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REVIEW ARTICLE

Trends of novel psychoactive substances (NPSs) and their fatal cases

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Abstract The abuse of novel psychoactive substances (NPSs) has been increasing dramatically since the late 2000s worldwide. Furthermore, variations of synthetic cannabinoids and other NPSs have been appearing in the market recently. The number of newly identified NPSs in 2013 was 42 in Singapore, 37 in Korea, and 23 in Indonesia. Even though the kinds and amounts of NPSs are increasing sharply, toxicological information regarding NPSs is not available and hard to obtain. When compared to classical controlled drugs, there are only a few fatal cases and a limited number of data in terms of metabolism and toxicity of NPSs. However there have been fatal cases of NPSs reported continuously in the USA, Europe, Japan and other countries, but not in Korea. Therefore, in this study, the fatal concentrations of NPSs have been reviewed through papers to predict the unexpected side effects or toxicological effects of NPSs. The blood concentrations of synthetic cannabinoids, synthetic cathinones and others in fatal cases are presented. JWH-018, JWH-073, MAM-2201, NNEI, MDPV, mephedrone, methylone, α-PVP, PV9, 25I-NBOMe, PMMA and methoxetamine were substances targeted. The fatal NPS cases will be of great help for forensic toxicologists in the research of the metabolism and toxicity of NPSs, and will also aid in establishing analytical methods for detecting NPSs in biological fluids.

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Keywords Novel psychoactive substances (NPSs) · Synthetic cannabinoids · Synthetic cathinones · Fatal cases · Blood concentrations

Introduction

Novel psychoactive substances (NPSs), also known as "legal highs" or "research chemicals", are a term used for synthetic materials or modified controlled drugs designed to evade existing regulations on narcotic drugs [1]. These substances include synthetic cannabinoids, synthetic cathinones, phenethylamines, piperazines, and tryptamines. With constant modification in chemical structure and rapid spread through the Internet, NPSs have become a serious social issue. Since the late 2000s, the abuse of synthetic cannabinoids, the most representative NPSs, has increased drastically throughout the world. To avoid regulations, NPSs are sold disguised as various herbal products through convenience stores, electronic cigarette stores and online. In terms of synthetic cannabinoids, the most common form found in Korea is JWH-018 and its variations. Since their first appearance in 2009, the spread of synthetic cannabinoids has been increasing in Korea [2].

Meanwhile, the recreational use of synthetic cathinones appeared in the USA since 2009. They are marketed to drug users as legal alternatives to methamphetamine, cocaine, and MDMA (3,4-methylenedioxymethamphetamine), packaged and sold as research chemicals, bath salts, jewelry cleaners, ice melters, hookah pipe cleaners or plant foods, labeled "not for human consumption". Synthetic cathinones include MDPV (3,4-methylenedioxypyrovalerone), mephedrone, methylone, α-PVP (α-pyrrolidinovalerophenone), pyrovalerone, etc. Drug users experience feelings of euphoria, alertness, talkativeness,

sexual arousal, and positivity 30–45 min after oral administration, and the effects last 1–3 h. The side effects include anxiety, insomnia, fatigue, mydriasis, agitation, aggression, combative behavior, panic, disorientation, confusion, memory loss, blackouts, myoclonus, excited delirium, paranoia, hallucinations, increased suicidal ideation, chest pain, and hypertension. According to the reports from hospital emergency rooms, synthetic cathinones users are often violent and out of control, showing paranoid behaviors and delusions [3]. Especially regarding "bath salts", the data reported by American Association of Poison Control Centers (AAPCC) has shown a drastic increase in abuse cases from 303 in 2010 to 6072 in 2011, indicating a critical situation in abuse [4]. Due to its constantly changing structure, the toxicological information on NPSs is not easy to obtain. When compared to the classical controlled drugs, there are a smaller number of fatal cases and a limited number of data in terms of metabolism and toxicity of NPSs. However there have been fatal cases of NPSs reported continuously in the USA, Europe, Japan and other countries, but not in Korea.

The purpose of this review is firstly to present the recent abuse trends of NPSs in Korea and other Asian countries and, secondly, to show their blood concentrations in fatal cases after substance intake together with the distribution of the concentrations in the human specimens. In addition, as many ass possible toxic symptoms before death are described. The target compounds in this review are JWH-018, JWH-073, MAM-2201, NNEI, MDPV, mephedrone, methylone, α-PVP, PV9, 25I-NBOMe, PMMA and methoxetamine.

Abuse trends

The 3rd generation synthetic cannabinoids

In response to physical toxicity and social problems of synthetic cannabinoids reported in 2009, many countries tried to regulate them with laws and prohibited their use. From 2009 to 2012, extensive variations of synthetic cannabinoids appeared and were abused. They are referred to as the 2nd generation synthetic cannabinoids, which are regulated by law.

In addition to new modified forms of synthetic cannabinoids that began to appear since 2013 to avoid regulations, unregulated substances have begun to appear. Because of their commercial use through electronic cigarettes and others, the abuse of such substances is now even more sophisticated. These substances are called the 3rd generation synthetic cannabinoids, a term first used in the report published by the Advisory Council on the Misuse of Drugs (ACMD) of United Kingdom in November 2014 [5].

