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MINI REVIEW

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From JWH-018 to OXIZIDS: Structural evolution of synthetic cannabinoids in the European Union from 2008 to present day

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Abstract

With new synthetic cannabinoids (SCs) appearing on the European drug market every year, early warning systems are key to detect, monitor, and respond to threats posed by them. The European Union Early Warning System (EU EWS) implemented by the European Monitoring Centre for Drugs and Drug Addiction has monitored these substances since their first European detection in 2008. Since then, national and international responses have been implemented, aimed at tackling risks posed by SCs. Throughout this time, new SCs have emerged on the European market containing diverse structural moieties, appearing to be designed in a way that circumvents existing legal controls, contributing to a complex public health scenario. This study provides an inventory of the SCs detected in the EU from 2008 to 2022, describing their structural evolution by analysing separately four structural features: their core, tail, linker, and linked groups. The range of structural changes is analysed considering key milestones, including the year of first report by the European Union Early Warning System to the key legislative changes that have occurred since. The analysis shows that from June 2021 to July 2022, 20 out of 23 newly emerged SCs evade the generic SC legislation introduced in China in May 2021. This supports the hypothesis that the protection of public health benefits from timely information exchange and careful assessment of the risks associated with these substances. Additionally, the introduction of legal responses, albeit an important instrument to reduce the availability of dangerous substances on the market, may also be accompanied by unintended consequences.

KEYWORDS
drug detection, early warning system, European drug market, new psychoactive substances, synthetic cannabinoids

1 | INTRODUCTION

Synthetic cannabinoids (SCs) are the largest category of new psychoactive substance (NPS) monitored by the EU Early Warning System (EU EWS), the EU mechanism responsible for information exchange on NPS[1] operated by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). According to the current legislation (Council Framework Decision 2004/757/JHA[2]), the first detection of a new SC in a European Member State is followed by an official report from that country to the EMCDDA, and a subsequent assessment of the extent of the substance characteristics including compliance with the legal definition of NPS, analytical and contextual information of

the detection, and a rapid review of open source information such as scientific and patent literature.[3] Following this, a "formal notification" is issued to the EU EWS Network on behalf of the reporting country, and the substance officially integrates the list of monitored substances by the EU EWS, towards which all EU Member States have reporting duties.

The first "formal notification" of an SC reported to the EU EWS occurred following the almost simultaneous detection of JWH-018 (Figure 1) in Austria and in Germany in December 2008.[1,4] By the end of 2021, the EMCDDA was monitoring a total of 224 SCs, with an additional 13 emerging between January and July 2022. These molecules are classified as SCs based on their pharmacological properties or, in the absence of that information, based on their structural similarities with other SCs. Although they are diverse, SC molecular structures can generally be divided into common building blocks. The approach adopted by the EMCDDA since 2013 focuses on four building blocks[5]: a **tail**, a **linker**, and a **linked group** that span from the **core** moiety (Figure 1). An alternative three-component approach was used by a private company, combining the linker and core groups into a single building block.[6] The advantage of separating them, as seen in the EMCDDA system, is that it allows for a more detailed description of the molecular diversity within the SC category, which is particularly useful in light of recently emerging substances.

Consistent and accurate naming of this growing group of chemically heterogenous substances represents a challenge, particularly considering the constant introduction of new structural modifications. A number of different and unrelated naming approaches have been used through the years, leading to a mixture of nomenclature for these compounds.[5,7] Older (so-called "first generation") SC compounds were mainly studied and named in academic settings, where they were developed typically with the purpose of finding therapeutic targets for the endocannabinoid system. Examples include the JWH series of compounds (denoted by JWH-XXX, with X being a numerical digit), synthesised by the John W. Huffman research group in Clemson

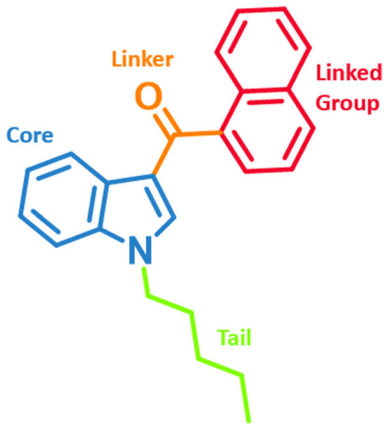


FIGURE 1 Molecular structure of the first synthetic cannabinoid notified to the European Monitoring Centre for Drugs and Drug Addiction: JWH-018. The general structure of synthetic cannabinoid compounds can be described in four building blocks: core in blue, tail in green, linker in orange, and linked group in red [Colour figure can be viewed at wileyonlinelibrary.com]

