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Postmortem findings of organ damage in novel psychoactive substances users: A comprehensive review

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ABSTRACT

Introduction: Despite the rising number of NPS-related deaths, comprehensive data on their prevalence, identification, and associated organ damage remain scarce.
Materials and methods: A literature search was conducted. Predefined inclusion and exclusion criteria were applied, resulting in the identification of 197 articles.
Results: We identified 446 cases of NPS-related deaths, involving a total of 176 different substances. Synthetic opioids were the most prevalent class (34 %), followed by synthetic cannabinoids (22 %) and cathinones (21 %). Co-ingestion of NPS with other substances occurred in 77 % of cases. Macroscopic findings varied across organs, with congestion and edema most observed in the brain (23 %) and lung (56 %), respectively.
Discussion: The existing literature lacks comprehensive descriptions of organs subjected to autopsy and histological examination in NPS-positive subjects. Despite this limitation, our findings underscore the prominence of lung pathology. Moreover, the prevalence of normal organs in cases of acute intoxication is a significant observation. We advocate for future research to provide more detailed insights to enhance our understanding of the multifaceted landscape of NPS-related deaths.

1. Introduction

Novel psychoactive substances (NPS) are recently utilized designer drugs, many of which are not yet regulated by the United Nations International Drug Control Conventions. These compounds, which include synthetic cannabinoids, opioids, stimulants, hallucinogens, and others (including natural products and their derivatives), have comparable chemical structures and associated health risks to traditional illegal drugs and, as a result, are often marketed as 'legal' substitutes for the latter. Due to the considerable number of novel compounds, their variety and the velocity with which they emerge, it is difficult to monitor and define effective responses. Indeed, these compounds interact pharmacologically with many targets and their chemical structures vary significantly to avoid inclusion on lists of prohibited substances (Liechti, 2015).

The chemical structure and pharmacokinetics of NPS may be utilized to predict not only their intended psychotropic effects but also their adverse effects and addictive potential.

Recently, there has been a surge in intoxications attributed to novel synthetic opioids (NSOs), with particular reference to illicitly manufactured fentanyl and its analogues. These substances act as μ-opioid receptor agonists in the central nervous system (CNS). Fentanyl, sanctioned for medical use since 1968, is extensively employed in anaesthesia and pain management. Fentanyl analogues (FAs), engineered

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with minor structural modifications, emerged in the 1970s for anaesthesia and research purposes and have since become entwined in the trend of NPS. They have resulted in numerous overdose cases and fatalities stemming from respiratory depression, cardiac arrest, or severe allergic reactions (Brunetti et al., 2021).

Stimulants such as amphetamines and methamphetamine-like cathinones typically inhibit the transport or induce the release of dopamine and noradrenaline, and their use often leads to unwanted, adverse effects. For instance, due to their sympathomimetic actions on the CNS, cathinone and cathine obtained from khat (Catha edulis), a shrub that grows in eastern Africa and south-west Arabian Peninsula, may exacerbate psychotic symptoms in individuals with pre-existing conditions and precipitate psychiatric disorders in vulnerable individuals (Corkery et al., 2011). In addition, approximately 56 % of mephedrone (the most popular cathinone derivative) users report at least one side-effect, which may include convulsions, gastrointestinal problems, tremors, headache, anxiety, aggression, short-term psychosis/mania, cardiovascular and respiratory disorders, and nephrotoxicity (Schifano et al., 2012). Additional classes of NPS act on the dopaminergic regulation; another example of a synthetic stimulant is 4-Fluoroethylphenidate (4F-EPH) (Corkery and Schifano, 2022). Moreover, phenmetrazine-derived stimulants (i.e., 3-fluorophenmetrazine, also known as 3-FPM) act as substrates at the norepinephrine and dopamine transporters (Luethi and Liechti, 2020).

Psychedelics (hallucinogenic phenethylamines, tryptamines) induce their psychoactive effects mainly by acting on the serotonergic system. The most common hallucinogenic phenethylamines (i.e., 2-C or 25x-NBOMe series) are mostly obtained through the addition of lipophilic substituents at the phenyl ring (Liechti, 2015). Tryptamine, on the other hand, is a naturally occurring monoamine alkaloid found in fungi and plants that functions as a serotonin releaser and enhancer of serotonergic activity. Chemical variants of tryptamines, such as 5-MeO-DALT (N,N-diallyl-5-methoxytryptamine), are obtained through the modification of side chains or functional groups (Corkery et al., 2012a).

Similar to the dissociative anaesthetic ketamine, designer dissociative agents (i.e., arylcyclohexylamine and diarylethylamine) exert their typical effects by acting on glutamatergic NMDA receptors (Luethi and Liechti, 2020).

Synthetic cannabinoids encompass a wide range of compounds with varying chemical structures, all capable of interacting with the body's cannabinoid receptors (CB1 and CB2), mimicking the effects of tetrahydrocannabinol (THC), the principal psychoactive component of cannabis. Due to their action as full agonists with heightened receptor affinity, these compounds often exert potent, and in some cases, lethal effects (Roque-Bravo et al., 2023).

Designer benzodiazepines stem from structural modifications of well-known benzodiazepine medications commonly used in medicine to treat sleep disorders and anxiety, likely acting by binding to the GABAa receptor. Their combined use with other drugs that act as depressants of the CNS can pose an increased health risk (Yu et al., 2023).

In most cases, the use of NPS leads to mild or moderate poisoning; nonetheless, significant consequences that frequently develop into medical emergencies and can even culminate in the death of the patient are not uncommon. Subjects under the influence of these drugs may exhibit violent behaviour, self-harm, and may be involved in accidents or even suicide attempts; nevertheless, medical consequences such as liver or kidney damage, neuropsychiatric symptoms, and panic attacks have also been recorded (Kamijo et al., 2016). Serotonergic drugs have been linked to the onset of acute serotonin syndrome, hyperthermia, convulsions, and hyponatremia, among other side-effects. Dopaminergic compounds, on the other hand, are extremely addictive and can cause insomnia, agitation, and psychosis.

