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Crawling into the Unknown: Unveiling Novel Psychoactive Substances (NPSs) in the Post Pandemic Era Utilizing the NPS*finder*®

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Abstract

Novel Psychoactive Substances (NPSs) and other psychoactive or misuse-relevant compounds present a persistent global public health threat, underscoring the critical need for real-time crawling and monitoring tools to investigate and provide valuable information assisting in the management and preparedness against that dynamic and evolving threat. This study utilized the NPS*finder*® web crawler to analyze NPS trends during the post-pandemic period, with data collected from selected highly trafficked psychonaut websites continuously monitored between January and September 2023. Following a comprehensive filtering process of screening, assessment, and evaluation, the dataset provided insights into the availability and characteristics of recently reported NPSs. Three hundred and sixty-eight molecules were analyzed, of which 158 were newly captured NPSs, suitable for inclusion in the NPS*finder*® database. Those substances were classified based on their chemical structure, pharmacological mechanism of action, therapeutic indication, if any, and abuse liability. The main NPS classes identified were natural origin/herbal substances (25; 16%), cannabinoids (23; 15%), prescribed medications (23; 15%), synthetic opioids (20; 13%), phenethylamines (14; 9%), cathinones (11; 7%), and anabolic substances (8; 5%). The findings highlight ongoing diversification in substances identified across selected online sources during the post-pandemic period. The study benefits from a timely focus, a substantial and systematically curated dataset, and the application of a continuous web-crawling methodology enabling near real-time detection of emerging substances. The integration of pharmacological and chemical classification further enhances the interpretability and potential clinical relevance of the findings. However, results should be interpreted cautiously. The reliance on predominantly English-language, open-web sources may introduce selection bias and limit geographic generalizability, and the descriptive design does not allow inference regarding prevalence, user behavior, or causal trends. Within these constraints, web-crawling approaches may serve as valuable complementary tools to established early warning systems, supporting early signal detection and informing future toxicological and public health responses.

Keywords

novel psychoactive substances, addiction, NPS*finder*®, web crawler, drug misuse, recreational use

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Introduction

Novel Psychoactive Substances as a Public Health Threat

The landscape of Novel Psychoactive Substances (NPSs) is highly dynamic and continues to evolve rapidly, posing major challenges for clinicians, toxicologists, policymakers, and drug-control systems.[1,2] The term NPSs refers to substances that are not scheduled under the international drug conventions but may produce effects similar to those of controlled drugs.[1,2] NPSs are often described as "designer drugs" or "research chemicals," although some street terms, such as "bath salts," apply to specific subclasses, particularly synthetic cathinones.[1,3] Many NPSs are structurally related to established illicit drugs, including cannabinoids, opioids, dissociatives, benzodiazepines, stimulants, and hallucinogens.[1,3] Small chemical modifications may generate analogues, derivatives, or stereoisomers with pharmacological properties that resemble, but do not exactly reproduce, those of the parent compound.[4,5] These differences may affect potency, onset and duration of action, toxicity, and adverse effects.[5] NPSs are not necessarily newly synthesized compounds; many were first described years earlier but have only recently appeared in recreational drug markets.[5,6] A major concern is the rapid proliferation of these substances, combined with limited pharmacological and toxicological evidence, uncertain mechanisms of action, and incomplete knowledge of short- and long-term harms.[7,8] In addition, the absence of manufacturing standards and quality control raises concerns about purity, potency, adulteration, and contamination.[9] NPSs may be sold as powders, tablets, liquids, capsules, herbal preparations, or vaping products,[10,11] and may be consumed by smoking, snorting, injecting, swallowing, or "bombing."[10,12] They may be obtained through head shops, street-level suppliers, online vendors, or the darknet, with digital communication platforms increasingly facilitating access.[1,13,14] Their low cost, wide variability, availability and difficulty of detection have contributed to growing concern regarding misuse, especially among adolescents and young adults.[15] Commonly reported NPS classes include synthetic cannabinoids (SCs), synthetic cathinones, phenethylamines, piperazines, tryptamines, dissociatives, depressants, stimulants, and hallucinogens.[16-18]

Early Warning Systems in NPSs Detection

Given the speed with which NPS appear, circulate, and diversify across markets, timely detection and risk assessment are essential.[4,7] Early Warning Systems (EWSs) play a central role in this context by monitoring emerging substances, identifying harms, and informing regulatory, clinical, and public health responses. At global level, the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) provides an important framework for monitoring NPSs trends, legal responses, toxicological risks, and geographic spread.[7] To date, more than 110 countries have contributed reports to the UNODC EWA, resulting in the identification of over 800 unique NPS worldwide.[7] These data support evidence-informed decision-making by clinicians, researchers, public health professionals, and law-enforcement authorities.[19] Similarly, in Europe, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), in collaboration with Europol, monitors emerging substances and maintains a database containing more than 1200 compounds.[4,20] In 2022, approximately 930 NPS were being monitored in Europe, including 41 substances newly notified that year.[21] Recent reports have highlighted several important threats, including the continuing emergence of novel synthetic opioids (NSOs), particularly fentanyl analogues and nitazene derivatives.[20,21] National EWS frameworks may further strengthen this response by integrating toxicology, forensic, clinical, and regulatory data streams. In this way, coordinated early warning activity can support faster identification of emerging harms and more timely public health action.[7]