Trends in Korea

The current situation of NPS identification in Korea is shown in Fig. 1. The number of NPSs identified by the National Forensic Service from 2009 to 2012 has steadily risen; synthetic cannabinoids were found at a considerable rate in them. A total of 37 kinds of NPSs were identified by the National Forensic Service in 2013 and, among them, 17 were synthetic cannabinoids, representing 46 % of total NPSs (Table 1).

Trends in Asian countries except Japan

NPSs identified from 2011 to 2013 according to the questionnaires conducted recently in nine Asian countries are indicated in Fig. 2. The nine surveyed countries were Korea, Singapore, Indonesia, Macau, Malaysia, Thailand, Brunei, Myanmar, and the Philippines. The number of identified NPSs in 2013 was 42 in Singapore, 37 in Korea, and 23 in Indonesia. Most countries showed annual increases in the number of NPSs identified.

Fatal case study

In 2014, the fatal cases caused by four types of NPSs from 2008 until now in Europe were reported [8]; 99 cases of synthetic cathinone MDPV (3,4-methylenedioxypyrovalerone), 20 of methoxetamine, 15 of synthetic opioid AH-7921, and 1 of substituted phenethylamine 25I-NBOMe. No fatal cases related to NPSs have been reported in Korea. Therefore, the fatal cases reported in foreign countries were investigated in this study.

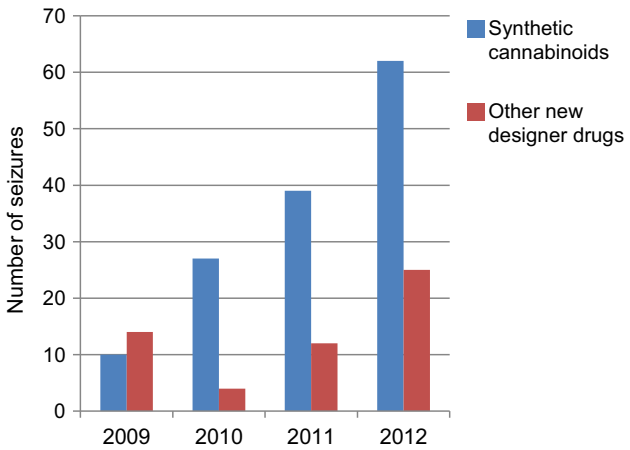

Fig. 1 Number of the seized novel psychoactive substances (NPSs) identified by the National Forensic Service during 2009–2012 [6]

Table 1 List of novel psychoactive substances (NPSs) identified by the National Forensic Service, 2013

Group (number of NPSs)	Name of NPSs
Synthetic cannabinoids (17)	JWH-203, AM-2201, UR-144, 5F-UR-144, MAM-2201, EAM-2201, APINACA, 5F-APINACA, AB-PINACA, 5F-AB-PINACA, STS-135, ADB-FUBINACA, PB-22, 5F-PB-22, FUB-PB-22, NNEI, 5F-NNEI
Synthetic cathinones (5)	α-PBP, α-PVT, FMC, MPHP, α-PHPP
Phenethylamines (4)	Methiopropamine, *N*,α-Diethylphenethylamine, 2C-B, 25I-NBOMe
Piperazines (2)	DBP, TFMPP
Tryptamines (2)	5-MeO-DALT, 5-MeO-MiPT
Others (7)	Ketamine, salvinorin A, psilocin, psilocibin, harmine, dimethyltryptamine, methoxetamine

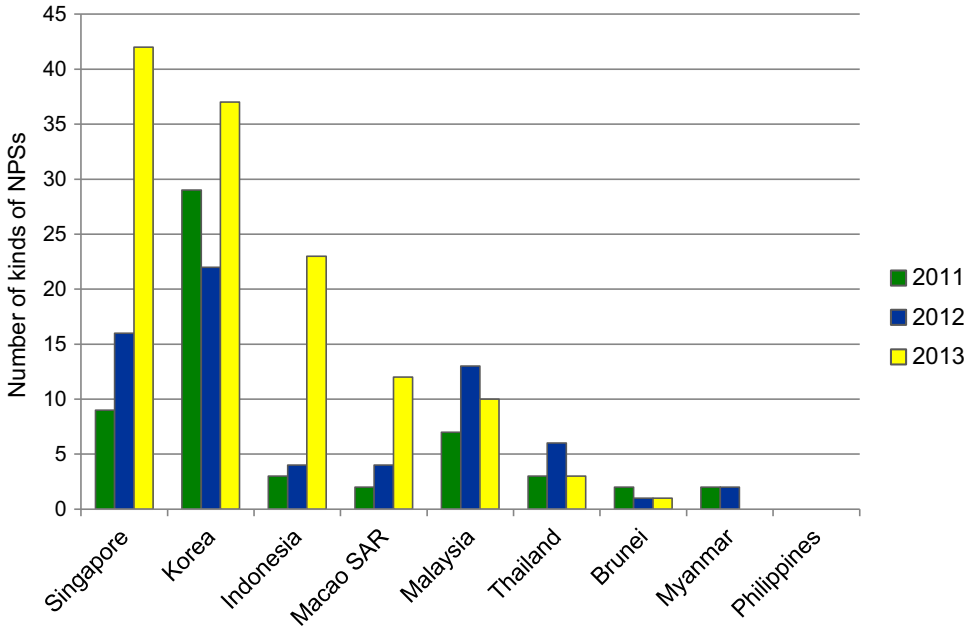

Fig. 2 Number of NPSs detected from 2011 to 2013 in nine Asian countries [7]

