XLR-11

Critical Review Report

Agenda Item 4.12

Expert Committee on Drug Dependence

Thirty-eighth Meeting

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Contents

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Summary

XLR-11 ([1-(5-fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone) is a synthetic constituent found in herbal smoking mixtures that are sold under a variety of brand names. It is common for retailers to purchase bulk quantities of the synthetic substance and to add the synthetic material to a variety of vegetable matter used as the plant base.

XLR-11 has been demonstrated to be a full agonist at human G-protein coupled CB_1 and CB_2 receptors. Investigations carried out *in vitro* demonstrated functional and mechanistic similarities to Δ^9-THC. In some assays, XLR-11 displayed a higher potency than Δ^9-THC in its ability to mediate Δ^9-THC-like effects. When investigated *in vivo,* XLR-11 also displayed Δ^9-THC-like effects (sometimes more potent) that were attenuated by rimonabant.

The available data suggest XLR-11 to display abuse liability. Further studies are needed to assess dependence potential. Severe adverse effects have been associated with a range of synthetic cannabinoids but the total numbers of cases that have been specifically linked to XLR-11 are more limited. Adverse effects associated with XLR-11 included acute kidney injury, low body temperature, rigid muscle tone, back or abdominal pain, elevated peak systolic blood pressure, slurred speech, lack of convergence, and body and eyelid tremors. One case of acute cerebral ischemia and infarction was reported although XLR-11 was not detected in blood and urine. Commonly reported adverse reactions associated with a range of synthetic cannabinoids frequently include agitation, cardiovascular events including tachycardia and hypertension, hallucination, nausea/hyperemesis, seizures and hypokalaemia. Chest pain, myoclonia and psychiatric complications were also reported. No therapeutic and medical use could be identified.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

1364933-54-9

C. Other Chemical Names

Not applicable (see Section 2).

D. Trade Names

Not applicable.

E. Street Names

XLR-11, 5F-UR-144, TMCP-2201, 5-FUR-144, 'Spice', 'synthetic cannabis'. This substance is a constituent found in a range of herbal mixtures that are sold using rapidly changing product names (e.g. 'Maya 2012', 'Peace', 'Vegas Titanium',[1] 'Bizarro Blueberry', 'Colorado', 'Funky Green Stuff (Reggie's Blend)', 'Hammer Head', 'iBlown 4G', 'Sunshine Daydream', 'Sunshine Nightmare',[2] 'Mr. Happy', 'Clown Loyal', 'Lava'[3], 'WTF'[4]).

F. Physical Appearance

XLR-11 is a white crystalline solid and forms large prismatic crystals.[5]

G. WHO Review History

XLR-11 has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that XLR-11 is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

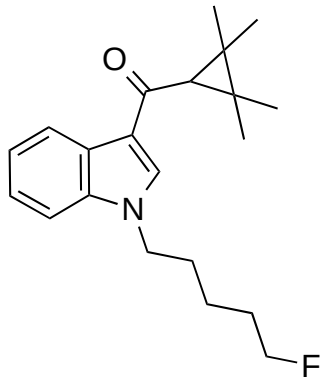
A. Chemical Name

IUPAC Name: [1-(5-Fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone

CA Index Name: [1-(5-Fluoropentyl)-1*H*-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone

B. Chemical Structure

Free base:



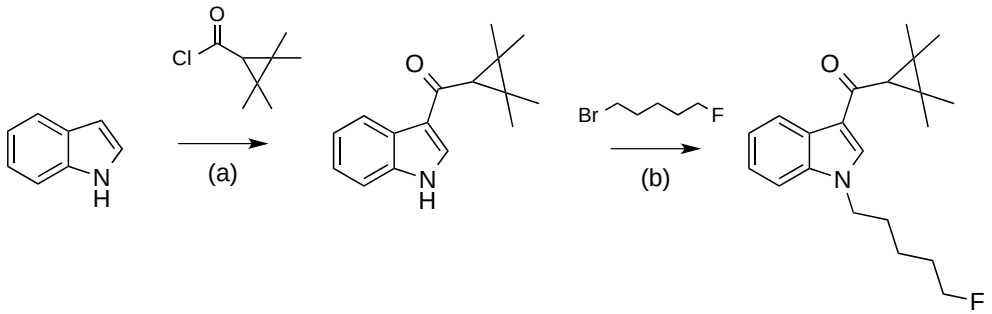
Molecular Formula: $C_{21}H_{28}FNO$
Molecular Weight: 329.46 g/mol

C. Stereoisomers

Not applicable.

D. *Methods and Ease of Illicit Manufacturing*

Information about illicit manufacturing is unavailable. One approach to XLR-11 synthesis is based on a standard acylation reaction of indole with 2,2,3,3-tetramethylcyclopropanecarbonyl chloride (a) followed by *N*-alkylation with 1-bromo-5-fluoropentane (b)[5] similar to the preparation reported for other 3-(2,2,3,3-tetramethylcyclopropanecarbonyl)indole analogs (e.g.[6, 7]). Illicit manufacturing of this substance is expected to be simple and straightforward.



E. Chemical Properties

Melting point: 76-77 °C (i-PrOH/H_2O)[5]
Boiling point: Not reported.
Solubility: ~0.2 mg/mL in 1:4 EtOH:phosphate-buffered saline (pH 7.2); ~30 mg/mL in EtOH, DMF, and DMSO.[8]

F. Identification and Analysis

A range of routine and standard methods can be applied for the chemical analysis of XLR-11 in bulk form (e.g. spiked plant matter, powder and liquids). More sensitive analytical techniques may be needed (e.g. single or multistage mass spectrometry) for the detection of this substance in biological matrices with low concentration. For the analysis of biological fluids such as urine, the detection of the unchanged parent molecule may be challenging, thus, requiring the detection of XLR-11 metabolites instead. Table 1 (Annex 2) provides a list of representative examples published in the scientific literature.

3. Ease of Convertibility Into Controlled Substances

No information available.

4. General Pharmacology

A. Routes of administration and dosage

XLR-11, in its pure form but mostly as a constituent in herbal mixtures, is most commonly smoked but reliable data about dosage are unavailable. The variations in drug composition and quantities frequently observed with many smoking mixtures (e.g.[1]) make such an estimation impossible for users as well despite what might be written on a product label.

