Forensic Toxicol (2015) 33:54–60
DOI 10.1007/s11419-014-0247-4

ORIGINAL ARTICLE

Inhomogeneities in herbal mixtures: a serious risk for consumers

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Received: 16 July 2014 / Accepted: 28 September 2014 / Published online: 22 October 2014

Abstract The most frequent form of consumption of cannabinoid receptor agonists (CRAs), often referred to as synthetic cannabinoids, is smoking of herbal mixtures often obtained via the Internet. However, because the plant material is either sprayed with or soaked in a drug solution, one of the main health risks in using these products is made up by the inhomogeneity in the content of active ingredient(s) and distribution within the mixtures. In the present study, 311 herbal mixtures covering 31 different brands seized from an online retailer in 2012 were analyzed quantitatively by high-performance liquid chromatography with diode array detection after screening by gas chromatography–mass spectrometry. Both interpackage and intrapackage CRA content variation were investigated by sampling without prior homogenization to reflect drug user behavior. The results showed that it is impossible for the consumer to safely dose these drugs, and that two joints of herbal mixture prepared from the same package could contain significantly different amounts of the active substance. Therefore, accidental overdosing is likely to occur frequently. In some products, interpackage variability of up to 33 % [standard deviation (SD)] and intrapackage variability of up to 20 % (SD) were observed. Another major health risk is posed by the substitution of a CRA in a herbal mixture without changing the brand name. In almost all cases when such a substitution was observed, there was a pronounced difference in the binding affinities of the respective CRA without a noticeable change in the amount added to the plant material. These findings can partly explain the high number of unintended intoxications that require hospitalization after use of these drugs.

Keywords Cannabinoid receptor agonist · Synthetic cannabinoid · Inhomogeneity of herbal mixture · HPLC-DAD · GC–MS · Legal highs

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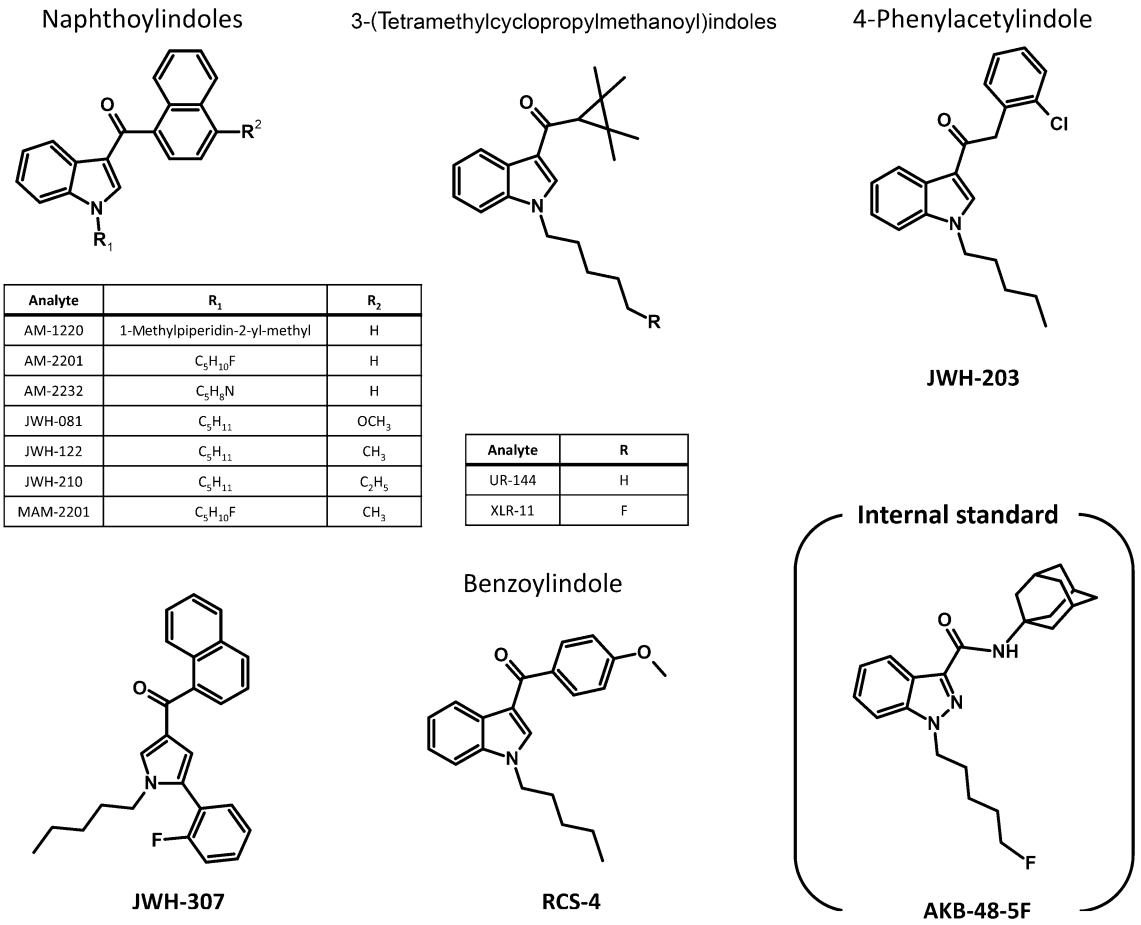
Introduction

