time, while no remarkable difference of FLI between the both reaction temperatures was observed. Therefore the following experiments were done at room temperature for 30 min.

To remove the excess reagent and interfering components derived from plasma, clean-up with an SPE cartridge (Varian Bond Elut® C_{18}) was introduced. The volume of CH_3CN for elution of labels was examined. In the range of 200–1000 µL, more than 500 µL of CH_3CN gave the maximum and constant FLI. The extraction recoveries of both DIB labels calculated on the peak height ratios with standards obtained with or without SPE were ca. 80%.

HPLC conditions

Owing to the remarkable difference in the chromatographic behaviors of both compounds on a reversed-phase column, their satisfactory separation from the interfering peaks within acceptable analysis time could not be obtained by an isocratic elution. Thus, a gradient elution was required in all previous methods (Vorce *et al.*, 2008; Elliott and Smith, 2008). We also used a gradient elution with the combination of 0.1 M acetate buffer (pH 3.5; MP 1) and CH_3CN (MP 2) and a good separation of DIB labels without interference of peaks from reagent and plasma components could be achieved (Fig. 1). The retention times of DIB-BZP and -TFMPP labels were 9.1 and 12.3 min, respectively. Total running time including washing and equilibration steps after eluting of DIB-TFMPP was *ca* 25 min.

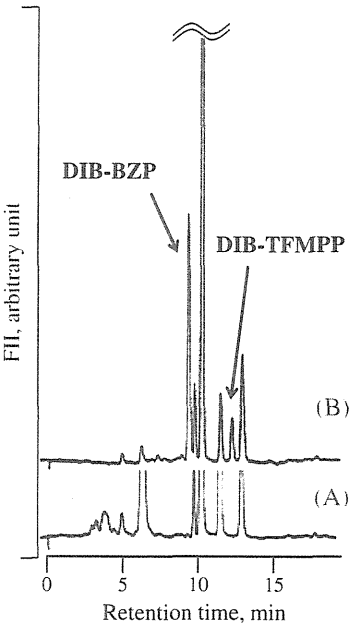

Figure 1. Chromatograms of rat plasma (A) and that obtained after 60 min of co-administration of BZP and TFMPP (B).

Method validation

Calibration curves obtained with a spiked plasma showed good linearities in the ranges of 25–1000 ng/mL for BZP ($r = 0.997$) and 50–2000 ng/mL for TFMPP ($r = 0.999$). The LODs of BZP and TFMPP were 0.9 ng/mL (20.4 fmol on column) and 4.6 ng/mL (69.0 fmol on column), respectively. The LOQs were 3.0 (BZP) and 15.2 ng/mL (TFMPP).

Accuracy, intra- and inter-day precisions of the proposed method were evaluated by analyzing plasma spiked with known concentrations of BZP (50 and 500 ng/mL) and TFMPP (100 and 1000 ng/mL), as shown in Table 1. Accuracy in the range of 94.4 ± 3.7 to 109.4 ± 5.3% was obtained. The intra-day precisions (relative standard deviations, RSDs) for BZP and TFMPP were 4.8% (50 ng/mL) and 3.7% (500 ng/mL), and 4.5% (100 ng/mL) and 4.4% (1000 ng/mL), respectively. Inter-day precisions (RSDs) of 6.3% (50 ng/mL) and 4.8% (500 ng/mL) for BZP were obtained, while those for TFMPP were 9.1% (100 ng/mL) and 7.6% (1000 ng/mL). These parameters of the proposed method were acceptable for the precise analyses of these compounds. However, recoveries of BZP and TFMPP were 37.9 and 49.8%, respectively. The reason for these low recoveries might be the low extraction yield of both compounds from the plasma matrix, because remarkable loss of DIB labels was not observed in the SPE procedure (extraction yield *ca* 80%). Little information on the recovery of BZP and TFMPP in plasma could be found in previous reports. Anyway, the simultaneous monitoring of both compounds after administration was demonstrated with such low recoveries.

The sensitivity of the proposed method was higher than that of HPLC-UV (312 ng/mL for BZP and 20 ng/mL for TFMPP; Elliott and Smith, 2008) and comparable to that of GC-MS methods (5 ng/mL for both substances; Peters *et al.*, 2003). The proposed method has the merit that the plasma volume required for measurement (20 µL) was smaller than those of HPLC-UV (500 µL; Elliott and Smith, 2008) and LC-MS (100 µL; Antia *et al.*, 2009a).

Monitoring of BZP and TFMPP after their sole or co-administration to rats

Furthermore, the proposed method was applied to monitor BZP and TFMPP concentration after a single sole or co-administration of BZP and/or TFMPP to rats. The dose for sole administration of BZP and TFMPP was 2 mg/kg, and 2 mg/kg each of dose was combined for co-administration. The dose used in this study may

Table 1. Accuracy, intra- and inter-day assay precision and recovery

Analyte	Spiked concentration (ng/mL)	Accuracy (%)[a]	Precision (RSD)%		Recovery (%)
			Intra-day	Inter-day	
BZP	50	109.4 ± 5.3	4.8	6.3	37.9
	500	99.4 ± 3.7	3.7	4.8	
TFMPP	100	103.3 ± 4.6	4.5	9.1	49.8
	1000	99.8 ± 4.4	4.4	7.6	

[a] Data presented as means ± SD ($n = 5$).

be suitable because the maximum dose of the BZP abuser in a previous report corresponded to 5 mg/kg (Tsutsumi *et al.*, 2006). The concentration–time profiles of BZP and TFMPP are shown in Fig. 2. The concentrations of BZP after sole administration in plasma were comparable to those of co-administration of BZP and TFMPP, whereas the TFMPP concentrations after co-administration trended to be higher than those after sole administration (AUC_{0-360}, mg·min/L: 51 ± 17 vs 71 ± 13, $P = 0.192$). By using the proposed method, BZP and TFMPP could be monitored at least 480 min after administration.

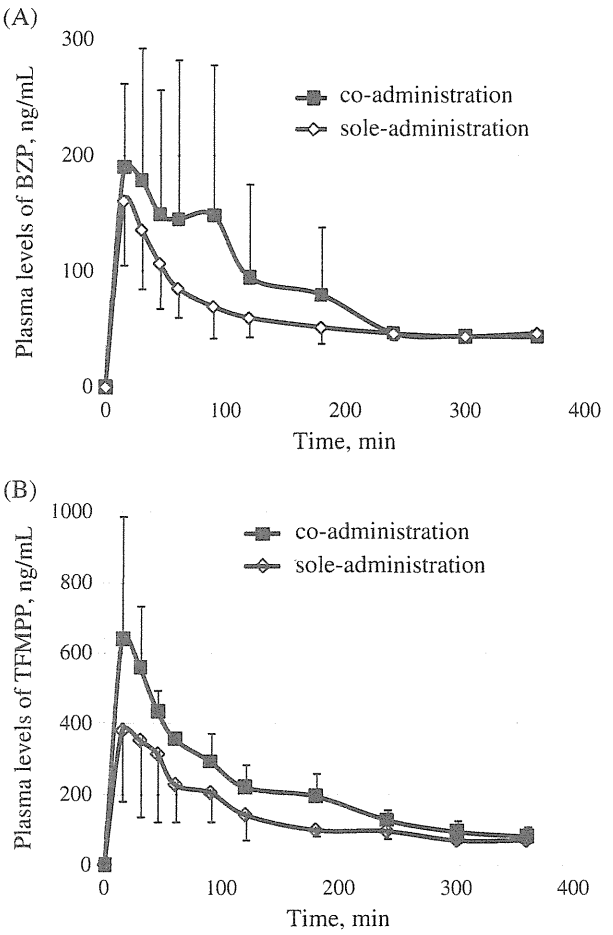

Figure 2. BZP (A) and TFMPP (B) level-time profiles in plasma after sole or co-administration of BZP and TFMPP to rats ($n = 3$).

The calculated pharmacokinetic parameters of BZP and TFMPP are summarized in Table 2. A significant difference in pharmacokinetic parameters of TFMPP (CL of TFMPP, L/min: 0.009 ± 0.001 vs 0.005 ± 0.002, $P = 0.047$) was found. Little useful information to compare with our results was available. Antia *et al.* studied on pharmacokinetics of BZP and TFMPP after their co-administration to humans (Antia *et al.*, 2009b). Metabolic profiles of both compounds were altered by co-administration. Changes to some pharmacokinetics of TFMPP were also noted and this agreed well with our result, although the dose ratio of BZP and TFMPP used, 3.3:1.0 (Antia *et al.*, 2009b), was different from ours (1:1). The metabolic pathway of each drug in rat was studied. BZP was not extensively metabolized and was mainly excreted as the unchanged parent compound (Staack *et al.*, 2002). In contrast to BZP, TFMPP was extensively metabolized and almost all excreted as metabolites (Staack and Maurer, 2005). So if the interaction of BZP and TFMPP occurred in the metabolic process, the pharmacokinetic parameter of TFMPP might be changed easily. The mechanism of interactions between BZP and TFMPP cannot be elucidated from the results obtained in this study because of the limitations of the study conditions: the dose (and dose ratio) of BZP and TFMPP were fixed and their metabolites were not considered.

Conclusions

The proposed HPLC-FL method with DIB labeling was useful for simultaneous determination of BZP and TFMPP in rat plasma. Using fluorescence labeling, SPE for a clean-up step and a gradient elution, sensitive and selective determination of these compounds was achieved. The obtained validation parameters of BZP and TFMPP in plasma were acceptable. Furthermore, this method could be successfully applied to monitor these compounds after a single sole or co- administration to rat. Under the conditions used, significant differences in

Table 2. Pharmacokinetic parameters of BZP and TFMPP

Pharmacokinetic parameter	Sole-administration, mean ± SD ($n = 3$)	Co-administration, mean ± SD ($n = 3$)
BZP		
K (min^{-1})	0.0037 ± 0.0016	0.0034 ± 0.0010
$T_{1/2}$ (min)	219 ± 108	222 ± 82
V (L)	5.1 ± 2.1	4.6 ± 2.7
Cl (L/min)	0.017 ± 0.0038	0.014 ± 0.0059
AUC_{0-360} (mg·min/L)	22 ± 5.1	27 ± 11
TFMPP		
K (min^{-1})	0.0061 ± 0.0039	0.0047 ± 0.0039
$T_{1/2}$ (min)	147 ± 78	237 ± 216
V (L)	2.0 ± 1.3	1.2 ± 0.34
Cl (L/min)	0.009 ± 0.001	0.005 ± 0.002*
AUC_{0-360} (mg·min/L)	51 ± 17	71 ± 13

* $P < 0.05$ (Student's *t*-test).

pharmacokinetic parameters of TFMPP could be found by their co-administration. From the results, the proposed method is sensitive and reliable, and thus might be suitable for studies in forensic toxicology and pharmaceutical sciences.

