Synthetic Cannabinoids and Cathinones: Prevalence and Markets

A. L. Bretteville-Jensen[1], S. S. Tuv[2], O. R. Bilgrei[1], B. Fjeld[2], L. Bachs[2*]

[1]Norwegian Institute for Alcohol and Drug Research
Sentrum, Oslo

[2]Norwegian Institute of Public Health
Nydalen, Oslo
Norway

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* Corresponding author: Dr. Liliana Bachs, Norwegian Institute of Public Health, P. O. Box 4404, Nydalen, Oslo 0403, Norway; +47 2107 7892 (voice); Liliana.Bachs@fhi.no.

1042-7201/25-1&2/March 2013/7–26/$20.00 •

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REFERENCE: Bretteville-Jensen AL, Tuv SS, Bilgrei OR, Fjeld B, Bachs L: Synthetic cannabinoids and cathinones; Prevalence and markets; *Forensic Sci Rev* 25:7; 2013.

ABSTRACT: Over the past few years, the phenomenon of new designer drugs has attracted much attention. Synthetic cannabinoids and cathinones are the two main classes of these drugs. Both are potent drugs of abuse, and several cases of severe toxicity and deaths are reported. The present work is based on a systematic review of studies that have assessed the market and prevalence of synthetic cannabinoids and cathinones, and integrates pharmacological, sociological, and epidemiological aspects of these two groups of emerging synthetic drugs. The review reflects that the Internet has made synthetic cannabinoids and cathinones widely available. Furthermore, aggressive and widespread marketing, as well as the low price level of these drugs, their juridical status and their lack of detection on standard drug tests may serve as major motivations for drug use. The number of prevalence studies is small and derived from a limited number of countries. In spite of the many methodological shortcomings, some conclusions may be cautiously drawn. Taken together, the results point toward higher prevalence of use for synthetic cathinones than for synthetic cannabinoids. In the general population, the prevalence of use of synthetic cathinones is reported to be around 4% compared to figures lower than 1% for synthetic cannabinoids. Among students, the prevalence varies from 1–20% for synthetic cathinones and 2–10% for synthetic cannabinoids. Among groups with high rates of drug use, the prevalence varies between 4% to more than 60% for synthetic cathinones and around 10% for synthetic cannabinoids.

KEY WORDS: Consumption, drug market, drug prices, head shops, Internet, legal highs, mephedrone, motives, prevalence, Spice, subjective effects, synthetic cannabinoids, synthetic cathinones.

INTRODUCTION

Over the past few years, the phenomenon of new designer drugs has attracted much attention. Designer drugs' compounds and chemical compositions are created to mimic the intoxicating effects of other well-known illegal substances. To circumvent existing drug laws, producers often make use of noncontrolled ingredients, with the desired "highs" being obtained by applying analogs or derivatives of existing drugs, using modifications of the original chemical structures. These alternative products are neither controlled by international drug conventions nor licensed for legal use [73]. The term "legal highs" is frequently used by market participants when referring to this group of new synthetic drugs, although the term also comprises plants such as kratom (*Mitragyna speciosa*), "magic mushrooms", and salvia (*Salvia divinorum*), all having psychoactive components. More recently, the term "research chemicals" has been introduced to denominate these groups of drugs.

Lately, there has been an increase in the range, potency, profile, and availability of "legal highs". The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Early Warning System has placed on its radar approximately 164 new psychoactive substances, within the EU, between 2005 and 2011 [20], with global estimations of more than 200 new drugs. Synthetic cannabinoids and cathinones are the two main classes of these drugs, representing two thirds of all new substances reported to the European Early Warning System [20].

Synthetic Cannabinoids

Synthetic cannabinoids constitute a large group of drugs with effects similar to those of cannabis, but which may in fact be considerably more potent. Some synthetic cannabinoids are analogs of Δ^9-tetrahydrocannabinol (THC), the main psychoactive substance in cannabis; however, most are structurally different [53]. Synthetic cannabinoids exert their effects by acting on cannabinoid receptors in the body, which are part of a complex endocannabinoid system that is not yet fully understood. There are currently two known subtypes of the cannabinoid receptor: The cannabinoid CB_1 receptor, which is located in the brain mostly; and the CB_2 receptor, which is mainly expressed in the immune system. The CB_1 receptor is thought to be one of the most widely expressed G-protein-coupled receptors in the brain, and is believed to play a significant role in the modulation of GABA and glutamate neurotransmission [59]. While THC is a partial agonist on both the CB_1 and the CB_2 receptors, synthetic cannabinoids are typically full agonists on the CB_1 receptor, thus leading to maximum activation, even at significantly lower doses [61,81]. Some synthetic cannabinoids show an affinity for the CB_2 receptor. In addition to having a higher potency than cannabis, some of these drugs also have active metabolites and long half-lives [60].

Synthetic cannabinoids have constituted an area of research since the 1960s, primarily for medical reasons. Due to difficulties in separating anti-inflammatory and analgesic properties from unwanted psychotropic effects,

only a few of the compounds are in medical use today. The synthetic cannabinoids have, however, found their way into the world of recreational drug use.

Synthetic cannabinoids were introduced into the market dissolved in a solvent and sprayed onto a dried plant-derived base for delivery. **Figure 1** illustrates the package and the herbal content of a sachet. In this case, the herbal content was laced with the synthetic cannabinoid NA1200 (Figure 1). These products are typically sold as "herbal blends" or "incense", and many different mixtures have been released under the generic brand name: Spice [31,72]. The same products are also distributed under other names such as K2 and K2 Summit, and even more exotic names like Spice Gold, Spice Silver, Spice Diamond, Genie, Zohai, Yucatan Fire, Banana Cream Nuke, Aroma, and Red X Dawn are in current use [22,28]. Mixtures created for smoking are commonly available in metal foil sachets, often containing a few grams [22]. The contents of the various Spice products vary with respect to potency and the number and types of additives, which imply a risk of unintentional overdose.

Some of the synthetic chemicals that were added clandestinely to Spice mixtures have, in a few months, gone from being virtually unknown research chemicals, for which forensic science laboratories have had difficulties in identifying and obtaining reference samples, to being commercially marketed in their own right [31]. These chemicals are known by names such as JWH-018, JWH-073, AM-2202, etc., and in a pure state, these substances are sold as either solids or oils [22]. The abbreviations refer to the initials of the researchers that first synthesized the substances: JWH — John William Huffman, professor of organic chemistry, Clemson University; AM — Alexandros Makriyannis, professor of biotechnology and bioorganic chemistry, Northeastern University, Boston; RM — Raphael Mechoulam, professor of medicinal chemistry, Hebrew University, Jerusalem.

Synthetic Cathinones

Synthetic cathinones are analogs of cathinone, one of the psychoactive compounds that are naturally present in the plant known as khat (*Catha edulis*). Structurally, cathinone derivatives are the β-keto analogs of a corresponding phenethylamine, and the group includes several substances [30]. These drugs are able to produce stimulating effects by increasing the synaptic concentrations of cathecholamines, such as dopamine, serotonin, and norepinephrine. The stimulating effects of synthetic cathinones have been compared to methylphenidate in lower doses, and to cocaine or amphetamine in higher doses [13,55]. Despite the widespread use, information on human pharmacodynamics and pharmacokinetics, for most of the cathinone derivates,

Figure 1. Seizure containing NA1200. (Reproduced with permission from the Norwegian Directorate of Customs and Excise, Oslo, Norway.)

is very limited. In vitro data indicate that ring-substituted cathinones, like mephedrone and methylone, act as nonselective substrates on monoamine transporters; whereas pyrolidinophenones, like MDPV, act as potent catecholamine-selective transporter blockers [5,55]. In this way, the profiles of mephedrone and methylone are most similar to that of MDMA, while the profile of MDPV is most similar to that of cocaine. Several cases of acute toxicity and deaths have been reported after the use of synthetic cathinones [54].

Synthetic cathinones are sold as powder or tablets, collectively called M-Cats (i.e., methcathinone, ephedrone, methylone, methedrone, ethcathinone, and fluoromethcathinone) [21], with pseudonyms like Meph, Drone, Mmcat, Miaow Miaow, Bubbles, Rush, Bounce, and Sub-coca [69,73]. Mephedrone is often advertised as "research chemicals", "bath salts", "plant food", or "hoover freshener".

Synthetic cathinones were first developed in the early to mid-20th century, and initially used to treat conditions such as obesity and fatigue. Methcathinone is a synthetic cathinone that has been abused for decades in the former Soviet Union, Russia, and in Eastern Europe [19,64]. This drug was developed as an antidepressant in the 1930s, but the strong addictive potential stopped it from ever being marketed. A large number of hospitalizations in Israel in the early 2000s, due to intoxications with khat-extracted cathinones, led to the outlaw of these substances [6]. In Europe, seizures of synthetic cathinones (mephedrone) were first reported in 2007 [12,18]. Mephredone's popularity increased during 2009–2010, initially in the United Kingdom and secondly in the rest of Europe. In 2010, synthetic cathinones were first identified in the United States.