Synthetic cannabinoid receptor agonists (CRAs) (Fig. 1), first identified in 2008 in herbal mixtures in Germany and Japan [1, 2] represent the fastest growing class of new psychoactive substances (NPS) in Europe, with 30 new compounds reported via the early warning system of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2012 [3] and 29 in 2013 [4]. A common mode of distribution of herbal products laced with these substances is the Internet, with online shops often offering a wide variety of "legal high" products. Similar to the increase in the number of identified CRAs, the number of online shops also continues to grow, with 693 shops identified in January 2012 by the EMCDDA [3]. Because the plant material is either sprayed with or soaked in a drug solution, a significant health risk arising from the use of these products is posed by the inhomogeneity of the herbal mixtures regarding the amount of active ingredient(s) per package and uneven distribution within each package [5–7]. Such variability in the product makes it impossible for consumers to safely dose these drugs, because two joints prepared from the same mixture could contain extremely different amounts of the active substance. Furthermore, the



Analyte	R_1	R_2
AM-1220	1-Methylpiperidin-2-yl-methyl	H
AM-2201	$C_5H_{10}F$	H
AM-2232	C_5H_8N	H
JWH-081	C_5H_{11}	OCH_3
JWH-122	C_5H_{11}	CH_3
JWH-210	C_5H_{11}	C_2H_5
MAM-2201	$C_5H_{10}F$	CH_3

Analyte	R
UR-144	H
XLR-11	F

Fig. 1 Chemical structures of the cannabinoid receptor agonists (CRAs) detected from the herbal mixtures and of the utilized internal standard AKB-48-5F

