Post-Mortem Toxicology: A Systematic Review of Death Cases Involving Synthetic Cannabinoid Receptor Agonists

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Background: Synthetic cannabinoid receptor agonists (SCRAs) have become the largest group of new psychoactive substances monitored by the European Union Early Warning System. Despite the wide diffusion on the market, data regarding effects, toxicities, and mechanisms as well as toxic/lethal doses are still scarce.

Methods: A comprehensive literature search for articles published up to January 2019 was performed in multiple electronic databases. Only cases of death in which toxicological analyses revealed the presence of SCRAs in blood or urine and at least an external examination was performed, including those occurred in emergency departments, were included.

Results: Of 380 studies identified, 354 were excluded, while 8 additional manuscripts were included through the screening of relevant references cited in the selected articles. A total number of 34 manuscripts (8 case series and 26 case reports) were included.

Conclusions: Typical toxic ranges for SCRAs have not been so far identified, and the results of toxicological analyses should be interpreted with caution. In death cases involving SCRAs, a thorough post-mortem examination is a prerequisite to assess the role of the substance use in the deceased and to identify a probable mechanism of death. Even after a comprehensive analysis of clinical, circumstantial, toxicological, and autoptic data, the cause and manner of death remain unclear in some cases.

Keywords: forensic toxicology, novel psychoactive substances, synthetic cannabinoids, post-mortem examination, toxicological significance score
INTRODUCTION

Synthetic cannabinoids or synthetic cannabinoid receptor agonists (SCRAs) are a heterogeneous group of compounds designed to mimic the effects of delta-9-tetrahydrocannabinol (Δ9-THC) by binding to the cannabinoid receptors CB1 and CB2. In contrast to Δ9-THC, a partial agonist at the CB1 and CB2 receptors, most of the SCRA market share is due to full agonists at these receptors and additionally show much higher potency (1, 2). Since their first detection in herbal blends in 2008 (3, 4), they have become the largest group of new psychoactive substances (NPS), with 190 compounds reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) until the end of 2018 and an extraordinary dynamic market (5), even though there has been a relative reduction of the rate of new compounds per year (5). It was initially claimed that SCRA could be "safe" alternatives to marijuana, due to similarities of their pharmacological profile to Δ9-THC and other phytocannabinoids, and lots of compounds binding to the cannabinoid receptors have been synthesized and evaluated regarding their binding affinities and activity in animal or cell models since then (6). However, a huge number of in-vitro and in-vivo studies, reports, and alerts have highlighted severe adverse events and enhanced toxicity (2, 7, 8) prompting the United States Drug Enforcement Administration to classify some of these compounds as Schedule I substances. Signs and symptoms of SCRA consumption include psychomotor agitation, euphoria, anxiety, confusion, and psychosis on the one side, sedation and loss of consciousness on the other (9, 10). Adverse cardiac effects are among the most frequently encountered adverse reactions after SCRA intake. Particularly, both tachycardia (more frequently) and bradycardia have been reported. Gastro-intestinal symptoms with nausea and vomiting are also common. Moreover, rhabdomyolysis, hyperthermia, and hypothermia, seizures, respiratory depression, nephro- and hepatotoxicity were described in combination with SCRA intake. Particularly, both tachycardia (more frequently) and bradycardia have been reported. Gastro-intestinal symptoms with nausea and vomiting are also common. Moreover, rhabdomyolysis, hyperthermia, and hypothermia, seizures, respiratory depression, nephro- and hepatotoxicity were described in combination with SCRA intake (11, 12). Some of these effects might be mediated also by interference with other neurotransmitter pathways, since certain SCRAs can also bind to glutamatergic, serotonin (5-HT), opioid, and both adrenergic and cholinerigic receptors and to calcium, sodium, potassium channels (13).

Several cases of intoxication have been reported caused by, e.g., MDMB-CHMICA and AB-CHMINACA, which can cause severe symptoms requiring hospitalization and prolonged recovery time (14). Other compounds, such as Cumyl-PEGACLONE, have been suggested as "relatively safe" due to the low number of poisonings despite the abundant presence in herbal blends (25–30% of tested products) and their widespread use (prevalence of 29% in samples positive for SCRAs, including testing for driving under the influence, insult, and threat, criminal offenses). Moreover, the role of the SCRA was scarce, making SCRAs one of the most "unpredictable" classes of substances (16). Moreover, only few studies regarding the time of detectability, the diffusion in tissues, and the post-mortem distribution of the drugs can be retrieved in the literature. The limited knowledge regarding the pharmacodynamics and pharmacokinetics of SCRA contributes to the difficulties of the interpretation of toxicological results. Furthermore, several aspects, such as interactions among SCRA or in the combination with other drugs, are difficult to assess in cases of SCRA-related deaths.

To our knowledge, there are no previous detailed review papers, which report fatalities caused by the misuse of synthetic cannabinoids providing circumstantial, analytical data, and complete results of post-mortem examination.

The aim of the present study is to offer an overview of thoroughly investigated fatalities involving SCRA, considering not only analytical results, but also an in-depth analysis on investigative data, analytical methods, and macro and microscopic findings.

MATERIALS AND METHODS

Literature Search and Inclusion/Exclusion Criteria

In February 2019 a literature search for articles published until January 2019 was performed in electronic databases (Pubmed, Scopus), using the following research terms: “synthetic cannabinoids” AND (death OR fatal OR fatalities OR autopsy OR forensic OR post-mortem). Search was done in English language and duplicates were manually deleted. Titles and abstracts were screened and only cases of death, in which toxicological analyses revealed at least one SCRA in blood or urine, and at least an external examination was performed were included. Patients rushed to the emergency department and subsequently died were also included in the selected cases.

Exclusion criteria were: irretrievability of a full-text; off-topic articles (e.g., death cases in which other NPS, but no SCRA, were detected); in vitro/animal model studies; herbal blends analyses; non-fatal cases of intoxication; books/reviews not including unpublished cases of death due to SCRA; autopsy/external examination not performed.

Data Extraction

An electronic database with the selected papers was built in Excel® (Microsoft Office, 2006). For each included manuscript, authors, title, journal, year, and type of publication (e.g., case report, case series), number of death cases and type of involved SCRA were extracted.

A separate database was built with the retrieved papers and, for each death case, the following information was extracted:

- type of victim, referring to age and sex;
- concentrations of SCRA retrieved during toxicological analyses in central and peripheral blood, urine, and tissues;
- other substances detected in blood;
- circumstantial data (and whatever relevant emerged during the death scene investigation), with particular reference to a history of drug abuse and to the availability of herbal blends/paraphernalia at the scene,
post-mortem gross and microscopic findings;
• cause, manner, and suggested mechanism of death;
• post-mortem interval (PMI)
• role of the SCRA as described by the authors.

Data Analysis/Interpretation
Only a descriptive statistic was applied. For each death case, two independent observers assigned a Toxicological Significance Score (TSS) to the involved SC, in accordance to the methodology proposed by Elliott et al. (17). When no agreement was achieved, a third person was consulted. This rating was compared with the likely role in death assigned by the authors.

Information related to toxicological analytical methodology (linearity, calibration curve, accuracy, precision, limit of detection/quantification, matrix effect), in accordance with what suggested by Welter-Luedeke and Maurer (18) were also noted and taken into consideration when evaluating the single cases.

RESULTS

Literature Review
The literature search resulted in 380 sources after elimination of duplicates. Of these, 354 were excluded applying the criteria listed in "Materials and Methods," while 8 additional manuscripts were included through the screening of references cited in the selected articles. Details of the literature search are listed in Figure 1.

Finally, a total of 34 manuscripts were included (authors, title, journal, date of publication, and involved SCRA(s) are shown in Table 1), corresponding to 74 published cases. Of the 34 manuscripts, 8 consisted in case series and 26 in case reports, including articles only providing new analytical data on previously reported death cases (Table 1). Tables 2 and 3 both refer to the single cases. Particularly, Table 2 displays the epidemiology of the victim, the involved SCRA(s), other substances detected, anamnestic/circumstantial, and clinical data, macroscopic and microscopic features, cause, and suggested mechanism of death, toxicological significance score, and role of SCRA as suggested by the authors of the paper. In Table 3, concentrations in peripheral, central blood, urine, and tissues, together with the PMI are shown.

Analytical Issues
Sample preparation and extraction procedures varied widely: liquid-liquid extraction was the most frequently used, though solid-phase extraction (24, 44, 47, 53) and QuEChERS dispersive solid-phase extraction (29, 30, 35, 50) were also reported. Only in a minority of the cases, the standard addition method was employed for quantification (19, 23, 28, 30). In two cases, liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QToF-MS) was used to detected and quantitate parent compounds and/or metabolites in blood and ante-mortem serum (38, 48).

Overall, 31 SCRA(s) (EAM-2201, AB-PINACA, 5F-PB-22, 5F- AKB-48, 5F-ADB, AB-CHMINACA, UR-144, XLR-11, JWH-022, MAB-CHMINACA, MDMB-CHMICA, 5F-AMB, Mepirapim, JWH-018, AM-2201, JWH-210, JWH-122, JWH-250, JWH-175, ADB-FUBINACA, AB-FUBINACA, 5F-APINACA, MAM-2201, STS135, THJ 2201, AM-1220, AM-2232, PB-22, NNEI, AM-604, and JWH-073) were detected, some being more frequently identified in the revised cases, such as 5F-ADB, XLR-11, and JWH-018.

Even if reported with lower rates, 5F-PB-22, UR-144 were also common. XLR-11 was mostly reported in 2016, while 5F- ADB showed a peak in 2017 and 2018. However, a clear trend cannot be determined on the sole basis of this data.