Challenges to the Analytical and Regulatory Agencies

The increase in abuse of these new drugs is a great challenge for analytical toxicologists, because most new drugs are not covered by established analytical methods. These drugs show a more-or-less poor cross-reactivity,

when using commercially available immunoassay tests, with related drug classes, but they may also be missed when using mass spectrometry-based screening techniques. Analyses in urine are further complicated by the fact that many of these substances are rapidly transformed into a large number of mostly unknown metabolites. A continuous adaptation of existing analytical methods, or the development of new methods, is therefore necessary. Methods for analyzing cathinone-derived drugs have been described for blood, serum, plasma, urine, and hair; and methods for analyzing synthetic cannabinoids have been described for blood, serum, urine, oral fluid, and hair [2,39].

The synthetic cannabinoid receptor agonist constituents of Spice were classified in the United Kingdom as Class B agents, under the Misuse of Drugs Act 1971, in 2009. At the same point in time, these substances were also banned in several other European countries. More than a year later, in March 2011, five of the most widely abused synthetic cannabinoids were scheduled by the US Department of Justice and placed on the Schedule I list, under the Controlled Substances Act.

In the United Kingdom, all substituted cathinones were made illegal in April 2010, under the Misuse of Drugs Act 1971. The same proceedings were followed by the Republic of Ireland. The US Department of Justice and the Drug Enforcement Administration (DEA) temporarily banned three synthetic cathinones (mephedrone, MDPV, and methylone) in October 2011; an action taken to control these substances for at least 12 months, while a more permanent ban was under consideration. The DEA placed the same substances on the Schedule I list in July 2012, permanently banning them. Highlights in the history of the legal status of these drugs are depicted in **Figure 2**.

Traditionally, new drugs have been taken under control individually, after risk assessments, and added to a list of substances already controlled by drug laws. During the last few years, new psychoactive substances have entered the market on a larger scale, challenging the traditional way of banning novel substances. Different attempts have been launched at making the control of these new substances more effective, as for example by listing substances under defined groups rather than individually, penalizing unauthorized distribution of psychoactive substances, or introducing refinements to old legislations.

To our knowledge, no previous work has reviewed the literature regarding market and prevalence of synthetic cannabinoids and synthetic cathinones. In this article, the current literature on this topic is systematically reviewed. The present work integrates pharmacological, sociological, and epidemiological aspects of the phenomenon of these two groups of emerging synthetic drugs.

I. METHODS

Test searches were conducted to find relevant terms and search words, and controlled vocabulary was examined using a few relevant articles. Search strategies were developed (**Table 1**), and literature searches were conducted, using the following databases to ensure comprehensive article retrievals: Medline, Embase, PsycINFO, and ISI Web of Science.

The searches were conducted during September and October 2012, using a combination of both controlled vocabulary and text word searching. The year of publication was limited to 2004 and up until the current date. No limitations were made as to publication language in the original searches. The search result revealed a total of 881 publications, after the removal of duplicates.

Abstracts from all of the 881 publications were read, and only publications involving prevalence and drug markets, for synthetic cannabinoids and cathinones, were selected. At this stage, articles with publication languages other than English, Norwegian, Spanish, or German were excluded. After this initial elimination, approximately 80 articles were read in full text, and the material reflects primarily publications from the western countries. Articles without an adequately defined methodology,

Table 1. Terms used as the basis for the search strategy. The terms in column A were searched separately and grouped together with the boolean operator 'OR' to broaden the search. The terms in column B were processed in the same way. Finally the results from columns A and B were combined using the boolean operator 'AND'.

A	B
4-MEC	Abuse trend
Bath salt	Current trend
Buphedrone	Drug abuse
Butylone	Drug market
Designer drug	Drug usage
JWH-018	Drug use
JWH-073	Emerging trend
K2 and (drug or cannabinoid)	Market monitor
Legal high	Market surveillance
MDPBP	Prevalence
MDPV	
Mephedrone	
Methylone	
Spice and (drug or cannabinoid)	
Synthetic cannabinoids	
Synthetic cathinone	
Methcathinone	

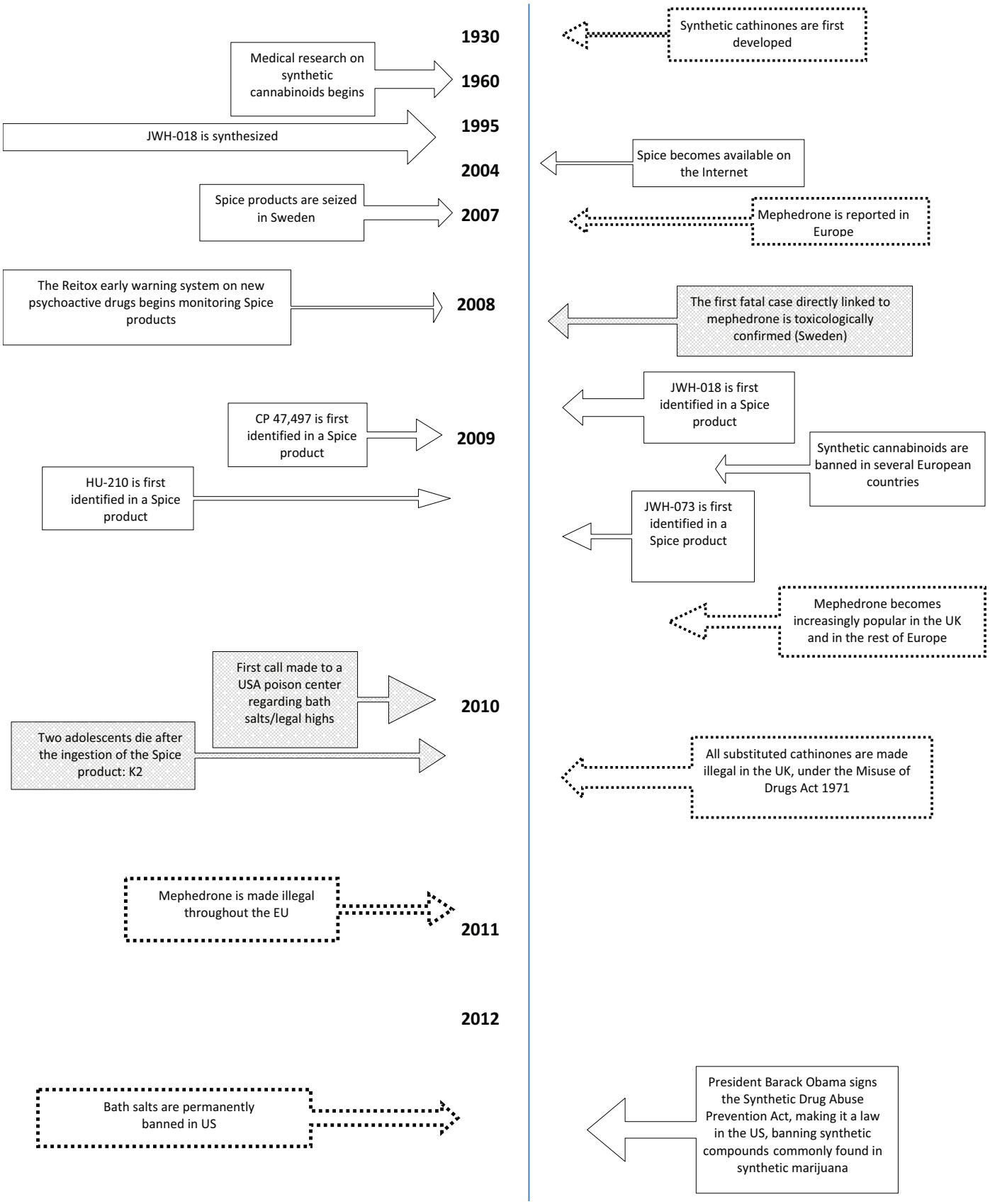

Figure 2. Timeline showing the development, from the early 1900s, when synthetic cannabinoids and cathinones first were developed for medical research, and up until today, with a current extended use of these substances as recreational drugs. The solid lines provide information on synthetic cannabinoids, while the dashed lines provide information on synthetic cathinones. The gray boxes refer to their toxicity.

study population, or drug classes were excluded. With the discovery of relevant references, which had not already appeared in the initial search result, these were added to the final review.

