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Monitoring and Analysis of Novel Psychoactive Substances in Trends Databases, Surface Web and the Deep Web, with Special Interest and Geo-mapping of the Middle East

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ABSTRACT

BACKGROUND

Novel or new psychoactive substances (NPS), also known as designer drugs and research chemicals, represent a relatively recent phenomenon which can be traced back to the last decade or even earlier. The growth of this phenomenon and its electronic trade (e-trade) has been logarithmic and alarming; its aftermaths are not limited to; the economy, individual and public health, or illicit drug trade. The discipline of NPS has been extensively studied since 2010. However, there are still deficits in; data from the Middle East and the developing world including Arabic countries (1), application of data science and inferential hypothesis testing (2), implementation of the principles and theories of social science (3), utilization of experimental designs including randomised controlled trials (RCT) and quasi-experimental studies (4), and ultimately the enactment of real-time web analysis and the realization of tools of *knowledge discovery in databases* (5).

AIM AND OBJECTIVES

This study will implement an innovative research approach by combining observational analyses and data science; the aim is to provide generalizable (inferential) data in relation to NPS e-commerce activities on both divisions of the web, surface and deep. The pinnacle objective is to; assess the proportional magnitude of NPS e-commerce activity in the Middle East (1), provide a thorough analysis of the e-vendors on the darknet, both globally and regionally (Middle East) (2), correlate change in trends of e-commerce with time (3), provide recommendations for future studies in relation to the e-commerce activity in the Middle East (4), and to discuss the colossal potential of data mining technologies (5).

MATERIALS AND METHODS

This dissertation embodies the integrative and combinatorial approach towards the investigation of the e-trade (e-commerce) of NPS; it is made of integrated studies allocated into eleven results chapters. The utilised investigative tools represent a mixed-breed of observational web analytics including; literature review (1), cross-sectional studies and surveys (2, 3), internet snapshots (4), retrospective analyses (5), and critical appraisal (6). These analyses took place in both appendices of the web (surface web and the anonymous deep web); the analyses specifically involved; Google Trends database (1), literature databases (2), drug fora (3), social communication e-media (3), news and media networks (4), Grams search engine of the deep web (5), the darknet and its e-marketplace (6), Alphabay, Agora, Valhalla, Hansa, other dedicated e-markets for NPS e-trade (7). Additional extrapolations were concluded via the use of surveys and e-surveys in a population of medical

students from Iraq. The potentials for *knowledge discovery in databases* (KDD) were also discussed in all chapters. Each chapter was thoroughly investigated via; data science tools (I), inferential statistics and hypothesis testing (II). The latter was dependent on using the *Microsoft Excel 2016*, the *Statistical Package for the Social Sciences* (SPSS), and some online tools of data science.

RESULTS AND DISCUSSION

A systematic review of approximately 600 PubMed-indexed articles of NPS literature showed; attempts of NPS research started to evolve after 2010, almost one-third of the research output (36%) was of relevance to toxicology and analytic chemistry, while reviews and cross-sectional studies were less common (15%, 18%). The analysis of the individual basis of power showed that NPS researchers, legislators, and policymakers are lagging behind, whereas terrorist possesses the highest possible power. Power scores of e-vendors scored highest in the UK, US, and eastern Europe, while being almost absent in the Middle East.

The complimentary usage of PubMed, drug fora, and Google Trends was successful in extrapolating the most trending and high-risk NPS; the contribution from the Middle East to incidents of intoxications and fatalities was absent except for Israel. Deep web analysis, including the darknet e-marketplace, has shown that the contribution of the Middle East never exceeded 7% of the total e-trade, data were limited to; Iran, Israel, Turkey, Afghanistan, Oman, United Arab Emirates, and Saudi Arabia. Other Arabic countries included; Egypt, Morocco, and Algeria. It was interesting to observe the e-vendors of NPS operating in the Middle East were highly involved in e-trade activities in other nations, primarily; the UK, Western Europe and Scandinavia, US, Canada, Australia, and New Zealand. Surveys and internet snapshots unveiled the lack of awareness and very low prevalence of (ab)use of NPS within the selected Iraqi population.

Captagon was highly prevalent in the Middle East, unlike NBOMe and octodrine. In summary, the contribution from the Middle East was *microscopic* when compared to the developed world; it did not exceed 7% of the entire NPS phenomenon e-trade. Similarly, the NPS research in the region of the Middle East can be described to be in its infancy. The overall level-of-evidence of this dissertation is assumed to be of level-2b according to the classification system imposed by the *Oxford Center for Evidence-Based Medicine* (2009).

CONCLUSION

The growth of the NPS phenomenon, including the e-commerce and its links to terrorism, are reaching unprecedented levels. Unless some reasonable efforts and ingenious upgrades of the current research methodologies, the NPS trade and e-trade will continue to prevail rendering all its counter-attempts fade into dust; these attempts are not only limited to NPS research but also into; legislative actions, policy planning, and counter-terrorism. Upgrades should affect these front lines; increasing the quality and quantity of studies in developed countries including Middle Eastern and Arabic countries (1), incorporation of efficient use of data science and advanced web analytics (2), compulsory training of data science, biostatistics, and basic neuroscience for all NPS researchers, chemists, and toxicologists (3), validation and incorporation of data mining and real-time analyses (4), inclusion of the rarely-used experimental studies including RCTs, pragmatic RCTs, and animal modelling (5), enhancement and potentiation of internet snapshot techniques (6), and full exploitation of trends databases of the surface web (7). Perhaps, the integration of real-time data mining and data crunching, and inferential data science technique will represent the climax armament to antagonise the alarming e-trade.

KEYWORDS

Novel psychoactive substances; New psychoactive substances; Designer Drugs; Research chemicals; Evidence-Based Medicine; Middle East; Arabic countries; Data mining; Knowledge discovery in databases; Captagon; Octodrine; NBOMe; Bases of power; Literature review; Drug fora; PubMed; Grey literature; Surface Web; Deep web; Darknet; AlphaBay; Google Trends; Inferential Statistics; Hypothesis testing; Observational studies; Cross-sectional analysis; Internet snapshot; Retrospective Studies; Case reports; Review article; Interdisciplinary Medicine; Neurosciences; Psychology; Psychoanalysis; Data Science; Critical appraisal; Information and communication technology.

TABLE OF CONTENTS

I. BACKGROUND AND LITERATURE REVIEW

A BRIEF HISTORY OF NPS

Novel or new psychoactive substances (NPS) are defined as newly used designer drugs, also known as internet drugs or research chemicals or legal highs. NPS are not controlled by the United Nations drug conventions, although they may pose a public health and economic threats comparable to those posed by classic (archetypal) illicit substances listed in these conventions (Cluver and Rheingold, 2014; United Nations Office on Drugs and Crimes, 2016). The rapid spread of the NPS, represents a major problem for the economy, policy makers, medical and paramedical experts, and information-communication technology experts.

The United Nations Office on Drugs and Crime (UNODC) has identified six main groups of NPS: synthetic cannabinoids, synthetic cathinones, ketamine, phenethylamines, piperazines and plant-based substances (Dargan and Wood, 2013). A seventh miscellaneous group of substances was also added later (Dargan and Wood, 2013). Despite the policies and current guidelines against the e-commerce of NPS, they continue to be a popular trend.

In the European Union (EU), 41 NPS were identified for the first time in 2010, 49 in 2011, 73 in 2012, 81 in 2013, and 37 by April 2014 via the European Early Warning System (Krabseth et al., 2016; World Health Organization, 2004). In 2013, It was estimated that almost a quarter of a billion people of age between 15 and 64 years used an illicit drug in 2013, which corresponds to an estimated global prevalence of 5.2% (DrugWiseUK, 2016). Similarly, the number of NPS of use reported in the European Union is increasing each year exponentially, for the period 2009 to 2014 (Novel Psychoactive Treatment UK Network, 2015).

In 2014, the UNODC via its World Drug Report indicated that the number of NPS on the global market more than doubled over the period 2009–2013 (United Nations Office on Drugs and Crimes, 2016). Between 2008 and 2015, a total of 644 NPS had been reported by 102 countries to the UNODC early warning advisory on NPS. The emergence of NPS was reported for the first time in 2015 in Kyrgyzstan and Mauritius. In 2015, the early warning advisory also registered the emergence of NPS in previous years in Belarus, Serbia, South Africa and Tajikistan. The majority of countries and territories that reported the emergence of NPS up to December 2015 were from Europe (41), followed by Asia (30), Africa (16), the Americas (13) and Oceania (2). Furthermore, there is a considerable lack of data in relation to the region of the Middle East (United Nations Office on Drugs and Crimes, 2016).

In March 2015, the EMCDDA published an update on the NPS situation in Europe. The report divides the NPS market into several categories: Legal Highs, research chemicals, food supplements, designer drugs, and medicines. All produced in clandestine laboratories (DrugWiseUK, 2016). Little is known about the diffusion of NPS in the Middle East. However, as the current civil war and terrorism in Syria continue, the demand for illicit drugs, including an amphetamine-related substance known as captagon is on the rise. This substance is also diffused in Iraq, Turkey, Iran, Jordan, Kuwait, Oman, UAE and Qatar (Al-Imam et al., 2016). Other substances of critical importance are; octodrine and NBOMe. Octodrine is a re-emerging old substance (the 1940s) with potential use as a mild performance enhancer and as an NPS. Octodrine has been marginally studied in literature; its physiological sympathomimetic effects enforce its use as an NPS. On the other hand, NBOMe is a hallucinogenic agent that was invented in 2003; it a is potent serotoninergic agonist (Ling et al., 2013; Nichols 2016; Rao and Hoffman, 2014). NBOMe is used by psychedelics users from the developed world despite its high rates of intoxications and death. There have been no documented reports from the Middle East neither on octodrine nor on NBOMe. Further, each of the three substances (captagon, octodrine, and NBOMe) belongs to a different category of chemicals and has a different; potency, mechanism of action, physiological effects, pharmacodynamics, and pharmacokinetics. Each substance is either relatively new (captagon and NBOMe) or re-emerging (octodrine) with the lack of prior studies, reviews, and potential medical indications of use. Additionally, there are no adequate data on their e-commerce on both divisions of the web including the darknet e-marketplace. The illicit drugs market strategies have significantly changed in recent years, and the Internet has become increasingly important as a distribution and communication modality, this method is also known as the electronic commerce (e-commerce) or electronic trade (e-trade). Additionally, potent substances can be easily purchased online, and in uncertain doses, they entail a high risk of serious poisonings, morbidities and chronic illnesses, and even sudden deaths (Krabseth et al., 2016).

Figure 1. The geographic mapping of NPS by 102 countries to the UNODC early warning advisory on NPS (United Nations Office on Drugs and Crimes, 2016).

