

AM-2201

Critical Review Report

Agenda item 4.7

Expert Committee on Drug Dependence
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**World Health
Organization**

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Summary

AM-2201 is an aminoalkylindole used as an active ingredient of products sold as cannabis substitutes. When smoked, AM-2201 produces cannabimimetic effects in doses lower than the doses of Δ^9 -tetrahydrocannabinol (THC) needed to produce effects of similar strength (higher potency). Many of the risks linked to cannabis use are also present in the case of AM-2201, among them complications in patients suffering from cardiovascular diseases and triggering of acute psychosis. Abuse potential and dependence potential seem to be similar to cannabis. One of the major differences between cannabis and this synthetic cannabinoid is the greater acute toxicity of AM-2201. Due to its full agonistic action at the CB1 receptor and extraordinarily high potency, the side effects of higher doses can be life-threatening. This is aggravated by the fact that dosing is very difficult due to changing contents of active ingredients in different products, different batches of the same product and even within one packet. Regarding chronic toxicity, risks are very difficult to estimate on the basis of the available data. However, there are concerns about potential carcinogenic effects. In contrast to JWH-018 and JWH-073, AM-2201 carries a fluorine atom at the 5 position of the alkyl side chain, which is subject to metabolic transformation and gives rise to additional concern with regard to potential toxicity.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable

B. Chemical Abstract Service (CAS) Registry Number

335161-24-5

C. Other Names

AM-2201, AM2201, 1-(5-fluoropentyl)-3-(1-naphthoyl)indole, JWH 2201

D. Trade Names (hydrobromide salt)

None

E. Street Names

‘Spice’, ‘K2’, ‘legal weed’, ‘synthetic cannabis’, ‘herbal incense’

AM-2201 was found as an additive in over 90 different brands of ‘herbal mixtures’ in Germany alone (own unpublished data). These products were carrying fantasy names like e.g.: ‘Agent Orange’, ‘Atomic Bomb’, ‘Green’, ‘Jamaican Gold Extreme’, ‘Manga Xtreme’, ‘New Bonzai’ and ‘XoXo’.

One should be aware of the fact that mixtures sold under specific brand names do not always contain the same substance or mixture of substances over time.

F. Physical properties

White crystalline solid (in pure form), soluble at ~5mg/ml in ethanol.

G. WHO Review History

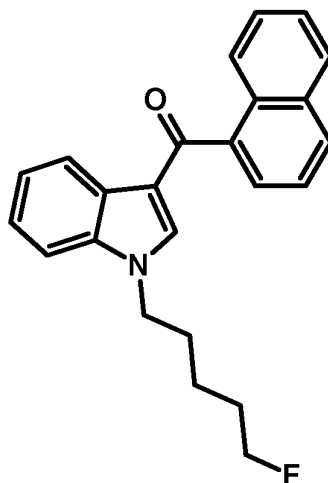
AM-2201 was not previously pre-reviewed or critically reviewed. A direct critical review is being proposed based on information brought to WHO’s attention that AM-2201 is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. 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

IUPACName: [1-(5-Fluoropentyl)-1H-indol-3-yl](naphthalen-1-yl)methanone

CA Index Name: [1-(5-Fluoropentyl)-1H-indol-3-yl]-1-naphthalenyl-methanone

B. Chemical Structure

Molecular Formula:	C ₂₄ H ₂₂ FNO
Molecular Weight:	359.43 g/mol
Melting point:	93.7 °C ^[1]
Boiling point:	n/a
Fusion point:	n/a