B. Pharmacokinetics

One key finding associated with the transformation of XLR-11 in biological fluids includes the fact that several metabolites are identical to those formed from UR-144 metabolism (including formation of UR-144 as a metabolite of XLR-11) and that the detection of XLR-11 metabolites in urine should be targeted rather than attempting to detect the parent, unchanged compound. XLR-11, equivalent to what is observed with UR-144, undergoes heat-induced degradation during smoking (and some forms of instrumental analysis such as gas chromatography), which yields the formation of 1-(1-(5-fluoropentyl)-1*H*-indol-3-yl)-3,3,4-trimethylpent-4-en-1-one, thus, presenting an additional target for bioanalytical applications. The extent to which the formation of UR-144 metabolites affects the detection window related to XRL-11 intake remains to be investigated.

Several *in vitro* metabolism studies have been published in the scientific literature, which included the use of human hepatocytes,[9] human hepatocellular carcinoma cells (HepaRG)[10], pooled human liver microsomes (pHLMs)[11, 12] and recombinant

human CYP enzymes.[12] In the case where human hepatocytes were employed (phase I and phase II, analysis after 1h and 3 h), more than of 25 biotransformation products were detected resulting from hydroxylation, carboxylation, hemiketal and hemiacetal formation, dehydration, and glucuronidation of some oxidative metabolites, including oxidative defluorination. Major metabolites identified included 2'-carboxy-XLR-11, UR-144 pentanoic acid, 5-hydroxy-UR-144, 2'-carboxy-UR-144 pentanoic acid, 2'-hydroxy-XLR-11 glucuronide and 1'-hydroxy-XLR-11 glucuronide, respectively.[9] The incubation of XLR-11 in HepaRG cells for 48 h followed by enzymatic hydrolysis revealed the detection of 12 metabolites, which included UR-144 pentanoic acid and 5-hydroxy-UR-144.[10] Incubation with pHLMs (analysis after 15 min and 90 min) confirmed the involvement of hydroxylation, dioxidation followed by internal dehydration, carboxylation, *N*-dealkylation, oxidative defluorination and various combinations thereof. Furthermore, it was shown that CYP3A4 was the major isozyme involved in the CYP mediated transformation of XLR-11.[12] In another *in vitro* study using pHLMs (2 h incubation), the dominating metabolite was identified as 5-hydroxy-UR-144. A comparison with UR-144 transformation under identical conditions suggested a different ratio between 5-hydroxy-UR-144 and 4-hydroxy-UR-144 that was not detected following XLR-11 incubation.[11]

The analysis of male ICR mice urine samples obtained from intravenous injection of XLR-11 in the tail vein revealed the presence of monohydroxylated metabolites along with their glucuronide conjugates including 5-hydroxy-UR-144. The defluorinated analog UR-144 and other carboxylated species have also been detected.[13] Interestingly, the main metabolites detected in an authentic urine sample obtained from a XLR-11 user included the *N*-(5-hydroxypentyl) and the *N*-pentanoic acid derivatives of the XLR-11 degradant mentioned above.[10] The analysis of six authentic urine specimens both (with and without enzymatic hydrolysis) revealed the detection of 19 metabolites, also displaying oxidative defluorination, hydroxylation, carboxylation, dehydrogenation, glucuronidation, and combinations of these reactions. The majority of metabolites were identified as the transformation products based on the XLR-degradant.[11]

The detection of the parent molecule in blood however, has been demonstrated in a number of clinical cases.[14, 15] In an analysis report on hair samples associated with XLR-11 consumption the detected species were XLR-11, UR-144, 5-hydroxy-UR-144, UR-144 pentanoic acid, 4-hydroxy-UR-144 and 4-hydroxy-XLR-11, respectively.[16] Unchanged XLR-11, hydroxylated metabolites and the XLR-11 degradant could also be detected in oral fluid samples associated with the presence of XLR-11 and UR-144.[17]

C. Pharmacodynamics

Information about the effects are currently available from a number of *in vitro* and *in vivo* assays is summarized in Tables 2 and 3, which demonstrate effects also observed with Δ^9-THC, which, when tested under *in vivo* conditions, could be attenuated with rimonabant.

For example, radioligand displacement studies with hCB_1 and hCB_2 (HEK-293) using [^{3}H]CP-55,940, [^{3}H]SR-144,528 and [^{3}H]rimonabant confirmed that XLR-11 showed higher affinity to both receptor subtypes in the low nanomolar range compared to Δ^9-THC (Table 2) with a ~11-fold selectivity toward CB_2. Both receptors were also activated at low nanomolar concentrations ([^{35}S]GTPγS binding) and XLR-11 acted as a full agonist.[13] XLR-11 was more potent and showed higher efficacy than Δ^9-THC in the ability to activate G protein-gated inwardly rectifying K^+ channels (GIRKs).[5] XLR-11 was also found to be more or less equipotent in the ability to inhibit CB_1 receptor mediated inhibition of glutamate release in mouse hippocampal slice preparations (blocked by CB_1 receptor antagonists AM251 or PIMSR1), although JWH-018 was about 67-fold more potent (Table 2).[18] *In vivo* studies revealed that the effects of XLR-11 were mechanistically consistent with Δ^9-THC (Table 3).

Similar to UR-144,[19] XLR-11 has been reported to convert into 1-(1-(5-fluoropentyl)-1*H*-indol-3-yl)-3,3,4-trimethylpent-4-en-1-one as a consequence of exposure to heat (e.g. during chemical analysis by gas chromatography-based systems) or smoking,[20] which means that it can also undergo biotransformation (see Section 4B). Information about the pharmacodynamic properties of this degradant is currently unavailable. Interestingly, the metabolite common to both XLR-11 and UR-144 (5-hydroxy-UR-144) was identified as a CB_2 selective agonist[5, 7] but the extent to which this impacts on the overall drug effects in users of XLR-11 is unclear.