Synthetic cannabinoids

JWH-018 and JWH-073

Shanks et al. [9] developed the method of analyzing the concentrations of JWH-018 and JWH-073 in human blood using ultra-performance liquid chromatography–tandem mass spectrometry (UPLC–MS-MS), and applied its use in postmortem forensic cases. JWH-018 and/or JWH-073 were detected in 18 of 45 forensic cases, showing a 40 % detection rate. Concentrations ranged widely from 0.1–199 ng/mL (average, 17.5 ng/mL) for JWH-018 and 0.1–68.3 ng/mL (average 8.7 ng/mL) for JWH-073. In one case, the sample was obtained from a 57-year-old male who died in the emergency room after arrival. According to a witness, the man had smoked "spice". By autopsy, signs of an enlarged heart were noted and the heart blood concentration of JWH-018 was 199 ng/mL. In addition, clonazepam, 7-aminoclonazepam and methadone were detected in the blood, but these were later identified to be prescribed drugs.

MAM-2201

Saito et al. [10] analyzed MAM-2201 from the sample of a 59-year-old man who was found dead in his house. The MAM-2201 concentration in the whole blood was 12.4 ng/mL, and those in the liver, kidney, brain and the adipose tissue were 18.1, 11.2, 4.3 and 1535 ng/g, respectively. The authors also reported that it was the first case of a fatal MAM-2201 poisoning.

NNEI (N-1-naphthalenyl-1-pentyl-1H-indole-3-carboxamide)

Sasaki et al. [11] reported the acute fatal poisoning case of NNEI, which is an analog of JWH-018. A man aged in his 20s was found dead in his room with an herbal product labeled "fairy evolution" and a smoking device. NNEI was detected from the extract of the herbal product, and the concentrations of NNEI in whole blood of the victim were 0.64, 0.75, 0.84 and 0.99 ng/mL in the left atrium, right atrium, left femoral vein and right femoral vein, respectively. In addition, the NNEI concentration in the adipose tissue was 42.9 ng/g. NNEI was also detected in the victim's hair, which was 40 cm in length. By segmental analysis, NNEI was detected in all segments of hair with the highest concentration of 781 pg/mg at a 10–12 cm segment.

Multiple drugs

Hasegawa et al. [12] reported the fatal case of multiple drugs, including AB-CHMINACA and 5-fluoro-AMB, which are newly emerging synthetic cannabinoids, and diphenidine, a known NMDA receptor channel blocker, from the specimens of a dead body. The deceased man was 30 years old, found dead in his car. An opened herbal product package labeled "herbal incense". The "super lemon" and another small package of herbal blend without any label were found in the car. AB-CHMINACA, 5-fluoro-AMB, and diphenidine were identified from the herbal products through gas chromatography–mass spectrometry (GC–MS) and liquid chromatography–tandem mass spectrometry (LC–MS-MS) analysis. AB-CHMINACA was detected in various tissues of the victim, such as the brain, heart, lungs, adipose tissue, spleen, etc., and postmortem concentrations ranged from 7.55–38.9 ng/g. However, AB-CHMINACA was not detected in the blood or urine.

5-Fluoro-AMB was detected only in the adipose tissue at a concentration of 18.7 ng/g. Diphenidine was detected at high concentrations in all specimens, at 715 ng/mL in the femoral blood, and at an especially high concentration (11,100 ng/g) in adipose tissue. Similar to the MAM-2201 case mentioned previously, a high detection of an unchanged form of synthetic cannabinoid is likely to be found in adipose tissues due to the high lipophilicity and low concentration or lack of metabolizing enzymes within the tissues. The concentrations of synthetic cannabinoids in fatal cases are summarized in Table 2.

Synthetic cathinones

MDPV (3,4-methylenedioxypyrovalerone)

Marinetti et al. [3] reported that the MDPV concentrations in blood of 23 postmortem cases ranged 10–640 ng/mL (average, 109 ng/mL). High concentrations of synthetic cathinones do not indicate intoxication as the cause of death. Among the cases, the highest MDPV concentration at 640 ng/mL was found in a suicide case by hanging, whereas death by MDPV intoxication indicated a much lower concentration at 91 ng/mL. In one fatal case from a traffic accident, the methylone concentration in the blood was 729 ng/mL, which is relatively high. Synthetic cathinones were detected in other four fatal suicide cases as well. As mentioned in the introduction, such findings show an increase in suicidal tendencies as a side effect of synthetic cathinones.

According to the report by Wyman et al. [13], the deceased 39-year-old white male with a history of schizophrenia, depression, and drug abuse was found in an unresponsive state. He was on prescription drugs such as lamotrigine, fluoxetine, risperidone, trazodone, benztropine, hydroxyzine, metformin, temazepam, and simvastatin. According to his family, he had snorted "bath salts" before he was found. By autopsy, a mildly enlarged heart (430 g) and edematous lungs were observed. MDPV was detected in the femoral blood and heart blood at concentrations of 440 and 500 ng/mL, respectively, and the lungs, kidney, and liver showed relatively even distribution of MDPV at 600, 840 and 980 ng/g, respectively. Because synthetic cathinones such as MDPV are structurally similar to amphetamine, it inhibits the re-uptake of dopamine and norepinephrine by neurons. Therefore, vasoconstriction, hypertension and tachycardia occurr following MDPV consumption. Consequently, it was assumed that the 39-year-old male died due to cardiac arrhythmia caused by MDPV intoxication.

