pharmacokinetics of 4-FA. User platforms indicate that varying amounts are consumed, ranging from 40 to 200 mg in a single dose. However, most users consume 100–150 mg (42%) (Linsen et al., 2015). Oral exposure is most frequently reported. Effects occur within 30–60 min after exposure and generally last 4–6 h (44%). However, some users report effects for more than 8 h after exposure. Nasal insufflation is also practiced, but is reported to be very painful (Erowid experience vault 4-fluoroamphetamine; Linsen et al., 2015). Animal models have shown a rapid increase in extracellular neurotransmitter levels in the brain following exposure to 4-FA, supporting the rapid onset of clinical effects in humans (Baumann et al., 2011; Marona-Lewicka et al., 1995).

3.2.3. Pharmacodynamics: mechanism of action. Exposure to 4-FA induces the release of NE, DA and 5-HT in the brain and inhibits their reuptake. *In vitro*, 4-FA most potently induces the release of NE, followed by DA and 5-HT (EC₅₀ respectively <50, <200 and <1000 nM) (Wee et al., 2005; Nagai et al., 2007). A similar potency was observed for the inhibition of reuptake of these neurotransmitters; IC₅₀ values for NE, DA and 5-HT were <0.4, <4 and <20 μ M, respectively (Nagai et al., 2007; Rickli et al., 2015a; Marona-Lewicka et al., 1995) (see Table 2 for overview). Likely, these mechanisms also occur during recreational use in humans, since micromolar serum concentrations are reached (see Section 3.2.4). *In vivo* (rat, nucleus accumbens), the effect on the dopaminergic system was also stronger than on the serotonergic system, although a larger difference in potency was observed compared to the *in vitro* data. For example, following 4-FA exposure (1 mg/kg, i.v.), DA levels increased by 300%, while 5-HT levels increased by only 30% (Baumann et al., 2011). In other brain areas, such as the striatum, increases in DA levels up to 800% were observed (7 mg/kg 4-FA, i.p.) (Marona-Lewicka et al., 1995).

3.2.4. Pharmacodynamics: clinical effects and toxicology. Users have reported a wide variety of effects following 4-FA exposure, including decreased appetite, dry mucosa, sweating, mydriasis, body tingles, coordination difficulties, jaw clenching, increased energy, hyperactivity and increased body temperature. In addition, psychological effects may occur, like increased happiness, empathy, euphoria, sleeplessness and anxiety (Erowid experience vault 4-fluoroamphetamine). In a survey amongst Dutch drug users, the subjective effects of 4-FA were found to be comparable to those of amphetamine and MDMA (Linsen et al., 2015).

Scientific data on the pharmacological effects of 4-FA in humans is limited. Interestingly, a study investigating the subjective effects following ecstasy exposure showed that in 35 samples (<1% of all samples), the actual substance was not MDMA, but 4-FA. In

half of these cases, social and entactogenic feelings were experienced. Overall, this study showed that 4-FA was likely to induce desirable subjective effects without a significant probability of experiencing adverse effects (Brunt et al., 2012). A survey amongst 4-FA users showed that stimulatory and euphoric effects were the most frequently reported positive effects (58 and 28% respectively). However, adverse effects were also reported, including jaw clenching (43%), elevated heartbeat (37%), tachycardia (12%) and elevated body temperature (33%). Unpleasant hallucinations were reported in only 1% of the users (Linsen et al., 2015). Additionally, the DPIC has reported nausea, vomiting, dysphagia, abdominal pain, dizziness, headache, a feeling of fainting, confusion, agitation restlessness, visual disturbances, tremors, tachycardia and tachypnea following 4-FA exposure (Hondebrink et al., 2015).

Adverse effects were also reported in case reports describing the observed effects in individuals suspected for driving under the influence of drugs (DUID). For example, 2 men suspected for DUID showed symptoms of mydriasis, slow pupil light reflexes, trembling fingers, tremors and restlessness. The presence of 4-FA was confirmed in serum (350 and 475 µg/L, respectively; ~2 and 3 µM) (Table 2) (Röhrich et al., 2012). Lower serum concentrations were detected in 2 different DUID subjects; both around 90 µg/L (~0.6 µM) (Table 2). Possibly the time between exposure and serum analysis contributes to the differences in serum concentrations. The first subject presented with a slow coordination, concentration deficiencies, slurred speech, agitation, restlessness, dry mouth, reddened and glassy eyes and pupil abnormalities. The second subject fell asleep while driving, resulting in a car accident. Notably, other psychoactive substances were detected in the serum of both subjects as well, that could have contributed to the reported symptoms (Maas et al., 2015). A case-series of 14 DUID cases reported a median 4-FA whole blood concentration of 21 µg/kg (~0.1 µM, range 6–430 µg/kg) (Table 2). However, no case histories or information about impairment and/or driving performance were reported (Johansen and Hansen, 2012).