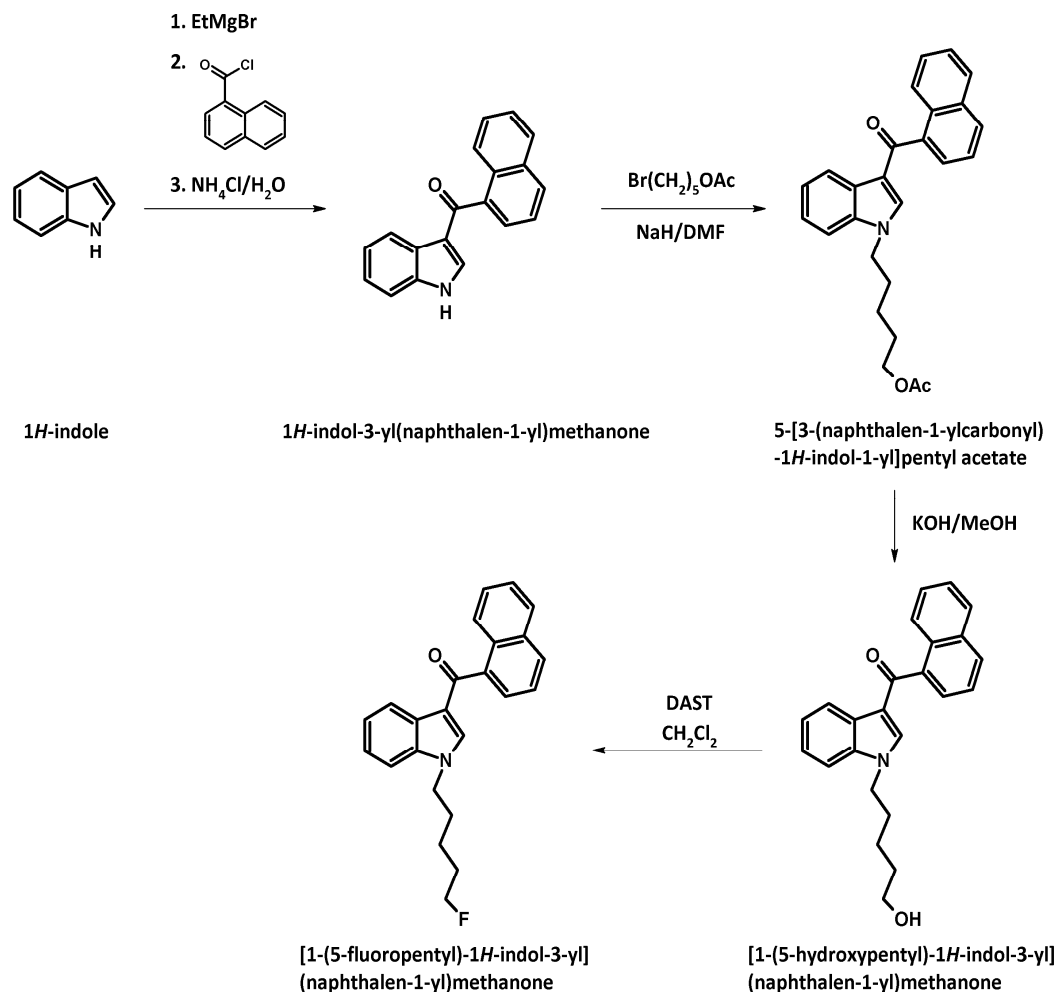
C. Stereoisomers

None

D. Synthesis

Synthesis of AM-2201 was first reported in 2001 by Alexandros Makriyannis and Hongfeng Deng [2]. Starting from a 1-H indole solution in acetic acid ethyl ester, a solution of methyl magnesium bromide in acetic acid ethyl ester is added. Then, naphthalene-1-carbonyl chloride (prepared from naphthalene-1-carboxylic acid and thionyl chloride) is added, followed by the addition of an aqueous solution of ammonium chloride. Afterwards, the obtained filtrate of 1H-indol-3-yl(naphthalen-1-yl)methanone is washed and recrystallized. This product is added to a suspension of sodium hydride in dimethylformamide (DMF) followed by the addition of 5-bromopentylacetate for N-alkylation. After cleavage of the acetate using a methanolic potassium hydroxide solution, fluorination of the pentyl side chain is performed utilizing diethylaminosulfur trifluoride (DAST) and dichloromethane (Figure 1)

Figure 1: Synthesis of AM-2201



Commercially available domestic or industrial products, which could be used for synthesis, may contain other potentially toxic substances, including heavy metals and organic solvents. Use of such products as reagents may result in serious toxic effects if the resultant impure product is consumed. The herbal material which is used as a basis for the smoking mixtures may contain toxicologically relevant substances like e.g. pesticides, too.

E. Chemical description

AM-2201 is a naphthoylindole alkylated at the indole nitrogen and carries a fluorine atom at the 5-position of the pentyl side chain.

F. Chemical properties

Chemically, AM-2201 can be regarded as relatively inert as it is substituted at the reactive C-3 position with the naphthoyl moiety. Due to the aromaticity of the indole system the nitrogen does not lead to considerable basicity. In contrast to non-fluorinated analogues, at higher temperatures AM-2201 may be converted into JWH-018 and JWH-022 to a minor extent [3, 4].

G. *Chemical identification*

The analytical profile of AM-2201 has been described in various papers. Utilized methods include LC-MS/MS [5], GC-EI-MS [1, 3, 6-12], LC-Q-ToF-MS [13], AccuTOF-DART [3], NMR [1, 8, 13], FTIR ATR [1, 6, 7] and UV-VIS detection [8, 10, 11, 13]. Detection in biological matrices was described in serum [14], whole blood [15-18], hair [19, 20] and oral fluid [21-23] targeting AM-2201. In urine samples, the main metabolites are the analytical targets [4, 24, 25].

3. **Ease of convertibility into controlled substances**

When heated (e.g. during smoking), AM-2201 may be converted into JWH-018 to a minor extent [3, 4], which was one of the first synthetic cannabinoids to be included into various national narcotics laws. However, AM-2201 is not considered an immediate precursor of any internationally controlled substance.

4. **General pharmacology**

4.1. **Pharmacodynamics**

In vivo data on pharmacodynamics of AM-2201 have not been published so far. However, AM-2201 possesses a relatively high binding affinity (expressed as IC₅₀ (occupation of 50% of the receptors)) towards the cannabinoid receptor type 1 (CB1) of 1.0 nM and towards the cannabinoid receptor type 2 (CB2) of 2.6 nM [2] compared to the binding affinities of delta-9 tetrahydrocannabinol (THC) of 40.7 ± 1.7 nM at the CB1 and 36.4 ± 10 nM at the CB2 receptor [26, 27]. Furthermore, Nakajima et al. and Chimalakonda et al. tested the biological effects by applying an in vitro [³⁵S] guanosine-5'-O-(3-thio)-triphosphate ([³⁵S]GTP γ S) binding assay, measuring an 50% effective concentration (EC₅₀) of 0.24 nM [8] and full agonistic properties [28]. Based on this data and clinical observations, it can be assumed that AM-2201 shows typical effects of CB1 agonists. These effects can include sedation, cognitive dysfunction, tachycardia, postural hypotension, dry mouth, ataxia, immunosuppression and psychotropic effects [29]

A pronounced difference with regard to THC is the formation of potentially pharmacologically active AM-2201 metabolites. While in the case of THC, only one of the major THC-metabolites is known to be psychoactive and retains binding affinity towards cannabinoid receptors (11-OH-THC: K_i at CB1 receptor: 38.4 ± 0.8 nM) [26], several AM-2201 metabolites retain high CB1 receptor binding affinity (relative rank of binding affinities: AM-2201 > AM-2201 N-(4-OH-pentyl) = JWH-018 N-(5-OH-pentyl) > THC > JWH-073 N-(4-OH-butyl)) [28, 30, 31]. Furthermore, similar efficacy for AM-2201 (a full agonist) and the two AM-2201 metabolites AM-2201 N-(4-OH-pentyl) and JWH-018 N-(5-OH-pentyl) has been shown and partial agonistic activity for JWH-073 N-(4-OH-butyl) [28, 30, 31]. The glucuronidated JWH-018 N-(5-OH-pentyl) metabolite retains binding affinity towards the CB1 receptor and activity as a neutral antagonist (K_i: 922 nM) [32]. No data is available concerning the question whether this metabolite of JWH-018 is capable of antagonizing pharmacological effects of JWH-018 in vivo, and if sufficient concentrations are formed at the site of action.

Neuropharmacology and effects on the central nervous system

No study data available.

Effects on cardiovascular, respiratory, gastrointestinal, liver, kidneys and genitourinary systems

No study data available.

Behavioural studies in animals

No study data available.

Effects on cognition in humans

No study data available.

Effects in humans

There is no data of systematic studies available for AM-2201 in the scientific literature so far. However, based on case reports and on user reports from the Internet, there is some evidence of bioavailability after smoking and oral uptake, and typical effects seem to mimic the effects of cannabis consumption. Adverse effects are summarized under section 6.