Table 2. XLR-11 *in-vitro* data	**Ref**
Receptor binding: [a] XLR-11: CB_1 K_i = 24 nM ([^{3}H]CP-55,940), 234 nM ([^{3}H]SR-144,528) and CB_2: K_i = 2.1 nM ([^{3}H]CP-55,940). Δ^9-THC (data from previous study): CB_1 K_i = 67 nM ([^{3}H]CP-55,940), 764 nM ([^{3}H]SR-144,528) and CB_2 K_i = 36 nM ([^{3}H]CP-55,940). Rimonabant (data partially from previous study): CB_1 K_i = 6 nM ([^{3}H]CP-55,940), 1.8 nM ([^{3}H]SR-144,528) and CB_2 K_i = 702 nM ([^{3}H]CP-55,940). CP-55,940 (data partially from previous study): CB_1 K_i = 1 nM ([^{3}H]CP-55,940), 31 nM ([^{3}H]SR-144,528) and CB_2 K_i = 0.7 nM ([^{3}H]CP-55,940). UR-144: CB_1 K_i = 29 nM ([^{3}H]CP-55,940), 368 nM ([^{3}H]SR-144,528) and CB_2 K_i = 4.5 nM ([^{3}H]CP-55,940). [^{35}S]GTPγS binding (all three tested compounds were full agonists at both receptors): [b] CB_1 receptors: XLR-11: ED_{50} = 159 nM; CP-55,940: ED_{50} = 25 nM; UR-144: ED_{50} = 98 nM. CB_2 receptors: XLR-11: ED_{50} = 145 nM; CP-55,940: ED_{50} = 23 nM; UR-144: ED_{50} = 334 nM.	Wiley *et al.*[13]
Functional activity: [c] CB_1 receptors: XLR-11: ED_{50} = 98 nM; WIN-55,212-12: ED_{50} = 284 nM; Δ^9-THC: ED_{50} = 250 nM; UR-144: ED_{50} = 421 nM. CB_2 receptors: XLR-11: ED_{50} = 83 nM; WIN-55,212-12: ED_{50} = 62 nM; Δ^9-THC: ED_{50} = 1157 nM; UR-144: ED_{50} = 72 nM. Efficacy relative to WIN 55,212-2 to stimulate hyperpolarization (= 100%): CB_1 receptors: XLR-11: 110%; Δ^9-THC: 51%; UR-144: 94% CB_2 receptors: XLR-11: 117%; Δ^9-THC: 13% (at 10 μM); UR-144: 104%	Banister *et al.*[5]
Receptor binding: [d] XLR-11: CB_1 IC_{50} = 7.92 nM; UR-144: IC_{50} = 578.5 nM. Functional activity: [d] XLR-11: CB_1 EC_{50} = 359 nM (efficacy 104.95%); UR-144: EC_{50} = 1295 nM (efficacy 95.28%).	Gatch *et al.*[21]
Functional activity: [e] cAMP inhibition assay: XLR-11: EC_{50} = 3981 nM (efficacy 65%); WIN 55,212-2: EC_{50} = 31.6 nM (efficacy 65%); CP-55,940 EC_{50} = 316 nM (efficacy 47%). CB1 agonist-mediated reductions in forskolin-stimulated cAMP levels were blocked in the presence of rimonabant. CB_1-induced suppression of Ca^{2+} spiking in cultured rat hippocampal neurons. XLR-11 addition (1 and 10 μM) suppressed Ca^{2+} spiking. WIN-55,212-2 significantly suppressed Ca^{2+} spiking frequency at 10 μM, but not at 1 μM. WIN 55,212-3 (10 μM) did not suppress Ca^{2+} spiking to confirm CB_1-induced suppression whereas CP-55,940 suppressed spiking frequency at 10 μM.	Costain *et al.*[22]
	Hoffman *et al.*[18]

Electrophysiological recordings in mouse hippocampal slice preparations: [f] Maximal inhibition of glutamatergic field excitatory postsynaptic potential (fEPSPs): Δ^9-THC: EC_{50} = 707 nM (39% at 1 μM). XLR-11: EC_{50} = 933 nM (41% at 2 μM). JWH-018: EC_{50} = 14 nM (46% at 100 nM). Effects were reversed by addition of the neutral CB_1 antagonist PIMSR1. Slices incubated for 90 min with XLR-11 (1μM) showed significantly reduced long-term potentiation.	
Functional activity: [g] CB_1-induced suppression of Ca^{2+} spiking in a hippocampal neurons grown on a multi-electrode array (MEA) dish. XLR-11 (10 μM) significantly reduced Ca^{2+} mediated spikes in neurons grown on MEAs compared to DMSO at the 40, 60 and 80 min time points. A CB_1-mediated mechanism was implicated given that rimonabant (5 μM) reversed the suppression.	Tauskela *et al.*[23]

[a] Ref[13]: hCB_1 and hCB_2 (HEK-293); [^{3}H]CP-55,940 (7.2 nM) or [^{3}H]rimonabant (2 nM) used for displacement (nonspecific binding determined by inclusion of 10 μM unlabeled CP-55,940 or rimonabant); concentration of [^{3}H]SR-144,528 not reported.
[b] Ref[13]: incubation of mixture containing test drug (0.25 nM to 20 μM), GDP (20 μM), GTPγ[^{35}S] (100 pM), and hCB_1 and hCB_2 membrane preparations from HEK-293 cells.
[c] Ref[5]: hCB_1 and hCB_2 receptors in stably transfected mouse AtT20 neuroblastoma cells; FLIPR membrane potential assay (blue) used for quantitative determination of K^+ flux (hyperpolarization) linked to G-protein activation: G-protein-gated inwardly rectifying K^+ channels (GIRKs); plates were incubated at ambient CO_2 for 45 min at 37 °C; WIN 55,212-2 produced maximal decrease in fluorescence, corresponding to hyperpolarization of 29% in AtT20-CB_1 cells and 31% in AtT20-CB_2 cells. Comparison of test drugs was normalized against the WIN 55,212-2 response. WIN 55,212-2 showed a 4-lod preference for stimulating hyperpolarization in AtT20-CB_2 cells compared to AtT20-CB_1 cells.
[d] Ref[21]: Assays carried out by NovaScreen (PerkinElmer, Waltham, Massachusetts, USA) under contract with the National Institute on Drug Abuse Addiction Treatment Discovery Program; hCB_1 receptors expressed in HEK-293 (binding) and CHO cells (functional activity). Further details not reported.
[e] Ref[22]: GloSensor™ cAMP assay; HEK293T cells transiently transfected with pGloSensor-22F and pcDNA6-CNR1; efficacy (% inhibition) relative to full agonist WIN-55,212-2. Synthetic cannabinoids were added 12 min prior to the addition of 10 μM forskolin. Luminescence was determined 15 min after forskolin addition; data were normalized to vehicle readings. Low-density primary hippocampal cultures were loaded with a Ca^{2+} indicator and exposed to low Mg^{2+} buffer to induce spontaneous, transient increases in intracellular Ca^{2+} levels (Ca^{2+} spikes).
[f] Ref[18]: Studies employed 4-to 6 week-old male wildtype C57BL6 mice or $CB1^{+/+}$ and $CB1^{-/-}$ mice bred on a C57BL6 background. The selective adenosine A1 receptor antagonist, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX, 200 nM), was included in the artificial CSF (aCSF) throughout incubation and recordings to avoid disruption CB_1R-mediated inhibition of glutamate release. During electrophysiological recordings, a switch between control aCSF and drug-containing aCSF was performed. Field excitatory postsynaptic potential (fEPSP) responses were monitored.
[g] Ref[23]: each multi-electrode array served as its own internal control: two 20 min baseline recordings were performed prior to acquiring four 20 min recordings with a cannabinoid or DMSO vehicle present; online extracellular spike detection was used.