Murrray et al. [14] reported a fatal MDPV case of a 40-year-old male who injected and snorted "bath salts" containing MDPV. Pasin et al. [15] detected MDPV in the urine and blood of a male who died after taking "synthetic cocaine", which is known to contain MDPV. The results of the urine sample showed a substantially higher peak for MDPV, which suggested that it existed largely as the parent drug through urine. The concentration of MDPV in the blood was less than the level of quantification (LOQ; 0.05 mg/L).

Mephedrone (4-methoxymethcathinone)

Fatal mephedrone cases have been reported in many countries, indicating its extensive abuse worldwide. Wikstrom et al. [16] reported two fatal mephedrone cases from Sweden. The first case was of a 23-year-old male who arrived at the hospital unconscious with a body temperature of 42 °C. He died after 16 h. The mephedrone concentration in the antemortem blood sample was 13,200 ng/mL and that in the postmortem femoral blood was 8400 ng/mL.

Table 2 Concentrations of synthetic cannabinoids in fatal cases

Substance (number of cases)	Matrix	Result (ng/mL or ng/g)	Other substance(s) (ng/mL or ng/g)	Reference
JWH-018 (18)	Blood	0.1–199	JWH-073 (8 of 18 cases): 0.1–68.3	[9]
MAM-2201 (1)	Blood	12.4		[10]
	Liver	18.1		
	Kidney	11.2		
	Brain	4.3		
	Adipose tissue	1535		
NNEI (1)	Plasma			[11]
	Right atrium	0.92		
	Left atrium	0.77		
	Whole blood			
	Right atrium	0.75		
	Left atrium	0.64		
	Right femoral vein	0.99		
	Left femoral vein	0.84		
	Urine	ND		
	Brain	0.76		
	Heart muscle	0.82		
	Lung	1.06		
	Liver	1.31		
	Kidney	0.92		
	Adipose tissue	42.9		
AB-CHMINACA (1)	Femoral blood	<LOQ	Diphenidine: 715 ± 28.3	[12]
	Right heart blood	<LOQ	Diphenidine: 707 ± 62.9	
	Left heart blood	<LOQ	Diphenidine: 923 ± 62.8	
	Urine	<LOQ	Diphenidine: 376 ± 23.7	
	Brain	15.6 ± 0.39	Diphenidine: 1550 ± 49.1	
	Heart muscle	20.0 ± 3.00	Diphenidine: 2070 ± 73.5	
	Lung	8.02 ± 0.71	Diphenidine: 1600 ± 13.9	
	Liver	21.2 ± 1.30	Diphenidine: 2960 ± 34.0	
	Spleen	7.55 ± 0.18	Diphenidine: 1300 ± 31.9	
	Kidney	24.7 ± 1.63	Diphenidine: 2510 ± 32.9	
	Pancreas	38.9 ± 4.55	Diphenidine: 1910 ± 38.1	
	Adipose tissue	24.8 ± 2.48	Diphenidine: 11,100 ± 1120	
			5-Fluoro AMB: 18.7 ± 1.10	

ND not detected, *LOQ* limit of quantification

The second case was a 19-year-old male who was found unconscious in the bathtub of his house. He died upon arrival at the hospital. The mephedrone concentration in the blood was 9600 ng/mL and was also detected in the hair (up to 5 cm in length), suggesting a chronic intake of mephedrone over several months before death. Adamowicz et al. [17] reported a fatal case from Germany, in which the body of an approximately 30-year-old male was found with eight small bags containing white powder. GC–MS and high-performance liquid chromatography analysis identified the powder as mephedrone with the purity in the range of 80.4–87.3 %. The concentrations of mephedrone in the blood and vitreous humor were 5500 and 7100 ng/mL, respectively. Lusthof et al. [18] reported a case from the Netherlands of a 36-year-old male who died after being arrested and sent to a hospital for self-mutilation. Ninety-six green tablets and white powder were found in his house. During the autopsy, severe superficial skin lacerations, bruises and minor brain swelling were found, though these were not the cause of his death. A high concentration of mephedrone in the femoral blood (5100 ng/mL) and traces of cocaine, MDMA, and oxazepam were detected by toxicological analysis. Mephedrone was identified in the tablet (approximately 140 mg/tablet) and a trace amount of

cocaine was detected in the white powder. Conclusively, his cause of death was determined as mephedrone overdose, which probably led him to a state of excited delirium. Cosby et al. [19] reported fatal cases from Ireland from 2009 to 2010, among which mephedrone was detected in 12 cases. In two cases among them, the cause of death was confirmed as mephedrone intoxication, where the blood concentrations were 2100 and 1940 ng/mL.

A fatal case of multiple drugs mixed with mephedrone was also reported. Dickson et al. [20] reported a case of a 22-year-old male, in which 60 ng/mL of morphine was detected in the victim's blood, and 6-acetylmorphine, morphine, codeine, and doxylamine were detected in the urine. Mephedrone was also confirmed in the victim's blood and urine at 500 and 198,000 ng/mL, respectively. Through a subsequent investigation, it was found that he had taken "black tar" mixed with heroin and mephedrone. Moreover, Gerace et al. [21] reported a fatal case from Italy in which cocaine and mephedrone were detected. The mephedrone concentrations in the blood and urine of a 25-year-old male were 1330 and 144,000 ng/mL, respectively, along with detection of cocaine and cocaethylene.