Interactions with other substances and medicines

No study data available.

4.2. Routes of administration and dosage

AM-2201 is mainly offered on the Internet either in the form of ‘herbal mixtures’, where the chemical has been sprayed on plant material (e.g. damiana), or as a powder [29]. Based on user reports and on the dosage forms offered, the primary route of administration is inhalation either by smoking the ‘herbal mixture’ as a joint or utilizing a vaporizer, ‘bong’ or pipe [33]. Furthermore, oral uptake of the compound was described by various users on internet fora [33]. Based on such information from the Internet, active doses start from 250 µg when smoked/vaporized [34]. Based on data from the EMCDDA, 250 µg is considered a light dose, 500-1,000 µg moderate, 1-2 mg a heavy dose and 3 mg can cause hallucinations and extreme anxiety [35]. When taken orally, Hutter et al. reported no physical or psychoactive effect after a 5 mg dose [4], which is most probably a consequence of a pronounced ‘first pass effect’ in combination with a relatively slow resorption in the gastro-intestinal tract.

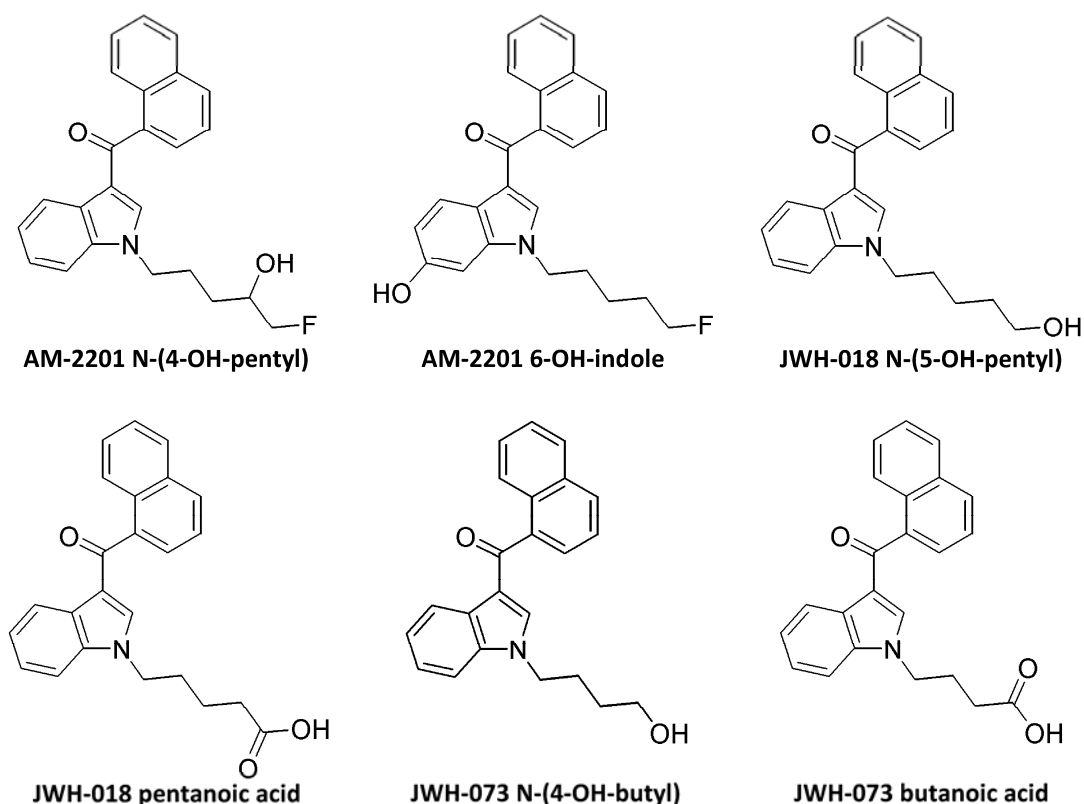
AM-2201 contents in various ‘herbal mixtures’ purchased in Germany [36], Japan [8], Korea [12] and the USA [37] varied from 0.9 to 303 mg/g.

It has to be considered that many of the ‘herbal mixtures’ are inhomogeneous with respect to the content of active ingredients, as it has been shown by Logan et al.[10], Ng et al. [38], Langer et al. [36] and Choi et al. [12]. The latter analyzed eleven samples of one ‘herbal mixture’ detecting an extremely high variation of the AM-2201 content, ranging from 0.9 to 36.6 mg/g (mean 14.5 mg/g).

4.3. Pharmacokinetics

AM-2201 is metabolized by various enzymes of the CYP450 family. Using human liver microsomes (HLM) and recombinant human protein, Chimalakonda et al. [28] identified CYP2C9 and CYP1A2 as the major enzymes involved in the oxidation of AM-2201, whereas the contribution of CYP2C19, 2D6, 2E1 and 3A4 was relatively small for this metabolic step. In addition to the metabolic reactions already known from the structurally closely related compound JWH-018, AM-2201 undergoes enzymatic defluorination, which Sobolevsky et al. [39] attributed to cytochrome P450 2E1. Chimalakonda et al. showed that CYP1A2, 2C9 and 2C19 all mediate the oxidative defluorination [28]. As a consequence, AM-2201 shows partly the same metabolites as JWH-018. However, experiments conducted in vitro [28] and in vivo [4, 40] demonstrated that JWH-018 N-(4OH-pentyl) is only formed after JWH-018 uptake, and may therefore be used as a diagnostic marker to differentiate uptake of JWH-018 and AM-2201. The primary metabolites detected both after incubation with human liver microsomes and in authentic urine samples were AM-2201 N-(4-OH-pentyl), AM-2201 6-OH-indole, JWH-018 N-(5-OH-pentyl), JWH-018 pentanoic acid, JWH-073 N-(4-OH-butyl) and JWH-073 butanoic acid (Figure 2) [4]. The main metabolites following HLM incubation were JWH-018 pentanoic acid (46%), JWH-018 N-(5-OH-pentyl) (37%) and AM-2201 N-(4-OH-pentyl) (9.5%). The reactions followed classic Michaelis Menten kinetics in case of the JWH-018 pentanoic acid and AM-2201 N-(4-OH-pentyl) or a biphasic kinetic profile in case of the JWH-018 N-(5-OH-pentyl) metabolite[28].