University, South Carolina,[8,9] and the AM- (Alexandros Makriyannis research group), HU- (Hebrew University), and CP- (Pfizer Cyclohexyl phenyls) series. In contrast, some of the common names of the SCs that appeared subsequently ("second generation" SCs) were associated with some attempts at marketing—either of the compound itself (e.g., XLR-11 named as after the first fuel rocket developed in the United States[10,11]) or of the private company that originally investigated the compound (e.g., SGT-13, alluding to Stargate International). To ensure a common language among the many stakeholders involved in the monitoring of these substances (including laboratory personnel, law enforcement, and hospital staff) and to facilitate international monitoring activities, in 2013, the EMCDDA developed a naming system that alluded to the structural features of the compounds, referred to as the "EMCDDA common name" (Tables S1 and S2). The syntax uses code names for the four building blocks in the order: (1) Linked Group, (2) Tail, (3) Core, and (4) Linker, always preceded by (0) Tail Substitution. The EMCDDA naming system has recently been revised ("EMCDDA framework name"; Tables S1 and S2) and expanded upon to allow for increased consistency and additional flexibility to cover the substitution of each building block, which in turn better covers recently emerged SCs.[12] The same building blocks are retained in the same order from the original syntax, with prefixes for substituents added with hyphens where necessary; however, more specifically, substitution is now indicated in front of the modified building block. Using the revised approach, the SC colloquially known as 5F-ADB (**m**ethyl2-[[1-(5-fluoropentyl)indazole-3-carbonyl]amino]-3,3-dimethyl-butanoate) becomes known as MDMB-5F-PINACA under the "EMCDDA framework name" (5F-MDMB-PINACA under the "EMCDDA common name"). In this case, (1) linked group = **m**ethyl-3,-3-**dim**ethyl**b**utanoate, that is, MDMB; tail substitution = 5-fluoro, that is, 5F; (2) tail = **p**entyl, P; (3) core = **ind**azole, INA; and (4) linker = **c**arbox**a**mide, CA.

The expansion of the number of SCs in the drug market over the last 14 years was accompanied by several responses, including legal responses. Across the world, many countries have controlled these compounds, using or amending existing legislation or introducing innovative legal instruments like generic definitions (by chemical structure or pharmacological effects). Controls have also been introduced at international and European levels. In Europe, regional control in all Member States can be implemented whenever cross-border risks to public health are identified, following a formal risk assessment of the substance and a decision by the European Commission and the European Council. As of July 2022, seven such controls were implemented (Table 1), with the first one occurring in 2016, for MDMB-CHMICA (methyl 2-[[1-(cyclohexylmethyl)indole-3-carbonyl]amino]-3,3-dimethyl-butanoate). At international level, scheduling of SCs occurs under Schedule II of the 1971 United Nations convention, following assessment by an independent group of experts, the Expert Committee on Drug Dependence, carried out by the World Health Organisation. Since 2015 and as of July 2022, 20 SCs have been placed under international control.[13,14] The main legal milestones referring to SCs are shown in Table 1. Chinese legislation is included, as the country has frequently been shown to be an important source

TABLE 1 List of legislative responses to synthetic cannabinoids between 2013 and 2021

Organisation	Date	Substances covered
Chinese government	Nov 2013	JWH-073, AM-694, AM-2201, JWH-250, and JWH-018
European Union	Jul 2014	SCRAs excluded from scope of medicinal products (Article 1 (2)(b) of 2001/83/EC)
United Nations	Mar 2015	AM-2201 and JWH-018
Chinese government	Sept 2015	5F-AB-PINACA, 5F-ADBICA, AB-CHIMINACA, and several JWH- and AM- SCs
EMCDDA	Jul 2016	Risk assessment: MDMB-CHMICA
European Union	Feb 2017	MDMB-CHMICA
United Nations	Mar 2017	XLR-11, 5F-APINACA, and MDMB-CHMICA
EMCDDA	Nov 2017	Risk assessments: AB-CHMINACA, ADB-CHMINACA, 5F-MDMB-PINACA, and CUMYL-4CN-BINACA
United Nations	Mar 2018	5F-PB-22, UR-144, AB-PINACA, 5F-MDMB-PINACA, and AB-CHMINACA
European Union	May 2018	CUMYL-4CN-BINACA and ADB-CHMINACA
Chinese government	Aug 2018	AMB-FUBINACA, FUB-APINACA, ADB-CHMINACA, ADB-FUBINACA, 5F-MDMB-PINACA, AMB-CHMICA, FUBIMINA, and NM-2201
United Nations	Mar 2019	ADB-CHMINACA, CUMYL-4CN-BINACA, AMB-FUBINACA, and ADB-FUBINACA
United Nations	Mar 2020	4F-MDMB-BINACA, 5F-MDMB-PICA, 5F-AMB-PINACA, and AB-FUBINACA
EMCDDA	Dec 2020	Risk assessments: MDMB-4en-PINACA and 4F-MDMB-BICA
United Nations	Mar 2021	CUMYL-PEGACLONE and MDMB-4en-PINACA
Chinese government	May 2021	Ban based on generic definitions (Figure 2) and other named SCs
European Union	May 2021	MDMB-4en-PINACA and 4F-MDMB-BICA

Notes: These include synthetic cannabinoid scheduling decisions made by the World Health Organisation (United Nations), council implementing decisions and European Commission's delegated acts by the European Union, and measures implemented by the Office of China National Narcotics Control Commission. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) risk assessments have also been included. Synthetic cannabinoid acronyms have been defined in Tables S1–S3.

of SCs to the EU market.[15] Given its role in the European supply of SCs, Chinese legislation is likely to influence the new SCs appearing in Europe. In 2021, the Office of China National Narcotics Control Commission announced a class-wide ban on SCs, encompassing the seven structural scaffolds depicted in Figure 2.