Impact of the COVID-19 Pandemic on NPSs Markets

The COVID-19 pandemic substantially affected daily life, mental health, healthcare systems, and global economies. It also disrupted drug production, trafficking, supply chains, and access routes.[22] In several settings, traditional illicit drug markets were affected by shortages, price fluctuations, and changes in purity, while online sourcing appeared to become more prominent.[23,24] In parallel, concern increased regarding the emergence of specific NPS categories, particularly NSOs such as nitazene derivatives.[23] Some reports also described increased use or online visibility of substances such as pregabalin, codeine, and tramadol during lockdown periods,[25] while use patterns for some traditional drugs appeared to decline or temporarily change.[22,26] These changes were not uniform across countries, substances, or user groups. Indeed, the pandemic restrictions seemed to affect the demand for specific NPS classes such as NSOs and cathinones.[22,27]

The NPSfinder® Tool

NPS*finder*® is a specialized web-crawling tool developed by Damicom, a small-to-medium enterprise based in Rome, Italy, and used in collaboration with the NPS Research Unit of the University of Hertfordshire, UK.[28] The tool was designed to support online early detection of emerging psychoactive substances by scanning selected websites and extracting substance-related information, including chemical names, street names, molecular features, and reported psychoactive effects.[28] The NPS*finder*® operates continuously and focuses on selected, open-surface, high-visibility psychonaut websites and forums.[19,22,27-29] Its purpose is to identify substances discussed, advertised, or described online in relation to

psychoactive effects, misuse, or recreational experimentation. Accordingly, the information extracted by the tool should be interpreted as a surveillance signal from selected online environments rather than as a direct measure of population prevalence or user behavior.[27,30] In addition to potentially novel compounds, the NPS*finder*® may also identify older or previously described substances that newly emerge in online discussions or reappear in changing misuse contexts.[22,29,30] This feature is particularly relevant for early warning activity, as online psychonaut environments may highlight substances before they are captured by more formal clinical, forensic, or regulatory systems.

Aim of the Study

This study aimed to identify and classify NPSs recently reported and newly captured by the NPS*finder*® during the post-pandemic period, focusing on their characteristics, mechanisms of action, and reported psychoactive properties. Data were extracted from selected open-surface psychonaut websites between January and September 2023. This study adopted a surveillance-oriented operational framework. Substances were considered relevant for inclusion when they were discussed online in relation to psychoactive effects, recreational use, or misuse potential. By targeting this timeframe, this study aimed to uncover potential shifts in the NPS landscape, reflecting current trends and emerging substances and classes in the continuously evolving drug market, especially during the transition out of the COVID-19 public health emergency.

Methods

NPSfinder® Crawling Tool and Database

For the purposes of this study, the password-protected NPS*finder*® software was used exclusively by registered researchers. The tool operated continuously on a 24/7 basis and scanned selected website addresses and uniform resource locators (URLs) in order to detect substances newly appearing in the monitored online environments. Further technical details of the NPS*finder*® tool have been reported previously.[28] When a potentially relevant substance was identified, it was added as a candidate entry for subsequent review and possible inclusion in the expanding NPS*finder*® database (Figure 1).

Data Collection, Screening, and Identification of Emerging Substances

The investigation focused on selected high-visibility, open-surface websites. Websites were chosen on the basis of predefined practical criteria, including Google indexing, high user traffic, frequency of access, and the volume of psychonaut-related content. The main websites included in this study were DrugsData, Chemicalfrog, and Legit-rcvendorsusa, as these platforms were considered prominent sources of NPS-related information at international level (Table 1).

The monitored period extended from January to September 2023. This timeframe was selected to capture substances appearing during the later phases of the COVID-19 period and the months immediately following the World Health Organization's declaration in May 2023 that COVID-19 no longer constituted a global public health emergency.[31] The predominant language of the monitored websites was English, although content in other languages, including Dutch, French, Turkish, Swedish, Spanish, German, Russian, and Italian, could also be encountered.[32] Following the crawling phase, Damicom IT exported the raw data into an Excel spreadsheet. The initial dataset contained 370 entries. After removal of two duplicate entries, 368 unique entries remained for manual screening and review (Supplemental Table 1). The first author (ED) reviewed the full dataset manually. This process was then reviewed, discussed, and validated by three co-authors (AV, FS, LL) with expertise in addiction medicine, psychiatry, and pharmacology in order to strengthen classification reliability. Disagreements or uncertainties regarding eligibility or classification were resolved through discussion and consensus among the reviewing authors.

Each entry underwent a structured multi-step review. First, duplicates and substances already present in the existing NPS*finder*® database were excluded. Second, entries without sufficient evidence of psychoactive properties or misuse potential were removed. Third, each remaining substance was assessed through literature searches and database checks to determine whether it was relevant to the online NPS scene and whether inclusion in the updated database was justified. For the purposes of this study, a substance was considered eligible for inclusion when it appeared in the monitored online environments in connection with psychoactive effects, recreational use, or misuse potential, and when the available information supported its relevance for surveillance. This approach was broader than a strict definition of NPS and therefore allowed retention of certain prescribed medications, natural-origin substances, anabolic agents, precursors, metabolites, and other compounds when relevant to online surveillance activity. For this study, "newly identified" refers to substances newly captured for potential inclusion in the NPS*finder*® database during the study period. This term does not imply that a substance was newly synthesized, available globally, or reported for the first time in the scientific literature or in formal early warning systems.