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Changes in the prevalence of new psychoactive substances before and after the introduction of the generic scheduling of synthetic cannabinoids in Japan

Ruri Kikura-Hanajiri,* Nahoko Uchiyama, Maiko Kawamura and Yukihiro Goda

To counter the spread of the many analogues of psychoactive substances, the Pharmaceutical Affairs Law in Japan was amended in 2006 to establish a new category – Designated Substances – in order to more promptly control these drugs. As of March 2013, 106 substances (including one plant, *Salvia divinorum*) were listed in the category of Designated Substances, and 13 of them had had their category changed from Designated Substances into the much stricter category, Narcotics. However, new analogues of controlled substances, especially synthetic cannabinoids, appeared one-by-one since the new category was introduced. To avoid a cat-and-mouse game between regulators and illicit drug manufacturers, a comprehensive system (generic scheduling) for designating naphthoylindole-type synthetic cannabinoids, with particular substituents, was introduced into the Designated Substances in 2013. Since late 2012, the naphthoylindole-type compounds have been gradually replaced by other types of synthetic cannabinoids, such as cyclopropylmethanones, cannabimimetic carboxamide derivatives, adamanthoyl indoles, and cannabimimetic quinolinyl carboxylates. After the enforcement of the generic scheduling for designating naphthoylindoles in March 2013, these naphthoylindoles have been completely replaced by other types and have rarely been detected in the products. New types of psychoactive substances, including opioid receptor agonists (e.g. AH-7921, MT-45), hallucinogenic phenethylamines (e.g. NBOMe-type compounds), and thiophene derivatives (e.g. methiopropamine, α-PVT) have also appeared. The almost infinite possibilities of altered structures of chemicals make it difficult to carry out effective and exhaustive scheduling. To prevent the widespread distribution and abuse of these new psychoactive substances, continuous and dedicated monitoring for the emergence of these substances is necessary.

Keywords: new psychoactive substances; synthetic cannabinoids; generic scheduling

Introduction

A wide variety of new psychotropic substances has emerged around the world over the past few years. The United Nations Office on Drugs and Crime (UNODC) reported that the number of new psychoactive substances reported to the UNODC rose from 166 at the end of 2009, to 251 by mid-2012, an increase of more than 50%.[1,2] Among these psychoactive substances, synthetic cannabinoid CB_1/CB_2 receptor agonists (synthetic cannabinoids), phenethylamines and cathinone derivatives are major classes of abused drugs.[1,2]

In particular, products of herbal smoking mixtures containing synthetic cannabinoids have been widely distributed since at least 2006, and new analogues appeared on the illegal drug market. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported that the number of synthetic cannabinoids detected by the EU Early Warning System (EWS) for new psychoactive substances has been increasing, with a total of 84 synthetic cannabinoids reported to the EMCDDA as of May 2013.[3,4] To counter the spread of these many analogues of psychoactive substances, some countries have been innovative in introducing new legislation.

In Japan, the Pharmaceutical Affairs Law was amended in 2006 to establish a new category – Designated Substances. Additionally, a comprehensive system (generic scheduling) for designating naphthoylindole-type synthetic cannabinoids, with particular substituents (Figure 1), was introduced into the Designated Substances category in March 2013.

We have been conducting an ongoing survey of new psychoactive substances on the Japanese illegal drug market since 2004.[5–36] With a focus on synthetic cannabinoids, we have obtained more than 1300 products sold via the Internet as 'legal herbs' or 'incense' for their expected cannabis-like effects since 2009.[20,23–36] We have also investigated many newly emerged substances (Table 1). As of March 2013, at least 59 types of synthetic cannabinoids have been identified through our survey. In this report, we describe the changes in the prevalence of new psychoactive substances and their legal status on the basis of our survey from 2009 to 2013, especially the changes before and after the introduction of the 2013 generic scheduling of synthetic cannabinoids in Japan.

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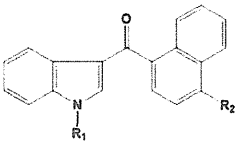
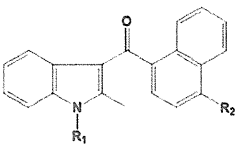
1) 3-(1-Naphthoyl)indole



R_1	*n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17} -CH=CHCH$_2$CH$_2$CH$_3$, -CH$_2$CH=CHCH$_2$CH$_3$, -CH$_2$CH$_2$CH=CHCH$_3$, -CH$_2$CH$_2$CH$_2$CH=CH$_2$ -(*n*-C_3H_6)X, -(*n*-C_4H_8)X, -(*n*-C_5H_{10})X [X=F, Cl, Br, I, CN, OH, OCOCH$_3$]
R_2	H, CH$_3$, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13} -OCH$_3$, -OC$_2$H$_5$ F, Cl, Br, I

Excluding the following substances and their salts;
(4-ethoxynaphthalen-1-yl)(1-octyl-1H-indol-3-yl)methanone,
(1-heptyl-1H-indol-3-yl) (4-hexylnaphthalen-1-yl)methanone,
(4-hexylnaphthalen-1-yl)(1-octyl-1H-indol-3-yl)methanone,
(4-methoxynaphthalen-1-yl)(1-octyl-1H-indol-3-yl)methanone,
1-naphthalenyl(1-pentyl-1H-indol-3-yl)methanone and
(1-octyl-1H-indol-3-yl)(4-pentylnaphthalen-1-yl)methanone.

2) 2-Methyl-3-(1-naphthoyl)indole



R_1	*n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15} (In case of [R_2=*n*-C_6H_{13}], limited to *n*-C_3H_7, *n*-C_4H_9) *n*-C_8H_{17} (Only where R_2 is C_2H_5 or *n*-C_3H_7) -CH=CHCH$_2$CH$_2$CH$_3$, -CH$_2$CH=CHCH$_2$CH$_3$, -CH$_2$CH$_2$CH=CHCH$_3$, -CH$_2$CH$_2$CH$_2$CH=CH$_2$ (Except [R_2=*n*-C_6H_{13}]) -(*n*-C_3H_6)X, -(*n*-C_4H_8)X, -(*n*-C_5H_{10})X (In case of [R_2=*n*-C_6H_{13}], limited to -(*n*-C_3H_6)X, -(*n*-C_4H_8)X) [X=F, Cl, Br, I, CN, OH, OCOCH$_3$]
R_2	H, CH$_3$, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13} -OCH$_3$, -OC$_2$H$_5$ F, Cl, Br, I

Except (2-methyl-1-heptyl-1H-indol-3-yl)(4-pentylnaphthalene-1-yl)methanone and its salts.

Figure 1. The structural range of the generic scheduling for designating naphthoylindole-type synthetic cannabinoids based on the provision of the Pharmaceutical Affairs Law in Japan.

The changes in the prevalence of designer drugs and their legal status in Japan

At the beginning of this century, many analogues of narcotic substances were widely distributed in Japan as easily available psychoactive substances, and they had become a serious problem. Products ranging from herbal mixtures to synthetic drugs, sold as 'aroma liquid', 'herbal incense', or 'research chemicals' were available in various forms via the Internet or head shops. [25] They were not controlled under the Narcotics and Psychotropics Control Law in Japan because their pharmacological effects had not yet been proven scientifically. Although these substances should have been controlled by the Pharmaceutical Affairs Law, enforcement was difficult because they were sold as non-pharmaceutical products.

To fight their distribution, the Ministry of Health, Labor, and Welfare of Japan amended the Pharmaceutical Affairs Law in 2006. The new psychoactive substances defined were more strictly controlled by the amended law as follows:

1. A new category – Designated Substances – was introduced under this law. The Minister designates the psychotropic substances with potential effects on the central nervous system, which are recommended by a committee in the Ministry, as Designated Substances. Full scientific data required for Narcotics is not necessary for designation and that makes it possible to control the concerned compounds quickly.
2. The manufacture, import, and sale of the Designated Substances are banned except for proper use (such as medicinal or industrial use, and use for research or testing purposes by the government or research institutes).
3. The examination of suspected substances is possible.
4. The strengthening of punishment for distribution of non-authorized pharmaceuticals is possible.

If the substances are still being distributed after the control as Designated Substances and their harmful effects, such as drug dependency, are proved scientifically, they should be re-categorized into Narcotics. The Narcotics and Psychotropics Control Law prohibits their distribution, possession and use.