Herein, the structural features are described of 224 SC compounds included in the monitoring of the EU EWS between December 2008 and December 2021 (15 of these 224 SCs do not fit the existing four-part model and are indicated under the category 'other'). A detailed structural analysis is also provided of those which emerged between June 2021 and July 2022, following important legal changes in China. The results have been clustered by core, tail, linker, and linked groups to explore whether patterns emerge over the last 13 years of EU EWS monitoring. A timeline is also shown, based on the dates of formal notification to the EU EWS Network, that is, the dates from which the compound was officially included in EU EWS monitoring. These dates typically shortly follow the first identification in Europe and are therefore taken as a proxy indicator of their emergence in the European market. Key legal responses in Europe and in source countries have been considered as possible drivers for structural innovation in the market in Europe. A list of all monitored substances, including their date of formal notification and chemical identifiers, is provided in Tables S1 and S2.

2 | METHODS

Data on the number and type of SCs under monitoring by the EU EWS were extracted from the European Database on new substances (EDND) in July 2022. The database is the information system that allows the reporting and management of information on NPSs reported by the EU Member States in the framework of Regulation (EU) 2017/2101 of the European Parliament and of the Council of 15 November 2017 amending Regulation (EC) No 1920/2006. Access to EDND is restricted to the Reitox EWS correspondents, the Reitox national focal points, nominated members of national EWS, and EU institutions. It focuses on event-based detections of NPSs and contains information on the chemistry and analysis of the substances under monitoring. Additionally, when available, the EDND details NPS substance manufacture, pharmacology, toxicology, epidemiology, trafficking, and distribution. The date of "formal notification" refers to the date following a rapid review of the data available on the substance, including analytical confirmation regarding its detection in at least one country of the EU EWS Network, the substance was included in EU EWS monitoring. Detections can occur in law enforcement seizures, collected sample, and test purchases.

3 | EXPLORING THE STRUCTURAL DIVERSITY OF SCs

All SCs under monitoring by the EMCDDA by the end of 2021 were categorised according to their four building blocks: core, tail, linker,

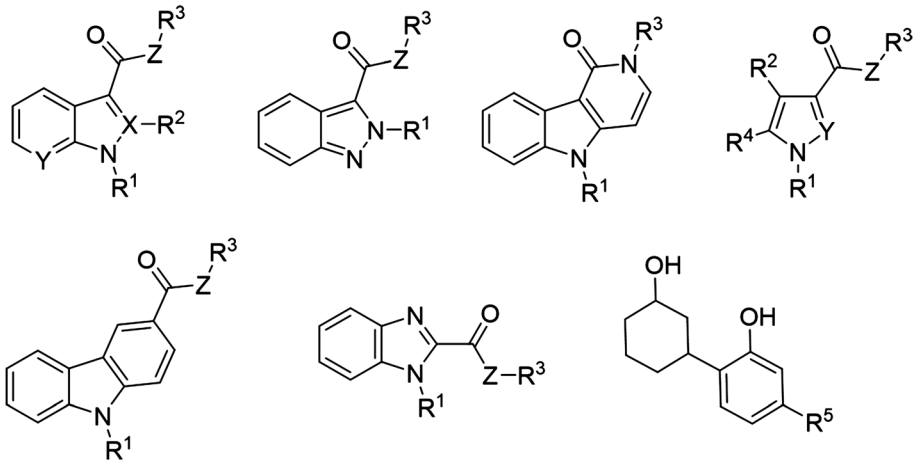


FIGURE 2 Generic core scaffolds covered under the synthetic cannabinoid Chinese legislation introduced in 2021. R^1 represents a substituted or unsubstituted C3–C8 hydrocarbon group; a substituted or unsubstituted heterocyclic group containing 1–3 heteroatoms; a substituted or unsubstituted heterocyclic group containing 1–3 heteroatoms; and substituted methyl or ethyl. R^2 represents hydrogen or methyl or no atom. R^3 represents a substituted or unsubstituted C6–C10 aryl group; a substituted or unsubstituted C3–C10 hydrocarbon group; a substituted or unsubstituted heterocyclic group containing 1–3 heteroatoms; substituted or unsubstituted heterocycle; and substituted methyl or ethyl containing 1–3 heteroatoms. R^4 represents hydrogen; substituted or unsubstituted phenyl; and substituted or unsubstituted benzyl. R^5 represents a substituted or unsubstituted C3–C10 hydrocarbon group. X represents N or C. Y represents N or CH. Z represents O or NH or no atom.

and linked groups. The 15 compounds under monitoring that do not fit with the existing four-part structure model were classified as "others." These compounds are CP 47,497, CP 47,497-C6 homologue, CP 47,497-C8 homologue, CP 47,497-C9 homologue, HU-210, CP 47,497 (C8, C2), Org 27569, Org 27759, Org 29647, HU-331, trans-CP 47,497-C8, URB-754, URB-597, LY2183240, and MCHB-1. All notified compounds have been listed in Tables S1 and S2, up until July 2022. Treemaps were built based on how many SCs under monitoring as of December 2021 featured the same type of core, tail, linker, or linked groups (Figure 3, left). Corresponding histograms (right) further describe the structural variation by year of introduction of the SC into monitoring, that is, a close proxy indicator of its first identification in Europe. Any tail or linked group that has only been observed in one SC has been included on the treemaps as their own entity but grouped into "other" on the corresponding histograms for visual clarity.