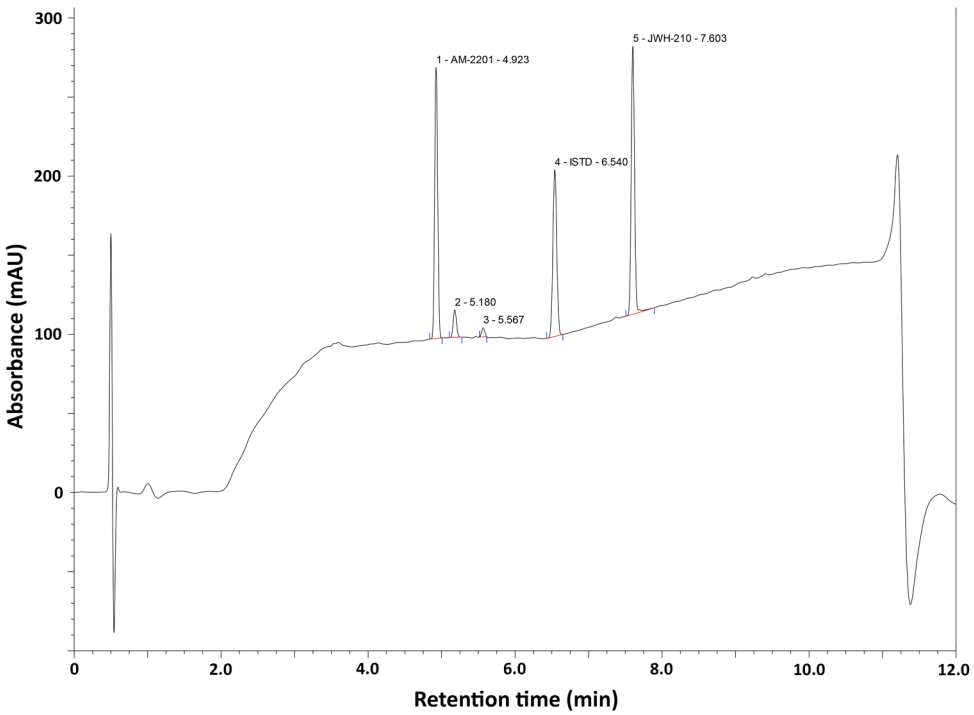


Fig. 2 High-performance liquid chromatography-photodiode array detection chromatogram of one extract from the herbal mixture "Manga Hot" containing 52 mg/g AM-2201 (peak *1*) and 73 mg/g JWH-210 (peak *5*). Peaks *2* and *3* are impurities from the HPLC system that were also present in blank samples (not shown). Peak *4* represents the internal standard AKB-48-5F

compositions of these herbal mixtures change rapidly over time, and a certain product name does not guarantee the same composition of compound(s) between batches [8].

Despite such an obvious risk, no investigation to date has been carried out on a large number of samples from one online shop to assess product variability. Most studies of these dubious products used a homogenization step prior to quantitation, and no intrapackage variability was assessed. Although homogenization is a necessary approach in a forensic chemical analysis, the results do not reflect the risk of these drugs for consumers who might be exposed to dangerous amounts upon consuming the product.

In the present study, 311 herbal mixtures covering 31 different brands seized from a single online retailer were quantitatively analyzed utilizing a high-performance liquid chromatography-photodiode array detection (HPLC-DAD) method after screening by gas chromatography–mass spectrometry (GC–MS). Following the death of a person after consuming the herbal mixture "ACME" (containing JWH-210) and the "bath salt" product "9/11" (containing 4-methylethcathinone), the aim of this study was to assess the danger of overdosing due to interpackage and intrapackage inhomogeneities of CRAs in these products.

Materials and methods

Chemicals and reagents

Formic acid (Rotipuran® ≥98 %) was purchased from Carl Roth (Karlsruhe, Germany); methanol (HPLC grade) from

Table 1 Interpackage inhomogeneity of cannabinoid receptor agonist (CRA) contents in the herbal mixtures

Product	Number of packages examined	CRA(s)	Mean CRA content (mg/g)	SD (%)	Range (mg/g)
ACME	19	JWH-210	96	9	87.5–112
Bonzai Citrus	5	JWH-307	134	14	111–154
Bonzai Summerboost	4	JWH-122	135	8	121–143
Bonzai Winterboost	5	JWH-307	153	8	143–172
Jamaican Gold Extreme	3	JWH-122	161	2	160–165
Jamaican Gold Supreme	3	JWH-122	164	2	162–166
Jazz	5	JWH-210	58	4	55–61
M.I.B	5	JWH-210	143	5	133–150
Manga Hot	4	AM-2201 and JWH-210	47 and 69	4.4 and 2.8	45–49 and 66–70
Maya 2012	7	UR-144	44	9	36–48
	2	XLR-11	40	–	39–41
MNK	55	JWH-210	102	14	56–125
Monkees 3D Afterlife	2	AM-1220 and JWH-122	23 and 45	–	18–28 and 35–55
Monkees Goes Bananas	33	JWH-122	92	21	51–122
No Name	10	MAM-2201	40	18	29–51
OMG	22	JWH-122	74	12	56–88
Peace	7	XLR-11	39	7	36–42
Pineapple Express	10	RCS-4	86	11	78–100
Push	10	AM-1220	62	12	48–72
Skunk	20	RCS-4 and JWH-081	6.0 and 45	2.5 and 10.5	n.d.–20 and 26–63
Soulman	10	AM-1220 and MAM-2201	24 and 77	3.8 and 12.5	17–31 and 52–95
Summerlicious	23	AM-2232	45	33	26–100
Vegas Chocolate	6	JWH-210	42	12	41–66
Vegas Premium Incense	5	JWH-210	32	20	22–37
Vegas Titanium	6	JWH-210	49	8	45–53
	7	XLR-11	46	33	37–76
XoXo	2	AM-1220 and MAM-2201	72 and 11	23 and 12	61–84 and 10–12
X-treme	4	RCS-4	54	27	37–71
ZIP	12	AM-2201	66	11	55–74