In addition to DUID cases, only two case reports of a 4-FA intoxication are available in the literature. The first case involved an 18 year-old man who presented to the emergency department (ED) with vomiting, shortness of breath, chest tightness and altered mental status, 5 h after exposure to an unknown amount of 4-FA (Al-Abri et al., 2014). Exposure was analytically confirmed; a urine concentration of 64 mg/L and a serum level of 118 µg/L (~0.8 µM) were reported (Table 2). Ten hours after exposure, the patient developed cardiogenic shock and required ventilation. The patient was hospitalized for 2 weeks and was discharged in good condition. The second case involved an 27-year old man who ingested 200 mg of 4-FA powder (Laskowski et al., 2015). Four hours after exposure he presented to the ED with sympathomimetic effects (e.g., agitation, tachycardia, diaphoresis, dilated pupils, hyperreflexia) and a core temperature of 41.4°C. Following treatment including ice water submersion and ICU admission, the patient left the hospital 1 day after exposure. Serum and urine analysis confirmed the presence of 4-FA. Unfortunately, actual 4-FA concentrations were not reported. In addition to these intoxication cases, one 4-FA-related fatality was reported in the literature (Johansen and Hansen, 2012). In this case, death was ascribed to a combination of 4-FA (580 µg/kg in whole blood; ~4 µM), amphetamine (300 mg/kg) and a high level of methadone (650 mg/kg) (Table 2). No information on clinical effects was reported.

3.3. Benzofurans: 5-APB and 6-APB

3.3.1. Class. 5-(2-Aminopropyl)benzofuran (5-APB) and 6-(2-aminopropyl)benzofuran (6-APB) (Table 1), also known as benzofury, are structural isomers first developed in the 1990s by researchers investigating non-neurotoxic MDMA analogues (Monte et al., 1993). These phenethylamines are structurally related to MDMA and 3,4-methylenedioxyamphetamine (MDA). 5-APB and 6-APB were first reported to the EMCDDA in 2010 (5-APB, UK) and 2011 (6-APB, Hungary) (EMCDDA, 2010a, 2011).

3.3.2. Pharmacokinetics. Limited literature is available on the pharmacokinetics of benzofurans. In general, more user reports are available for 6-APB than for 5-APB. For both substances, oral amounts range from 60 to 150 mg. Effects occur within 1–2 h after dosing and generally last long; users report effects up to 7 h with both substances (Erowid experience vault 6-APB; Erowid experience vault 5-APB). 6-APB is usually consumed orally since nasal insufflation is very painful (Jebadurai et al., 2013).

Data on the metabolism of 5- or 6-APB in humans is not available. However, animal studies have detected several metabolites in rat urine samples following very high oral doses of 5- and 6-APB (20 mg/kg, comparable to 3 mg/kg for a human adult (using the body surface area (BSA) normalization method; Reagan-Shaw et al., 2008)). The metabolism of 5- and 6-APB was comparable and involved hydroxylation of the furan ring, followed by ring cleavage and reduction of the resulting unsaturated aldehyde. The aldehyde was oxidized to carboxylic acid or reduced to alcohol, which was then hydroxylated. Phase II metabolism consisted of glucuronidation. In rats, the main metabolites of 5-APB and 6-APB were 3-carboxymethyl-4-hydroxy-amphetamine and 4-carboxymethyl-3-hydroxy-amphetamine respectively. In accordance, 3-carboxymethyl-4-hydroxy-amphetamine was the most abundant metabolite found following exposure of human hepatocytes to 5-APB (150 µM). Other detected metabolites included hydroxy-5-APB and hydroxy-dihydro-5-APB (Welter et al., 2015a, 2015b).