II. RESULTS FROM THE INCLUDED PAPERS

A. Drug Markets and Production

1. The Sale of Synthetic Cannabinoids and Cathinones

Synthetic cannabinoids and cathinones are sold over the Internet, in so-called "smart shops" or "head shops", in gas stations, in convenience stores, by tobacco specialists and by street dealers [23,67,72]. A "smart shop" or "head shop" is a legal retail outlet that usually sells paraphernalia for drug use, such as pipes, rolling machines, rolling papers, vaporizers, and bongs [69]. Many shops also trade counterculture books, magazines, and music, in addition to commodities like cannabis seeds and cultivation equipment. Head shops originated in the United States in the 1960s, and are now also found in Canada, Australia, New Zealand, and many European countries [23]. Although many head shops offer "legal" psychoactive substances for sale, this is not the case for every retailer.

The extent of drug sales through regular drug dealers and local retailers is unknown, but seems to vary extensively between countries and across different regions [7,72]. Furthermore, the number of head shops has also varied substantially over time, and in response to changes in legal status and regulations; e.g., in Poland, where the number of head shops reached an all-time high of more than 1,400 shops, before a new legislation was introduced [7]. However, the main marketplace for drugs like synthetic cannabinoids and cathinones appears to be the Internet [17,58,73], with the Internet playing an important role for sales, marketing, and exchange of consumer experiences. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) registered an increase in the number of Internet shops from 314 in January 2011 to 693 in January 2012 [20], and a study of the online availability of "legal highs" in Europe indicated a presence of more than 500 different products [37]. The traded goods are sent to customers by mail, and "discrete packaging" is sometimes emphasized in the shops' advertisements [58]. Some sites accept only payment by bank transfer or Internet payment accounts, while others offer a range of payment options, including credit and debit cards, as well as mail order [67].

2. Marketing

Synthetic cannabinoids and cathinones products have often been marketed by using names aiming to reflect that the drugs are "legal", "safe", and "natural", applying words such as: "herbal highs" or "legal highs", etc. [23,80]. However, the products do not usually come with any consumer information that explicitly declares or explains the uses and effects [70]. A study of all "legal high" products offered by UK-based Internet retailers (including plants like salvia and kratom), found that in 92% of the cases, the Internet shops failed to list side effects, and in 82% and 86% of the cases, contraindications and drug interactions were not listed, respectively [58]. On the contrary, the distributors, to circumvent regulatory frameworks, often label the package or the container with "not for human consumption", and sell it as either "plant food", "fertilizer", "bath salts", or "hoover freshener" [69]. In consequence, the drugs subsequently fall outside of the medicinal product regulations; meaning harm reduction information about dosage, administration, risks, and contraindications is no longer required. The warning messages, stating that the drug is "not intended for human consumption", stands in sharp contrast to the sophisticated packaging, marketing, and promotion of the product as an alternative intoxicant, undetectable by conventional drug-testing methodology [24].

Despite the frequent lack of consumer guidance, the products may still come with a content declaration. The declaration, however, has often been proved misleading, as it does not list the true contents, with subsequent analyses having frequently revealed that the synthetic cannabinoid or cathinone substances are omitted from the list, and that the listed ingredients are missing [10,23,31,67]. For example, Piggee [52] notes that the herbal ingredients listed on the packaging of Spice did not appear to contribute to the drug's psychoactive effects, and were not even present in most of the samples tested. **Figure 3** illustrates a product without declaration of ingredients containing both JWH122 and 250.

The Internet, and the new ways of social networking, play an important role in reaching potential customers, and thereby also in the marketing of new drugs [17,37]. Aggressive marketing is thereby made possible toward large groups of potential buyers that may not have been

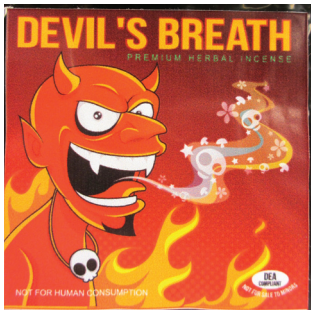

Figure 3. Seizure containing JWH122 and 250. (Reproduced with permission from the Norwegian Directorate of Customs and Excise, Oslo, Norway.)

reached without the Internet sites selling the drugs. Further, the Internet shops have fancy advertisements and often adopt marketing strategies from traditional businesses by offering discounts on individual or bulk purchases of the products [67]. Many shops also mislead their consumers by incorrectly marketing their products as legal alternatives to drugs like cannabis, ecstasy, amphetamine, and cocaine [21,22,73]. Moreover, suppliers of synthetic cannabinoids and cathinones can further make use of early adopters and trend leaders in their marketing strategies, and Griffiths et al. [31] draw a parallel with modern viral marketing techniques, that employ social networking as a tool for encouraging new brands to be adopted.

3. Consumers' Exchange of Information

The extensive exchange of user information on the Internet is another particular feature of the recent developments in drug use. On these forums, drug users share their experiences and knowledge regarding what drugs to buy, what effects to expect from the different types of drugs, the recommended doses, common side-effects and how to deal with them, etc. For many, these forums serve as their main source for updated and, what is believed to be, trustworthy information on drugs, as user-orientated sites have often been rated more useful and reliable than the official sources, among drug users [67]. Furthermore, these sites are often ranked higher in the search engine results than the official sources. Sumnall et al. [67] also point out that it is through the user forums that new substances start becoming better known, in the general population of users, and that these general discussions of subjective experiences probably play an important role in the rapid spread of new drug-using trends. Altogether, the many Internet shops, user forums, and the like, imply that anyone curious about drugs may search the Internet, and thereby become exposed to thousands of sites emphasizing the drugs' positive effects, and simultaneously downplaying or denying any of the negative effects.

4. Producers

Producers of the precursors are sometimes, but not necessarily always, the same as the producers of the end products. According to the EMCDDA [20,21] and others [67] China is identified as the main country of production, and to a lesser extent India is also mentioned. Some of the precursors of synthetic cannabinoids and cathinones are legally and easily available on the world market [20]. Concerns exist, however, about the quality of some of the wholesale precursors and bulk active substances, as regulatory oversight and enforcement may be limited [67]. The lack of quality standards and control suggest great product variability, and any given precursor may not keep the same quality or contain the same ingredients over time. Chemical additives are sometimes clandestinely combined with these substances, so that both the producers of the end products and the retailers may be unaware of the actual contents of their commodities [8,67].

The producers seem to be consistently updated on local drug legislations and very flexible. For instance, the banning of some of the synthetic cannabinoid and cathinone products in the UK and in Germany, resulted in a very rapid emergence of new types of commodities, with chemical structures and intoxicating effects very similar to, but not exactly the same as, the banned goods [8,45].

5. Potency and Prices

In line with the extensive variability observed among the precursors of synthetic cannabinoids and cathinones, the end products also show great variations in content [8,16]. This implies that potential consumers have no means of assessing the actual potency of the dried herbal mixtures, powder, or tablets, before ingestion, not even with products or brands they have previously consumed. In particular, because of the difficulty in making a homogeneous mixture of dried vegetable matter and small quantities of synthetic additives, it is likely that there are considerable interbatch differences in the concentrations of cannabinoids in Spice-like products [23]. This claim is supported by the scientists who first revealed the true contents of the Spice products: The combinations and the concentrations of the synthetic cannabinoids present in Spice products can produce markedly different effects, even within separate batches of the same brand [3,18].

The synthetic cannabinoid and cathinone products are priced competitively compared with their more well-known illicit counterparts [1,11]. Prices collected from different Internet sites confirm the relatively low price level, although prices are reported within a wide price range [58]. Even so, if the prices collected in a study on UK-based Internet sites are representative for the general international price level, the results suggest that the drugs are affordable, even for initial experimentation among young people [37,58]. EMCDDA (2011) reports that sachets of Spice smoking mixtures (at about 3 g), which is sufficient for around eight joints, can be purchased for 26 to 30 EUR from Internet sites or specialist shops. For a synthetic cathinone product, like mephedrone, one usually has to pay between 18 and 25 Euros for 1 g [22]. This implies that the cathinones products are cheaper that more well-known substances like MDMA. Furthermore, many Internet retailers and local street dealers offer great bulk-buying discounts, meaning that the unit price becomes considerably lower than that of the price of one sachet or 1 g of powder [22,67].

B. Motives for Use, Modes of Consumption, and Subjective Effects

To this date, most of the available papers focusing on synthetic cannabinoid or cathinone use have been limited to toxicology reports, identifying the chemical constituents of commercial products, or case reports, on individuals who present to hospitals following adverse drug effects [72]. For this reason, there is only a limited body of literature focusing on micro-level analysis of the individual motives for use, the modes of consumption, and the subjective and behavioral effects of synthetic cannabinoids and cathinones [12]. A total of 17 papers, exploring the motives for use, the modes of consumption, or the perceived effects, were included.

