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Understanding the evolving nature of novel psychoactive substances: Mapping 10 years of research

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ABSTRACT

Novel psychoactive substances (NPS) is an umbrella term used to describe a heterogeneous group of compounds that mimic the effects of existing drugs and whose demand and use rapidly emerge, change, or even vanish in the drug market. The novelty of this global phenomenon and its dynamic nature represent major challenges for the scientific community that constantly requires timely evidence-based inputs. Our aim is to review the literature on NPS and compare its temporal evolution according to the topics presented at the International Conference series on NPS over the past decade. Our analysis shows that some new clusters of research recently emerged in comparison to a previous review and that the material presented at the NPS Conferences anticipates the scientific literature by approximately 2.5 years. Such findings not only provide new original insights on the latest NPS trends but also address existing knowledge gaps in the NPS field, while emphasizing the importance of face-to-face thematic events supported by faster publication processes to inform prompt interventions and policy making.

Novel psychoactive substances (NPS) are a group of compounds that mimic the effects of existing drugs and that are purposely designed to elude drug legislation (Kuypers et al., 2021; Tracy et al., 2017). Although the toxicological profile of NPS is scarcely known, their use is oftentimes linked with adverse medical outcomes (Baumann and Volkow, 2016; Logan et al., 2017; Zawilska, 2015). For this reason, the spread of NPS represents a public health emergency that requires scientific investigation (Peacock et al., 2019; Simão et al., 2022). However, requests and use of specific NPS rapidly emerge, change, or even vanish in the drug market. Their dynamic nature represents a major challenge for the scientific community (Skinnider et al., 2021), which is in constant need of effective methods for the prompt detection and the pharmacological/toxicological profiling of the new products available on the market. This, in turn, does not allow timely design and evaluation of the efficacy of national drug policies and management of NPS users.

A previous study from Neoh et al. (2023) reviewed all the scientific literature on NPS using for the first time a scientometric approach. A sample of 2365 documents published in the past 12 years was analyzed in a data-driven fashion to identify the major thematic domains in the literature. A total of 10 major thematic clusters were identified. The largest cluster, "Mechanisms of NPS action", explored the neuropharmacological and neural effects of NPS use (Miliano et al., 2016). This cluster was followed by "Synthetic cathinones", a group of works on the availability and use of mephedrone and other cathinones (Wood and Dargan, 2013), and by "Neuropharmacology of NPS", a cluster in which documents elucidated the neuropharmacological effects of NPS (Papaseit et al., 2016). The next thematic cluster by size was "Intoxication profile and detection of NPS use", where documents mainly focused on the intoxication profiles of NPS users and substance detection methods (Salomone, 2015). This theme was followed by "New synthetic opioids", which represents a response to the rising use of synthetic opioids globally as well as the surge in opioid overdose deaths in the United States of America (Vandeputte et al., 2022). "New synthetic opioids" was the most recent theme in the NPS literature. The following major cluster was "Legal aspects of NPS use", a collection of works interested in characterizing the legal status of emerging NPS (Bilinski et al., 2012; McNabb et al., 2012). Subsequently, in response to the widespread use of synthetic cannabinoid receptor agonists and their penetration into the

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recreational drug market, the cluster "Synthetic cannabinoid receptor agonists" examined the effects of the recreational use of these compounds (Cannaert et al., 2020). Other groups of documents investigated the application of chemical methods to NPS detection (cluster "Metabolite profiles for drug screening"; e.g., Welter et al. (2014)). Ultimately, the last two thematic clusters by size were "NPS and the Internet", a cluster of documents focused on the role of the Internet as a virtual marketplace/source for information on NPS (Corazza et al., 2014; Deluca et al., 2012), and "NPS as a New Public Health Problem", where clinical data is presented to highlight the harmful effects associated with NPS use (Karila et al., 2015; Zawilska, 2015).