In forensics terms, numerous studies in the literature report and emphasize how these substances can have harmful, if not lethal, effects on animal models (Foti et al., 2019) and humans (Corkery et al., 2012b). The effects of NPS described in the scientific literature appear to be multifaceted. For instance, some authors provide valuable information on specific NPS, ranging from the pharmacokinetics of the substance to its marketing, and from the route of intake to toxicity profiles. Others, in their observation of acute events and deaths caused by NPS or polydrug use, tend to focus more on characterizing the individual aspects of substance abuse (Loi et al., 2015).

There is no doubt that the use of these substances is becoming more and more important, with the number of deaths attributable to NPS increasing year by year; additionally, there is currently insufficient information concerning the number of marketed and consumed drugs, how these substances are identified, and the amount and type of organ damage caused by the latter.

In this review, we focused on the information currently available in the literature regarding the occurrence and types of organ damage associated with the use and abuse of NPS. Additionally, we explored the demographic characteristics of the individuals involved and details of their abuse history to extract valuable insights for preventive interventions.

2. Materials and methods

As a preliminary step, a search was conducted on the PROSPERO database to assess the existence of similar studies. This inquiry, conducted on May 5, 2024, revealed the presence of 25 reviews under the entry 'Novel psychoactive substances' but none of these reviews addressed the topic of the present study (post-mortem observation of organ damage related to the consumption of NPS).

The search was carried out from April 1–30, 2024, on the following database: PubMed, Scopus, Web of Science. We entered pertinent key terms previously divided into two main groups and then connected in pairs using the Boolean operator 'AND'. Additional operators such as 'OR' and '*' were used to extend and optimize the research. We included both Mesh terms and free-text protocols. For the first group "Novel Psychoactive substances" the following terms were searched: 'NPS', 'new psychoactive substance*', 'new psychoactive drug*' 'novel psychoactive drug*' while for the second one we used 'autopsy', 'hystolog*', 'hystopatholog*', 'immunohysto*'. We used the following Mesh terms on PubMed database: ("Autopsy" [Mesh]) AND ("Designer Drugs"[Mesh] OR "Synthetic Drugs"[Mesh]). The research was conducted in the Title, Abstract, and Keywords fields of the Scopus and Web of Science databases.

The "related articles" algorithm was also used to identify additional relevant articles, as well as the references of each article which were thoroughly screened.

At this stage, each article was carefully evaluated, reviewing the text in its entirety, by distinct teams of two authors, each composed by one forensic pathologist and one toxicologist with expertise on novel psychoactive drugs.

The following pre-determined eligibility criteria were applied:

- Inclusion criteria: (1) studies and case reports concerning NPS-related fatalities, (2) experimental studies conducted in animal models and including examination of the viscera after animal sacrifice, and (3) studies that included autopsies and analysis of organ samples and/or histological studies conducted on human NPS consumers (4) English language;
- Exclusion criteria: (1) systematic reviews of the literature, and (2) studies lacking post-mortem organ examination in NPS users (i.e., studies containing only data on the measurement of the concentration of NPS metabolites in organic tissues, both *in vivo* and post-mortem; studies containing only information on the clinical manifestations of NPS intake in living subjects; studies without autoptic description of main organs) (3) aggregate data.

Any possible disagreement was resolved by a consensus process with a third author, until unanimous agreement.

The search across the three databases yielded 1312 results. After removing duplicates, this number was reduced to 1084. The application of the inclusion and exclusion criteria resulted in a further refinement of the results to 117. Additionally, bibliographic screenings of sources from the reviews contributed an extra 83 results (other sources), bringing the total to 200 articles. Among these, articles did not have the full text available, resulting in a total of 196 articles (Adamowicz et al., 2020, 2019, 2013; Adamowicz and Hydzik, 2019; Ameline et al., 2019; Andreasen et al., 2015; Angerer et al., 2017; Anne et al., 2015; Anzillotti et al., 2020, 2019; Archer et al., 2015; Arndt and Gray, 2022; Aromatario et al., 2012; Atherton et al., 2019; Bailey et al., 2010; Bakota et al., 2016; Ballesteros et al., 2018; Barnett et al., 2014; Barrios et al., 2016; Behonick et al., 2014; Benedicte et al., 2020; Boland et al., 2020; Bottinelli et al., 2017; Braham et al., 2021; Brockbals et al., 2019; Butler et al., 2018; Byard et al., 2016; Carbone et al., 2013; Cartiser et al., 2021; Chan et al., 2019, 2021; Coopman et al., 2016a, 2016b; Copeland et al., 2022; Corkery, 2018; Corkery et al., 2013; Cosbey et al., 2013; Cunningham et al., 2016; Curtis et al., 2003; Dams et al., 2003; Di Candia et al., 2022; Domagalska et al., 2021; Domingo et al., 2017; Dussy et al., 2016; Dybowski and Dawidowicz, 2020; Eiden et al., 2013; Ellefsen et al., 2017; Elliott et al., 2016, 2015; Epain et al., 2024; Ewelina et al., 2021; Fagiola et al., 2019; Fels et al., 2019, 2017; Fogarty et al., 2018; Fort et al., 2016; Freni et al., 2019; Fujita et al., 2016; Fulga et al., 2020; Garneau et al., 2020; Gerace et al., 2018, 2014; Gevorkyan et al., 2021; Gieroń and Adamowicz, 2016; Gillespie et al., 1982; Giorgetti et al., 2022, 2020; Guerrieri et al., 2017b, 2017a; Hasegawa et al., 2018, 2015a, 2015b, 2014; Helland et al., 2017; Hess et al., 2015; Hobbs et al., 2022; Hofmann et al., 2022; Holler et al., 2011; Ivanov et al., 2019; Johansson et al., 2017; Karinen et al., 2014b, 2014a; Kesha et al., 2013; Kinoshita et al., 2017; Kraemer et al., 2019; Kristofic et al., 2016; Kronstrand et al., 2014, 2013, 2011; Krotulski et al., 2021, 2020, 2018; Krpo et al., 2018; Kudo et al., 2015; Kueppers and Cooke, 2015; Kusano et al., 2018; Langford and Bolton, 2018; Lehmann et al., 2019, 2018; Lelievre et al., 2022; Levasseur et al., 2023; Liveri et al., 2016; Lowe et al., 2015; Lusthof et al., 2011; Maeda et al., 2018; Majchrzak et al., 2018; Margasińska-Olejak et al., 2019; Marinetti and Antonides, 2013; Martucci et al., 2018; Maskell et al., 2011; Matey et al., 2020; McIntyre et al., 2017, 2016, 2015c, 2015a, 2015b, 2015d, 2015e, 2013; Minakata et al., 2020; Mochizuki et al., 2021; Mohr et al., 2016; Moss et al., 2019; Mueller et al., 2021; Nakamura et al., 2022; Namera et al., 2013; Nash et al., 2019; Neerman et al., 2013; Neukamm et al., 2024; Nowak et al., 2021; Ojanperä et al., 2006; Palazzoli et al., 2021; Papsun et al., 2017, 2016; Paul et al., 2018; Pearson et al., 2012; Pellegrini et al., 2019; Pieprzyca et al., 2018; Poklis et al., 2016, 2014; Potocka-Banaś et al., 2017; Rock et al., 2023; Rohrig et al., 2018; Rojek et al., 2014, 2012; Romanńczuk et al., 2022; Saito et al., 2013a, 2013b; Sasaki et al., 2015; Schaefer et al., 2013; Seetohul and Pounder, 2013; Sellors et al., 2014; Shanks et al., 2016, 2015b, 2015a; Shanks and Behonick, 2017, 2016; Shoff et al., 2019; Simon et al., 2022; Smith et al., 2016; Sofalvi et al., 2019; Staeheli et al., 2016; Steele et al., 2022; Strehmel et al., 2018; Swanson et al., 2017; Sykutera et al., 2015; Sykutera and Bloch-Bogusławska, 2015; Takase et al., 2016; Tanaka et al., 2006; Theofel et al., 2019; Thirakul et al., 2017; Tiemensma et al., 2021; Tomczak et al., 2018; Truver et al., 2023; Tusiewicz et al., 2023; Usui et al., 2018, 2014; Vevelstad et al., 2012; Vignali et al., 2019; Vorce et al., 2014; Wachholz et al., 2023; Walle et al., 2023; Walterscheid et al., 2014; Wang and Walker, 2018; Warrick et al., 2012; Waters et al., 2016; Westin et al., 2016; Wiergowski et al., 2014; Wikström et al., 2013, 2010; Wright et al., 2013; Wyman et al., 2013; Yonemitsu et al., 2016; Zaitsu et al., 2015; Zawadzki et al., 2021, 2020).