In April 2007, 31 compounds (11 tryptamines, 11 phenethylamines, 6 nitrites, 2 piperazines and salvinorin A) and one plant (*Salvia divinorum*) were first listed as Designated Substances. However, simultaneous with the control of these designer drugs, new analogues of the controlled substances began to appear on the illegal drug market and the identification and control of these compounds rapidly devolved into a cat and mouse game. In particular, the recent spread of products containing various analogues of synthetic cannabinoids and/or cathinone derivatives has been a matter of great concern in Japan. [20–36]

Before 2007, the major psychoactive substances distributed on the Japanese illegal drug market were tryptamine-type derivatives (such as 5-MeO-DIPT, 'Foxy'), phenethylamine-type derivatives (such as the 2C series, for example, 2C-T-7), and piperazine-type derivatives (such as BZP). Nitrites, such as isobutyl nitrite and isopentyl nitrite ('Rush'), were also widely distributed in Japan. [25] After these compounds were listed as Narcotics or Designated Substances in 2007, they quickly disappeared from the market and cathinone derivatives were distributed widely, as well as phenethylamine-type and piperazine-type designer drugs. [25]

Although the tryptamine-type designer drugs decreased, non-controlled psychotropic plants, such as 'Kratom' (*Mitragyna speciosa*), 'San Pedro' (*Trichocereus pachano*), 'Peyote' (*Lophophoria williamsii*), 'Hawaiian baby woodrose' (*Argyreia nervosa*), 'Fly Agaric' (*Amanita muscaria*), and 'Ayahuasca' (*Psychotria viridis, Banisteriopsis caapi, etc.*) became popular in place of the chemical psychotropic substances. [11,13,16–18,22] The herbal products

originally consisted of plant mixtures with psychoactive effects. However, these products have changed over the past few years to include potent new psychoactive compounds such as synthetic cannabinoids. Most plant species identified by DNA sequence analyses in the products, were different from the plants indicated on the labels and no reliable psychoactive effects have been reported. Therefore, these plant materials would be used mainly as diluents for the psychoactive synthetic substances.[32]

The changes in the structures of synthetic cannabinoids after the introduction of generic scheduling

After the introduction of the category Designated Substances into the Pharmaceutical Affairs Law in 2007, the conventional designer drugs (such as tryptamines and piperazines) disappeared from the illegal drug market in Japan, as described above. However, since 2008, herbal-type products containing various synthetic cannabinoids have appeared in Japan under names such as 'legal herbs' and 'incense'. The active entries of various synthetic cannabinoids dramatically changed the situation in the market. [25,29,30] These compounds were originally invented as cannabinoid receptor probes. Their numerous analogues were synthesized during the development of new medicine affecting the central nervous system, and only some of these analogues have appeared as designer drugs on the illegal drug market. We were therefore sure that other analogues with strong activities would appear one after another.

At present, the synthetic cannabinoids and cathinone derivatives are the most popular designer drugs sold on the illegal drug market in Japan. [25,30] Among the 84 Designated Substances which were listed from 2011 to September 2013 (2 tryptamines, 9 phenethylamines, 23 cathinone derivatives, 1 piperazine, 43 synthetic cannabinoids, and 6 others, including the substances which had their category changed from Designated Substances to Narcotics), approximately 80% of the compounds were either synthetic cannabinoids or cathinone derivatives. These new psychoactive substances mimic the effects of illicit drugs and are produced by introducing slight modifications to the chemical structure of controlled drugs to circumvent drug controls. In fact, the actual composition in terms of synthetic additives in the products was dynamically changing and rapidly responding to the newly implemented control measures. This made it difficult to effectively control these compounds. An alarming increase in emergency hospitalizations caused by these synthetic cannabinoids and/or cathinone derivatives has been observed since 2011. [29,37] Several fatalities related to these products have occurred, [29,38,39] and car accidents caused by impaired consciousness after smoking the products have been a serious problem throughout Japan since 2012. [29]

To counteract the emergence of the many analogues of these compounds, Japan's Ministry of Health, Labor, and Welfare implemented three legislative measures in 2012. In the first instance, the Ministry listed new psychoactive substances as Designated Substances with greater speed. From 2007 to 2011, a total of 69 substances were listed in the category of Designated Substances. In 2012 and the first half of 2013, another 61 substances were added, excluding the compounds designated by the generic scheduling. Figure 2 shows the new psychoactive substances listed as Designated Substances under the Pharmaceutical Affairs Law since 2007.

For the second measure, the Ministry re-categorized Designated Substances as Narcotics in 2012. From 2009 to the first half of 2013, 15 compounds had their category changed from Designated Substances to Narcotics. Twelve of these 15 compounds have been changed since 2012. These 12 compounds include 6 synthetic cannabinoids (cannabicyclohexanol, JWH-018, JWH-073, JWH-122, AM2201 and MAM-2201) and four cathinone derivatives (ethcathinone, MDPV, mephedrone and α-PVP). For the third measure, generic scheduling for designating naphthoylindole-type synthetic cannabinoids, with particular substituents, was introduced into the Designated Substances (Figure 1). The structural range of the generic scheduling was decided according to the substances' possible pharmacological activities, which were estimated using the Quantitative Structure-Activity Relationship (QSAR). As a result, a total of 759 compounds, excluding the already controlled compounds, were newly added to the Designated Substances. This was enforced in March 2013. As of 1 September 2013, the total number of Designated Substances is 881 substances and one plant.

Figure 3 shows the changes in the structures of synthetic cannabinoids detected in the herbal products from 2009 to 2013. In 2009, only cyclohexylphenols (e.g. cannabicyclohexanol)

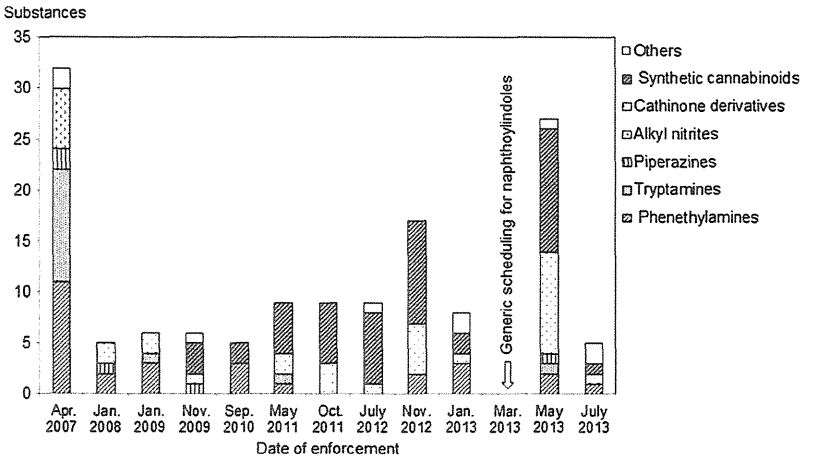


Figure 2. New psychoactive substances controlled as Designated Substances under the Pharmaceutical Affairs Law in Japan.

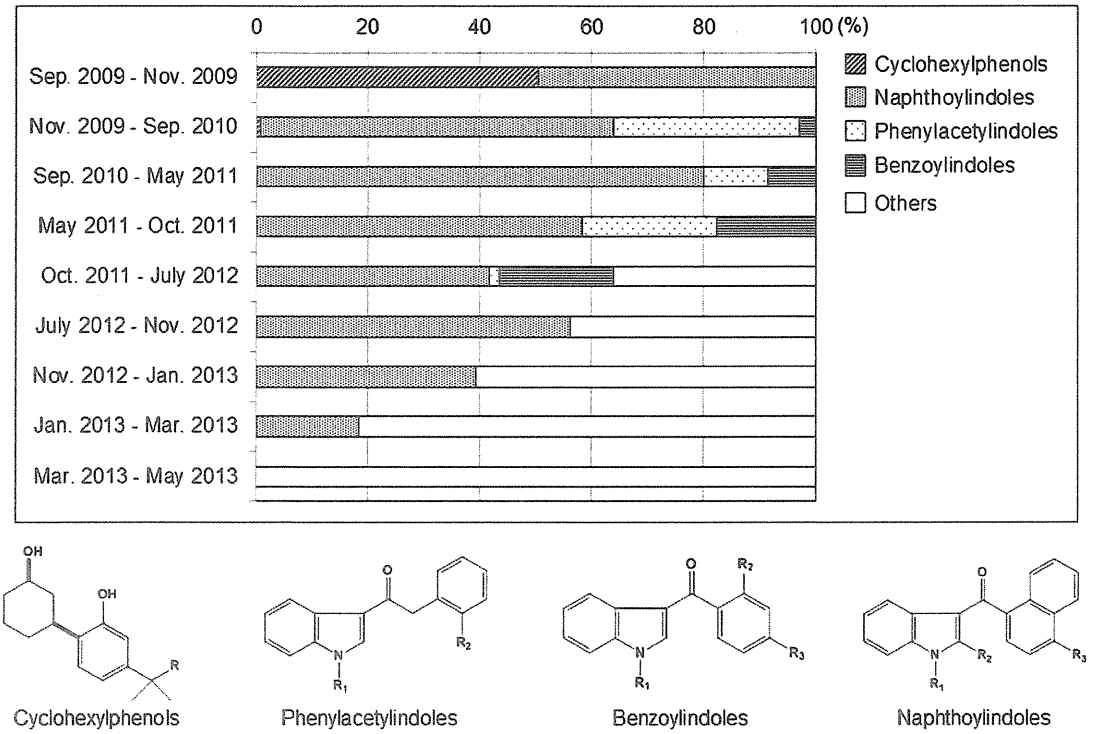


Figure 3. Changes in the rates of various types of synthetic cannabinoids, i.e., cyclohexylphenols, naphthoylindoles, phenylacetylindoles, benzoylindoles and others, detected in 1,349 herbal-type products that were sold as 'legal herbs' or 'incense' on the Internet between September 2009 and May 2013.

and naphthoylindoles (e.g. JWH-018) were found. However, following the control of these compounds, the cyclohexylphenols disappeared from the illegal drug market and various analogues of the naphthoylindoles (e.g. JWH-081, JWH-210 and AM2201), phenylacetylindoles (e.g. JWH-203) and benzoylindoles (e.g. AM694) were widely distributed. [29,30] Other compounds that