Methylone

Cawrse et al. [22] reported four postmortem cases related to methylone: (case 1) a 19-year-old male collapsed at a gym and was sent to a hospital but died. The cause of his death was cardiac arrest associated with methylone; (case 2) a 38-year-old male was found dead on his bed with a gunshot wound to the head, which was the cause of death; (case 3) a 21-year-old female with a history of substance abuse drove a car into a river and died; (case 4) this case was related to case 2. A 35-year-old female was found dead with her boyfriend with a stab wound to the neck and a gunshot wound to the head, which was the cause of death (homicide). Methylone was detected in all four cases. In case 1, the methylone concentration in the femoral blood was 670 ng/mL and in cases 2, 3 and 4, methylone concentrations in the heart blood ranged from 60 to 1100 ng/mL. MDPV was also detected in cases 3 and 4, in which MDPV concentrations in the heart blood were 470 and 30 ng/mL respectively. Pearson et al. [23] reported three fatal cases due to methylone intoxication. In case 1, a 23-year-old male was arrested for screaming in public in the state of hallucination and transported to a hospital, where his body temperature was measured to be 41 °C. He showed symptoms of intoxication, such as rhabdomyolysis, acute renal failure, acute respiratory failure, fever, confusional state and seizure. He died from cardiac arrest approximately 24 h after admission. In case 2, a 19-year-old female took a pill named "Molly" and had a seizure. She was transported to a hospital but died. Her auxiliary temperature was 39.9 °C. In case 3, a witness stated that the 23-year-old male was tied to a chair for 3–4 h because of his excessive sweating, irrational and erratic behaviors. The victim was having a seizure when he was found, transported to a hospital but died after 45 min. The body temperature was 41.6 °C. By GC–MS analysis, methylone concentrations in the femoral blood of cases 1, 2, and 3 were 840, 3300 and 560 ng/mL, respectively. The cause of death for all three cases was methylone intoxication. Interestingly, all three cases had elevated body temperature from 39.9 to 41.6 °C. Pearson et al. [23] reported that other fatal cases of "bath salts" need to be investigated for elevated body temperature, as it may be an indicator of "bath salts" toxicity.

α-PVP (α-pyrrolidinovaleorophenone)

Saito et al. [24] analyzed α-PVP in blood using GC–MS and reported a fatal case of the substance. A 32-year-old male was observed being extremely excited and violent on top of a car. Three policemen suppressed him and transported him to a hospital, but he died after 22.5 h. Using GC–MS, 486 ng/mL of α-PVP was detected in the heart blood. Later, Hasegawa et al. [25] developed a new analytical method of analyzing α-PVP, as well as its metabolite OH-α-PVP using LC–MS-MS. This method was used to identify a fatal case relating to α-PVP. The police found a naked and agitated 41-year-old male upon arrival. After minor altercation, his sudden silence alerted the police and was transported to a hospital but was later pronounced dead. By autopsy, no serious injuries related to the death were found. Some subcutaneous hemorrhages were found but no damages were observed in the organs. No outstanding substances were detected through the general drug screening of the blood, however, α-PVP was detected in the victim's urine. By LC–MS-MS analysis, α-PVP and its metabolite OH-α-PVP were detected in body fluid and solid tissues, and the concentration of α-PVP in the femoral blood was 654 ng/ml. As shown in Table 3, the concentrations of α-PVP and OH-α-PVP in solid tissues were higher as compared to the concentration in the blood. Also, the α-PVP concentration in the heart blood was lower as compared to the femoral blood, suggesting postmortem diffusion of α-PVP and OH-α-PVP from the heart blood into the heart muscle.

PV9 (α-POP)

Hasegawa et al. [26] identified a new synthetic cathinone, PV9, in a biological specimen, and reported a fatal poisoning case. A couple purchased "aroma liquid" and "bath salts" at a suspicious drug shop, and although the amount taken is unknown, the female (18 years old) began shivering, went into convulsions, and became unconscious

Table 3 Concentrations of synthetic cathinones in fatal cases

Substance (number of cases)	Matrix	Result (ng/mL or ng/g)	Other substance(s) (ng/mL or ng/g)	Reference
MDPV (23)	Blood	10–640		[3]
MDPV (1)	Femoral blood	440		[13]
	Heart blood	500		
	Urine	>5000	Methylone: Pos	
	Gastric	>2000		
	Bile	880		
	Cerebrospinal fluid	410		
	Lung	600		
	Kidney	840		
	Liver	980		
	Skeletal muscle	560		
	Spleen	640		
	Brain			
	Parietal	360		
	Cerebellum	420		
	Lentiform nucleus	300		
	Frontal	300		
	Occipital	420		
	Medulla	420		
	Heart muscle	120		
	Hair	11.6	Methylone: 1.3 ng/mg	
MDPV (1)	Heart blood	1200	α-PBP: 200	[28]
Mephedrone (2)	Femoral blood	8400/9600		[16]
Mephedrone (1)	Blood	5500		[17]
	Vitreous humor	7100		
Mephedrone (1)	Femoral blood	5100	Cocaine, MDMA, oxazepam: trace	[18]
Mephedrone (2)	Blood	2100/1940		[19]
Mephedrone (1)	Blood	500	Morphine: 60	[20]
	Urine	198,000	6-Acetylmorphine, morphine, codeine, doxylamine: Pos	
Mephedrone (1)	Blood	1330	Cocaine, cocaethylene: Pos	[21]
	Urine	144,000		
Methylone (2)	Central blood	740/110		[22]
	Peripheral blood	670/NR		
	Urine	38,000/250		
	Liver	1800/550		
	Kidney	2300/260		
	Spleen	2100/NR		
	Bile	1800/520		
Methylone (2)	Heart blood	60/1100	MDPV: 470/30	[22]
	Liver	140/1300	MDPV: 530/ND	
	Kidney	160/910	MDPV: 490/ND	
	Bile	520/NR	MDPV: 580/ND	
	Urine	NR/220	MDPV: ND	
Methylone (3)	Peripheral blood	560–3300		[23]
α-PVP (1)	Blood	486		[24]