While some laboratories applied national or international validation guidelines, such as those of the German Society of Toxicological and Forensic Chemistry (GTFCh), "in house" methods have also been adopted, stating overall good results.
TABLE 1 | Characteristics of the included studies: authors, titles, journal, and year of publication, number of cases reported and type of SCRs involved (semisystematic names).

| Title                                                                 | Journal                  | Year | No. of cases | SCRA                                      | Author                          |
|----------------------------------------------------------------------|--------------------------|------|--------------|-------------------------------------------|----------------------------------|
| A case of intoxication with a mixture of synthetic cannabinoids EAM-2201, AB-PINACA and AB-FUBINACA, and a synthetic cathinone e-PFP. | Leg Med (Tokyo)          | 2018 | –            | EAM-2201, AB-PINACA, AB-FUBINACA          | Yamagishi et al. (19)            |
| Synthetic cannabinoids: variety is definitely not the spice of life. | J Forensic Leg Med       | 2018 | 1            | 5F-PB-22, 5F-AKB-48                       | Langford and Bolton (20)         |
| Teens and Spice: A review of adolescent fatalities associated with synthetic cannabinoid use | J Forensic Sci           | 2018 | 2            | UR-144, XLR-11, JWH-022                   | Paul et al. (21)                 |
| Identification and quantification of predominant metabolites of synthetic cannabinoid MAB-CHMINACA in an authentic human urine specimen. | Drug Test Anal           | 2018 | –            | MAB-CHMINACA                              | Hasegawa et al. (22)             |
| Fatal intoxication by 5F-ADB and diphenidine: Detection, quantification, and investigation of their main metabolic pathways in humans by LC/MS/MS and LC/Q-TOFMS. | Drug Test Anal           | 2018 | 1            | 5F-ADB                                    | Kusano et al. (23)               |
| Post-mortem distribution of the synthetic cannabinoid MDMB-CHMICA and its metabolites in a case of combined drug intoxication. | Int J Legal Med          | 2018 | 1            | MDMB-CHMICA, EG-018                       | Gaunitz et al. (24)              |
| Identification and quantification of 5-fluoro-ADB, one of the most dangerous synthetic cannabinoids, in the stomach contents and solid tissues of a human cadaver and in some herbal products | Forensic Toxicol         | 2017 | 1            | 5F-ADB, MAB-CHMINACA                      | Minakata et al. (25)             |
| Three fatalities associated with the synthetic cannabinoids 5F-ADB, 5F-PB-22, and AB-CHMINACA | Forensic Sci Int         | 2017 | 3            | 5F-ADB                                    | Angerer et al. (27)              |
| Postmortem distribution of MAB-CHMINACA in body fluids and solid tissues of a human cadaver | Forensic Toxicol         | 2015 | 1            | 5F-ADB, 5F-ADB-PINACA, MAB-CHMINACA       | Hasegawa et al. (28)             |
| Postmortem distribution of AB-CHMINACA, 5-fluoro-AMB and diphenidine in body fluids and solid tissues in a fatal poisoning case: usefulness of the adipose tissue for detection of the drugs in the unchanged forms | Forensic Toxicol         | 2015 | 1            | AB-CHMINACA, 5F-AMB                       | Hasegawa et al. (29)             |
| Fatal poisoning with the synthetic cannabinoid AB-CHMINACA and ethyl alcohol – a case study and literature review | Problems of Forensic Sciences | 2016 | 1            | AB-CHMINACA                               | Giron et al. (31)                |
| Death after use of the synthetic cannabinoid 5F-AMB | Forensic Sci Int         | 2016 | 1            | 5F-AMB                                    | Shanks and Behonick (32)         |
| Synthetic cannabinoid drug use as a cause or contributory cause of death | Forensic Sci Int         | 2016 | 25           | JWH-018, AM-2201                          | Labay et al. (33)                |
| Death associated with the use of the synthetic cannabinoid ADB-FUBINACA | J Anal Toxicol           | 2016 | 1            | ADB-FUBINACA                              | Shanks et al. (34)               |
| Clinical and toxicological findings of acute intoxication with synthetic cannabinoids and cathinones | Acute Med Surg           | 2016 | 1            | Mepirapim                                 | Fujita et al. (35)               |
| Case report: fatal intoxication with synthetic cannabinoid MDMB-CHMICA | Forensic Sci Int         | 2016 | 1            | MDMB-CHMICA                               | Adamowicz (36)                   |
| Death due to diabetic ketoacidosis: Induction by the consumption of synthetic cannabinoids? | Forensic Sci Int         | 2015 | 1            | AB-CHMINACA, AB-FUBINACA, AM-2201, 5F-AMB, 5F-APINACA, EAM-2201, JWH-018, JWH-122, MAM-2201, STS135, THJ2201, UR-144, XLR-11-MAM-2201, AM-1220, AM-2232 | Hess et al. (37) |
| High-resolution mass spectrometric determination of the synthetic cannabinoids MAM-2201, AM-2201, AM-2232, and their metabolites in postmortem plasma and urine by LC/Q-TOFMS. | Int J Legal Med          | 2015 | 1            | AB-CHMINACA, AB-FUBINACA, EAM-2201, JWH-018, JWH-122, MAM-2201, STS135, THJ2201, UR-144, XLR-11-MAM-2201, AM-1220, AM-2232 | Zaitsu et al. (38) |
| Case reports of synthetic cannabinoid XLR-11 associated fatalities. | Forensic Sci Int         | 2015 | 2            | XLR-11                                    | Shanks et al. (34)               |
| Deaths linked to synthetic cannabinoids. | Forensic Sci Med Pathol  | 2015 | 3            | PB-22                                     | Gerostamoulos et al. (39)        |
Analytical details were not always given and not all of the above-mentioned parameters, especially matrix-effects, were systematically assessed (19, 27, 31, 37, 38, 41, 44, 52).

According to previously published cases (33, 43), concentrations of SCRs in post-mortem cases covered a wide range, from 0.01 to 199 ng/mL (43), although lower concentrations, in the range 0.5 to 2.5 ng/mL, were most frequently encountered.

Peripheral blood was analyzed in 53 cases out of 74 (72%). In 8 cases (11%) only heart blood concentrations were stated, while both peripheral and central concentrations were published in 10 cases (14%). Other biological matrices, apart from urine, were quantitatively analyzed in only 8 cases (11%) (Table 3). Other substances were found in 44 out of 74 cases (59%).

As regard other xenobiotics detected, ethanol was detected in 13 cases (17%), though levels ≥ 1.5 g/L were found only in 6. A co-consumption of NPS, as synthetic cathinones (pentedrone, α-PVP, DL-4662), hallucinogens (6-APB, 6-MAPB, methoxetamine), anesthetics (diphenidine), and synthetic opioids (AH-7921) was seen in 11 cases (15%). Common drugs of abuse detected included antidepressive/neuroleptics/antipsychotics (quetiapine, trimipramine, olanzapine, sodium valproate, mirtazapine, amitriptylne, phenytoin, paroxetine, aripiprazole, citalopram, valproate, mirtazapine, amitriptyline, phenytoin, paroxetine, aripiprazole, citalopram, fluoxetine, haloperidol, trazodone, venlafaxine, pregabalin, topiramate) (12/74, 16.2%), cannabinoids (10/74, 13%), amphetamines, benzodiazepines (both 6/74, 8%) and opioids (5/74, 7%).

**Case Reports**

The age of the deceased ranged from 14 to 61 (19). Mean age was 32, median 29. The 38.5% belonged to the 20 to 29 decades. Teenagers were also represented (15.4%) (Figure 2). With reference to the gender of the victims, 88.1% were male and 11.9% were female. A past use of drugs and/or alcohol was reported in 18 out of 74 cases (24%), while poor mental health was only reported in 5 cases (7%).

Herbal blends, smoking devices (e.g., pipes) and other paraphernalia were found during the death scene investigation (DSI) in 30 out of 74 cases (41%) and were variably labeled as “Aladdin platinum/limited,” “Herbal incense, the super lemon,” “F1,” “Hammer Head,” “Magic Gold,” “Desert Premium Potpourri,” “AL 37,” “AP 31,” “Strongman,” “GM sapphire,” “Heart Shot Black,” “Apollo,” “Mocarz,” “Smoke XXX. A potent potpourri,” “Mad Hatter Incense,” “Fairy evolution,” “Mary Joy Annihilation,” “Passion Flower Herb – Zonk,” “Stoner Pot-Pourri K11,” “Supanova Pot-Pourri,” “K2 Cherry,” “Space Cade Flight Risk,” “Game over,” “Orange Flame,” “Legal Phunk,” “Mojo.” Clinical data was available in 15 cases (20%) and mostly included the detection of cardiac arrest/assystolia/fibrillation at the arrival to an Emergency Department.