Figure 2: Major metabolites of AM-2201 (modified from Hutter et al. [4])



No data regarding the phase II metabolism of AM-2201 has been published so far. However, conjugation to glucuronic acid via various UDP-glucuronosyltransferase enzymes (predominately hepatic UGT1A1, UGT1A9 and UGT2B7) has been shown for the metabolites common with JWH-018 and JWH-073, namely JWH-018 N-(5-OH-pentyl), JWH-018 pentanoic acid, JWH-073 N-(4-OH-butyl) as well as JWH-073 butanoic acid [41].

Serum concentration over time profiles of AM-2201, as well as concentrations of various AM-2201 metabolites detected in serum and urine samples after oral ingestion of 5 mg AM-2201 by one volunteer were published by Hutter et al. [4]. In this study, a peak serum concentration of 0.56 ng/ml was detected in the sample taken 1h 35 min post intake. AM-2201 was detectable for five days in serum (limit of detection: 0.8 pg/ml), indicating a terminal elimination half-life of at least several days as it has also been observed for other synthetic cannabinoids [42]. The concentration of the JWH-018 pentanoic acid metabolite in serum exceeded the AM-2201 concentrations in serum in all obtained samples in this study, indicating a very fast metabolic transformation. Furthermore, the concentrations of the metabolites shared in common with JWH-018 were much higher than the AM-2201 metabolites still carrying the fluorine atom in all samples and could be detected in urine for up to 10 days post consumption. The absence of physical and psychotropic effect after the 5 mg dose may be explained by a combination of a strong first-pass effect and a much slower resorption when compared with inhalational uptake. Therefore, pharmacokinetics of AM-2201 after smoking may differ significantly.

5. Toxicology

Toxicity of AM-2201 has so far only been investigated on primary neuronal cells of the forebrain, showing an induction of cytotoxicity in a concentration-dependent manner [43]. Using preincubation with the CB1 selective antagonist AM-251, AM-2201 cytotoxicity (30 μ M) was suppressed, indicating an important role of CB1 receptors in the induction of cytotoxicity in this cell line rather than other mechanisms. Furthermore, the AM-2201 cytotoxicity proceeded via apoptosis and was mediated by caspase enzymes, revealing a strong neurotoxic effect according to the authors. However, considering the concentrations tested in the above study (10 μ M and 30 μ M AM-2201), conclusions on the cytotoxicity in vivo have to be drawn with care, as serum concentration levels published in the literature or from routine sample analysis (own unpublished data) were not higher than 33.4 nM (12 ng/ml) and are therefore about 300-fold lower than the concentrations applied by Tomiyama et al.; Nevertheless, due to the lipophilic character of AM-2201, it can not be excluded that higher concentrations may occur in deeper compartments (accumulation) or in epithelial cells of the aerodigestive tract (which are directly exposed to smoke or pure substance).

Apart from this study, no data regarding the toxicity of AM-2201 is published in the literature so far, and in particular there is no data on potential teratogenic effects. However, it has to be noted that the endocannabinoid system is present from conception onwards in the developing central nervous system and that THC, as well as the cannabimimetic WIN-55,212-2, interfere with the endocannabinoid system to cause anencephaly and neurobehavioural deficiencies in the offspring [44]. It is not known whether AM-2201 crosses the placental barrier. However, based on its physico-chemical properties, it can be assumed to effectively reach the fetal tissues via the placenta.

6. Adverse reactions in humans

Cases of AM-2201 intoxications in humans published in the literature:

Non-fatal Cases

Adverse effects described in the literature after the consumption of synthetic cannabinoids include tachycardia, agitation, hallucination, hypertension, minor elevation of blood glucose, hypokalemia, vomiting, chest pain, seizures, myoclonia, extreme anxiety leading to panic attacks and acute psychosis (risk of suicide) [45].

In cases with analytically verified AM-2201 consumption convulsions, vomiting, drowsiness, tachycardia, cannabinoid hyperemesis syndrome, and diffuse pulmonary infiltrates were reported. A 19-year-old man suffered from two generalized convulsions lasting for 1-2 min, and vomited soon after smoking an 'herbal mixture' containing JWH-018, JWH-081, JWH-250 and AM-2201 [46]. A 40 year old man was admitted to the hospital after he was found drowsy and in a slow reacting condition at home after smoking of self-estimated 0.5 g of a 'herbal mixture' (AM-2201 and trace amounts of AM-2232), and consumption of α -methyltryptamine and a benzodiazepine-like substance. In this case 3.1 ng/ml AM-2201 was detected in the obtained serum samples [15]. A diffuse pulmonary infiltrate was diagnosed in a 21-year-old male and an infectious etiology appeared unlikely. Blood, urine and saliva analysis confirmed the uptake of AM-2201 (blood level: 0.75 ng/ml), JWH-122 and JWH-210 and it emerged that the patient smoked multiple brands of 'herbal mixtures' during the preceding four months [47]. Hopkins et al. report a case of cannabinoid hyperemesis syndrome in a consumer with a self-reported highly frequent synthetic cannabinoid consumption who had developed recurring and severe crampy abdominal pain associated with intractable nausea and vomiting. Urine samples of the patient tested positive for JWH-018, JWH-073 and AM-2201, and negative for THC. Furthermore, the patient reported that after two weeks of sobriety his symptoms completely resolved [48].

Fatal cases

Three fatal cases in which AM-2201 could be detected in post-mortem blood samples were published so far. One occurred in Germany, where a 36-year-old man collapsed after smoking a 'herbal mixture'. He suffered from seizures and died after admission to the hospital despite continued resuscitation attempts. The residue of the joint he had consumed contained JWH-122, AM-2201, MAM-2201 and UR-144. AM-2201 could be detected in the femoral blood sample of the deceased at a concentration of 1.4 ng/ml as well as in the brain (~0.1 ng/g), lung (~2.0 ng/g), bile fluid (~5.9 ng/ml), gastric content (~270 μ g absolute), hair (~ 3.0 ng/mg) and adipose tissue (~ 180 ng/g). Furthermore, the synthetic cannabinoids JWH-018 (0.1 ng/ml), JWH-122 (0.3 ng/ml), MAM-2201 (1.5 ng/ml) and UR-144 (6 ng/ml) as well as a relatively high concentration of amphetamine (250 ng/ml) were also detected in the femoral blood, indicating an acute influence of several synthetic cannabinoids and amphetamine [49]. In this case, the presence of various substances in the femoral blood prevents a realistic estimation of the contribution of AM-2201 to the lethal outcome.

