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REVIEW ARTICLE

# Acute, chronic, and *post-mortem* toxicity: a review focused on three different classes of new psychoactive substances

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## Abstract

**Purpose** New psychoactive substances (NPS) are not controlled under the Single Convention on Narcotic Drugs of 1961 or the 1971 Convention, but they may pose a public health threat. Knowledge of the main properties and toxicological effects of these substances is lacking. According to the current Drugs Law (Law n. 11.343/2006), the Brazilian Surveillance Agency issues directives for forbidden substances in Brazil, and structural classes of synthetic cannabinoids, cathinones, and phenylethylamines are considered illicit drugs. Considering that data on these controlled substances are scattered, the main objective of this work was to collect and organize data to generate relevant information on the toxicological properties of NPS.

**Methods** We carried out a literature review collecting information on the acute, chronic, and post-mortem toxicity of these classes of NSP. We searched info in five scientific databases considering works from 2017 to 2021 and performed a statistical evaluation of the data.

**Results** Results have shown a general lack of studies in this field given that many NPS have not had their toxicity evaluated. We observed a significant difference in the volume of data concerning acute and chronic/post-mortem toxicity. Moreover, studies on the adverse effects of polydrug use are scarce.

**Conclusions** More in-depth information about the main threats involving NPS use are needed**.**

**Keywords** Toxicology · New psychoactive substances · Amphetamine-type stimulants · Synthetic cannabinoids · Phenylethylamine

## Abbreviations

| | |
|---|---|
| AAFS | American Academy of Forensic Sciences |
| ANVISA | Agência Nacional de Vigilância Sanitária |
| $CB_1$ | Cannabinoid-1 receptor |
| $CB_2$ | Cannabinoid-2 receptor |
| CBD | Cannabidiol |
| DAT | Dopamine transporter |
| EMCDDA | European Monitoring Centre for Drugs and Drug Addiction |
| INCB | International Narcotics Control Board |
| $LD_{50}$ | Lethal Dose to 50% of a population |
| LSD | Lysergic acid diethylamide |
| MDA | Methylenedioxyamphetamine |
| MDPV | Methylenedioxypyrovalerone |
| NET | Norepinephrine transporter |
| NPS | New psychoactive substances |
| SCs | Synthetic cannabinoids |
| SERT | Serotonin transporter |
| SOFT | Society of Forensic Toxicologists |
| SWGTOX | Scientific Working Group on Forensic Toxicology |
| THC | Tetrahydrocannabinol |
| UKIAFT | United Kingdom and Ireland Association of Forensic Toxicologists |
| UNO | United Nations Organization |
| UNODC | United Nations Office on Drugs and Crime |
| WHO | World Health Organization |

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## Introduction

Compounds known as new psychoactive substances (NPS) were detected around the 2010s. According to the United Nations Office on Drugs and Crime (UNODC), NPS are "substances of abuse either in a pure form or a preparation that are not controlled under the Single Convention on Narcotic Drugs of 1961 or the 1971 Convention, but which may pose a public health threat. In this context, the term "new" does not necessarily refer to new inventions but to substances that have recently become available" [1].

Until now, over 950 NPS have been identified in about 120 countries [2, 3]. The fast emergence of these new drugs has created an unprecedented public health concern of unknown consequences because knowledge about their main chemical properties and toxicological effects is lacking.

Toxicokinetics and toxicodynamics describe the concepts and properties that are used to understand the toxic effects exerted by xenobiotics on the body [4]. Toxicokinetics concerns the processes that take place from the moment that xenobiotics are absorbed by the body until they are excreted. Whereas toxicokinetics studies the movement of these substances in the body, toxicodynamics assesses the targets, effects, and mechanisms that happen in case of poisoning [5]. Besides these parameters, the time of exposure to these substances is crucial.

Regarding toxicity, xenobiotics may exert acute and chronic effects. Acute intoxication is observed when a single exposure event occurs, or several exposure events take place within a brief period. In contrast, chronic intoxication happens when exposure lasts a long period, such as months or even years. Several substances do not cause negative effects if the exposure period is short. However, they can promote slow but aggravating effects as the contact period increases [6].

In the forensic context, guidelines related to the establishment of practice standards for validating toxicology methods were published in 2013. The guidelines were designed by the Scientific Working Group on Forensic Toxicology (SWGTOX), and the methods were divided into four categories of analyses: immunoassay-based screening, screening (all others), qualitative confirmation/identification, and quantitative analysis [7]. In the United States, toxicological analyses published by the Committee of the Society of Forensic Toxicologists (SOFT) along with the Toxicology Section of the American Academy of Forensic Sciences (AAFS) have been advocated [8]. The document contains general recommendations for analytical procedures based on screening tests and confirmatory tests. In addition, the United Kingdom has issued general recommendations on the analytical procedures for presumptive screening tests and chromatographic tests, published by the United Kingdom and Ireland Association of Forensic Toxicologists (UKIAFT) [9].

Toxicological analysis laboratories worldwide play a key role in the so-called Early Warning System. This system is defined as a multidisciplinary and interinstitutional network that allows information to be exchanged between the main agents directly and indirectly involved in the field of drugs. This system assumes that countries have different structural characteristics. Among other actions, the main functions of a toxicological analysis laboratory in an Early Warning System include (i) detecting new and known substances and the combinations between them, which can all pose a potential threat; (ii) improving NPS analytical characterization; and (iii) providing intelligence information about the changes in drug market trends [3].

Here, we have conducted a focused review of the toxicity issues of three NPS groups, to collect information about the acute, chronic, and *post-mortem* conditions from scientific databases, aiming to provide the reader with the main toxicity features of these NPS.

## Background

The first step of a toxicokinetic study is to understand how organisms absorb chemical substances. Basically, there is dermal, oral, and respiratory absorption [10]. Skin is a large organ composed of several layers and serves as a barrier between the environment and the interior of an organism. Chemical substances cross the external skin layer by passive means or small fissures. After overcoming the external barrier, the chemical substance reaches the internal skin layers, which are in direct contact with the blood and lymphatic vessels. When absorbed into the bloodstream, chemical substances are distributed throughout the organism [11]. Oral absorption is a very relevant way for chemical substances to enter an organism. Their ingestion may be accidental, through contaminated water or food, or intentional, in cases of suicide or drug abuse. Then, the chemical substance is absorbed in either the stomach or the intestine and is distributed through the body via blood and lymphatic circulation [12]. The respiratory system is another relevant absorption means through which chemical substances may enter an organism. First, gases in the atmosphere as well as volatile compounds are aspired. Then, depending on size, they stop in different parts of the respiratory system. Smaller particles reach the pulmonary alveoli, where they are absorbed into the bloodstream, or they can be removed by different means [13]. Removed particles and larger particles are taken to the mouth, where they are either eliminated from the organism or reabsorbed via the gastrointestinal system.

Numerous factors influence the absorption of a toxic substance, including its oil/water partition coefficient, pH, $pK_a$, $pK_b$, and particle size [4]. After being absorbed, toxic substances are transported in the blood and lymphatic streams throughout the compartments of an organism. Because these substances are distributed via the bloodstream, more irrigated organs and tissues establish a chemical equilibrium faster, thereby accumulating more toxic substances at the beginning of an intoxication. Some of the organs with these characteristics are the brain, heart, and liver. As for the less irrigated sites, they take longer to establish a chemical equilibrium with the bloodstream, so they have smaller concentrations of toxic substances in the early intoxication stages. The bones, fatty tissues, nails, and teeth are some of the less irrigated organs and tissues [14]. Larger concentrations of toxic substances cause more harmful effects, so stronger toxic effects are expected in regions with more blood vessels [5]. However, this scenario may change: the absorbed toxic substances may migrate and accumulate in less irrigated places as time passes. Given that these substances have a stronger affinity for less irrigated tissues, as time elapses, they accumulate therein. Just like there are factors that interfere in toxic substance absorption, there are factors that influence their distribution, including oil/water partition coefficient, pH, $pK_a$, $pK_b$, biological barriers (which can be any membrane present in the organism), and complexation with free proteins in the bloodstream, among other factors [15, 16].

Following the distribution, toxic substances are biotransformed and excreted. Biotransformation reactions are often accompanied by excretion. Biotransformation primarily aims to modify the structures of molecules, to make them more water-soluble and to facilitate their excretion [14]. Renal excretion happens when the kidneys filter toxic substances and eliminate them with urine. Most hydrophilic substances are eliminated via this mechanism because they are soluble in water and can be filtered from the organism with water. Gastrointestinal elimination is responsible for removing hydrophobic toxic substances that are not absorbed when ingested. Besides hydrophobic substances, gastrointestinal elimination removes hydrophobic substances that cannot be filtered by the kidneys, that are dissolved in biliary solutions, and that passively migrate through the stomach and intestine walls to the feces [17, 18]. Lastly, there is respiratory excretion, which eliminates gaseous and volatile compounds. These compounds are eliminated in exhaled air when they are not absorbed in the lungs or when they are excreted by gaseous transferences taking place in the alveoli [10]. Besides these excretion routes, there are some alternative routes, such as tears, sweat, and saliva, to eliminate chemical substances from an organism [4].

While toxicokinetics studies the movement of xenobiotics in organisms, toxicodynamics studies the targets, effects, and mechanisms that take place during intoxication. These studies provide important data for (i) determining whether substances can cause harmful effects and which populations can be affected, (ii) establishing pre-emptive procedures and mitigation measures in case of accidents, and (iii) developing less toxic and more selective substances that would harm to a lesser extent populations other than the targeted ones [19].

When we discuss toxicological action mechanisms, we seek to understand the process through which the toxic substance reaches its target organ or tissue and remains there long enough to elicit any significant harmful effect [20]. Concerning the toxicity of chemical substances, acute and chronic effects exist. Acute intoxication occurs when a single exposure event or several exposure events happen within a brief period [21]. The harmful effects caused by acute intoxication manifest in the organism within a maximum of 2 weeks. The lethal dose to 50% ($LD_{50}$) of a population, obtained for at least three animal species, is a toxicological parameter that is commonly used to evaluate acute toxicology [22, 23]. Chronic intoxication happens when the exposure event lasts for a long period, such as months or even years. Various chemical substances do not promote any adverse effects if the contact period is short. Nevertheless, they can cause slow but aggravating effects as the contact period gets extended [4].

Numerous chemical substances can be toxic to many organisms, so properties such as molecular structure, biochemical behavior, and pharmacological behavior, among others, are used to classify them. Some of these substances act on specific organs and tissues, while others act indiscriminately, targeting whatever organ or tissue they meet. Action selectivity happens due to physiological and biochemical differences among organisms [24]. For example, bacteria are affected by antibiotics, while animals are not harmed by them because their cell membranes have a different composition.

To establish therapeutic and preemptive measures, it is necessary to understand how the toxic substances act and what their targets in the organisms are. Xenobiotics often exert harmful effects by interacting with biochemical receptors. These interactions interfere in membrane function, inhibiting oxidative phosphorylation, forming chemical complexes with enzymes, proteins, and nucleic acids, and disturbing calcium homeostasis [25–27]. Identifying through which of these mechanisms a toxic substance acts is important given that harmful effects can be avoided by anticipating symptoms and concocting antidotes.

Toxic effects occur when xenobiotics disrupt physiological and biochemical functions in organs and tissues [28]. If the intoxication effects are extensive enough, cell death induced by them may severely damage organs and tissues or might not cause any significant harm. Just as in

toxicokinetics, toxicodynamic studies consider that the higher the concentration of a toxic substance in the organism, the greater its toxic effect [29]. The severity of the harmful effects will also vary according to the affected organ or tissue; for example, if a vital organ is afflicted, the intoxication effects will likely be more significant. To analyze the damage extent, the organ regenerative capacity must also be considered—if an organ with high regenerative capacity is affected, the toxic effect will probably be less severe [4].

Toxicokinetics and toxicodynamics are essential for toxicological studies because they help to understand how xenobiotics behave when in contact with different organisms. Together, toxicokinetics and toxicodynamics provide the knowledge needed to understand the toxic properties of different substances and to develop effective antidotes and preemptive measures to avoid or to reduce the damage caused by intoxication.