CRITICAL APPRAISAL OF RESEARCH OUTPUT

The hierarchy of evidence can be described as a pyramid were low-level of evidence studies (weakest evidence) are located at the base of the pyramid (Daly et al., 2007; Olivia, 2014; Tang and Wan, 2014). In the current era of evidence-based medicine (EBM), an integrative approach is required in seeking out original studies of high level-of-evidence (Every-Palmer and Howick, 2014; Greenhalgh, 2014; Smith and Rennie, 2014; Montori et al., 2013). On the other hand, dozens of critical appraisal tools of literature exist, including; *CASP* appraisal tools, *CEBM* appraisal tools, and *JBI* tools (Ciliska, 2008; Crowe and Sheppard, 2011; Hannes et al., 2011; Sanderson et al., 2007). As will be seen in subsequent chapters, several studies in the established body of literature for NPS discipline, have been declared to be of high level-of-evidence, although that was not always correct. Some studies lack rigour standards, including inferential analyses and hypotheses testing.

Current NPS-related web analytic studies are frequently reliant on internet snapshots, retrospective studies, reviews, and other observational analyses. To date, there are no significant interventional studies, animal and physiologic models, or proper (ethical) human experimentations with NPS. In fact, all web analyses are purely observational, though attempts for quasi-experimental studies are emerging (Hegde et al., 2013; Van den Brink, 2012). Furthermore, observational methods are not only highly time-consuming and require excellent resources, but they are also observations which are obsolete beyond the point of time in which they were taken (Nizar et al., 2015; Vermette-Marcotte et al., 2014; Wood and Dargan, 2014). Hence, observational and internet snapshot techniques might be considered as “endangered” methods, unless some drastic upgrades are introduced.

The upgrades should serve to reduce time and efforts. Here, we propose three methods and these will be carried out in this dissertation. The 1st method should aim at finding the most popular NPS on the web, both surface and deep web. The 2nd method is dependent on the 1st one; it includes extracting data in relation to the high-risk NPS among the most popular (prevalent) NPS (Schifano et al., 2015; Moore et al., 2013). The 3rd method implies the inclusion of data mining and knowledge discovery in databases (KDD). These three methods should be implemented in a hierarchical way to extract data principally from; the predominant medical and paramedical databases, including PubMed and the Cochrane Library (1), most popular drug fora (2) Google Trends database (3), high-rank e-markets on darknet, including AlphaBay (4), and Grams search engine (5) (Berry and Linoff, 1997; Butte and Kohane 1999; Buxton and Bingham, 2015; Davey et al., 2014; Martin, 2014). The varied array of the sets of data and resources should be successful to build a successful database; the aim is a reduction of time and effort, in parallel with the application of the automation principle of KDD.

Numerous studies have failed to produce a satisfactory level of data and statistical analyses, particularly inferential (Bordens and Abbott , 2002; Lowry, 2014). Statistical analyses should be inherent and fundamental in all research output of high-rank of evidence; these analyses are basically divided into; descriptive and inferential (Clarke and Warwick, 1994; Dixon and Massey; 1969; Ferguson, 1959). In one of the chapters (chapter: Extrapolations Based on Literature review – Evidence-Based Analysis of Literature), there will be an implementation of extensive systematic analyses of the NPS research output in relation to the embedded level-of-evidence and statistical analyses upon which recommendations for the following chapters will be extrapolated accordingly. These recommendations can also give an insight into the overall trends of research output, nationally and internationally.

THE COMMITTED INTERDISCIPLINARY APPROACH FOR NPS RESEARCH

The growth of NPS discipline and drug (ab)use problem was phenomenal in the past decade; it was also paralleled by the effort of NPS researchers to keep pace with this ever growing problem (Krabseth et al., 2016; Orsolini et al., 2016; Wood et al., 2012). Regulating bodies like the United Nations Office on Drugs and Crime (UNODC), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), World Anti-Doping Agency (WADA), World Health Organization (WHO), and Food and Drug Administration (FDA) (Griffiths et al., 1997; Hanstad; et al., 2008; Mackey and Liang, 2013). These global organisations invested in the process aiming to contain or limit the inevitable consequential sequelae of this malady; regulating bodies aim to interfere at legislation levels (legal status), and policy is making either to regulate, control or completely ban a particular substance (Ayres et al., 2012; Corazza et al., 2013).

Researchers in the field of NPS are from multiple backgrounds, involving multiple disciplines; these are not limited to analytic chemistry, molecular biology, toxicology, biostatistics and data science, web analytics, animal modelling, and neuroscience (Dargan and Wood, 2013). All these disciplines should be interlinked with each other; researchers of NPS should be integrative, holistic, and innovative. Hence, a multi-talented researcher is an imperative and an essential building block of an effective NPS research team (Marcus, 2002; Smith and Robert, 2014). It is also highly appreciable that an NPS researcher is confident of his analytic tools, particularly data science tools and inferential statistics (Corazza et al., 2013; Wood and Dargan, 2012). Researchers should be effectively communicated in a cross-talk to share the experience on a global scale (Goldacre et al., 2000; Simon et al., 2000; Wong et al., 2000).

THE NPS PHENOMENON IN THE MIDDLE EAST

There have been exhaustive attempts to map the epidemiology of the NPS (ab)use and its e-commerce in the developed world, particularly in the United States, the United Kingdom, Canada, the European Union, Eastern Europe, Australia, and New Zealand. Historically, mapping has been done via observational analyses, both cross-sectional and longitudinal. The cross-sectional analysis includes surveys and questionnaires, and Internet snapshots. Most of these studies were used to assess the prevalence of use and misuse the western societies and the developed countries, while few attempts were prosecuted in the developing world, and even a fewer attempts were committed for the region of the Middle East and the Arabic countries. For example, the research efforts carried out by Al-Hemiary and colleagues, and Corazza and coworkers (Bigdeli et al., 2013; Al-Diwan et al., 2015; Al-Hemiary et al., 2014; Al-Hemiary et al., 2015; Al-Hemiary et al., 2016; Corazza et al., 2014). However, the advent of intranet networks and virtual social communication media will enable these observational studies to be carried out with more ease and promptness in the Middle East nowadays (Hadgar, 2016; Joh et al., 2017; Moorhead et al., 2013).

A question remains unanswered; how to estimate the prevalence of the use of NPS in this region (Middle East)? Can the prevalence of NPS use be estimated by modalities other than observational studies of the web? The answer is yes; it can be inferred by modes other than web analytics, for example; cross-sectional studies and survey in a real (non-virtual) population of users, and retrospectively from; seized batches and databases from criminal records, hospital emergency units, border patrol agencies, police departments, intelligence and counter-terrorism units. These modalities of research have been already extensively implemented by the aforementioned regulating bodies (Burns, 2014 Ferri et al., 2015; Mackey and Liang, 2013; Toohey and Beaton, 2017).

TERRORISM AND NPS IN THE MIDDLE EAST

It seems that the use of NPS and terrorism are somehow interlinked. According to the *UN Security Council*, terrorism is defined as the use of violence to frighten the people to achieve a political goal, and the systematic use of terror especially as a mean of coercion and the consistent use of violence and intimidation to achieve some goal (Saul, 2005). On the other hand, the *Federal Bureau of Investigation* (FBI) defines terrorism according to its type, international or domestic, based on some diagnostic criteria (Federal Bureau of Investigation, 2016; Greene et al., 2014). Terrorism is a dynamic phenomenon; it usually exploits the use of NPS phenomenon under unusual settings; areas of conflicts, war zones, and civil unrest. Terrorist organisations currently active in the Middle East include *the Islamic State of Iraq and the Levant* (ISIL) and Al-Qaeda; they aim for high profits and leverage in the battlefield by taking advantage of the pharmaceutical properties of stimulant NPS, which can highly boost performance, physical and cognitive abilities, and aggression of their fighters (DrugWiseUK, 2016).

The majority of the terrorist organisation are domestic (Global Terrorism Database, 2016). Statistical data from the Global Terrorism Database (GTD) revealed that Iraq is infested by terrorism, it ranks on the top of the list (rank 1st), with a total number of attacks of 7807, and fatalities of 26998 (Global Terrorism Database, 2016). In the region of the Middle East, particularly in areas of political instability and civil conflict as in Iraq, Syria, and Lebanon; there are dozens of terrorist organisations and militias; the most famous two are Al-Qaeda and ISIL (University of Maryland, 2016). Cumulatively, these two organisations have been the most active and the most lethal in the Middle East in the past few decades, and it has grown even more since the defeat of the Saddam Hussein regime upon the United States military invasion of Iraq on 2003 (Global Terrorism Database, 2016; University of Maryland, 2016).

ISIL is a predominantly “Sunni” jihadist organisation that deviates from the original spirit of Islam, ISIL seeks to induce civil instability in Iraq and the Levant (Greater Syria) with the aim of establishing a caliphate state based on the application of the Sharia (Islamic law). ISIL, formerly known as ISIS, is mainly operational in Iraq, Syria, Lebanon, Yemen, and more recently Egypt. However, there are indicators that many of its sleeping cells are found in other regions of the world including Europe (The British Broadcasting Corporation, 2016; The Cable News Network, 2016). Al-Qaeda, unlike ISIL, adhere strictly to applying Sharia law, according to which a Muslim should be in absolute abstinence from Alcohol and the use of any sort of drugs, unless for medicinal or therapeutic purposes, that may alter the natural status of the mind (Alshaer, 2016; Al-Yassini, 1985; Sattari, 2012). Therefore, ISIL is selective when it comes to applying the Sharia law, to justify its own agenda.

Within the pharmaceutical “family” of NPS and of particular relevance in the Middle East is the use of phenethylamines. Phenethylamines are chemicals that can form naturally inside the human body in minute quantities; It can also be synthesised in a chemical laboratory. Phenethylamines are taken by some individuals for; improving athletic performance, treating depression, achieving weight loss, and improving mood and attention (Dargan and Wood, 2013). Phenethylamine stimulates the body to make certain chemicals, including monoamines, which play a great role in depression and other psychiatric conditions (Hall, 2015). The human body normally does not naturally produce enough phenethylamine, and some extreme cases, phenethylamine can be taken as a supplement to support normal body functions (Fischman, 2016). Amphetamines and Amphetamines-type Stimulant are phenethylamine derivatives; a quintessential example is a captagon (Dargan and Wood, 2013; Fischman, 2016). These chemical compounds seem to be favoured by members of militias and terrorist organisations. For instance, the use of Captagon by members of ISIL during terrorist activities in the Middle East and other regions including the EU (Al-Imam et al., 2016).