Results of post-mortem examination, as for macroscopical or gross findings, were available in 55 cases (74%), including those cases in which only a short referral to “unremarkable findings” was reported. In most cases in which a SC was later discovered during toxicological analysis, the post-mortem examination had revealed only non-specific signs of intoxication, such as pulmonary edema and congestion, brain edema, hemolysis, and signs of aspiration (34, 40). In some cases, stomach and gastroduodenal erosions (20, 35), abundant hypostasis coupled to petechiae (27, 29, 37) and intracutaneous skin bleedings (vibices) (30) were reported. Lastly, cardiac abnormalities, such as cardiomegaly (33, 43), dilatative or hypertrophic cardiomyopathy (21), stenosis due to atherosclerosis (33, 46) or acute thrombosis of the coronary arteries were seen (32).
| Age, sex | SCRA(s) in peripheral blood (ng/mL) | SCRA(s) in blood (ng/mL, ethanol g/L) | Anamnestic and circumstantial data | Clinical data | Gross findings | Histopathology | Cause of death | Suggested mechanism | TSS | Role of SCRA(s) (authors) | Study |
|----------|-------------------------------------|--------------------------------------|---------------------------------|--------------|----------------|---------------|---------------|-----------------|-----|-------------------------|-------|
| 17, M    | UR-144: 12.3 (subclavian), XLR-11: 1.3 (subclavian), JWH-022: 3 (subclavian) | Ethanol: 0.3 | Quetiapine: pos Nicotine: pos | Severe drug dependence with multiple admission to mental health hospital; found dead in his room | No history of any other substance use, or any relevant medical, surgical or family history | Dilated cardiomyopathy, cardiomegaly (520 g), bilateral pulmonary edema, bilateral pleural effusion and ascites | Cardiomyocyte hypertrophy, contraction band necrosis, pulmonary edema and pulmonary vascular congestion | SCRA intoxication | Sudden cardiac death and dilated cardiomyopathy | TSS 3 | SCRA intoxication | Paul et al. [21] |
| 14, M    | AB-CHMINACA: 8.2 (subclavian) | - | - | Daily SC intake for 6 months, last use an hour before experiencing sudden cardiac death following an un witnessed collapse in his bathroom | No history of any other substance use, or any relevant medical, surgical or family history | Dilated cardiomyopathy, cardiomegaly (520 g), bilateral pulmonary edema, bilateral pleural effusion and ascites | Cardiomyocyte hypertrophy, contraction band necrosis, pulmonary edema and pulmonary vascular congestion | SCRA intoxication | Sudden cardiac death and dilated cardiomyopathy | TSS 3 | SCRA intoxication | Paul et al. [21] |
| 53, M    | 5F-ADB: 0.19 ± 0.04 (”) | Diphenidine: 12 ± 5.05 | Quetiapine: pos | Severe drug dependence with multiple admission to mental health hospital; found dead in his room | No history of any other substance use, or any relevant medical, surgical or family history | Dilated cardiomyopathy, cardiomegaly (520 g), bilateral pulmonary edema, bilateral pleural effusion and ascites | Cardiomyocyte hypertrophy, contraction band necrosis, pulmonary edema and pulmonary vascular congestion | SCRA intoxication | Sudden cardiac death and dilated cardiomyopathy | TSS 3 | SCRA intoxication | Paul et al. [21] |
| 30, F    | 5F-ADB: 0.12 (lou) | AB-PINACA: 0.0126 ± 0.0001 | Ethanol 3.11 | History of schizophrenia, alcohol and alcohol withdrawal, seizures; he was found dead in an alleyway within 30 min of having been given a smoking pipe | Shock advisory deliriblator | Lungs congestion, scattered erosions within the mucosa of the stomach | Confirmation of macroscopic findings | Combination of alcohol and SCRA(s) | Sudden onset of cardiac arrhythmias or cardiac death | TSS U | Possible contributory role in emotional and mental imbalance | Langford and Bolton [23] |
| 20s, M   | 5F-ADB: 0.23 (lou) | - | - | The decedent was lying on the floor in a supine posture. An opened sachet labeled “Heart Shot BLACK” was found on a table. | No medication history | Ischemic heart disease | Acute circulatory failure after drug inhalation | NP | TSS 2 | The SCRA involvement on death is unknown | Usui et al. [50] |
| 50s, M   | 5F-ADB: 0.16 (lou) | - | - | The decedent was lying on the floor in a supine posture. An opened sachet labeled “Heart Shot BLACK” was found on a table. | No medication or medical history | Unremarkable | NP | TSS 2 | The SCRA involvement on death is unknown | Usui et al. [50] |
| 50s, M   | 5F-ADB: 1.38 (lou) | 14 – 34 | History of schizophrenia under medication, he was found dead in his car in a parking lot while he was holding a plastic pipe and with an unsealed “Heart Shot BLACK” package in his hands | For the treatment of schizophrenia he was taking risperidone, biperiden, and olanzapine. | Unremarkable | NP | Acute circulatory failure after drug inhalation | NP | TSS 2 | The SCRA involvement on death is unknown | Usui et al. [50] |
| 17, M    | 5F-PB-22: pos 5F-ADB: 0.16 (lou) | AB-PINACA: 0.0126 ± 0.0001 | Ethanol 3.11 | History of schizophrenia, alcohol and alcohol withdrawal, seizures; he was found dead in an alleyway within 30 min of having been given a smoking pipe | Shock advisory deliriblator | Lungs congestion, scattered erosions within the mucosa of the stomach | Confirmation of macroscopic findings | Combination of alcohol and SCRA(s) | Sudden onset of cardiac arrhythmias or cardiac death | TSS U | Possible contributory role in emotional and mental imbalance | Langford and Bolton [23] |
| 34, M    | 5F-ADB: 0.19 ± 0.04 (”) | AB-PINACA: 0.0126 ± 0.0001 | Ethanol 3.11 | History of schizophrenia, alcohol and alcohol withdrawal, seizures; he was found dead in an alleyway within 30 min of having been given a smoking pipe | Shock advisory deliriblator | Lungs congestion, scattered erosions within the mucosa of the stomach | Confirmation of macroscopic findings | Combination of alcohol and SCRA(s) | Sudden onset of cardiac arrhythmias or cardiac death | TSS U | Possible contributory role in emotional and mental imbalance | Langford and Bolton [23] |
| 35, M    | 5F-PB-22: pos 5F-ADB: 0.16 (lou) | AB-PINACA: 0.0126 ± 0.0001 | Ethanol 3.11 | History of schizophrenia, alcohol and alcohol withdrawal, seizures; he was found dead in an alleyway within 30 min of having been given a smoking pipe | Shock advisory deliriblator | Lungs congestion, scattered erosions within the mucosa of the stomach | Confirmation of macroscopic findings | Combination of alcohol and SCRA(s) | Sudden onset of cardiac arrhythmias or cardiac death | TSS U | Possible contributory role in emotional and mental imbalance | Langford and Bolton [23] |
| Age, sex | SCRA(s) in peripheral blood (ng/ml) | Other substances in blood (ng/ml, ethanol g/L) | Anamnestic and Circumstantial data | Clinical data | Gross findings | Histopathology | Cause of death | Suggested mechanism | TSS | Role of SCRA(s) (authors) | Study |
|----------|-----------------------------------|-----------------------------------------------|-----------------------------------|--------------|---------------|--------------|---------------|-------------------|-----|--------------------------|-------|
| 27, M    | MDMB-CHMICA: 1.7                  | Amphetamine: 1050                             | Eyewitnesses reported that the man fell from the 24th floor of a building. | NP           | Multiple injuries to head (including partial debraining), left lung and internal bleeding due to rib fractures. | NP           | Fall from height | Psychosis-induced or loss of attention | TSS 1 | Under the influence | Gaunitz et al. (24) |
| 30, M    | AB-CHMINACA: pos 5F-AMB: pos      | Diphenidine 715                               | Found dead in a parked car       | NP           | NP            | NP           | NP            | NP                | TSS U | NP | Minakata et al. (25) |
| 30s, M   | 5F-ADB: pos MAB-CHMINACA: pos     | –                                             | Found dead at home               | NP           | NP            | NP           | NP            | NP                | TSS U | NP | Minakata et al. (25) |
| 16, M    | UR-144: 2.1                      | –                                             | He smoked “dope” and a cigarette with UR-144, experienced hallucinations and psychosis, lost control of himself and jumped out of the window from the second floor of the building | NP           | Multiple fractures to skull, thoracic and lumbar spine, public and ischial bones and multi-organ injuries | NP           | Fall from height | Psychosis-induced | TSS 3i | NP | Rojek et al. (26) |
| 22, M    | UR-144: 1.4                      | Pentedrone: 2500                             | History of alcohol and drugs abuse, previous suicidal ideations; showed mental disorders and aggressive behavior, injured a witness with an axe | NP           | NP            | NP           | Asphyxia due to hanging | Behavioral abnormalities | TSS 1i | NP | |
| 40, M    | UR-144: 4                        | Pentedrone: 290                              | History of mental instability; psychomotor agitation, aggressive behavior, after smoking a legal high called Orange Flame | NP           | Acute toxic liver damage, kidney failure, rhabdomyolysis, disseminated intravascular coagulation, bleeding in the gastrointestinal tract and traumatic hematomas; cardiac arrest | NP           | Massive multi-organ failure due to the effect of toxic substances | Behavioral abnormalities with desire of enhancing stimulating effects | TSS 1i | NP | |
| 25, M    | 5F-PB-22: 0.37                   | Ethanol: 2.6                                  | History of alcohol and illicit drug use, found dead in his apartment; witnesses reported that the decedent had drunk a lot of alcohol on the evening before his death. Packages of products named “F1,” “Hammer Head,” and “Magic Gold” were found at the scene | NP           | Cerebral edema, pulmonary edema, acute blood congestion of internal organs, petechial hemorrhage in eyelids, facial skin and on the lungs | NP           | Partial or complete obstruction of the upper airways | Sufocation in presence of SC and ethanol in a state of unconsciousness | TSS 2 | Direct contribution | Angerer et al. (27) |
| 28, M    | AB-CHMINACA: 4.1                 | Ethanol: 1.45                                 | Extensive consumer of alcohol and illicit drugs, found dead in his flat. Three packages of the herbal blend “Desert Premium Potpourri 2 g” were located besides the decedent | NP           | Cerebral edema and pulmonary edema | NP           | Mixed ethanol and SC intoxication with fatal outcome | NP | TSS 2 | Direct contribution | |
| 41, M    | 5F-ADB: 0.38                     | Ethanol: 0.09, Trimipramine: 170, Olanzapine: 41 | Methamphetamine user, found at home | NP           | Cerebral edema, pulmonary edema, acute blood congestion of myocardial cells death, morphological material in alveoli as a sign of aspiration of stomach content | NP           | Coma and subsequent aspiration of vomit | NP | TSS 3 | Direct contribution | |
| Age, sex | SCRA(s) in peripheral blood (ng/ml) | Other substances in blood (ng/ml, ethanol g/L) | Anamnestic and Circumstantial data | Clinical data | Gross findings | Histopathology | Cause of death | Suggested mechanism | TSS | Role of SCRA(s) (authors) | Study |
|----------|-----------------------------------|-----------------------------------------------|----------------------------------|---------------|---------------|----------------|----------------|---------------------|-----|------------------------|-------|
| 26, M    | AB-PINACA: 26 - PVP: 9900          | MDPV: 55                                     | NP                              | NP            | NP            | NP             | Fall from height | TSS U               | NP  | Kubo et al. (47)        |       |
|          | 5F-AMB: 8 - PVP: 90               | AH-7901: 1100                                | NP                              | NP            | NP            | NP             | Intoxication     | TSS U               | NP  |                       |       |
|          | Mespipirin: 157                  | 6-APB: 2.7                                   | NP                              | NP            | NP            | NP             | Intoxication     | TSS U               | NP  |                       |       |
|          | -                                 | DL-6662: 138, Sodium valproate: pos          | NP                              | NP            | NP            | NP             | Intoxication     | TSS U               | NP  |                       |       |
|          | -                                 | DL-6662 <1, α-PHP: 338, 6-MAPB: <1           | NP                              | NP            | NP            | NP             | Intoxication     | TSS U               | NP  |                       |       |
| 30s, M   | AB-CHMINACA: 1.5 (**)             | Ethanol: 1.8                                 | Alcohol addiction. After smoking a pipe with a herbal mixture ("Strongman"), he collapsed and had a slurred speech. An hour later, was found with vomit, weak pulse, shallow breathing. About half an hour later, was declared dead by the emergency doctor | NP            | Congestion of internal organs and pulmonary edema | NP             | Acute cardiopulmonary failure | SNC depression | TSS 3 | Intoxication due to alcohol and SCRA consumption | Gieron and Adamowicz (31) |
| 22, M    | MDMB-CHMICA: 1.4 (ante-mortem serum) | Mirtazapine: 5.3, THC: 1.5, Cetirizine: pos | Found lifeless 15 minutes after smoking a brown organic powder | Asystole, declared dead due to brain hypoxia | Anoxic brain damage and pneumonia | NP             | Sudden cardiac death | NP | TSS 3 | Overdose | Westin et al. (48) |
| 44, M    | MDMB-CHMICA: 1 (**)               | Amtriptyline: 130                           | History of poor mental health   | NP            | NP            | NP             | Suicidal by hanging | NP | TSS 1 | Not attributable to SCRA | Seywright et al. (49) |
| 38, M    | MDMB-CHMICA: <1 (**)              | Ethanol: 2.37, Acetone: < 100, BHB: 249     | History of alcoholism: found dead at home | NP            | NP            | NP             | Complications of chronic alcohol abuse and acute alcohol toxicity | NP | TSS 1 | Not attributable to SCRA | Seywright et al. (49) |
| 34, M    | 5F-AMB: 0.3 (subclavian)          | -                                            | History of ethanol abuse, found supine on the floor. An opened bag of "Apollo" brand herbal incense was found in his pocket | Unremarkable medical history | NP             | NP             | SC toxicity | TSS 2 | Related (SCRA toxicity) | Shanks and Benorick (51) |
| 41, M    | JWH-018: 0.11, AM-2201: 2.5       | Phenytoin: 9800                             | Enratic and aggressive behavior, restrained by the police | Cardiomegaly with four chamber dilation | NP             | NP             | Complications of excited delirium associated with synthetic marijuana use following police arrest and restraint procedures | Delirium-induced | TSS 2 | NP | Labay et al. (53) |
| 23, M    | JWH-210: pos                      | Fentanyl: pos                                | Single motor vehicle crash, no significant injuries, restrained by the police | NP             | NP             | NP             | Agitated delirium associated with SCRA use following police arrest and | Delirium-induced | TSS 1 | NP |                       |       |
| Age, sex | SCRA(s) in peripheral blood (ng/ml) | Other substances in blood (ng/ml, ethanol g/L) | Anamnestic and Circumstantial data | Clinical data | Gross findings | Histopathology | Cause of death | Suggested mechanism | TSS | Role of SCRA(s) (authors) | Study |
|----------|-----------------------------------|-----------------------------------------------|----------------------------------|--------------|--------------|--------------|--------------|-------------------|-----|-------------------------|-------|
| 25, M    | AM-2201: 0.21 JWH-018: 0.65 JWH-122: pos JWH-210: pos | Amphetamine: 730 Amphetamine: 90 | Unresponsive after a party, recent binge drinking and jumping from a patio. He was found "frozen" after the jump. | Asystole at emergency arrival | No evidence of head, chest or abdomen injury. | Macrosteatosis, chronic active hepatitis | | restraint procedures Complications of acute ethanol toxicity, acute SCRA toxicity, possible hypothermia Mixed drug intoxication | TSS 2 | NP | |
| 42, M    | XLR-11: pos | Methamphetamine: 0.15 THC-COOH: 6.0 | Seizure-like activity after methamphetamine and K2 intake | | | | | | TSS 1 | NP | |
| 55, M    | AM-2201: 17 JWH-018: 0.47 | Chlorpheniramine: < 100, Paroxetine: pos, Benzodiazepines: pos, Alprazolam: < 0.5, Aripiprazole pos | Recent chest pain and heart palpitations in history of cardiac problems | Diagnosed type 2 diabetes | No evidence of diabetes, obesity, abdominal aortic aneurysm | Ischemic heart disease, obesity, diabetes SCRA toxicity | | | TSS 1 | NP | |
| 34, M    | XLR-11: pos UR-144: pos | Ethanol 0.03 Lidocaine pos | Collapse on public street, after intake of alcohol and drugs | Presence of a needle puncture in the left antecubital fossa | | SCRAs and alcohol | | | TSS U | NP | |
| 21, M    | JWH-018: pos | Ethanol: 0.01 Tramadol: pos, Delta-9-THC: 7 THC-COOH: 17 Caffeine: pos Theophylline: pos Atropine: 110 | Decedent found unresponsive in bed | Decedent found unresponsive in bed | Pulmonary congestion, vomiting in upper airway, aspiration pneumonia, patchy alveolar hemorrhage | Mixed drug intoxication, aspiration pneumonia | | | TSS 1 | NP | |
| 24, M    | JWH-122: pos JWH-210: pos AM-2201: 0.16 | Delta-9-THC: 2.7 THC-COOH: 6.4 Caffeine: pos Nicotine: pos Cotinine: pos | Learning disability, found lying prone on floor of his bedroom | No evidence of head, chest or abdomen injury | Bloodly froth in airway, cardiomegaly | SCRAs adverse effects | | | TSS 2 | NP | |
| 38, M    | UR-144: pos | Amphetamine: pos Alprazolam: pos Citalopram/escitalopram: 300 Hydrocodone: 26 Morphine (free): pos | Found deceased lying on bed, after "partying" with others | No evidence of head, chest or abdomen injury | | Mixed drug intoxication | | | TSS U | NP | |
| 24, M    | JWH-210: pos AM-2201: 1.1 | Fluoxetine: 620 Norfluoxetine: 520 Phenobarbital: pos Benzodiazepines: pos Diflunisal: pos Methadone: pos | Found unresponsive in bed, after taking methadone | No evidence of head, chest or abdomen injury | | Mixed drug intoxication | | | TSS U | NP | |
| 56, F    | XLR-11: pos | Delta-9-THC: 4.3 THC-COOH: 26 Oxycodone 420 Haloperidol 4.7 Fluoxetine 1300 Norfluoxetine 370 Trazadone 250 | Death in private residence | | | Mixed drug intoxication | | | TSS 1 | NP | |