Table 3. *In vivo* assay data for XLR-11	
Behaviour / physiology / neurochemistry	**Ref**
Tetrad test: [a] Spontaneous activity: XLR-11: ED_{50} = 0.9 µmol/kg Δ^9-THC: ED_{50} ED_{50} = 15 µmol/kg (positive control) UR-144: ED_{50} = 1.0 µmol/kg Drop in total counts compared to vehicle condition with significant difference ($p < 0.05$): XLR-11: 3 mg/kg Δ^9-THC: 30 mg/kg UR-144: not considered significant. Percent maximum possible antinociceptive effect: XLR-11: ED_{50} = 3.3 µmol/kg Δ^9-THC: ED_{50} = 12 µmol/kg (positive control) UR-144: ED_{50} = 2.6 µmol/kg Compared to vehicle condition with significant difference ($p < 0.05$): XLR-11: 3 mg/kg Δ^9-THC: 3, 10 and 30 mg/kg UR-144: 3 mg/kg Rectal temperature (hypothermia): XLR-11: ED_{50} = 0.6 µmol/kg Δ^9-THC: ED_{50} = 4 µmol/kg (positive control) UR-144: ED_{50} = 0.6 µmol/kg Drop in rectal temperature compared to vehicle condition with significant difference ($p < 0.05$): XLR-11: 0.1, 1 and 3 mg/kg Δ^9-THC: 1, 3, 10 and 30 mg/kg UR-144: 1 and 3 mg/kg Ring immobility (catalepsy): XLR-11: ED_{50} = 0.6 µmol/kg Δ^9-THC: ED_{50} = 3 µmol/kg (positive control) UR-144: ED_{50} = 1.0 µmol/kg Percentage increase in immobility compared to vehicle condition with significant difference ($p < 0.05$): XLR-11: 0.3, 1 and 3 mg/kg Δ^9-THC: 1, 3, 10 and 30 mg/kg UR-144: 1 and 3 mg/kg With the exception of the effects of XLR-11 in the ring immobility test, the cannabinoid effects of XLR-11 (3 mg/kg) and UR-144 (3 mg/kg) were blocked in the tetrad tests by prior administration of rimonabant (3 mg/kg). The effects of Δ^9-THC (10 mg/kg) were also attenuated by rimonabant but statistical significance ($p<0.05$) was not reached in the hypothermia test. Drug discrimination: [b] XLR-11: ED_{50} = 3.5 µmol/kg Δ^9-THC: ED_{50} = 5.4 µmol/kg (positive control)	Wiley *et al*.[13]

UR-144: ED_{50} = 7.4 μmol/kg Rimonbant (3 mg/kg) significantly antagonized substitution of 5.6 mg/kg doses of XLR-11 and UR-144. Response rates following agonist-antagonist combination were not significantly affected for XLR-11 but significantly decreased (compared to vehicle) for UR-144.	
<u>Body temperature:</u> [c] A moderate, dose-dependent decrease in body temperature was observed for XLR-11 and UR-144 at 10 mg/kg levels. Terminal fluorination did not induce a change. In comparison, a large hypothermic effect (-1.5 °C) was observed following JWH-018 administration (3 mg/kg). <u>Heart rate:</u> [c] A decrease in heart rate was observed for XLR-11 and UR-144 (and other test drugs studied) when administered between 0.3 and 10 mg/kg.	Banister *et al*.[5]
<u>Locomotor activity:</u> [d] XLR-11 (ED_{50} = 10.29 mg/kg), Δ^9-THC (ED_{50} = 11.14 mg/kg) and UR-144 (ED_{50} = 7.68 mg/kg) decreased locomotor activity as dose increased. Depressant effects of XLR-11 occurred within 10 min after administration and lasted 40-60 min. Maximal depressant effects of 10 and 30 mg/kg occurred 10-40 min after injection. Depressant effects of Δ^9-THC occurred within 10-50 min after injection and lasted 90-140 min. Maximal depressant effects were observed 30-60 min after 10 and 30 mg/kg. Depressant effects of UR-144 occurred within 10 min after administration and lasted 40-60 min. Maximal depressant effects of 10 and 30 mg/kg occurred 10-40 min after injection. <u>Drug discrimination</u>: [e] XLR-11 (ED_{50} = 0.18 mg/kg), Δ^9-THC (ED_{50} = 0.85 mg/kg) and UR-144 (ED_{50} = 0.45 mg/kg), amongst other synthetic cannabinoids tested, fully substituted for the discriminative stimulus effect of Δ^9- THC (3 mg/kg). XLR-11 (1 mg/kg) fully substituted from 5 to 15 min after administration, and drug-appropriate responding was nearly absent by 60 min. No effect on response rate was observed for this dose of XLR-11. UR-144 (2.5 mg/kg) fully substituted at 15 and 60 min after administration, and drug-appropriate responding was diminished to <40% after 4 h. No effect of UR-144 on the response rate was observed. No other adverse effects were observed at the doses and time points tested.	Gatch *et al*.[21]

[a] Ref[13]: Male ICR mice; intravenous injection in tail vein; spontaneous activity measured 5 min after drug injection for 10 min (two 4-beam infrared arrays, horizontal movement); warm water tail withdrawal procedure assessed with 55 °C warm water and tested at 20 min post-injection; rectal temperature measured with digital thermometer 30 min after injection; ring immobility: at 40 min post-injection, mice were placed on elevated ring set-up and the amount of time the animals remained motionless during a 5 min period was recorded.

[b] Ref[13]: Male C57/Bl6J inbred mice; trained to respond on one of the two levers following intraperitoneal (i.p.) administration of 5.6 mg/kg Δ^9-THC and to respond on the other lever following i.p. vehicle injection according to a fixed ratio 10 (FR10) schedule of food reinforcement, under which 10 consecutive responses on the correct (injection-appropriate) lever resulted in delivery of a food pellet; 15 min daily training sessions were held; once substitution tests with each compound were completed, a further assessment of rimonabant antagonism of the effects of 5.6 mg/kg XLR-11 and UR-144 was included. Three mg/kg rimonabant was injected i.p. 10 min prior to i.p. injection of XLR-

11 or UR-144.