REGULATING ORGANIZATIONS AND EARLY WARNING SYSTEMS

There are several existing bodies which are responsible for the; monitoring, regulation, and establishing guidelines concerning NPS. For example; the World Health Organization (WHO, established in 1948), the United Nations Office on Drugs and Crime (UNODC, 1997), World Anti-Doping Agency (WADA, 1999), and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 1993) (Hanstad, 2008; Network NP, 2015; Sedefov, 2010; United Nations Office on Drugs and Crime, 2010; World Health Organization, 2010). These international organisations also contribute efficiently and consistently to the process of policy-making in relation to the legal status of NPS substances (Des Jarlais, 1995; Simpson and Friend, 1989; Stevens et al., 2006).

Two empirical initiatives (early warning system) were launched by the EMCDDA and the UNDOC in relation to the monitoring of the global NPS phenomenon. The 1st is *the EU Early Warning System*, in which when a new psychoactive substance is detected, detailed data on the manufacture, traffic and use, including additional information on the possible medical purposes is sent by the EU Member States to the EMCDDA in Portugal and to the Europol in the Netherlands. Accordingly, the EMCDDA and Europol will collect the data and communicate immediately with; each other, to the representatives of the Member States and the Europol National Units, to the European Commission, and to the London-based European Medicines Agency (European Monitoring Centre for Drugs and Drug Addiction, 2017).

The 2nd initiative is *the Global SMART Program*. The Global Synthetics Monitoring: Analyses, Reporting and Trends (SMART) programme was launched in 2008. The programme has strengthened online data-sharing mechanisms and provided training on how to improve data gathering and analysis of synthetic drugs and NPS. SMART primarily evaluate the needs of EU Member States in high-priority regions in relation to the systematic collection of drug-related data including; seizures, trafficking, use, and forensic drug analysis capabilities. All these activities are implemented to ensure that the Member States can generate and manage information on NPS (United Nations Office on Drugs and Crime, 2017).

THE DEEP WEB AND THE DARKNET

The e-trade (e-commerce) activities of NPS existing on the surface web represent only *the tip of the iceberg* (Gilani, 2016; Heyerdahl et al., 2014; Smith and Morley, 2017). The incognito deep web is virtually an endless place for e-trade of NPS and several other illicit and inhumane activities; including child pornography, human and slave trafficking, unethical experimentation, weapons e-trade, and even terrorism-related activities (Al-Imam et al., 2016; Dalton, 2014; Maddox et al., 2016; Spurlin and Garry, 2009; Taylor and Fritsch, 2014; Weimann, 2016). The deep web, also known as the invisible web, seems to be of supreme importance for the e-commerce. This is due to anonymity in this division of the internet, and the use of an anonymous payment system (Chen, 2012; Grams, 2016). The deep web utilize technologies to provide anonymity for users' identities and their online purchases; these technologies include: the use of distinct Internet browsers (Tor Browser, etc.), login credentials specific to each e-market, secure routing protocols, virtual private networks (VPN), Internet Protocol Masking (IP masking), and the Bitcoin payment system (Fifield et al., 2015; Prouff et al., 2014; Reid and Harrigan; 2013). Furthermore, the deep web represents the online content which is not indexed by the standard search engines (including Google, Yahoo, MSN, etc.). Many marketplaces (e-marketplace) exist on the deep web, for examples: 'Silk Road', 'Black Market Reloaded', 'The Armory' and the 'General Store' (Christin et al., 2013; Van Hout et al., 2013).

By the end of 2015, in excess of 700 NPS had been reported by a large number of countries in the world. These include synthetic cathinones; synthetic cannabinoids; phenethylamines; and psychedelics account for the vast majority of these substances (Dargan and Wood, 2013; United Nations Office on Drugs and Crimes, 2016). This thriving growth was facilitated and promoted by the "online drug culture" which finds its expression; in chat rooms, drug fora, blogs, and e-markets, on both the surface and deep web. The deep web, with high-level of anonymity, has progressively modified this phenomenon into a private virtual one. The rapid pace of change in the NPS online market constitutes a major challenge to the provision of current and reliable scientific knowledge on these substances (Corazza et al., 2011; Corazza et al., 2013a; Corazza et al., 2013b).

The darknet is a vital component of the deep web; it's a huge virtual (e-)marketplace where several illicit activities exist including the NPS e-trade (Bailey et al., 2006; Bancroft and Reid, 2016; Fachkha and Debbabi, 2016). Dozens of e-markets are operational on the darknet e-marketplace, including; Hansa, Darknet Hero League, AlphaBay, Agora, Nucleus Market, Majestic Garden, Real Deal Market, Oasis, Abraxas, Outlaw Market, Middle Earth, Silkkitie, Oxygen, Tochka Market, and Arsenal (Al-Imam et al., 2016; Biddle et al., 2002; Van Buskirk et al., 2016). Those e-markets can be systematically and thoroughly mapped not only from an NPS perspective but also from a social science perspective; the aim is to analyse the marketing strategies and the properties of the e-commerce (Dahl, 1957; Spekman, 1979; Wrong, 1980). The characteristics of e-vendors from the Middle East have been marginally studied in the literature (Van Hout et al., 2013; Van Hout et al., 2014); the analysis of the individual basis of power for e-vendors was never carried out before (French et al., 1959; Wrong, 1980). Power scoring of e-vendors should also of value to explain the geographical context (geo-mapping) of shipping countries of NPS.

Several methods have been used by researchers to observe and analyse the e-trade on the deep web and its darknet; most are relying either on the observational cross-sectional or retrospective analyses; the most common analytic tool is known as the *Internet snapshot method*. However, this technique is not only time consuming, having modest accuracy, and of low level-of-evidence, but it is also photographic (ionic), representing an absolute brief point in time. Further, snapshots for the deep web requires the dedication of time, financial resources, and considerable human efforts (Pastor-Satorras et al., 2001; Siddiqi et al., 2015). Therefore, a strive to improve the internet snapshot will be discussed in this dissertation to; enhance the accuracy of the snapshot method (1), improve the implied level-of-evidence (2), reduce time and efforts (3), implement the application of inferential statistics (4), and potentially be applied in combination with techniques of data mining (Berry and Linoff, 1997; Fayyad et al., 1996).

APPLICATION OF THEORIES AND PRINCIPLES OF PSYCHOLOGY AND SOCIAL SCIENCE

Concepts and theories of psychology and social science can be applicable to the discipline of NPS research (Moore et al., 2013; Wood et al., 2012). Social science has been very successful in explaining occurrences, including; economics, game theory, political events, casting a vote, gambling, and even in explaining the theory of evolution (Campbell, 1975; Frey 1999; Morrow 1994; Plides 2001; Shubik 1984). Hence, the application of social science principles is both innovative and complementary to explain events related to the NPS discipline. One of the critically acclaimed principles of social science is known as *the individual basis of power* (Bourdieu, 1994; Katz and Khan, 1978; Wrong, 1980).

The individual basis of authority (power) includes three main elements; personal, structural and cognitive (University of Michigan, 2017; Wrong, 1980). The same basis of power can be implemented to explain the unbalance within the NPS industry and e-commerce market between opposers of the NPS phenomenon (anti-NPS) and protagonist and enthusiast of it (pro-NPS) (Al-Imam et al., 2016; Dargan and Wood, 2013). NPS opposers include NPS investigators and researchers, legislators, policy makers, regulating bodies, and collateral organisations and research institute. For example, the *Novel psychoactive treatment: UK Network* (NEPTUNE) (David, 2013; EMCDDA, 2016, Mackey and Liang, 2013). On the other hand, NPS protagonist may include; vendors and e-vendors, e-markets on the surface and deep web, NPS chemists, terrorists and terrorist organisations. Terrorist organisations have been recently incriminated in using NPS stimulants including phenethylamines and amphetamines, for example, the use of captagon fenethylline by ISIL in the Middle East and in the terror attacks across Europe in 2015 and 2016 (Al-Imam et al., 2016; Ekici and Ozbay, 2013; Ganor and Halperin, 2013; Kravitz and Nichols, 2016; Mackey and Liang, 2013; Ward and Mabrey, 2013).

There are also dozens of e-markets of darknet on the deep web; the most popular are AlphaBay, Valhalla, and HANSA (Broséus et al., 2016; Celestini et al., 2017; Grisham et al., 2016; Wehinge, 2011). These e-markets and their e-vendors can be analysed using social science models. These analyses can be used to infer data in relation to the main promoters of the booming NPS industry. Furthermore, the objective of these inferences is to grasp a solid an idea, rather than a mere speculation, on the power within the mega market of NPS e-commerce and NPS industry. Therefore, the inclusion of concepts of social science can serve as a cornerstone modality of NPS research. Unfortunately, it was not fully considered seriously to counteract the extraordinary evolution of the NPS phenomenon including both regular trade and e-trade (e-commerce) (Fayyad et al., 1996; Jelen and Laexander, 2006; O'Leary Z, 2004). This dissertation will take a venturing step into these concepts, which can also be used to explain the lack of presentation, e-vendors, and NPS investigators from the region of the Middle East and Arabic countries.

POTENTIAL EMERGING TECHNOLOGIES

There are numerous technologies that are either novel or futuristic, these are not limited to; cloud computing (1), data mining and knowledge discovery in databases (2), virtual reality (VR) and mixed virtual reality and augmented reality (AR) (3), three-dimensional printing (4), nanotechnology (5), the use of drones (6), tissue engineering and regenerative medicine (7), the anonymous Bitcoin payment system (8), and the brain-computer interface (BCI) concepts (9) (Androulaki, et al., 2013; Armburst et al., 2013; Bhushan, 2010; Earnshaw, 2014; He et al, 2013; Lipson and Kurman, 2013; Nakamoto, 2008; Ohta and Tamura, 2014; Ong and Nee, 2013; Vincent and Loave, 2014; Witten et al., 2016; Yoo and Lee, 2002). These novel technologies are evolving not only rapidly but also co-dependently and exponentially in parallel with the logarithmic growth of the ICT. Just to imagine; how will the combination of cloud computing and 3D printing work for protagonists of the NPS industry? how can 3D printing be revolutionary in relation to NPS? enabling an average user with no background knowledge in chemistry to print and customise his (or her) “own” substance based on the timely desires, how virtual reality (VR) and augmented virtual reality (AVR) will enhance the user subjective experience of a psychedelic trip? by adding a personalised virtual world of his (or her) own. This future is inevitable, and it seems daunting and frightening.

In fact, all of the current efforts to regulate and control the NPS phenomenon may become limited or obsolete. Therefore, serious efforts and far-reaching enhancements should be adopted to counteract the supremacy of NPS protagonists and emerging technologies. Data mining can be one of the promising solutions; it is an interdisciplinary division of computer science, which lies at the intersect of; data science and statistics, machine learning, databases systems, and artificial intelligence. The application of data mining is vital for the discovery of patterns within large sets of data. Mining techniques are not seriously considered yet for the discipline of NPS research.