Following this filtering process, 158 substances were suitable for inclusion as newly relevant entries in the NPS*finder*® database update (Figure 2). The substances were then grouped according to their main psychoactive or pharmacological characteristics into the following categories: natural-origin substances, cannabinoids, prescribed medications,

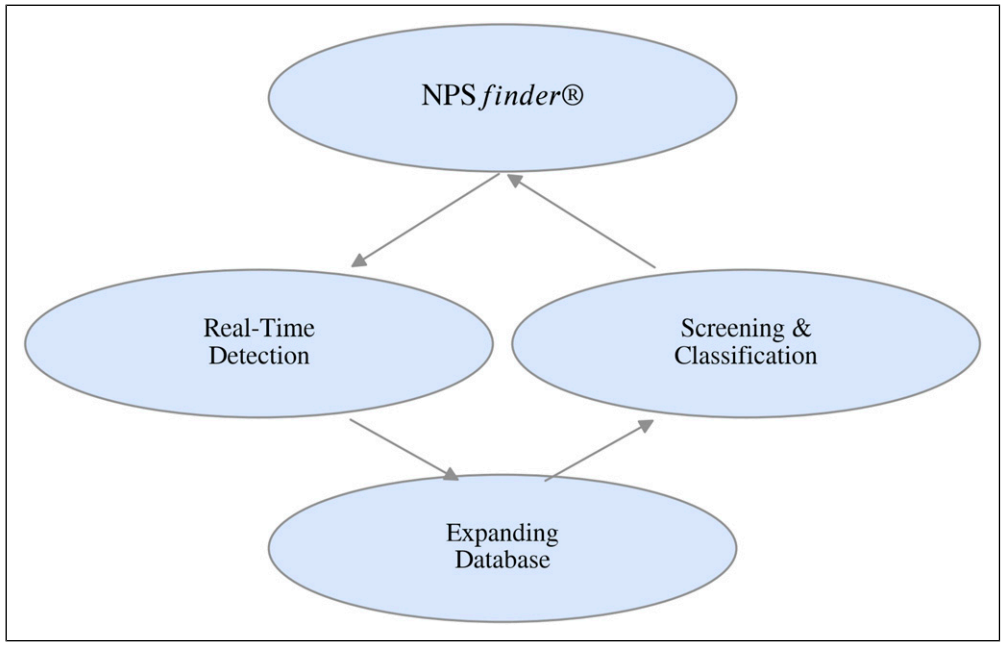

Figure 1. The NPS*finder*® tool and its main features

Table 1. Open-Surface Websites Monitored by the NPS*finder*® Web-Crawling Tool Between January and September 2023

N	Website name	URLs
1	DrugsData	https://www.drugsdata.org/
2	Chemicalfrog	https://chemicalfrog.com/
3	Legitrcvendorsusa	https://legitrcvendorsusa.com/

synthetic opioids, cathinones, anabolic substances, and other classes.[19,28] Where uncertainty arose regarding classification, the final decision was reached through discussion among the authors. All extracted information was stored in a restricted-access online environment protected by advanced firewalls.

Results

During the study period, the NPSfinder® detected 370 entries. After removal of two duplicate entries, 368 unique entries remained for review. The complete list and screening outcomes of all 368 unique entries are provided in Supplemental Table 1. Following manual screening and application of the study inclusion criteria, 158 substances were considered suitable for inclusion as newly captured or surveillance-relevant entries in the NPS*finder*® database update (Supplemental Table 2; Figure 4). Of the 368 unique entries screened, n = 120 were excluded because they were already present in the existing NPS*finder*® database; while n = 90 were excluded because they did not meet the eligibility criteria, since available evidence did not support their psychoactive or misuse relevance, or the available information was insufficient to justify inclusion.

Among these 158 substances, the most frequently represented categories were natural-origin substances/herbals, cannabinoids, prescribed medications, synthetic opioids, and phenethylamines (Figure 3).

A total of 158 substances were classified into 14 groups (Figures 3 and 4). The most frequent categories were natural-origin substances/herbals (25; 16%), cannabinoids (23; 15%), and prescribed medications used in recreational or misuse contexts (23; 15%), followed by synthetic opioids (20; 13%) and phenethylamines (14; 9%). Additional categories included cathinones (11; 7%), anabolic substances (8; 5%), PCP-like substances, piperidines, and psychostimulants (4 each; 2%). Fourteen substances (9%) were included in an "other" category, which comprised research chemicals, drug metabolites, nootropics, precursors, and compounds that could not be confidently assigned to a single pharmacological class (Figure 4).

All 158 substances were listed alphabetically in Supplemental Table 2 together with available information on molecular formula, chemical structure, mechanism of action, and relevant characteristics. Assignment to known NPS classes was based on previously published classification approaches.[33,34] Chemical names and molecular formulas were completed with support from PubChem,[35] and chemical structures were generated using PubChem Sketcher V2.4.

For a number of compounds, including DKAPBP, 5ABB, ISO-F, and X-PV, complete information on chemical structure, molecular formula, mechanism of action, or characteristics was not available. In these cases, the substances appeared to have been identified through preliminary forensic