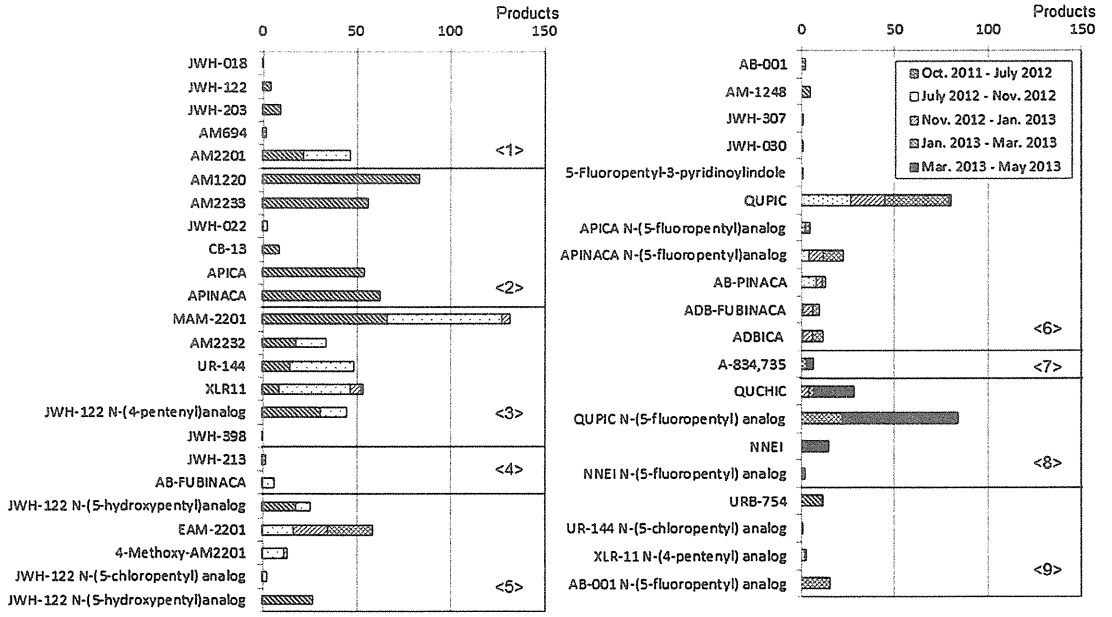


Figure 4. Changes in the prevalence of synthetic cannabinoids and their legal status on the basis of our survey of 775 herbal-type products sold as 'legal herbs' or 'incense' on the Internet between October 2011 and May 2013, The horizontal axis shows the number of products. ▨: Numbers of compounds detected in the products purchased from October 2011 to July 2012, ▨: from July 2012 to November 2012, ▨: from November 2012 to January 2013, ▨: from January 2013 to March 2013, ▨: from March 2013 to May 2013. <1>: Compounds controlled as Designated Substances before July 2012. <2>: since July 2012. <3>: since November 2012. <4>: since January 2013. <5>: since March 2013. <6>: since May 2013. <7>: since July 2013. <8>: compounds requested for public comment as of September 2013. <9> compounds not yet controlled.

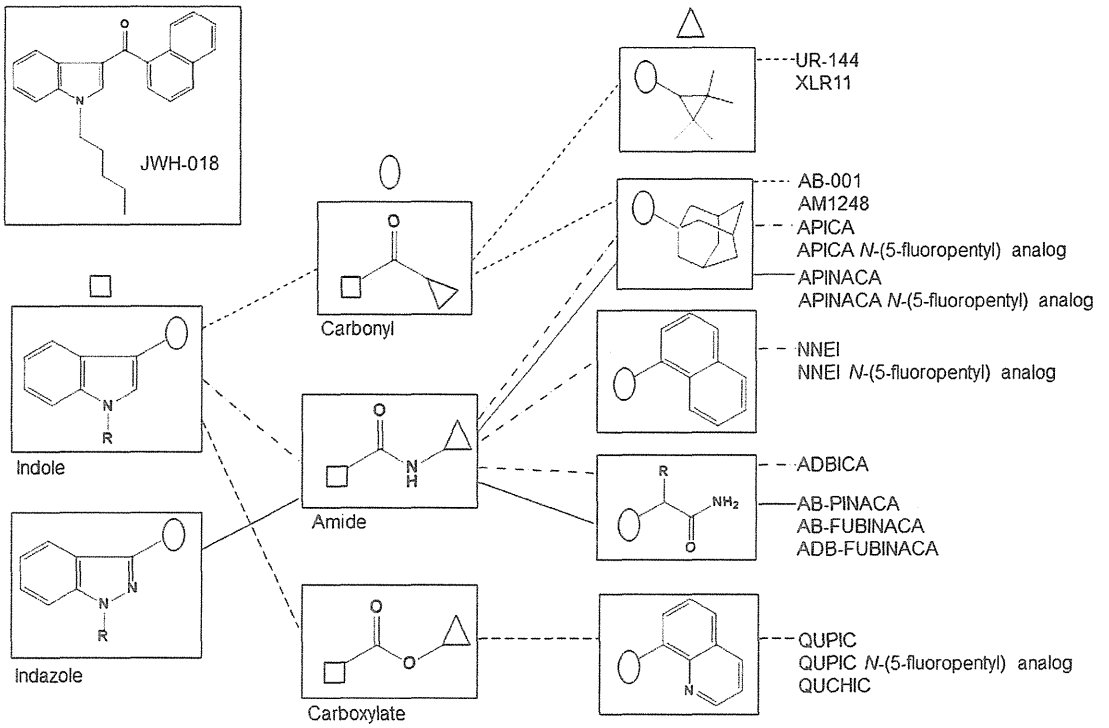


Figure 5. Chemical structures of new types of synthetic cannabinoids emerging since 2012.

do not have the four structures described above had never been detected prior to 2011, and 63% of the compounds detected from 2009 to 2011 were naphthoylindoles. [29,30] However, after the official announcement of the generic scheduling in November 2012, other types of synthetic cannabinoids increased dramatically [28,31,33–36] and the naphthoylindoles were rarely detected. Moreover, after enforcement of the generic scheduling for designating naphthoylindoles in March 2013, this structure has been completely replaced by other types.

Figure 4 shows the changes in the prevalence of synthetic cannabinoids since 2012. Before the introduction of the generic scheduling, most compounds detected in the products were naphthoylindole-type compounds. Among them, MAM-2201 was the most frequently detected in 2012, and some health problems, possibly caused by this compound, were reported. [29,30,39] However, in the second half of 2012, new types of synthetic compounds, such as carboxyamide derivatives (e.g. APICA and APINACA) and quinolinyl carboxylates [e.g. QUPIC (PB-22)] increased, [28–31,33,34] and they accounted for 71% of the detected compounds. After the introduction of the generic scheduling, 5-fluoro QUPIC was the most detected synthetic cannabinoid in the products obtained in early 2013. [36] It has been reported that some of these recent emerging synthetic cannabinoids have higher cannabinoid CB_1/CB_2 receptor binding affinities than that of JWH-018 or Δ^9-tetrahydrocannabinol which is an active component of marijuana, and potential serious health damage may be expected. [33,36,40,41]

Figure 5 summarizes the structures of various types of synthetic cannabinoids that have appeared since 2012. Instead of naphthoylindole-type compounds, adamanthoylindoles (e.g. AB-001), carboxyamide derivatives (e.g. APICA and APINACA), and di-carboxamide derivatives (e.g. AB-PINACA, AB-FUBINACA, ADBICA and ADB-FUBINACA) have appeared in the illegal drug market one after another. [28,31] As well as carboxyamide

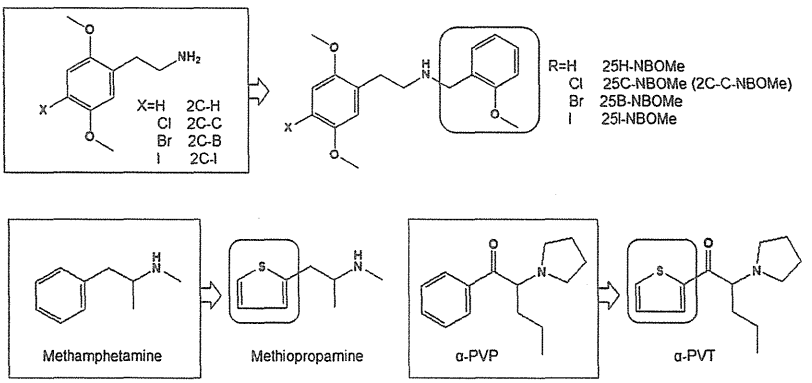


Figure 6. The emergence of new psychoactive substances as alternatives to controlled drugs.

and di-carbocyamide derivatives, cyclopropylmethanone-type compounds (e.g. UR-144 and XLR11) and quinolinyl carboxylates [e.g. QUPIC and QUCHIC (BB-22)] and their fluoro-derivatives have also been widely distributed since 2012. [34,36]. These substances have been listed as Designated Substances as of September 2013. As shown in Figures 4 and 5, as soon as generic scheduling was introduced by the Ministry, new types of psychoactive substances appeared.

The recent emergence of other new psychoactive substances

With the marked increase in the detection of new synthetic cannabinoids, other substances belonging to an expanding range of chemical families, that are derivatives of controlled drugs, have appeared since 2012 (Figure 6). For instance, there are potent hallucinogenic NBOMe-type compounds (e.g. 25I-NBOMe and 25C-NBOMe) and stimulant thiophene analogs (e.g. methiopropamine and α-PVT). [29,34] AH-7921 and MT-45 also emerged as new types of designer drugs. [34,35] These compounds have been classified as opioid analgesics with high addictive liability. [42–46] These designer drugs were detected together with several synthetic cannabinoids and cathinone derivatives in the products. In the last 3 years, the types of designer drugs and their combinations in illegal products have been diversifying, and we expect that more serious health risks will be associated with their use.

Conclusions

To counter the spread of the many analogues of psychoactive substances, the Pharmaceutical Affairs Law in Japan was amended in 2006 to establish a new category, Designated Substances. Additionally, the generic definition for designating naphthoylindole-type synthetic cannabinoids was introduced into the Designated Substances category in 2013. The almost infinite possibilities of altered structures of chemicals make it difficult to carry out effective and exhaustive scheduling. Because of the continuing diversity of new emerging substances, information-sharing among international laboratories will be crucial in the fight against these dangerous substances. The test purchasing of products for sale is one method of keeping track of how the substances contained in a product change over time, and it contributes to the early detection of new psychoactive substances that appear on the market. To prevent the widespread distribution and abuse of these new psychoactive substances, continuous and dedicated monitoring of the emergence of these substances is essential.

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Appendix

Table 1. Abbreviations and their chemical names of new psychoactive substances mentioned in this study.