Table 3 continued

Substance (number of cases)	Matrix	Result (ng/mL or ng/g)	Other substance(s) (ng/mL or ng/g)	Reference
α-PVP (1)	Right heart blood	458 ± 20.0		[25]
	Left heart blood	442 ± 11.1		
	Femoral vein blood	654 ± 34.2		
	Urine	11,200 ± 1350		
	Stomach contents	1030 ± 92.6		
	Brain	518 ± 20.2		
	Lung	1070 ± 37.2		
	Heart muscle	1360 ± 11.2		
	Liver	681 ± 77.9		
	Kidney	1580 ± 87.1		
	Pancreas	1780 ± 70.4		
	Spleen	318 ± 19.1		
PV9 (1)	Femoral vein blood	180 ± 18.9		[26, 27]
	Brain	212 ± 11.9		
	Lung	337 ± 16.0		
	Heart muscle	258 ± 5.78		
	Liver	377 ± 10.1		
	Spleen	269 ± 5.57		
	Kidney	907 ± 19.5		
	Pancreas	628 ± 28.2		
	Skeletal muscle	686 ± 14.0		
	Adipose tissue	526 ± 20.0		

Pos positive, *NR* not recorded

immediately after taking the "aroma liquid". She was transferred to a hospital but died after 20 h. The consumed "aroma liquid" was identified as PV9 by GC–MS, and using LC–MS-MS, the PV9 concentration in antemortem blood was found to be 45.7 ng/mL and that of the postmortem femoral blood was 180 ng/mL. In addition, in a recent publication, Hasegawa et al. [27] quantitated PV9 in solid tissues of the victim. The highest concentration of PV9 was observed in the kidney (907 ng/g), followed by skeletal muscles (686 ng/g), pancreas (628 ng/g), adipose tissue (526 ng/g), liver (377 ng/g), lung (337 ng/g), spleen (269 ng/g), heart (258 ng/g), and brain (212 ng/g). The concentrations in all nine tissues were higher than that of postmortem femoral blood, suggesting the usefulness of tissue analysis in determining the cause of death regarding PV9 (Table 3).

Multiple drugs

Namera et al. [28] detected MDPV, α-PVP and α-PBP (α-pyrrolidinobutiophenone) in blood and hair of a 35-year-old female. The quantitative analysis of heart blood showed concentrations of MDPV and α-PBP at 1200 and 200 ng/mL, respectively. By segmental analysis (10 mm) of the hair, both MDPV and α-PVP were detected. MDPV was detected in hair segments up to 10 cm in length with the highest concentration in the 1–2 cm segment (22 ng/10 mm hair), α-PVP was detected in segments up to 5 cm, and α-PBP was detected in the 0–1 cm segment (less than 0.05 ng), indicating long-term abuse of MDPV and α-PVP. The concentrations of synthetic cathinones in fatal cases are summarized in Table 3.

Phenethylamines

25I-NBOMe[2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-mehoxyphenyl)methyl]ethanamine]

Poklis et al. [29] reported a fatal case of 25I-NBOMe, a "2C" class designer drug. A healthy 19-year-old male ingested blotter paper infused with "acid" the day before his death. His body was found near the swimming pool of his apartment complex. According to his friends, he had behaved abnormally that night and the police assumed his death from falling from his apartment balcony. The autopsy revealed no special causes other than organ damages and fractures caused by the fall. Toxicological analysis of the victim's specimen revealed 25I-NBOMe, and concentrations were

Table 4 Concentrations of phenethylamines in fatal cases

Substance (number of cases)	Matrix	Result (ng/mL or ng/g)	Other substance (ng/mL or ng/g)	Reference
25I-NBOMe (1)	Heart blood	0.41		[29]
	Peripheral blood	0.40		
	Urine	2.86		
	Vitreous humor	0.099		
	Brain	2.78		
	Liver	5.64		
	Bile	12.1		
PMMA only (12)	Peripheral blood	170–3300	PMA: ND–260	[30]
			MA: ND–3580	
			AM: ND–3110	

PMA paramethoxyamphetamine, *MA* methamphetamine, *AM* amphetamine

Table 5 Concentrations of methoxetamine in a fatal case

Substance (number of cases)	Matrix	Result (ng/ml or ng/g)	Other substance (ng/ml or ng/g)	Reference
Methoxetamine (1)	Femoral blood	8600	Venlafaxine: 300	[31]
			Tetrahydrocannabinol: 1	
			AM-694: 0.09	
			AM-2201: 0.3	
			JWH-018: 0.05	

calculated using a direct quantification method; 0.41 ng/mL in heart blood, 0.40 ng/mL in peripheral blood, 2.86 ng/mL in urine, 0.099 ng/mL in vitreous humor, 2.78 ng/g in the brain, 5.64 ng/g in the liver, and 12.1 ng/g in bile. It was determined that the victim had hallucinated by taking 25I-NBOMe, which had contributed to his fall (Table 4).