The general goal of this study is to thematically characterize the evolving nature of the studies on NPS during the past decade. This was done by analyzing the thematic domains of the scientific works presented at the International Conference on NPS, which started as part of a series in 2012 in Budapest and established itself as the largest event in the field attracting experts from over 50 countries (Corazza et al., 2017b). The series, now at its 10th edition, aims to present the state-of-the-art on NPS with the strength of an interdisciplinary and international approach (Substances, 2023). The specific aims of the current study are: *(i)* starting from the thematic clusters identified in the article by Neoh et al. (2023), to classify all the works presented during the previous nine editions of the International Conference on Novel Psychoactive Substances; and *(ii)* to compare the clusters that emerged in the scientific literature with the temporal trends of topics in the contributions presented at the International Conferences on Novel Psychoactive Substances.

To conduct the study, we downloaded the titles and retrieved the abstracts of all the works presented during all nine editions of the International Conference on Novel Psychoactive Substances, from 2012 to 2022. For the analysis, we did not differentiate between oral and posters presentation. The reason for this choice is that the Conference did not have a traditional poster session. Conversely, posters were presented as oral talks. All data was downloaded from the conference's main website on the date 25 October 2022 (Substances, 2023). A total of 515 contributions (M = 57.22; SD= 28.81 contributions per edition) were presented during the nine editions of the International Conference on Novel Psychoactive Substances. All the contributions were coded based on their main focus of research based on their title and abstract. To classify the contributions, we used the labels referring to the ten main domains of research previously identified by Neoh et al. (2023) in the NPS literature. Specifically, the ten labels used were: "Mechanism of action", "Synthetic cathinones", "Neuropharmacology of NPS", "Intoxication profile and detection of NPS use", "New synthetic opioids", "Legal aspects of NPS use", "Synthetic cannabinoid receptor agonists", "Metabolic profiles for drug screening", "NPS and the Internet", "NPS as a New Public Health Problem". Contributions that did not fit in the previous thematic domains were coded using the label "Others".

Two coders independently assigned each contribution to one of the 11 labels. Coders were instructed to choose only the most fitting label for each contribution. Cronbach's alpha was assessed on 25% of the sample as an index of inter-coder reliability and was considered acceptable (α >.85). The category of "Others" was then thematically analyzed to identify further common thematic subcategories. Three labels, which were not identified in the scientometric study from Neoh et al. (2023), emerged and were called: "Response to NPS", "Sports/-Doping/Enhancement" and "Covid-19".

The most frequent research theme that appeared in the nine editions of the International Conference on Novel Psychoactive Substances resulted to be "Synthetic cathinones" (total contributions = 105). This central theme was followed by "Legal aspects of NPS use" (total contributions = 58), "Neuropharmacology of NPS" (total contributions = 57), and "Mechanism of action of NPS" (total contributions = 52).

From the relative frequency of themes by years, it emerges that contributions on synthetic cathinones were highly prevalent throughout all the editions of the conference (relative frequency = 0.20 of the total contributions). Only in 2013, 2014, and 2020 synthetic cathinones were not the most frequent theme of the conference. In 2013, the main focus of the conference was the investigation of the mechanisms of action of novel psychoactive substances (relative frequency = 0.31 in 2013). In 2014, the focus was more on framing the novel psychoactive substances as a new public health problem (relative frequency = 0.25 in 2014) as well as the understanding of their neuropharmacology and the definition of detection methods. Ultimately, in 2020, the main thematic focus of the conference was the presentation of results regarding new synthetic opioids and synthetic cannabinoid receptor agonists (see Fig. 1 for the frequencies of themes computed by year/conference edition).

Next, we compared the temporal trends between the clusters that emerged in the scientific literature in Neoh et al. (2023) and the topics presented at the International Conferences on Novel Psychoactive Substances. Accordingly, the average year in which clusters' documents were published was used as a proxy to identify the peak of interest for the specific theme in the NPS literature. The temporal trajectory of themes in the International Conferences on Novel Psychoactive Substances was outlined by means of the relative frequency of each topic by year/edition of the conference. Except for two themes (i.e., synthetic cathinones and legal aspects of NPS use), the peak of interest for all main research domains, as identified by Neoh et al. (2023), was preceded on average by 2.5 years by some initial contributions in the International Conference on Novel Psychoactive Substances (see Fig. 2). Noteworthy, the peaks in the number of Conference's contributions regarding the mechanisms of NPS action, intoxication profile and detection of NPS use, and NPS as a new public health problem were all before the research peak identified in the published scientific literature. As regards synthetic cathinones and legal aspects of NPS use, these thematic clusters have their peak in 2012, the year in which the first edition of the Conference took place in Budapest. For this reason, it was not possible for the Conference's contributions to anticipate these lines of research.