1. Motives for Use

Different studies have identified several qualitative motives for using both synthetic cannabinoids and cathinones, with some motives overlapping. In general, the perceived lack of long- or short-term harm, as well as good ratings from peers or on the Internet, seemed to be the most important attractions to the new psychoactive substances [29,67]. One paper also reported a level of protection and a distance from the illegal drug trade, offered by the legal status prior to the ban of several of the available compounds, as important motives for use [70]. The widespread user availability also seemed to be an important factor [11,67,71], in addition to the economical motivation, linked to the low pricing [11,67,69,71,73]. Some users also stated the lack of detection on standard drug tests as their main motive for using synthetic cannabinoids or cathinones [12,24,73,75].

The papers further identified a few specific motives for use linked to each of the two drug groups. For synthetic cathinones, there were several reports linking mephedrone's rising popularity to a dissatisfaction with the purity and consistency of the available cocaine and ecstasy at the time, among regular stimulant users [11,73]. For this reason, synthetic cathinones escalated as a favorable drug in comparison to the dominating club stimulant drugs (MDMA and cocaine), and gained huge popularity in the drug using club scene, especially in Ireland [68].

The subjective motives found for using synthetic cannabinoids stands in contrast to those of synthetic cathinones, the former being associated with curiosity and pleasurable feelings of rebellion [24,72]. The legal availability appeared to serve as a stronger motivator among the synthetic cannabinoid users, than what was the case for the users of synthetic cathinones [75].

2. Modes of Consumption

The modes of consumption for the new psychoactive substances do not differ greatly from that of the more "traditional" drugs. Synthetic cannabinoids are primarily administered the same way as cannabis: Being mostly smoked (via a pipe, in a cigarette/joint/blunt, or by using a hookah/water pipe/bong), although administration via vaporization, in addition to oral and rectal ingestion, has also been reported [12,38,72]. During an average episode of use, participants in a study reported consuming a mean of 1 g of "herbal blend" (which is much more than when smoked "clean"), resulting in an average duration of subjective intoxication lasting for 93 min [72].

On the other hand, mephedrone and other forms of synthetic cathinones are usually available as powders or tablets, and can be consumed orally, by nasal insufflation, by intramuscular/intravenous injection, or by rectal insertion. The powder can also be dissolved in water, or it may also be swallowed, after wrapping it in tissue paper [73]. Even though there are several modes of use, the most common route is via snorting [68,71,77]. Dosages were usually gauged, based on users' experience of the drug, spanning from 0.5–2 g, over the course of 6–12 h [68,77]. Each dosage appeared to consist of approximately 100–200 mg or more, with users re-dosing to prolong the euphoric experience, leading to the consumption of 1-2 g per session [73,77]. The amounts used in a typical session were significantly larger for those who snorted the drug compared with those who consumed the drug orally [80].

3. Subjective Effects

a. Synthetic Cannabinoids

Studies focusing on the subjective effects after intoxication with synthetic cannabinoids are scarce, and our search generated only three papers focusing on this perspective. Several other studies have focused on the clinical effects, related to the use of synthetic cannabinoids, but these studies are not included in this review.

The use of synthetic cannabinoids normally takes place at home, either alone or in small groups, as opposed to larger social gatherings [72,75]. Most studies indicate that the subjective effects of synthetic cannabinoids are similar to those of cannabis [33]; but despite producing similar effects, many users still have reported that synthetic cannabinoids produce subjective effects that are unique, and discernible from other licit or illicit drugs [72]. An anonymous Internet-based survey in the United States recruited participants with a history of synthetic cannabinoid use ($n = 168$), with survey questions focusing on targeting the subjective effects after intoxication. The subjects perceived effects that were largely positive, though

negative or unwanted effects were reported by some. The positive subjective effects of synthetic cannabinoids were: Feeling of a pleasant "high", increase in appetite, producing a dreamlike state, feeling stimulated or energetic, having a floating feeling, inability to control laughter, and feeling more focused than usual. The negative effects reported were: Dry mouth, feeling drowsy or tired, feeling lightheaded, having trouble remembering things, feeling the heart racing, feeling clumsy, having a heavy or sluggish feeling, feeling nervous or anxious, feeling paranoid, feeling dizzy, feeling nauseous, slurred speech, hallucinations, decrease in appetite, hearing a ringing sound, and vomiting. Withdrawal symptoms, following cessation, were most prevalent among the frequent users. The most common symptoms of withdrawal were: Headaches, anxiety/nervousness, coughing, insomnia/sleep disturbances, anger/irritability, impatience, difficulty concentrating, restlessness, nausea, and depression [72].

Another North American study examined 11 adolescents' experiences with synthetic cannabinoids, aiming to describe the psychoactive and physical effects, as reported by the users. Although positive mood changes were noted, the adolescents also experienced negative emotional effects. All subjects noted feeling euphoric, but 9 out of 11 also noted negative mood changes, such as irritability and anxiety, following the use of synthetic cannabinoids. In addition, all users reported having difficulties with memory, with some describing auditory or visual perceptual distortions, and two describing paranoid thoughts [12].

A German online survey, targeting individuals with a history of synthetic cannabinoid use ($n = 860$), showed that a considerable share of the respondents had experienced acute side effects, or aftereffects, at least once. These effects appeared to occur more frequently among the regular consumers. The most frequently reported conditions, in descending order, were: Increased heart rate, circulation problems, headaches, nausea, and anxiety. According to the survey, most of the respondents were concerned about a high risk of acute physical symptoms, as well as the possibility of long-term damage. One third reportedly declined to continue using this group of drugs because of the possible side effects [75].

b. Synthetic Cathinones

Studies focusing on the subjective effects of synthetic cathinones, in the same way as with the synthetic cannabinoids, are scarce. The only available papers concerning the use of synthetic cathinones, have aimed specifically on the use of the β-keto-amphetamine mephedrone (4-methylmethcathinone) [78]. Our search generated a total of eight papers, all focusing on the subjective effects of mephedrone intoxication.

A UK-based online cross-sectional survey ($n = 890$) showed a range of mephedrone-related physiological effects, including: Increased sweating, palpitations, nausea, headache, increased sex drive, and cold blue fingers. The results revealed a significant dose-response relationship for the incidence of increased sex drive and excessive sweating. Still, the majority of the respondents who had previously used cocaine reported that mephedrone provided a longer-lasting and better "high" than that of cocaine, with the same level of risk as cocaine, albeit being less addictive [77].

Another UK-based telephone survey, based on 100 people reporting using mephedrone at least once during the past 12 months, described increase in energy, euphoria, and talkativeness, as the most prevalent and intense acute effects. Tiredness, insomnia, nasal congestion, and impaired concentration were the most prevalent withdrawal-related effects reported [79].

A Web-based survey in the United Kingdom, targeted at mephedrone users ($n = 1406$), showed that the users considered the effects to best compare with those of MDMA. Some users described feelings of warmth and empathy after consumption, and stated that they considered the drug to be less harmful than alcohol or tobacco, but more harmful than Class A drugs, such as LSD, psilocybin, and MDMA. Twenty percent of the respondents reported having experienced a significant negative reaction after taking mephedrone. The most prevalent negative effects reported were anxiety, panic, and heart palpitations. Approximately half of the respondents said that they had found mephedrone to be addictive [11].

An Irish qualitative study [71] with a total of 22 mephedrone users described the drug outcomes as: Feeling "loved up", experiencing heightened senses, increase in sensuality and sex drive, and feelings of elation. The negative physical side effects reported during the "rush" were few, and the "comedowns" stated as manageable, but the subjects still described immediate negative effects, such as: A burning sensation in the nostrils, an unpleasant acidic chemical taste in the sinuses, and a slight disorientation when snorting or bumping. Some subjects also reported: Increased sweating, restlessness, insomnia, anxiety, feeling "down", and having regrets over "out-of-character behavior". Even so, the majority of the user experiences were positive, with a strong preference for mephedrone, as opposed to other illicit party drugs, such as ecstasy, amphetamine, or cocaine [71]. Later on, the authors conducted a follow-up study, focusing on the postlegislative mephedrone consumerist patterns. A total of 10 of the previous participants reported continued mephedrone consumption after the drug had been regulated, the rest switching back to ecstasy or cocaine. The subjects also reported observing an improvement in the availability and

quality of the cocaine and the MDMA, after the regulation of mephedrone. In contrast to the prelegislative study, postlegislative users described an emergence of negative effects with a continued use of mephedrone [69].

In another Irish qualitative study, including 32 people having used mephedrone for the last six months, the users' experiences reported were conflicting, with many of the subjects describing variations in the strength of effect, gauging their dosage to achieve the desired effect, and describing the use of other drugs to counteract the negative effects of strong "comedowns" [70].