THE PROSPECTIVE DATA MINING TECHNOLOGIES

What if the existing early warning systems implemented by the UNODC and the EMCDDA can be further perfected to unprecedented levels? Can this be done via the implementation of ICT technologies including the concepts of data mining and the application of artificial intelligence? That would be a fascinating evolutionary step. Designer drugs represent an extraordinary neuro-chemical phenomenon of the 21st century, the escalating rise in the NPS spectacle seems to be ahead of efforts of NPS researchers and regulating bodies combined (Rolles et al., 2014; Saniotis, 2010; Simonato et al., 2013; Tracy et al., 2017). There have been numerous attempts to restrict the spread of designer drugs and “research chemicals”. However, most of these were limited. The NPS global “industry” is not only driven by money, human desire, terrorism and extremism, but also by the booming progress in the field of information and communication technologies (Burchardt et al., 2014; Fettweis, 2014; Webster, 2014). Furthermore, the advent of the anonymity and the Bitcoin payment system on the deep web, led to a more aggressive and unrestrained spread of these illicit substances and illegal trading bodies on the Internet (2014; Jha et al., 2014; Lee and Wei, 2016; Reid and Harrigan, 2013; Van Hout et al., 2013; Van Hout et al., 2014).

Despite all these encountered difficulties, there are still some bright expectations in the horizon; this thesis will explore the implementation of generalizable (inferential) statistics, extra-large databases, data crunching, and the concepts of data mining and knowledge discovery in databases (Fan and Bifet, 2013; Larose, 2014; Wu et al., 2014). The best way to understand a trend for a phenomenon, like that of the NPS, is to study a large or an extra-large database; Google Trends database fits this purpose perfectly. This database already permits the use of specific keywords in addition to the application of specific filters for time and geographic location. These keywords can be used to derive statistical inferences (Google Trends, 2017). The potentials of this technique are very promising; the aim is to apprehend the overall trends on the surface web, and to test if these trends are compatible with the other trends on the deep web, specifically on the e-markets of the darknet (Miranda, 2014; Lederman, 2016 ;Rudesill et al., 2015). Automation and real-time analysis of databases should achieve much more progress when compared to research attempts prior to the implementation of data mining technologies.

AIMS AND OBJECTIVES

1) RESEARCH QUESTIONS

The prime rationale behind this study is the paucity of literature and the lack of data based on original studies in connection to the NPS and NPS e-phenomena in the region of the Middle East (Al-Imam et al., 2016; Corazza et al., 2013; Corazza et al., 2014). There is a considerable lack of data in relation to the; methods of commerce and e-commerce of NPS, the relative role of the surface web and the deep web in connection with the e-commerce activities, degree of spread and (ab)use of NPS in the Middle East (epidemiological studies), data in relation to incidents of intoxication and death due to (ab)use of NPS, potential exploitation of NPS by extremists and terrorists organizations, role of national regulating bodies, and measures used to prevent and manage these NPS-related threats.

The study will focus on the spread of the NPS and its e-commerce on the web, both surface and deep web. The contribution of the Middle East to the global phenomenon will be assessed in relation to; its magnitude compared with the global NPS electronic trade activities, geographic mapping, and the collateral research output to counteract this dangerous phenomenon. Thorough mapping of the deep web and the darknet will be carried out with an aim to understand the e-marketing strategies, the e-vendors and their relevant characteristics, the categories of promoted NPS, the total number of NPS per e-market, the dominant (trending) NPS on these e-markets, and to reach a conclusion in relation to the most prominent e-markets that are steering the trends on the darknet e-marketplace.

Special focus will be directed towards amphetamines, amphetamine-type stimulants (ATS), and hallucinogens (Farré et al., 2015; Fischman, 2016; Hoffer and Osmond, 2013; Weiss and Laties, 1962). The analyses will focus on; the surface web (1), Google Trends database (2), the deep web (3), and the darknet e-marketplace on the deep web (4). These analyses will be integrated and hierarchical, starting from the surface web, including the trends database and the drug fora, culminating eventually towards exploring the deep web. Research questions to be addressed are;

1. Are there any deficits in the established body of NPS literature and previous research attempts? how can the research efforts be further enhanced and upgraded? Can the literature databases be used in an integrative way with data retrieved from drug fora and social communication media? Is it possible to attain collateral and corresponding data from these resources to reach an estimate in relation to the incidents of intoxications and fatalities caused by particular and potent NPS? can similar inferences be drawn in relation to the Middle East? (Helander et al., 2013; Hohmann et al., 2014; Schifano et al., 2015)

2. Is it possible to utilise theories of social science including the basis of the power analyses for protagonists of NPS (pro-NPS) and compare them to those who oppose, control, or regulate it (anti-NPS)? will it be possible to analyse the basis of power for each? are there any restrictions for applying these analyses? How can these obstacles be overcome (Spekman, 1979; Wrong, 1980)
3. In relation to NPS (ab)use, how can the cultural and ethnic backgrounds of the Middle East, be of a differential effect when compared to that of the developed world, for example; the European Union (EU), North America, and Australasia? Is it possible to use inferential statistical models, for this purpose? Can other factors be correlated, for example; religious affiliation, atheism, and agnosticism, population count, sexual abuse and rape, and geographic mapping (geo-mapping)? From a cultural perspective, are there any geo-ethnic or religious biases, in relation to NPS (ab)use? can these be inferred from specific populations of NPS (ab)users, for example in a population of psychedelics users? Is it possible to implement retrospective analysis of incidents of NPS-related intoxications and death to infer the demographics of (ab)users for the most popular and high-risk substances? Is there a pattern (specific demographics) unique for these substances? Can valid inferences, based on data science, be applied?
4. Is it valuable to use analyses based on trends databases of the surface web, primarily Google Trends database? Can these analyses be utilised for the purpose of statistical inferences and hypothesis testing? Will these inferences be applicable (generalizable) to the deep web? Will it be feasible to retrieve data of value in geo-mapping? if so, can geo-mapping be carried out in relation to the Middle East (Carneiro and Mylonakis, 2009; Choi and Varian, 2012)? What are the potentials for data crunching and data mining? Where mining techniques applied before? Are there specific obstacles? Can data mining technologies be functional on the deep web and the darknet e-marketplace? (Fayyad, 1996; Han et al., 2011).
5. The ultimate question is to understand the contribution of the Middle East and Arabic countries in relation to the electronic commerce and trade (e-commerce and e-trade) of NPS on the web. This will include inferences derived from both divisions of the internet; the surface web, and the anonymous deep web (Cali et al., 2016; Liu et al., 2016). Will it be possible to estimate the proportional contribution of the two divisions of the web to the NPS e-commerce? Which division is the principal contributor? Can it be deducted if the e-trade in the Middle East, alone by itself, is responsible for the spread of the NPS phenomenon in that region? Or are there other modalities of NPS distribution other than the electronic commerce via the web?

2) HOLISTIC OBJECTIVES

From short-term towards the long-term, the main objectives are;

1. To carry out a systematic critical appraisal of the published literature in relation to the NPS phenomenon, and to estimate the magnitude of the research output originating from the Middle East, its quality, country and Institute of origin (geographic mapping), level-of-evidence, and the implemented statistical analyses. The aim is to assess how far the Middle Eastern researchers are lagging behind their peers from the developed world primarily in the European Union, the United Kingdom, the United States, Canada, and Australasia.
2. To infer data in relation to the most popular categories (chemical categories) of NPS based on information retrieved from Google Trends database. Geographic mapping (geo-mapping) will be implemented to reach an inference in relation to the contribution of the Middle East.
3. To provide data on high-risk NPS via integrative analyses of literature, drug fora, and social communication media. Geo-mapping will also be established with an aim to assess the contribution and prevalence of high-risk NPS in the Middle East. Incidents of intoxication and fatalities in the published literature and drug fora will be analysed for this purpose.
4. To shed light on selected NPS of interest; captagon, octodrine, and NBOMe(s). Each substance belongs to a different chemical category of NPS. Captagon is a potent amphetamine-type stimulant; it was linked to several terror attacks in the Middle East and Europe. Octodrine is a re-emerging NPS; it is utilised as a supplemental agent in weight loss and pre-workout formula. Very few manuscripts have been published in relation to octodrine; the substance is vague and long-forgotten since the 1940s. NBOMes are potent hallucinogens with frightening incidents of intoxications and fatalities. The incidence of intoxications and deaths induced by each of these substances is lacking; there is a considerable lack of original studies of relevance, including epidemiological studies, chemical characterization, web analytics, preventive and therapeutic measures, and data in relation to the national regulating bodies in the region.
5. Implement a thorough Mapping of the deep web, and the anonymous e-markets found on the darknet to; extrapolate the commonest (trending) NPS in e-commerce on the deep web, geographically map the e-vendors on the darknet, estimate the proportional contribution of the e-vendors from the Middle East, and conclude the most dominant e-market(s).
6. To gather data, via cross-sectional analyses and surveys, in relation to the level-of-awareness and prevalence of (ab)use in selected populations from Iraq, including a population of undergraduate medical students at the College of Medicine, University of Bagdad.
7. Present the research output in seminars and conference events, nationally and internationally, and to add to the existing body of published literature of relevance to the NPS,

its e-commerce in the Middle East, and its collateral e-phenomena on the web. Publications will include; case reports, review articles, and original studies.

8. The long-term and ultimate objective will be the elaboration on the potential of exploiting data mining tools and data crunching of the surface web for real-time analyses of; trends databases, the surface web, the deep web, and the darknet e-marketplace. Real-time analyses will represent a breakthrough in the field of NPS research. For instance, real-time analyses and geo-mapping of; attentiveness of surface web users towards specific NPS, incidents of intoxication and fatalities due to either some potent trending NPS and and the comparable magnitude of the Middle Eastern contribution in relation to the global geo-map.