(Continued)
| Age, sex | SCRAs in peripheral blood (ng/ml) | Other substances in blood (ng/ml, ethanol g/L) | Anamnestic and Circumstantial data | Clinical data | Gross findings | Histopathology | Cause of death | Suggested mechanism | TSS | Role of SCRAs (authors) | Study |
|----------|-------------------------------|-----------------------------------------------|----------------------------------|--------------|---------------|---------------|--------------|-------------------|-----|------------------------|-------|
| 15, M    | XLR-11: pos                   |                                |                                |              |              |               |              |                   |     |                       |       |
| 42, F    | AM-2201: 2.8                 | JWH-018: 0.11                   | Cartoon monoxide: 4300         |              |              |               |              |                   |     |                       |       |
| 25, M    | JWH-122: pos                 | JWH-250: 0.23                   | Caffeine: pos                  |              |              |               |              |                   |     |                       |       |
| 15, F    | XLR-11: pos                  |                                |                                |              |              |               |              |                   |     |                       |       |
| 52, M    | JWH-018: 0.28                |                                |                                |              |              |               |              |                   |     |                       |       |
| 15, F    | XLR-11: pos                  |                                |                                |              |              |               |              |                   |     |                       |       |
| 30, F    | XLR-11: pos                  |                                |                                |              |              |               |              |                   |     |                       |       |
| 31, F    | JWH-175: 105                 |                                |                                |              |              |               |              |                   |     |                       |       |
| Age, sex | SCRA(s) in peripheral blood (ng/ml) | Other substances in blood (ng/ml, ethanol g/L) | Anamnestic and Circumstantial data | Clinical data | Gross findings | Histopathology | Cause of death | Suggested mechanism | TSS | Role of SCRA(s) (authors) | Study |
|----------|-------------------------------------|-----------------------------------------------|-----------------------------------|--------------|---------------|---------------|---------------|-------------------|-----|-------------------------|-------|
| 58, M    | JWH-210: pos –                      | –                                             | Collapse in a parking after a wavering gait, after smoking K2 | Seizure      | Acute myocardial infarction due to coronary artery thrombosis | NP            | Nellie          | TSS 1             | NP  | Shanks et al. (51)      |
| 41, F    | ADB-FUBINACA: 7.3 (1) THC: 1.1 THC-COOH: 4.7 | –                                             | Aggressive after smoking SC known as “Mojo,” physically restrained by her children, then became unresponsive. | NP           | NP            | Acute circulatory failure due to SCRA intoxication | Acute circulatory failure | TSS 2 | Fujita et al. (55)     |
| 23, M    | Methaprin: 950 (serum) A-EAPP 3100 | –                                             | Fell asleep after ingestion of the drugs in the restroom; he was found without respiratory signs and was transferred to a hospital | Cardio-pulmonary arrest and confirmed dead approximately 3.5 h after drug use | Congestion of the organs (particularly the lungs) and gastrointestinal bleeding from the stomach into the duodenum | NP            | Nellie          | TSS 1             | NP  | Shanks et al. (51)      |
| 25, M    | MDMB-CHMICA: 5.6 (ante-mortem blood), MDMB-CHMICA: < 0.2 (post-mortem blood) Ethanol: 1.48 (ante-mortem blood), Ethanol: 0.81 (post-mortem blood) | –                                             | History of alcohol and NPSs abuse. After smoking two different SCRAs in a day and drinking a beer, he was wheezing, vomited and then lost consciousness. He was found lying on the floor, without a circulation and a pulse | On hospital admission, he was deeply unconsciousness, limp, circulatory and respiratory inefficient, without deep tendon, pharyngeal and tracheal reflexes. During hospitalization, severe redness of the skin, pathological muscle contraction of chest were observed. Purulent and watery content was expelled and dianhea and bleeding diathess | Pulmonary edema, vascualr congestion, thrombotic occlusion of the lumen of the left anterior descending coronary artery by hemorrhagic disruption of coronary arterial plaque, ischemia of the anterior left ventricular myocardium | NP            | Unremarkable    | TSS 1             | NP  | Hess et al. (57)        |
| 25, M    | AB-CHMINA: 2.8 AB-FUBINACA: 0.97 AM-2201: <0.1 SF-AMB: 0.19 SF-APINACA: 0.51 EAM-2201: <0.1 MAM-2201: <0.1 STS 135: 0.16 THJ 2201: 0.16 MAM-2201: 16.3, AM-1220: 140, AM-2232: 0.86 | –                                             | History of SCRA use with previous intoxications, insulin dependent diabetes, Found dead in his apartment | Brain edema, pulmonary edema, subependimal petechial hemorrhages, hepatic steatitis, aorta angusta, small myocardial scars | Pulmonary congestion and edema, microvesicular steatosis of the liver, Armanii-Ebstein cells in kidneys | Diabetic ketoacidosis, probably following SCRA consumption | SKipping of insulin doses due to intoxicated state or SCRAs induced hyperglyceremia | TSS 1 | Contributory | Zaitsu et al. (30) |
| 29, F    | XLR-11: 1.4 | Diphenhydramine: 81 | Known user of SC, found dead on the floor of the bedroom | Lungs, heart and liver congestion | NP | SCRA intoxication | NP | TSS 2 | Causative | Shank et al. (54) |
| 32, F    | XLR-11: 0.6 | – | History of drug abuse (methamphetamine, heroin and SCRAs), The day before, presented to the emergency room with chest pain, nausea, and agitation, diagnosed | Pulmonary edema and congestion, acute visceral congestion and mild pulmonary anthracosis | Pulmonary edema and congestion | NP | TSS 2 | Probable contributory | Shank et al. (54) |