A study researching the cognitive and subjective effects of mephedrone revealed that users had experienced: An increase in self-confidence, hearing a buzzing sound, dizziness, and impaired concentration and memory. Acute ingestion of mephedrone primed the wanting of more of the drug. When drug-free, the users revealed elevated depression scores, in addition to scoring higher on symptoms of schizotypal behavior, particularly on impulsive behavior, anhedonia, and lack of intimacy, and showed disruptions in attention and concentration [29].

C. Prevalence

The studies of the prevalence of use for synthetic cannabinoids and cathinones are scarce and heterogeneous. The results are presented grouped by methodology: Questionnaires/surveys, results from analysis of biological material, and results from calls to poison centers. A summary of prevalence studies are presented in **Table 2**.

1. Prevalence of the Use of Synthetic Cannabinoids

A total of 17 papers, exploring the prevalence of synthetic cannabinoids, were included in this review.

a. Results from Questionnaires/Surveys

Seven papers based on questionnaires or surveys, exploring the prevalence of the use of synthetic cannabinoids, were included.

The first published paper is from England, and was surveyed in 2009 [79]. A cross-sectional anonymous online survey was posted on a website, promoting dance-club events, targeting the population associated with the dance music scene. From a total of 2,295 respondents, 12.6% reported having used Spice, Magic, or Warrior smoking blend.

Another survey, originating in Germany, is from the same time period [49]. The design of this 2009 Epidemiological Survey of Substance Abuse (ESA) included 8,030 subjects (aged 18–64), drawn from population registers. A mixed-mode design including questionnaires, by using telephone and Internet interviews, was applied, with a 12-month prevalence of Spice consumption reported to 0.8% (with a response rate of 50.1%).

The Centre for Drug Research has published drug trends in Frankfurt am Main from the year 2010, based on questionnaires answered by pupils aged 15–18. The center found a lifetime prevalence of 9% for the use of "Spice and other smokable blends". A total of 2% of the pupils reported that they had used the drug during the last 30 days [76].

A study from the United States explored the use of synthetic cannabinoids among college students in Florida, in 2010 [38]. A mailed questionnaire, with an invitation to participate, was sent to 2,396 students, with 852 (36%) responding. In addition to questions regarding the smoking of tobacco, the students were asked if they had ever smoked "Spice, also known as K2 or legal weed". The use of synthetic cannabinoids was reported by 8% of the sample population.

A survey [83] undertaken by 315 customers in gay-friendly night clubs in London, in 2011 showed a prevalence for lifetime use of Spice/K2 of 9%. Responders reported a prevalence of the use of Spice on "the same night" of 0.6%.

A study based on declared drug use, in the context of the British Crime Survey 2010–2011 [62], which yearly retrieves information on drug prevalence among individuals aged 16–59, living in households in England and Wales, since 1996, revealed that the prevalence for the use of Spice was 0.2%. Among those aged 15–24 the prevalence was 0.4%, and among those aged 25–59 it was 0.1%.

The latest study presents data from 2012 [40]. This study is based upon a yearly survey performed among adolescents in the United States. The 2012 national sample included 45,449 students, attending 395 public and private schools, aged 13–18. The past year's prevalence for the use of synthetic cannabinoids was 4.4%, 8.8%, and 11.3%, for the age groups 13–14, 15–16, and 17–18, respectively. The prevalence for the adolescents aged 17–18 was unchanged from the previous year. For the other age groups, the question of the use of Spice was included for the first time.

b. Results from Analysis of Biological Material

Six studies, exploring the prevalence of the use of different synthetic cannabinoids, by analyzing biological materials, were included in this review. Three of the studies are based upon the analysis of urine samples from doping controls, and consequently the population explored consisted of young athletes.

The first study, from Germany [48], was performed in 2009, as a part of the analytical work in identifying JWH-018 metabolites, in order to develop effective screening

Table 2. Summary of prevalence studies

Drug	Case no.; time	Description of study	Summary of study results	Ref.
Questionnaires/Surveys				
MDPV; Mephedrone	693; 2010	Australian national cross-sectional surveys among regular ecstasy users	Lifetime use: 21% mephedrone, 1% MDPV; Past 6-month use: 17% mephedrone, 0.5% MDPV	[10]
Synthetic cannabinoids (K2)	852; 2010	University of Florida students	Use at least once: 8% (69 out of 852)	[38]
Mephedrone	315; 2011	Survey in two dance clubs in London	41% took or planned to take mephedrone on the night of survey	[84]
Mephedrone	572; 2010	Online survey recruited from various online forums	Used mephedrone at least once: 4% (23 out of 572). Average age: 20.87 years; 14 male, 9 female; 8 user during the past month, 4 during 6 months, 4 during past year, 7 more than one year ago	[44]
Mephedrone	308; 2010	Questionnaire in gay nightclubs in South London	Lifetime, 54%; past year, 52%; past month, 41%; same night, 21%; planning on consuming same night, 22%	[47]
Mephedrone	1006; 2010	Questionnaire among students	Previous use, 20.3%; 23.4% previous use once, 23.4%; daily use, 4.4%	[14]
Mephedrone Spice/K2	313; 2011	Questionnaire in gay nightclubs in South London	Mephedrone: lifetime, 63.8%; past month, 53.2%; same night, 41% Spice/K2: lifetime, 9.0%; past month, 2.2%; same night, 0.6%	[83]
Mephedrone Spice	2295; 2009	Online survey among readers of the dance magazine MixMag in UK	Lifetime use rate: mephedrone, 41.3%; MDVP, 1.9%; methylone, 10–8%; synthetic cannabinoids, 12.6%	[79]
Mephedrone Synthetic cannabinoids	2010–11	Survey: 16–59 years	Past year use rate. Mephedrone: 6–59 years, 1.4%; 16–24 years, 4.4%. Spice: 6–59 years, 0.2%; 16–24 years, 0.4%	[62]
Synthetic cannabinoids Synthetic cathinones	45,000–50,000; 2012	National samples of students from three grades	Synthetic cannabinoids: 12th graders, 11.3%; 10th graders, 8.8%; 8th graders, 4.4%. Synthetic cathinones: 12th graders, 1.3%; 10th graders, 0.6%; 8th graders, 0.8%	[40]
Smokable blends (Spice)	2010	Questionnaire among pupils aged 15–18 years in Frankfurt am Main	Lifetime, 9%; last 30 days, 2%	[76]
Synthetic cannabinoids	8030; 2009	Mixed mode of questionnaires, telephone and Internet interviews in Germany	12-month use rate among 18–64 years: 0.8%	[49]
Biological Material				
Cathinones[a]	325; 2009–10	Hair collected for assessing driving ability, tested positive for MDMA or amphetamine	New psychoactive drugs found in 37% (120 of 325) samples; mephedrone in 3%, while methylone in 1 single case	[57]
MDPV	4570; 2009–10	DUID in Finland (excluding cases with acohol only)	5.7% of all DUID cases tested positive for MDPV	[43]
JWH-018 JWH-073	5956; 2011	Urine from athletes: Jan. 24 for JWH-018; Oct. 28, JWH-073	Positive for JWH-018 or JWH-073: 4.5%	[36]
Mephedrone Methylone	209; 2010	Urine from users of methadone in a substitution treatment program in Northern Ireland	Positive for mephedrone, 7.5%; positive for methylone, 1.2%	[46]
JWH-018 JWH-073	25; 2010	Urine from athletes suspected of using synthetic cannabinoids	Positive for JWH-018 and/or JWH-073, 92%	[35]
JWH-018	7500; 2009	Randomly selected urine from athletes in doping controls	Positive for JWH-018: 0.03%	[48]
JWH-018 JWH-073 JWH-250	679, 50,000; 2010	Oral fluid, urine	679 oral fluid samples, 15% positive; 50,000 urine samples, 18% positive	[66]
JWH-018 JWH-073	2060; 2010–11	Urine samples from suspected users	Positive for at least one compound, 29.6%; positive for JWH-018 metabolites, 20.3%; 8.9% positive for metabolites from both, 8.9%; 1 case positive only for JWH-073	[41]
Mephedrone	318	Students, hair and questionnaire	Hair, 3.9% positive; combined hair and questionnaire, 5.7%	[51]

Table 2. (Continued)

Drug	Case no.; time	Description of study	Summary of study results	Ref.
Poison Center data				
Bath salts	2009–12	Comparative UK/US exposure study	Mean exposure counts per month per million population: 0.438 in the UK and 0.457 in US	[63]
Synthetic cannabinoids	2011	Study on rural and urban areas	334 calls in 2011. Cases per 100,000: large metropolitan, 1.37; medium metropolitan, 3.12; small metropolitan, 3.12 metropolitan/rural, 8.43	[50]
Cathinones	362; 2010–11	All calls to Texas poison centers	Exposure rate: 5.2–69 per 100,000 (different regions)	[25]
Synthetic cannabinoids	2010–11	Calls to Texas poison centers	Exposure rate per 100,000: 2.79–7.14 (11 health regions in Texas); city, 4.02; rural area, 4.90	[26]
Synthetic cannabinoids	2010–11	Callers to the poison control center at the border of Mexico and far from the border of Mexico	Exposure rate: 4.1 per 100,000. No difference between counties	[27]
Synthetic cannabinoids	2010	Emergency department visits	Rate per 100,000: 12–29 years, 11.1; 12–17 years, 14.9; 18–20 years, 13.9; 21–24 years: 11.8; 25–29 years, 4.1	[65]

[a] Psychoactive drugs tested include: 4-MMC (mephedrone), butylone, cathinone, ethylone, MDPV, methcathinone, and methylone.

methods for urine. A total of 7,500 samples, from doping controls, were reanalyzed for the presence of JWH-018 or its metabolites. Two samples were found to test positive.