The current work characterized the main themes of interest in the past 10 years of research on NPS. Furthermore, it presented a comparison between the temporal trajectories of the main themes in the scientific literature and in the contributions at the International Conference on Novel Psychoactive Substances. Some limitations need to be considered before moving on to the discussion of the results. First, the results are limited to contributions presented at the International Conference series on Novel Psychoactive Substances. However, the analysis of contributions presented at the Conference is highly informative on the trends of research in NPS. A second limitation of the work is that we instructed the two independent coders to classify the Conference's contributions by identifying only one main research interest. Although an acceptable inter-rater reliability was computed on the 25% of the sample, using a combination of labels could expand the results of this work.

In agreement with the scientometric review by Neoh et al. (2023), the past ten years of research on NPS show a strong interest in synthetic cathinones as well as the legal status, the mechanisms of action and the neuropharmacology of NPS. Synthetic cathinones (e.g., mephedrone) are stimulant compounds that represent the vast majority of the NPS observed in clinical settings and they seem to pose a serious risk in terms of adverse medical outcomes for the users (Tracy et al., 2017). In the literature, the definition of the legal status of NPS classes and the investigation of their mechanisms of action emerges as pivotal and it highlights the close dialogue between local governments and the scientific community in tackling the NPS epidemics (Wilkins et al., 2017).

Some contributions presented at the International Conference on Novel Psychoactive Substances did not fit any of the research domains identified by Neoh et al. (2023). By inspecting these works using a qualitative approach, three further research themes were identified. Particularly, these contributions investigated the users' response to NPS, the use of NPS as performance-enhancers in sport activity, and the misuse of NPS during the Covid-19 pandemic. We believe these three clusters were not captured in Neoh et al. (2023)'s review for different

Reearch theme	2012	2013	2014	2016	2017	2019	2020	2021	2022	Total
Mechanism of NPS action	27.27	31.25	3.92	20.27	12.26	5.26	5.26	8.51	1.39	10.10
Synthetic cathinones	31.82	12.50	1.96	25.68	22.64	18.95	13.16	27.66	29.17	20.39
Neuropharmacology of NPS	4.55	12.50	21.57	1.35	8.49	14.74	5.26	14.89	12.50	11.07
Intoxication profile and detection of NPS use	13.64	6.25	23.53	9.46	1.89	3.16	5.26	8.51	8.33	7.38
New synthetic opioids	0.00	3.13	0.00	1.35	10.38	7.37	21.05	12.77	8.33	7.77
Legal aspects of NPS use	9.09	3.13	3.92	10.81	17.92	12.63	10.53	6.38	12.50	11.26
Synthetic cannabinoid receptor agonists	4.55	3.13	5.88	5.41	8.49	13.68	21.05	4.26	5.56	8.54
Metabolic profiles for drug screening	4.55	0.00	0.00	2.70	0.94	3.16	0.00	0.00	5.56	1.94
NPS and the Internet	4.55	9.38	11.76	8.11	3.77	5.26	5.26	2.13	1.39	5.44
NPS as a New Public Health Problem	0.00	15.63	25.49	6.76	3.77	3.16	5.26	2.13	5.56	7.18
Response to NPS	0.00	0.00	0.00	2.70	5.66	5.26	0.00	0.00	2.78	2.91
Sports/Doping/Enhancement	0.00	3.13	1.96	5.41	3.77	7.37	5.26	4.26	2.78	4.47
Covid-19	0.00	0.00	0.00	0.00	0.00	0.00	2.63	8.51	4.17	1.55

Fig. 1. Heatmap from the percent frequencies computed by year for the thematic domains in the novel psychoactive substances research.