[c] Ref[5]: male Wistar rats; biotelemetry transmitters placed in the peritoneal cavity; drugs administered (i.p.) in an ascending dose sequence (0.1, 0.3, 1, 3 mg/kg) (10 mg/kg if required) at the same time of day; data for heart rate and body temperature gathered at 1000 Hz (15 or 30 min bins). Data were corded for 6 h post-injection.

[d] Ref[21]: Male ND4 Swiss-Webster mice (~8 weeks old); 16 infrared beams were located in the horizontal direction; dose range tested: Δ^9-THC (1-30 mg/kg), UR-144 (1-30 mg/kg), XLR-11 (1-30 mg/kg), and others, immediately before testing. Horizontal activity (interruption of photocell beams, ambulation counts) was measured for 8 h within 10-min periods; behavioural observations of each mouse were recorded at 30, 120, and 480 min after the highest dose tested.

[e] Ref[21]: Male Sprague-Dawley rats; trained to discriminate Δ^9-THC (3 mg/kg) from vehicle using a two-lever choice methodology; each training session lasted 10 min; test drugs (amongst others): intraperitoneal injections of UR-144 (0.1-5 mg/kg, 30 min before start) and XLR-11 (0.05-1 mg/kg, 15 min before start). Δ^9-THC (3 mg/kg) controls were tested before the start of each compound evaluation.

5. Toxicology

The potential genotoxic properties of XLR-11 have been investigated using a variety of genotoxicity systems.[24] Gene mutations were not induced in bacterial mutagenicity tests with *Salmonella typhimurium* strains. *In vitro* single cell gel electrophoresis (SCGE) assays with human lymphocytes and with buccal- and lung-derived human cell lines revealed induction of DNA damage but was considered unrelated to oxidative damage. The addition of liver enzyme homogenate (S9 mix) confirmed that DNA-reactive intermediates were not formed as a consequence of XLR-11 biotransformation and that the addition of bovine serum albumin might have contributed to potential detoxification *via* protein binding. XLR-11 (tested between 25 μM and 150 μM) caused the formation of micronuclei in human mitogen-stimulated lymphocytes and in TR-146 cells at high doses, which reflected chromosomal aberrations. Furthermore, 5 mg and 20 mg samples of XLR-11 were vaporized to assess DNA stability in human-derived lung fibroblasts (A-549) and buccal (TR-146) cells *via* implementation of a gas-liquid interface in order to mimic drug exposure by inhalation. The observation of DNA instability suggested that exposure of drug vapor to cells in the respiratory tract may cause tumors and that further studies were needed to investigate further.[24]

6. Adverse Reactions in Humans

Adverse reactions associated with products determined to contain XLR-11 are summarized in Table 4 below. The total number of cases reported in the scientific literature is relatively small. The non-fatal cases feature the association with acute kidney injuries but the ability to identify a casual link in all cases with XLR-11 proved challenging and other possible etiologies might have to be considered as well. Commonly reported adverse reactions associated with a range of synthetic cannabinoids frequently include agitation, cardiovascular events including tachycardia and hypertension, hallucination, nausea/hyperemesis, seizures and hypokalaemia. Chest pain, myoclonia and psychiatric complications were also reported.[25, 26]

Table 4. Case reports associated with the involvement of XLR-11 reported in the scientific literature.

Year	Cases	Patient, age	Context/clinically related comments (examples)	Ref
2012	16	15M, 1F	Fifteen males aged 15-33 years (median: 18.5 years) and one female aged 15 years; Acute kidney injury associated with the intake of products containing synthetic cannabinoids in six US States between March 2012 and December 2012; all 16 patients initially visited emergency departments and subsequently were hospitalized. Clinical features: Nausea and vomiting in 15/16 cases; Twelve patients reported abdominal, flank, and/or back pain. None reported pre-existing renal dysfunction or use of medication that might have caused renal problems. The highest serum creatinine concentrations (creatinine peak) among the 16 patients ranged from 3.3 to 21.0 mg/dL (median: 6.7 mg/dL; normal 0.6–1.3 mg/dL) and occurred 1-6 days after symptom onset (median: 3 days). Urinalysis for 15 patients showed variable results: proteinuria (eight patients), casts (five), white blood cells (nine), and red blood cells (eight). Twelve patients underwent renal ultrasonography, nine of whom had a nonspecific increase in renal cortical echogenicity; none had hydronephrosis. Six of eight patients with a renal biopsy demonstrated acute tubular injury, and three of eight patients demonstrated features of acute interstitial nephritis. Kidney function recovery was apparent within 3 days of creatinine peak in most patients. However, five of the 16 patients required haemodialysis, and four patients received corticosteroids; none died. Other infectious, autoimmune, pharmacologic, or other toxic causes of AKI were not found. Product used by 5/16 patients, including two patients who used the same product, contained XLR-11. XLR-11 and/or the *N*-pentanoic acid metabolite) was detected in five of the seven cases for whom clinical specimens were available. The consistent finding of XLR-11 in product samples and clinical specimens was suggested to include alternative explanations: XLR-11, a metabolite, or a contaminant associated with it might be responsible for AKI in these patients, or its presence might simply reflect the widespread use of this particular compound in SC products during the study period rather than a causal association with AKI.	CDC[3]
2013	1	26M	Acute kidney injury. Case also included in CDC report above.[3] Patient presented to the emergency department with one day of abdominal pain, nausea, vomiting and lower back pain. Vital signs: 97.7° F; heart rate: 54 bpm; blood pressure: 151/40 mmHg; respiratory rate: 16 breaths per min with 100% SatO2. Laboratory evaluation proved to be remarkable for a 14.4 K/mm3 WBC, 5.38 mg/dL serum creatinine, 30 mg/dL blood urea nitrogen (BUN), and urinalysis with 1+ protein and trace blood. On Day 2 in the hospital, creatinine and BUN peaked at 7.74 and 39 mg/dL; discharged after six days in the hospital with AKI of unknown etiology and serum creatinine of 3.09 mg/dL. Twenty three days later his serum creatinine was 1.1 mg/dL. Product and biofluids analysis confirmed the presence of XLR-11 and UR-144; patient reporting use of this branded product two or three times a day for approximately one year and had used the product on the morning of his presentation.	Thornton *et al.*[27]