## Methods

According to the current Drug Law (Law n. 11.343/2006), the Brazilian National Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA) is the institution that decides which chemical substances are forbidden in Brazil. ANVISA's guidelines include the structural class of synthetic cannabinoids, cathinones, and phenylethylamines. Prohibition of these substances has motivated us to organize this review given that toxicological information about these three classes of substances and their homologous structures is lacking.

During this research, we focused on a bibliographic review during which we aimed to collect information about NSP toxicity. This type of review aims to identify and fill gaps regarding a particular issue. Thus, the main reason for carrying out research based on bibliographic reviews is the possibility of integrating and relating knowledge from different scientific areas that would be scattered in the literature [30].

We surveyed the bibliographic platforms Google Scholar, SCOPUS, PubMed, and Dimensions, as well as the complete Web of Science collection, which includes seven different databases, namely Web of Science Core Collection, Data Citations Index, Derwent Innovations Index, KCl-Korean Journals Database, Russian Science Citation Index, SciELO Citation Index, and Zoological Record [31]. Because the surveyed topic is comprehensive and rich in different perspectives, we decided to define descriptors to guide our research. We used the terms "toxicity", "acute", "chronic", "*post-mortem*", "*postmortem*", and their combinations by employing the Boolean operator "AND" [32]. In addition to this descriptor, we use the asterisk (*) at the end of the name of each substance [31]. This procedure allowed us to include both singular and plural terms, making the search more powerful.

The inclusion criteria were (a) articles in any language and (b) articles published between 2017 and 2021. This time window used whole years for the research and considered the most recent articles on the proposed topic.

The exclusion criteria were (a) articles that did not belong to the focus of the review, (b) materials that did not deal with the evaluated substances, (c) articles that did not provide input to the discussions, and (d) articles that did not discuss toxicology.

After we evaluated the articles, we analyzed them for their abstracts and keywords. From this reading, if the materials fit the research objective, we read them in full for inclusion in the review. However, even though these articles did not present the basic elements of the subject, we analyzed them to avoid exclusion problems. Thus, to analyze the results, we used descriptive analysis to integrate this information.

Figure 1 systematically gathers the articles that respected the eligibility criteria, to fall within the scope of this research.

## Results

### Amphetamines and cathinones

The various structural possibilities of amphetamines and cathinones pose a challenge to toxicological analysts that seek to understand how these substances act within a short time [33], as reflected in the articles published in indexed journals. We analyzed different indexing platforms, which all indicated that there have been more articles on cathinone toxicity than on amphetamine toxicity over the past 5 years (Fig. 2). We verified that the platform Google Scholar had

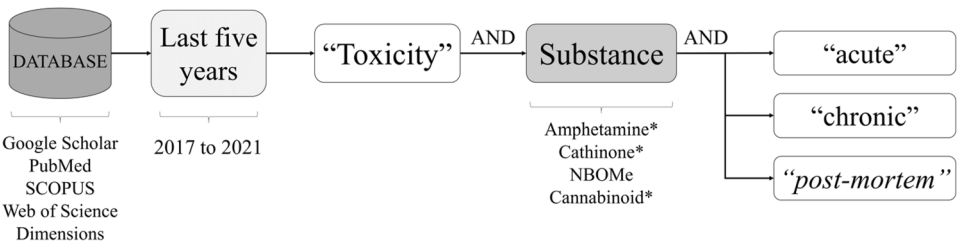


**Fig. 1** Simplified flowchart of the methodology applied herein to retrieve articles published from 2017 to 2021

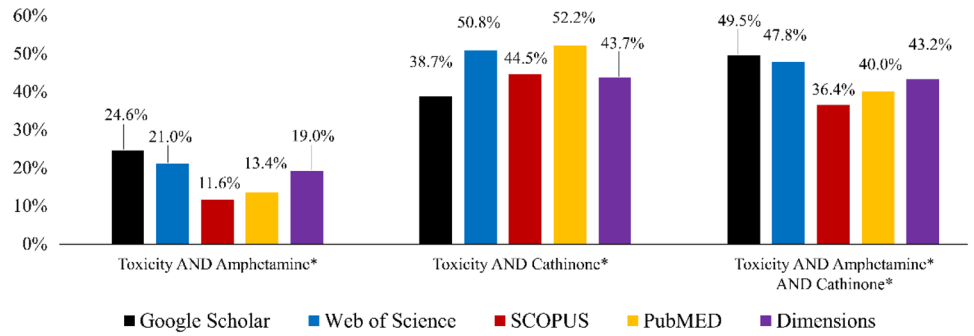


**Fig. 2** Number of indexed studies about amphetamine and cathinone toxicity published in the last 5 years retrieved from the platforms PubMED (yellow), Web of Science (blue), Google Scholar (black), SCOPUS (red) and Dimensions (purple) s for the evaluated descriptors

the lowest percentage of indexed studies about cathinone toxicity over the last 5 years compared to all the studies about this topic indexed on the platform to date: 1911 out of 54,690 (38.7%) studies. As for amphetamine toxicity, 303 out of the 2612 (11.6%) studies indexed on the platform SCOPUS to date were published in the last 5 years. The platform that had the highest percentage of indexed studies about cathinone toxicity in the last 5 years was PubMed; more specifically, this platform had 52.2% (133 of 255) of all its indexed studies about cathinone toxicity published in this period. In contrast, only 13.4% (345 of 2573) of the indexed studies about amphetamine toxicity were published in the past 5 years. These data demonstrate the interest in understanding the action of these substances in the body and the urgency to fill the information gap of the first decade of the 2000s.

Figure 2 shows that data regarding amphetamines were published mainly before the period analyzed herein, indicating that these substances have been studied for many years not only for recreational purposes but also for therapeutic purposes. Regarding cathinones, the importance of this class increased with the appearance of NPS in the early 2010s.

To assess the characteristics of each platform using the evaluated descriptors, we calculated the linear coefficient correlation between the volume of indexed articles over time. The results are listed in Table 1, and the arrows indicate the trends.

Table 1 shows a positive trend, i.e., constant indexing of articles on the platforms Google Scholar and Dimensions for all the descriptors related to amphetamines and cathinones. For the joint descriptors "Toxicity AND amphetamine*" the coefficient of correlation was high (> 0.9), suggesting that the volume of indexed articles was homogeneous and proportional over the years, indicating constant activity. Additionally, on the basis of the number of published articles, research into amphetamine toxicity increased [34]. However, the platform Google Scholar underestimated data because it had an unstable way of accurately reporting data [31]. The other descriptors indicated rising trends in research [34]. The platform PubMED showed that the number of published studies decreased over the years. We did not find any trending standards for the platform SCOPUS. In the case of the platform Web of Science, correlation was positive only for the descriptors "Toxicity AND amphetamine*".

When we evaluated the descriptors "Toxicity AND amphetamine*", 2021 was the year when the largest number of studies was indexed by the platforms Google Scholar, Dimensions, and SCOPUS platforms. As for the platforms Web of Science and PubMed, 2020 and 2017 were the years with the largest number of indexed studies, respectively. These data help to understand the relationship between the descriptor and the evaluated bibliographic platforms more precisely. In addition to these articles, some review and/or update articles published before the evaluated period may be a source for other researchers in the area [35–42]. Data and Graphics are shown in the Supplementary Material (Tables S1–S5 and Figures S1–S4).

**Table 1** Linear coefficient of the correlation between data obtained for amphetamines and cathinones along time

| Correlation ($R^2$) | Toxicity AND amphetamine* | | Toxicity AND cathinone* | | Toxicity AND amphetamine* AND cathinone* | |
|---|---|---|---|---|---|---|
| Google Scholar | 0.9893 | ↑ | 0.6941 | ↑ | 0.5346 | ↑ |
| Web of Science | 0.7449 | ↑ | 0.0023 | → | 0.0851 | ↑ |
| SCOPUS | 0.2237 | → | 0.1008 | → | 0.5000 | ↑ |
| PubMED | 0.7517 | ↓ | 0.4808 | ↓ | 0.6364 | ↓ |
| Dimensions | 0.9781 | ↑ | 0.4440 | ↑ | 0.5281 | ↑ |

↑ increase with years; → flat in the analyzed period; and ↓ decrease with years [34]

## Structure and international restrictions

Amphetamines and cathinones are sympathomimetic derivatives of phenylethylamine [43]. This group of molecules acts on the central nervous system, and their molecules are intended to mimic the effects of the hormones adrenaline and noradrenaline, which are endogenous molecules [44, 45]. Among these derivatives, there are natural and synthetic ones. In the former group, ephedrine and pseudoephedrine stand out. The latter group can be further divided into two other groups—classic synthetics and new compounds. Classic synthetics are represented by methylenedioxyamphetamine (MDA) and methamphetamine. The second subgroup includes mephedrone, methylone, and methylenedioxypyrovalerone (MDPV) [46].

Amphetamines and cathinones have gained global prominence from the first decade of the 2000s onwards. When they appeared in the recreational drug market, they were sold as "bath salts", "fertilizers", "plant food", or "research chemicals". On all of them, there was mention of "not being suitable for human consumption" to evade criminal sanctions [47]. However, despite these different names and the indication that consumption was not appropriate, some factors contributed to their increased consumption, including the association of recreational effects with the effects of classic substances, the greater availability of varieties at more affordable prices, and a false sense that they were safer for consumption and legally accepted [48].

Given the variety of amphetamines and cathinones that have emerged in the recreational drug market and the false sense of legality, several countries have established regulations to curb the increase in these substances. The United Nations Convention on Psychotropic Substances of 1971, which is constantly updated, gives an international indication of this control [49]. The signatories to this Convention, such as the United Kingdom (UK *Misuse of Drugs Act 1971—Class B),* Brazil (ANVISA's Ordinance n. 344/1998), and the United States (Schedule *I in the USA Controlled Substances Act*), have incorporated these indications into their lists [46]. Restrictions may be specified in terms of the substance, or they may be generic and refer to the basic structure.

Amphetamines and cathinones share a standard basic structure, and changes can occur at four different positions: (i) aromatic ring ($R_1$), (ii) alkyl chain ($R_2$), and (iii and iv) amine group ($R_3$ and $R_4$). Furthermore, a structural feature of all cathinones, which distinguishes them from amphetamines, is the presence of the ketone group at the β position of the side chain [50] (Fig. 3).

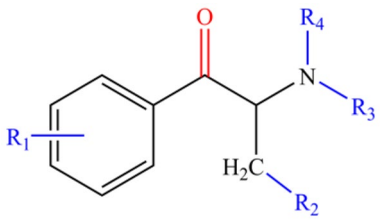


**Fig. 3** Basic structure of amphetamines and cathinones. The substituents are in the respective positions in blue color, and the ketone group bond at the β position of the side chain is in red

## Forms of consumption

As much as research into amphetamines and cathinones has increased significantly in recent years, their structures are not new to the therapeutic and pharmaceutical market. Amphetamine has been known since 1886 [51]; mephedrone was first synthesized in 1929; MDPV was first synthesized in the 1960s [52]; and other cathinones and amphetamines have been designed more recently to circumvent world recommendations. However, for a false legal character to exist, the way these substances are made available has not changed, with the most common marketed forms being tablets, crystalline or colored powders, and, less commonly, capsules [53].

Amphetamines and cathinones share physical characteristics that are known mainly from internet forums or sales sites [54]. Though not explicitly mentioned on these forum and sites, there have been reports of product tampering that could result in more serious risks to consumers than the substance of interest [55]. In addition, these tablets are commonly used in combination with alcohol, ketamine, cannabis (natural or synthetic), and prescription drugs for psychiatric illnesses [52]. All these factors, plus the absence of assertive information about these substances and the scarcity of studies on their action in the human organism, constitute a problem whose real social dimension and health impact are unknown.