SD standard deviation; *n.d.* not detected

J.T.Baker (Deventer, The Netherlands); acetonitrile (ACN), ammonium formate (99.995 %), ethanol (analytical grade), and ethyl acetate (analytical grade) from Sigma Aldrich (Steinheim, Germany). Deionized water was prepared using a cartridge deionizer from Memtech (Moorenweis, Germany). RCS-4 [(4-methoxyphenyl)(1-pentyl-1*H*-indol-3-yl)methanone] was purchased from Cayman Chemical (Ann Arbor, MI, USA). AKB-48-5F, UR-144, and XLR-11 were kindly provided by Ilmari Szilvay (Finnish Customs Laboratory). AM-1220 [(1-[(1-methyl-2-piperidinyl)methyl]-1*H*-indol-3-yl)-1-naphthalenyl-methanone] was obtained by purification of a research chemical using thin-layer chromatography (TLC) [9], and MAM-2201 ([1-(5-fluoropentyl)-1*H*-indol-3-yl](4-methyl-1-naphthalenyl)-methanone) was extracted from a herbal mixture [10, 11]. All other synthetic cannabinoids, JWH-081 [(4-methoxy-1-naphthalenyl)(1-pentyl-1*H*-indol-3-yl)-methanone], JWH-122 [(4-methyl-1-naphthalenyl)(1-pentyl-1*H*-indol-3-yl)-methanone], JWH-203 [2-(2-chlorophenyl)-1-(1-pentyl-1*H*-indol-3-yl)-ethanone], JWH-210 [(4-ethyl-1-naphthalenyl)(1-pentyl-1*H*-indol-3-yl)-methanone], JWH-307 ([5-(2-fluorophenyl)-1-pentyl-1*H*-pyrrol-3-yl](naphthalen-1-yl)methanone), AM-2201 ([1-(5-fluoropentyl)-1*H*-indol-3-yl]-1-naphthalenyl-methanone), and AM-2232 [3-(1-naphthalenylcarbonyl)-1*H*-indole-1-pentanenitrile] were provided by the German Federal Criminal Police Office (BKA), the State Bureaus of Criminal Investigation (LKA) Baden-Württemberg and Niedersachsen, or purchased as "research chemicals" over the Internet. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, GC–MS, and TLC were used to verify the identity and purity (≥98 %) of substances not obtained as certified standards.

Samples

All investigated herbal mixtures investigated were part of a single seizure conducted in March 2012, covering a total of 4,127 packages (31 different brands) from an online shop selling "legal highs". From this seizure, 311 packages were quantitated as an adequate sample for interpretation of the homogeneity. Furthermore, 34 packages (21 different brands) were completely analyzed (in 200-mg portions) to investigate intrapackage inhomogeneities.

Extraction of synthetic cannabinoids

Two hundred milligrams of each herbal mixture was accurately weighed into a test tube and extracted three times by addition of 2 ml of methanol and ultrasonication for 15 min; the extracts were combined and filtered through a 0.22-µm filter (Carl Roth, Karlsruhe, Germany). The filtrate was used for in-house screening by GC–MS and quantitation by HPLC-DAD as described below. In order to mimic the usual conditions of actual drug use, no homogenization was carried out prior to sampling.