3.3.3. Pharmacodynamics: mechanism of action. Following 5-APB exposure (10 µM), vasoconstriction and increased DA brain levels were observed in *ex vivo* animal studies (Dawson et al., 2014). In addition, monoamine release was also observed *in vitro* following exposure to high levels of 5-APB and 6-APB (100 µM) (Rickli et al., 2015b), as well as inhibition of the reuptake of DA, 5-HT and NE (IC₅₀ < 7.0 µM). The reuptake of 5-HT and NE was most potently inhibited by both substances (IC₅₀ < 3.2 µM) (Monte et al., 1993; Rickli et al., 2015b) (see Table 2 for overview). On a receptor level, affinity has been reported for 5-HT receptors (5-HT_{2A}/5-HT_{2B}/5-HT_{2C}, K_i < 1 µM) and adrenoceptors (α_{2C}, K_i = 45 nM, α_{1A/2A} K_i < 10 µM) (Iversen et al., 2013; Dawson et al., 2014; Patent; Rickli et al., 2015b). Likely, these mechanisms also occur during recreational use, since low µM serum concentrations are reached (see Section 3.3.4).

3.3.4. Pharmacodynamics: clinical effects and toxicology. According to users, the effects of benzofurans are comparable with MDA and MDMA and are therefore used as stimulants or entactogens because of their euphoric and empathogenic effects (ACMD, 2013b). However, users have also reported multiple adverse effects, e.g., nausea, jaw and teeth clenching, dry mouth, dry eyes, insomnia, diarrhoea, sensitivity to light, palpitations, hot flushes, headache, drowsiness and clonus of the hands and feet. Also, psychological symptoms were reported, like visual and auditory hallucinations, depression, anxiety, panic attacks, insomnia, severe paranoia and psychosis. Furthermore, some users report an unpleasant 'come-down' that can exist for several days (Jebadurai et al., 2013; Chan

et al., 2013). The National Poisons Information Service in the UK has reported agitation, aggression, anxiety, insomnia, tachycardia, palpitations and hypertension as common clinical features after 6-APB exposure. Remarkably, clinical features persisted for more than 48 h in 53% of the cases (James et al., 2011). In addition, the DPIC has reported aggression, confusion, hallucinations, general discomfort and hypertension after benzofuran (5-APB/6-APB) exposure (Hondebrink et al., 2015).

Only 4 scientific reports on clinical effects following non-fatal human benzofuran exposures are available in the literature, which all reported severe clinical effects. The first case report is a very limited description of 7 patients who visited the ED following exposure to 2-APB, a structural analogue of 5-APB and 6-APB. Although exposure was not analytically confirmed, the patients developed tachycardia, hypertension and hyperpyrexia (ACMD, 2013a). The second case involved a 21-year old male who ingested 0.4 g 6-APB (confirmed in urine at 2 ng/L) and was admitted to hospital for 3 days (Chan et al., 2013). He developed agitation, but maintained a normal temperature, heart rate and blood pressure. Although he had no previous psychiatric history, he did develop severe psychiatric symptoms; i.e., self-harm, paranoid behaviour, psychosis and suicidal thoughts. Notably, 6 other substances were detected in urine, which could have contributed to the observed symptoms. The third report involved a 42-year old male who snorted 750 mg of benzofury (unknown which specific APB) and 500 mg of methoxetamine and consumed 1.5 L beer (Wood et al., 2012a,b). Serum levels of methoxetamine amounted up to 0.12 mg/L, whereas 5- or 6-APB were only measured qualitatively. The patient collapsed and developed a reduced consciousness (Glasgow Coma Scale of 6/15), tachycardia, hypertension and hyperthermia. All vital signs returned to normal within 2 h and the patient was discharged the same day. The fourth case report concerns a 40-year old man who was brought to the ED for severe psychomotor agitation, confusion and disorientation (Locatelli et al., 2013). At physical examination, severe agitation, mydriasis, profuse sweating, diffuse clonus, tachycardia and hyperthermia were observed. Initially, meningocephalitis/septicemia was suspected, but after awakening (12 h after admission) the patient admitted the regular consumption of 'benzofury'. Analysis of the product used revealed the presence of benzofurans and 4-methylethcathinone (4-MEC). In addition, benzofuran isomers were detected in blood (302 µg/L, ~2 µM) and urine (14.6 mg/L) (Table 2). Urine analysis was also positive for MDMA and amphetamine, but the chromatographic confirmation was negative for these substances. In addition to these 4 case reports, benzofuran blood levels of 0.11 and 0.14 mg/L (~0.6–0.8 µM) (Table 2) were determined in 2 DUID cases (Elliott and Evans, 2014).