## Pharmacological aspects and toxicity

**Pharmacokinetics** Co-ingestion with other substances makes the symptoms caused by amphetamine and cathinone consumption more complex and a public health challenge [52]. These substances can be consumed in different ways, mainly by oral ingestion and nasal insufflation. Less common ways of consumption include subcutaneous, rectal, and eye insertions in aqueous suspension. The doses normally depend on how the substances are consumed and range from a few milligrams to grams. Moreover, in a single session, multiple uses can occur by various means [56]. Depending on the chemical structure of the substance, it will be bet-

ter dissolved or have better permeability in the membranes. For instance, amphetamines are normally more soluble in lipids than cathinones, so the former can permeate biological membranes more easily [57]. On the other hand, cathinones are more water-soluble, which allows for their more effective dissolution. The combination of these and other properties accounts for dose variations among the substances, and indications for users can be from 1 to 125 mg of mephedrone by nasal insufflation and reach 50–799 mg of *N*-ethylpentylone in tablets. The wide diversity of amphetamine- and cathinone-derived substances creates uncertainties regarding their purity, increasing the probability of unwanted effects or even overdose [58].

In general, P450 mediates amphetamine and cathinone metabolism. Depending on the structure of the substance, a specific isoform will mediate its metabolism. For example, CYP2D6 metabolizes mephedrone, while CYP2C19, CYP2D6, or CYP1A2 metabolize pentedrone. Furthermore, metabolism is stereoselective, as in the case of cathinone. CYP2D6 metabolizes S-(-)-cathinone to (1R,2S)-(-)-norephedrine and R-(+)-cathinone to (1R,2R)-(-)-norpseudoephedrine [53] (Fig. 4). In this way, these biotransformations generate metabolites that are biologically active in the body, which is the case when MDMA is converted to MDA. This stereoselective metabolism is expected to occur for other amphetamines and cathinones, but further research is needed. Phase I processes include *N*-demethylation, hydroxylation, oxidation, and *O*-reduction, whilst Phase II processes include glucuronidation and succinylation. Nevertheless, these steps are not a rule—for the synthetic cathinones MDPV and MDPPP, glucuronidation and/or sulfonation occur in Phase I in animal models [48]. Finally, these metabolites are excreted mainly through urine, but they can be eliminated by alternative ways such as sweat [59], hair, and vitreous humor [60].

**Pharmacodynamics** On average, the effects of amphetamines and cathinones start 20–60 min after they are ingested. Because amphetamines and cathinones share a homologous structure, they act similarly on the central nervous system [53] by increasing the synaptic concentrations of endogenous amines (dopamine, serotonin, and norepinephrine) [61]. This response normally occurs by two sequential mechanisms. The first is the inhibition of monoamine uptake transporters (DAT, SERT, and NET), which decreases synapse neurotransmitters. In the second mechanism, this inhibition and the increase in vesicular pH cause intracellular neurotransmitters to be released [62].

Neurotransmitters represent established targets for many pharmacological agents (including psychostimulants, antidepressants, and neurotoxins) that affect brain function [63]. As for other neurotransmitters such as AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), the cannabinoid receptors $CB_1$ and $CB_2$, and $GABA_A$ (γ-aminobutyric acid type A), they have not been reported yet [58, 64].

In the case of transporters that have an affinity for amphetamines and cathinones and are affected by them, the greatest difference between amphetamines and cathinones lies in how long the effect lasts. Cathinones have less intense effects than amphetamines because the former are less stable in the biological cavity and are inactivated early [65]. Therefore, stimulation of different monoamine systems results in distinct clinical and toxicological effects. For example, substances that stimulate the dopaminergic system the most cause psychostimulant effects and reinforcing properties (high potential for abuse and addiction), whereas substances that stimulate the noradrenergic system the most have more cardiac and psychostimulant effects [66]. Finally, substances that increase serotonergic stimulation commonly generate hyperthermia, paranoia, and hallucinations [67]. Practically speaking, these effects can increase dopamine and serotonin concentrations in relation to endogenous ligands in the synaptic cleft. Amphetamine increases the dopamine and serotonin concentrations by 412 and 165%, respectively, and mephedrone increases the dopamine and serotonin concentrations by 496 and 941%, respectively [52].

Apart from the classification of these substances according to their action on monoamine systems, there is also the classification according to their potency of inhibition or to their ability to act as a substrate for these transporters. In

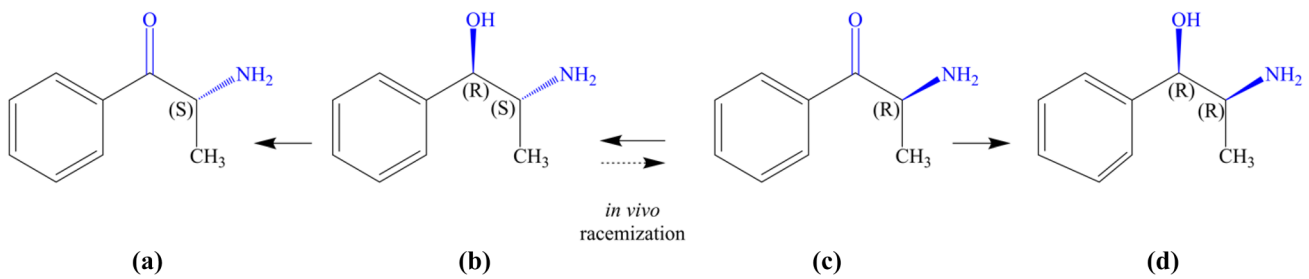


**Fig. 4** Stereoselective cathinone metabolism by CYP2D6; the groups responsible for chirality are highlighted in blue. The reactants and products of this process are **a** S-(-)-cathinone, **b** (1R,2S)-(-)-norephedrine, **c** R-(+)-cathinone, and **d** (1R, 2R)-(-)-norpseudoephedrine [53]

general, there are substances that will "block" the reuptake activity or will act as "substrate" to increase monoamine release [68, 69]. The modulation of these effects and the affinity for specific transporters is intrinsically linked to the chemical structure of the substance given that substitutions in the structure can potentiate or reduce the effects on the body [70]. This observation has been made for amphetamines with and without substituents at the "para" position of the aromatic ring. The modified structures had their potency to inhibit NET and DAT reduced compared to the corresponding non-para-substituted amphetamines [69, 71].

Although this series of factors and complex processes are different for each amphetamine and cathinone structure, consumers seek the psychoactive effects of a positive response, which include improved mood, self-confidence, reduced sleepiness, and establishment of a state of euphoria [70, 72]. However, amphetamines and synthetic cathinones can exert several adverse or even toxic effects on the human body. Among these effects, the most reported have been cardiovascular symptoms (tachycardia, increased blood pressure, palpitations, and chest pain) [66, 73], neurological symptoms (insomnia, headaches, seizures, visual disturbances, and paresthesia) [62], and other symptoms like skeletal muscle breakdown (rhabdomyolysis), bowel problems [74], and kidney damage. In more severe cases, disseminated intravascular coagulation (DIC) and multiple organ failure leading to death have been reported [75].

**Acute toxicity** Acute amphetamine and cathinone toxicity occur due to an excessive increase in extracellular monoamines (dopamine, serotonin, and noradrenaline), causing three physiological alterations: hyponatremia, hyperthermia, and oxidative stress [51, 72, 76].

Each physiological response occurs to a greater or lesser degree according to the structure of the amphetamine or cathinone derivative. Hyponatremia is caused by the increased concentrations of antidiuretic hormones elicited by these substances. The liver begins to reabsorb fluids excessively, leading to the alteration [77]. In the case of hyperthermia, the great stimulus of activity in the central nervous system increases the body temperature [78]. Finally, oxidative stress is due to reactive nitrogen and oxygen species being formed [73]. Both species affect the nervous system, from the central nervous system to the nerve terminals and peripheral organs.

These alterations have been studied with pure substances in animal models other than humans. However, actual consumption is markedly different because there is concomitant use of other stimulants such as cocaine, MDMA, other amphetamines, and cathinones [43, 77, 79]. Some emerging evidence has indicated that synthetic cathinones have increased toxicity [74, 80] or even increased fatality rate [81] under these circumstances.

In addition to the possibility of mixing, when an overdose of amphetamines or cathinones occurs, the first acute toxic effect happens in the central nervous system, as mentioned. In a second moment or even in parallel, the cardiovascular system (anginal pain, headache, palpitations, and arrhythmias, among other symptoms) [66, 73] and the gastrointestinal system (dry mouth, diarrhea, and nausea, among other physiological responses) are affected [74].

The effects related to acute amphetamine and cathinone toxicity have been the subject of numerous studies (Fig. 5). The articles on acute amphetamine and cathinone toxicity indexed on the platforms vary. To get an idea of the recent interest in this topic, of all the articles published to date on the platform Google Scholar about acute amphetamine and cathinone toxicity, 73.2% (9840 out of 13,440) and 70.6% (1349 of 1911) were published in the last 5 years, respectively. For the other indexing platforms, the results were different. On the platform Web of Science, 24.7% (57 of 231) and 26.7% (35 of 131) of all the articles published to date about acute amphetamine and cathinone toxicity were published in the last 5 years, respectively. On the platform SCOPUS, 23.8% (72 out of 303) and 24.8% (32 out of 139) of all the articles published to date about acute amphetamine and cathinone toxicity were published in the last 5 years, respectively. On the platform PubMed, 21.2% (73 of 345) and 25.6% (34 of 133) of all the articles published to date about acute amphetamine and cathinone toxicity were published in the last 5 years, respectively. Finally, for the platform Dimensions, 72.2% (7352 of 10,181) and 73.4% (1258 of 1714) of all the articles published to date about acute amphetamine and cathinone toxicity were published in the last 5 years, respectively. This volume of data demonstrates the most immediate interest in understanding the effects of these different substances on the human organism and animal models.

**Chronic toxicity** When we evaluated chronic amphetamine and cathinone toxicity, we were met with a lack of information about these symptoms due to the rapid appearance of these substances in the illegal market. However, the chronic amphetamine effects are already known due to the clinical interest in these substances. Symptoms are expected to resemble acute toxicity symptoms, but the nervous system may be damaged, leading to the mental condition of amphetamine psychosis [48, 52, 53].

Chronic toxicity may occur because, after repeated amphetamine and/or cathinone use, the body may become less susceptible to physiological responses, a phenomenon known as tachyphylaxis. As a result, dependence on the mesolimbic dopaminergic system may occur, with external reinforcements being needed to maintain standard levels [82]. Dopamine together with serotonin acts on this