All selected articles, including internet page link identifiers or digital object identifiers (DOIs), were entered into an explanatory multiparametric table that included age and gender of the individuals, type of drug assumed, whether autopsy and/or histological examinations were performed, both general and specific pathological findings on individual organs examined (brain, heart, kidney, lung, liver). To better understand the mechanisms by which NPS can produce organ damage and to identify NPS-independent factors that may have contributed to the pathological findings, additional parameters were included, such as: substance abuse/dependence and/or drug-use history, NPS-intake related to *in vivo* symptoms, and concurrent use of drugs (including therapeutic medications).

We categorized NPS into various classes, including synthetic opioids, cathinones, synthetic cannabinoids, amphetamines and their derivatives, designer benzodiazepines, phenethylamines and their analogues, arylcyclohexylamines, phenmetrazine analogues, tryptamines, and others. Any case in which multiple NPS classes were involved was labeled as "multiple NPS".

Statistical analyses were performed using OriginPro (OriginLab Corporation, Northampton, MA, USA). Pearson's Chi-Square Analysis was used to assess associations between categorical variables, including the relationship between gender and multiple drug use, as well as between gender and NPS usage. The Kruskal-Wallis ANOVA was used to determine significant differences in the age of subjects across different NPS classes. Dunn's Post Hoc Test was subsequently employed for pairwise comparisons to identify specific differences between groups. Graphical representations were also generated using OriginPro.

3. Results

The research conducted using the specified methodology has identified 446 cases of deaths related to the intake of NPS. In total, 176 substances belonging to the class of NPS were identified.

3.1. Class of substances

The class most commonly present in the reviewed cases is synthetic opioids (34 %), followed by synthetic cannabinoids (22 %) and cathinones (21 %) *(*Fig. 1*)*.

Additionally, we extracted data regarding the simultaneous presence in at least one biological sample of NPS and another substance (therapeutic drugs or substances of abuse, including alcohol). We found that such co-ingestion occurs in 77 % of cases.

For the class of synthetic opioids (SO), the following substances were identified: a-methylfentanyl, AH-7921, 4-FIBF, MT-45, flunitazene, piperidylthiambutene, thff, U-47700, fentanyl, furanylfentanyl, cyclopropylfentanyl, carfentanyl, norfentanyl, methoxyacetylfentanyl, acetylfentanyl, acrylfentanyl, 4-ANPP, isotonitazene, metonitazene, 3-methylfentanyl, ocfentanil, butyrylfentanyl, U-49900, despropionyl-p-fluorofentanyl, fluorofentanyl, acetylnorfentanyl, n-methyl U-47931, p-fluoro(iso)butyrylfentanyl, U-47931, valerylfentanyl.

For the class of synthetic cannabinoids (SCB**)**, the following substances were identified: mepirapim, 5F-ADB, Cumyl-PEGACLONE, AB-CHMINACA, AM-2201, ADB-FUBINACA, 5F-PB-22, JWH-122, JWH-018, 5F-AMB, MAM-2201, AB-FUBINACA, MDMB-CHMICA, XLR-11, JWH-210, 5F-AKB-48, THJ-018, UR-144, AMB-CHMICA, AMB–FUBINACA, 5F-Cumyl-P7AICA, AM-694, AM-1220, 5F-MDMB-P7AICA, AB-PINACA, Cumyl-4CN-BINACA, EAM-2201, EG-018, 5F-MDMB-PICA, 5F-Cumyl-PEGACLONE, FUB-PB22, JWH-022, JWH-250, JWH-019, MDMB-CHMCZCA, MDMB-FUBICA, EMB-FUBINACA, MMB-2201, AM-2232, NNEI, PB-22, 5F-ADBICA, STS-135, THJ-2201.