(Continued)
| Age, sex | SCRA(s) in peripheral blood (ng/ml) | Other substances in blood (ng/ml, ethanol g/L) | Anamnestic and Circumstantial data | Clinical data | Gross findings | Histopathology | Cause of death | Suggested mechanism | TSS | Role of SCRA(s) (authors) | Study |
|----------|----------------------------------|-----------------------------------------------|-----------------------------------|---------------|---------------|---------------|---------------|-----------------|------|---------------------|-------|
| 15–35 PB-22: pos – | – | Unremarkable, later found unresponsive at a friend’s house. Found at home | Unremarkable | Unascertained | NP | TSS U | Unknown, no competitive cause | Gerostamoulos et al. (39) |
| 15–35 PB-22: pos – | – | Found at home | Unremarkable | Unascertained | NP | TSS U | Unknown, no competitive cause |
| 15–35 PB-22: pos – | – | Found at home | Unremarkable | Unascertained | NP | TSS U | Unknown, no competitive cause |
| 20s M NNEI: 0.99, 0.64 (*) – | | Found dead on the floor of his room, a package containing dried herbal blend labeled “Fairy evolution” was found in the room, previous history of weight loss | No medical history | Marked lungs congestion | Organs and lungs congestion. Lungs: marked congestion and edema, alveolar macrophage infiltrations. Liver: slight lymphocytic infiltrations in the Glisson’s sheath. Spleen: arteriolar hyalinizations and severe congestion. Brain: Corpora amylacea. Heart: arteriolar wall hypertrophy, slight interstitial fibrosis and contraction bands. | Acute circulatory disturbance induced by NNEI | Hypertension and hyperactivity of cardiac function | TSS 2 | SCRA poisoning | Sasaki et al. (45) |
| 17, M 5F-PB-22: 1.1 Ethanol: 0.033, Amiodarone Caffeine (not quantified) | | His friends reported that he began gasping for air and then fell to the ground, after SCRA consumption and ethanol intake | Unremarkable | SCRA intoxication | Possible anaphylactic etiology characterized by sudden onset cardiac dysrhythmias or seizure | NP | TSS 2 | Behonick et al. (45) |
| 27, M 5F-PB-22: 1.3 (anti-mortem serum) THC-COOH | | History of marijuana use of several times per week. | Acute liver injury, severe coagulopathy, acute kidney injury, acute respiratory failure, hypoxemia, severe anion gap metabolic and lactic acidosis. Brief episode of cardiac arrest, and pulseless electrical activity and poor oxygenation secondary to acute respiratory distress syndrome likely the result of aspiration and pulmonary contusions following chest compressions. | NP | Fulminant liver failure in the setting of THC and SC exposure | TSS 2 | NP |
| 18, M 5F-PB-22: 1.5 (iliac) | | Found dead at home after a night of partying, with alcohol intake and SCRA smoking (K2/Spice) | NP | Sudden death, in association with synthetic cannabinoid use | NP | TSS 2 | Contributory Schaefer et al. (46) |
| 19, M 5F-PB-22: 1.5 (*) – | | Bilateral pulmonary vasocongestion and congestion in the abdominal organs (liver, spleen and kidneys) | Necrotizing granulomatous inflammation with histoplasma microorganisms | NP | TSS 2 | NP |
| 36, M JWH-018: 0.1 JWH-122: 0.39 AM-2201: 1.4 MAM-2201: 1.5 LR-144: 6 (estimated) Amphetamine: 250 | | Sudden collapse after smoking herbal blend named “Mary Joy Annihilation” | Seizures, multiple attempts of resuscitation | Necrotizing granulomatous inflammation with histoplasma microorganisms | Acute drug intoxication using the synthetic cannabinoid SF-22 | NP | TSS 1 | Contributory Schaefer et al. (46) |

(Continued)
| Age, sex | SCRA(s) in peripheral blood (ng/ml) | Other substances in blood (ng/ml, ethanol g/L) | Anamnestic and Circumstantial data | Clinical data | Gross findings | Histopathology | Cause of death | Suggested mechanism | TSS | Role of SCRA(s) (authors) | Study |
|----------|-----------------------------------|-----------------------------------------------|-----------------------------------|--------------|---------------|----------------|---------------|-------------------|-----|--------------------------|-------|
| 17, M    | JWH-210: 12                        | –                                             | Found dead outdoors (temperature during the night was 6-8°C), after having smoked a mixture of herbs labeled “Smoke XXX. A potent potpourri” | NP           | Low BMI (16.4), lung edema | NP             | Hypothermia in combination with SCRA intoxication | Hypothermia | TSS 2 | Significant role | Kronstrand et al. (52) |
| 23, M    | AM-2201: 12, AM-2201 m: 2.47, JWH-018 m: 123, 50.8 (*) | –                                             | A sibling heard 30 minutes of “stomping noises.” Significant damage to a wall and glass window at the scene, a large volume of blood covered the floor, windows and walls | NP           | No known history of mental illness, seizures disorder, previous psychiatric care or past or current use of illicit drugs or over-the-counter medication (OTC) | Multiple blunt-force injuries to both hands and sharp force wounds on the head and upper extremities, including a fatal stab wound at the neck | NP | Self-inflicted fatal wound due to SC use, No evidence indicating the intent of self-harm | Psychiatric complications caused by AM-2201 use | TSS 2 | Psychiatric complications caused by SCRA | Patton et al. (41) |
| 26, M    | AM-694: 0.09 (0.00009 µg/g), AM-2201: 0.3 (0.0003 µg/g), JWH-018: 0.05 (0.00005 µg/g) | Methoxetamine: 8600 | Found on the floor in his apartment | History of drug abuse and depression (treated with venlaxafine) | Pulmonary edema | NP | Acute fatal intoxication with methoxetamine | TSS 1 | Possible contributory | Wikström et al. (42) |
| 59, M    | MAM-2201: 12.4 (*) | –                                             | Found dead on a sofa at home The man had smoked herbal incense (Spice) and a white powder presumably containing JWH-018 | NP           | Unresponsive to Narcan, asystole | Unremarkable | Acute intoxication | NP | TSS 3 | Fatal intoxication | Saito et al. (44) |
| 57, M    | JWH-018: 199 (*) | Clonazepam: 5.5 | Avid herbal incense user, found nude and unresponsive at home | Unresponsive to Narcan, asystole | Enlarged heart | NP | Acute intoxication | NP | TSS U | NP | Shanks et al. (43) |
| 52, M    | JWH-018: 19.6, JWH-073: 68.3 (*) | –                                             | Avid herbal incense user, found nude and unresponsive at home | NP           | NP | NP | NP | TSS U | NP | |
| 29, M    | JWH-018: 83.3 (*) | –                                             | Avid SCRA user, history of suicidal tendencies | NP           | NP | NP | Suicide by exsanguination | NP | TSS 3i | NP | |

Ref, reference; age, -s: decade (e.g., 30s: from 30 to 39 years old); PBC, peripheral blood concentration; m, metabolites; pos, positive; NP, not provided; TSS, Toxicological Significance score.