The second fatality occurred in the USA, where a 23-year-old man with no history of mental illness, seizure disorder, previous psychiatric care or past or current use of antipsychotic or illicit drugs was found dead lying supine on the floor. The 'herbal mixture' found in the decedent's shirt pocket contained 0.8 ± 0.2 % of AM-2201 by weight and the found smoking device contained high concentrations AM-2201 and trace

amounts of JWH-073. In the post-mortem blood sample 12 ng/ml AM-2201 along with 2.5 ng/ml of an oxidized metabolite of AM-2201 were detected, and no further drugs of abuse (opiates, benzodiazepines, amphetamines, cocaine, THC) or alcohol were found. A post-mortem examination of the decedent revealed many self-inflicted blunt and sharp force wounds, including a self-inflicted stab wound to the right side of the neck considered fatal, thus concluding the manner of death to be related to psychiatric complications after AM-2201 use [37].

The third case describes a fatal methoxetamine intoxication of a 26-year-old male in Sweden, where it cannot be ruled out that the presence of three synthetic cannabinoids (femoral blood: AM-2201 0.3 ng/g, AM-694 0.09 ng/ml and JWH-018 0.05 ng/g) may have contributed to the lethal outcome. [50]

Cases of persons driving a motor vehicle under the suspected influence of synthetic cannabinoids:

Three cases of persons driving a vehicle after uptake of AM-2201 were reported by Musshoff et al. [51]. The symptoms of all three cases are listed in Table 1. Similar to most other cases, several synthetic cannabinoids were detected in the serum of the respective person, suggesting synergistic effects.

Table 1:

Case No.	Patient Details	Clinical Presentation	Comments
1	19 y, m	Arrived with car in a very intoxicated state, police noted: 'not able to follow instructions, retarded sequence of movements, lazy, cumbersome, confused and disorientated, slurred and babbled speech, inappropriate freezing, reduced breathing and enlarged pupils'. At the hospital very dizzy and nearly unconscious.	Uptake of AM-2201 and JWH-018
2	20 y, m	General road traffic control. Police noted: 'vestibular disorder, disturbance of fine motor skills, enlarged pupils and blunt mood'. 80 min later: 'finger-to-finger test doubtful, obviously enlarged pupils and delayed reaction of the pupils to light'	Uptake of AM-2201, JWH-019, JWH-122 and JWH-210
3	22 y, m	On a motorbike, about to be checked at a general road traffic control. Firstly, escaped by overrunning red traffic lights, later he skedaddled by foot. Police noted after arrest: 'retarded sequence of movements, apathetic, nervous, inert, delayed reactions of pupils. One hour 35 min later, physician noticed no abnormalities.	Uptake of AM-2201, JWH-018, JWH-122, JWH-210, JWH-307, MAM-2201 and UR-144

Intoxication cases reported to the Poisons Information Center Freiburg, Germany

Cases of intoxications in humans, which included uptake of AM-2201, that were reported to the Poisons Information Centre Freiburg are summarized in Table 2 (own unpublished data).

Table 2: all concentrations determined in serum (ng/ml), n.d.: not detected, latency gives an estimate of the time distance between blood sampling and consumption.

Sex	Age	AM-2201	JWH-018	JWH-122	JWH-203	JWH-210	JWH-307	Latency	Symptoms	Other drugs
m	27	6.1	0.13	n.d.	n.d.	0.57	n.d.	unknown	Drowsiness, convulsion, mydriasis	Immunoassay: THC-COOH
m	16	0.34	n.d.	0.38	n.d.	3.0	n.d.	unknown	Somnolent, vomiting	Immunoassay: THC-COOH, amphetamines
m	16	0.15	n.d.	0.48	n.d.	3.3	n.d.	unknown	Somnolent, vomiting	THC-COOH: 5.1 ng/ml
m	16	0.48	n.d.	2.8	1.1	12	n.d.	1.5h	Repeated vomiting, somnolence, hypokalemia	-
m	13	0.44	n.d.	1.6	1.1	10	n.d.	1.5h	Severe nausea, repeated vomiting, drowsiness, hypokalemia	-
m	17	0.21	n.d.	n.d.	n.d.	2.1	n.d.	1-2h	Hyperventilation, restlessness, mydriasis, hypokalemia	THC 1.2 ng/ml; 11-OH-THC 0.5 ng/ml; THC-COOH 4.15 ng/ml; immunoassay: benzodiazepines
f	17	0.18	n.d.	n.d.	n.d.	n.d.	n.d.	3.5h	Tachycardia, hallucinations, change of perception, delayed reaction of the pupils	THC 0.1 ng/ml; 11-OH-THC 0.15 ng/ml; THC-COOH 6.3 ng/ml
unknown	19	0.58	n.d.	n.d.	n.d.	3.0	n.d.	3h	Dyspnea	-
m	17	1.3	n.d.	n.d.	n.d.	1.8	0.11	1-2h	Tachycardia, angina pectoris	-
m	18	9.5	n.d.	n.d.	n.d.	20	n.d.	1h	Nausea, tachycardia, syncope	-
m	18	2.0	0.24	n.d.	n.d.	n.d.	n.d.	45min	Tachycardia, dyspnea, thoracic constriction, vertigo	-
m	17	0.37	n.d.	n.d.	n.d.	n.d.	n.d.	4h	Strong burning sensation in the respiratory tract, vertigo, collapsing, restlessness, later somnolent, amnesia	-
m	15	0.50	n.d.	n.d.	n.d.	n.d.	n.d.	4h	Burning sensation in the respiratory tract, repeated vomiting, restlessness, hallucinations, increasingly somnolent	-

In the latter two of these thirteen cases, AM-2201 was the only synthetic cannabinoid detected in serum and no further drugs could be detected (comprehensive screening methods were applied covering a wide range of legal and illegal drugs). This indicates

that in these cases AM-2201 was responsible for the observed effects, confirming many of the adverse reactions summarized earlier in this section. It is therefore plausible to assume that in analogy to JWH-018, life-threatening conditions can be caused by AM-2201 uptake.