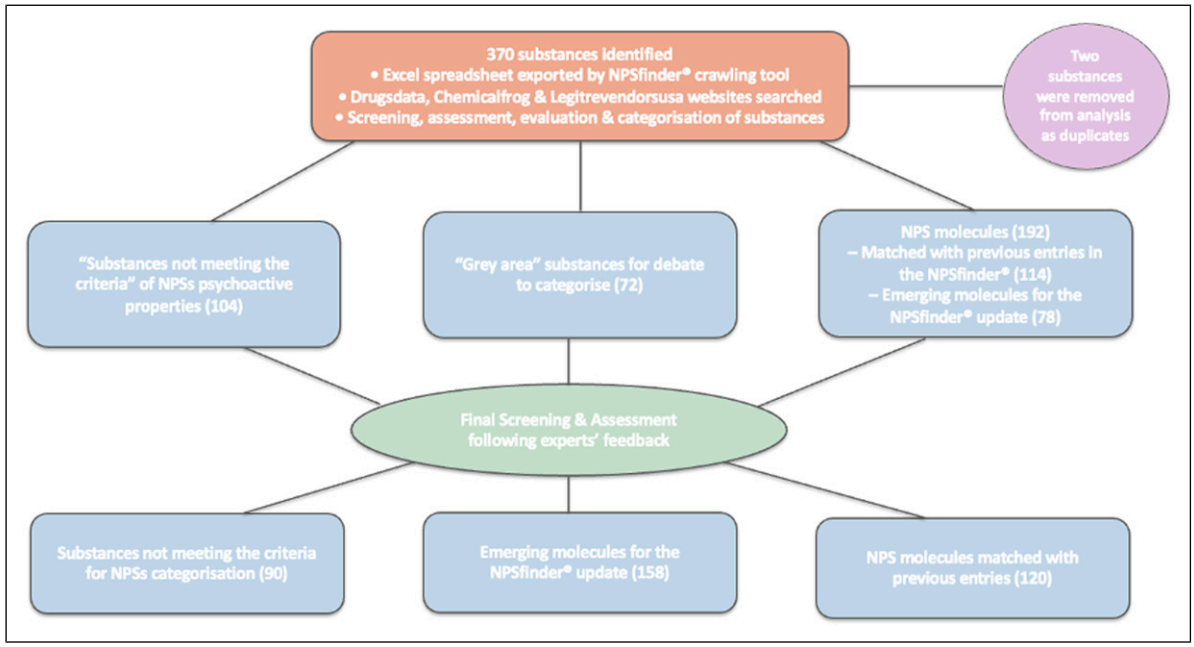

Figure 2. NPS*finder*® methodology. Flowchart displaying the data handling, systematic filtering, screening and analysis process

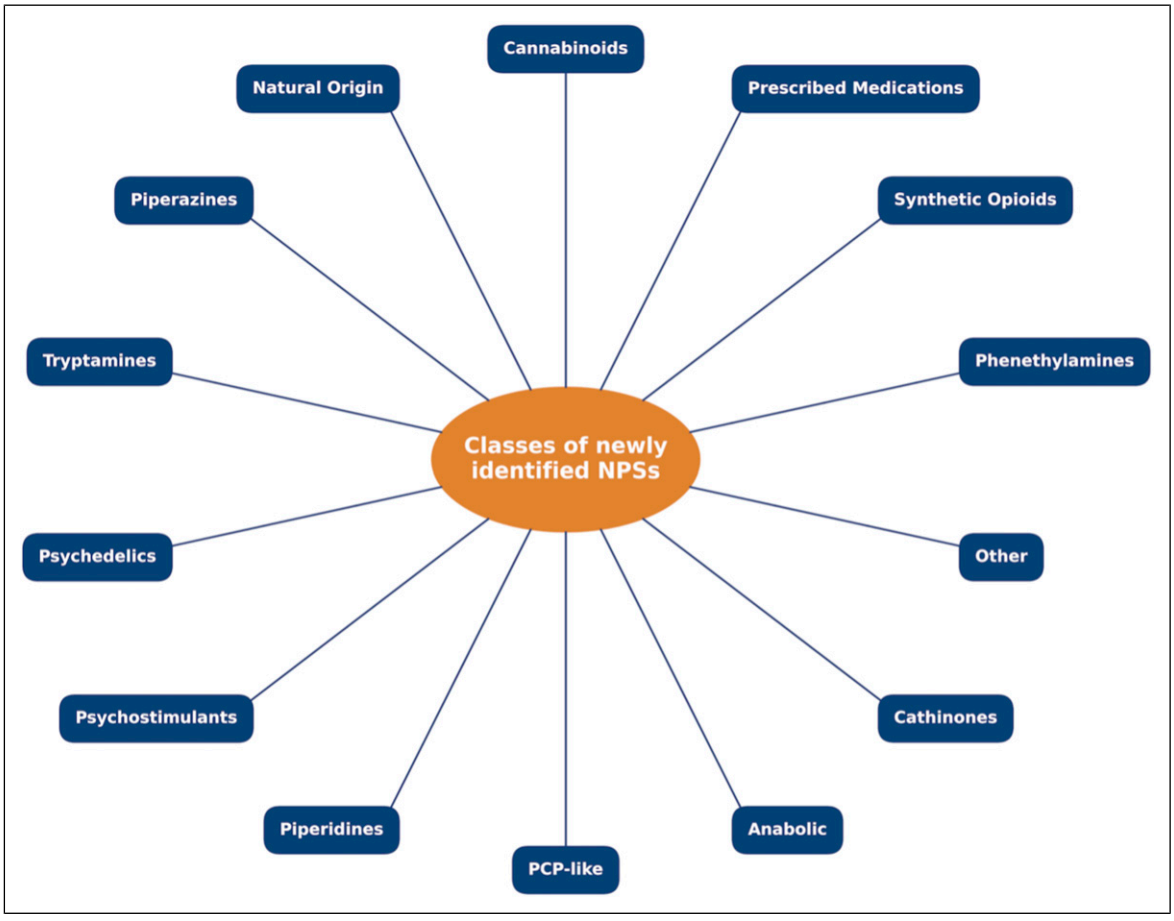

Figure 3. Classification of newly captured NPSs meeting the criteria for the NPS*finder*® Update. Flow chart displaying the class categorization of newly reported NPSs. *Other: Research chemicals, chemical compounds, nootropics, drug metabolites, precursors