3.1 | Overview

The structural diversity of SC compounds is vast with hundreds of thousands of potential combinations, considering the four main building blocks. Overall, the 224 SCs under monitoring by the EU EWS between December 2008 and December 2021 that fit the four-part model feature 30 different linked groups, 27 tails, 14 cores, and 8 linkers. From the treemaps in Figure 3, it is evident that both the tail and linked groups (panels b and d, respectively) are far more diverse than the core and linker groups (panels a and c, respectively). Indeed, around 80% of the SCs under monitoring contain one of two linker groups (carboxamide and methanone; panel c) and one of two core groups (indole and indazole; panel a).

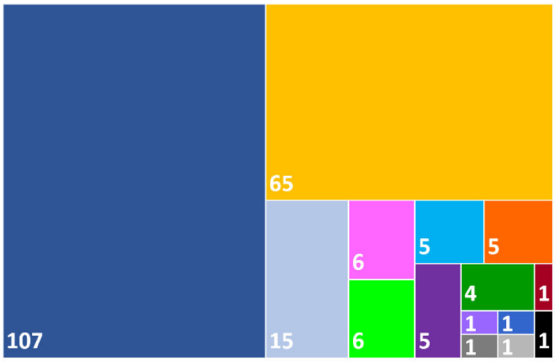
The timing of introduction of the structural changes can be followed in the histograms in Figure 3, with the height of the histograms reflecting the number of new substances detected for the first time in each year and the shading reflecting the category and type of building block. In terms of rate of introduction of new SCs in the European market, there was clearly a sharp increase in the number of SCs identified for the first time between 2008 and 2011. This was followed by a period where new SCs were steadily detected at the rate of roughly 27 per year between 2011 and 2015. Since 2016, this number has dropped to 10 new SCs annually, on average. Potential reasons behind this trend have been previously explored.[16]

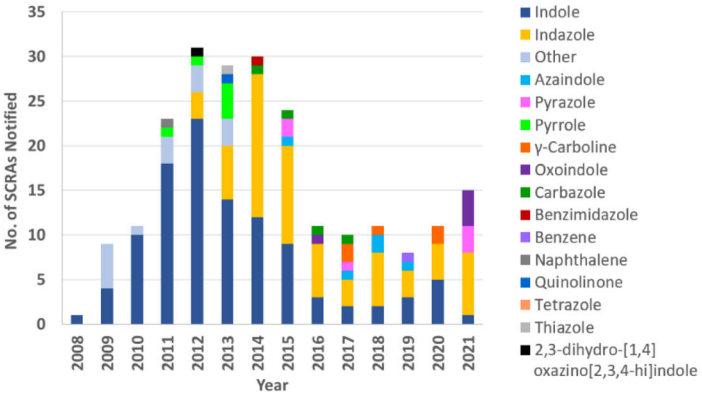
In the phase between 2008 and 2011, the SCs detected typically featured an indole core, a pentyl tail, a methanone linker, and a naphthyl linked group—the "building blocks" of JWH-018. During this period, SC producers seemed focused on mimicking the first compound brought to the drug market, which was then sold in herbal smoking mixtures touted as "legal" alternatives to cannabis. Since then, the type of products, potency, and structure of these compounds have varied considerably.

3.2 | The core moiety

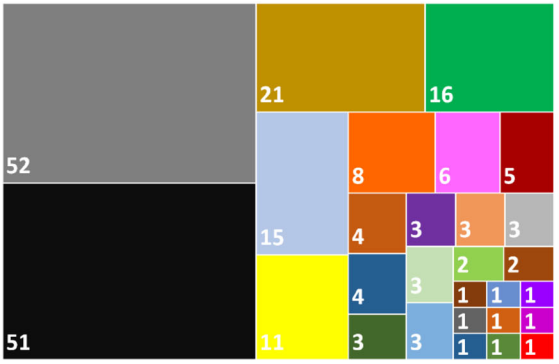
Figure 3a describes the structural variations in SC core elements. Most of the cannabinoids monitored contain indole cores (107), followed by indazole cores (65). Both indole and indazole derivatives are commonly found in pharmaceuticals due in large part to their diverse biological activities. Consequently, it is no surprise that these moieties are observed in SCs. Although the predominant core group until 2014, a general decline of indole cores can be observed from 2013 onwards. This coincided with an increase in the implementation of