Quantitation of synthetic cannabinoid receptor agonists

For quantitation, 5 µl of filtrate was transferred into an HPLC vial containing 1 ml of mobile phase B as well as 25 µg/ml of CRA AKB-48-5F as internal standard (IS) and analyzed by HPLC-DAD utilizing a Dionex UltiMate 3000 RSLC HPLC system (Thermo Fisher Scientific, Dreieich, Germany). The system consisted of an HPG-3400RS binary pump, an SRD-3600 solvent rack degasser, a WPS-3000TRS autosampler, a TCC-3000RS column compartment, and a DAD-3000RS diode array detector (DAD). Separation was carried out by a method similar to that described by Huppertz et al. [12]. Mobile phase A consisted of deionized water with 1 % ACN, 2 mM ammonium formate, and 0.1 % formic acid. Mobile phase B was ACN containing 2 mM ammonium formate and 0.1 % formic acid. Gradient elution was performed on a Kinetex C18 column (100 × 2.1 mm i.d., 1.7 µm particle size) with a corresponding guard column (both columns from Phenomenex, Aschaffenburg, Germany). Gradient elution was started with 20 % mobile phase B for 1 min, increased to 60 % B within 1.5 min, increased to 65 % B within another 1.5 min, held for 1.5 min, increased to 99 % B within 2.5 min, and held for 2 min. Starting conditions were restored within 0.2 min, and the system was allowed to re-equilibrate for 1.8 min prior to injection of the next sample. The flow rate was set to 0.5 ml/min and the injection volume was 2 µl. The autosampler tray temperature was 10 °C and the column oven temperature was

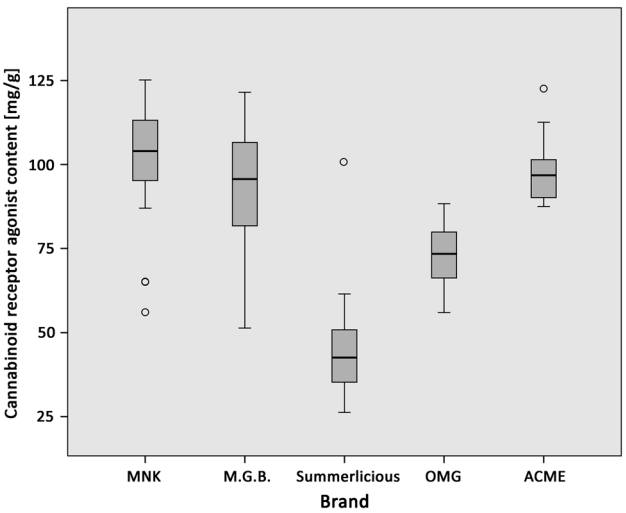


Fig. 3 Box whisker plots of the CRA contents in five different brands of herbal mixtures [MNK $n = 55$; Monkees Goes Bananas (M.G.B.) $n = 33$; Summerlicious $n = 23$; OMG $n = 22$; ACME $n = 19$]. *Small open circles* indicate outliers

40 °C. Wavelengths of the DAD were set to 209 and 217 nm for analysis of CRAs according to the United Nations Office on Drugs and Crime manual [13]. Five-point calibration curves (1–50 μg/ml) were prepared by fortifying 1 ml of mobile phase B containing 25 μg/ml of IS (AKB-48-5F) with the corresponding amounts of CRAs. An HPLC-DAD chromatogram of one extract from a herbal mixture containing two CRAs is shown in Fig. 2.

Verification of synthetic cannabinoid receptor agonists

Considering that many CRAs have similar absorption maxima, one filtrate of each CRA composition detected in the products was verified using GC–MS analysis before quantitation by HPLC-DAD. For this purpose, 4 μl of filtrate was transferred into a GC vial and evaporated to dryness under a gentle stream of nitrogen. The dry residue was reconstituted in 100 μl of ethyl acetate, and a 1-μl aliquot was injected into the GC–MS system, which consisted of a 6890 series GC with a 5873 mass selective detector, a 7638 B series injector, and used Chemstation G1701GA version D.03.00.611 software (Agilent, Waldbronn, Germany). GC–MS conditions were: injection, splitless mode; injection port temperature, 270 °C; column, HP-5-MS capillary (30 m × 0.25 mm i.d., 0.25 μm film thickness; Agilent); carrier gas, helium; flow rate,