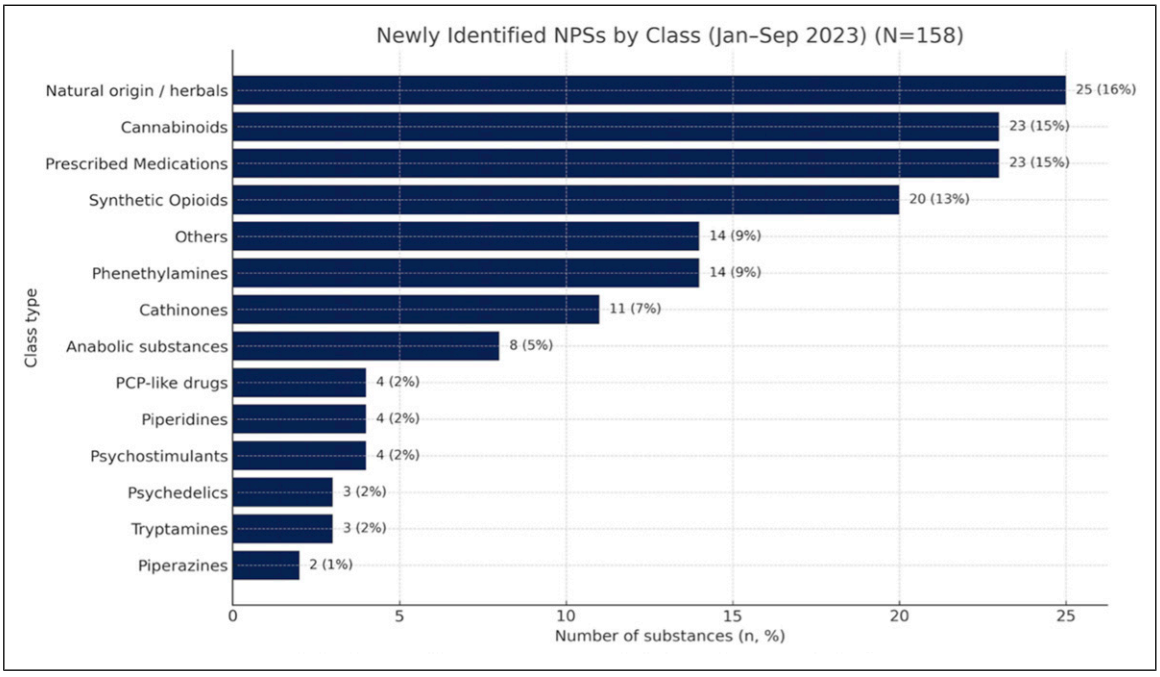

Figure 4. Distribution of the 158 newly captured NPSs from January to September 2023. The histogram shows the number and percentage of substances per class. *Other: Research chemicals, chemical compounds, nootropics, drug metabolites

toxicology alerts, laboratory reports, or early online reports, with little or no peer-reviewed literature available at the time of analysis. Examples of the newly detected substances included natural-origin products (e.g., methylecgonine cinnamate, myristic acid, mitragynine, piperine), synthetic cannabinoids (e.g., ADB-FUBIATA, EDMB-PINACA, 4F-APINACA, 5F-MDMB-BINACA), prescribed medications discussed in psychoactive or recreational contexts (e.g., buspirone, carbamazepine, doxepin, levamisole), synthetic opioids (e.g., fluoro-norfentanyl, metonitazene, 4-ANBocP, protonitazene), and phenethylamines (e.g., MDA 2-amido analog, MMDPPA, N-formylamphetamine), as detailed in Supplemental Table 2.

Discussion

Principal Findings and Comparison With Other Early Warning Systems

Since its launch in November 2017, the NPS*finder*® has identified and recorded a large number of substances from selected open-surface online environments.[28] The substances identified in this study reflect the breadth and dynamics of the online NPS markets, including cannabinoids, synthetic opioids, phenethylamines, cathinones, prescribed medications used for recreational purposes, natural-origin psychoactive products, and anabolic substances. These findings reinforce the public health importance of timely online monitoring, especially given the speed with which psychoactive substances appear, reappear, or are repurposed within web-based environments. This study distinguishes between a narrow definition of NPS and a broader surveillance-relevant category of psychoactive or misuse-related substances detected in selected online environments. Although the formal definition of NPS generally refers to substances not scheduled under the international drug conventions, early warning activities may also encounter prescribed medications, natural-origin products, precursors, metabolites, and other relevant substances when these appear in online discussions related to psychoactive effects, recreational use, or misuse.

In the present study, 158 substances met the surveillance-oriented inclusion criteria for addition to the updated database during the January-September 2023 period. Within the same timeframe, the EMCDDA described 26 newly identified NPSs in Europe, while the UNODC reported 31 NPSs worldwide, compared with 44 emerging psychoactive substances recorded in 2022. The EMCDDA and UNODC reported smaller numbers of newly notified NPSs than those captured by the NPS*finder*®. However, the systems differ substantially in geographic scope, data sources, evidential thresholds, inclusion criteria, and surveillance methods. Formal EWSs rely heavily on forensic, toxicological, clinical, and regulatory reporting, whereas the NPS*finder*® captures signals from selected psychonaut and vendor-facing online environments. For this reason, the larger number of substances recorded by the NPS*finder*® should not be interpreted as direct superiority over formal EWSs, but rather as evidence that web-based monitoring can complement established systems by detecting broader and earlier online signals.