PMMA (paramethoxymethamphetamine)

Vevelstad et al. [30] reported 12 fatal intoxications related to PMMA in Norway during a 6-month period (July 2010–January 2011). PMMA is the 4-methoxy analogue of methamphetamine, and PMA (paramethoxyamphetamine), its toxic metabolite, is the 4-methoxy analogue of amphetamine. In the 12 PMMA fatal cases, the mean concentrations of PMMA and PMA were 2020 ng/mL (range 170–3300 ng/mL) and 90 ng/mL (range not detected–260 ng/mL), respectively. The concentrations of phenethylamines in fatal cases are summarized in Table 4.

Other

Methoxetamine [2-(3-methoxyphenyl)-2-(ethylamino)-cyclohexanone]

Wikstrom et al. [31] reported a fatal case of methoxetamine, a new recreational drug with a similar structure to ketamine. A 26-year-old male with a history of drug abuse and depression was found dead with some plastic bags labeled "2-(3-methoxyphenyl)-2-(ethylamino)-cyclohexanone" and "haze". In the analysis, a considerably higher concentration of methoxetamine at 8600 ng/mL was detected in the femoral blood. In addition, a therapeutic concentration of venlafaxine at 300 ng/mL was also detected. Even though traces of synthetic cannabinoids (tetrahydrocannabinol, AM-694, AM-2201 and JWH-018) were also detected, the cause of death was acute fatal intoxication of methoxetamine (Table 5).

Conclusions

This study examined the recent trend of NPSs and reviewed fatal cases of NPSs. Since the late 2000s, NPS abuse has been rapidly increasing in Asian countries with newly synthesized NPSs showing up every year. Due to the variety and evolution of NPSs, it is necessary to identify their structures and develop analytical methods for detection in biological specimens. In addition, the lack of clinical studies on the effects and toxicity of these substances has caused difficulties in interpretation of toxicological findings. Although no fatal cases of NPSs have been reported in Korea, the number of cases in the USA, Europe, and Japan are extensive in each country. Through this

article, fatal cases of synthetic cannabinoids, synthetic cathinones, phenethylamines and methoxetamine were reviewed. The number of reported fatal cases is still limited as compared to the classical controlled drugs and lack studies regarding metabolism and toxicity. However, reported fatal NPS case studies will be useful for forensic toxicologists to understand the characteristic symptoms (or behaviors) developed by substances of abuse. Furthermore, a reference of case studies will assist research and enhance understanding of the metabolism and toxicity of NPSs to be emerging in the near future.

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Compliance with ethical standards