For the class of cathinones (C), the following substances were identified: N-ethylpentylone, a-PVP, a-PHP, a-PiHP, a-PVT, 4-MeO-α-PVP, 4-Fluoro-3-methyl-α-PVP, a-PNP, a-PBP, 4-F-α-PVP, α-EAPP, α-propylaminopentiophenone, MDPV, 4-MMC, 3-MMC, 4-MEC, methylone, 4-CMC, butylone, ethylone, eutylone, MDPBP, MDPHP, MDPPP, methcathinone, N-Ethylhexedrone, PV8, Pentedrone MPHP, 4-MEAP, 3,4-DMMC, Methedrone, 4F-MPH, 4-methoxyPV8, PV9, mexedrone, 4-MPD, 4-FMC, 4-methoxy PV9, 5-DBFPV, 4-CIC, 4-BMC, N-etylnorhexedrone, PVP, 4-MPD, MMMP.

For the class of amphetamines derivatives (A), the following substances were identified: PMA, PMMA, MDA, MPA, 2-FMA, DMAA, 2-FA,

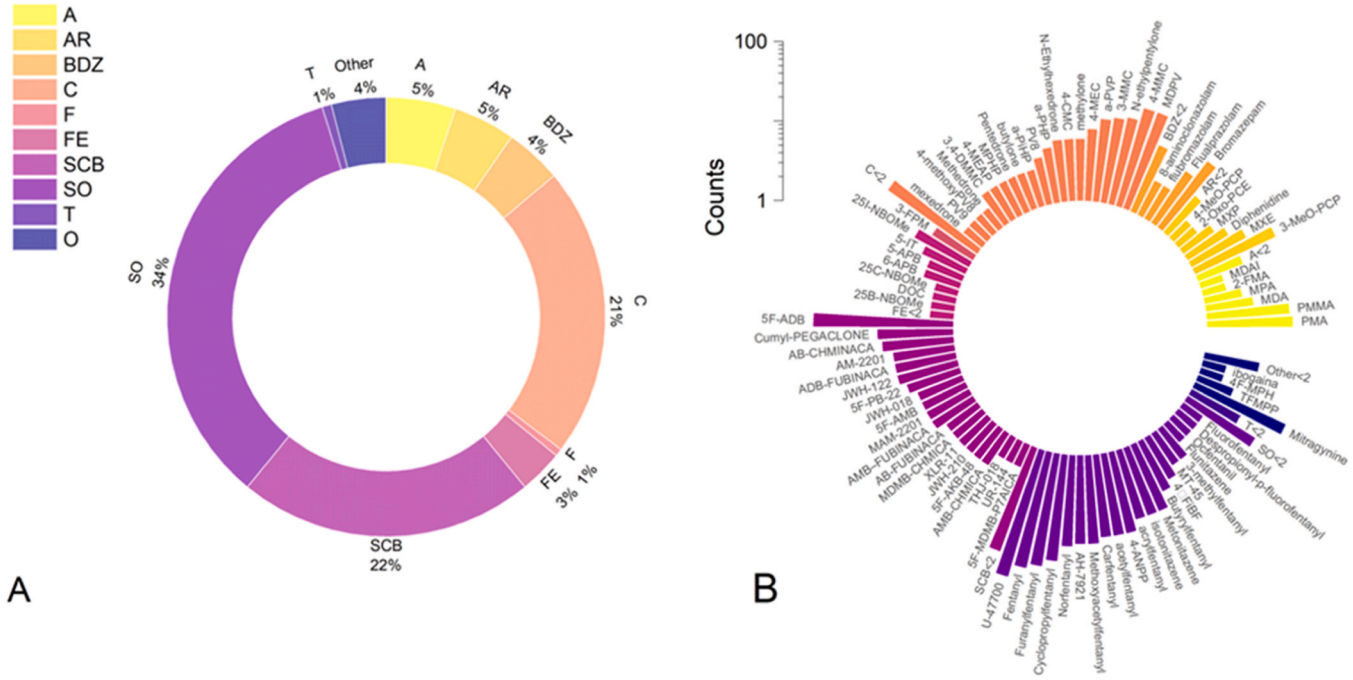

Fig. 1. Distribution of NPS classes among deceased individuals positive for NPS in included literature, represented as percentages and approximated to the nearest percentage point. Each substance assumed by individuals, even in cases of multiple assumptions, was considered a separate count (A); corresponding circular bar plot on a logarithmic scale, color-coded by NPS class. Substances with fewer than 2 counts are grouped into single categories labeled A<2, AR<2, BDZ<2, C<2, FE<2, SCB<2, SO<2, and Other<2, respectively (B). Abbreviations: A – Amphetamines, AR – Arylcyclohexylamines, BDZ – Benzodiazepines, C – Cathinones, F – Phenmetrazine analogues, FE – Phenethylamines, SCB – Synthetic Cannabinoids, SO – Synthetic Opioids, T – Tryptamines, O – Other substances.

MDAI, 5-MAPB, PMMMA.

For the class of designer benzodiazepines (BDZ), the following substances were identified: flualprazolam, flubromazolam, 8-aminoclonazolam, desalkylflurazepam, diclazepam, flubromazepam, flunitrazepam, hydroxyflubromazepam, clonazolam, bromazepam, phenazepam, pyrazolam.

For the class of phenethylamines and their analogues (FE), the following substances were identified: 25I-NBOMe, 25C-NBOMe, DOC, 25B-NBOMe, 2C-T-7, 25IB-NBOMe, 5-IT, 5-APB, 6-APB.

For the class of arylcyclohexylamines (AR), the following substances were identified: 3-MeO-PCP, MXE, MXP, diphenidine, 2-Oxo-PCE, 4-MeO-PCP, MeO-PCP, N-Ethylnorketamine, 3,4-MDPHP, 2-MXP.

For the class of tryptamines (T) the following substances were identified: 5-MeO-DIPT, 5-MeO-MiPT, psilocin, 4-HO-MET, AMT.

For the class of phenmetrazine analogues (F) the following substance was identified: 3-FPM.

The "others" category encompassed substances such as poppers, xylazine, phenibut, 4-Fluoromethylphenidate (4F-MPH), mitragynine, 7-hydroxymitragynine, ibogaine, 3-Trifluoromethylphenylpiperazine (TFMPP), and benzylpiperazine (BZP).