2014	9	All M	Acute kidney injury. Cases appear to be related to those mentioned in CDC report above.[3] Males aged 15-27 years (median, 18 years). Nine patients: initial symptoms acute onset of severe nausea, emesis, and back or abdominal pain (89%). In cases who recalled their last exposure, they reported symptom onset between approximately 30 min and 24 h (median: 8-12 h) after smoking a synthetic cannabinoid product. One patient reported gross hematuria, and one presented with uremic encephalopathy (blood urea nitrogen, BUN. 177 mg/dL). All required hospitalization. All patients had elevated peak systolic blood pressure (median, 154 mm Hg; range, 138-172 mm Hg). Initial BUN concentration ranged from 24 to 177 mg/dL (median, 42 mg/dL), and peaked at 28-177 mg/dL (median, 42 mg/dL). Initial serum creatinine concentration ranged from 2.6 to 17.7 mg/dL (median, 6.6 mg/dL); it peaked 2-7 days (median, 4 days) after symptom onset (median peak Cr, 7.9 [range, 2.6-17.7 mg/dL]). Eight patients demonstrated leukocytosis (89%). Renal ultrasound performed on eight patients revealed a nonspecific increase in cortical echogenicity without hydronephrosis for seven (88%) patients. For two patients, peak creatinine persisted for 4 days, and recovery of renal function occurred after patients received corticosteroids or hemodialysis. Four patients had smoked the synthetic cannabinoid product with a total of five other contacts, none of whom reported illness to the cases. Synthetic cannabinoid products (n=2) and clinical specimens (n=9) were obtained from five patients. XLR-11 and the *N*-pentanoic acid metabolite was detected in one serum sample with an interval of last use and sampling of 44 h. Treatment for the majority of cases: fluid management. Whether XLR-11 caused acute kidney injury could not be unambiguously concluded.	Buser *et al.*[28]
2014	1	22M	Intoxication and involvement in a road traffic accident. Driver displayed a lethargic attitude and behavior with slow speech, low body temperature, rigid muscle tone, normal pulse, lack of horizontal and vertical gaze nystagmus, nonconvergence of the eyes, dilated pupil size, and normal pupillary reaction to light. Blood analysis revealed a blood concentration of 1.34 ng/mL.	Lemos *et al.*[15]
2014	18	All male	Intoxication and impaired driving. Mean age: 25 y (range 17-42, median 23.0). Eight cases revealed detection of XLR-11 (blood) and 4 cases showed the presence of UR-144 and XLR-11 (blood). Slurred speech, lack of convergence, and body and eyelid tremors were most consistently noted during interview. Horizontal gaze nystagmus, bloodshot and watery eyes were also described.	Louis *et al.*[14]
2014	1	33M	Acute cerebral ischemia and infarction following consumption of a herbal product containing XLR-11. His vital signs upon arrival were BP, 163/63 mmHg; pulse, 100/ min; respiration, 16/min; oxygen saturation, 99% on room air; and afebrile. The patient was right-handed, and his initial physical examination was significant with right facial weak-ness/flattening of the right nasolabial fold, minor right hemiparesis, dysarthria, aphasia, and a mild right pronator drift. The National Institutes of Health Stroke Scale (NIHSS) score was 5, which improved to a score of 3 within an hour. A repeat head CT, performed the next day, showed acute infarction in the left insular cortex. Analysis of herbal product revealed the presence of XLR-11 but it was not detected in blood	Takematsu *et al.*[4]

			and urine collected 1 h after inhalation.	
2015	2	29F, 32F	Case 1: 29F found dead with reported signs of intoxication and agitation the day before; known to be user of synthetic cannabinoid products; diphenhydramine (81 ng/mL) and XLR-11 (1.4 ng/mL) detected in peripheral blood. Medical examiner certified the cause of death as synthetic cannabinoid toxicity and the manner of death as accident. Case 2: 32F with history of drug abuse, including methamphetamine, heroin, and synthetic cannabinoids, presented to the emergency room with chest pain, nausea, and agitation. She was diagnosed with anxiety and left the hospital; was later found unresponsive and died. Remarkable pathological findings at autopsy were significant pulmonary edema and congestion, along with acute visceral congestion and mild pulmonary anthracosis. XLR-11 detected (0.6 ng/mL). Naloxone was administered during resuscitation attempts. Medical examiner ruled the cause and manner of death as undetermined, with significant findings of positive toxicology for XLR-11.	Shanks *et al*.[29]

7. Dependence Potential

A. Animal Studies

No information available.

B. Human Studies

No information available.

8. Abuse Potential

A. Animal Studies

The *in vivo* data summarized in Table 3 suggest that XLR-11 displays abuse liability.

B. Human Studies

No information available.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Not applicable.

10. Listing on the WHO Model List of Essential Medicines

XLR-11 is not listed on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

XLR-11 is not marketed as a medicine.

12. Industrial Use

XLR-11 has no reported industrial use.

13. Non-Medical Use, Abuse and Dependence

Household or subpopulation surveys that specifically probe for prevalence of XLR-11 are currently not available in the published literature.

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

The majority of available synthetic cannabinoid products (including those identified to contain XLR-11) is sold in the form of herbal mixtures, and designed for smoking purposes. It is common for retailers to purchase bulk quantities of the synthetic substance and to add the synthetic material to a variety of vegetable matter as the plant base. Products sold as herbal smoking mixtures frequently change in drug composition and quantity, often without indications on product labels.[1, 30]

The consumption of these products might be attractive to a variety of users, such as regular users of cannabis and those who might wish to avoid drug-testing procedures resulting in positive cannabis findings. Ease of access, and perceived lack of control might equally be of interest to some users. The high potency associated with many synthetic cannabinoids carries the risk of accidental overdose and potentially severe adverse events but information specific to XLR are limited. Cases specific to XLR-11 have been summarized in Table 4 of Section 6 including examples of impaired driving under the influence of XLR-11.

15. Licit Production, Consumption and International Trade

XLR-11 is available as standard reference material and produced for scientific research by a number of commercial suppliers. Other uses are not known.