*Quantiﬁed in central blood.

"Unclear if central or peripheral concentration.

-: no other compounds detected.

TSS indexed with "i" marks an indirect mechanism.
**TABLE 3 | Post-mortem concentrations in peripheral blood (PBC), central blood (CBC) and other tissues.**

| Cannabinoid(s) | PBC (ng/mL) | CBC (ng/mL) | PMI | Urine | Other organs concentration (ng/g) | Author, Year |
|----------------|-------------|-------------|-----|-------|-----------------------------------|--------------|
| EAM-2201, AB-PINACA, AB-FUBINACA | EAM-2201: 0.0566 ± 0.0042; AB-PINACA: 0.0126 ± 0.0001 | EAM-2201: right heart 0.0287 ± 0.0045; left heart 0.031 ± 0.0056; AB-PINACA: right heart 0.0196 ± 0.0038; left heart 0.0206 ± 0.001 | 2 days | EAM-2201: lung 0.35, liver 0.13; kidney 0.12; AB-PINACA: lung 0.36; liver 0.17; kidney 0.14; AB-FUBINACA: lung 0.12, liver 0.05, kidney 0.02 | | Yamagishi et al. (19); Minakata et al. (25) |
| 5F-PB-22, 5F-AKB-48 | unquantified | unquantified | 8 h | | | Langford and Bolton (20); Paul et al. (21)|
| AB-CHMINACA | (subclavian) 8.2 | | | | | Paul et al. (21) |
| UR-144, XLR-11, JWH-022 | (subclavian) 12.3; XLR-11: (subclavian) 1.3; JWH-022: (subclavian) 3 | | | | | |
| 5F-ADB, 5F-ADB-PINACA, MAB-CHMINACA | MAB-CHMINACA: right heart 10.6; left heart 9.30 | MAB-CHMINACA: right heart 1.92 | 35-40 h | m | | Hasegawa et al. (22, 29); Kusano et al. (23); Gaunitz et al. (24); Usui et al. (50) |
| 5F-ADB | 0.19 | 2.1 | 2 days | m | Brain: 5.5; lung: 2.6; liver: 2.6; stomach content: 2.4; kidney: 3.8; psoas muscle: 1.2 | |
| MDMB-CHMICA | 6.05 | 1.7 | 12 h | 0.01 + m | | |
| 5F-ADB (iliac) | 0.12 | right heart 0.24; left heart 0.45 | | | | |
| 5F-ADB (iliac) | 0.23 | right heart 1.35 | | | | |
| 5F-ADB (iliac) | 0.16 | right heart 0.14; left heart 0.11 | | | | |
| 5F-ADB (iliac) | 1.38 | right heart 1.102 | | | | |
| AB-CHMINACA, 5F-AMB | 2 days | AB-CHMINACA, 5F-AMB | | | | Minakata et al. (25); Hasegawa et al. (29) |
| 5F-ADB, MAB-CHMINACA | 2.1 | MAB-CHMINACA | 1 day | 5F-ADB, MAB-CHMINACA | | Minakata et al. (25); Rojek et al. (26) |
| UR-144 | 1.4 | | | | | Angerer et al. (27) |
| UR-144 | 4 | | | | | |
| 5F-PB-22 | 0.37 | 0.38 | 0.37 | m | | Kubo et al. (47) |
| AB-CHMINACA | 4.1 | 5F-AMBI | | | | |
| 5F-ADB | 0.38 | 0.16 | 1 day | 5F-ADB, MAB-CHMINACA | | Minakata et al. (25); Rojek et al. (26) |
| AB-PINACA | 26 | 5F-AMBI: 8 | | | | |
| 5F-AB-PINACA, 5F-AMB | 5F-AMB: <1 | 5F-AMB: 176; 5F-AB-PINACA: 152; 5F-AMB: 28; 5F-AB-PINACA: 21 | | | | |
| 5F-AMB | 0.3 | Mepirapim 157; 5F-AMB: <1 | 3 days | 0.1 | Brain blood 2.2, lung blood 2.7, liver blood 0.3, kidney blood 1.3, intestines blood 1.0 | Gieron et al. (31); Shanks and Behonick (32); Labay et al. (33) |
| 5F-AMB (subclavian) | 0.3 | JWH-018, AM-2201; JWH-210; JWH-018, AM-2201, JWH-122, JWH-210; XLR-11; JWH-018, AM-2201; JWH-210; XLR-11; JWH-012, AM-2201; JWH-210; XLR-11 | | | | |
| JWH-018, AM-2201; JWH-210; JWH-018, AM-2201, JWH-122, JWH-210; XLR-11; JWH-018, AM-2201; JWH-210; XLR-11 | JWH-016: 0.11; AM-2201: 2.5 | JWH-016: 0.65; AM-2201: 0.21; JWH-210: pos; JWH-210: pos | | | | |
| 5F-AMB | | | | | | |
| 5F-AMB | | | | | | |
| 5F-AMB | | | | | | |
| Cannabinoid(s) | PBC (ng/mL) | CBC (ng/ml) | PMI | Urine | Other organs concentration (ng/g) | Author, Year |
|----------------|-------------|-------------|-----|-------|----------------------------------|--------------|
| XLR-11, UR-144 | pos         |             |     |       |                                  |              |
| JWH-018        | pos         |             |     |       |                                  |              |
| JWH-122, JWH-210, AM-2201 | JWH-122: pos; JWH-210: pos; AM-2201: 0.16 |             |     |       |                                  |              |
| UR-144         | pos         |             |     |       |                                  |              |
| JWH-210, AM-2201 | JWH-210: pos; AM-220: 1.1 |             |     |       |                                  |              |
| XLR-11         | pos         |             |     |       |                                  |              |
| XLR-11         | pos         |             |     |       |                                  |              |
| AM-2201, JWH-018 | AM-2201: 2.8; JWH-018: 0.11 |             |     |       |                                  |              |
| JWH-122, JWH-250, AM-2201 | JWH-122: pos; JWH-250: 0.23; AM-2201: 7.3 |             |     |       |                                  |              |
| JWH-122        | pos         |             |     |       |                                  |              |
| JWH-122, JWH-210, AM-2201 | JWH-122: pos; JWH-210: pos; AM-2201: 0.22 |             |     |       |                                  |              |
| AM-2201        | 0.13        |             |     |       |                                  |              |
| JWH-122       | pos         |             |     |       |                                  |              |
| XLR-11         | pos         |             |     |       |                                  |              |
| XLR-11         | pos         |             |     |       |                                  |              |
| JWH-175        | 105         |             |     |       |                                  |              |
| JWH-210        | pos         |             |     |       |                                  |              |
| ADB-PUBINACA   | 1**         | inferior vena cava 7.3 |     |       |                                  | Shanks et al. (51) |
| MDMB-CHMICA    | <1**        |             |     |       |                                  | Seywright et al. (49) |
| Meprapim       | 950 (serum, 3.5 h after use) |             |     |       |                                  | Fujita et al. (35) |
| MDMB-CHMICA    | 5.6 (ante-mortem), <0.2 post-mortem | brain 2.6, stomach content 0.2, bile < 0.2, kidney 0.2 |     |       |                                  | Adamowicz (36) |
| MDMB-CHMICA    | (ante-mortem serum) 1.4 | spleen 0.1 |     |       |                                  | Westin et al. (48) |
| AB-CHMINACA, AB-FUBINACA, AM-2201, 5F-AMB, 5F-APINACA, EAM-2201, JWH-018, JWH-122, MAM-2201, STS135, THJ2201, UR-144, XLR-11 | AB-CHMINACA: 2.8; AB-FUBINACA: 0.97; 5F-AMB: 0.19; 5F-APINACA: 0.51; STS 135: 0.16; THJ 2201: 0.16 | AB-CHMINACA: 1.1 m |     |       |                                  | Hess et al. (37) |
| MAM-2201, AM-1220, AM-2232 | MAM-2201: 16.3; AM-1220: 140; AM-2232: 0.86 + m | MAM-2201: right ventricle 30.7, left ventricle 85.8; AM-1220: right ventricle 222, left ventricle 438; AM-2232: right ventricle, 1.76 left ventricle 1.95 | 20 h | AM-1120: traces | Zaitsu et al. (38) |
| XLR-11         | 1.4         |             |     |       |                                  | Shanks et al. (34) |
| XLR-11         | 0.6         |             |     |       |                                  | Gerostamoulos et al. (39) |
| PB-22          |             |             |     |       |                                  | Behonick et al. (40) |
| 5F-PB-22       | 1.1         |             |     |       |                                  |               |
| 5F-PB-22       | (ante-mortem) 1.3 (iliac) 1.5 |                                  |     |       |                                  |               |

(Continued)
Histological data, as a specific result of a microscopical analysis, was clearly described only in 13 cases (18%).

Cause of death was stated in all but 4 cases (5%). Cardiac arrhythmias and cardio-circulatory acute effects were listed in 17 cases (23%) as cause of death or as underlying mechanisms in a group of mono and poly-drug intoxications, involving both teenagers and adults (20, 21, 35, 40, 48). A number of death cases were associated with excited delirium and police restraints (33), as well as fall from height, either due to drug-induced psychosis or reduced awareness with accidental falling (24, 26).

Behavioral effects could also lead to suicide (26), self-inflicted self-injuries (41) and further consumption of other drugs (26, 55). Respiratory depression (27), especially in the setting of mixed intake of xenobiotics (33, 51), and asphyxia due to aspiration of gastric content in a state of coma (22, 27, 28) were also declared.

Manner of death was mostly accidental or not given and 4 cases of suicide (5%) were recognized.

Post-mortem interval (PMI) was stated in 11 cases (15%) and ranged from 8 hours to 4 days (Table 3).