In the UK, 5- and 6-APB have been implicated in several deaths since 2011 in which the presence of 5- or 6-APB was confirmed in post-mortem samples. However, often other substances were detected also, hampering attribution of death to 5- or 6-APB only (Clemente et al., 2012; Elliott and Evans, 2014). Post-mortem femoral blood concentrations of 5- or 6-APB in 10 cases ranged from 0.11 to 4.19 mg/L (~0.6–24 µM) (Table 2) (Elliott and Evans, 2014). An additional fatality, with analytically confirmed 5-APB exposure but without other relevant exposures, was recently reported in the United States. In this case, the post-mortem 5-APB femoral blood concentration was 2.5 mg/L (~14 µM) and the urine concentration was 23 mg/L (McIntyre et al., 2014) (Table 2). Finally, a case report was published, which describes a fatality in which 3-methyl-N-methylcathinone (3-MMC, 1.6 mg/L) and 5-APB (5.6 mg/L, ~32 µM) were detected in post-mortem blood samples (Adamowicz et al., 2014) (Table 2). In addition, an ethanol level of 1.4 g/L was measured antemortem. The 20-year old man involved experienced psychomotor agitation within minutes after exposure. At the hospital, his clinical course quickly deteriorated and tachycardia,

hypertension, tachypnea and seizures were reported. Cardiac arrest occurred and, despite intensive treatment, the patient died.

4. Discussion

2C-B, 4-FA and benzofurans are all phenethylamines, structurally related to common illicit drugs like amphetamine and MDMA. This resemblance is reflected in both the clinical course these NPS provoke as well as their mechanism of action. For example, 2C-B, 4-FA and benzofurans all increase DA, NE and 5-HT levels by inducing the release, preventing the breakdown or inhibiting the re-uptake of these neurotransmitters. As a result, exposure to 2C-B, 4-FA and benzofurans can result in a wide range of clinical effects, but typically include sympathomimetic symptoms like tachycardia, hypertension, hyperthermia, agitation, tremors and mydriasis. However, there are also remarkable differences between these NPS. Surprisingly, 2C-B and benzofurans have been reported to cause severe psychological effects such as hallucinations and psychosis, whilst this has not been described for 4-FA. In addition, while 5- and 6-APB have been implicated in more than 10 deaths, only one 4-FA-related and no 2C-B-related fatalities were reported in literature.

Fewer fatalities could indicate that exposure to 2C-B and 4-FA results in less severe toxic effects compared to benzofurans. However, a number of potential confounders could also contribute to a lower number of fatalities. First of all, the difference in the number of fatalities could also be due to differences in availability or analytical difficulties in the detection of these substances (Archer et al., 2011; Elliott and Evans, 2014; Helander et al., 2014). Secondly, factors such as mislabelling of drugs or the presence of multiple drugs in 1 tablet or powder (Zamengo et al., 2014) could play a role. However, recent studies have shown that there is a high degree of consistency (93%) between the self-reported use or product labelling of a certain NPS and the actual content in drug analysis (Bäckberg et al., 2015). Thirdly, concomitant exposures to other illicit substances or alcohol hamper an estimation of the severity of clinical effects. In fact, multiple-drug intoxications of NPS with other drugs or alcohol seem to occur frequently. For instance, in 9 out of 10 5-APB or 6-APB-related deaths, other illicit substances were detected (Clemente et al., 2012). Moreover, a survey amongst mephedrone users showed that only 14% of the respondents use mephedrone without other drugs or alcohol (Carhart-Harris et al., 2011). Forensic casework detected other drugs or alcohol in 84% of NPS cases (Elliott and Evans, 2014). Furthermore, 44% of the cases presenting at emergency departments in Sweden involved multiple-drug intoxications with more than one NPS, or a mixture of new and/or classic drugs being detected (Helander et al., 2013). Finally, variable effects may be seen as a result of interindividual differences due to genetic polymorphisms of enzymatic activity or medical conditions. For example, *in vitro* experiments using human hepatocytes revealed large interindividual differences in 2C-B cytotoxicity (1 mM, Carmo et al., 2005). As a result, specific individuals with a disadvantageous genetic profile may be at higher risk for 2C-B-induced toxicity. Differences in human susceptibility to the toxicity of other amphetamine-like designer drugs has been reported previously (Carmo et al., 2004; Tucker et al., 1994; Colado et al., 1995; Jones and Simpson, 1999; Malpass et al., 1999). Furthermore, comparable 5- or 6-APB concentrations were detected in deceased individuals and in DUID cases, indicating the importance of interindividual differences in response to a similar exposure. However, factors such as the time of sample collection, the stability of the drug, post-mortem redistribution, the cause of death and poly-drug use should also be considered when interpreting post-mortem concentrations (Elliott and Evans, 2014).