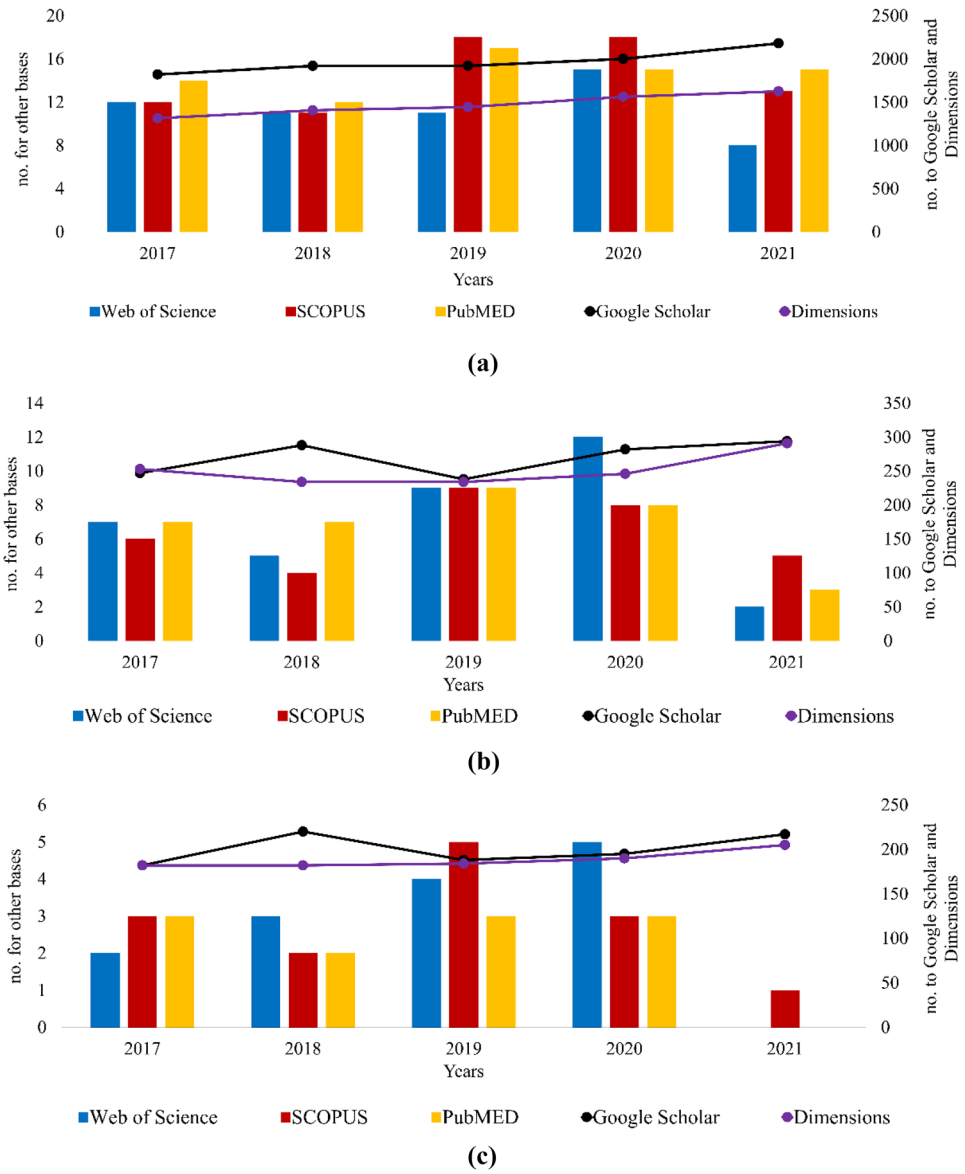


**Fig. 5** Result for the last 5 years (2017–2021) for the descriptors **a** Toxicity AND amphetamine AND acute; **b** Toxicity AND cathinone AND acute; and **c** Toxicity AND cathinone AND amphetamine AND acute

system, leading to possible cases of aggression and paranoia, changes in spatial perception, and psychotic behavior [83].

Despite these indications, gaps in the knowledge about the chronic toxicity of these substances remain (Fig. 6), as seen from the volume of data indexed on the platforms. As in the case of acute toxicity, the number of published articles on chronic amphetamine and cathinone toxicity vary significantly. A search of the platform Google Scholar showed that 67.3% (9050 out of 13,440) and 52.7% (1007 out of 1911) of all the articles published to date about chronic amphetamine and cathinone toxicity were published in the last 5 years, respectively. As for the other platforms, a search of the Web of Science showed that 7.8% (18 of 231) and 5.3% (7 of 131) of all the articles published to date about chronic amphetamine and cathinone toxicity were published in the last 5 years, respectively; a search of the platform SCOPUS showed that 8.3% (25 out of 303) and 4.7% (6 out of 129) of all the articles published to date about chronic amphetamine and cathinone toxicity were published in the last 5 years, respectively; a search of the platform PubMed showed that 11.6% (40 of 345) and 2.3% (3 of 133) of all the articles published to date about chronic amphetamine and cathinone toxicity were published in the last 5 years, respectively; and a search of the platform Dimensions showed that 67.8% (6899 of 10,181) and 52.3% (897 of 1714) of all the articles published to date about chronic amphetamine and cathinone toxicity were published in the last 5 years, respectively. There was a noticeable difference and a clear scarcity of longitudinal studies on the use of these substances.

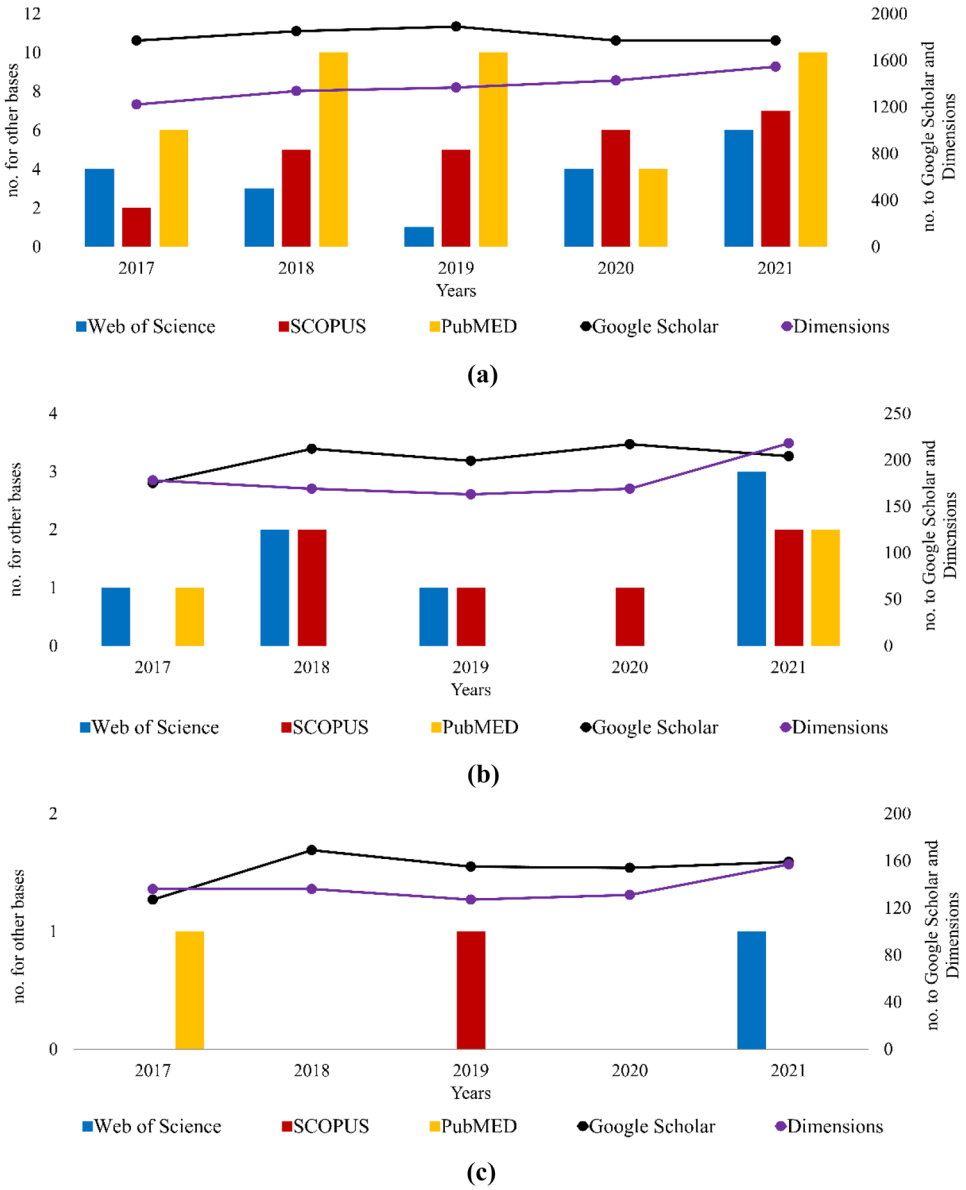


**Fig. 6** Result for the last 5 years (2017–2021) for the descriptors **a** Toxicity AND amphetamine AND chronic; **b** Toxicity AND cathinone AND chronic; and **c** Toxicity AND cathinone AND amphetamine AND chronic

**Post-mortem toxicity** *Post-mortem* toxicological data can be a valuable source of information to help elucidate the causes of deaths [55], and they provide the basis for more assertive public policies for different consumer niches. However, being able to determine an exact number of fatal intoxications due to amphetamine and/or cathinone use is a challenge for several reasons: toxicological tests are not mandatory in several countries; toxicological studies are not performed on all cases of unknown death; and not all laboratories have standards to attest to the presence of NPS [58].

On the other hand, when these studies are carried out, important information is observed. A study on suicide carried out in the United States (37 States) showed greater chances of cases involving amphetamines and serious mental illnesses (schizophrenia and/or bipolarity) both in men and women compared to cases involving other mental disorders or no mental disorder [84].

This lack of discussion can be observed in the articles indexed on the platforms (Fig. 7). However, these articles have indicated that mixing substances, or poly-use, happens frequently and is a challenge for toxicology [43, 77, 79]. The main results have indicated the detection of substances, but not their toxicological effects because substances and samples are complex. On the platform Google Scholar, of all the articles published about *post-mortem* amphetamine and cathinone toxicity to date, 26.6% (3581 of 13,440) and 43.2% (825 of 1911) were published in the last 5 years, respectively. In the other platforms the results diverged, but the number of articles remained small when compared to acute and chronic toxicity. On the platform

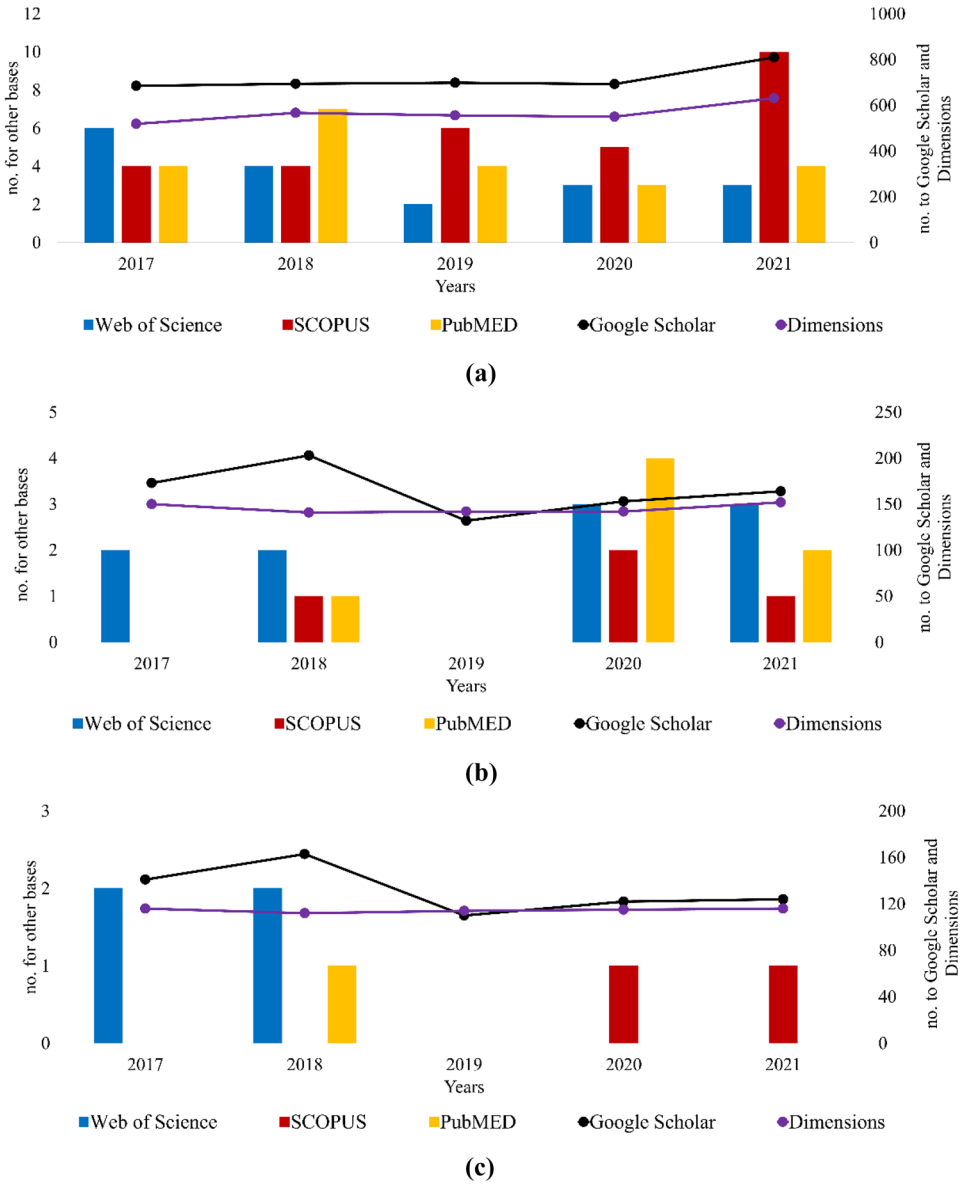


**Fig. 7** Result for the last 5 years (2017–2021) for the descriptors **a** Toxicity AND amphetamine AND *post-mortem*; **b** Toxicity AND cathinone AND *post-mortem*; and **c** Toxicity AND cathinone AND amphetamine AND *post-mortem*

Web of Science, of all the articles published about *post-mortem* amphetamine and cathinone toxicity to date, 7.8% (18 of 231) and 7.6% (10 of 131) were published in the last 5 years, respectively. On the platform SCOPUS, of all the articles published about *post-mortem* amphetamine and cathinone toxicity to date, 9.6% (29 out of 303) and 3.1% (4 out of 129) were published in the last 5 years, respectively. On the platform PubMed, of all the articles published about *post-mortem* amphetamine and cathinone toxicity to date, 6.4% (22 out of 345) and 5.3% (7 out of 133) were published in the last 5 years, respectively. On the platform PubMed, of all the articles published about *post-mortem* amphetamine and cathinone toxicity to date, 27.7% (2823 out of 10,181) and 42.4% (727 out of 1714) were published in the last 5 years, respectively.