In our study, the main classes of NPSs included natural NPSs/herbals (16%), prescribed medications used recreationally as NPSs (15%), cannabinoids (15%), and NSOs (13%). Similarly, the UNODC main NPS classes included a range of NSOs (36%), SCs (24%) and stimulants (24%), whilst the EMCDDA identified a range of SCs (35%), NSOs (27%), and phenethylamines (15%). There was also meaningful overlap between the databases in the main NPS classes identified, particularly cannabinoids, synthetic opioids, and stimulant-type compounds. This supports the value of the NPS*finder*® as a complementary surveillance tool capable of capturing categories that are also of concern to established international monitoring systems.[7,20,21] Conversely, SCs have been on the decline since 2020, likely due to the impact of both the COVID-19 pandemic and restriction measures on cannabinoids' resourcing.[36] In addition, the consistent rise of NSOs visibility highlights the preference of users for highly potent synthetic alternatives to traditional illicit substances. This constitutes a severe risk for public health due to unpredictable toxicity, complex pharmacodynamics, risk of dependence, and overdose.[7,21] According to the 2023 EMCDDA report, fentanyl derivatives and SCs were highlighted as the most hazardous NPS categories in Europe. Also, the detection of stimulant-type NPSs, such as cathinones and phenethylamines, here described is in line with previous reports, showing a persistent interest in stimulant NPSs. Indeed, both stimulants and SCs have featured among the most prevalent NPS classes since 2008 in Europe.[36,37] A significant presence of prescribed medications and products of natural origin/herbals used as NPSs suggests that online psychoactive discourse extends beyond classical NPS classes and users' shift, possibly being perceived as "safer options."[38] These data are in line with a reported increased popularity of self-medication use and alternative herbal treatments.[38–40] Stimulant-type substances remained as popular choices in the online environments due to euphoric, psychoactive effects and use as party drugs, consistent with their continued relevance in broader surveillance reports.[41] Finally, the anabolic agents' current identification may suggest an overlap between recreational NPSs and performance-enhancing drug markets.[42]

*Classes Detected From the NPS*finder®

NPSs of Natural Origin/Herbals. Natural-origin psychoactive compounds such as kratom, *Salvia divinorum*, and hallucinogenic mushrooms continue to present surveillance challenges, particularly because they may be perceived as more accessible or less risky than synthetic drugs.[43] In our dataset, natural-origin substances represented the largest category, accounting for 25 of the 158 included entries (16%). This class included aromatic esters, alcohols, organic acids, essential oils, spices, and other naturally derived products. Their identification is important from a surveillance perspective, especially because "natural" products might carry significant toxicological risks, may be adulterated, and used in combination with other psychoactive substances.[43-46] Some natural NPSs have been known for their historical and traditional medicinal use, although their contemporary recreational use has remained largely unregulated, leading to unpredictable psychological, physiological and toxicological effects.[44,47] Preference for natural NPSs is associated with the desire of users to experience hallucinations, dissociation, and altered perception. Severe intoxication, overdose risk, addiction, and even fatalities may occur from natural NPS use, especially when combined with other drugs, increasing health risk.[43,46] Despite herbal smoking mixtures being among the most popular NPSs forms of abuse,[48] there are still underreporting issues from other EWSs. For instance, a vitamin E synthetic derivative, called Vitamin E Acetate, has been an emerging adulterant in many e-vaping mixtures smoked for recreational purposes, posing a serious risk for lung damage. This product has been reported as the potentially causative agent in the 2019 outbreak of e-cigarette/vaping product use-associated lung injury (EVALI) in the United States.[49] Another urgent issue is the polysubstance misuse reported by kratom users; when the compound is ingested in combination with prescribed opioids and benzodiazepines, the intoxication risk severity may well increase.[50,51] Therefore, the development of organized health promotion strategies and raising of public awareness about the potential risks of natural NPSs are of utmost importance.

Synthetic Cannabinoids (SCs). Synthetic cannabinoids (SCs) remain one of the most dominant NPS classes in international surveillance systems.[19,21,33,52] Their continued emergence reflects rapid structural modification, high potency, and the capacity of producers to generate new analogues that complicate detection and control.[37,53,54] In our dataset, 22 synthetic cannabinoids and one entry classified as a natural cannabinoid were identified, representing approximately 15% of all included substances. This made cannabinoids the second most frequent category. Most of the identified compounds belonged to indazole- or indole-based carboxamide/carboxylate groups and included MDMB-/ADB-derived structures, as well as compounds with 5F substitutions and other side-chain modifications (e.g., 5F-MDMB-BINACA, 5F-PB-22 analogue, ADB-4en-PINACA, MDMB-3en-BUTINACA, MDMB-4en-PICA, MDMB-5Br- INACA, ADB-5Br-INACA, 8Cl-ADB). We noted the presence of FUB-/benzyl-derivative structures (e.g., FUB-MDMB, ADB-FUBIATA). SCs remain among the most frequently identified NPSs worldwide, with more than 209 compounds reported in the European Union member states since 2008, accounting for approximately 60% of all NPS seizures by 2020.[54] Seizures of cannabinoid-infused herbal materials have increased, with a peak in 2021.[21] SCs' popularity is driven by their high potency, perceived euphoric mood and relaxation, but also misleading marketing as "legal highs" and easy access, especially among young adults.[55,56] SCs are found in various

formulations, such as herbal mixtures (e.g., wrapped in foil packages), powder, tablets, capsules, and liquid for e-cigarettes.[56] SCs mimic the effects of THC from natural cannabinoids but due to high potency and unknown pharmacodynamics, they may lead to more intense and unpredictable outcomes such as addiction, sleep disturbances, obsessive-compulsive disorder, depression, anxiety, paranoia, psychosis and fatal intoxications.[57] Cases of acute intoxication may lead to neurological and cognitive impairment, memory loss, suicidal ideation, seizures, and cardiovascular arrest risk as well.[37,55] Chronic SCs use has been associated with increased risk of persistent neuropsychiatric symptoms, especially in vulnerable individuals.[37,55,56] Withdrawal symptoms can be intense with commonly reported restlessness, irritability, cravings, high blood pressure, nausea, tremor and nightmares. SC users also tend to be polysubstance users, ingesting other NPSs or prescription drugs as well,[38-40,58,59] hence running a high risk of severe intoxication, organ failure, and death.[37,56] Some SCs could arguably play a potential protective role in inflammation, neurodegenerative diseases (e.g., Alzheimer's; Parkinson's disease), arthritis and cancer,[56,60] but only in tightly controlled clinical settings. The compounds dominating our dataset have been strongly associated with unpredictable adverse effects and severe toxicity at even low doses.[61-63]