We emphasize that none of the selected cases involved the intake of phenmetrazine analogues or tryptamines as a single substance; hence, in the final analysis, they were included under the class "multiple NPS".

3.2. Demographic data

Demographically, males are the most affected group, accounting for 392 cases (87.9 %), compared to 54 cases (12.1 %) involving females. Analysing the age of the selected subjects, the following gender differences were recorded: females have a median age of 30 years with an interquartile range (IQR) of 20 years (from 10 to 50 years), while males have a median age of 32 years with an IQR of 17 years (from 15 to 49 years).

Statistical analysis showed no statistically significant association between gender and multiple drug use, in contrast to the statistically significant association between NPS usage and gender. Specifically, the count distribution revealed that males were more frequently associated with the use of SO (n = 119 males, 13 females), SCB (n = 80 males, 4 females), C (n = 78 males, 11 females), and multiple NPS (n = 65 males, 10 females). Pearson's Chi-Square Analysis was conducted to determine if the distribution of NPS use differed significantly by gender. The results indicated a significant association (chi-square statistic= 42.3, p= 1.2e-4) suggesting that the use of NPS classes was not independent of gender.

The age distribution of subjects by NPS class reveals statistically significant differences between the pairs: C and FE (p = 0,00318), FE and Multiple NPS (p = 0,01324), FE and SCB (p = 3,59E-5), FE and SO (p = 2,05E-4) *(*Fig. 2*)*.

Additionally, we observed that among all cases examined, 53 % of the deceased had a documented history of substance abuse, including alcohol. In the remaining cases, this information was unknown.

Data regarding the *in vivo* clinical presentation of the subjects under study were reported in only 22 % of cases.

3.3. Autoptic and histological data

Initially, we highlight that histological examination was performed only in 22 % of cases.

3.4. Brain

The most evident macroscopic findings are congestion and edema, present in 23 % of the cases examined, followed by the absence of pathological findings (19 %). In rare cases, signs of ischemia were present (2 %).

At the microscopic level, the brain is the least described organ compared to others (92 % of cases had no available description). In cases where a description was available, the most common finding was within normal limits (23 %), followed by congestion (3 %) and ischemia (1 %).

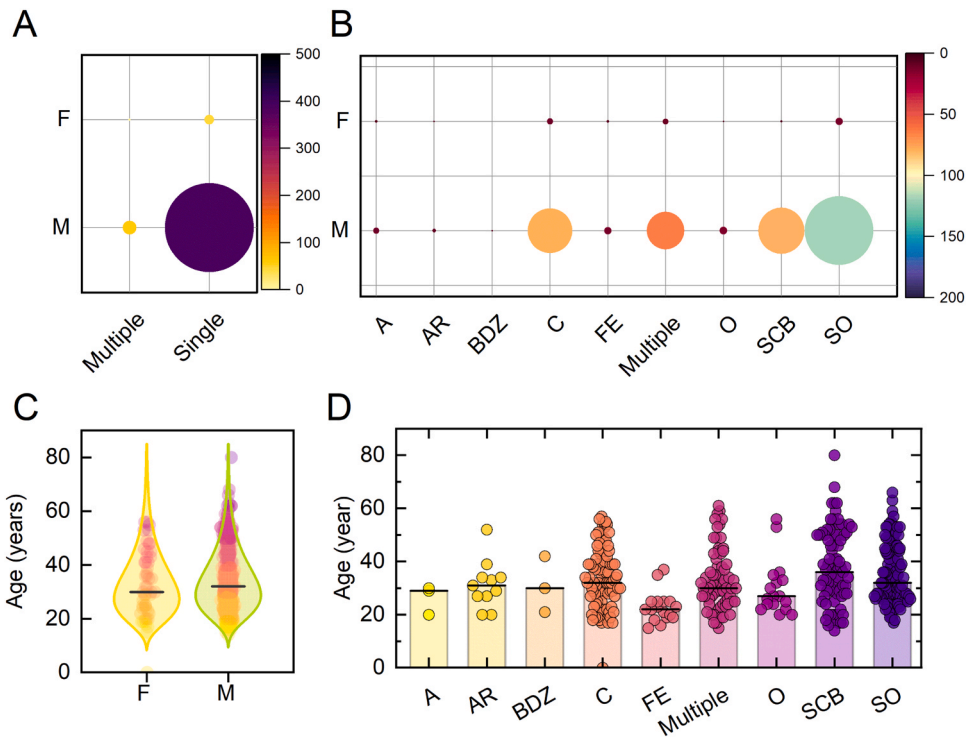

Fig. 2. Overview of literature investigating substance types in relation to parameters such as gender and age in post-mortem organ damage cases Panel A displays the distribution of single versus multiple NPS usage by gender in absolute counts. Pearson's chi-square analysis reveals no significant association between gender and multiple drug use (chi-square statistic = 0.208; p-value = 0.649). Panel B shows the count distribution for different classes of NPS substances by gender, where Pearson's chi-square analysis reveals a significant association between NPS use and gender (chi-square statistic = 42.3; p-value = 1.2e-4). Panel C details the age of subjects stratified by gender, with median ages (IQR) of 30 (20) for females and 32 (17) for males; no significant differences in age distribution are observed. Panel D illustrates the age of subjects by NPS class, where Kruskal-Wallis ANOVA identifies significant differences among groups (p = 1.6e-4). Dunn's post hoc test indicates significant differences between the pairs: C and FE (p = 0,00318), FE and Multiple NPS (p = 0,01324), FE and SCB (p = 3,59E-5), FE and SO (p = 2,05E-4). Abbreviations: A – Amphetamines, AR – Arylcyclohexylamines, BDZ – Benzodiazepines, C – Cathinones, FE – Phenethylamines, SCB – Synthetic Cannabinoids, SO – Synthetic Opioids, O – Other substances.

3.5. Kidney

The kidney is the least described organ macroscopically (71 % of cases with no available description). However, the most frequently described finding corresponds to normal morphology (20 %). Less frequently described are congestion (4 %) and sclerosis or scarring (3 %).