Abbreviations	Chemical names
A-834,735	{1-[(Tetrahydropyran-4-yl)methyl]-1*H*-indol-3-yl}(2,2,3,3-tetramethylcyclopropan-1-yl)methanone
AB-001	1-Adamantyl(1-pentyl-1*H*-indol-3-yl)methanone
AB-FUBINACA	*N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide
AB-PINACA	*N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide
ADB-FUBINACA	*N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide
ADBICA	*N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indole-3-carboxamide
AH-7921	3,4-Dichloro-*N*-{[1-(dimethylamino)cyclohexyl]methyl}benzamide
AM694	[1-(5-Fluoropentyl)-1*H*-indol-3-yl](2-iodophenyl)methanone
AM1220	{1-[(1-Methylpiperidin-2-yl)methyl] -1*H*-indole-3-yl} (naphthalen-1-yl)methanone
AM1248	1-Adamantyl{1-[(1-methylpiperidin-2-yl)methyl]-1*H*-indol-3-yl}methanone
AM2201	[1-(5-Fluoropentyl)-1H-indol-3-yl](naphthalen-1-yl)methanone
AM2232	5-[3-(1-Naphthoyl)-1*H*-indol-1-yl]pentanenitrile
AM2233	(2-Iodophenyl){1-[(1-methylpiperidin-2-yl)methyl]-1*H*-indole-3-yl}methanone
APICA	*N*-(1-Adamantyl)-1-pentyl-1*H*-indole-3-carboxamide
APINACA	*N*-(1-Adamantyl)-1-pentyl-1*H*-indazole-3-carboxamide
25B-NBOMe	2-(4-Bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine
BZP	1-Benzylpiperazine

(Continues)

Table 1. *(Continued).*

Abbreviations	Chemical names
Cannabicyclohexanol	(1RS, 3SR)-3-[2-Hydroxy-4-(2-methylnonan-2-yl)phenyl]cyclohexan-1-ol
2C-B	2-(4-Bromo-2,5-dimethoxyphenyl)ethanamine
CB-13	Naphthalen-1-yl[4-(pentyloxy)naphthalen-1-yl]methanone
2C-C	2-(4-Iodo-2,5-dimethoxyphenyl)ethanamine
2C-C-NBOMe	2-(4-Chloro-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine
2C-H	2-(2,5-Dimethoxyphenyl)ethanamine
2C-I	2-(4-Iodo-2,5-dimethoxyphenyl)ethanamine
2C-T-7	2-(2,5-Dimethoxy-4-propylsulfanylphenyl)ethanamine
Ethcathinone	2-Ethylamino-1-phenylpropan-1-one
EAM2201	(4-Ethylnaphthalen-1-yl)(1-(5-fluoropentyl)-1*H*-indol-3-yl)methanone
5-Fluoropentyl-3-pyridinoylindole	[1-(5-Fluoropentyl)-1*H*-indol-3-yl](pyridin-3-yl)methanone
25H-NBOMe	2-(2,5-Dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine
25I-NBOMe	2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine
JWH-018	Naphthalen-1-yl(1-pentylindol-3-yl)methanone
JWH-022	Naphthalen-1-yl[1-(pent-4-en-1-yl)-1*H*-indole-3-yl]methanone
JWH-030	Naphthalen-1-yl(1-pentyl-1*H*-pyrrol-3-yl)methanone
JWH-073	(1-Butyl-1H-indol-3-yl)(naphthalen-1-yl)methanone
JWH-081	1-(4-Methoxynaphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone
JWH-122	(4-Methylnaphthalen-1-yl)(1-penthyl-1H-indol-3-yl)methanone
JWH-203	2-(2-Chlorophenyl)-1-(1-penty-1*H*-indol-3-yl)ethanone
JWH-210	(4-Ethylnaphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone
JWH-213	(4-Ethylnaphthalen-1-yl)(2-methyl-1-pentyl-1*H*-indol-3-yl)methanone
JWH-307	[5-(2-Fluorophenyl)-1-pentyl-1*H*-pyrrol-3-yl](naphthalen-1-yl)methanone
JWH-398	(4-Chloronaphthalen-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone
MAM-2201	[1-(5-Fluoropentyl)-1H-indol-3-yl](4-methylnaphthalen-1-yl)methanone
MDPV	1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one
5-MeO-DIPT	*N,N*-Diisopropyl-5-methoxytryptamine
Mephedrone	2-(Methylamino)-1-(4-methylphenyl)propan-1-one
Methiopropamine	2-Methylamino-1-(thiophen-2-yl)propane
MT-45	1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine
NNE1	*N*-(Naphthalen-1-yl)-1-pentyl-1*H*-indole-3-carboxamide
α-PVP	1-Phenyl-2-(pyrrolidin-1-yl)pentan-1-one
α-PVT	2-(Pyrrolidin-1-yl)-1-(thiophen-2-yl)pentan-1-one
QUCHIC	Quinolin-8-yl 1-(cyclohexylmethyl)-1*H*-indole-3-carboxylate
QUPIC	Quinolin-8-yl 1-pentyl(1*H*-indole)-3-carboxylate
UR-144	(2,2,3,3-Tetramethylcyclopropan-1-yl)(1-pentyl-1*H*-indol-3-yl)methanone
URB-754	6-Methyl-2-[(4-methylphenyl)amino]-1-benzoxazin-4-one
XLR11	[1-(5-Fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropan-1-yl)methanone

—Review—

違法ドラッグを取り巻く国内外における現状と規制について

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Prevalence of New Designer Drugs and Their Legal Status in Japan

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In recent years, many analogs of narcotics have been widely distributed as easily available psychotropic substances and have become a serious problem in Japan. To counter the spread of these non-controlled substances, the Pharmaceutical Affairs Law in Japan was amended in 2006 to establish a new category; Designated Substances in order to more strictly control these substances. In April 2007, 31 compounds and 1 plant were first controlled as Designated Substances. Before 2007, the major compounds distributed in the Japanese illegal drug market were tryptamines, phenethylamines and piperazines. Alkyl nitrites, such as isobutyl nitrite and isopentyl nitrite, were also widely distributed. After they were listed as Narcotics or Designated Substances in 2007, these compounds, especially the tryptamines, quickly disappeared from the market. In their place, cathinone derivatives have been widely distributed, as well as different phenethylamines and piperazines. Additionally, in recent years, new herbal products containing synthetic cannabinoids have appeared globally. As at July 2012, 78 substances (including 1 plant; *Salvia divinorum*) were listed in the category of Designated Substances. They were 13 tryptamines, 17 phenethylamines, 11 cathinones, 4 piperazines, 23 synthetic cannabinoids, 6 alkyl nitrites, 3 other compounds and 1 plant. In this review, we show our survey of the spread of new designer drugs in Japan, focusing especially on synthetic cannabinoids and cathinone derivatives. Also, the prevalence and legal status of these substances in other countries will be presented.

Key words——designer drug; synthetic cannabinoid; cathinone derivative; Designated Substance

1. はじめに

深刻化する違法ドラッグ問題に対応するため，厚生労働省は2006年に薬事法を改正し，興奮等の作用を有する蓋然性が高く，保健衛生上の危害が発生する恐れがある薬物や植物を厚生労働大臣が「指定薬物」として指定し，医療等の用途以外の製造，輸入，販売等を禁止することとなった．2007年4月に31化合物1植物が最初に指定薬物として規制されて以来，計8回の指定薬物指定が行われ，2012年7月時点で77化合物1植物が指定薬物として規制されている（トリプタミン類13，フェネチルアミン類17，カチノン誘導体11，ピペラジン類4，合成カンナビノイド23，亜硝酸エステル類6，その他3，植物1）（Table 1）．

The authors declare no conflict of interest.

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本総説は，日本薬学会第132年会シンポジウムS09で発表したものを中心に記述したものである．

国立医薬品食品衛生研究所（国立衛研）では，業務の一部として，指定薬物制度に対応し，問題となる化合物や植物の規制化に必要な評価手法及び科学的データを監視指導・麻薬行政に提供することを目的とした試験研究を行っている．特に，違法ドラッグ製品の流通実態を把握することを目的とし，2002年度より，厚生労働省が全国都道府県に委託して買い上げた違法ドラッグ製品及び国立衛研が独自に行っているインターネット等買上違法ドラッグ製品の含有成分分析調査を実施している．2011年度までに国立衛研が調査した違法ドラッグ製品は，2002年度から2011年度の10年間に全国都道府県で買い上げた違法ドラッグ製品（収去品，地方衛生研究所等の公共分析機関からの分析依頼品を含む）が691製品，2004年から2007年の3年間に国立衛研が試買した *Salvia divinorum* や kratom (*Mitragyna speciosa*) 等の植物製品が127製品（合成カンナビノイド含有製品を除く），また脱法ハーブやアロマリキッドを標榜してインターネット上で販売していた製品の試

Table 1. Psychotropic Substances Controlled as Designated Substances in Japan (as of July 2012)

Enforcement	Tryptamines	Phenethylamines	Cathinone derivatives	Piperazines	Synthetic cannabinoids	Others	Total
1 April 2007	MIPT DPT DIPT 5-MeO-AMT 5-MeO-DMT 5-MeO-DET 5-MeO-MIPT 5-MeO-DPT 5-MeO-DALT 4-OH DIPT 4-AcO-DIPT	(2C-I)* (2C-T-2)* (2C-T-4)* 2C-C 2C-E TMA-6 PMMA 4-FMP MMDA-2 BDB HMDMA		4MPP MBZP		Isopropyl nitrite Butyl nitrite Isobutyl nitrite *t*-Butyl nitrite Isopentyl nitrite Cyclohexyl nitrite Salvinorin A [*Salvia divinorum*]	32(29)
11 January 2008		Indan-2-amine DOI	bk-MDEA bk-MBDB	MDBP			5
16 January 2009	5-MeO-EIPT	ALEPH-2 DOC *N*-Me-4-FMP	Ethcathinone MDPV				6
20 November 2009			Mephedrone	4FPP	Cannabicyclohexanol CP-47, 497 JWH-018	Diphenylprolinol	6
24 September 2010		DON 2C-C-3 *N*-Me-2-FMP			JWH-073 JWH-250		5
14 May 2011	5-MeO-EPT	ALEPH-4	3-Fluoromethcathinone Methedrone		JWH-015 JWH-081 JWH-122 JWH-200 JWH-251		9
20 October 2011			4-Fluoromethcathinone Naphyrone 4-Methylethcathinone		JWH-019 JWH-203 JWH-210 AM-694 AM-2201 RCS-4		9
1 July 2012			3,4-dimethylmethcathinone		JWH-022 AM-1220 AM-2233 CB-13 Cannabipiperidiethanone APICA APINACA	Methoxetamine	9
Total	13	20(17)	11	4	23	9+1 plant	80(77) +1 plant

* 2C-I, 2C-T-2 and 2C-T-4 had their category changed from "Designated Substances" to "Narcotics" from January 2008.