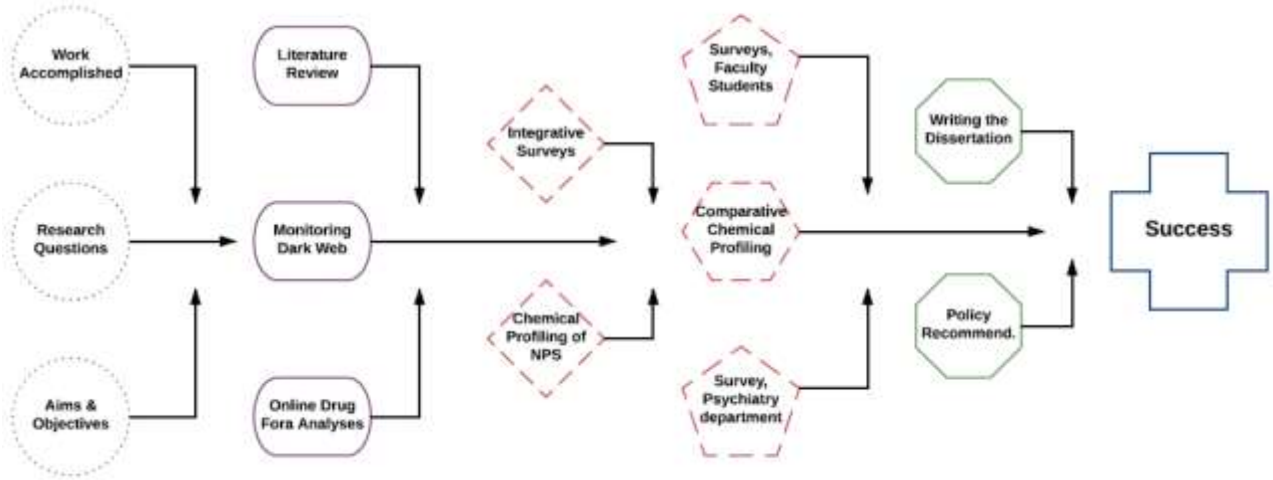


Figure 1. Concept Map of the Research Activities.

3) OBJECTIVES PER CHAPTERS

Extrapolations Based on Literature review – Evidence-Based Analysis of Literature

1. To contrive a database made of hundreds of prior publications which will form a solid basis for hierarchical analyses of literature, to be integrated later with data retrieved from; drug fora, social communication media, trends databases, and the deep web.
2. To infer the overall characteristics of the established (published) NPS research, its strength, weaknesses and limitations, and to provide recommendations for future endeavours in NPS research, to achieve more accurate studies and to seek higher level-of-evidence.

Analysis of Bases of Power of Key Players in the NPS Industry

1. To introduce concepts from social science to the discipline of NPS research; this will validate the key players in the NPS *business* via contrasting the predicted power of pro-NPS versus anti-NPS.
2. To establish a conclusion, based on quantification methods, on the power within the mega market of NPS e-commerce on the deep web and the darknet.

Extrapolations Based on Literature review – Most popular NPS

1. To apprehend the overall trends of attentiveness (interest) of surface web users towards NPS substances; these will be based primarily on data retrieved from the published literature in parallel to data extrapolated from Google Trends database.
2. To geographically map the attentiveness of surface web users towards the major chemical categories of NPS, and to test if these trends are compatible (analogous) with the trends observed on the deep web, specifically on the e-markets of the darknet.

Spotting High-risk NPS; Integrative Analyses of PubMed, Drug Fora, and the Surface Web

1. To infer and define the high-risk NPS, these will be based on data from the previous chapter (the most popular NPS).
2. To test multiple hypotheses, among which the determination of the age and gender of (ab)users of these high-risk NPS.

Darknet – Part 1

1. To estimate the attentiveness of surface web users in the deep web and its *incognito* e-markets, and to infer the geographic location (countries) of those surface web users. Geographic mapping will establish a comparison in between the Middle East and other regions of the world, which will eventuate in estimating the proportional contribution of the Middle East to the NPS e-commerce on the deep web.

2. To quantitatively score the e-markets on the darknet by assessing the e-markets' power, and inferring the most popular categories of NPS within these e-markets, in addition to the data in relation to NPS-related substances including the traditional psychoactive substances.

Darknet – Part 2

1. To test the hypothesis if a particular e-market is a proper representative (the most dominant) for the darknet e-marketplace, and to infer the most important determinant parameter of power ratings for e-markets on the darknet.
2. To deduct specific conclusions in relation to the spread of specific NPS in the world. Special correlations can be tested for particular demographic parameters, which can serve as a potential blueprint for an early warning system to anticipate particular events including; the religious affiliation, the population count for a specific region of the world, and sexual assault and rape incidents.

A Tale of A Survey and Two Internet Snapshots

1. To infer an estimate in relation to the level of awareness and NPS (ab)use in a selected population of undergraduate medical students from Baghdad, Iraq. Additional correlations can be tested with other parameters including demographics, social status, medical illnesses, and past psychiatric history.
2. To infer the most commonly used terms for psychedelics (hallucinogenic substances) in a selected population of NPS (ab)users. The deduction will be based on thematic analyses and psychoanalysis of comments and subjective experiences of (ab)users who are interacting and commenting on the drug fora and the social communication media.

Integrative Analyses of Captagon, Octodrine, and NBOMe

1. To visualise the extent of spread (e-prevalence) for each of the three substances, and to assess the extent of e-commerce activities on the web, both surface and deep.
2. To infer data on the basis of the power of e-vendors of these NPS on the darknet e-marketplace of the deep web.

Captagon

1. To extract up-to-date data, concerning the captagon e-commerce and use in the Middle East, and to analyse the attentiveness of surface web users in relation to captagon, by relying on data from Google Trends database, drug fora, and social media. Analyses will also explore the geo-mapping of captagon e-vendors on the deep web.
2. To assess and analyse the use of captagon in correspondence with extremism and terrorism in the region of the Middle East and Europe, and to provide future recommendations.

Octodrine

1. To carry out the first ever conducted systematic literature review in relation to octodrine, in an aim to reach out a conclusion of this re-emerging substance which is currently used in pre-workout formula and as a weight-reducing agent.
2. To analyse the attentiveness of surface web users based on data derived from Trends database, and to compare the popularity (abundance of data) on octodrine on the surface web and the deep web.

NBOMe(s)

1. To infer an estimation for the epidemiologic magnitude of the NBOMe e-commerce based on data retrieved from trends databases, case series, case reports, review articles, and online drug fora. The aim is to reach an estimate on the electronic spread of NBOMe(s) and the change in these trends for the past five years (2012-2016).
2. To review the incidents of intoxications and deaths related to the (ab)use of NPS, and to create a blueprint for an early warning system to be activated based on changes in trends' data; the aim is to anticipate imminent cases of fatalities worldwide. This will also enable a correlation of the changes in trends in correspondence with cases of intoxications and deaths.

Critical Appraisal, Limitations of Studies, Conclusion, and Future Recommendations

1. To assess the quality and the level-of-evidence of research output of this dissertation via the implementation of critical appraisal tools and principles of Evidence-based Medicine
2. To provide key point conclusions, present limitations of the carried out analyses, and suggest recommendations for future studies.

4) CONTRIBUTION TO FUTURE RESEARCH

The analysis of strengths, weaknesses, opportunities, and threats, also known as *SWOT analysis* (Table 1), is an inseparable component of the critical analysis of this study. This research is integrative, Opportunities include; a comparative approach of Middle East versus other regions including; developed countries and the European Union (1), Integrative analyses of trends databases and the darknet e-marketplace (2), geo-mapping based on data retrieved from; medical and paramedical literature database, Google Trends database, drug fora, deep web, and the darknet (3), Integrative analyses of published literature, drug fora, social communication media. For instance, in relation to incidents of intoxication-death due to specific NPS (4), Innovative analysis of the reviewed literature via; critical appraisal tools, assessment of the level-of-evidence, and evaluation of the conveyed statistical analyses (5), application of inferential hypothesis testing (6), implementation principles of social science in relation to the NPS e-commerce activities, e-markets, e-vendors, and (ab)users (7), conducting thematic psychoanalysis in relation to NPS (ab)users based on data originating from drug fora, blogs, and social e-media (8), and ultimately the exploration of the role of data mining and knowledge discovery in databases (9).

There will also be some threats including; liability for hacking attempts during the process of surfing the web, primarily the deep web (1), none-response or low response rate while conducting cross-sectional surveys (2), and biases while carrying out observational analyses, including internet snapshots, surveys, web analysis, and critical appraisal of the published literature. Other biases (interpretive and cultural-related) may eventuate while implementing thematic psychoanalysis of contents of the drug fora and social e-media (4).

Strengths include; Inferences in relation to the Middle East, including; the most popular NPS, high-risk NPS, e-vendors and e-markets analyses (1), exploration via observational analyses of Google Trends, surface web, published literature and unpublished literature, drug fora, deep web, and darknet e-marketplace (2), application of statistical analyses (3), implementation of a wide variety of observational studies; cross-sectional analyses, surveys, internet snapshots, and retrospective analyses (4), and an Interdisciplinary mode of study, involving; neuroscience, addiction studies, data science, information technology, psychology, and social science (5). On the other hand, weaknesses include; lack of chemical analytics and toxicological characterization of NPS substances (1), lack of prospective observational analyses (2), internet snapshots and surveys are cross-sectional in time. Hence, obsolete beyond that moment (3), Lack of experimental studies including; quasi-experimental studies, physiologic studies, animal models, and randomised controlled trials (RCTs), including pragmatic RCTs (4), and reliance on one specific trends database (5).

Table 1. SWOT Analysis.

STRENGTHS	WEAKNESSES
• Inferences in relation to the Middle East, including; the most popular NPS, high-risk NPS, e-vendors' and e-markets' analyses. • Exploration and observational analyses of Google Trends, surface web, published literature, grey literature, drug fora, deep web, and the darknet e-marketplace. • The Application of statistical analyses; descriptive and inferential • The Implementation of a wide variety of observational studies including; cross-sectional analyses and surveys, internet snapshots, and retrospective analyses. • A multidisciplinary approach to study, involving; neuroscience, addiction studies, data science and statistics, information and communication technology, psychology and psychoanalysis, and social science.	• Lack of chemical analytics and toxicological characterization of NPS substances. • Lack of the prospective studies, a category of observational analysis. • Internet snapshots and surveys are cross-sectional in time. Hence, obsolete beyond that point in time. • Lack of experimental studies including; quasi-experiments, physiologic animal models, and randomised controlled trials (RCTs), including pragmatic RCTs. • Reliance on one trends database, which is Google Trends database.
OPPORTUNITIES	**THREATS**
• Comparative approach to the Middle East versus other regions including; developed countries and the European Union (EU) • Integrative analyses of trends databases and the darknet e-marketplace. • Geo-mapping opportunities during analyses of; medical literature databases, Google Trends, drug fora, the deep web, and the darknet. • Integrative analyses of published literature, grey literature, and data from drug for.a • Innovative analysis of the reviewed literature via; critical appraisal, assessment of its level-of-evidence, and evaluation of its implemented statistical analyses • The application of innovative techniques of data science including inferential hypothesis testing. • The application of principles of theories of social science in relation to the analysis of NPS e-commerce phenomenon on the deep web. • Application of thematic psychoanalysis in relation to the comments and subjective experiences of NPS (ab)users; these analyses were done via drug fora and social communication media. • The exploration of the potential role of data mining and knowledge discovery in databases.	• Hacking attempts during the process web analytics on the surface web, and a higher risk while surfing the deep web. • Non-response or a low response rate during cross-sectional surveys. • Biases during observational analyses, including internet snapshots, surveys, and trends' analysis. • Biases (interpretive) during thematic psychoanalysis of drug fora.