AM-2201 serum / blood concentrations found in the literature

Table 3: Blood concentrations of AM-2201 from case reports and studies.

Case No.	Patient Details	Reference	Drugs detected	AM-2201 concentration	Comments
1	43 yr, m, 75 kg	Hutter et al. 2013	AM-2201	0.56 ng/ml (peak serum)	Oral intake of 5 mg AM-2201
2	21 yr, m	Alhadi et al. 2013	AM-2201, JWH-122, JWH-210	0.75 ng/ml (blood)	
3	40 yr, m	Holm et al. 2013	AM-2201	3.1 ng/ml (serum)	α -methyl-tryptamine and 'benzodiazepine-like substance' (self-reported)
4	unknown	Kneisel et al. 2013	AM-2201, JWH-122	0.18 ng/ml (serum)	
5	unknown	Kneisel et al. 2013	AM-2201, JWH-122, JWH-210	0.22 ng/ml (serum)	
6	unknown	Kneisel et al. 2013	AM-2201, JWH-122, JWH-210	1.9 ng/ml (serum)	
7	unknown	Kneisel et al. 2013	AM-2201, JWH-018, JWH-122, JWH-210	0.33 ng/ml (serum)	
8	18 yr, m	Musshoff et al. 2013	AM-2201, JWH-018	4.6 ng/ml (serum)	See case no. 1 Table 1 (JWH-018: 0.17 ng/ml)
9	20 yr, m	Musshoff et al. 2013	JWH-019, JWH-122, JWH-210, AM-2201	0.31 ng/ml (serum)	See case no. 2 Table 1 (JWH-019: 1.7 ng/ml, JWH-122: 7.6 ng/ml, JWH-210: 4.4 ng/ml)
10	22 yr, m	Musshoff et al. 2013	JWH-018, JWH-122, JWH-210, JWH-307, MAM-2201, AM-2201, UR-144	< 0.1 ng/ml (serum)	See case no. 3 Table 1 (JWH-018: 1.9 ng/ml, JWH-122: 28 ng/ml, JWH-210: 2.5 ng/ml, JWH-307: < 0.1 ng/ml, MAM-2201: < 0.1 ng/ml, UR-144: < 0.1 ng/ml)
11	31 yr	Yeakel et al. 2013	AM-2201, JWH-081, JWH-122, JWH-210	1.4 ng/ml (whole blood)	Impaired driver; walk and turn test: leg tremors, cannot keep balance; one-leg stand test: swayed, raised arms; Romberg: eye tremors; (JWH-081: 0.12 ng/ml, JWH-122: 2.5 ng/ml, JWH-210: 0.1 ng/ml)

Case No.	Patient Details	Reference	Drugs detected	AM-2201 concentration	Comments
12	27 yr	Yeakel et al. 2013	AM-2201, JWH-018, JWH-122, JWH-210	0.43 ng/ml (whole blood)	Impaired driver: Romberg test: eye tremors (JWH-018: 0.1 ng/ml, JWH-122 and JWH-210: positive)
13	21 yr	Yeakel et al. 2013	AM-2201, JWH-250	3.1 ng/ml (whole blood)	Impaired driver; accident: walk and turn test: leg, body tremors; one-leg stand test: swayed, leg, body tremors; Romberg test: swayed, leg, body eyelid tremors (JWH-250: 0.38 ng/ml)
14	26 yr	Yeakel et al. 2013	AM-2201	0.94 ng/ml (whole blood)	Impaired driver
15	18 yr	Yeakel et al. 2013	AM-2201	3.6 ng/ml (whole blood)	Impaired driver, accident, walk and turn test: raised arms, leg tremors; one-leg stand test: swayed, raised arms, foot down; Romberg test: swayed, leg tremors
16	21 yr	Yeakel et al. 2013	AM-2201, JWH-081, JWH-122, JWH-210	2.8 ng/ml (whole blood)	Impaired driver, accident, walk and turn test: nearly fell at turn (JWH-081, JWH-122, JWH-210: positive)
17	19 yr	Yeakel et al. 2013	AM-2201, JWH-210	4.0 ng/ml (whole blood)	Impaired driver, accident, walk and turn test: leg tremors; one-leg stand test: leg tremors (JWH-210: positive)
18	17 yr, m	Tuv et al. 2014	AM-2201, methamphet-amine, clonazepam	0.07 ng/ml (whole blood)	Impaired mildly (methamphetamine: 100 ng/ml, clonazepam: 60 ng/ml)
19	31 yr, m	Tuv et al. 2014	AM-2201, methamphet-amine, THC, diazepam, nordiazepam	0.25 ng/ml (whole blood)	Suspicion of DUID (methamphetamine: 90 ng/ml, diazepam 600 ng/ml, nordiazepam 600 ng/ml, THC 2 ng/ml)
20	41 yr, m	Tuv et al. 2014	AM-2201, diazepam, nitrazepam, alprazolam, oxazepam, THC	0.25 ng/ml (whole blood)	Suspicion of DUID (diazepam 90 ng/ml, nitrazepam 100 ng/ml, alprazolam 40 ng/ml, oxazepam 1,500 ng/ml, THC 0.9 ng/ml)
21	30 yr, m	Tuv et al. 2014	AM-2201, methylphenidate, clonazepam, THC	0.40 ng/ml (whole blood)	Impaired greatly (methylphenidate 5 ng/ml, clonazepam 40 ng/ml), THC 0.6 ng/ml)
22	17 yr, m	Tuv et al. 2014	AM-2201, clonazepam, THC	1.33 ng/ml (whole blood)	Impaired mildly (clonazepam 20 ng/ml), THC 2 ng/ml)

Based on the analysis of 128 AM-2201 positive serum samples in Germany (mainly from forensic psychiatric hospitals for abstinence control), the concentrations ranged from < 0.1 to 12 ng/ml (mean: 1.3 ng/ml; median: 0.4 ng/ml) (own unpublished data).