Table 2 Intrapackage inhomogeneities of CRA contents in the herbal mixtures

Product	Actual amount per package (g)	Samples analyzed	CRA(s)	Mean CRA content (mg/g)	SD (%)	Range (mg/g)
ACME	2.03	10	JWH-210	98	15	73–127
	1.86	9	JWH-210	97	7	89–111
	1.95	10	JWH-210	93	8	83–107
	2.09	10	JWH-210	123	16	91–165
	1.98	10	JWH-210	102	10	87–121
Blaze	3.14	16	JWH-307	151	11	103–173
Bonzai Citrus	3.16	16	JWH-307	138	8	124–161
Bonzai Summerboost	2.88	14	JWH-122	149	8	128–170
Bonzai Winterboost	2.92	14	JWH-307	150	9	112–175
Green	1.83	9	AM-2201 and JWH-203	48 and 67	8 and 8	42–52 and 58–75
Jamaican Gold Extreme	3.3	16	JWH-122	161	8	138–182
Jamaican Gold Supreme	3.34	16	JWH-122	154	9	125–189
Jazz	1.92	10	JWH-210	59	7	53–69
M.I.B	3.04	15	JWH-210	141	6	150–117
Manga Hot	2.71	14	AM-2201 and JWH-210	51 and 73	5 and 4	46–55 and 68–77
MNK	0.69	3	JWH-210	112	6	107–119
	0.71	3	JWH-210	105	17	87–124
	0.61	3	JWH-210	122	17	107–146
	0.53	3	JWH-210	106	20	86–127
	0.89	4	JWH-210	119	17	101–148
Monkees Goes Bananas	2.02	10	JWH-122	96	11	83–117
	1.86	9	JWH-122	97	9	83–113
	2.01	9	JWH-122	93	16	71–118
OMG	1.71	9	JWH-122	79	16	65–105
	1.99	10	JWH-122	63	13	48–75
Peace	2.05	10	XLR-11	41	2	40–42
R&B	3.12	16	JWH-307	108	13	81–125
Vegas Chocolate	1.99	10	JWH-210	42	12	34–48
Vegas Premium Incense	1.99	10	JWH-210	21	7	19–23
Vegas Titanium	2.21	11	JWH-210	48	10	42–55
	2.01	10	XLR-11	43	5	40–46
VIP	2.97	15	JWH-307	131	10	102–150
ZIP	2.85	14	AM-2201	66	15	57–91
	3.15	16	AM-2201	70	14	47–85

1 ml/min; oven temperature, 100 °C for 3 min, ramped to 310 °C at 30 °C/min, and held at 310 °C for 10 min; transfer line heater and ion source temperatures, 280 and 230 °C, respectively; ionization energy, 70 eV in electron impact ionization mode. The obtained mass spectra were compared with those of the Cayman Spectral Library [14] and with spectra from an in-house library containing a wide range of CRAs.

Results and discussion

Interpackage inhomogeneity

Interpackage inhomogeneities in CRA content in the 29 products analyzed (27 brands) and those of the five representative brands are listed in Table 1 and in Fig. 3, respectively. The highest standard deviation (SD) detected was in the product "Summerlicious," with the AM-2232 content ranging from 26 to 100 mg/g ($n = 23$). It is particularly concerning that the highest measured concentration (100 mg/g) was an outlier and could lead to severe intoxication in consumers who are accustomed to using an amount of drug material adjusted to the median CRA content. Considering the high receptor binding affinity of AM-2232 at 0.28 nM toward the CB_1 receptor [15], this wide range is even more worrying. Interpackage inhomogeneities observed by Choi et al. [6] in five South Korean products (2–12 packages) were higher in most of the products investigated by them as compared to those of the present study.