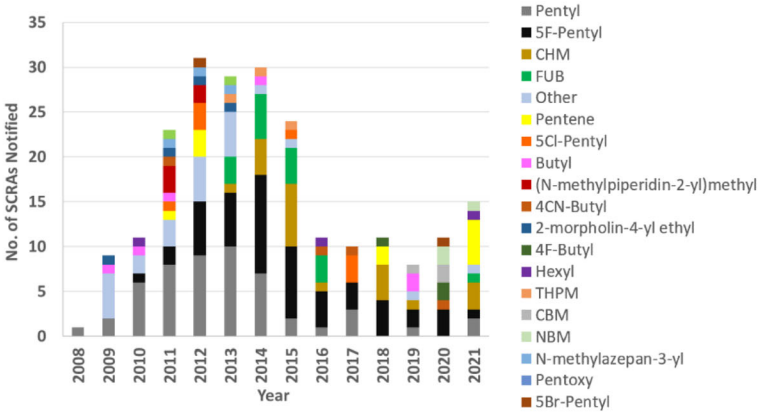
(a) – Core groups



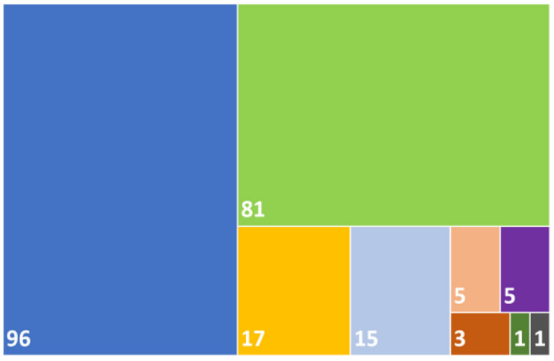


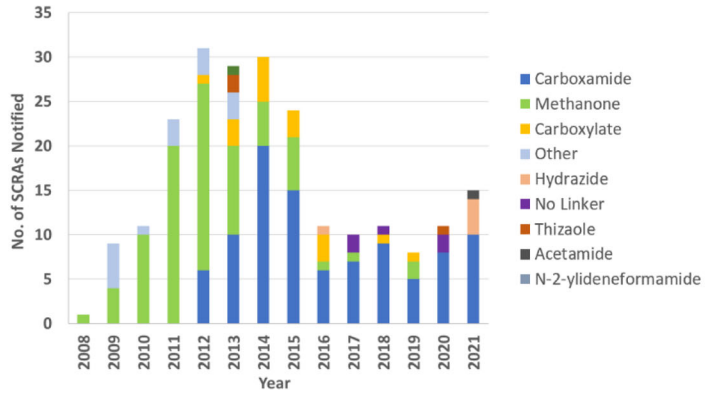
(b) – Tail groups



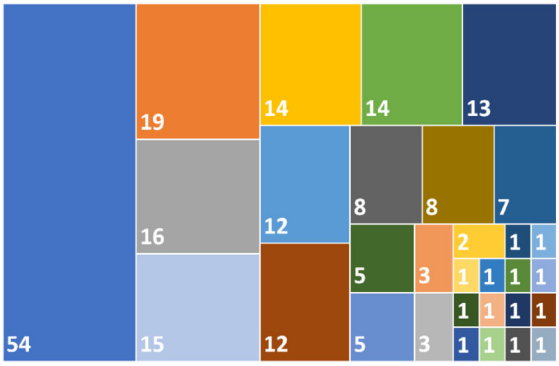


(c) – Linker groups





(d) – Linked groups



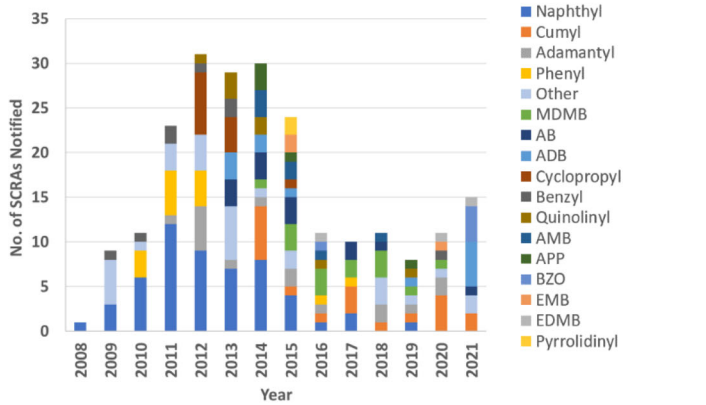


FIGURE 3 Treemap (left): Number of synthetic cannabinoids monitored by the European Monitoring Centre for Drugs and Drug Addiction, according to structural element (total number: 224). Histogram (right): Cannabinoids monitored by the European Monitoring Centre for Drugs and Drug Addiction, according to the year of first detection (notification), distributed by structural element. (a) Core groups; (b) linker groups; (c) tail groups; (d) linked groups. Tail and linked group acronyms have been defined in Table S3. [Colour figure can be viewed at wileyonlinelibrary.com]

responses to the emergence of these substances in Europe (and internationally, including more capacity for analytical detection and some national legal controls). An additional driver for the introduction of SCs with indazole cores may also have been their inferred pharmacological properties. In fact, evidence suggests that indazole rings are capable of stabilizing type 1 and 2 cannabinoid receptor (CB1R and CB2R) interactions with specific G-proteins, therefore increasing the potency for some of these compounds.[17–19]

Aside from indoles and indazoles, 12 additional cores are observed in the set of monitored SCs. Most of these appeared from 2013 onwards, alongside the decline in SCs containing indole cores. Interestingly, in 2021, four new oxoindole cores and three new pyrazole (substituted with a fluorophenyl ring) cores were seen for the first time. Oxoindole cores are found in the OXIZID series, with the name referring to the **OX**o**I**ndole core and the hydra**ZID**e linker.[20] MDA-19 (also known as BZO-HEXOXIZID) was the first of these compounds to be notified in 2016, but no further OXIZIDs were seen until 2021. This reemergence of old cores was also seen with fluorophenyl-substituted pyrazole moieties, whereby before 2021, only one other pyrazole SC had been notified, in 2017.