## Phenylethylamines (NBOMes)

NBOMes are relatively new substances that have recently become more popular. Therefore, the number of articles about NBOMe toxicity indexed on the analyzed platforms in the last 5 years is still small [85]. We retrieved a larger number of articles from the platforms Google Scholar (1060 articles) and Dimensions (966 articles), which provided almost four-times more results for articles with the terms "NBOMe" and "toxicity" than the platform Web of Science (54 articles). The platforms PubMed (47 articles) and SCOPUS (47 articles) had even smaller numbers of articles (Fig. 8). When we restricted the search to the last 5 years, the main findings clearly occurred in this period. Overall, the results indicated that 43.9% (18 out of 41), 51.1% (24 out of 47), 66.6% (706

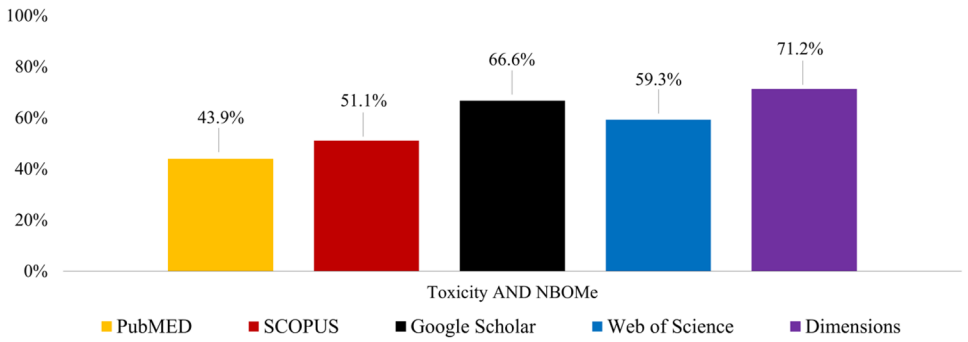


**Fig. 8** Percentage of studies about NBOMe toxicity published to date that were indexed in the last 5 years on the platforms PubMED (yellow), Web of Science (blue), Google Scholar (black), SCOPUS (red), and Dimensions (purple) for the evaluated descriptors

out of 1060), 59.3% (32 of 54), and 71.2% (688 out of 966) of the articles about NBOMe toxicity found on the platforms PubMED, SCOPUS, Google Scholar, Web of Science, and Dimensions were published in the last 5 years, respectively.

Analysis of Fig. 8 shows that information on the toxicity of NBOMe has been a subject of recent research: 43.9% (PubMED) and 71.2% (Dimensions) of all the studies on NBOMe toxicity were published in the last 5 years. By using this dataset, we calculated a linear coefficient of correlation ($R^2$) for the number of indexed articles over the years. We obtained $R^2$ of 0.8264 (Dimensions—↓ slight decrease along years), 0.6282 (Web of Science—↓ decrease along years), 0.2353 (SCOPUS—↓ non-linear decrease along years), 0.1591 (Google Scholar—↓ slight rise along years), and 0.0313 (PubMED—↓ non-linear decrease along years). In all cases, data dispersion indicates that research into this topic is growing [34].

When we used the descriptors "Toxicity" AND "NBOMe" to obtain the year with the largest number of indexed studies, we found 2017 for the platform Web of Science, 2017 and 2018 for the platform SCOPUS, and 2018 for the platform Dimensions. More recently, the platforms that indexed the most significant volume of articles were PubMED and Google Scholar, in 2019 and 2021, respectively. In addition to these articles, some review articles before the evaluated period may be a source for other researchers in the area [86–92]. Data and Graphics are presented in the Supplementary Material (Table S6 and Figure S6).

## Structure and international restrictions

NBOMes, also known as "*N*-Bombs" or "*N*-Bomb", consist of substituted class 2C phenethylamine derivatives. Like LSD, they have potent hallucinogenic effects. Despite having been recently discovered, their consumption has increased over the years, and adverse effects have been linked to their toxicity [85, 93, 94].

These molecules consist of phenethylamines substituted with methoxy groups at positions 2 and 5 of the benzene ring; at position 4, they normally bear a halogen. On the other ring, there is a methoxy group at position 2' [95]. NBOMes are commonly found in blotter papers, but they can also be marketed in ampoules, pills, and freebase powder [85].

NBOMes have already been catalogued by the UNODC Convention on Psychotropic Substances of 1971, Schedule I. This convention aims to establish international control of psychotropic substances and is constantly updated according to the expansion and appearance of new substances of abuse, thereby allowing new synthetic drugs to be controlled, and their therapeutic and abuse potential to be compared [49, 96].

The list of substances controlled by the Convention is called the Green List, and it contains four control schedules for psychotropic substances. The list also provides information about changes in substance name, as well as synonyms, conversion factors to calculate the purity of salts and bases, and restrictions and prohibitions on the import and export of such substances. The body responsible for updating this list is the INCB (International Narcotics Control Board), which independently and quasi-judicially monitors the implementation of such conventions [97].

The NBOMes on the green list includes 25B-NBOMe, 25C-NBOMe, and 25I-NBOMe. These substances were added on March 13, 2015, during the 10th Meeting, and have not undergone inspection or review by the World Health Organization (WHO). The information provided to the WHO on this date was that such substances had no therapeutic or medical use. In addition, preliminary data from several countries were obtained and indicated serious damage, showing a risk to public health. Forty-six of 48 countries voted for including 25B-NBOMe and 25C-NBOMe in Annex I, one country voted against, and one country abstained. As for 25I-NBOMe, 47 countries voted in favor and only one voted against its inclusion in Annex 1. Therefore, the substances were added to the Green List, being the first NBOMes to be recognized as psychotropic substances [98].

However, NBOMes include a great diversity of other derivatives that are not on the Green List and which pose the same health risks [99, 100].

### Forms of consumption

The NBOMe effects resemble the LSD effects. NBOMes are also commonly consumed in blotter papers, and they act more slowly when they are ingested by the buccal and sublingual routes compared to insufflation. Unlike LSD, which normally has no taste at all, NBOMes cause a metallic taste and numbness in the mouth and tongue, which last for approximately 1 h [99].

### Pharmacological aspects and toxicity

**Pharmacokinetics** There are no conclusive studies on the NBOMe pharmacokinetics in humans or animals. However, there is some evidence that their action starts faster after they are insufflated compared to the buccal and sublingual consumption routes. Nevertheless, insufflation offers more toxicity risks. With respect to intravenous injection, there has been only one record of a single clinical case, which presented higher levels of toxicity than those recorded in other types of consumption routes [99].

NBOMes undergo hepatic metabolism, and their metabolites are excreted in the urine. These metabolites have been classified into phase I and phase II metabolites in both human and rodent urine. For 25I-NBOMe, 25B-NBOMe, and 25C-NBOMe, phase I metabolites are mostly metabolized by *O*-demethylation, *O,O*-bis-demethylation, and hydroxylation. The P450 cytochromes underlying biotransformation include CYP2C9 and CYP2C19 (*O*-demethylation), CYP1A2 and CYP3A4 (hydroxylation), and CYP3A4 (*N*-demethoxybenzylation). There are also records of CYP2B6 being involved in NBOMe metabolism (Fig. 9). Thus, at this stage, the most common metabolites are 2-*O*-desmethyl-25X-NBOMe, 25X-NBOH, and 5-*O*-desmethyl-25X-NBOMe. During phase II, sulfonation and glucuronidation occur, but *O*-methylation, glutathione conjugation, and *N*-acetylation have also been verified [99, 101].

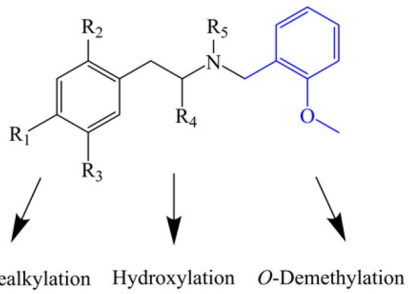


**Fig. 9** Scheme for the possible NBOMe metabolic processes by action of different CYPs [102]

**Pharmacodynamics** Besides hallucinations, NBOMes cause euphoria, increased alertness and self-esteem, heightened emotions, tachycardia, hypertension, aggressive behavior, seizures, vasoconstriction, hyperthermia, levitation perception, involuntary motor activity, psychedelic effects, rhabdomyolysis, and, in some cases, death. These effects are due to the serotonergic toxicity exerted by these molecules [94, 103, 104].

Because NBOMes are good agonists, their hallucinogenic activity is related to their affinity for 5-HT receptors: NBOMes can interact with the 5-HT2A, 5-HT2C, and 5-HT1A receptors. Most 25X-NBOMe analogs (where X represents a halogen) have a high affinity for the 5-HT2A receptor, and it is through this receptor that the psychoactive effects emerge, so much so that molecules belonging to the NBOMe family were initially synthesized for researching these receptors. Although the 5-HT2A receptor is the main target of 25X-NBOMes (due to an *N*-benzyl substitution), agonists of other receptors exist. For example, there is 25I-NBOMe, which also has an affinity for the 5-HT1A and 5-HT2C receptors (studies performed in vitro), as well as 25D-NBOMe, 25E-NBOMe, 25H-NBOMe, and 25 N-NBOMe, which also have an affinity for the 5-HT2C receptor. Some affinity for 5-HT2B receptors has also been reported, but they are less required by NBOMes compared to 2C molecules. In addition to 5-HT receptors, 25I-NBOMe in particular has moderate affinity for α1 and α2 adrenergic receptors, which may explain some symptoms caused by 25I-NBOMe use, such as vasoconstriction [94, 99, 100, 104–106].

Besides the effects on the serotonergic system, NBOMes affect the dopaminergic system. Because NBOMes are psychoactive phenethylamines, they inhibit dopamine (DAT) and serotonin (SERT) transporters, increasing dopamine and extracellular 5-HT [107].

**Acute toxicity** Acute intoxication by NBOMes occurs more easily than acute intoxication by LSD because NBMOs exert their effects at smaller doses. In addition, overdose with NBOMes is also possible. NBOMes are normally detected in blood, urine, plasma, or serum. When intoxication occurs, patients should be treated with benzodiazepines and intravenous fluids, but the treatment of patients in these conditions is still very vague in the literature. One of the most serious and most reported symptoms of NBOMe toxicity is rhabdomyolysis, which refers to the damage that the release of electrolytes, myoglobin, creatine kinase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase into circulation elicits, causing renal failure, hypotonia, and potentially fatal associated acute kidney injury. One of the markers of rhabdomyolysis is high blood CK activity (exceeding 10 to 25 times the threshold value). Associated with this,

multiple organ failure, sepsis, and severe coagulopathies can occur [85, 103, 108, 109].