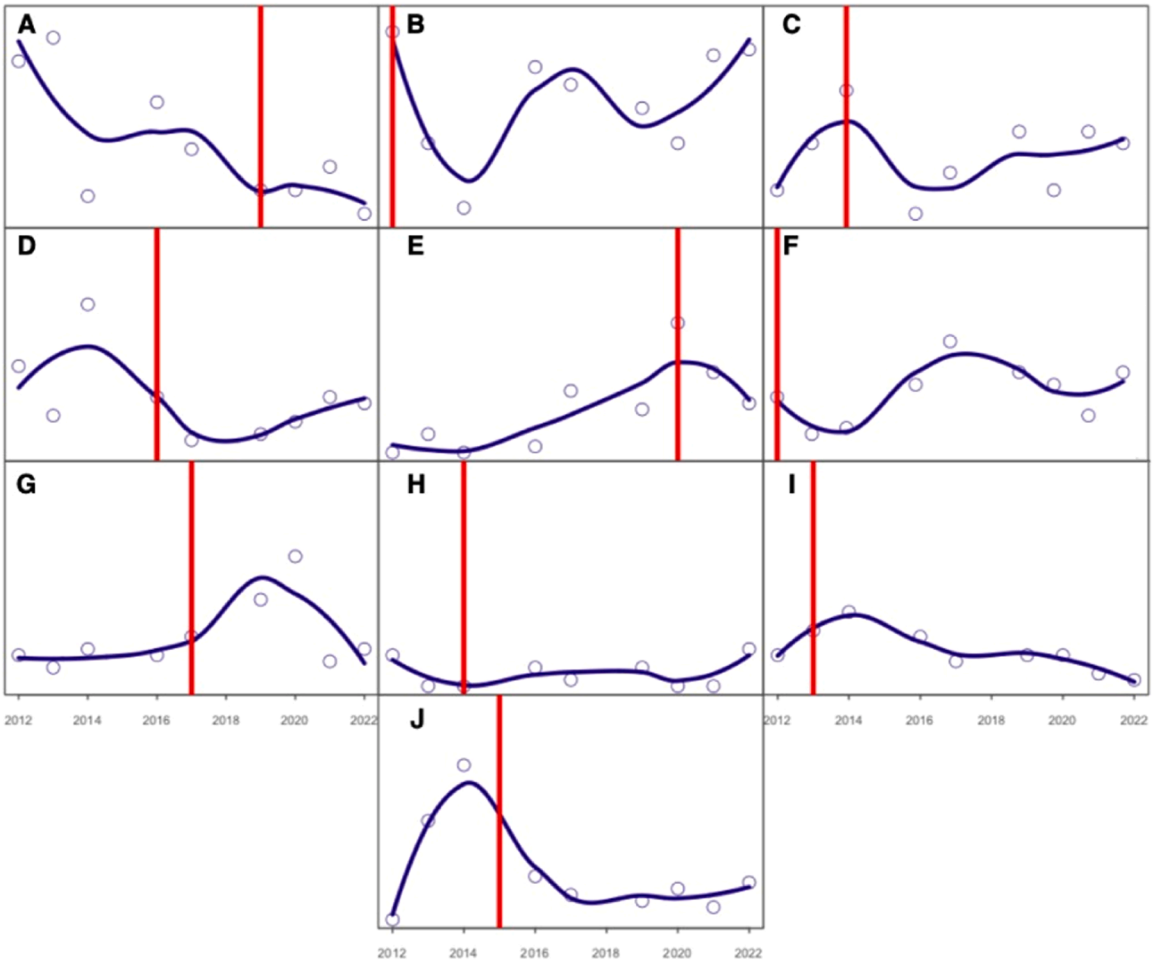

Fig. 2. Temporal trajectories of research themes in the literature on novel psychoactive substances (NPS) by year. The research themes identified by Neoh et al. (2023) are reported in the figure. (**A**) Mechanisms of NPS action; (**B**) Synthetic cathinones; (**C**) Neuropharmacology of NPS; (**D**) Intoxication profile and detection of NPS use; (**E**) New synthetic opioids; (**F**) Legal aspects of NPS use; (**G**) Synthetic cannabinoid receptor agonists; (**H**) Metabolic profiles for drug screening of NPS use; (**I**) NPS and the Internet; (**J**) NPS as a New Public Health Problem. In all panels, the red lines represent the research peak for the thematic domain, as identified by Neoh et al. (2023).