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. National Forensic Service (2014) Special report. The type of new psychoactive substances abused in Korea: case report and recent trend. National Forensic Service, Seoul, pp 6–7
2. Kim E (2014) Understanding of drug analysis in hair (in Korean). Design MIP, Seoul
3. Marinetti LJ, Antonides HM (2013) Analysis of synthetic cathinones commonly found in bath salts in human performance and postmortem toxicology: method development, drug distribution and interpretation of results. J Anal Toxicol 37:135–146
4. Bronstein AC, Spyker DA, Cantilena LR, Rumack BH, Dart RC (2012) 2011 annual report of the American Association of Poison Control Centers' national Poison Data System (NPDS): 29th Annual report. Clin Toxicol 50(10):911–1164. https://aapcc.s3.amazonaws.com/pdfs/annual_reports/2011_NPDS_Annual_Report_-_Final.pdf. Accessed 25 Feb 2015
5. ACMD (Advisory Council on the Misuse of Drug) (2015) ACMD's report on 'third generation' synthetic cannabinoids. https://www.gov.uk/government/publications/third-generation-synthetic-cannabinoids. Accessed 15 Jan 2015
6. Chung H (2013) New designer drugs seized in Korea; forensic identifications by NFS during 2009–2012. Annu Rep NFS 45:166–177
7. Yap A (2014) Traditional drugs and NPS abuse in Asia. 5th AFSN meeting, Oct 12–18, Seoul
8. EMCDDA (2014) European drug report 2014: trends and developments. http://www.emcdda.europa.eu/publications/edr/trends-developments/2014. Accessed 20 Jan 2015
9. Shanks KG, Dahn T, Terrell AR (2012) Detection of JWH-018 and JWH-073 by UPLC–MS-MS in postmortem whole blood casework. J Anal Toxicol 36:145–152
10. Saito T, Namera A, Miura N, Ohta S, Miyazaki S, Osawa M, Inokuchi S (2013) A fatal case of MAM-2201 poisoning. Forensic Toxicol 31:333–337
11. Sasaki C, Saito T, Shinozuka T, Irie W, Murakami C, Maeda K, Nakamaru N, Oishi M, Nakamura S, Kurihara K (2015) A case of death caused by abuse of a synthetic cannabinoid *N*-1-naphthalenyl-1-pentyl-1*H*-indole-3-carboxamide. Forensic Toxicol 33:165–169
12. Hasegawa K, Wurita A, Minakata K, Gonmori K, Nozawa H, Yamagishi I, Watanabe K, Suzuku O (2015) Postmortem distribution of AB-CHMINACA, 5-fluoro-AMB, and diphenidine in body fluids and solid tissues in a fatal poisoning case: usefulness of adipose tissue for detection of the drugs in unchanged forms. Forensic Toxicol 33:45–53
13. Wyman JF, Lavins ES, Engelhart D, Armstrong EJ, Snell KD, Boggs PD, Taylor SM, Norris RN, Miller FP (2013) Postmortem tissue distribution of MDPV following lethal intoxication by "bath salts". J Anal Toxicol 37:182–185
14. Murray BL, Murphy CM, Beuhler MC (2012) Death following recreational use of designer drug "bath salts" containing 3,4-methylenedioxypyrovalerone (MDPV). J Med Toxicol 8:69–75
15. Pasin D, Bidney S, Fu S (2015) Analysis of new designer drugs in post-mortem blood using high-resolution mass spectrometry. J Anal Toxicol 39:163–171
16. Wikstrom M, Thelander G, Nystrom I, Kronstrand R (2010) Two fatal intoxications with the new designer drug mephedrone (4-methoxymethcathinone). J Anal Toxicol 34:594–598
17. Adamowicz P, Tokarczyk B, Stanaszek R, Slopianka M (2013) Fatal mephedrone intoxication-a case report. J Anal Toxicol 37:37–42
18. Lusthof KJ, Oosting R, Maes A, Verschraagen M, Dijkhuizen A, Sprong AGA (2011) A case of extreme agitation and death after the use of mephedrone in The Netherlands. Forensic Sci Int 206:e93–e95
19. Cosby S, Peters KL, Quinn A, Bentley A (2013) Mephedrone (methylmethcathinone) in toxicology casework: a Northern Ireland perspective. J Anal Toxicol 37:74–82
20. Dickson AJ, Vorce SP, Levine B, Past MR (2010) Multiple-drug toxicity caused by the coadministration of 4-methylmethcathinone (mephedrone) and heroin. J Anal Toxicol 34:162–168
21. Gerace E, Petrarulo M, Bison F, Salomone A, Vincenti M (2014) Toxicological findings in a fatal multidrug intoxication involving mephedrone. Forensic Sci Int 243:68–73
22. Cawrse BM, Levine B, Jufer RA, Fowler DR, Vorce SP, Dickson AJ, Holler JM (2012) Distribution of methylone in four postmortem cases. J Anal Toxicol 36:434–439
23. Pearson JM, Hargraves TL, Hair LS, Massucci CJ, Frazee CC, Garg U, Pietak BR (2012) Three fatal intoxications due to methylone. J Anal Toxicol 36:444–451
24. Saito T, Namera A, Osawa M, Aoki H, Inokuchi S (2013) SPME–GC–MS analysis of α-pyrrolidinovalerophenone in blood in a fatal poisoning case. Forensic Toxicol 31:328–332
25. Hasegawa K, Suzuki O, Wurita A, Minakata K, Yamagishi I, Nozawa H, Gonmori K, Watanabe K (2014) Postmortem distribution of α-pyrrolidinovalerophenone and its metabolite in body fluids and solid tissues in a fatal poisoning case measured by LC–MS-MS with the standard addition method. Forensic Toxicol 32:225–234
26. Hasegawa K, Wurita A, Minakata K, Gonmori K, Nozawa H, Yamagishi I, Suzuki O, Watanabe K (2014) Identification and quantitation of a new cathinone designer drug PV9 in an "aroma liquid" product, antemortem whole blood and urine specimens, and a postmortem whole blood specimen in a fatal poisoning case. Forensic Toxicol 32:243–250
27. Hasegawa K, Wurita A, Minakata K, Gonmori K, Nozawa H, Yamagishi I, Watanabe K, Suzuki O (2015) Postmortem distribution of PV9, a new cathinone derivative, in human solid tissues in a fatal poisoning case. Forensic Toxicol 33:141–147
28. Namera A, Urabe S, Saito T, Torikoshi-Hatano A, Shiraishi H, Arima Y, Nagao M (2013) A fatal case of 3,4-methylenedioxypyrovalerone poisoning: coexistence of α-pyrrolidinobutiophenone and α-pyrrolidinovelerophenone in blood and/or hair. Forensic Toxicol 31:338–343

29. Poklis JL, Devers KG, Arbefeville EF, Pearson JM, Houston E, Poklis A (2014) Postmortem detection of 25I-NBOMe [2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-mehoxyphenyl)methyl]ethanamine] in fluids and tissues determined by high performance liquid chromatography with tandem mass spectrometry from a traumatic death. Forensic Sci Int 234:e14–e20
30. Vevelstad M, Øiestad EL, Middelkoop G, Hasvold I, Lilleng P, Delaveris GJM, Eggen T, Mørland J, Arnesta M (2012) The PMMA epidermic in Norway: comparison of fatal and non-fatal intoxications. Forensic Sci Int 219:151–157
31. Wikstrom M, Thelander G, Dahlgren M, Kronstrand R (2013) An accidental fatal intoxication with methoxetamine. J Anal Toxicol 37:43–46