16. Illicit Manufacture and Traffic and Related Information

Reports have been received from the EMCDDA's European Early-Warning System on new psychoactive substances that XLR-11 (first reported in 2012) was encountered in seizures or as a used substance in Greece, France, Bulgaria, United Kingdom, Cyprus, Ireland, Romania, Italy, Czech Republic, Latvia, Finland, Croatia, Sweden, Denmark, Spain, Belgium, Germany, Norway, Austria, Slovenia, and Hungary.[31]

In 2012, XLR-11 has been reported to UNODC by Norway and Portugal.[32] XLR-11 was reported 97 times to the UNODC Early Warning Advisory on New Psychoactive Substances by 39 Countries since 2012 (2015 data not complete yet at the time of this writing). The highest number of reports was received in 2014 (Dr. Justice Tettey, UNODC, personal communication).[33] In South Korea, XLR-11 has been reported to represent the most frequently seized synthetic cannabinoid in 2013 with a total number of synthetic cannabinoid seizures reaching more than 40.[34]

Between 2009 and June 2013, 26 species of synthetic cannabinoids were identified by the the National Forensic Service in South Korea in materials seized mainly by the Police Agency and the Prosecutor's Office in South Korea.[34] Another report stated that until 2014, XLR-11 was identified in 75 seized materials in 24 cases submitted to the National Forensic Service by the police or public prosecutor's office.[11]

XLR-11 appeared to be particularly prevalent in the United States since 2012. The National Forensic Laboratory Information System (NFLIS), which is dedicated to the collection of drug cases submitted by State and local laboratories in the United States, registered 19,795 reports linked to XLR-11 in the period between January 2010 and June 2013. The January - June 2013 period alone accounted for 11,273 reports.[35] The NFLIS 2014 midyear report (revised in March 2016) documented that XLR-11 featured in 6,316 out of 18,823 reports on synthetic cannabinoids compared to a total number of 660,078 reported for the top 25 drugs (e.g. cannabis/THC = 230,330 reports).[36] In comparison, the NFLIS 2015 midyear report documented that XLR-11 featured in 3,769 out of 17,053 reports on synthetic cannabinoids. The total number of reports for the top 25 was 659,842 (cannabis/THC = 204,030 reports).[37]

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current International Controls and Their Impact

XLR-11 is not controlled under the 1961, 1971 or 1988 United Nation Conventions.

18. Current and Past National Controls

The EMCDDA received information from the National Focal Points that XLR-11 is controlled in the following countries:[31] Belgium, Czech Republic, Denmark, Estonia, Finland, Hungary, Lithuania, Portugal, Romania, Turkey, United Kingdom. XLR-11 is also controlled in China[38] and the United States.[39-41]

Also refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

Not applicable.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 38th ECDD: Evaluation of XLR-11

Data was obtained from 47 Member States (6 AFR, 2 EMR, 26 EUR, 7 PAH, 1 SEAR and 5 WPR).

A total of 39 Member States (4 AFR, 2 EMR, 20 EUR, 7 PAH, 1 SEAR and 5 WPR) answered the questionnaire for XLR-11. Of these, 23 respondents (1 AFR, 2 EMR, 17 EUR, 2 PAH and 1 WPR) had information on this substance.

LEGITIMATE USE

There were 20 countries that reported no approved medical products containing XLR-11 for human or veterinarian indications. There was also no reported industrial use in 17 countries.

XLR-11 is currently being used in medical or scientific research in one country for metabolism and abuse potential research. Importation is the origin/source of XLR-11 when used for legitimate non-medical/non-scientific use.

XLR-11 was not reported to be used for any cultural, religious or ceremonial purposes in 19 countries.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

There were 13 countries that reported XLR-11 as being misused for its psychoactive properties (as a recreational drug). Common routes of administration for non-medical/non-scientific purposes are smoking (9 countries), oral (2 countries), inhalation (2 countries) and sniffing (1 country). The main route of administration for XLR-11 was reported as smoking (5 countries) and oral (1 country).

The most common formulation reported for non-medical/non-scientific purposes was powder (5 countries), followed by tablets (1 country). Another common formulation reported was herbal mixtures or plant material impregnated with the XLR-11 (11 countries). One country mentioned that it was prepared in this way to resemble cannabis.

There were 9 countries which reported that the source of XLR-11 for non-medical/non-scientific use was smuggling.

Specific subpopulations known to misuse XLR-11 included cannabis users (1 country) and youth (1 country).

The level of negative health-impact originating from this substance's non-medical consumption was reported as either negligible (3 countries), substantial (1 country) or serious (4 countries). For the countries that indicated a substantial or serious level of negative health-impact, they specified

that it was due to the association of XLR-11 with adverse effects (including intoxications, kidney injuries/toxicity, collapses, psychosis) and fatalities.

One country reported emergency room/department visits related to the non-medical use of XLR-11. They had 1 case in 2012 and 1 case in 2013, in both instances other substances were detected.

The adverse effects which presented for XLR-11 at the emergency room/department included dizziness, cardiac and circulatory troubles, vomiting, acute psychosis. One country commented that neurological and cardiovascular adverse effects have been noted following XLR-11 ingestion. They also stated that an association between XLR-11 and acute kidney injury has been reported.

In regards to the mortality rate, data was provided by 1 country where they had a case in 2013 where only XLR-11 was involved. Another country reported 10 cases in 2010 to 2015 where other substances were also involved. One country commented that there may be a higher number of cases because in their country there is no reporting obligation by hospitals, poison centers etc.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

There were 19 countries reported that XLR-11 was under national control. The legislation the control is based upon included Medicines Act (3 countries), Controlled Substances Act (12 countries), Criminal Law Act (1 country) and other specific legislation (2 countries stated that it was specific legislation for new psychoactive substances). In two countries the current control is a temporary measure. Another country reported that it is not currently under control but an amendment to their legislation on new psychoactive substances is currently in preparation. There were no challenges to implementing controls for XLR-11 reported.

The scope of the controls includes production (16 countries), manufacturing (17 countries), exporting (16 countries), importing (18 countries), distribution (17 countries), use (11 countries) and possession (16 countries).

Reported illicit activities involving XLR-11 include manufacture of the substance by chemical synthesis (1 country), production of consumer products (2 countries), trafficking (8 countries), smuggling (1 country), diversion (1 country), domestic internet sales (1 country), internet sales from abroad (5 countries), internet sales from unknown locations (4 countries) and finally sales to people who use this substance (4 countries).

There were 14 countries which completed the section on the number of seizures. The combined number of seizures was 11,109 (2014), 7,111 (2015) and 1,227 (2016 to date). One country commented that they had noticed a decline of cases as soon as the substance was placed under control by national legislation.

If XLR-11 was placed under international control, 22 countries responded that they would have the capacity to enforce the control at the national level. There were 22 countries which responded that they would have the forensic laboratory capacity to analyse the substance.

Annex 2: Representative examples of studies associated with the detection and chemical analysis of XLR-11 (amongst other substances) published in the scientific literature.