II. MATERIALS AND METHODS

The web mapping and analytics, including that of the deep web, has been approved by the University of Hertfordshire (November 2013; PHAEC/10-42). The survey targeting the undergraduate medical students from Iraq (Chapter: A Tale of A Survey and Two Internet Snapshots) has been approved by; the University of Hertfordshire (Protocol no. LMS/PGR/UH/02723) and the University of Baghdad (IRB meeting no.7, 20/12/2016).

The research will be articulated into a number of overlapping and simultaneous activities (Figure 1). Each chapter will be integrated with those chapters that follow; there will be a cumulative build-up of data, and expansion of results leading to an ultimate conclusion. Each chapter will rely on; graphical presentations, data analysis and inferential statistics, and innovative methods of observational and quasi-experimental analyses. These analyses will involve the surface web, trends databases, the deep web, the darknet and its e-markets, *Grams* search engine, online drug fora, medical and paramedical databases, and social communication media. The chapters will be in the following sequence;

- Background and Literature Review
- Aims and Objectives
- Materials and Methods
- Extrapolations Based on Literature review – Evidence-Based Analysis of Literature
- Analysis of Bases of Power of Key Players in the NPS Industry
- Extrapolations Based on Literature review – Most popular NPS
- Spotting High-risk NPS: Integrative Analyses of PubMed, Drug Fora, and the Surface Web
- Darknet – Part 1
- Darknet – Part 2
- A Tale of A Survey and Two Internet Snapshots
- Integrative Analyses of Captagon, Octodrine, and NBOMe
- Captagon
- Octodrine
- NBOMe
- Critical Appraisal, Limitations Of Studies, Conclusion, and Recommendations

- Background and Literature Review

The background will represent the portal to the research project and its pertinent research questions. The literature review will be carried out across medical, paramedical, and technical databases. There will be an emphasis on the PubMed/Medline database (Foltz 1936; US Department of Health and Human Services, 2005). The literature review will be systematic and responsive to the research questions for the intended chapters. Pre-determined keywords and Boolean operators will be implemented to; expand, narrow down, or minimise irrelevant and redundant data. The literature review will be accompanied by validation and verification of the level-of-evidence for the retrieved manuscripts; this will be accomplished by using the appropriate appraisal tools and the level-of-evidence Classification system imposed by the *Oxford Center for Evidence-Based Medicine* (CEBM, 2009; Sackett, 1997). Each retrieved manuscript will be screened in the following sequence; title (1), abstract (2), results and conclusions (3), and the full article (4). The purpose of this screening is to determine if a given manuscript is responsive to the researching questions or not.

- Aims and Objectives

This chapter will include details about; the research questions to be answered, objectives, and the goals of component studies. Each of these will be explained from a hybrid perspective of sociology, data science, neuroscience and psychiatry, and medical sciences.

- Materials and Methods

  (this chapter)

- Extrapolation Based on Literature review – Evidence-Based Analysis of Literature

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). PubMed/Medline has been systematically searched for publications specific to the discipline of NPS. The aim of the search was to establish a database which is representative of the majority of publications in NPS research globally. Specific keywords were used; *novel psychoactive substances* (1), *novel psychoactive substance** (1), *new psychoactive substance* (3), *new psychoactive substance** (4), and *(novel psychoactive substance*) OR (new psychoactive substance*)* (5). The systematic search took place in January and February 2017; the use of the keywords and a boolean operator (OR) was intended to expand the number of hits (publications) found on PubMed. Furthermore, no filters were used, in an attempt to avoid biases in relation to geographic location, researchers, date of publication, or countries (of research institution). Only one duplicate article was found and then excluded. Hence, the number of hits (publications indexed in PubMed) was sufficient and reliable enough to deduct a statistical inference in relation to the overall and global trend of NPS-related research output for the period from 2010 to 2017.

The typology of this observational analysis is retrospective; it will go back in time to 2010 where very few publications in the field of NPS were existent; NPS research was still in its infancy. This was followed later by an exponential growth of publications, paralleled by the more escalating growth of the NPS "business". This analysis will aim to provide a snapshot of a time of the available literature by criticising its strengths, potential weakness, and limitations. The critics will be the tools of *Evidence-based Medicine* (EBM) and *critical appraisal* (CEBM, 2009; Reynolds, 2008; Norman and Shannon, 1998). The number of hits retrieved from PubMed will be used to compile an extensive database made of nine tabulated parameters; Number of authors per a publication (1), name of the 1st author (2), the research institute of 1st author (3), Country of the research institute (4), year of publication (or indexing) in PubMed (5), type of the study (6), type of the implemented statistical analysis, if any (7), the level-of-evidence (8), and the journal of publication (9). The categorization of the level-of-evidence will be based on; the classification system implemented by the *Oxford Centre for Evidence-Based Medicine* (CEBM, 2009), and *CASP critical appraisal tools* (Norman and Shannon, 1998; Rosenberg and Donald 1995). The CASP analysis will be based on reading through each article (title, abstract, and full length), with a particular focus on; the nature of the study, and the application of statistics and data sciences. The implemented statistics will be categorised into; none, descriptive, or inferential (Ryon, 2013; Spriensma, 2016). The level-of-evidence will be ranging from 5 (weakest evidence) to 1 (strongest evidence).

The analysis will enable us to; derive a "formula" on the global and regional research in connection to the discpline of NPS research, conclude the major contributing countries to this discipline, and apprehend the average level-of-evidence. The final outcome is to assess if the retrospective research output was up to the expectation (of strong evidence), and to understand the potential limitations. There will also be attempts to correlate the geographical distribution of the publications with the spread of NPS on darknet e-markets; to reach a conclusion if the research output is keeping pace with the NPS phenomenon on the deep web, and if there are sufficient research activities from the Middle Eastern. In this study, statistical analyses will be implemented, both descriptive and inferential. Inferential tests will include; regression models, Student's t-test, and the analysis of variance and covariance (ANOVA). Descriptive statistics will aim to discover exceptional cases (outliers) within the compiled database of publications. Statistical significance was considered at an alpha (α) value of 0.05 and a confidence interval of 95% (95% CI).

- Analysis of Bases of Power of Key Players in the NPS Industry

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). The basis of power (authority) will be analysed in relation to the key players in the NPS "industry"; these players will be divided into; NPS protagonists (pro-NPS) and NPS antagonists (anti-NPS). Pro-NPS include vendors, e-vendors on surface web, e-vendors on the deep web, NPS (ab)users, chemists, and terrorists. All those agents (key players) interact with each other within the NPS markets, e-markets, legislation and policy making, and even in terrorism and counter-terrorism. The individual basis of power are divided into three broad categories; structural, personal, and cognitive (University of Michigan, 2017; Spekman, 1979). Each of these has sub-components; personal basis power is based on expertise, information, and referent power; cognitive power relies on *priming* and *beliefs*; structural power relies on legitimate power, reward, and coercion. The details of these belong to the realm of social science.

Power scores will be established for e-vendors on the deep web, specifically on the e-markets of the darknet. Analogous scores will also be generated for e-markets on the darknet, including three of the most dominant markets on the darknet; AlphaBay, Valhalla, and Hansa. Generally speaking, power scores for e-vendors will be based on similar parameters, including vendor level, trust level, membership length in the e-market (vendor's antiquity), number of positive and negative feedbacks from e-customers, number of sold orders (NPS items), number of subscribers, and e-vendor scoring on Grams search engine (Agichtein et al., 2001; Nakov and Hearst, 2005). All these parameters will generate highly accurate power scores for e-vendors; this will be followed by performing statistical inferences and special correlations. The aim of these scoring and inferences is to grasp an apprehension on the power within the NPS industry. Statistical tests will include linear regression and Student's t-test (paired and independent). Alpha (α) value of 0.05 will be considered as the cutoff point for statistical significance. These analyses will be visually presented and geographically mapped whenever possible.

The bases of power for NPS researcher are to be more thoroughly explored; fifty researchers were chosen at random, using a *random number generator*; researchers were selected from an established database; the database has 587 entries. This selection process led to the creation of the 2nd database with 50 entries; each entry (NPS researcher) has 14 determinant parameters including the researcher name (1), academic title or status (2), number of indexed publication on PubMed/Medline (3), ResearchGate (RG) score (4), number of research items on RG (5), number of citations on RG (7), number of followers on RG (8), percentile RG scoring (9), *h-index* score on RG (10), direct and indirect reach on RG (11, 12), body language and speech analysis which are based on Youtube videos (13, 14).

Speech analysis was done in relation to the *Han's Rosling* effective range (University of Michigan, 2017). To summarise, each researcher had parametric data collected from; surface web, research institute, PubMed, ResearchGate, and Youtube (Burgess et al., 2013; Martín-Martín A et al., 2016; US National Library of Medicine National Institutes of Health. PubMed, 2017). These data were "corrected" (numerically scored in ascending order); these scores were later treated mathematically to calculate a *power score* specific for each researcher. The power score is expressive to the individual basis of power (strength of authority).

Another scoring system, a *certainty scoring*, was also created. The certainty score was also established for each of the same 50 researchers. Certainty score was calculated mathematically as a representative of another 14 parameters; researcher title (1), facial features (2), number of publications (3), his/her research institute name (4), country (5), previous research institute(s) names (6), academic backgrounds and expertise (7), his/her network on PubMed (8), networking on RG (9), availability of Youtube videos (10), email and phone number (11, 12), social status (13), and funding bodies (14). Hence, it can be deduced that the certainty score may also be considered as a determinant of the power. However, it's fundamentally different from power score; certainty score is a measure (index) of how much data, on the web, can be easily retrieved for a particular NPS researcher. In other words, the availability of redundant information on a particular researcher can be considered a weakness; the stronger a researcher, the more he (or she) should be anonymous on the web. To summarise, both power score and certainty score are indices for the basis of power. Each of the power and the certainty scoring was further analysed using descriptive and inferential statistics.