As highlighted, the amount of information about NBOMes is incipient because this class of NSP is relatively new in the drug market compared to amphetamines and cathinones. Figure 10 indicates the number of published articles year by year. In general, 69.3% (541 out of 781), 47.1% (8 out of 17), 42.9% (6 out of 14), 55.6% (10 out of 18), and 72.9% (551 out of 756) of all the articles about acute NBOMe toxicity on the platforms Google Scholar, Web of Science, PubMED, SCOPUS, and Dimensions to date were indexed in the last 5 years, respectively.

**Chronic toxicity** In vivo studies have shown that the chronic use of substances acting as 5-HT2A receptor agonists desensitizes and downregulates this receptor, creating a certain resistance of this receptor to these substances. Some users have reported some resistance to the psychoactive effects of these substances after using them for 3 days, and a few weeks of abstinence were necessary for them to obtain the previous effects with the same dose [110].

Another study has compared the use of small NBOMe doses over a few days and a single larger NBOMe dose, given to rats. The study showed that the chronic use of 25I-NBOMes implied a loss of responsiveness of the neuronal dopamine, 5-HT, and glutamate pathways in the frontal cortex of rats. This loss was much more pronounced than the loss observed with an acute dose [105].

Of all the evaluated substances and of all the employed sets of descriptors, chronic NBO toxicity resulted in the smallest number of articles on the platforms Web of Science, SCOPUS, and PubMED (Fig. 11). Of all the articles on chronic NBOMe toxicity published to date on the platforms Google Scholar, SCOPUS, Web of Science, PubMED, and Dimensions, 74.4% (320 out of 430), 0.0% (0 out of 0), 100.0% (1 out of 1), 0.0% (0 out of 0), and 75.8% (395 out of 521) were published over the past 5 years.

**Post-mortem toxicity** The presence of NBOMes *postmortem* can normally be verified in fluids, tissues, heart blood, peripheral whole blood, vitreous humor, liver content, stomach, serum, and mainly urine. The amount found in *postmortem* cases is usually very small—there have been cases of death with up to 0.50 ng/mL substance present in the samples. Actually, the corresponding NBOMe metabolites were detected (the main metabolic pathways being hydroxylation, *N*-debenzylation, and *O*-demethylation), and not the parent compound [85, 100].

As in the previous cases, the workload related to *postmortem* studies of NBOMes has been small (Fig. 12). Of all the articles published to date on *post-mortem* NBOMe toxicity on the platforms Google Scholar, Web of Science, PubMED, SCOPUS, and Dimensions, 70.5% (365 out of 518), 57.1% (4 out of 7), 50.0% (2 out of 4), 25.0% (1 out of 4), and 76.8% (503 out of 655) were published over the last 5 years, respectively.

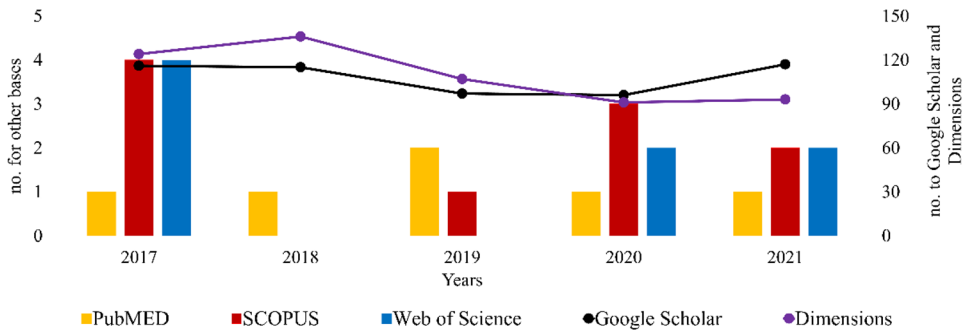


**Fig. 10** Result for the last 5 years (2017–2021) for the descriptors Toxicity AND NBOMe AND acute

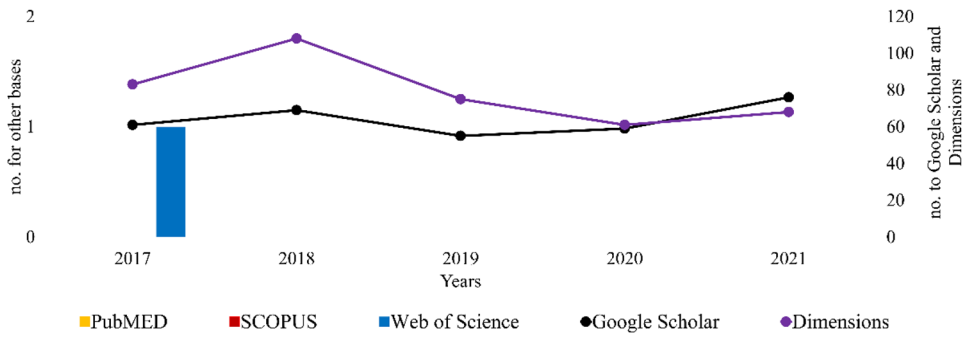


**Fig. 11** Result for the last 5 years (2017–2021) for the descriptors Toxicity AND NBOMe AND chronic

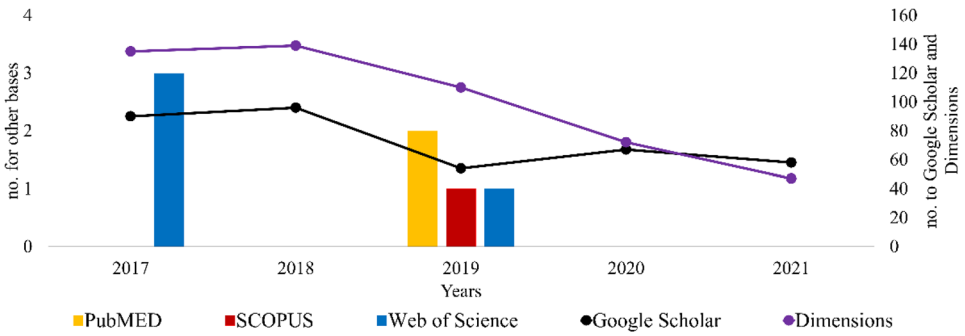


**Fig. 12** Result for the last 5 years (2017–2021) for the descriptors Toxicity AND NBO AND *post-mortem*

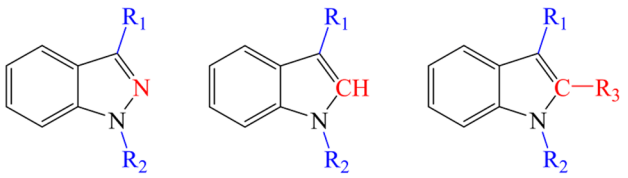


**Fig. 13** Possible generic structures of synthetic cannabinoids. The homologous carbon atoms, called the core, are in black; the distinctions among the cores are in red; the possible ramifications (linked $R_1$ group and $R_2$ tail) are in blue

## Synthetic cannabinoids

Synthetic cannabinoids (SCs) seek to question the effects provided by cannabis. SCs are the most diverse group among the existing NSP chemical structures (Fig. 13). They seek to mimic the effects of THC, the main psychoactive cannabinoid in *Cannabis sativa*. SCs are largely SC agonists, and the synthetic additives present in these products can vary significantly in terms of quantity, as well as the types of SCs used in them. Some of these substances may have a higher addictive potential than cannabis due to faster development of tolerance, which can lead to increased acute and long-term toxicity [111].

Structures such as JWH-018, 5F-APINACA, and AM-2201 were the first SCs to appear. Despite their quite diverse structures, some trends have been observed, such as the simple replacement of halide in various positions in the alkyl chain or the variation in the length of the alkyl chain, as well as changes in the group linking naphthalene to groups like adamantyl and methoxyphenyl. An evolution in the SC structure has been the presence of indazole heterocycles and the use of amide and binding groups, which has dramatically increased the number of such substances since 2013 [111, 112].

Given that various SC structures are possible, understanding the responses of toxicological analyses over a short period of time (the past 5 years, as described for amphetamines and cathinones [33]), is challenging. In this way, the number of articles about SC toxicity indexed on the different platforms evaluated here was larger than the number of articles on amphetamine and cathinone toxicity. In the last 5 years, a lot of information has been obtained, and a lot has been discovered about SC toxicity compared to the years before 2017 (Fig. 14). The platform SCOPUS had the smallest number of indexed articles, and 34.5% (419 out of 1213) were published in the last 5 years. The platform Web of Science had the largest number of articles on SCs, and the highest percentage of articles published over the last 5 years: 51.0% (395 out of 775), followed by the platforms Google Scholar—49.7% (15,410 out of 31,010), Dimensions—45.4% (366 out of 806), and PubMED—39.0% (696 out of 1784).

Figure 14 shows that, on average, half of the studies on cannabinoids were produced before 2017, and the other half were produced within the last 5 years. The amount of information in the previous 5 years ranged from 39.5%

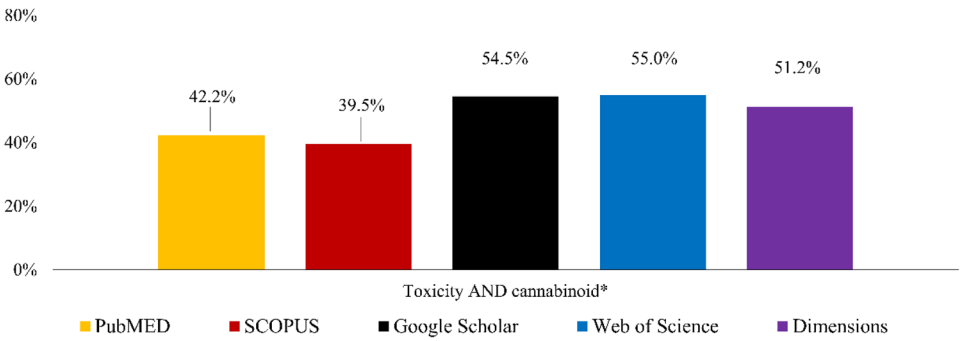


**Fig. 14** Percentage of indexed studies about SC toxicity published to date that were indexed in the last 5 years on the PubMED (yellow), Web of Science (blue), Google Scholar (black), SCOPUS (red) and Dimensions (purple) platforms for the evaluated descriptors

(SCOPUS) to 55.0% (Web of Science). By basing the analysis further on this dataset, we used a linear correlation ($R^2$) between the volume of indexed articles and the evaluated years, to obtain correlations of 0.9474 (SCOPUS—↑ slight increase along years), 0.7222 (Google Scholar—↑ linear increase along years), 0.4808 (Web of Science—↓ non-linear decrease along years), 0.0384 (Dimensions—↑ slight increase along years), and 0.0313 (PubMED—↓ slight decrease along years). Data and Graphics are shown in the Supplementary Material (Table S7 and Figure S7). According to these correlations, because of the intrinsic differences of each platform, some of them are in a rising stage, whereas others are in a burst stage [34]. This difference may be due to the advent of SCs, which started to drive new studies, changing the format of the projections.

The year with the largest number of articles indexed for the descriptor "Toxicity" AND "cannabinoid*" was 2017, 2018, and 2019 on the platforms Web of Science, Dimensions, and PubMED, respectively. In 2021, the platforms SCOPUS and Google Scholar had the most indexed articles on this topic. In addition to these articles, some review articles before the period evaluated may be a source for other researchers in the area [113–118].

### Structure and international restrictions

Marijuana is the most used illicit drug worldwide. The United Nations Organization (UNO) estimates that nearly 4% of the global population aged between 15 and 64 used the drug at least once in 2019, which amounted to 200 million. Between 2010 and 2019, the number of marijuana users increased by almost 18 percent, and the global number of users had reached 209 million by 2020 [1, 119].