Similar results are evident at the histological level, with a normal kidney in the majority of cases (4 % of the total), but with 91 % of data unavailable. Additional findings include acute tubular necrosis (2 %), congestion (1 %) and scarring (1 %).

3.6. Heart

Macroscopically, the heart appeared normal in the majority of cases (16 %). The most frequently described pathological finding was hypertrophy and/or cardiomegaly (11 % of cases). Atherosclerosis was present in 7 % of cases. No data were available in 47 % of cases.

Microscopically, in the vast majority of cases (87 %), no data were available. Reported pathological findings included myocardial hypertrophy, fibrosis, and fatty replacement (4 %).

3.7. Lung

It is the most frequently described organ in our reported cases, both at macroscopic and microscopic levels.

Macroscopically, congestion and/or edema were reported in 56 % of cases. In 15 % of cases, the finding was described as normal, while in 14 %, the result was not available. In 6 % of cases, multiple pathological findings were present. Other results present in smaller percentages included emphysema (3 %) and hemorrhage or petechiae (1 %).

Histologically, congestion and/or edema were the most frequently observed findings (6 %). In this case as well, data were not available in 84 % of cases.

3.8. Liver

At the macroscopic level, it mostly appeared normal (18 % of cases). Additionally, congestion (6 %), steatosis (4 %), and hepatomegaly (3 %) were documented, in decreasing order. Data were absent in 62 % of cases.

At the histological level, data were absent in 87.4 % of cases. However, the organ appeared normal in 3.8 % of cases. Hepatitis was less frequently observed in 2.2 % of cases, as was steatosis (2.2 % of cases). (Fig. 3)

4. Discussion

Despite a general decrease in the number of new compounds introduced in the illicit drug market (EMCDDA, 2024), the total number of NPS monitored by the policymakers (i.e., "bath salts" or "legal highs") increase every year, along with their usage (Zaami et al., 2018) (Chiappini et al., 2015). In the ongoing battle against new drugs of abuse, institutions and research laboratories are struggling to keep up with the development of ever new compounds. Consequently, obtaining information on these substances, including their toxicity, effects, and potential organ damage, is challenging.

The first three categories of NPS, within our sample of deceased

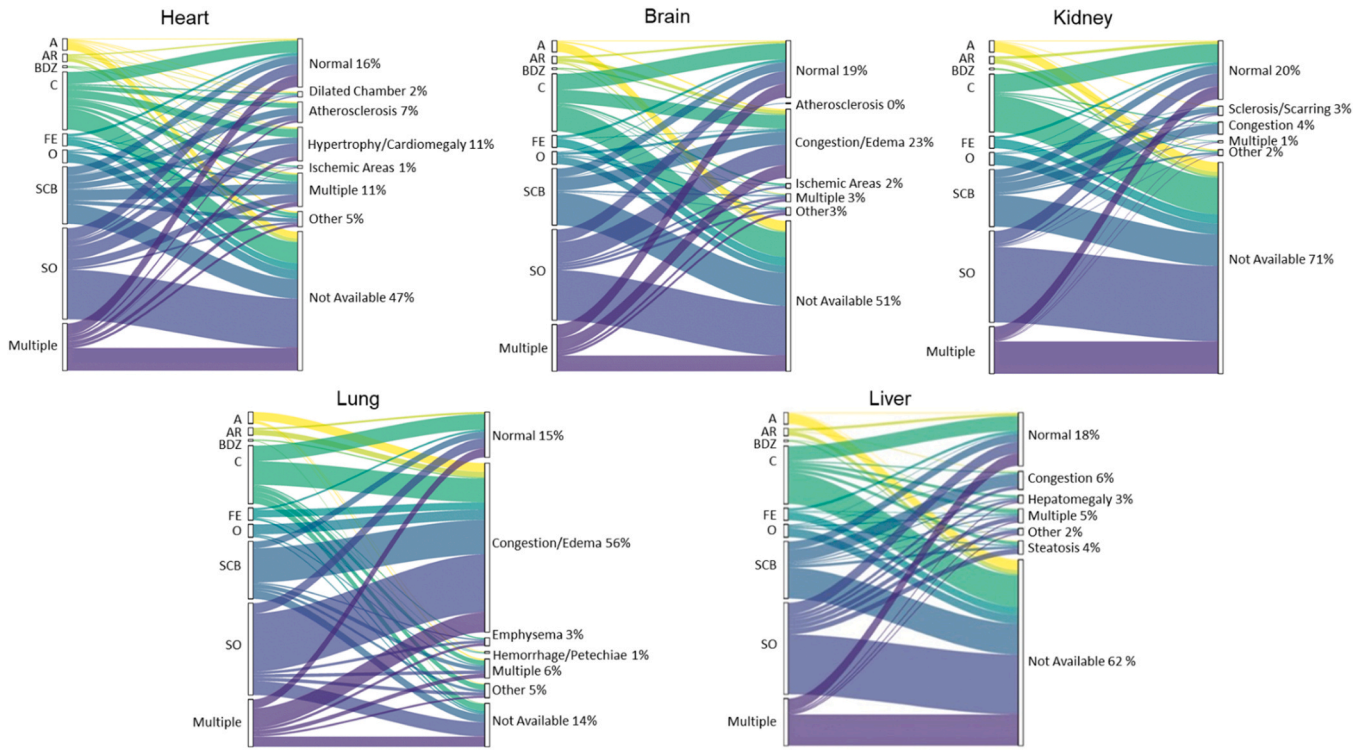

Fig. 3. Alluvial plot illustrating the connections between NPS class and types of autopsy-determined organ damage in the heart, brain, kidney, lungs, and liver.

individuals, reflect a tendency among consumers towards frequent usage of substances belonging to the classes of synthetic opioids, synthetic cannabinoids, and cathinones. This trend aligns with existing literature findings (Papaseit et al., 2014). The prominence of synthetic opioids as the substance most frequently associated with individuals' deaths aligns with the high risk posed by these drugs, attributed to their depressive effects on the respiratory system. This lethal effect has been highlighted in both fentanyl derivatives and non-fentanyl derivatives, such as U-47700 (Hasegawa et al., 2022), which ranks highest in the SO category, followed by fentanyl and its main derivatives. It is noteworthy that recent cases of deaths caused by the polydrug use of substances within the SO class – including both fentanyl and non-fentanyl analog – have emerged, suggesting a likely synergistic action in causing fatal respiratory failure (Giorgetti et al., 2024).