Prescribed Medications. Misuse of prescribed and over-the-counter medications represents an increasingly important concern of the broader psychoactive substance landscape, contributing to a growing public health concern turning into an epidemic; this may be especially an issue in developed countries.[40,64] One would argue that there was a clear increase in prescribed medications' misuse during the pandemic[22]; this has likely been associated with an increase in the "doctor shopping" phenomenon, whereby prescriptions for the same drug from multiple prescribers are recorded.[65] Well-known examples of abused prescribed substances include antidepressants, anxiolytics, opioid analgesics, and gabapentinoids.[40,64,66] Medications can be misused for their sedative, euphoric, anxiolytic, or hallucinogenic effects.[33,58,59,67] In line with our findings, the last two decades have seen a large increase in medication misuse; twenty-three compounds were recorded, constituting 15% of total emerging NPSs identified. This class included substances such as buspirone, carbamazepine, doxepin, levamisole, and xylazine. Their appearance in the dataset is noteworthy because prescribed medications may be diverted, combined with other substances, or used outside therapeutic indications, with resulting risks of dependence, toxicity, polypharmacy, hospitalization, and death.[58,68–73] These compounds appeared in the monitored websites in recreational, misuse-related, or psychoactive contexts. Their presence, therefore, reflects relevance to the online NPS trends and shifts rather than formal reclassification as conventional NPSs. An emerging substance of interest here identified is xylazine, a prescribed veterinary medication, which has been recently reported as a misused drug[69,70]; its low cost and ready availability may be a reason for global concern.[71] Regulatory prescription-monitoring interventions are crucial to tackle this issue, as well as better strategies for raising awareness of prescription drugs' misuse and abuse.[1,40,72] Healthcare professionals, and especially pharmacists, could play an important role in preventing and reducing the misuse of prescribed substances by recording suspicious prescription requests.[40,64,73] These findings reinforce the need for closer integration between web-based surveillance, prescription-monitoring activity, and public health communication.

Novel Synthetic Opioids. Novel Synthetic Opioids (NSOs) remain among the most concerning emerging drug categories because of their very high potency and association with overdose and fatal intoxication.[21,33,74,75] In our dataset, twenty synthetic opioids were identified, accounting for 13% of all substances. These compounds included nitazenes (e.g., etonitazepyne, metonitazene, protonitazene, N-piperidinyl etonitazene), fentanyl analogues (e.g., iso-butanoyl-4-fluorofentanyl, propionyl-fluoronorfentanyl), and a range of precursors, intermediates, and metabolites. The presence of nitazenes is consistent with recent alerts highlighting their growing relevance in drug-related harms.[21,76–78] The identification of both end-products and precursor-related compounds also suggests rapid adaptation within illicit production and supply chains.[78,79] Substances in this class may be active at very low doses and may be sold deceptively as heroin, oxycodone, or other opioids, increasing the risk of accidental exposure and fatal overdose.[76,80] The nitazenes and fentanyl analogues we detected are related to severe low-dose toxicity, respiratory depression and overdose fatalities often requiring multiple naloxone doses.[28,76–78] The high proportion of fentanyl precursors/intermediates we detected aligns with the rapid and adaptive illicit manufacturing processes.[78,79] NSOs are possibly the most potent, dangerous, rapidly evolving and lethal NPSs.[33] Characterized by structural diversity, they may be hundreds of times more potent than heroin.[21] Well-known compounds belonging to the NSO class include fentanyl analogues, nitazenes, brorphine, and etonitazepyne.[74,75] NSOs are frequently sold online and are, at times, mixed with other drugs, often without their users being aware, hence significantly increasing the risk of overdose, intoxication and death.[21] As with other NPSs, some NSOs have been studied for potential benefit in pain management; such clinical applications remain, however, controversial.[81]

Phenethylamines. Phenethylamines form a large and structurally diverse class of psychoactive substances that may produce stimulant, empathogenic, hallucinogenic, or mixed effects.[41,82] In the present study, 14 phenethylamines were identified, accounting for 9% of the identified substances. The class in our dataset included MDMA/MDA analogues,

amphetamine- and methamphetamine-related derivatives, and psychedelic compounds such as 2C-B-related analogues. These findings are in keeping with surveillance reports showing that phenethylamines remain relevant within the European and broader NPS landscape.[7,21] From a pharmacological perspective, many phenethylamines act through monoaminergic pathways and, in some cases, serotonergic receptor systems, contributing to stimulant and psychedelic effects.[41,82] At the same time, this class remains clinically important because dose uncertainty, mis-selling, and variable potency may increase the risk of toxicity. High or uncertain doses, though, can induce psychosis, agitation, paranoia, hyperthermia, cardiovascular complications and, eventually, genotoxicity.[41,83] There have also been cases of overdoses and fatalities.[41,84] Some phenethylamines have been explored in clinical research for their potential therapeutic use in treating depression, PTSD and anxiety, showing a potential therapeutic interest.[85,86]

Cathinones. Synthetic cathinones, commonly referred to as "bath salts," remain a persistent class within the NPS landscape.[12,21,36] They are commonly marketed as stimulants and are often used for effects such as increased energy, alertness, and euphoria.[12,87] They are popular among young adults, mainly because of their ability to mimic the effects of traditional psychostimulant drugs such as cocaine, MDMA and amphetamines.[88] In the present study, 11 cathinones were identified, accounting for 7% of the substances identified. Although this class was not among the most frequent in our dataset, its continued presence is consistent with previous surveillance data showing sustained circulation of cathinones in drug markets.[21,36] Their potential harms are associated with acute toxicity, behavioral disturbance, cardiovascular complications, and polysubstance use.[89] On the other hand, potential therapeutic applications include depression and fatigue.[90,91]