The discussion about prohibiting *Cannabis sativa* began in 1925 at the International Opium Convention, where it was proposed that the use of "Indian hemp" be restricted to medical and scientific purposes. However, countries opposed this rule, citing social and religious traditions and the growth in the prevalence of hybrid cannabis plants, which would prevent the rules from being imposed. Cannabis legality for general or recreational use varies from country to country. It is illegal in almost all countries, but this scenario has been changing because some countries have decriminalized the possession of small amounts of *Cannabis sativa* [120, 121].

In addition to the cultural and social challenges met throughout the course of cannabis legislation, the increase in the number of NPS in recent years has made discussions about the subject more complex. These new substances, produced in laboratories, have been changing the profile of cannabinoids consumed by the population, consequently affecting how public authorities should act. Countries have used various approaches to deal with the emergence of SCs and other NPS groups, including individual listings or generic controls, analogous legislation, temporary bans, and rapid procedures [122, 123].

As markets witness the introduction of new compounds that are unpredictable and poorly understood, NPS add another challenge to the study of cannabinoids worldwide. SCs are the NPS category with the largest number of substances—by the end of 2017, there were at least 251 SCs. In 2008, these products grew in popularity in Germany and other European countries. In low-income countries, their use is also becoming more popular: between 2015 and 2019, South and Central America recorded a five-fold increase in the amount of seized NPS. Reported seizures have also increased in Africa, South and South-West Asia, and the Near and Middle East [2, 3].

### Forms of consumption

The trade names are diverse, and the most common are *Spice*, *K2*, and *Spice gold*. Synthetic substances are sprayed into herbal products to reproduce the aspects of cannabis. According to the labels, the packages contain between 0.5 and 3.0 g of different plant species, constituting a mixture of exotic herbs and aromatic plant extracts. However, the psychoactive effects exerted by these products resemble the effects of *Cannabis sativa* because the products are sprayed with SC solutions. The SC concentration is usually between 1 and 30 mg/g of sample [3, 124].

The synthetic additives present in these products can vary significantly in terms of quantity and type of SCs.

### Pharmacological aspects and toxicity

Given that neither the mechanisms nor the effects of the most studied natural cannabinoids, THC and CBD, have been fully elucidated, the increasing number of SCs poses a great challenge when it comes to measuring their effects and toxicity in relation to their consumption. Moreover, toxicity due to SC use is not only related to their effects, but also to the effects of additives that can contaminate these products and potentiate the SC effects. Between March and April 2018, there was an outbreak of severe bleeding events in patients who had ingested SCs contaminated with a rodenticide [125].

**Pharmacokinetics** Cannabinoids are consumed by two main routes: oral and inward. Regarding oral consumption, absorption is slower and incomplete. Effects appear about 30 to 60 min after ingestion and last up to 3 h. As for consumption through the inward approach, absorption is immediate. Effects appear after 20 to 30 min and may last from two to three hours, so this is the most used and effective route [114, 125, 126].

After SCs are inhaled, maximum blood concentrations close to 10 µg/mL are rapidly reached. However, the concentrations decay fast, but they may be detectable for hours or days. For example, JWH-018 is detectable up to 48 h after consumption [127].

Once SCs are administered, they enter the bloodstream and are distributed to some body organs. They are biotransformed by pulmonary and brain-liver enzymes of the CPY450 system, which catalyze their hydroxylation, oxidation, or conjugation with glycanic acid. Because SCs are highly lipophilic, they can easily penetrate the blood–brain barrier. If consumed chronically, SCs can accumulate in adipose tissue, prolonging their permanence in the body [128].

Drug metabolism essentially involves two steps. Phase I (oxidation), which basically consists of adding an oxygen atom to the substrate, creates a functional group that is used in phase II conjugation reactions. Phase II (conjugation) is performed predominantly by gut system enzymes (uridine-diphosphate-glucoronyl transferase), which bind glucoronic acid to substrates such as steroids, bilirubin, and drugs, increasing their solubility and facilitating their renal excretion [129].

Phase I (oxidation) is affected by cytochrome P450 or CYP450 family enzymes. Among the CYP450 proteins present in the human body, six (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) are involved in the metabolism of 90% of the drugs [129, 130].

The THC half-life time can range from 20 h to 13 days. Over 100 THC metabolites have been identified; most of them are monohydroxyl compounds. These metabolites undergo glucuronidation or, less commonly, conjugation with amino acids, fatty acids, sulfate, and glutathione [128].

When the liver metabolizes THC in phase I, it generates the metabolite 11-hydroxy-THC (11-OH-THC) by hydroxylation. In turn, 11-OH-THC has a greater ability to activate the cannabinoid receptor and, because it is more lipophilic, it crosses the blood–brain barrier faster. Subsequently, in the liver, 11-OH-THC is transformed into other inactive metabolites, the main one being 11-nor-carboxy-THC (TCHCOOH) (Fig. 15) [130, 131].

JWH-018 SC bears an indole ring or oxidized *N*-alkyl chain, so it can give monohydroxylated compounds. For example, there is the active metabolite JWH-018 4-hydroxyindol, which subsequently undergoes conjugation mediated by glucuronosyltransferases and is excreted as phase II glucoronid conjugates in urine [133].

Over 65% of cannabinoids are excreted in feces, and approximately 20 percent of them are excreted in the urine. Between 80 and 90% of cannabinoids are excreted in the form of hydroxylated and carboxylated metabolites within about 5 days. Some metabolites can be reabsorbed (enterohepatic circulation), which prolongs their action. Total disposal can take up to 30 days [130].

**Pharmacodynamics** Despite their variability, all SCs act on the same target, so they belong to the same family of substances. Like THC, SCs bind to $CB_1$ and $CB_2$. Because structure plays a key role in this process, the SC effects can vary. For instance, HU-210 is about 60–100 times more powerful than THC at both the $CB_1$ and $CB_2$; CP4497 is around 20 times more powerful than THC at the $CB_1$; and JWH-018 is 4–6 times more powerful than THC at the $CB_1$ [112].

$CB_1$, a cannabinoid receptor that is coupled to the G protein, occurs predominantly in the central nervous system, but it can also be found in the lungs, liver, kidney, heart, muscle, and vasculature. The $CB_2$ is found mainly in the lymphatic system, where it attenuates inflammation signals, but it also occurs in the kidney. In addition, studies have suggested that endogenous cannabinoids act not only via the $CB_1$ and $CB_2$, but also by directly inhibiting $Na^+$ and $Ca^{2+}$ channels in ventricular myocytes, thus decreasing muscle contractility. The $CB_1$ seems to affect the actions of neurotransmitters such as acetylcholine, norepinephrine, dopamine, 5-hydroxytryptamine, α-aminobutyric acid (GABA), glutamate, and D-aspartate [126, 134].

Responses of the central nervous system to THC and $CB_1$ agonists include beneficial analgesic effects, attenuation of nausea and vomiting in cancer chemotherapy, reduction of intraocular pressure, stimulation of appetite in exhausting

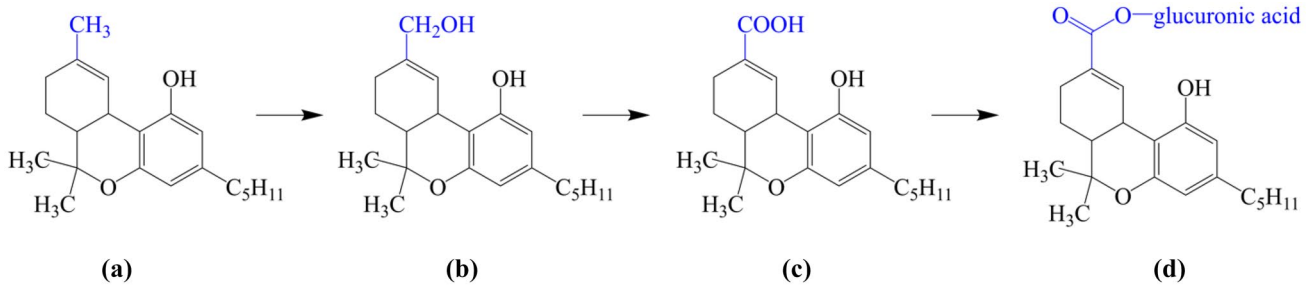


**Fig. 15** Main biotransformations of **a** Δ9-tetrahydrocannabinol and the products **b** 11-hydroxytetrahydrocannabinol, **c** 11-nor-Δ9-tetrahydrocannabinol carboxylic acid, and **d** 11-ort-Δ9-tetrahydrocannabinol carboxylic acid conjugated with glucuronic acid [132]

syndromes, relief of muscle spasms/spasticity in multiple sclerosis, and decreased intestinal motility. However, undesirable side effects, including changes in cognition and memory, dysphoria/euphoria, and sedation, accompany these therapeutic responses [135].

**Acute toxicity** Acute exposure to cannabis increases the heart rate and blood pressure and can cause hypotension. Reports of complications of cases of severe cardiovascular diseases, including acute coronary syndromes and strokes, have been reported by cannabis users. Studies that reviewed a broad spectrum of cognitive functions reported that attention, concentration, decision-making, impulsivity, reaction time, risk taking, verbal fluency, and working memory were acutely impaired in a dose-dependent manner, but these effects were not consistently observed [114, 116, 125].

Even long-term users may have negative experiences if they use more potent cannabis products than usual, or if they use cannabis in an unknown way. Hallucinations may occur after the use of very high THC doses and may occur at even lower doses in individuals with pre-existing vulnerability to psychosis [114, 116, 136].

Acute cardiac toxicity is relatively common among users that go to medical centers seeking emergency care. Supraventricular tachycardia with a heart rate of up to 172 beats per minute has been reported in a 24-year-old after ingestion of electronic cigarette fluid mixed with SCs. In addition, acute myocardial infarction (MI) has been associated with the use of SCs in adolescents and adults [125].

The search for acute toxicity and SCs on the platforms PubMED, Google Scholar, SCOPUS, Web of Science, and Dimensions showed that 44.8% (152 out of 339), 45.0% (10,500 out of 23,320), 40.8% (111 out of 272), 52.4% (97 out of 185), and 24.3% (18,463 out of 76,028) of the articles indexed on these platforms were published over the last five years (Fig. 16).

**Chronic toxicity** Studies about brain structure and function in chronic cannabis users have provided some support for the epidemiological findings. Magnetic resonance analysis has shown structural changes in the hippocampus, prefrontal cortex, and cerebellum in chronic cannabis users. These changes were greater in people who had used cannabis longer. A recent systematic review has found a consistent reduction in the hippocampus volume of long-term daily cannabis users. Moreover, users can develop cannabis addiction syndrome characterized by loss of control over use. Additionally, these changes can be exacerbated in prone individuals. Furthermore, airway injury, pulmonary inflammation, and impaired lung defense can occur [137, 138].

That abuse of SCs may cause neurotoxicity has also been documented in the literature. In a recent case report, a 25-year-old presented stroke symptoms the morning after using a product called *Freeze*. In addition, two cases of ischemic stroke were reported a few hours after the first use of SCs, suggesting a possible association [125].

As for published studies, 45.5% (10,710 out of 23,430), 33.5% (66 out of 197), 47.5% (38 out of 80), 44.3% (109 out of 246), and 24.5% (18,437 out of 75,284) of the articles indexed on the platforms Google Scholar, SCOPUS, Web of Science, PubMED, and Dimensions were published in the last 5 years (Fig. 17).

The number of articles on chronic toxicity was smaller than the number of articles on acute toxicity because research into chronic toxicity requires more time and resources for solid data to be obtained.

**Post-mortem toxicity** A pharmacokinetic study in mice exposed to 200 mg of the smoke of the product known as "*Buzz*", containing 10.8 mg of JWH-018, was conducted. Six mice were sacrificed after exposure for 20 min. JWH-018 concentrations of 82 ± 42 mg/kg, 1990 ± 72 mg/kg, and 510 ± 166 mg/kg were found in the blood, liver, and brain of the mice [127].