7. Dependence potential

Animal studies:

Ginsburg et al. performed a study in monkeys and came to the conclusion that the shorter duration of action of JWH-018 and JWH-073 could evoke a more frequent use, and might therefore increase abuse and dependence liability [52].

Further studies conducted by Hrubá et al. in rhesus monkeys suggested that there may be differences in the dependence liability between JWH-018 and THC, as cross-tolerance was observed after 3 days of THC treatment for THC but not for JWH-018 [53].

Human data:

There is evidence that synthetic cannabinoids can produce tolerance and withdrawal symptoms when the substance is abruptly discontinued following a regular use of high doses.

A case report from Germany describes the withdrawal symptoms of a 20-year-old male who had consumed the herbal mixture ‘Spice Gold’ on a daily basis. He developed tolerance and increased the dose to 3 g per day. The patient felt a continuous desire for the drug and kept on using it despite the development of persistent cognitive impairment. During withdrawal he developed inner unrest, drug craving, nocturnal nightmares, profuse sweating, nausea, tremor, and headache. The authors interpreted the symptoms as a dependence syndrome corresponding to ICD-10 and DSM-IV criteria, resembling the withdrawal syndrome in cannabis dependence [54]. Although the composition of the ‘herbal mixture’ was not determined by the authors, it can be assumed that it contained either CP47,497-C8 or JWH-018 or both (based on analytical data from a product monitoring program, own unpublished data). Extrapolation from this report to potential effects of AM-2201 may not be appropriate. However, it suggests that structurally related drugs acting in the same way may put users at similar risks.

Rominger et al. describe the withdrawal symptoms of a 23-year-old male who smoked 10 g of a herbal mixture (containing synthetic cannabinoids not stated in the article) on a daily basis [55]. Symptoms included anxiety, unstable mood, crying fits, feeling of inner emptiness, spatial disorientation, hyperacusis, somatic pain, shortness of breath, hyperventilation, intense sweating and sensations of motor and inner restlessness.

The most commonly reported withdrawal effects from synthetic cannabinoids in an internet based survey study were headaches, anxiety, coughing, insomnia, anger, impatience, difficulties in concentrating, restlessness, nausea, and depression [56].

The US Department of Health and Human Services expect that the physical dependence liability of synthetic cannabinoids will be similar than the one of THC as they act through the same molecular target [56]. The EMCDDA states that ‘user consider its effects to be short acting and describe an extreme urge to redose’ [35].

8. Abuse potential

Animal studies:

Drug discrimination studies conducted with JWH-018 and JWH-073 in rats and monkeys suggest that synthetic cannabinoids administration produces similar effects like THC [57, 58] [52] [56]. As a consequence, AM-2201 is very likely to have a high potential to be abused e.g. as a substitute for cannabis due to its structural and functional similarity to JWH-018.

Human data:

One of the main reasons for abuse of synthetic cannabinoids is the difficulty of detecting consumption by analysis of biological samples. The non-detectability of these

compounds makes them very attractive for persons undergoing regular drug tests (e.g. patients of forensic clinics/withdrawal clinics, workplace drug testing or driving licence re-granting candidates). In a survey conducted by Vandrey et al. including adults from 13 different countries who reported at least one lifetime use of synthetic cannabinoids, 38% of the study completers were subject to drug testing procedures [59].

The US Department of Health and Human Services review states that the synthetic cannabinoids JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol exhibit a high potential for abuse similar to that of marijuana [56]. Due to structural and functional similarity of AM-2201 to these compounds, the same can be assumed for this drug.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

AM-2201 has not been used in therapy.

10. Listing on the WHO Model List of Essential Medicines

AM-2201 is not listed on the WHO Model List of Essential Medicines.

11. Marketing authorizations (as a medicine)

Not applicable.

12. Industrial use

AM-2201 has no industrial use.

13. Non-medical use, abuse and dependence

AM-2201 is still prevalent as an additive in commercially available 'herbal-mixtures'. However, most reports and surveys are based on products containing synthetic cannabinoids in general, without identifying the particular substance (consumers usually do not know the composition of the products).

At present, synthetic cannabinoids appear to be mainly consumed in Europe, Japan, Russia and the USA. They have a wide-ranging abuse potential as substitutes for cannabis due to their non-detectability, easy availability and strong effects.

Synthetic cannabinoids are monitored through the European early-warning system (EWS). The main aim of the EWS is the rapid collection, analysis and exchange of information on new synthetic substances as soon as they appear in Europe. Seizures of AM-2201 are reported from Austria, Belgium, Bulgaria, Croatia, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Norway, Poland, Slovakia, Slovenia, Spain, Sweden, UK, Turkey [35, 60]. The first reports of AM-2201 seizures occurred in 2010 (Latvia and Belgium) [61]. In 2012, 30 new synthetic cannabinoids were formally notified to the EWS [62]. In the 2012 UNODC survey on

new psychoactive substances, JWH-018 was identified as the most widespread synthetic cannabinoids.

In a nation-wide survey regarding ‘herbal mixture’ consumption among 14- to 18-year-old pupils in Spain in 2010, 1.1% for lifetime prevalence and 0.8% for last year prevalence were reported. In the USA 12% last year prevalence for synthetic cannabinoids among 12th graders was reported [60]. A representative survey conducted among students aged between 15 and 18 years at schools in the area of Frankfurt/Main, Germany, found that about 6% of respondents reported having used ‘Spice’ at least once, and 3% had used it during the last 30 days [61]. Heltsley et al. analyzed urine samples from 5,956 U.S. athletes (collected: 24.01.2011 – 28.10.2011) of which 4.5% were tested positive for metabolites of JWH-018 and/or JWH-073 [63].

The Drug Abuse Warning Network (DAWN), a public health surveillance system monitoring drug-related emergency department (ED) visits in the USA, reports 11,406 synthetic cannabinoids related ED visits and 28,531 in 2011 [64]. In 2010, 2,906 calls to poison centers for exposure to synthetic cannabinoids were reported across the USA by the American Association of Poison Control Centers. This number increased to 6,968 in 2011 and slightly declined to 5,228 calls in 2012. The Texas Poison Center Network further reported 1,869 calls regarding exposure to synthetic cannabinoids and three deaths from January 1, 2010 through June 30, 2013 [64].

The US Department of Health and Human Services reports of 5,450 reports from state and local forensics laboratories in 39 States of JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol for a period from January 2009 to December 2011 [56].