買品が2009年から2012年2月までに686製品，合計1504製品にもおよぶ．

本稿では，全国都道府県買上違法ドラッグ製品及び脱法ハーブやアロマリキッドを標榜してインターネット上で販売していた製品の国立衛研試買品の成分分析調査結果を基に，指定薬物指定による規制と違法ドラッグ流通実態の変化について論じる．また，これら化合物の海外における規制状況についても簡単に解説する．

2. 指定薬物制度と違法ドラッグ流通実態の変化

2-1. 全国都道府県買上違法ドラッグ製品の成分分析調査 Figure 1 に，2002 年度から 2011 年度に全国都道府県で買い上げた違法ドラッグ 691 製品（収去品，地方衛生研究所等の公共分析機関からの分析依頼品を含む）の成分分析調査の結果，違法ドラッグ成分が検出された製品数の推移を示した．過去 10 年間に検出された違法ドラッグ成分は，主に亜硝酸エステル類，トリプタミン類，フェネチルアミン類，ピペラジン類，カチノン誘導体，合成カンナビノイド，その他に分類される．これら化合物の中で，10 年間の検出総数としては，トリプタミン類（23%）及び合成カンナビノイド（32%）が最も多い結果となった．[1-3]

制度制定前に流通していた違法ドラッグの主流は *Salvia divinorum* 等の幻覚成分を含む植物，[4-9] 5-MeO-DIPT（Foxy; *N*,*N*-diisopropyl-5-methoxytryptamine, 2005 年 4 月麻薬として規制）等のトリプタミン類，2C-T-7 (2-[2,5-dimethoxy-(4-propylsulfanyl)phenyl] ethanamine, 2006 年 4 月麻薬として規制）等のフェネチルアミン類及びピペラジン類等であった．[10-13] また，RUSH 等の名で知られた亜硝酸エステル類も違法ドラッグとして広く流通した．これらの化合物が麻薬若しくは指定薬物として規制されるとその流通は激減したが，規制された化合物に代わり，構造類似化合物が市場に出現した．[14] 現在では，カチノン誘導体やカンナビノイド受容体作動薬（合成カンナビノイド）が流通の主流となっているが，特に，2008 年度にその存在が明らかとなった合成カンナビノイドが添加された植物製品の登場は，従来の違法ドラッグの概念を大きく変えた．

合成カンナビノイドは，医薬品開発途上でメディシナルケミストリーによって大量に誕生したカンナビノイド受容体に対し高い活性を有する化合物群の総称である．もともとは医薬品開発が目的で誕生したものであるが，これら化合物を乾燥植物細片に混合した，いわゆる「脱法ハーブ」と呼ばれる製品が，大麻様の作用を標榜して違法ドラッグ市場に次から次へと登場している．この 1, 2 年の間にインターネット販売のみならず，都市部において店舗型販売店が著しく増加している．厚生労働省のまとめによると，「脱法ハーブ」などを店頭やインターネットなどで販売している業者数は 2012 年 3 月末現在，29 都道府県で 389 業者に上る．また，警視庁の発表によると 2012 年 1 月から 5 月に東京都内において「脱法ハーブ」吸引が関与した救急搬送事例が 94 件，愛知県の発表では 2012 年 2 月から 6 月に県内で 73 件報告されており，正式には報告されていない事例も含めると，件数はさらに増えるものと考えられる．既に違法ドラッグが関与する可能性が指

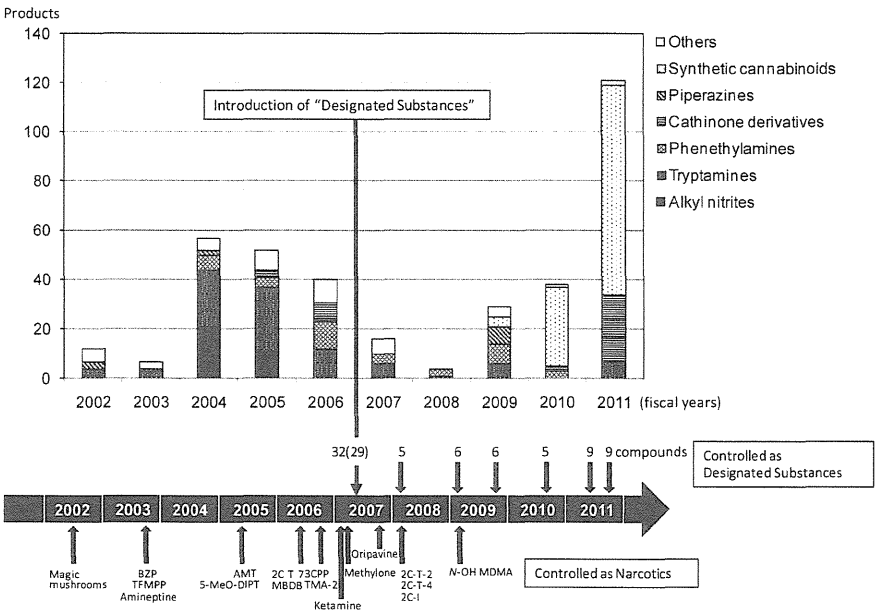


Fig. 1. Prevalence of Psychotropic Substances Based on Our Survey in the Last 10 Years

摘されている死亡例も報告されており，深刻な状況となっている．同様に，カチノン誘導体やその他化合物についても，アロマリキッドやバスソルト等を標榜して，溶液や粉末状態で，様々な構造類似化合物が違法ドラッグ市場に続々と登場している．これら違法ドラッグについては，指定薬物や麻薬に指定されると同時に構造類似化合物が新たに市場に登場し，規制とのイタチごっこが続いている．

2-2. いわゆる「脱法ハーブ」製品等の成分分析調査 2009年11月にcannabicyclohexanol(CCH), CP-47,497及びJWH-018の3化合物が合成カンナビノイド類として初めて指定薬物として薬事法下で規制されて以来，2012年7月時点で，合計23種類の合成カンナビノイドが指定薬物として規制されている（Fig. 2）．Figure 3に，国立衛研の違法ドラッグインターネット試買製品（2009年1月から2012年2月まで）のうち，合成カンナビノイドを主に含有する562製品（合法ハーブ，脱法ハーブ等標榜製品，乾燥植物細片，粉末等）から検出された化合物の変化を示した.[15]

日本において初めて合成カンナビノイドが違法ドラッグ製品中から検出・同定されたのは2008年後半であるが,[16] それ以後，2009年11月にCCH, JWH-018, CP-47,497が指定薬物として規制されるまでに流通が認められた化合物は，CCH及びJWH-018が主で，その他oleamideとJWH-073であった.[17-19] CCH, JWH-018, CP-47,497が指定薬物として規制されると，これら化合物は速やかに違法ドラッグ市場から消え，替わりにJWH-073, JWH-250, またJWH-081等が主流となった.[20] さらに2010年9月に，JWH-073及びJWH-250が指定薬物として規制されると，JWH-081, JWH-122, JWH-210等を中心とした構造類似化合物が主に流通した．2011年度には2回の指定薬物指定が行われ，合計11種類の合成カンナビノイド類が指定薬物として規制されたが，その間，JWH-203やAM-2201, AM-694等のハロゲン置換基を有する化合物の流通が広く認められるようになった．また，JWH-122（CB_1受容体に対するK_i値0.69 nM),[21] JWH-210 (0.46 nM)[22] 及びAM-694（0.08 nM)[23]のように，カンナビノイドCB_1受容体に対する親和性が極めて高い化合物も登場し，これら化合物による健康被害が懸念された．

2011年10月に上記化合物を含む6種類の合成カ

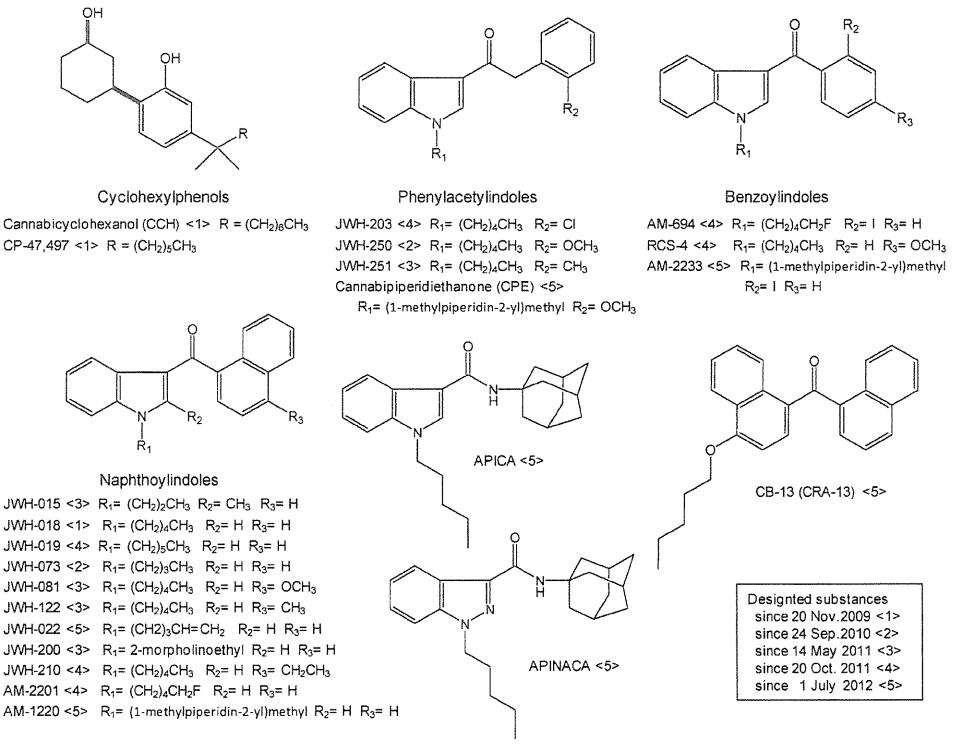


Fig. 2. Structures of Synthetic Cannabinoids Controlled as Designated Substances in Japan (as of July 2012)