Intrapackage inhomogeneity

The intrapackage inhomogeneity of the 34 packages (21 brands) analyzed is shown in Table 2, and intrapackage inhomogeneity of the five packages of the herbal mixture ACME is also shown in Fig. 4. Surprisingly, the highest standard deviation of 20 % was detected in a package of the product with the lowest amount of herbal material, "MNK". This product contains JWH-210, a CRA with a very high binding affinity toward the CB_1 receptor (0.46 ± 0.03 nM) [16].

Uniqueness of brand names

In 5 of the 31 brands, the CRA composition was not identical in the packages tested (Table 3). Comparing the binding affinities of the different CRAs (Table 3) detected in a particular brand, such variability can pose severe health risks to consumers. As an example, for the herbal mixture "Blaze," one package contained JWH-307, while the another contained JWH-210, a CRA with a more than tenfold higher binding affinity toward the CB_1 receptor. Despite such a large difference in binding affinity, both CRAs were added by the manufacturer in a similar percentage. Similar results were found for the most of the other brands, in which the amounts of CRAs sprayed on the plant material were similar, but the CB_1 receptor affinities were up to 50-fold different. Similar substitutions were also observed by Shanks et al. [8]; however, CRA contents were

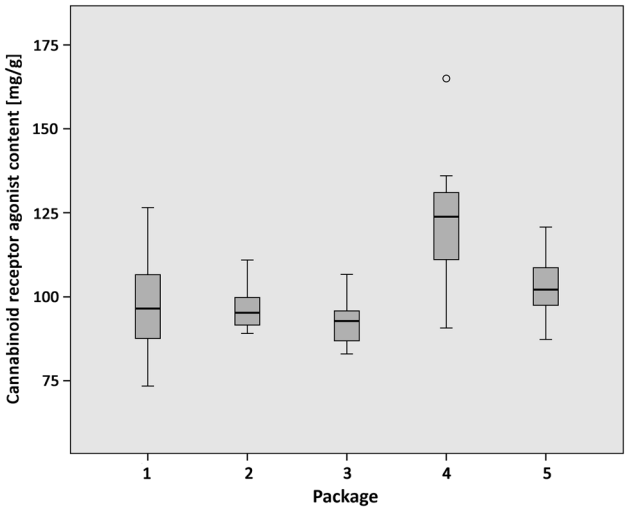


Fig. 4 Box whisker plots showing intrapackage inhomogeneity of JWH-210 content in five different packages of the herbal brand "ACME". All packages were analyzed completely in portions of 200 mg of herbal mixture leading to 10 samples per package ($n = 9$ for package No. 3)

Table 3 Herbal mixtures marketed under identical brand names with different CRA compositions together with the binding affinities of the respective CRAs for the CB_1 receptor

Product	Number of packages examined	Mean CRA content (mg/g)	CRA	K_i CB_1 (nM)[a]
Blaze	1	161	JWH-307	7.7 ± 1.8
	1	153	JWH-210	0.46 ± 0.03
Peace	1	59	JWH-210	0.46 ± 0.03
	7	39	XLR-11	24
Vegas Titanium	6	49	JWH-210	0.46 ± 0.03
	7	46	XLR-11	24
Maya 2012	7	44	UR-144	150[b]/29[c]
	2	40	XLR-11	24
X-treme	4	54	RCS-4	n.t.
	1	28	AM-2201	1.0

n.t. not tested/no results published

[a] According to [15–19]

[b] According to Frost et al. [17]

[c] According to Wiley et al. [18]

not quantitated and the products might have been purchased from different vendors.

Conclusions

Based on the obtained results, we conclude that it is impossible for users of dubious herbal mixtures to accurately dose the drugs they contain, and accidental overdoses are likely to occur frequently. Another aggravating factor is the intrapackage inhomgeneity of up to 20 % (SD) in some of the products. A third major health risk is the substitution of CRAs in herbal mixtures without changing the brand name. In almost all of these cases observed; there was a pronounced difference in the binding affinities of the respective CRA without any noticeable change in the amount added to the plant material.

Acknowledgments The authors thank the Drug Prevention and Information Programme of the European Union (JUST/2011/DPIP/AG/3597), the German Federal Ministry of Health, and the City of Frankfurt/Main for financial support.

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

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