- Extrapolations Based on Literature review – Most popular NPS

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). This study will analyse the web (surface web) contents in relation to the most popular classes based on chemical characterizations of NPS; the analysis will form the basis for more advanced inferences on the surface web including medical literature databases particularly PubMed/Medline, drug fora, deep web, and the e-markets on the darknet. The aim of this approach to intertwine the interest (or the attentiveness) of web users on the surface web in parallel with their attentiveness towards NPS on the deep web. The attentiveness of surface web users have been observed and studied via Google Trends databases by a series of snapshots (Internet snapshots); these were taken from the 14th to the 18th of February 2017 (Google Trends, 2017). Six keywords representative for each category of NPS were used across Google Trends; these are; *Cannabinoids*, *Phenethylamines*, *Cathinones*, *Tryptamines*, *Piperazines*, and *Pipradrol*.

The analysis, via Google Trends, was done for the period from the exact beginning of 2012 to the definite end of 2016, a whole duration of five (5) years. Hence, this study is observational and longitudinal (retrospective). Filters were used for the purpose of geographic mapping (geo-mapping) in; worldwide (Global), United States (US), United Kingdom (UK), Australia, and Canada. Data from the Middle East or Arabic country were not retrievable due to limitations of the database itself. However, these data were sought after during the global (worldwide) analysis using specific filters and whenever the database allowed it. Similarly, data were not attainable from regions of high population density including China and India. In fact, it seems that China does not permit the use of Google or its related applications (O'Rourke et al., 2007; Stevens, 2015; Thompson, 2006). Therefore, this analytic study was limited to developed western countries. In fact, the "Interest by region" shown by default on Google Trends permitted the data access to four countries only, namely; US, UK, Canada, and Australia

The analyses were carried out using descriptive and parametric inferential statistics; tests included; the analysis of variance (ANOVA), Student's t-test (paired and independent), and chi-square test. Significance was considered at an alpha (α) value of 0.05 and a confidence interval of 95% (95% CI). The test for significance was done; in between the different categories of NPS (1), within the same NPS category along the years from 2012-2016 (2), and in between the various geolocations (3).

- Spotting High-risk NPS; Integrative Analyses of PubMed, Drug Fora, and the Surface Web

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). The most popular categories (chemical categories) of NPS will be assessed across the darknet; these will be evaluated primarily on the AlphaBay e-market. NPS items included under each category will also be screened and scored (number of items) in an aim to find the most popular NPS. These will be later visually presented in an ascending order of popularity (availability). Each individual item (NPS) will be thoroughly evaluated for safety (risks, side effects and adverse reactions); these are expressed in the form of cases of intoxications (morbidities) and fatalities (mortalities). Precarious NPS will be labelled as red (dangerous) on visual illustrations (Figures). The screening will include shipping countries; which will expose if there are some suspicious activities in the region of the Middle East on the deep web. The mapping (screening) concept is original in relation to previous research attempts.

Discovering health-threatening NPS will be thorough and systematic; it will rely on a hybrid of evidence from; surface web (1) media networks and social media (2), drug fora reports (3), and medical and paramedical databases (4), and Google Trends (5). Hence the study is also a mixed-breed observational study made of retrospective and multiple internet snapshots. The data resources will be cross-referenced in an attempt to eliminate duplicate reporting of cases of intoxications and deaths. PubMed/Medline will be the principal representative of medical and paramedical databases (Sayers et al., 2015). Filters in medical and paramedical databases will be used to include manuscripts of; case reports (1), case series (3), reviews (4), and systematic reviews (5); Duplicate reporting of incidents in literature databases will be avoided. Data extracted from documented intoxications and fatalities will include; date of incidence, gender, age, geographic location or country, the number of incidents, and the outcome. The outcome of each incident includes; intoxication (1), suicide (2), homicide (3) pharmacological fatality (4), and Behavioural fatality (5). The date of the incident will be the actual date. However, if that information was not available, the date of publication (of the manuscript) will be considered as the alternative. These tabulated data will be later compared analysed using descriptive and inferential statistics. Alpha (α) value of 0.05 will be considered as cutoff margin for statistical significance; tests will include independent student's t-test and the analysis of variance and covariance (ANOVA). The aim is to test if the age and gender are uniquely specific to a particular NPS. This study is to be considered as an evidence-based review for the most popular and high-risk NPS based on data extracted from the surface web with a particular interest in drug fora and PubMed database. These comprehensive and systematic reviews can be effectively used in future studies for more integrative analyses with the darknet and its e-markets. Attention will also be directed towards the Middle East.

- Darknet – Part 1

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). The e-commerce activities on the deep and the darknet have been monitored for NPS and NPS-related substances including the traditional psychoactive substances, for instance, benzodiazepines, cannabis and hashish, and classical opioids; the aim is to provide a realistic snapshot of the advertised psychoactive substances, traditional and novel, on the e-marketplace of the darknet in specific and the deep web as a whole. Usually, e-vendors advertise several substances under specific chemical categorization (cannabinoids, psychedelics, etc.). However, the exact nature (ingredients) of these substances is either unknown or to be confirmed via chemical analytics methods (chemical characterization). Hence, it was critical to include traditional as well as novel psychoactive substances in the studied snapshots of the deep web. Further, this will provide a more realistic observation to the categorization system imposed by the e-vendors themselves and the e-markets within the deep web.

The e-trade of NPS on the deep web has been assessed via observing the anonymous e-markets on the deep web; this systematic analysis has been initiated by studying the surface web users' interest (attractiveness) in connection with the deep web and its darknet e-marketplace. This has been assessed by observing the time-related (chronological) changes of five keywords on Google Trends; the keywords are; *Deep web*, *Darknet*, *Tor*, *Bitcoin network*, and *Bitcoin* (Google, 2017). These terms are representative for the deep web, the darknet, the Tor web browsers, and the Bitcoin payment system (McCoy et al., 2008; Reid and Harrigan, 2013). This historical analysis (2012-2016) of keywords was followed by geographic mapping (geo-mapping) in an attempt to; localise surface web users of strongest tendencies to use the deep web and its e-markets (1), and assess the contribution of users from the Middle East and Arabic country, if any exist, to the global e-trade activity (2). This analysis is observational and retrospective (longitudinal), it was done for the period from the beginning of 2012 to the end of 2016 (2012-2016).

Analysis of the majority of contributing e-markets on darknet was done; these e-markets include; Hansa, Darknet Hero League, AlphaBay, Agora, Nucleus Market, Majestic Garden, Real Deal Market, Oasis, Abraxas, Outlaw Market, Middle Earth, Silkkitie, Oxygen, Tochka Market, and Arsenal (Biddle et al., 2002; Al-Imam et al., 2016). Assessing each market relied on the concept of the basis of power implemented in social sciences (Spekman, 1979; French et al., 1959). Each e-market has been assessed for its power (authority) by analysing three indices; overall rating (1), support rating (2), and the number of votes (3); these data were extracted from the Grams search engine of the darknet (Laura and Me, 2015; Nakov, 2005). Tabulation of the three power indices was followed by a digital *correction* (standardisation) and mathematical calculation of a power score unique for each e-market. Hence, the analysis is observational, and it is based on an Internet snapshot; the shot was taken on the 9th of February 2017.

The 3rd and final step was the analysis of the advertised (e-commerce) NPS on five of the most popular e-markets; the e-markets are; AlphaBay, Valhalla, HANSA, Acropolis, and Tochka, these e-markets were randomly selected. The e-trade of NPS on the darknet were usually classified them into eight categories or less (depending on the e-market); categories was as follows; Benzodiazepine (1), Cannabis, Hashish, and Cannabimimetics (2), Dissociative substances (3), Ecstasy and other empathogens (4), Opioids (5), Prescription substances (6) Stimulants and psychostimulants (7), and Psychedelics (8). A subsequent analysis involved the NPS enlisted under each of these categories. This step (3rd step) has led to the inferences about the most popular (trending) categories of NPS on darknet e-markets, which was preceded by identifying the biggest (dominant) e-markets of the darknet.

Each of the steps (above) was paralleled by thorough statistical analysis (descriptive and inferential), statistical inference implemented several tests including; the analysis of variance and covariance (ANOVA), student's t-test (paired and unpaired), regression models, and nonparametric test (when applicable); an alpha (α) value of 0.05 was set as the cutoff margin to adopt statistical significance. Descriptive statistics endeavoured to point out unique data events (statistical outliers), and to explain why these events occurred whenever feasible. A visual presentation of geo-mapping will also be used for the region of the Middle East, Arabic Countries, and the European Union (EU).

- Darknet – Part 2

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). Same as in the previous chapter (Darknet – Part 2), the implemented snapshots and analyses will include traditional psychoactive substances as well as novel psychoactive substances; this method will provide data with higher authenticity by mimicking the ways by which e-vendors categorize their advertised psychoactive substances within the darknet. This study will implement a hybrid observational analysis of Google Trends (retrospective) database and the darknet (cross-sectional). Multiple internet snapshots were taken on the 13th and the 14th of February 2017. Most e-markets on the darknet adopt an NPS categorization system made of eight classes (Dargan and Wood, 2013). The same classification scheme has been used to map the darknet via using the Grams search engine (Grams, 2017). Each category of NPS was mapped for; the total number of advertised hits/items (1), shipping country or geographic location (2), and the number of hits per location (3). These were later further analysed to provide a *fingerprint* of the darknet e-marketplace at the time the snapshot was taken. Similarly, hazardous NPS were mapped on darknet using a set of specified keywords via Grams search engine, mapped parameters included; total number of hits (1), e-markets promoting the NPS (2), number of hits per e-market (3), Shipping country or location (4), and the total number of hits per location (5).

It was also found that only five NPS contribute approximately 55% of the total e-trade output on the darknet, these substances were; cannabis, hashish, and cannabimimetic (1), MDMA (2), methamphetamine (3), crack (4), and LSD (5). Each of these substances was also mapped via Grams search engine for shipping country, and a number of hits per country. Additionally, Google Trends database was utilised to retrieve data in retrospect in relation to each of these five substances to infer the corresponding global attentiveness of surface web users. Geo-mapping was also analysed using Google Trends. The keywords used for Google Trends were; *MDMA*, *Cannabis*, *Methamphetamine*, *Cocaine* , and *Lysergic acid diethylamide*.

A specific analysis was conducted in relation to AlphaBay e-market, the aim was to test the hypothesis if this particular e-market is a proper representative for the entire darknet e-marketplace. The hypothesis has been tested via analysing the major categories of NPS on both AlphaBay and Grams search engine, the number of hits on both were analysed to reach an inference via regression models. The most popular and most toxic (high-risk) NPS substance were also analysed in relation to the Middle East. It was based on a snapshot for the darknet via Grams engine, mapping included; a total number of hits (1), geographic location (2), and the number of hits per location (3). Some specific (special) statistical correlations were later carried out.