DISCUSSION

The systematic review of the literature has resulted in an unexpectedly high number of cases of death involving SCRAs. Though, given the widespread use of the compounds, similar fatalities might be under-reported (publication bias) or under-recognized as a result of the challenges of post-mortem analyses. Indeed, the delay in developing and updating analytical methodologies affects the capability of many laboratories to detect and report cases of SCRA-related death, particularly when novel compounds which just entered the market are involved (55). Accordingly, the results here presented cannot be taken to estimate the prevalence.

Circumstantial Data

In almost the totality of cases, a possible involvement of SCRA's was suggested by either a past history of drug/alcohol abuse, by
witnesses’ statements of partying or smoking shortly before collapse, or by the DSI, which revealed paraphernalia and herbal residues. Depending on the market availability, it emerged that the content of such packages varied over time (31, 36, 55). Thus, it must be kept in mind that the product names do not validly predict the ingested substances.

Although e-cigarettes and e-liquids represent an innovative and attractive way to consume SCRAs (56, 57), no vaping liquids were reported in the circumstantial data of the reviewed death cases. The link between e-cigarettes and SCRAs consumption might be less familiar and known to the investigators, possibly resulting in such liquids not being systematically seized and/or analyzed. When such paraphernalia are found, an analysis of vaping liquids collected at the DSI should be strongly encouraged.

SCRAs are not detected by common immunoasays and require a target analysis, which is usually only requested by authorities and conducted when a suspicion is raised, due to analytical limitations and economic reasons (21). This factor could lead to a failure to recognize such cases and consequently to a massive underestimation of the number of death cases involving SCRAs. This underlines the importance of an appropriate awareness and of an in-depth experience in forensic toxicology during DSI and when interviewing witnesses.

Analytical Issues

The data extracted from the revision of the literature regarding toxicological analyses once again highlights the role of liquid chromatography-mass spectrometry (LC-MS/MS) for the quantification of SCRAs in biological specimens, although a singular preferred method for sample extraction is not known, given the variety of chemical differences among analytes (52). The use of standard addition methods, as recently suggested in a series of intoxications (58) is limited, possibly due to the low amount of post-mortem blood collected at the autopsy.

Only a small number of SCRAs emerged from the literature review, compared to the quantity of compounds included in the NPS category. We do not believe that this is a bias due to an attention to recent molecules, since the follow-up period ended in 2019 and more recent molecules, such as SCRAs bearing a γ-carbolimone core, were not found. This observation could be on the contrary related to difficulties in detecting SCRAs in the absence of a dedicated and updated method. The main challenge in forensic toxicology from an analytical point of view resides indeed in keeping methods updated, in order to detect novelties as soon as they are involved in death cases. Although there was a decrease in the last years, the frequent emergence of novel compounds might lead to missing relevant analytes. This was clearly demonstrated by cases where re-analysis of samples with novel and more sensitive methods allowed for identification of substances previously undetected (19, 22, 25). Very sensitive methods are needed in blood, given the low concentrations reported in the literature (52) and urine analysis can reveal a previous intake even when nothing is detected in blood (22, 23).

Once a new methodology for the analysis of biological specimens has been established, even in case reports, a so-called short validation, including selectivity, linearity, accuracy, precision, and matrix effect, is strongly recommended even if not always performed or published (59). In the case described by Langford et al., for example, the analyses were granted by a private licensed forensic laboratory, and no information was disclosed due to alleged “competition and market issues” (20). The absence of a clearly stated methodology and validation process questions the reliability of the analytical results and limits the comparability of the data. The validation could be further hampered by the lack of material for re-analysis and/or by the lack of isotopically labeled standards (27, 33). Lack of material represents a serious limitation particularly in the case of measured concentrations being far above the linear range of the calibration, even though results might be estimated by extrapolation (27, 38, 43). It has to be underlined that the vast majority of the methods for SCRAs quantification were validated in serum and not in post-mortem blood.

When evaluating the concentrations, several aspects need to be considered, including site of sampling, post-mortem interval, possible tolerance of the user, co-consumption of other drugs, potency of the compounds, chemical characteristics, and time delay between intake and death.

Some compounds, such as 5F-ADB, are known to be particularly unstable (29) and this could explain the extremely low concentrations of the highly potent SCRAs in our review (27). Rapid degradation due to pyrolysis, ante-mortem drug metabolism, as well as post-mortem redistribution and degradation (due to remaining esterase activity) were considered as further main factors for reduced concentrations and should be considered for all SCRAs, though with different weighting (19, 23, 44).

When compared to others SCRAs, mean concentrations were relatively higher for AB-CHMINACA, despite its high potency (21, 27). This could be due to the narrow time interval between drug smoking and death, approximately an hour in the case described by Paul et al. (21), or to a high tolerance of the subject implying high doses (21).

Concerning post-mortem redistribution (PMR), disparities among central and peripheral blood levels were mostly slight (19, 45) (PMI: 2 days). A 1.2 quotient of central/peripheral blood (C/P ratio) was found in a case of MDMB-CHMICA 12 h after death, and this result was interpreted as not indicative of PMR (24). Similarly, concentrations were in the same range in all tissues in a case described by Yamagishi et al. (19). On the contrary, cardiac blood levels strongly exceeded the peripheral ones in the case of Zaitse et al. (38) for MAM-2201, AM-1220, and AM-2232 (PMI: 20 h), where left and right ventricle blood levels were 2 to 5 and 1.5 to 2 times higher than femoral blood concentrations. Quantification employed LC-QTOF, a full validation was not performed and concentrations of some analytes were far above the highest calibration point. Nevertheless, C/P ratios appear to tend to values above 1 especially in the case of short time intervals between smoking and death (in this case 1.5 h). A death shortly after smoking, with high concentrations of SCRAs in lungs being released to the surrounding vessels and tissues could explain the higher levels in the blood of the left ventricle (60), although the authors...
suggested a myocardial accumulation instead (38). C/P ratios of 1.75 to 1.54 were also seen by Hasegawa et al. (29) (PMI: 2 days).

Divergences among compounds suggest that the chemical characteristics (e.g., greater or lower lipophilicity) as well as the pattern of use should be considered when hypothesizing PMR (45). Ingestion and smoking probably result in higher concentrations in stomach content and lungs, respectively. This could lead to a release into nearby vessels of the central compartment. Since femoral blood levels increase mostly due to release/redistribution from fat and muscle tissues, an inversed central/peripheral ratio would suggest a greater lipophilicity of the compound and/or chronic accumulation of SCRA in deep compartments. However, the scarce information regarding time between last consumption and death as well as the PMI complicates the situation. Stability and matrix effects additionally limit the capability of drawing valid conclusions based on blood concentrations.

The distribution of SCRA in tissues varied widely. Concentrations in tissues have been assessed only in a minority of cases and results may strongly depend on the employed methods of analysis, the description of which is beyond the scope of this article. Given the rarity of this type of measurement, which afford a time-demanding standard addition method (19), the available data regarding tissue distribution does not allow for general conclusions. However, they can be used to evaluate the specific case and might allow identifying potential sites of accumulation. For example, extremely high levels in the adipose tissue were seen for MAM-2201 (124 fold higher than blood concentration), leading to the suggestion of fatty tissue as a suitable target specimen for analysis (PMI: 4 days) (44). High adipose levels were also found for NNEI (45) (PMI 3 days) and might be interpreted as a result of continued substance use. According to Kusano et al. (23) adipose tissues are a suitable matrix for the detection of the parent compound, while other tissues (with higher esterase activity) could contain higher levels of metabolites.

High levels in liver and kidney tissue could be found in the case of more hydrophilic compounds (e.g., MAB-CHMINACA; PMI: 2–3 days) (29), especially when the interval between intake and death was short. In these cases, an accumulation in fatty tissue might not have occurred yet, requiring longer time (24, 29). Brain concentrations were high for MDMB-CHMICA in a case described by Gaunitz et al. (PMI: 12 h) and this allowed to confirm that the victim was under the effect of cannabinoids at the moment of death (24). High concentrations in lungs were also reported, pointing towards an intake through smoking.

In summary, blood and tissue concentrations should always be interpreted with caution, due to the multiple factors which have to be taken into account (e.g., PMR, PMI, active metabolites, stability, chemical characteristics, plasma/blood ratio, tolerance etc.) (61).

Pathology and Histopathology

The un-specificity of gross pathological findings heightens the risk of missed deaths involving SCRA. Vomiting and aspiration of gastric content are highly suggestive for drug-induced coma or loss of consciousness in otherwise healthy and young subjects (22, 29). This was also seen in a case in which, originally, only urine was found positive for SCRA, and further analyses demonstrated high blood concentrations of MAB-CHMINACA (22, 29). It should always be kept in mind that acute gastrointestinal bleedings could be due to several diseases and factors, such as Mallory-Weiss disease or hypothermia, and an accurate differential diagnosis remains fundamental before attributing such findings directly to SCRA consumption. For example, erosions seen in the case described by Langford and Bolton (20), could have been the result of ethanol intake, which was in his fatal ranges (3.11 g/L).

Bleedings and abundant hypostasis could raise the suspicion for a recent intake of SCRA. In 2018, fatal and life-threatening bleedings were connected to superwarfarin-type drugs such as brodifacoum added to products allegedly containing SCRA as reported by the Centers for Disease Control and Prevention (CDC), which released a health advisory. Long-acting anticoagulant rodenticides (LAARs) were occasionally found as adulterants in herbal blends (62). A case of death connected to anticoagulants is described in the literature (63), even though the case was not included in the review, since the past use of SCRA emerged only from circumstantial data (thus, the paper did not fit into the inclusion criteria). It is not clear if hemolysis, abundant hypostasis, and intracutaneous or soft tissue bleedings can be caused by such adulterants or represent a hematological effect, maybe liver-mediated, of SCRA themselves (40). As LAARs are usually not detected by urine screening analyses, highly sensitive LC-MS/MS methods are required for their detection (62).