Table 1. Representative examples of studies published in the scientific literature associated with the analysis of XLR-11 amongst other substances [a, b]

Techniques [c]	Comment	Reference
GC-MS, LC-TOF-MS, NMR	Analysis of herbal products seized in June/July 2012.	Choi *et al*.[1]
ELISA	XLR-11 showed cross-reactivity with JWH-200 calculated at a 0.03% level.	Rodrigues *et al*.[2]
GC-MS	Analysis of 3481 items seized between January 2010 and December 2012 (1321 cases). XLR-11 was detected in ~25% of the items.	Seely *et al*.[3]
LC-TOF-MS	Analysis of herbal samples.	Shanks *et al*.[4]
GC-MS, LC-QTOF-MS, NMR	Characterization of seized samples.	Shevyrin *et al*.[5]
GC-MS, LC-DAD, LC-MS, DART-TOF-MS, NMR	Analysis of herbal samples purchased *via* the Internet between October 2011 and April 2012.	Uchiyama *et al*.[6]
LC-QTOF-MS/MS	Urine analysis of XLR-11 and UR-144 metabolites following administration of test drugs in male ICR mice.	Wiley *et al*.[7]
LC-QqQ-TOF-MS	*In vitro* metabolism study using pooled human hepatocytes.	Wohlfarth *et al*.[8]
LC-QTOF-MS, GC-MS, FT-IR	Analysis of seized resinous samples.	Zuba *et al*.[9]
CE, MEKC-MS/MS	Method development and application to herbal samples.	Akamatsu *et al*.[10]
LC-MS/MS	Method development and application to 498 authentic oral fluid samples.	Amaratunga *et al*.[11]
LC-TOF-MS	Detection of XLR-11 in two products and one clinical serum sample from 2012.	Buser *et al*.[12]
Immunoanalysis	Method validation for synthetic cannabinoids in urine and application to authentic urine samples.	Castaneto *et al*.[13]
GC-MS	Analysis of 140 samples species seized between 2009 and 2013.	Chung *et al*.[14]
LC-MS/MS	Method development and application to authentic serum samples.	Huppertz *et al*.[15]
Presumptive color test	Evaluation of Brady's reagent (2,4-dinitrophenylhydrazine).	Isaacs[16]
GC-MS, LC-MS/MS, NMR	Analysis of herbal plant products obtained from test purchases.	Langer *et al*.[17]
EI-MS, LC-MS/MS	Detection in whole blood from an impaired driver.	Lemos *et al*.[18]
LC-MS/MS	Detection of XLR-11 in clinical samples obtained from impaired driving cases collected between June 2012 and September 2013.	Louis *et al*.[19]
ELISA, LC-MS/MS	Method validation and application to authentic urine samples.	Mohr *et al*.[20]
LC-MS/MS	Method development for analysis in urine.	Scheidweiler *et al*.[21]
GC-MS	Detection of XLR-11 in a product involved in serious adverse reaction.	Takematsu *et al*.[22]
TLC, NMR, m.p., elemental analysis; ESI-MS	General characterization following synthesis.	Banister *et al*.[23]
IMS, DART-QTOF-MS	Analysis of standard reference material.	Gwak *et al*.[24]
GC-(EI/CI)-MS/MS	Analysis of standard reference material.	Gwak *et al*.[25]
LC-IT-MS	*In vitro* metabolism study using HepaRG cells and analysis of clinical urine sample.	Kanamori *et al*.[26]

Miniature MS	Analysis of standards using two ambient ionization methods (paper spray and extraction spray).	Ma *et al*.[27]
LC-TOF-MS, GC-MS	Analysis of standards.	Marginean *et al*.[28]
LC-DAD, GC-MS	Analysis of 4,127 packages (31 different brands) seized in March 2012. XLR-11 was detected in some but not all items.	Moosmann *et al*.[29]
LC-MS/MS	Analysis of hair samples obtained from laboratory personnel handling herbal mixtures containing synthetic cannabinoids. XLR-11 detected in hair samples from 2/8 participants.	Moosmann *et al*.[30]
LC-MS/MS	Analysis of hair samples obtained from users and detection of XLR-11 in 14 samples.	Park *et al*.[31]
LC-MS/MS	Analysis of biofluids in two fatalities associated with XLR-11.	Shanks *et al*.[32]
Immunoanalysis	Application to herbal products.	Uchiyama *et al*.[33]
LC-MS/MS	Method development and application to authentic samples (XLR-11 not detected in case samples).	Adamowicz and Tokarczyk[34]
LC-Q-MS	Evaluation of matric effects in spiked blank blood samples.	Adamowicz and Wrzesień, [35]
LC-DAD, LC-Q-MS, SFC-MS	Method development using standards.	Breitenbach *et al*.[36]
LC-MS/MS	Method development and screening of 526 urine samples obtained from suspects of impaired driving between June 2012 and August 2013.	Davies *et al*.[37]
Electroanalysis, GC-MS, LC-MS	Method development and application to seized samples.	Dronova *et al*.[38]
LC-QTOF-MS	*In vitro* metabolism study and application to 18 authentic urine samples obtained from users.	Jang *et al*.[39]
ATR-IR, Raman, NMR	Analysis of 221 seized samples.	Jones *et al*.[40]
FT-ICR-MS	Analysis of nine herbal samples.	Kill *et al*.[41]
LC-Q-Orbitrap	*In vitro* metabolism study using human liver microsomes and recombinant CYP enzymes.	Nielsen *et al*.[42]

[a] As of August 2016.

[b] The term 'herbal' product typically refers to a variety of vegetable plant matters that have been spiked with the synthetic drug and do not refer to a natural product containing these substances.

[c] GC: gas chromatography; MS: mass spectrometry; LC: liquid chromatography (various forms); TOF: time-of-flight; NMR: nuclear magnetic resonance spectroscopy; ELISA: enzyme-linked immunosorbent assay; DAD: diode array detection; DART: direct analysis in real time; QTOF: quadrupole-time-of-flight; QqQ: triple quadrupole; FT-IR: Fourier transform infrared spectroscopy; CE: capillary electrophoresis; MEKC: micellar electrokinetic chromatography; MS/MS: tandem mass spectrometry; EI: electron ionization; m.p.: melting point; IMS: ion mobility spectrometry; CI: chemical ionization; IT: ion trap; Q: quadrupole; SFC: supercritical fluid chromatography; ATR-IR: attenuated total reflectance IR; FT-ICR-MS: Fourier transform ion cyclotron mass spectrometry.

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