A selection of urine samples collected in 2010, in the United States [35], from athletes suspected of synthetic cannabinoid use, were analyzed for JWH-018, JWH-073, and their metabolites. A total of 25 samples were reanalyzed, and 23 (92%) were found positive for one or more of the synthetic cannabinoid metabolites.

A wider study, performed by the same group, in 2011 [36], screened urine samples from 5,956 athletes without a suspicion of use. The prevalence of JWH-018, JWH-073, or any of their metabolites, in the tested material, was 4.5%.

From a toxicology laboratory in California [66] were reported prevalences of 18% positive findings among 50,000 urine samples, and 15% positive findings among 679 oral fluid samples, as collected during 2010–2011. The population from which the samples were collected is poorly defined in the meeting abstract, but is most probably sampled from a population of drug abusers. The drugs that were analyzed for in urine were JWH-18, JWH-073, and its metabolites, and in oral fluid they were JWH-018, JWH-073, and JWH-250.

In a material consisting of 2,060 urine samples, collected during 2010–2011, in Pennsylvania, from suspected users of synthetic cannabinoids [41], 30% of samples were found to be positive for at least one compound. The compounds analyzed for were JWH-018, JWH-073, and its metabolites.

A study conducted in Norway (Tuv, article in preparation), reported a prevalence of 2.2% for synthetic cannabinoids among drivers suspected of drugged driving. A total of 726 blood samples were analyzed for 18 different synthetic cannabinoids, collected during 2011–2012.

c. Results from Calls to Poison Centers/Visits to Emergency Departments

Four studies exploring the prevalence of calls to poison centers or visits to an emergency department, as a consequence of human exposure to synthetic cannabinoids, were identified.

In a sample of calls received during 2011 at the Illinois Poison Center in the United States [50], the distribution of the calls between rural and urban areas was studied. The prevalence of synthetic cannabinoid exposure cases was 8.43 per 100,000 inhabitants in the rural areas, and 1.37 per 100,000 inhabitants in the large metropolitan areas.

In a study from the Texas Poison Centers, of calls received during the time period 2010–2011 [27], the prevalence of the exposure to synthetic cannabinoids was 4.1 per 100,000 inhabitants. A further examination of the same material [26] revealed that the exposure rates in the different areas varied from 2.79 to 7–14 exposures per 100,000, and that the prevalence was higher in the rural counties (mean 4.9) than in the urban counties (mean 4.02).

A study from the Drug Abuse Warning Network in the United States reported on visits to the emergency department involving synthetic cannabinoids in 2010 [65]. Among the emergency department visits linked to synthetic cannabinoids, 75% were made by patients aged 12–29. The rate per 100,000 inhabitants for patients aged 12–29 was 11.1, representing a total of 8,557 visits.

2. Prevalence of the Use of Synthetic Cathinones

a. Results from Questionnaires/Surveys

Eight papers on the prevalence of the use of synthetic cathinones, based on questionnaires or surveys, were identified. The first study to be published is from England in 2009 [79]. A cross-sectional anonymous online survey was posted on a website promoting dance club events, targeting the population associated with the dance music scene. From a total of 2,295 respondents, 41.3% reported having at least once used mephedrone, 10.8% reported having used methylone, and 1.9% reported having used MDPV.

In Australia in 2010, a cross-sectional survey explored the use of different emerging psychoactive substances among regular ecstasy users [10]. The prevalence for the use of mephedrone, at least once, among 693 responders, was 21%. The prevalence for the use of MDPV was 1%.

Another study from Australia, conducted in 2010 [44], was an online survey among same-sex–attracted men and women, collecting information on drug use, as a part of a larger study on sexuality and nightlife. The prevalence for the use of mephedrone, at least once, among 572 respondents, was 4%.

Another survey, in a similar population, was undertaken in England in 2010 [47]. The population consisted of customers from two gay-friendly night clubs in London. Eight percent of those approached by the interviewers rejected participation. Among the 308 respondents, 54% reported use of mephedrone at least once, and 27% had already consumed or planned on taking mephedrone on the night of the survey. Less than 2% had tried mephedrone one year previous to the study. A new survey, conducted by the same group [84], undertaken one year later, among 315 customers at the same gay-friendly night clubs in London, showed an increase in the prevalence of reported use on the night of the questioning, from 27% to 41%, and for the lifetime use, from 54% to 63.8%. Mephedrone was rated as the favorite drug by 20.4% of the respondents, followed by cocaine (14.9%).

A survey performed in 2010 collected data on mephedrone use from a population of college or university students in London, England [14]. At the time of the investigation, mephedrone was not a controlled substance in the United Kingdom. The survey was voluntary and anonymous. Among 1,006 respondents, 20.3% reported use at least once, and 4.4% reported daily use. The age group reporting the highest prevalence of daily use was the group aged 13–15.

Targeting the use in the general population, one study was based on declared drug use in the context of the British Crime Survey 2010–2011 [62]. This survey retrieves yearly information on drug prevalence from individuals aged 16–59, living in households in England and Wales, since 1996. The prevalence of the use of mephedrone, during the past year, was 4.1%. Among those aged 15–24, the prevalence was 4.4%, and the prevalence was 0.6% among those aged 25–59.

The last study presents data from 2012, and is a yearly survey conducted among adolescents in the United States [40]. The 2012 national sample included 45,449 students, attending 395 public and private schools, aged 13–18. The last year prevalence for the use of "bath salts" was 0.8%, 0.6%, and 1.3%, for the age segments 13–14, 15–16, and 17–18, respectively. The question of the use of "bath salts" was included for the first time in 2012.

b. Results from Analysis of Biological Material

Four studies, exploring the prevalence of the use of different synthetic cathinones, based on results from analysis in biological materials, were included in this review.

One study [51] recruited volunteers from social arenas outside the higher educational institutions, from a metropolitan area in England and a rural area in Wales in 2010. The aim of this study was to test a new questionnaire model, to be used on sensitive issues, and combining both questionnaire answers and biological measurements. The use of mephedrone was chosen as an example of a "sensitive issue". The questionnaire was answered by 318 subjects, with roughly 50% of the subjects collected from each location. Samples of hair from 153 of the participants were analyzed for mephedrone. Too short or chemically treated hair was excluded. Most of the hair samples (93%) were collected from the Wales rural area. Both the questionnaire and the hair lengths estimated the use of mephedrone in the last 3 months. The analysis of hair yielded an estimated prevalence of 3.9% for mephedrone use. Combining the testing of hair and questionnaire answers increased the prevalence to 5.7%.

A similar prevalence for the use of mephedrone (4%) was found when testing 325 hair samples from a population of drug users in Switzerland [57]. Only one of the samples tested positive for methylone. The samples were collected during 2009–2010, in the context of assessing driving ability in relation to drugs of abuse. Only hair samples positive for amphetamines or MDMA (methylenedioxymethamphetamine) were screened for synthetic cathinones, the results thus representing only that of a group of active drug users.

A higher prevalence was found with the analysis of 163 random urine samples collected from patients attending methadone maintenance programs in Ireland, in 2010 [46]. The prevalence for mephedrone use was 7.4%, and 1.2% for methylone use. Most of the samples were also positive for other drugs.

Between 2009 and 2010, 3,000 blood samples collected from drivers suspected of driving under the influence of drugs (DUID) were analyzed for MDPV (3,4-methylenedioxypyrovalerone) in Finland [43]. The screening was performed in selected samples, where the presence of MDPV was suspected, not necessarily representing the general DUID population. The prevalence of MDPV in the screened samples was 8.6%, representing 5.7% of all DUID cases where analysis for drugs other than alcohol was requested ($n = 4,570$). As a consequence, the prevalence of the use of MDPV in subjects suspected of drugged driving can be estimated to 5.7% or higher.

c. Results from Calls to Poison Centers

Two studies were identified exploring the prevalence of calls to poison centers, with regard to synthetic cathinones.