Anabolic Substances. Eight anabolic substances (5%) were identified in the monitored dataset. These compounds appeared in online contexts relevant to misuse, enhancement, or broader due to availability in drug markets. Their identification may indicate some intersection between psychonaut, image- and performance-enhancing drug, and broader gray-market substance environments.[42,92]

Implications for Public Health, Research, and Policy

The present findings support the value of web-based monitoring as a complementary component of contemporary early warning activity. The NPS*finder*® cannot replace formal systems based on toxicology, clinical reporting, seizures, or laboratory data. However, it may provide rapid descriptive signals regarding substances that are becoming visible in selected online environments before they are fully reflected in established datasets.[22,28,29,93] This study also builds on earlier work from our group examining online drug-related activity during the COVID-19 period.[32] Compared with previous crawling exercises, the current dataset captured a broader range of substances, including a marked presence of prescribed medications, natural-origin products, cannabinoids, and synthetic opioids. These differences may reflect changing online visibility across time, although direct causal conclusions should not be drawn. From a public health perspective, the findings highlight the importance of maintaining adaptive monitoring strategies capable of detecting not only classical NPS classes but also boundary substances that may emerge in misuse contexts. For clinicians, toxicologists, and addiction specialists, such data may help prioritize awareness of compounds likely to appear in presentations of intoxication, dependence, or polysubstance use. For policymakers and regulatory agencies, these findings support the value of integrating digital surveillance with toxicology, forensic, and public health reporting systems. Public health communication should also reflect the fact that substances discussed online may include products marketed as "natural," "legal," or "pharmaceutical," which may nonetheless carry substantial risks when misused, combined with other substances, or consumed in uncertain formulations.[94] A major burden in NPS landscapes is how quickly they diversify, making it challenging to control. The traditional forensic, toxicological and clinical case study assessments and reports often pose limitations concerning real-world patterns, preferences, and trends of NPSs use, creating important gaps in public health promotion and harm risk preparedness.[95,96] The outcomes of this study have shown that web-based surveillance tools can bridge this gap by offering real-time updated information on emerging threats; this may enable policymakers to implement a range of strategic preventative interventions based on real-world data evidence.[22,97] Insights into NPSs availability, trends, patterns of use, and preferences can facilitate the development of targeted public health interventions.[98]

Strengths and Limitations

This study provides a timely contribution to understanding the evolving NPS landscape in the post-pandemic period, addressing a high-impact area of relevance for public health and drug surveillance. The use of the NPS*finder*® web-crawling platform enabled continuous monitoring of online environments and facilitated the identification of a substantial number of candidate substances, supported by a structured filtering process and expert validation. The additional pharmacological and chemical classification of identified compounds enhances the translational value of the findings for toxicological research and clinical awareness. Furthermore, the study illustrates how web-based surveillance tools may complement established early warning systems, such as those coordinated by EMCDDA and UNODC, by capturing early online signals that may precede formal reporting.

Nevertheless, several limitations should be acknowledged. The reliance on selected open-web, predominantly English-language sources may introduce selection bias and restrict the generalizability of the findings to a global context. In addition, the descriptive nature of the study limits the ability to perform quantitative trend analyses or establish causal relationships, and the data do not allow conclusions regarding real-world prevalence, patterns of use, or associated harms. Accordingly, the findings should be interpreted as indicators of online visibility rather than direct measures of substance use. Despite these constraints, the study supports the role of web-crawling methodologies as complementary components of NPS surveillance frameworks, offering timely insights that may inform future research, policy development, and public health preparedness.

Conclusions

This analysis supports the utility of the NPS*finder*® as a significant complementary real-time surveillance tool for continuously monitoring, updating, and classifying newly captured NPSs appearing in online environments. The 158 newly included entries reflect the diversity of compounds captured during the relatively short post-pandemic timeframe, underlining the rapidly evolving NPSs landscape and market adaptability towards regulatory restrictions, showcasing the urgent need for advanced and organized digital early warning monitoring systems.[22,27,30] These findings represent descriptive early warning signals rather than direct indicators of demand or population-level prevalence.

Future Research

Integrating real-time NPSs surveillance findings with forensic toxicology information, clinical case study reports and epidemiological analysis on NPSs users' patterns will better inform harm minimization strategies to enhance early detection, clinicians' practices and regulatory response efforts. This multi-source data approach could enhance the robustness of surveillance tools and suggest predictive models for identifying emerging high-risk NPSs. Furthermore, it is crucial to consider employing pharmacoepidemiology approaches and analytical methods, enabling researchers to compare findings from the NPS*finder*® with other sources of real-world data (RWD), real-world evidence (RWE), and outputs from other established EWSs. Future studies may also integrate findings from multiple diverse EWSs monitoring NPSs to develop a more comprehensive, systematic and representative picture of the NPSs trends globally. Finally, due to regional differences in NPSs availability and market trends, it would be of interest to use geographically-targeted surveillance tools to better inform and update regulatory agencies, raise public awareness, and hence enable timely policy interventions.

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Deligianni, E. contributed to conception and design, contributed to acquisition, analysis, and interpretation, and drafted manuscript; Vento, A. contributed to conception and design and critically revised manuscript; Papazisis, G. and Goulas, A. contributed to interpretation and critically revised manuscript; Lione, L. and Schifano, F. contributed to conception and design, contributed to acquisition, analysis, and interpretation, and critically revised manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

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Supplemental Material

Supplemental material for this article is available online.

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