The SCB and C classes are almost equally represented in our sample of deceased individuals. This data indicates the widespread use of these substance classes. Several factors may explain this phenomenon: a lack of awareness about the harmful potential of these compounds, with particular mention to SCBs consumed as "legal" replacement of phytocannabinoids (Cohen and Weinstein, 2018), coupled with a strong tendency for poly-drug use, particularly among opioid addicts (Alías-Ferri et al., 2022), and the high availability and appealing characteristics of these substances in the online market (Zangani et al., 2020; Carhart-Harris et al., 2011).

Furthermore, we consider demographic information about the users of psychoactive substances to be meaningful. We have observed that men are more commonly involved in deaths related to NPS consumption compared to women. This finding aligns with existing scientific literature, which indicates that males are more frequently affected by substance use disorders (SUD), although the gender gap has been narrowing in recent years (McHugh et al., 2018). Therefore, our observation of a higher number of male deaths compared to female deaths is consistent with expectations.

Several studies have investigated, especially using animal models, the different behavioural responses to drug use in terms of craving, adverse effects, rewarding effects, also in relation to NPS. Among the most significant results, females show a greater sensitivity to the rewarding effects of the SCB class compared to males. They are also more at risk of developing anxious symptoms related to the consumption of cathinone drugs compared to males (Fattore et al., 2020). Thus, these findings suggest that it needs to be clarified whether the gender gap resides in a different vulnerability to effects or in the different rate of consumption.

Regarding deaths related to the intake of NPS, previous studies (Webb et al., 2022) have highlighted a greater gender homogeneity among NPS deaths compared to common drugs, along with a tendency for a younger age of intake compared to conventional drugs. One possible explanation for these findings lies in the context of NPS intake, which often occurs in recreational settings accompanied, typically, by concurrent use of multiple psychoactive substances or medications, a pattern notably prevalent in our sample (77 % of cases involved at least two or more drugs, including alcohol).

Additionally, we have highlighted a correlation between the gender of deceased individuals and the class of NPS consumed, along with an association between the age of subjects and NPS classification, notably prominent for the FE class. This finding is consistent with previous literature, which has indicated a lower median age within this particular NPS class compared to others (Srisuma et al., 2015).

According to the statistics on drug-induced deaths in the European Union (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). "European Drug Report 2024: Trends and Developments." Last Accessed: September 30, 2024)), most fatalities occur within the age group of 25–44 years. This data aligns with the median age calculated in our sample, which is 30 years (IQR: 20 years) for females and 32 years (IQR: 17 years) for males.

Another noteworthy finding is the percentage of individuals with a history of drug or alcohol abuse. Scientific evidence suggests a high prevalence of NPS use among individuals with substance use disorder, particularly in cases reporting young subjects, documented mental disorders diagnosis, suicide attempts, and polysubstance abuse. The association between NPS use and a history of substance addiction is a negative prognostic factor (Dal Farra et al., 2022). Therefore, the high

frequency of polydrug use in our sample of deceased individuals, with a significant presence of CNS acting medications, including antidepressants and anxiolytics, is easily explainable. A comparison with the valuable literature highlighted that, in a particular case series of deaths related to the use of synthetic benzodiazepines, 80 % of the cases had a history of substance abuse (Darke et al., 2022a).

Only a limited number of publications (22 % of our reviewed cases) reported data on the in vivo clinical presentation of the studied subjects. This can be attributed to the fact that many studies document cases of individuals being found dead inside their homes, with no witnesses to specify what occurred in the moments immediately preceding death. Despite the inconsistency and wide variation in the information gathered from these articles, the majority can be categorized into three main groups: (a) symptoms such as chest pain, nausea, wheezing, shortness of breath, etc., (b) atypical behaviors (e.g., aggressive behavior, disorientation, signs of intoxication, agitation, etc.), and (c) loss of consciousness followed by a non-shockable rhythm/cardiac arrest/other.

Regarding the results of post-mortem examinations, it is first noted the absence of a substantial number of complete and detailed descriptions pertaining to the autopsy findings. This data assumes significant proportions, especially concerning histological examination, which, in the best-case scenario, that of the lung, is still absent in 83.6 % of cases. This lack of information is partly attributable to the authors' focus on specific aspects of reported cases, such as the analysis technique used or the blood values of individual metabolites. However, we believe that it constitutes a serious deficiency in the scientific information currently available in an area of extreme interest for public health, such as the consequences of NPS use.

We can still assert that, overall, the autopsies revealed nonspecific signs of intoxication. However, we noticed that certain findings are recurrent across examinations.

At the macroscopic level, the phenomena of congestion and edema assumes significant aspects for organs such as the brain, liver, and, predominantly, the lungs (56.1 %). Indeed, the lungs appear to be the focus of the autopsy descriptions currently available in the most relevant scientific literature, both concerning NPS (Corkery et al., 2019) and common drugs of abuse (Todorović et al., 2011). This finding can be explained by the physiological mechanisms of death due to drug intake, where respiratory failure is a primary cause. This data is also consistent with findings from an Australian study, which highlighted the presence of pulmonary edema in 82.6 % of cases involving deaths related to novel synthetic opioids (Darke et al., 2022b).

Numerous studies conducted on animal models have indeed highlighted the respiratory consequences of synthetic cannabinoids (Bilel et al., 2019) intake, such as bradypnea and hypoxia. Similarly, synthetic opioids are related to the well-known opioid-induced respiratory depression (OIRD), mediated by the presence of μ-, δ-, and κ-opioid receptors located in both the central and peripheral nervous systems (Frisoni et al., 2018). An animal study has shown an interesting enhancement effect of hypoxia associated with the consumption of heroin and fentanyl with xylazine, increasingly identified as adulterant in opioid synthetic drugs (Kiyatkin and Choi, 2024). These *in vivo* studies show good correlations with our post-mortem findings, which demonstrate the association between the intake of synthetic opioids and synthetic cannabinoids and the presence of pulmonary congestion and edema.