reasons, such as keyword selection and timing. It might be plausible to think that selection of keywords played a role in the identification of studies on NPS as performance-enhancers in sports. As for the cluster on the misuse of NPS during the Covid-19 pandemic, we believe it was not identified by Neoh et al. (2023) because, by the time the review was conducted, there were not enough published studies on the topic to create a relevant cluster within the established scientific literature. The results of the scientometric review would be probably different should the analysis be conducted now or in the near future. Lastly, the dynamic nature of NPS market might explain why the investigation of users' responses to NPS did not emerge as a core thematic cluster in Neoh et al. (2023). The ever-changing nature of the availability and use of these substances might prevent researchers to study and consolidate the literature on the users' response to NPS. When new compounds emerge,

they tend to capture the attention, with most studies trying to identify these substances and characterize them from an epidemiological point of view. The result is that the knowledge about the users' response to NPS is still limited in the scientific literature (Fattore et al., 2020).

Furthermore, the temporal trajectory of research themes in the International Conference on Novel Psychoactive Substances in most cases preceded the scientific literature by 2.5 years. In fact, only research domains that, accordingly to Neoh et al. (2023), had their peak of interest in 2012 were not anticipated by contributions at the Conference. This is most likely because 2012 was the year in which the first edition of the International Conference on Novel Psychoactive Substances took place. Considering this pattern of results, we could hypothesize that in, the next future, the scientific literature on NPS will be enriched by publications examining the use of NPS as performance-enhancers in sports as well as the misuse of NPS during the Covid-19 pandemic. For anti-doping authorities, the NPS phenomenon already represents a major challenge in order to guarantee fair competition among athletes (Corazza et al., 2017a; Mazzoni et al., 2017; Rabin and Corazza, 2022). In some cases, NPS might be included and masked in dietary supplements. The challenge, in this case, is that the parent compound or the metabolite are rarely detected in anti-doping tests (Mazzoni, 2022). As regards the use of NPS during the Covid-19 pandemic, some recent publications (e.g., Catalani et al. (2021); Di Trana et al. (2020)) have documented some changes in the drug market. Catalani et al. (2021) used a web crawler to investigate the discussion about NPS in a group of psychonaut websites and NPS online resources during the Covid-19 pandemic. With this approach, the authors identified 18 NPS that were previously unknown. Of these 18 NPS, the authors reported six cathinones, six opioids, two synthetic cannabinoid receptor agonists, two phenylcyclohexylpiperidine-like molecules, and two psychedelics.

In conclusion, the analysis showed that the NPS Conference's contributions tend to precede the peak of interest in the scientific literature by approximately 2.5 years. Such a result emphasizes the paramount importance of rapid information sharing among experts in the field supported by faster publication processes as well as face-to-face thematic events such as the NPS conference series to support timely policy responses and interventions at the global level. Further, the fact that the NPS Conference has recently included dedicated sessions on the increased use of performance-enhancers in sporting and other environments as well as the use of NPS during the Covid-19 pandemic make us hypothesize that these topics will consolidate in the scientific literature and develop as major thematic domains of NPS research in the next future. This observation is significant given that the ever-changing nature of the NPS market poses a serious challenge when trying to scientifically characterize NPS in time and anticipate the next trends.

CRediT authorship contribution statement

Alessandro Carollo: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Ornella Corazza:** Writing – review & editing. **Olivier Rabin:** Writing – review & editing. **Aurora Coppola:** Writing – review & editing. **Gianluca Esposito:** Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest. Two of the authors of this study (O.C.; O.R.) have been involved in the organization of the International Conferences on Novel Psychoactive Substances. However, there was no personal financial gain in the organization of the event.

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