The interpretation of cardio-vascular findings is discussed in the following subsection.

Cause and Mechanism of Death, TSS

Several preclinical studies and case reports addressed the increased cardiovascular risk related to SCRA use, though scientific evidence is still limited (14, 64–68). This was reflected by our literature review, since abnormal findings in heart were seen and death related to acute cardiovascular arrest or collapse certified. However, it could be unclear if these deaths are actually related to SCRA or not (69). Marijuana exerts some cardiovascular effects, acutely resulting in increased catecholamine release and, consequently, increased heart rate and vasodilation, with orthostatic hypotension (68). Cannabis is told either to exert negligible effects on blood pressure or an increase in blood pressure, and might increase the risk of myocardial infarction, particularly in predisposed subjects (68, 70–72). SCRA, being more potent cannabinoid receptor agonists, have been linked to the occurring of myocardial infarction (64) even in the absence of coronary artery disease, and of arrhythmia-related sudden cardiac death (65–67). Sasaki et al. (45) found signs of hypertension and aging in a 20-year-old victim, coupled to myocardial suffering, and thus hypothesized a cardio-circulatory hyperactivity due to prolonged SCRA use. The diversity of potential injury mechanisms (between myocardial infarction and arrhythmia) may explain why in some cases band necrosis proved a myocardial damage (21, 45), while in others neither macroscopic nor microscopic signs were noted (20, 21, 35).

In the cases where post-mortem examination failed to identify signs of heart diseases, the attribution of cardiac death to the
SCRA was mostly based on circumstantial data, e.g., the victim reported having smoked shortly before dying and/or a sudden collapse after smoking occurred (20, 35, 40). In a similar case, the possible role of SCRAs was confirmed by a serum sample collected only 2 h after a sudden collapse with asystolia, revealing 1.4 ng/mL of MDMB-CHMICA (48).

Moreover, asystole was initially noted in a case of death where, after resuscitation, a multi-organ failure finally led to cardiac arrest (36).

Atherosclerotic disease and other cardiac abnormalities, such as cardiomegaly and dilatative cardiomyopathy, pose an additional challenge to the assessment of the role of SCRAs in death cases (50, 61). In fact, drugs can either exacerbate a pre-existing condition, or be considered an irrelevant finding (33). In a case described by Tse et al. (64) a triple-vessel coronary thrombosis was found and death was attributed to myocardial infarction with a possible contributory role of SCRAs, despite the absence of analytical confirmation. In a case involving ADB-FUBINACA, Shanks et al. (51) concluded that, due to occurrence of behavioral effects followed by a sudden death, a SCRA-induced dysrythmia contributed to the death, notwithstanding the presence of a potentially fatal thrombolytic occlusion. Similarly, a contributory role was stated by Tse et al. (64) despite morphological findings which could have explained the death by themselves. These cases demonstrate that it can be difficult to assess the cardiac effects of SCRAs, particularly in the presence of findings potentially constituting a cause of death on their own. In such cases, a TSS of “1,” which does not exclude a partial contribution, seems to be appropriate (17).

In cases of polydrug abuse, the evaluation of role cannot leave aside concentrations of xenobiotics, leading to attribution of different TSS on a case-by-case basis, e.g., TSS U with 3 g/L of ethanol, positive unquantified SCRAs and suspected arrhythmias (20) vs TSS 3 with 1.8 g/L ethanol, 1.5 ng/mL AB-CHMINACA and acute cardiorespiratory depression (50).

Coma/somnolence can lead to death directly, through vomiting/aspiration or indirectly due to environmental exposure and hypothermia (54). In a case presented by Kronstrand et al. (52), death occurred due to “hypothermia and SCRA use,” despite the absence of typical hypothermia-related signs such as freeze-erythema and Wischnewsky spots (52). Hypothermia after the use of SCRAs was seen in experimental studies on animals (e.g., male rats and monkeys) (73, 74) and has been partially related to the effects of cannabinoids on dopamine receptors (75), but has not been confirmed in humans yet. However, in a case described by Adamowicz (36) a cadaveric temperature of 35.1°C was measured, despite the victim was at home and the measurement took place only 30 minutes after the sudden collapse. This finding would be in line with the animal experimental data regarding the effect of SCRAs on body temperature and highlights the need to evaluate body and ambient temperatures in cases of death possibly related to such compounds. An “intoxicated-state” was also considered as the underlying mechanism of a death due to ketoacidosis, even though an AB-CHMINACA-induced hyperglycemia was also possible (37).

A behavioral contribution of SCRAs to the death appears to be an additional source of concern. Anxiety and psychosis might be also explained by the affinity of SCRAs to dopaminergic (D2), serotoninergic (5-HT2A) or glutamatergic (NMDA) receptors (76, 77). In a case described by Labay et al. (33), the victim fell from a high building after feeling sick and vomiting several times and was found intoxicated with MDEA, MDA, and JWH-175. While psychiatric consequences of SCRAs intake are clear in the absence of other drugs (41), the evaluation of role in polydrug consumption is puzzling, as in the case of low levels of both SCRAs and phencytoin, which can induce psychosis (78). Data on toxic/fatal levels might lack for NPS (e.g., for co-consumption of pentedrone resulting in behavioral abnormalities) (26) and even therapeutic or negligible levels of common drugs of abuse could assume relevance in combination with SCRAs. The influence of SCRAs on non-cannabinoid receptors and on serotonin, dopamine, catecholamine levels further complicate potential interpretations. In such cases of polydrug abuse, it is possible that the death would not have occurred without SCRA consumption, although no direct causality can be established. A TSS of “1” (“i” indicating the indirect role) is suggested due to the presence of multiple drugs with unknown contributory role, despite behavioral toxicity being an important risk factor for fatal outcome (33).

On the other hand, in the first case reported by Rojek et al. (26), the victim jumped from a building after a reported “loss of control” and no other drug was detected. Thus, notwithstanding the behavioral toxicity and the indirect mechanism, a contribution to death is likely (TSS of “3” was assigned).

Finally, cases of acute liver and/or kidney failure have been described (40, 55).

In general, if only toxicological results are listed in the absence of macroscopical and microscopical data, uncertainties regarding the role of the substance increase, as in the case reported by Kusano et al. (23). However, the mechanism of death could remain unclear, despite having a more complete data set (40) and the agreement between independent reviewers judging the very same pieces of information could be weak (e.g., unanimous agreement in 2 cases out of 25 submitted to multiple evaluations) (33, 40). Thus, a multidisciplinary evaluation should be recommended for each case, in order to possibly limit such uncertainties.

Most of the publications identified a possible contributory role of SCRAs, even in the absence of findings clearly pointing towards a drug-related death (32, 34, 39, 45, 48). In the present review, a TSS of 3 was assigned when no competitive cause was seen, and the hypothesized mechanism of death was in line with the most frequently reported SCRA toxicities. Affinity and activity of new compounds are often unknown, and unexpectedly severe or idiosyncratic effects may occur (19). Given the uncertainty regarding toxic levels and toxic effects, even when the mechanism of death remains unclear and/or other substances might have played role, the possibility of a
contribution of SCRAs should not be ignored, and a TSS of “2” justified.

The likelihood of a high significance score is greater when multiple compounds with potentially synergic effects are detected, despite low concentrations of each single compound (19).

On the contrary, even though SCRAs could exacerbate an intoxication due to alcohol or other drugs, in cases with relatively very low SCRA concentrations or with concentrations of the competitive drug above the toxic threshold, a TSS of “1” is suggested. This does not necessarily mean that the SCRA has not exerted any negative effect, and the stability of the analyte of interest should further be considered as a cause of low concentrations.

TSS was rated “U” in cases with lack of sufficient data, as for example in the case described by Langford and Bolton (20), where high alcohol concentrations were retrieved, and no quantification of SCRAs was possible, or in the case of Minakata et al. (25) and Kusano et al. (23), where the effects of the other substance detected was difficult to assess.

LIMITATIONS

There are several limitations in this study. First of all, despite the extensive research involving multiple databases, the process of inferring scientific evidence is strongly limited by the possibility of under-reporting of similar cases and by the necessity of establishing a temporal limit for the review. Thus, the information presented have to be regarded as incomplete. Secondly, no weighting of selected articles regarding their quality was undertaken. A third significant limitation resides in establishing the TSS (16) of the selected cases, since the TSS is so far a non-validated scale. However, given the lack of criteria for establishing the role of substance(s) in death cases, the TSS appeared to be a flexible tool to assign a contributory weight to SCRAs, and thus to evaluate and compare different cases. In order to avoid misinterpretations and to appreciate the point of view of the authors of the manuscripts, in each death case the role of the substance was also supplied in their own words. Finally, only death cases in which at least one SCRA was analytically confirmed, and in which an autopsy was presumably performed, were included.

The authors are aware that this could have resulted in a partial loss of information, but on the other hand our aim was to possibly achieve a higher level of evidence.

CONCLUSIONS

Several mechanisms could lead to death after SCRAs consumption, and behavioral risks as well as cardiovascular effects or central nervous system depression appear to play important roles. Given the limited pharmacodynamic and pharmacokinetic data and the overlap between fatal and non-fatal concentrations, typical toxic ranges for SCRAs have not been identified so far. The results of toxicological analyses should be interpreted with caution, considering the many confounding and influencing factors, particularly regarding the reliability of LC-MS/MS methods validated insufficiently or validated only in serum. Furthermore, pattern of consumption (e.g., occasional vs. chronic) and tolerance of the subject should be estimated or evaluated on a case by case basis.

A complete and accurate post-mortem examination is a fundamental part in the evaluation of death cases involving SCRAs, since a comprehensive and multi-disciplinary evaluation of clinical, circumstantial, toxicological, and autoptic data is the only possibility to assess the toxicological significance of a substance and to tentatively identify a plausible mechanism of death, which could remain unclear despite an in-depth analysis of all data available.

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All authors materially participated in the article preparation and have approved the final article.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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