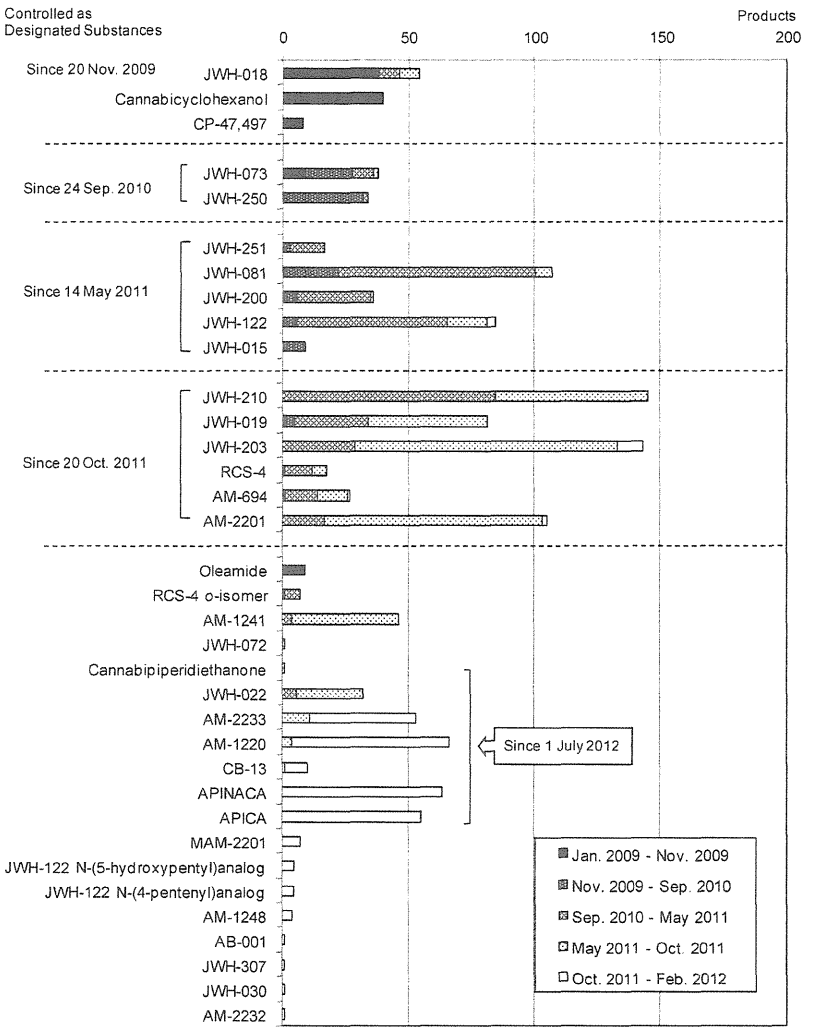


Fig. 3. Synthetic Cannabinoids Detected in 562 Dried, Cut Leaves or Powdery Products Obtained *via* the Internet between January 2009 and February 2012[15]

ンナビノイドが指定薬物として規制された直後から，それ以前には検出が認められていなかったAPICA, APINACA, AM-1220, AM-2233, CB-13等の流通が広く認められるようになった.[24–26] 2011年以前までは，Fig. 2に示したように，検出されるほとんどの合成カンナビノイドの構造は，cyclohexylphenols, naphthoylindoles, phenylacetylindoles若しくはbenzoylindolesのいずれかの基本骨格を有していた．しかし，APICA, APINACA及びCB-13は今まで流通していた化合物にはない基本骨格を有している．特にAPICA及びAPINACAは，adamantylcarboxamide構造を有し，APINACAはindole構造の代わりにindazole構造を有している.[24] Adamantyl構造に関しては，ほぼ同時期に流通が確認されたAB-001，2011年5月に新たな指定薬物規制が行われた前後から流通が認められたAM-1248においても同様の構造が認められる（Fig. 4）．また，AM-1220, AM-2233は，2011年5月の指定薬物規制が行われた前後から流通が認められたAM-1241やcannabipiperidiethanone（CPE）[25]と同様に，(1-methylpiperidin-2-yl) methyl基を有する化合物である（Fig. 4）．なお，2012年7月1日よりこれらAPICA, APINACA, AM-1220, AM-2233, CB-13, JWH-022, CPEの7種類の合成カンナビノイドは指定薬物として規制された．その他，Fig. 4に示した通り，2012年には，JWH-307, JWH-030, UR-144, URB754等のように，従来の合成カンナビノイドとは異なる骨格を有する化合物が続々と登場してい

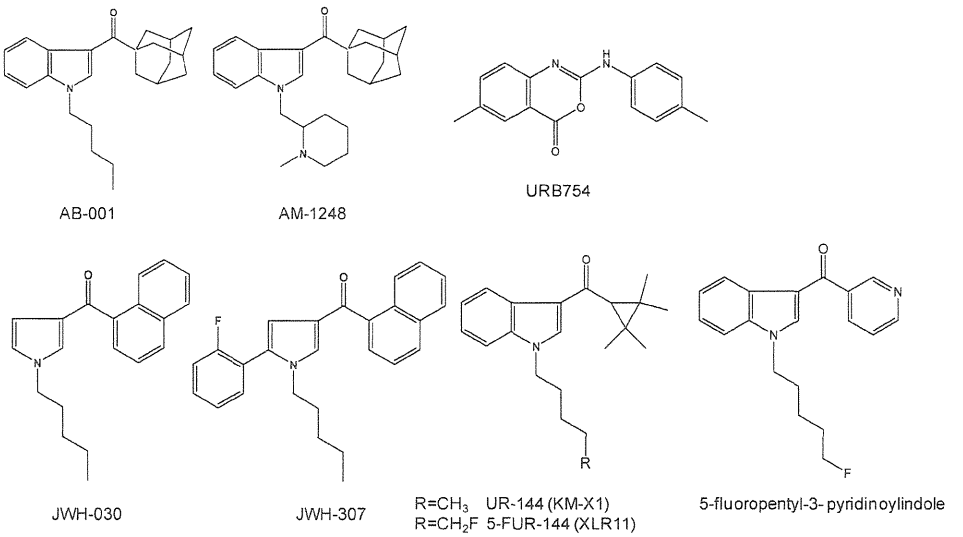


Fig. 4. Synthetic Cannabinoids, Having Structures Different from Those of Cyclohexylphenols, Naphthoylindoles, Phenylacetylindoles and Benzoylindoles, Detected in Our Survey since 2011[26]

る.[26] URB754 はカンナビノイド受容体作動薬ではないが，内因性カンナビノイドの分解に関与する monoacylglycerol lipase の阻害剤として開発された化合物である[27]（ただしその後，本活性は不純物によるものであることが報告されている）.[28] さらに，これらの化合物とともに，JWH-213，AM-2201 の 4-methylnaphtyl 体（MAM-2201）及び 4-ethylnaphtyl 体（EAM-2201），JWH-122 の *N*-(4-pentenyl) 体及び *N*-(5-hydroxypentyl) 体，JWH-018 の *N*-pentanenitrile 体（AM-2232）など，規制化合物の誘導体についても，2011 年 10 月以降に広く流通が認められている.[26]

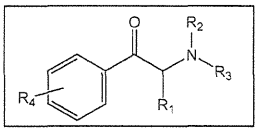
合成カンナビノイドを主に含有する乾燥植物細片若しくは粉末製品の中には，2011 年以降，合成カンナビノイドと同時に，カチノン誘導体，フェネチルアミン類，トリプタミン系化合物，dimethocaine 等の局所麻酔作用を有する中枢興奮薬，また 2011 年に新たに流通が認められた麻薬ケタミンの誘導体 methoxetamine 等，異なる作用を有する化合物を含有する製品も複数認められている.[15] また，1 製品に 10 種類もの化合物が添加された製品も存在し，各化合物自体の含有量及び薬理作用が大きくない場合でも，合計の化合物含有量を考慮すると，健康被害が懸念される.