At present, no specific guidelines are available for the treatment of NPS intoxications. However, given the apparent pharmacological similarity of 2C-B, 4-FA and benzofurans to amphetamine and MDMA, clinicians can reasonably rely on the guidelines provided for intoxications with these drugs (Miotto et al., 2013; Ricaurte and McCann, 2005). Initial treatment should consist of stabilization of the patient, monitoring of vital functions, establishing vascular access, collecting blood and urine samples and observation in a calm environment until clinical effects decline. Symptomatic treatment may be necessary and includes sedation, fluid resuscitation and aggressive reduction of hyperthermia, preferably by submersion in ice water (Dean et al., 2013; Ricaurte and McCann, 2005; Miotto et al., 2013; Laskowski et al., 2015). Antipsychotics could be administered in case of severe psychotic events (Ambrose et al., 2010; Huang and Bai, 2011). All in all, treatment should be based on clinical effects instead of the specific NPS involved, i.e. treat the patient and not the poison, since interindividual differences and concomitant exposures can occur.

Since data on the health risks of the current generation of NPS is limited, *in vitro* research could aid in predicting clinical effects through insight in their mechanism of action. In fact, 4-FA and benzofurans, and possibly 2C-B, increase neurotransmitter levels and affect neurotransmitter receptors at concentrations also reported in intoxication cases. For example, 4-FA inhibited the reuptake of NE, DA and 5-HT at concentrations of 0.4, 0.8 and 7 μ M, respectively, while a concentration of $\sim$ 3 μ M was reported in two DUID patients (Nagai et al., 2007; Röhrich et al., 2012). Some mechanisms of action correlate well with the reported clinical effects, while others do not. For instance, increased DA and NE levels likely contribute to the development of sympathomimetic effects like tachycardia and hypertension (Carlsson, 1987). On the other hand, as 2C-B has strong hallucinogenic properties (Dean et al., 2013), it would be expected that 2C-B activates 5-HT_{2A} receptors. However, *in vitro* studies have shown that the activation of this receptor is strongly inhibited by 2C-B (Villalobos et al., 2004). Therefore, although *in vitro* assays could facilitate in predicting clinical effects of NPS, such assays should always be validated prior to their use in risk assessment, for example by comparing the assay outcomes to health effects that occur in exposed individuals.

The use of NPS is increasing, of which 2C-B, 4-FA and benzofurans are frequently detected NPS in drug monitoring systems. Limited information is available on the health effects following exposure to these substances and information is often confounded by difficulties in analytical detection, mislabelling of drugs, concomitant exposures and interindividual differences. Our review showed that clinical effects are comparable to more commonly used illicit drugs and therefore, treatment of NPS toxicity can be similar.

Collaboration efforts on a European level are already in place that monitor trends and prevalence of NPS use; e.g., the Early Warning System of the EMCDDA (EMCDDA, 2007). To monitor the health risks of NPS use, risk assessment of NPS newly entering the market could be performed by combining (*in vitro*) screening methods with data on clinical effects originating from poison centres and user fora. Combining information on the prevalence and potential health risks of NPS could aid in early legislation before published case reports become available. Therefore, international collaboration of scientific institutes performing (*in vitro/in vivo*) research as well as poison centres is important. As a result, NPS posing a risk for public health can be detected more quickly.

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Contributors

JJNL and LH designed the study, reviewed all available literature and wrote the first draft of the manuscript. JJNL, LH, TMB and AJHPR interpreted the data and all authors contributed substantially to the revision of the first draft. All authors have approved the final article.

Conflict of interest

No conflict declared.

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