Also refer 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

A major health problem arises from inhomogeneities of the mixtures with regard to the content of active ingredients [10, 12, 36, 38]. As a consequence, it is not possible for the consumer to individually dose the compound. Two joints prepared from the same mixture could contain significantly different amounts of the drug. Furthermore, the composition of the ‘herbal mixtures’ change rapidly over time and therefore a certain product name does not guarantee the same composition of compounds between batches [5]. Apart from that, various authors identified further pharmacologically active substances in ‘herbal mixtures’, such as the benzodiazepine phenazepam [65], the kratom alkaloid mitragynine [11] or potent hallucinogens like N-(2-methoxy)benzyl phenethylamines [66]. These additives bear potential health risks of their own and may potentiate the risks connected to the use of the synthetic cannabinoids.

A public health alert was issued on a specific ‘herbal mixture’ (‘Annihilation’) by the EMCDDA after a series of non-fatal intoxications in Scotland, United Kingdom. The United Kingdom national focal point analyzed five samples of ‘Annihilation’ and revealed the presence of mixtures of synthetic cannabinoids. The contents of different

packages of the same product were not the same. The results of these analyses are presented in Table 4 [60].

Table 4: Synthetic cannabinoids found in ‘Annihilation’, October 2012

Source of data	UR-144	MAM-2201	AM-2201	JWH-122 pentenyl derivative	AM-1248
UK	positive	positive		positive	
UK	positive	positive			
UK	positive	positive	positive	positive	
UK	positive		positive		
UK	positive	positive			
Germany	positive	positive			positive

During 2010, 418 synthetic cannabinoids exposures without involvement of other substances were reported to the Texas poison center network, in comparison to 99 sole marijuana exposures. Forrester et al. further state that significantly more synthetic cannabinoid exposures were classified as ‘moderate effect’, while more marijuana exposures were classified as ‘no effect’[67]. Out of the ten most frequently reported adverse clinical effects, nine were similar to the ones reported for marijuana. Tachycardia, agitation, hallucinations, and hypertension were significantly more frequently associated with the use of synthetic cannabinoids.

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

15. Licit production, consumption and international trade

Not applicable.

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

16. Illicit manufacture and traffic and related information

Up to 2012 AM-2201 ranged fifth among the top synthetic cannabinoids reported to UNODC with 34 reports.[68] Based on data retrieved from the UNODC Early Warning Advisory on NPS, 27 countries reported the emergence of AM-2201 up to December 2013. In 2012 45 countries reported seizures of synthetic cannabinoids making them the most frequently seized NPS. Furthermore the number of countries reporting seizures of larger quantities (more than 1 kg) increased from 3 in Europe in 2009 to 16 in 2011 covering regions worldwide. One large seizure was also reported from the United States counting 4.8 million packages in one operation 2012.

The primary source of origin for synthetic cannabinoids is identified to be Asia (China and India), followed by Europe (Czech Republic, Hungary, Netherlands, Portugal, Spain, Ukraine and United Kingdom), the Americas, Africa and Oceania. Availability over the Internet is high in general and online shops seem to play the most important role in marketing and distribution worldwide. This can also be seen in the number of online shops selling ‘legal highs’ which increased from 170 in 2010 to 690 in 2012 in Europe only [68].

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

17. Current international controls and their impact

Not applicable.

18. Current and past national controls

Controlled in Austria, Czech Republic, Denmark, Germany, Hungary, Ireland, Italy, Lithuania, Luxembourg, Norway, Portugal, Slovenia, Sweden (according to the EDND of the EMCDDA) [35]. Also controlled in Japan, Switzerland and the USA.

Also refer 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

No data.

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Annex 1:

Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of AM-2201

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 66 Member States answered the questionnaire for AM-2201. Of these, only 31 respondents (AFR 1, AMR 5, EUR 21, WPR 4) had information on this substance.

LEGITIMATE USE

None reported that AM-2201 was currently authorized or in the process of being authorized/registered as a medical product in their country. Four respondents stated that this substance was used in medical and scientific research including as standard in analyses. There was no use stated for AM-2201 in animal/veterinary care

HARMFUL USE

Twenty-two respondents confirmed that there was recreational/harmful use of AM-2201; common routes of administration stated as oral by one, inhaling/sniffing by 14 and oral, injection, inhaling/sniffing by two. Twelve respondents stated this was obtained only via trafficking, one only via diversion, one via diversion and trafficking, one via clandestine manufacturing and three via trafficking and clandestine manufacturing. Twelve reported powder as the available formulation, and one each tablet; powder and tablet; powder, liquid and powder, tablet, liquid forms. Six respondents also mention that AM-2201 is often found in herbal mixtures. Five respondents state that it is used only in the general population, three only in clubs and one that it was used both by the general population and in clubs, and. In 2012 one respondent reported 2 deaths due to AM-2201. This same respondent reported 10 emergency room visits in 2012 and another reported 5 visits. Five respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by AM-2201. These included vomiting, anxiety, agitation, paranoia, irritability, seizures, tachycardia, self-inflicted injuries, hallucinations (visual and acoustical), dyspnoea, apnoea, spasms, cardiac arrest, panic attacks, somnolence, hypokalemia, concentration and coordination difficulties, elevated blood pressure, and loss of consciousness. One respondent reported drug related crimes involving postal delivery of NPS.

CONTROL

Of those with information on this substance, 26 reported that AM-2201 was controlled under legislation that was intended to regulate its availability; 18 under “controlled substance act”, five under “medicines law”, one “temporary ban” and two under “other” laws. Only four respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving this substance, four respondents reported clandestine manufacture. Eleven respondents reported processing into the consumer product, 18 reported trafficking, three reported diversion and 16 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	7,815 (14)	16,471 (19)
Total quantity seized (kg)	245.36 (9) some include other cannabinoids	654.41 (14) some include other cannabinoids
Total quantity seized (tablets/pills)	72 (1)	1,851 (1)
Others seized	wraps (1), plant and herbal products also reported	wraps (1), plant and herbal products also reported

IMPACT OF SCHEDULING

Twenty-seven respondents reported that if AM-2201 was placed under international control, they would have the laboratory capacity to identify the substance. There is no medical use reported.