なお，いわゆる「脱法ハーブ」と呼ばれる製品は，乾燥植物細片に合成化合物が添加されているが，使用されている植物についての情報は極めて乏しい．われわれは，合成カンナビノイドを含有する「脱法ハーブ」62 製品について，含有植物細片の遺伝子分析を行い，使用されている植物の基原種調査を行った.[29,30] その結果，含有植物は，製品の包装に表示されていた植物名とは異なり，向精神活性が報告されている植物はほとんどの場合で認められなかった．植物自体は，合成化合物の賦形剤のような役割で使用されているものと考えられる．しかし，大麻や *Salvia divinorum*, kratom 等，実際に活性成分を含有する植物も数製品から検出されている.[29,30]

2-3. いわゆる「アロマリキッド」製品等の含有成分調査　日本においては「アロマリキッド」等を標榜して広く流通しているカチノン誘導体についても，構造類似化合物が次々と市場に登場している．基本構造となる cathinone は元来，東アフリカやアラビア半島で酒の代用嗜好品として使用されるニシキギ科植物カート（*Catha edulis*）の主活性成分として知られている．本化合物は，興奮性のアミンとして，methcathinone（cathinone の *N*-methyl 体），2007 年に新たに規制された methylone とともに麻薬に指定されている．また，amfepramone 及び pyrovalerone は向精神薬としての規制を受けている (Table 2)．Figure 5 に，2009 年 9 月から 2012 年 2 月までにインターネットを通じて試買した，カチノン系化合物を主に含有する 124 製品（アロマリキッド等標榜製品，溶液，粉末等）から検出された化合物の変化を示す.[15]

Table 2. Cathinone Derivatives Detected in Our Survey[15] (as of May 2012)

Common name	R_1	R_2	R_3	R_4	Regulation category in Japan (as of July 2012)
Cathinone*	CH_3	H	H	H	Narcotic
Methcathinone (Ephedrone)*	CH_3	CH_3	H	H	Narcotic
3,4-Dimethylmethcathinone	CH_3	CH_3	H	3,4-dimethyl	Designated Substance (since 1 July 2012)
Ethcathinone	CH_3	CH_2CH_3	H	H	Designated Substance (since 16 January 2009)
Amfepramone (Diethylpropion)*	CH_3	CH_2CH_3	CH_2CH_3	H	Psychotropic
4-Methylmethcathinone (Mephedrone)	CH_3	CH_3	H	4-CH_3	Designated Substance (since 20 November 2009)
4-Methylethcathinone	CH_3	CH_2CH_3	H	4-CH_3	Designated Substance (since 20 October 2011)
4-Fluoromethcathinone (Flephedrone)	CH_3	CH_3	H	4-F	Designated Substance (since 20 October 2011)
3-Fluoromethcathinone	CH_3	CH_3	H	3-F	Designated Substance (since 14 May 2011)
4-Methoxymethcathinone (Methedrone)	CH_3	CH_3	H	4-OCH_3	Designated Substance (since 14 May 2011)
4-Methoxy-*N*,*N*-dimethylcathinone	CH_3	CH_3	CH_3	4-OCH_3	
Buphedrone	CH_2CH_3	CH_3	H	H	
4-Methylbuphedrone	CH_2CH_3	CH_3	H	4-CH_3	
4-Methyl-*N*-methylbuphedrone	CH_2CH_3	CH_3	CH_3	4-CH_3	
N-Ethylbuphedrone (NEB)	CH_2CH_3	CH_2CH_3	H	H	
Pentedrone	$CH_2CH_2CH_3$	CH_3	H	H	
Methylone (bk-MDMA)	CH_3	CH_3	H	3,4-methylenedioxy	Narcotic (since 3 February 2007)
Ethylone (bk-MDEA)	CH_3	CH_2CH_3	H	3,4-methylenedioxy	Designated Substance (since 11 January 2008)
BMDP (bk-MDBZ)	CH_3	benzyl	H	3,4-methylenedioxy	
Butylone (bk-MBDB)	CH_2CH_3	CH_3	H	3,4-methylenedioxy	Designated Substance (since 11 January 2008)
Pentylone	$CH_2CH_2CH_3$	CH_3	H	3,4-methylenedioxy	
α-PBP	CH_2CH_3	pyrrolidinyl		H	
α-PVP	$CH_2CH_2CH_3$	pyrrolidinyl		H	
Desethylpyrovalerone (4-MePPP)	CH_3	pyrrolidinyl		4-CH_3	
Pyrovalerone	$CH_2CH_2CH_3$	pyrrolidinyl		4-CH_3	Psychotropic
MDPBP	CH_2CH_3	pyrrolidinyl		3,4-methylenedioxy	
MDPV	$CH_2CH_2CH_3$	pyrrolidinyl		3,4-methylenedioxy	Designated Substance (since 16 January 2009)
Naphyrone	$CH_2CH_2CH_3$	pyrrolidinyl		(naphthyl structure)	Designated Substance (since 20 October 2011)



* Cathinone, methcathinone and amfepramone have never been detected in our survey.

世界的に多くの関連死亡事例が報告されている4-methylmethcathinone（mephedrone）は2009年11月に指定薬物に指定される以前に最も検出数が多かったカチノン誘導体である．本化合物規制後は，カチノン誘導体流通の主流は，構造類似化合物である4-methoxymethcathinone(methedrone)や，3-fluoromethcathinone, 4-fluoromethcathinone(flephedrone), naphyrone等であった．これらの化合物は，2010年後半から流通の主流となった4-methylethcathinoneとともに，2011年に指定薬物に指定された．2012年7月までに11種類のカチノン誘導体が指定薬物に指定されている（Table 2).

カチノン誘導体と同時に，溶液，粉末製品からは，フェネチルアミン類や，AMT（麻薬），5-MeO-DALT（指定薬物），*N*,*N*-diethyl-4-hydroxytryptamine（4-OH DET）等のトリプタミン系化合物，diphenylprolinol（指定薬物），2-diphenylmethylpyrrolidineや，procaine, lidocaine, dimethocaine, benzocaine等の局所麻酔作用を有する中枢興奮薬，methoxetamine等，異なる作用を有する様々な化合物を含有する製品も数多く認められている.[15] なお，合成カンナビノイドについては，溶液製品から

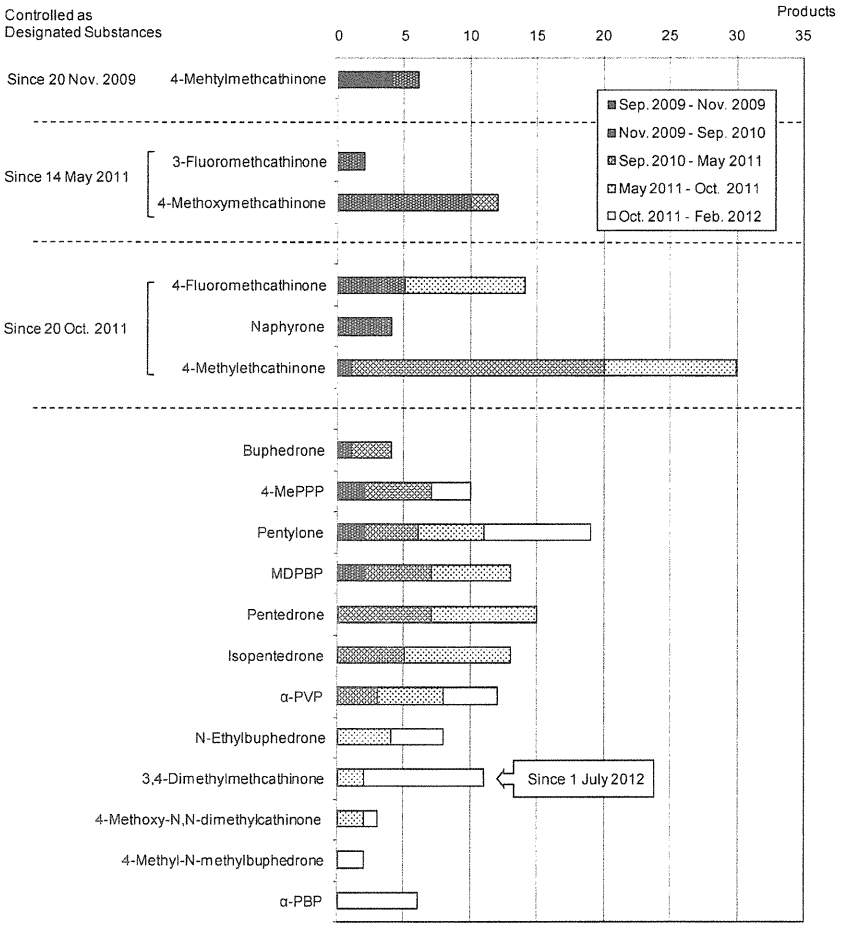


Fig. 5. Cathinone Derivatives Detected in 124 Different Liquid or Powdery Products Obtained *via* the Internet between September 2009 and February 2012[15]

は検出されなかった．これは，これら化合物の脂溶性が高いため，水系の溶媒には溶解不可であることが起因していると考えられる．

3. 海外の規制状況

欧米諸国においても，これら化合物の流通は大きな問題となっている．英国では，2009 年 12 月に合成カンナビノイド類，2010 年 4 月に 4-methylmethcathinone とその他関連カチノン誘導体，そして 2010 年 7 月には naphyrone 及びその関連化合物を Schedule I, Class B 薬物として包括規制している．米国においては，2011 年 3 月 1 日から CCH, CP-47,497, JWH-018, JWH-073, JWH-200 の 5 化合物を（2012 年 8 月 29 日まで延長），2011 年 10 月 21 日から MDPV, 4-methylmethcathinone, methylone の 3 化合物を，それぞれ暫定的に Schedule I 物質として規制している．さらに，2012 年 6 月に 26 化合物（合成カンナビノイド 15 種類，カチノン誘導体及びフェネチルアミン類 11 種類）を Schedule I 物質に追加することが議会において承認されている．薬理作用及び基本骨格に基づいた「カンナビノイド類」の範囲も規定されており，構造類似化合物の規制根拠がより明確になっている．

4. おわりに

指定薬物制度の導入により，路上等において従来流通していた違法ドラッグ販売数は表面上減少した．しかし，近年，いわゆる「脱法ハーブ」と呼ばれる合成カンナビノイド類が添加された植物製品や，アロマリキッド，バスソルトと呼ばれるカチノン誘導体等を添加した溶液製品，粉末製品の流通が広まっている．これら製品は，本調査結果においても示した通り，規制を逃れるため，含有成分が指定薬物に指定されると，速やかに構造類似化合物に置換して販売されるため，規制とのイタチごっこが続いている．指定薬物や麻薬と構造が類似している成

分が含まれていても規制することが困難なこれら「脱法ドラッグ」に対し，2012年4月に開催された厚生労働省薬事・食品衛生審議会の指定薬物部会では，違法薬物の指定手続きの迅速化（部会開催頻度の増加）や，海外で流通実態がある薬物を国内流通前に違法薬物に指定し，規制を可能にする等の対策強化を行うことが審議された．また，成分構造が似ていれば一括して規制や摘発をすることができる「包括指定」の導入について，具体的な検討に入ることが決まっている．これら違法ドラッグ含有製品による健康危害を防止するために，今後も継続的に新規違法ドラッグの出現を監視し，迅速に規制化を行っていく必要がある．

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