At the cardiac level, it's interesting to delve into the data regarding the high number of cases described as macroscopically normal. This could be attributed to the high percentage of arrhythmias associated with NPS abuse, which, due to their lethal action in a very short time frame, may not produce macroscopically significant evidence. For instance, in the case of synthetic cannabinoids (SCBs), effects such as long-lasting bradycardia, bradyarrhythmia interspersed with tachyarrhythmias, along with an increase in blood pressure, have been described (Marchetti et al., 2023). These events, especially in high-risk individuals or in cases of polyabuse with other potentially cardiotoxic substances, can lead to acute fatal phenomena such as cardiogenic shock or cardiac arrest. In cases of prolonged NPS intake, chronic cardiotoxicity phenomena have also been described, such as hypertension, coronary vasospasm, and heart failure, consistent with our findings of hypertrophy and/or cardiomegaly (Groenewegen et al., 2024).

Other organs described in a high percentage of autopsy examinations with characteristics entirely overlapping those of a healthy individual are the kidneys (20 % of total samples) and the brain (19 % of total samples). This data appears to be partially inconsistent with the current literature available. Indeed, preclinical evidence is available regarding the use of synthetic cannabinoids (SCBs) and acute kidney injury (Buser et al., 2014), the association between fentanyl analogues and renal toxicity (Ono et al., 2023), and the correlation between amphetamines like drugs and kidney damage (Foti et al., 2019). However, the specific cases reviewed in our study show samples without pathological alterations in 19.7 % of cases. This difference could be validly explained by the disparity between animal and human samples, which are the focus of our study.

Regarding the brain, there is a nearly equal representation of normal conditions (19.3 %) and congestion and edema (23.1 %). Currently, there is limited scientific knowledge available about the molecular mechanisms of neurotoxicity related to NPS consumption. In vitro studies have shown that mephedrone, belonging to the cathinone class, can cross the blood-brain barrier and causing endothelial damage (Buzhdygan et al., 2021). Potential harmful effects on neurogenesis have also been demonstrated for the same class (Roda et al., 2023). However, the use of animal samples represents a limitation in current knowledge (Pantano et al., 2017); therefore, future studies could provide valuable insights to increase understanding in this field. Data on animal samples related to neurotoxicity associated with dopamine release have also emerged for the SCB category (Ossato et al., 2017). Currently, in vivo study of NPS intoxications in human subjects shows symptoms attributable to neurotoxicity mediated by the monoaminergic system in association with increased oxidative stress (headache, seizures, cerebral edema, stroke), along with a range of cognitive disturbances including agitation, panic attacks, hallucinations, and delirium, common to all stimulant NPS (Rudin et al., 2021). Regarding our post-mortem samples, we therefore believe that the higher prevalence of highly nonspecific signs such as congestion and edema may be an indirect consequence of rapid deaths due to primary failure of the cardiac and respiratory systems, as well as direct neurotoxicity from the aforementioned mechanisms.

Regarding the association between hepatotoxicity and NPS use, literature data are available specifically concerning piperazines (Arbo et al., 2016), amphetamine analogues (Nakagawa et al., 2009), with cellular mechanisms linked to increased oxidative stress of hepatocytes. Autopsy findings in our reported cases predominantly showed normal liver characteristics along with congestion. Other observed signs such as steatosis and hepatomegaly are attributable to chronic organ damage, which is particularly common in all drug users, also due to the association with ethanol consumption (Louvet and Mathurin, 2015). In this regard, signs of chronic damage are also noted in other organs, such as the presence of sclerosis and/or scarring in the kidneys (3.1 %) and emphysema in the lungs (2.7 %).

Histological data currently available are scarce and of limited relevance; however, we still observe a general consistency with the findings highlighted at the macroscopic level.

In conclusion, our findings are consistent with forensic recommendations (Osborn et al., 2018) that emphasize the need for thorough investigations to detect any indicators of recent and chronic drug use and abuse. During the internal examination, several findings are identified as 'non-specific but potentially associated with drug use', including dilated cardiomyopathy (particularly linked to alcohol consumption), cirrhosis and fatty liver (also associated with ethanol abuse), cerebral edema, and severe pulmonary edema. These findings have also emerged in our reported cases. Regarding the high percentage of organs without

pathological findings, the same authoritative source states that the absence of significant alterations at autopsy can occur in many deaths caused by drugs, especially in young individuals.

5. Limitations

To address some of the limitations of our review, further studies investigating the mechanism underlying NPS-related organ damage and the association between individual substance and specific organ damage are needed. One of the limitations of our research stems from the relatively limited availability of studies in the current literature that meet our criteria. Indeed, most studies focused on determining tissue concentrations of NPS metabolites from a toxicological point of view, rather than on NPS-related macro- and/or microscopic organ damage; consequently, autopsies and/or histopathological examinations were often not performed at all. Furthermore, we observed that, even when available, a detailed description of all major organs of autopsy interest was lacking in most cases. Histological examination was performed in a low percentage of studies, leading to an inevitable loss of potentially significant information.

Secondly, the subjects of the articles included in our review were predominantly chronic or occasional users of multiple substances. This complicates the delineation of the underlying mechanism(s) of organ damage and, more importantly, the identification of the relationship between a specific substance and particular organ damage. This factor poses a challenge to the interpretation of data derived from autopsies, histology, toxicology, emergency care, and other sources.

It is also worth noting the prevalence of impure NPS or those sold as mixtures, sometimes even mislabelled: this data increases the difficulty of accurately estimating the prevalence of usage and associated health risk across various classes (Guirguis et al., 2017).

6. Conclusions

To the best of our knowledge, the current scientific literature contains few papers with a complete and detailed description of all organs subjected to autopsy and histological examination in subjects with at least one positive NPS. From the available data, we have nevertheless highlighted the frequency of pathological alterations in the lungs, which appear to be the most described organ in autopsy cases, both at the macroscopic and microscopic levels. Additionally, the frequency of normal organs in the presence of acute intoxication is noteworthy. We believe that such data should be supplemented in the future with more detailed information to improve the currently available understanding of the complex realm of NPS-related deaths.

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