A fatal case of myocardial ischemia after an overdose of the SC ADB-FUBINACA has been reported. *Post-mortem* toxicological analysis detected a high concentration of carboxamide indazole derived from the SC ADB-FUBINACA in the peripheral blood (105 ng/mL), as well as a low concentration of the synthetic cathinone, *N*-ethylpentylone. The high concentration of ADB-FUBINACA suggested oral consumption. This is among the strongest SCs, with

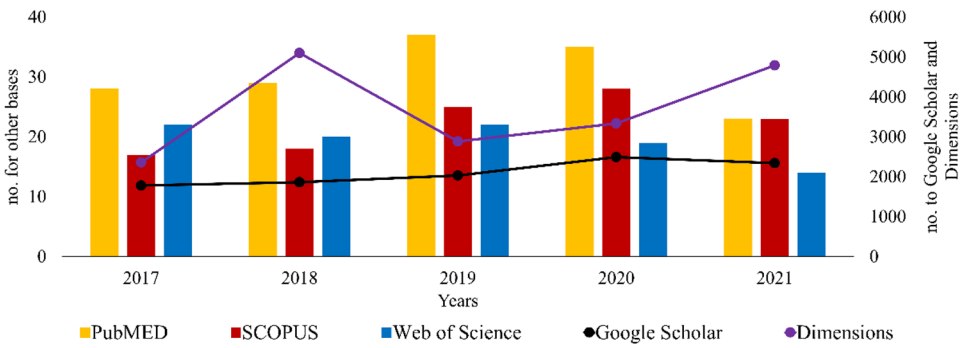


**Fig. 16** Result for the last 5 years (2017–2021) for the descriptors Toxicity AND SCs AND acute

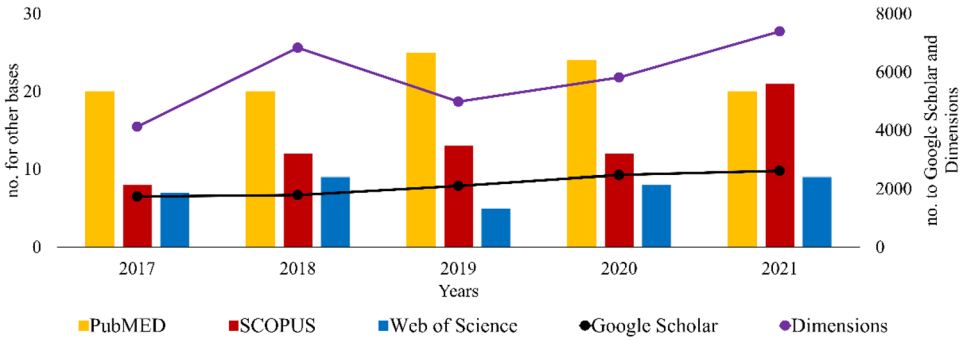


**Fig. 17** Result for the last 5 years (2017–2021) for the descriptors Toxicity AND SCs AND chronic

a binding affinity value (Ki) of 0.36 nM and an $EC_{50}$ of 0.98 mM [139].

As for published articles, 27.85% (2682 out of 9660), 47.2% (17 out of 36), 52.2% (12 out of 23), 40.6% (13 out of 32), and 25.7% (8219 out of 31,991) of the articles indexed on the platforms Google Scholar, SCOPUS, Web of Science, PubMED, and Dimensions were published in the last 5 years (Fig. 18). However, a clear trend cannot be established with these percentages and data because the volume is small.

## Discussion

When we discuss the mechanisms of toxicological action, we seek to understand the processes through which a toxic substance reaches its target organ or tissue and there remains long enough to cause any significant harmful effect. Many substances can be toxic to several organisms. Therefore, properties such as molecular structure, biochemical behavior, and pharmacological behavior, among others, can be used to classify them. Some of these substances act on specific target organs and tissues, while others act indiscriminately, targeting any organ or tissue they encounter. Action selectivity occurs due to physiological and biochemical differences between organisms. For example, bacteria are affected by antibiotics, while animals are not harmed by them because their cell membranes have different composition.

The data set available on indexing platforms allows the trends of the last 5 years and the consumption flow to be evaluated. Amphetamines are well-known substances and have been used for various purposes apart from recreational consumption. This previous knowledge is clear from the volume of papers published before 2017. According to the platform Google Scholar, about 24.6% of what has been published about amphetamine toxicity was published before 2017. Bearing the information published about amphetamine toxicity in mind, the trend in cathinone toxicity is a little more predictable because they share a similar chemical structure with amphetamines. However, even if the structures are homologous, the effects might not be necessarily the same. Thus, after this class of substances appeared for recreational purposes, the studies gained more prominence.

A similar idea can be applied to NBOMes. They share part of the structure with amphetamines, but their effects are more comparable to the LSD effects. On the platforms explored herein, over 40% of what is known about this NPS class has been discovered in the last 5 years. When you look at the number of published articles, this becomes more evident because the first thousand papers were only indexed on the platform Google Scholar, while on the other platforms the number of papers did not reach the hundreds, demonstrating that many studies can still be conducted. Indeed, the NPS market is dynamic, and research into this topic tries to keep pace. However, the demand for information has become more urgent.

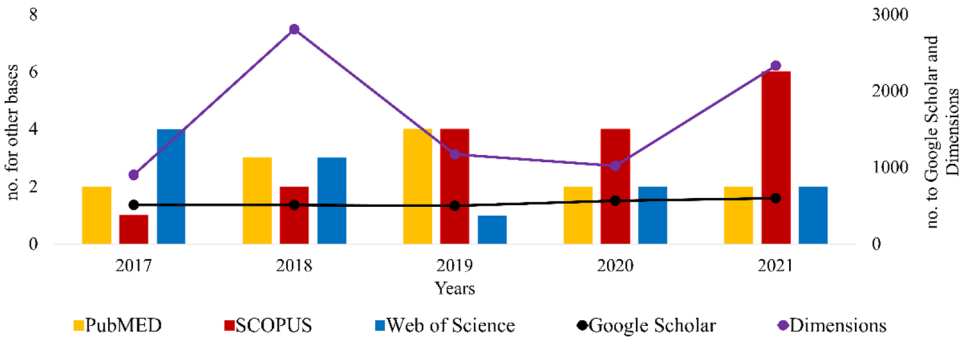


**Fig. 18** Result for the last 5 years (2017–2021) for the descriptors Toxicity AND SCs AND *post-mortem*

Along with amphetamine and cathinone toxicity, SC toxicity has also gained prominence. The compartmentalized SC structure (head, core, and tail) allows different structural arrangements, which maintain the constant interest in them. Of all the evaluated databases, SCs have the greatest uniformity of indexed articles. The platform Google Scholar has the most publications on SCs, indicating that over 50% of what is known about these substances has been discovered from 2017 to date.

For all the NPS classes evaluated here, acute toxicity returned the most information available because obtaining information about this type of toxicity is faster. In addition, the volume of data on acute toxicity demonstrates that it is possible to learn about NPS effects on both the human body and animal models. Cannabinoids presented the largest volume of available data, followed by amphetamines, cathinones, and NBOMes. Studies that seek to understand the combined toxicity of amphetamines and cathinones are still incipient.

Data on chronic toxicity followed the same trend. Google Scholar and Dimensions were the platforms with the largest data volume, whereas the platform Web of Science had the smallest data volume. On the basis of these data, the volume of published articles has been constant, except for cannabinoids, for which the number of published articles has risen. When assessing chronic toxicity, we noticed the lack of information on these symptoms due to the rapid NPS appearance in the illegal market. In the specific case of amphetamines, chronic effects are already known due to the clinical interest in them. Thus, symptoms are expected to resemble the symptoms of acute toxicity, but with the difference that chronic toxicity will probably damage the nervous system and lead to the mental condition of amphetamine psychosis [48, 53].

For all the NPS classes evaluated here, there was less information about *post-mortem* data. In some databases, there was no information at all. Such data could be a valuable source of information to help to elucidate the causes of deaths [55], and they could provide the basis for more assertive public policies for different consumer niches. However, being able to determine an exact number of fatal poisonings is challenging for several reasons: (i) toxicological tests are not mandatory in various countries; (ii) toxicological studies are not conducted for all cases of unknown death; and (iii) not all laboratories have standards to attest to the presence of NPS [58].

This lack of discussion can be observed in the articles indexed in the platforms for all the NPS in the scope of this review. However, some published articles indicated that mixing substances, or poly-use, happen frequently and are a challenge for toxicology [43, 70, 79].

The combined use, conscious or not, of substances has gained prominence in recent years. One of the main points regards drug purity. In the case of amphetamines, approximately 400 MDMA tablets were evaluated in the context of electronic music festivals. In 2019, over 90% of these tablets had MDMA in their composition, with few occurrences of caffeine and synthetic cathinones. However, in 2021, these numbers changed significantly. Only 54.6% of the analyzed materials contained MDMA, and 19.4% contained a synthetic cathinone, indicating adulteration [140]. These changes in a composition may aim to potentiate the effects, as observed for NBOMes. There are reports of NBOMe samples being complexed with hydroxypropyl-b-cyclodextrin (HP-b-CD) to potentiate the NBOMe effects given that HP-b-CD facilitates NBOMe penetration into body membranes [85].

These observations agree with the findings of West et al. [141]: 47.4% of the substances analyzed by these authors contained only one drug, but 39% had two, 12% had three, and 1.6% had four. The mixtures were not restricted to substances of the same class, and cocaine and MDMA were present in one tablet. In general, purity has been a source of interest and monitoring. Through the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the European Union observes the variation in the purity of different substances. Some of the data are summarized in Table 2 [142–147].

Therefore, people who make regular use of or who do not use these substances do not know about or have little information about the actual composition of these products. Moreover, the high rate at which NPS emerge does not allow information to be obtained in a timely manner. In a clinical-pharmacological context for a possible drug, the time for the drug to leave the bench and hit the shelves is about 10 to 12 years, and costs can reach up to $500

**Table 2** Variation in the concentration of different substances analyzed by the EMDCCA from 2017 to 2021

| Substance | | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|---|
| Cannabis (%THC herbaceous) | Max | 22 | 18 | 15 | 15 | 20 |
| | Min | 3 | 2 | 3 | 4 | 5 |
| Amphetamine (% Purity) | Max | 50 | 61 | 50 | 64 | 67 |
| | Min | 7 | 14 | 13 | 15 | 13 |
| Methamphetamine (% Purity) | Max | 79 | 73 | 90 | 100 | 94 |
| | Min | 16 | 22 | 12 | 21 | 16 |

million [148]. Thus, in a controlled context, there is a considerable amount of time for a substance to reach who will consume them, besides being a very costly process. In the forensic context, there is still an incipient amount of information on drug effects and risks both in the short and long term. Studies on NPS potency and toxicity are required [149–151]. However, time and resources are very limited for acquiring assertive information within a very short time, which is why these studies are a challenge.

## Conclusion

The toxicity of synthetic drugs is a current concern worldwide. When we collected the data presented here, we observed a general lack of studies given that many substances have not been evaluated for their toxicity. There is more information about amphetamine and cathinone toxicity compared to other NPS classes. A lot of information about cannabinoids has been reported over the last 5 years, indicating researchers' interest in this class.

In general, for the NPS included in this review, there is a significant difference between the volume of data about their acute and chronic/*post-mortem* toxicity. Obtaining information about chronic/*post-mortem* toxicity is important, but it has not been the subject of many studies over the last 5 years. In addition, proposals for longitudinal and multi-professional studies on the use of these substances are scarce. Nevertheless, the main challenge we observed throughout the review has been the lack of studies relating polydrug use and adverse effects. Although articles have reported adulterants or discussed purity, the effects of drug combinations have been little investigated.

In conclusion, there are gaps to be filled in the knowledge about NPS toxicity. The field for investigating NPS toxicological features is broad, and more confident and feasible information about them is desirable.

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**Data availability** The data provided in this study are available in the Supporting Information.

## Declarations

**Conflict of interest** The authors declare no competing financial interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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