3.3 | The tail moiety

Figure 3b shows the significant variation of chemical structures seen in SC tail groups. This variation is expected, given that—particularly for indoles and indazoles—changing the tail moiety tends to be synthetically trivial.[21–23] Often this is achieved inexpensively in one step[24] and in high yields by using a halogenated leaving group on the tail compound to attach to the N-1 position. This was evident with the "first generation" JWH series, which featured multiple examples where identical "core–linker–linked group" moieties were produced, with varying tails. Pentyl and a corresponding fluorinated tail, 5-fluoropentyl (5F-pentyl), are by far the most dominant tail groups observed in SCs, with 52 and 51 occurrences, respectively. Following the same pattern seen with cores, pentyl tails are dominant until 2013 and were "overtaken" by 5F-pentyl tails in 2014. Halogenation is a common strategy in medicinal chemistry. Research has shown that halogenated compounds can display certain pharmaceutical and physicochemical properties when compared with their nonhalogenated counterparts, including increased binding affinity to some target proteins and enhanced metabolic stability.[25] Although the available pharmacological data do not allow for wide generalisations, this also appears to be the case for some SCs with halogenated tails (e.g., 4-fluoro MDMB-BINACA) which have been shown to be potent agonists at the cannabinoid receptors, particularly when compared with their nonhalogenated counterparts.[17,26] Thus, it is possible that the ease of synthesis which allows producers to evade legislation and the potential increase in potency of the resultant products may have driven the diversity of SC tails and the slight preference towards halogenated versions. Indeed, the introduction of new structural features to SCs as a method to evade national legislation has been observed in Germany. This included γ-carboline cores appearing after the 2015 New Psychoactive Substance Act (NpSG) and new tail groups including cyclobutylmethyl, cyclohexylsulfonyl, norbornyl methyl, and tosyl, appearing after the 2019 NpSG amendment, based on generic SC structures.[27,28] Cyclic tails, mainly cyclohexyl methyl (CHM) and fluorobenzyl (FUB) groups, emerged concomitantly with the halogenated tails around 2013. The limited evidence available suggests that both FUB[29] and CHM tails[30] result in SCs which are more potent agonists of the CB_1 and CB_2 receptors than their acyclic analogues.

3.4 | The linker moiety

Figure 3c shows the variety in linker moieties of the SCs under monitoring, with carboxamide linkers (present in 96 SCs) and methanone linkers (81 SCs) featured most frequently, followed by carboxylate linkers (17 SCs). Although a number of factors may be behind the choice to introduce any particular compound in the drugs market, the prevalence of these linker groups may be connected to the fact that common routes may be used to synthesise these compounds. Amide and ester coupling reactions are common in pharmaceutical manufacturing, with amide compounds being generally more stable than their ester counterparts due to electron donation from the amide nitrogen. With 3-substituted indole and indazole carboxylic acids commercially available, addition of a tail to the 1-position and a simple amide coupling with a corresponding amine, $R\text{-}NH_2$ ($R =$ linked group), would afford the desired SC.[19]

Five monitored SCs fall into the category of "no linker," all of which contain γ-carboline-1-one cores. This group is structurally analogous to a cyclized indole and carboxamide linker. The first of these was notified in February 2017. Although only a few variations of these compounds have been detected in Europe, it should be noted that two of them—Cumyl-PEGACLONE and 5F-Cumyl-PEGACLONE—have rapidly spread and have already been identified in seizures occurring in multiple European countries, as well as in forensic casework regarding multiple fatalities across the world.[7,31–33]

3.5 | The linked group moiety

Figure 3d focuses on linked groups. Although there is greater structural diversity in this group in comparison with cores, tails, and linkers,

naphthyl is the predominant linked group, which is present in 54 out of 224 monitored SCs. Other linked moieties include CUMYL (19), adamantyl (16), and phenyl (14) groups. A total of 57 SCs contain linked moieties which are derivatives of amino acids. These include L-valinamide (AB), L-*tert*-leucinamide (ADB), D-valine methyl ester (AMB), L-phenylalaninamide (APP), and L-*tert*-leucine methyl ester sidechain (MDMB), all of which are commercially available as amino acid hydrochlorides. Once again, ease of synthesis, coupled with higher potency of the resulting SCs, may influence the introduction of some of these compounds in the market. For example, SCs with ADB linkers are more frequently introduced in Europe than those with AB and APP groups, and the available evidence suggests that ADB-linked SCs may result in higher binding affinity to both CB1R and CB2R than analogues with AB and APP groups (ADB > AB > APP).[19]

4 | IMPACT OF LEGISLATION ON THE SC MARKET

A timeline of the main structural changes in SCs introduced in the European market is shown in Figure 4, alongside some of the most relevant legal milestones in the field (as described in Table 1), which are provided for context. Generally, and as expected, the structural variety of SCs increased dramatically in the period between 2011 and 2015 with the increase in new substances introduced in the market. However, this variation has not diminished in the years following, despite the smaller numbers of first identifications of new SCs in Europe.