One study compared the exposures to "bath salts" in the US population with the UK population [63], during the time period 2009–2012. The mean exposure counts per month per million population served were similar in both countries, with 0.457 for the United States and 0.438 for the United Kingdom. A peak of 2.46 calls per month per million served occurred in the United Kingdom in March 2010, while in the United States, the peak of 1.64 calls per month per million served occurred in June 2011, more than a year later.

A study of the calls made to Texas Poison Centers, during 2010–2011 [25], reported the prevalence for questions regarding synthetic cathinones at between 5.2 and 69 per 100,000 inhabitants, distributed among the different geographical regions. Most of the calls (76%) were due to exposures, the rest were made for general information. The reported exposures increased during the first part of the time period examined, then declined after the products were banned in the state of Texas.

III. DISCUSSION

Synthetic cannabinoids and cathinones represent two-thirds of all new substances reported to the EMCDDA Early Warning System during the last few years, equating to the two largest groups of drugs in the emerging phenomenon of "legal highs" [20]. Synthetic cannabinoids constitute a group of drugs mimicking the effects of cannabis, while synthetic cathinones are analogs of cathinone, one of the psychoactive compounds that are naturally present in the khat plant (*Catha edulis*), with effects similar to drugs like cocaine and ecstasy. The pharmacology and toxicology of each individual synthetic compound is still largely unknown, although several deaths related to the use of both synthetic cannabinoids and cathinones have been reported.

The presented review summarizes studies exploring the market, the motives for use, and the prevalence of the use of these drugs.

A. Motives for Use and Modes of Consumption

Papers focusing on the subjective motives for use, the modes of consumption and the subjective effects after synthetic cannabinoid or cathinone intoxication are scarce [12]. The lack of in-depth qualitative studies, aimed at identifying these perspectives, can be partly explained by the only recent history of the recreational use of these psychoactive substances. Still, a small handful of papers serve as a basis for understanding why synthetic cannabinoids and cathinones are deemed attractive by users. In general, the perceived lack of long- or short-term harm, as well as good ratings from peers or on the Internet, seem to be the most important attractions [29,67]. Peer views mediated through the Internet is an example of the important role of the new digital technology in this ever-changing and dynamic market. The Internet constitutes a significant source of information on new psychoactive substances, and serves as a virtual space, where users can contribute with their own experiences regarding specific substances, creating a massive body of user-generated information related to new psychoactive substances. The positive experiences, mediated through the plethora of drug-related forums, seem to serve as a major motivator for the uninitiated. Other motivational factors, as cited by the users, are the drugs juridical status, the widespread user availability, the low price, as well as the lack of detection on standard drug tests [11,24,70,71,73,75].

The modes of consumption for synthetic cannabinoids and cathinones were in most cases identical with those of the drugs that they mimic. Synthetic cannabinoids are primarily smoked in the same way as cannabis [12,38,72], while synthetic cathinones are usually snorted [69,70,78]. The social arenas linked to the usage of these substances also exemplify the links to the drugs that they mimic. Synthetic cathinone use, and especially the use of mephedrone, is heavily linked to club-goers and the night-life scene [69,82], while the use of synthetic cannabinoids usually takes place at home, either alone or in small groups [72,75]. Mephedrone users considered the effects of the drug to best compare with those of MDMA, a dominating club stimulant drug [69], while the subjective effects of synthetic cannabinoids were reported most similar to those of cannabis [33]. The foregoing may explain the differences in the social settings where the use occurs. Even though positive effects were noted, several negative side effects that are unique and discernible from other drugs were reported.

B. Markets

The "cat-and-mouse" game played between the producers of the drugs and the drug lawmakers is reflected in the various aspects of production and trade of the synthetic cannabinoids and cathinones, and the market appears to change quite rapidly in response to attempts of regulation. The initiative, seen in many countries, to implement generic legislation and control (meaning that groups of drugs are placed under legal control, not only separately named substances) may work, even though profit-seeking drug suppliers will probably continue to search for new and clever ways of circumvention.

The Internet has made synthetic cannabinoids and cathinones available to almost everyone, and the accessibility has increased to an extent one would never think possible only a few decades ago. Even very young individuals can now order any product, using their laptop or mobile phone, and during any time of the day. Because the traded goods are sent by mail to the home address of the buyer, the traditional street dealers have, in many cases, been exchanged for the public mail system, implying that numerous transactions take place without the seller and buyer meeting in person. Consumers do not have to search for local dealers, and previous experience, or knowledge of the drug market and its participants, is no longer required. This widespread accessibility, through the Internet, is a new feature of recreational drug use, and can, according to general economic theory, increase sales and consumption of drugs.

Furthermore, the aggressive and widespread marketing made possible by application of the Internet, as well as the low price level of synthetic cannabinoid and cathinone substances, may also increase drug use. Economic literature confirms that drug consumption is price sensitive and that even addicts substantially change their pattern of use in response to changes in prices [9,32]. The low prices imply that there will be few economic arguments hindering young people from ingesting large quantities of the drugs. In summation: The easy accessibility, the aggressive marketing, the "almost legal" status, and the low price level of substances with intoxicating qualities, deemed "very good" by many users, suggest that substances like synthetic cannabinoids and cathinones have a great potential for widespread use and popularity.

C. Prevalence

In general, there is substantial heterogeneity to the estimates of prevalence. Part of this may be due to the methodological questions, but another part may reflect the different prevalence rates among the different geographical areas and populations. In spite of the methodological drawbacks, some conclusions may be cautiously drawn. Taken together, the results point toward higher prevalence of use for synthetic cathinones than for synthetic cannabinoids. In the general population, the prevalence of use of synthetic cathinones is reported to be around 4% compared to figures lower than 1% for synthetic cannabinoids. Among students, the prevalence varies between 1–20% for synthetic cathinones and 2–10% for synthetic cannabinoids. Among groups with high rates of drug use, the prevalence varies from 4% to more than 60% for synthetic cathinones and around 10% for synthetic cannabinoids.

The prevalence of synthetic cathinone use, and in particular, the use of mephedrone, is clearly higher than the use of synthetic cannabinoids in the United Kingdom, both among club-goers and in the general adult population. Especially among club-goers in London, it appears that mephedrone has largely replaced the use of MDMA, and partly the use of cocaine. A concomitant factor is that MDMA has been substituted for other, less attractive compounds (e.g., mCPP) [74], as the active ingredient in ecstasy, during the last few years. The use of mephedrone in the population of club-goers increased between 2010 and 2011, with mephedrone being reported as the "favorite" drug of choice, before cocaine, GHB, alcohol, and cannabis. This occurred despite the fact that mephedrone had been classified as an illegal substance during the time interval between these two surveys. Among the general population aged 16–24, the prevalence for the use of mephedrone is similar to that of cocaine, and the drug was ranked as the second most consumed recreational drug, after cannabis. The prevalence of the use of synthetic cannabinoids, however, is lower than most other drugs reported.

Data from the United States, regarding the prevalence of synthetic cathinones compared with synthetic cannabinoids, are not so clear-cut. Synthetic cathinones were introduced in the United States at a later point in time compared with that of Europe, and data on the prevalence of the use of synthetic cathinones in the United States is scarce. Apparently, the use of synthetic cathinones among college students is higher than that of many other drugs of abuse, commonly monitored among college students, such as cocaine, and the results have remained stable between 2010 and 2012. The prevalence of the use of synthetic cathinones is clearly higher than the prevalence of use of synthetic cannabinoids in the same population, in 2012, as reported by one survey. However, a study comparing calls to poison centers regarding the use of synthetic cathinones, between the United States and the United Kingdom, found similar rates; suggesting that the prevalence figures estimated for the use of synthetic cathinones in the United States from surveys may in fact

be underestimations. Supporting this possibility, calls to poison centers in Texas regarding exposure to synthetic cathinones show a higher prevalence than calls regarding synthetic cannabinoids, in the same region and in the same period of time.