The period between 2011 and 2015 was characterized by a large expansion in number, type, and availability of NPS in the European market, largely facilitated by globalisation (internet and fast international shipping) and driven by the open sale of these substances as "legal" alternatives to illicit drugs.[34] As the number of SCs increased, producers expanded the products on offer, typically choosing SCs with small variations of the JWH-018 structure (e.g., by introducing different tails) or SCs already available in the scientific literature. These were then mostly supplied sprayed on herbal smoking mixtures, sold in branded bright-coloured packaging. As concerns grew, mostly due to an increase in reports of harms associated with these products, so did the legal controls placed on these compounds. In 2014, China—a recognized source country for these substances to Europe's drug market[35]—legally banned five SCs (three from the JWH series and

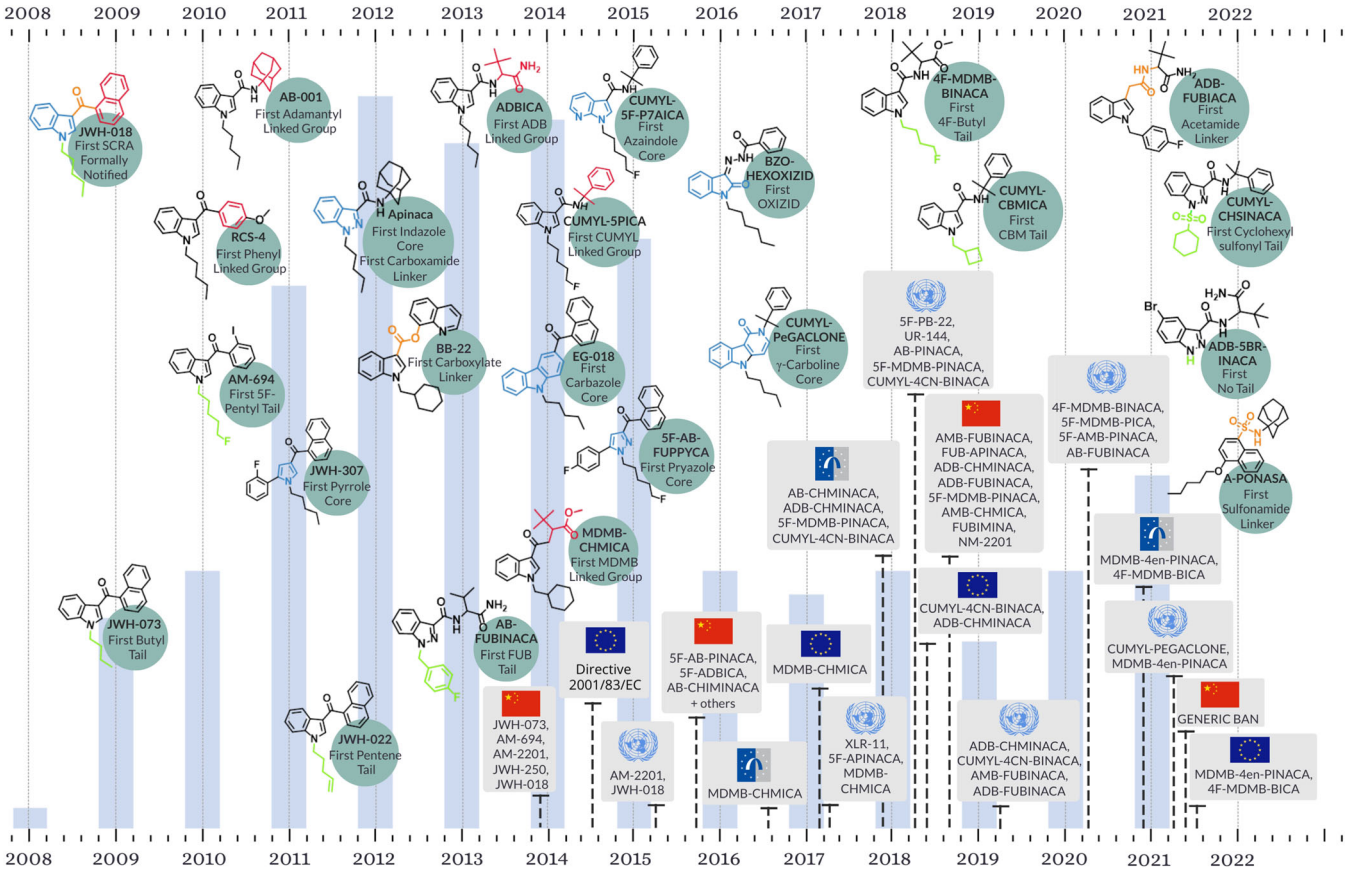


FIGURE 4 A timeline illustrating key structural developments in synthetic cannabinoid core, tail, linker, and linked group moieties from 2008 to 2022. European Monitoring Centre for Drugs and Drug Addiction risk assessments and key legislative responses from Table 1 have been indicated on the timeline. Histogram of new synthetic cannabinoids reported to the European Monitoring Centre for Drugs and Drug Addiction has been underlaid on the background. Acronym definitions for structural groups can be found in Tables S1–S3. [Colour figure can be viewed at wileyonlinelibrary.com]

two from the AM series). At the same time in Europe, increased investment was made in monitoring and responding to these substances, culminating in the first risk assessment and subsequent EU wide control of an SC in 2016, for MDMB-CHMICA.[36] At international level, a number of compounds were evaluated by the World Health Organisation's Expert Committee on Drug Dependence with recommendations for the control of AM-2201 and JWH-018 being issued in 2015. Together, these responses appeared to have contributed to a deceleration of the rate of introduction of new SCs. This was evidenced by the reduction in the number of formal notifications of SCs in Europe from approximately 27 per year during 2011 and 2015, to approximately 10 per year from then onwards. In this period, structural variations abounded, from the introduction of new cores (carbazole, azaindole, and pyrazole) to new linked groups (Cumyl, MDMB, etc.). Nonetheless, up until 2021, the number of structural variations somewhat followed a pattern, with a key structural feature (core or linker) being introduced, followed by several slightly changed chemical derivatives (with different tails or at times linked groups). These changes appeared to be motivated by three factors: ease of synthesis, a search for more potent compounds, and an avoidance of existing (and at times announced) legal controls.

In 2021, for the first time since 2016, an increase in first identifications of new SCs in Europe was observed, with 15 new substances being identified. This trend appears to continue in 2022 with 13 SCs being notified between January and 31st of July 2022. Importantly, these new compounds seen since mid-2021 are structurally very diverse and contain new or rarely seen cores, tails, and/or linker groups. These include four OXIZID compounds and some substituted indazole cores (including five indazole-containing compounds featuring a bromine substitution at the 5-position). SCs with new or rarely seen naphthalene (A-PONASA) and quinoline cores (ADB-FUBH-QUCA) were notified. In terms of tails, two new moieties, cyclohexyl sulfonyl and the 10-carbon decyl have been observed in three notified SCs in the first half of 2022. Additionally, four notified compounds (ADB-5Br-INACA, ADB-IACA, MDMB-5Br-INACA, and CUMYL-INACA) in 2022 do not contain a tail group at all. The impact of the absence of the tail in the pharmacological activity of SCs is yet to be assessed. Finally, with regard to linkers, acetamide (ATA) moieties were identified for the first time (e.g., in ADB-FUBIATA formally notified by the EMCDDA in December 2021). Since then, two other compounds have been identified in both Europe and the United States, CH-PIATA (also known as CH-PIACA) and CH-FUBIATA (also known as CH-FUBIACA), both containing acetamide linkers.[37,38] Another new linker, sulfonamide, has been identified in 2022, found in a newly detected SC, A-PONASA.

It is important to note that, in the absence of pharmacological data, some SCs are formally notified on a precautionary basis. Although in previous years, the structural similarity between new compounds and studied substances was sufficient to infer that the new compounds may display some degree of activity and/or affinity towards cannabinoid receptors, the new structural variations are such that such inferences are increasingly more difficult. An example of this is the unexpectedly low potency observed with the tosyl-substituted Cumyl-TsINACA.[39] This unpredictability is particularly true for compounds which are missing one of the "classical" building blocks, which may be seen as "precursors" for the synthesis of the more traditional four-part SCs, rather than SCs themselves. In fact, it appears that some surface web shops are trading some of these new, "atypical" compounds as "semifinished" products, alongside instructions on how to complete the synthesis (e.g., reaction instructions to attach haloalkane tails). These developments require attentive and careful monitoring, given the significant added risks associated with "DYI SCs" (incomplete or side reactions, uncertainty regarding the products, among other personal, environmental, and social risks).

Although the reasons for the greater structural variety in SCs emerging on the European market from June 2021 may be varied, these changes coincide with the introduction of legislation in China in May 2021 which banned all SCs with certain core structures (restricted core scaffolds shown Figure 2). Out of the 23 new SCs notified between June 2021 and July 2022, at least 20 are not covered by the new Chinese legislation. Market adaptability to control measures is not uncommon and reflects its dynamic and resilient nature. Structural evolution following the introduction of generic legislation has been previously seen after the 2019 update to the NpSG in Germany, similar to the phenomenon observed in 2021–2022.[28]

5 | CONCLUSION

SCs are the largest category of NPS monitored by the EMCDDA, with 224 different substances detected in Europe until December 2021 and a further 13 between January and July 2022. Although displaying comparable pharmacological profiles, their chemical structures are very diverse. In Europe, this diversity appears to be expanding through the years, with structures increasingly diverging from the "classical" four building block seen in the early years of monitoring, beginning in 2008. The analysis of the variation in building blocks appears to be driven by three main factors: ease of synthesis, a search for more potent compounds, and an avoidance of existing and announced legal controls. Until 2021, structural variations tended to be concentrated around the introduction of different tails and/or different linked groups in the molecules, which allowed to group new substances under "series" or "generations." Although the properties of the resulting compounds were often unknown, there was a small degree of predictability to the changes, which allowed forensic and toxicology labs to have some preparedness for upcoming derivatives.

Since June 2021, a number of SCs containing previously unseen or rare tails, cores, and linkers have been detected for the first time in Europe. Interestingly, 20 out of the 23 new compounds are not encompassed in the generic legislation which was introduced in China in May 2021. Although this may be due to a number of factors, it is likely that the introduction of legislation around certain structural building blocks of the "typical" SC scaffold in this source country may have played a role in the emergence of "atypical" scaffolds in Europe. These "atypical" compounds present challenges in many fronts given the many unknowns around them—analytical, forensic, toxicological,

pharmacological, just to name a few. Analysis of public health and social risks associated with these substances is therefore becoming more complex and demands higher levels of preparedness from all the actors in the field. National, regional, and international early warning systems are essential to support the responses to these challenges and to help mitigate potential unintended effects of supply reduction legislation at local or global level.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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