Other US data concerning the prevalence of use of synthetic cannabinoids, collected from laboratories testing for metabolites in urine, are especially difficult to interpret. These studies report testing of specimens upon suspicion, and confirm that the substances are in use, but say little about the prevalence of use. Testing random specimens from doping controls has reported prevalence of use as high as 4.5%. This way of testing implies most likely the use of synthetic cannabinoids within the last week before testing, which seems high in comparison with previous figures for use, at least once, at around 8%, among college students. Many factors may play a role in contributing to these figures: Firstly, the estimated prevalence from voluntary surveys among college students may be too low due to a selection of respondents; secondly, the prevalence among doping-tested athletes may be particularly high due to the subjects' confidence in that the laboratory will not be able to detect these new compounds, contrary to that of "regular" cannabis or other more "classical" recreational drugs. The same may apply, to some extent, to the general population, where the use of synthetic cannabinoids and cathinones has been popular, in part, due to the fact that these drugs could be legally possessed. The sharp fall in calls to poison centers in Texas after the synthetic cathinones were made illegal may be an example that supports this point of view. On the other hand, the fall in calls to poison centers may rather be due to health personnel becoming more knowledgeable about these new substances, seeing that a comparatively large share of the calls to poison centers comes from health care facilities. Another finding, from the studies on the US poison centers, worth mentioning is the higher prevalence of calls regarding synthetic cathinones from rural areas, compared with that of metropolitan areas; usually, as is the case with other drugs, rural counties appear to have a lower utilization of poison centers than that of the larger urban areas. Findings from wastewater analysis in Norway support this result, with JWH-018 being more abundant in wastewater from smaller communities than from larger cities [56].

Users of synthetic cannabinoids or cathinones appear to be younger than users of other drugs, and there is also a tendency toward a lesser degree of concomitant use of other drugs, although the latter may be a mere covariance with the younger age. The staircase pattern of drug initiation, as first pointed out by Kandel [42], supports the finding of younger users of synthetic cannabinoids, than of other substances. Cannabis is usually one of the first illegal intoxicants to be tested by youngsters, followed at some point by stimulants and opioids. Due to synthetic cannabinoids mimicking the effect of cannabis, Spice and other synthetic cannabinoid products may appeal to the same young age group. Furthermore, with the mean age of initiating drug use other than cannabis being higher, it may explain why poison centers report less polydrug use among the users of synthetic cannabinoids, than what is observed among users of the more "traditional" drugs.

Shortcomings and Limitations of the Data

The current prevalence of synthetic cannabinoids and cathinones, in the general population, is, however, largely unknown. The included studies provide "snapshots" of the prevalence of the use of these drugs, in different geographical areas, at different times, and in different subgroups of the general population. The time aspect is especially relevant for drugs that have recently been introduced to the market and in those cases where the legal status of the drug has changed shortly before or after the study period. Consequently, the prevalence rates, as reported by the different cross-sectional surveys, have to be interpreted in the context of the availability of the drug on the market and the legal status of the drug. In a similar manner, the extensive heterogeneity in the prevalence rates across subgroups of the population has to be taken into account when assessing the results.

There are also some general methodological issues to bear in mind during interpretation. Selection bias is a well-known problem in data from population surveys. The samples may not represent the study population aimed for, if the selected subjects are hard to reach or if the subjects contacted decline to participate. If the contact information is of poor quality, or if drug users are more prone to deny participation than nonusers, then prevalence estimates of the investigated drug use will be biased. The presence of false negatives, or false positives, is another weakness of surveyed data. As drug use, in general, is a socially less accepted behavior, and the use of some of the synthetic cannabinoid or cathinone products is illegal, some drug users may underreport or renounce actual drug consumption. Others, however, may report drug experiences that they have not actually had. Recall bias may be yet another problem if the questions relate to drug use happening a long time ago, or if the drug users, for any other reason, are incapable of recapturing the actual consumption. Furthermore, the respondents may not be certain as to what drug or drugs they have consumed. This confounding factor is probably of greater importance for the new synthetic drugs, than for the more "classical" recreational drugs. In consequence, some users

may respond affirmatively to having used a particular new drug, even though this may not be the case, while others may have been unaware of their consumption.

Compared to population surveys, studies based on the analysis of biological material do provide unbiased answers, but have other drawbacks, such as limitations in the analytical repertoire, varying sensitivity of the different methods, and specific time windows for the different matrices. For example, a positive result detected in blood represents drug intake during the course of the last few hours or days, whereas results in urine may represent intake in the last few days or weeks, and a positive result in hair may represent several intakes during the course of many months. To what extent results from analyses of biological materials can be interpreted as useful prevalence indicators will further depend on the sampling procedures that have generated the testing. No studies have, so far, collected biological material from the general population, the data included in this study representing different subgroups, as for example athletes, individuals suspected of drugged driving, or individuals with other drug-related behaviors.

Data from poison centers differs greatly from both population surveys and biological samples, as it reflects mainly the drugs' toxicity, or the users' concerns regarding health consequences of the drugs in use, and not the mere use itself. This type of data is still useful for revealing emerging trends.

CONCLUSIONS

Our results show a clear need for more research on prevalence in the different groups of users and geographical regions, as well as a need for exploring eventual cohort effects in relation to the age of users of synthetic cannabinoids and cathinones compared with users of other substances, by applying longitudinal studies.

From a public health perspective, the emergence and the increasing use of new psychoactive substances are worrying. There are substantial indications of serious harm associated with the use of synthetic cannabinoids and cathinones. The risks are not yet fully known, however, as research on the harmful effects, in particular on long-term use, is still in a premature state. The lack of clinical trials evaluating the safety of human consumption is of serious concern, as are the frequently misleading content declarations. If the lack of safety information leads to erroneous assumptions of synthetic cannabinoids and cathinones being safe for consumption, uninformed users may risk serious adverse effects. Health authorities may aim at confining use through well-known means of prevention, treatment, and control, but there are, in this case, particular challenges, especially given the widespread availability and international market for these new drugs. More research is required, and continuously updated and correct information must reach potential consumers. It seems important to promote human studies, exploring the toxicity profile of these drugs, by making available high-quality laboratory testing to the clinicians evaluating the potential cases of suspected poisoning, in the emergency rooms. Some projects in the field are already going on, for example the STRIDA project in Sweden [34]. To reach potential consumers with the information required for rational decision-making, perhaps user forums, which are currently the main source of information for many people, should be employed by health professionals to provide objective and updated facts on the various aspects of these new substances.

ACKNOWLEDGMENTS

We want to thank Wenche Jacobsen and Johanne Longva for help with the bibliographic searches and Stine Havig for language editing.

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ABOUT THE AUTHORS

A. L. Bretteville-Jensen; S. S. Tuv; O. R. Bilgrei; B. Fjeld; L. Bachs

Anne Line Bretteville-Jensen received her B.S. and M.S. degrees from the University of Oslo, Norway, and a Ph.D. degree in economics from the University of Bergen, Norway. She is currently a research director at the Norwegian Institute for Alcohol and Drug Research, Oslo, and has worked for the institute for more than 20 years.

Dr. Bretteville-Jensen has published a number of papers in health economics, epidemiology, and drug policy. She has held research positions at the Department of Economics at the University of Bergen and the Institute of Health Economics and Health Managements at the University of Oslo and has been a visiting scholar at the Centre for Health Economics, University of York (England), and the Department of Economics, University of Melbourne (Australia).

Silja Skogstad Tuv has an M.D. degree from the University of Tromsø, Norway (2004). She is currently a resident doctor at the Department of Toxicological and Pharmacological Assessment at the Division of Forensic Medicine and Drug Abuse, Norwegian Institute of Public Health.

Dr. Tuv has a particular interest in the pharmacology and toxicology of new drugs, and she has three years of professional experience in forensic toxicology.

Bente Fjeld received her M.D. degree from the University of Oslo (Oslo, Norway). She is currently a resident doctor at the Department of Toxicological and Pharmacological Assessment at the Division of Forensic Medicine and Drug Abuse, Norwegian Institute of Public Health.

Dr. Fjeld has three years of professional experience in Forensic Toxicology. She has been active in studies focusing on drug-impaired driving and drug stability.

Ola Røed Bilgrei holds a master's degree in sociology from the University of Oslo, Norway. He joined the Norwegian Institute for Alcohol and Drug Research in 2011, where he is currently working as an advisor. Mr. Bilgrei's work mainly consists of qualitative research with people using new psychoactive substances, as well as studies on the Norwegian tobacco policy, smoking-related norms, and stigmatization.

Liliana Bachs received her M.D. degree from the Autonomous University of Barcelona (Barcelona, Spain) and a Ph.D. degree in pharmacology from the University of Oslo (Oslo, Norway). She is currently Department Director at the Department of Toxicological and Pharmacological Assessment at the Division of Forensic Medicine and Drug Abuse, Norwegian Institute of Public Health.

Dr. Bachs has 15 years of professional experience in forensic toxicology. Her professional activities have focused on drugs and driving, opiate pharmacology, and behavioral pharmacology of drugs of abuse. She is a certified specialist in clinical pharmacology by the Norwegian Medical Association and has wide experience as an expert witness in the field of forensic toxicology.