The e-vendors (darknet) characteristics were also mapped and thoroughly analysed. Mapping included some e-vendor's related parameters; e-markets (1), Geographic location (2), the number of hit pers location (3), type of advertised-sold NPS (4), and the e-vendor's rating on Grams engine (5). The e-vendors found on AlphaBay e-market were further analysed for power scoring; the power scoring relied on five parameters; vendor level, trust level, e-customers' positive feedbacks percentage, e-vendor score, and e-vendor antiquity in the AlphaBay. The strongest e-vendors were pointed out via the power scoring. Furthermore, the power score for e-vendors was later correlated with the determinant parameters of the score itself; the purpose was to infer the most important determinant parameter of power ratings. The power scores were also correlated with the total number items sold by the e-vendors on the darknet; this correlation is another way to infer how AlphaBay is dominating the e-marketplace.

Special correlation, using inferential statistics, were implemented, these included; GHB substance geo-mapping versus sexual assault rate in GHB-shipping countries (1), high-risk and popular NPS versus religious affiliation in the shipping countries (2), and the number of hits in the Middle East and Arabic countries versus those in countries from the European Union (3). The aim of these analyses is to deduct specific conclusions in relation to the spread of certain NPS in the world, both developed and developing. This analytic approach is simple yet powerful; it can provide much insight and also serve as a base for an early warning system to anticipate particular events, for example; sexual assault and rape , shift in the religious affiliation for a specific geographic location, and the patterns of trending NPS substances in correlation with the population count in different countries. The statistical tests included; regression models, student's t-test, analysis of variance and covariance (ANOVA), and nonparametric tests. A confidence interval of 95% (95% CI) and an alpha value of 0.05 was set as the cutoff margin to determine the statistical significance.

- A Tale of A Survey and Two Internet Snapshots

This chapter is made of three individual studies, including one survey and two internet snapshots. Several techniques have been used by researchers to observe and analyse the e-trade on the deep web and its darknet; most were relying either on the observational cross-sectional or retrospective analysis; the most common analytic tool is known as the *Internet snapshot* method. However, this technique is not only time consuming, having modest accuracy, and of low level-of-evidence, but it is also; ionic (an absolute brief point in time), and requires the dedication of time, financial resources, and human efforts (Pastor-Satorras et al., 2001; Siddiqi et al., 2015). Therefore, in this chapter, a strive to improve the internet snapshot will be enacted to; enhance the accuracy of the snapshot method (1), improve the implied level-of-evidence (2), reduce time and efforts (3), implement the application of inferential statistics (4), and potentially be applied in combination with techniques of data mining (Berry and Linoff, 1997; Fayyad et al., 1996). This chapter will study NPS in addition to some NPS related substances (traditional psychoactive substances) of interest including benzodiazepines, cannabis, nicotine and tobacco, opioids, and some phenothiazines. The aim is to provide a realistic insight to the pattern of (ab)use of substances, including the NPS, and the existence of polypharmacy.

In the previous chapters, the collected data and results derived an undoubted conclusion of the limited contribution of the Middle East to the e-trade phenomenon of NPS on the web, both surface and deep. However, a question remains unanswered; how to estimate the prevalence of the use of NPS in this region? Can the prevalence of NPS use be estimated by modalities other than observational studies of the web? The answer is yes; it can be inferred by modes other than web analytics, for example; cross-sectional studies and survey in a real (non-virtual) population of users, and retrospectively from; seized batches and databases from criminal records, hospital emergency units, border patrol agencies, police departments, counter-terrorism units. These modalities of research have been already extensively implemented by regulating bodies including; the World Anti-Doping Agency (WADA), the United Nation Office on Drugs and Crime (UNODC), the INTERPOL, and the European Monitoring

Centre for Drugs and Drug Addiction (EMCDDA) (Burns, 2014 Ferri et al., 2015; Mackey and Liang, 2013; Toohey and Beaton, 2017).

1. NPS Prevalence in a Population of Iraqi Medical Students (Survey)

This study has been ethically approved by; the University of Hertfordshire (Protocol no. LMS/PGR/UH/02723) and the University of Baghdad (IRB meeting no.7, 20/12/2016). The nature of the study is observational and cross-sectional; it is based on a survey targeting a population of undergraduate medical students at the College of Medicine, University of Baghdad. It is estimated that the study will reach out to 1/4th of the total students' population at the College of Medicine. The aim of the survey is to infer an estimate about; the level of awareness of medical student about NPS (1), the prevalence of (ab)use of NPS, if any exist (2), and the correlation with other parameters including demographics, social status, medical illnesses, and past psychiatric history (3). A population of approximately 1800 students was targeted; the survey was made available to students starting from the 17th of March 2017 to the 28th of March 2017. The electronic form (e-form) was made of three main sections; demographic parameters of participants (1), awareness and prevalence of use of NPS (2), and the smoking, alcohol drinking habits, and other social habits (3). The estimated time required to complete the survey was estimated to be around 10 minutes. The survey questionnaires were addressing; age, gender, handedness, ethnicity, religious affiliation, number of siblings, place of residence, marital and social status, past medical and psychiatric history, the awareness on the topic of NPS, the awareness about specific NPS substances, the use of NPS, the experienced adverse effects, drinking and smoking habits, and other related social habits. All responses were anonymous; personal data including name and physical address were neither required nor asked for via the e-survey. The e-form was *pilot-tested* by a group of 20 randomly-selected students to ensure there are no errors, and to estimate the average duration of time required to complete the survey.

The survey itself (e-survey) was created using Google Forms tool; then it was distributed to students electronically (e-survey) via the University's bit-encrypted intranet system, the intranet is known as the *Iraqi Network Learning Environment* (INLE) (Iraqi Ministry of High Education and Scientific Research, 2017). The students have been prompted about the nature and the topic of the survey prior to its distribution. Once it was distributed, each student had only one attempt to fill and submit the e-form (e-survey). Afterwards, responses were not accepted, and the e-form was electronically locked. Responses were later downloaded as *comma-separated values* (.csv) file format, which was converted into a database on Microsoft Excel 2017, upon which graphical presentations and statistical analyses were carried out. Inter-group analyses were done between year-1 medical students versus other medical students from year-2, 3, 4, 5, and 6. The implemented statistical analyses were both descriptive and inferential; inferential statistics included both parametric and non-parametric tests. Alpha (α) value of 0.05 was set as the cutoff margin for statistical significance. Data in relation to this survey were stored on a secure 256-bit encrypted personal computer (PC) with an effective firewall deploying anti-virus and anti-malware technologies. The PC is password-protected, and only one user (the researcher, Ahmed Al-Imam) have access to it.

2. Psychedelic User and the Abuse of Power (Internet Snapshot no.1)

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). This internet snapshot will be taken for the comments of (ab)users of psychedelics substances (hallucinogens); these observations were systematically analysed in specific groups on social communication medium and drug fora (Erowid.org, 2017; Facebook, 2017). The comments of (ab)users of psychedelics substances have been systematically analysed in specific groups on the Facebook social communication medium (Erowid.org, 2017; Facebook. Magic Mushroom (Psilocybin), 2017; Facebook. Psychedelic Experience, 2017; Facebook. Psychedelic Heaven, 2017; Facebook. Psychedelics & Philosophy 2, 2017; Facebook. The Adult Psychedelic Sweet Shop, 2017; Facebook. The Terance McKenna Experience, 2017). These groups were dedicated for psychedelic users where they interact socially, share subjective experiences about psychedelic "trips", and post on a variety of other philosophical topics (Boyer et al., 2007; Van Hout et al., 2013; Van Hout et al., 2014). The number of members of these groups ranges from thousands to tens of thousands (per group). This study is observational and cross-sectional in nature; it is based on an internet snapshot taken on the 5th of March 2017. Some interesting threads were noticed, and followed-up; the topics of these threads were related the same theme, including questions like; *What will you do if you become God?*, *What will you do if you were given unlimited powers?* These topics can be evaluated via thematic analysis of comments (De Ganck et al., 2015; Pérez et al., 2015). The aim is to find whether psychedelic users tend to abuse some granted high power. In a former chapter (*Analysis of Bases of Power of Key Players in the NPS Industry*), the individual basis of power has been explored, including; structural, personal, and cognitive (French and Raven 1959; Wrong, 1980). In this chapter, a critical component of structural power, known as coercion and punishment, will be explored in relation to a specific subset of e-customers (psychedelic users). Threads of a total of 264 users were analysed for; gender (1), country or location (2); the number of words per comment (3), and the content (theme) of the comment (4). The gender for each of the commenting psychedelic users was concluded from the name, whenever possible, by using an already established mega-databases for correlation of names and gender. The country (location) was deducted from the profile page of each user whenever disclosed publically. The content (theme) for each comment was assessed via thematic analysis and psychoanalysis; comments were categorised into three main themes; positive (P), negative (N), and uncategorizable/unspecific (U). The age was rarely possible to be concluded. Hence, it was discarded as a tabulating parameter. A database was constructed for the formerly specified parameters, the total number of entries was 264 (n=264). These were later further analysed using pivot tables, graphical presentation, and statistical analyses. The geographic location (geo-mapping) was explored based on contributing countries for each user. Implemented statistical analyses were descriptive and inferential, the alpha (α) value of 0.05 was considered as the cutoff limit for statistical significance of Inferential statistics tests.

3. The Terminology Implemented by Psychedelic Users (Internet Snapshot no.2)

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). This Internet snapshot will target another population of psychedelic users, also on drug fora and social communication media. An observational cross-sectional analysis was conducted in a number of drug fora and groups on Facebook social e-medium (Erowid.org, 2017; Facebook, 2017). The internet snapshots were taken from the 8^{th} to the 25^{th} of February 2017; the purpose was to infer the most commonly used terms for a class of NPS known as psychedelics (hallucinogens). A number of terms have been observed during an initial screening; these terms have been tabulated for each psychedelic users, creating a database of 239 entries (n=239). Furthermore, threads (on drug fora and groups) with these terms were scanned whenever possible and by accessing the profile page of each contributing users (authors and contributors to the thread) for; age (1), gender (2), handedness (3), and sexual orientation (4). Handedness (right versus left-handedness) can be potentially correlated either with certain substance abuse or linguistic (verbal) preference for terms. Handedness represent a somato-neurological reflection for the patterns of *cerebral dominance*, also known as the *lateralization of brain functions*. Hence, it was hypothesised that verbal skills (terminology) may have some correlation with handedness (manifested cerebral dominance). Similarly, sexual orientation could be; straight (heterosexual), Gay or Lesbian (homosexual), and bisexual. Gender included; male, female, and transgender. A number of hypotheses have been proposed of the potential correlation of handedness or sexual orientation with the affinity to (ab)use psychedelics. These hypotheses will be analysed via descriptive and tested via inferential statistics at an alpha value of 0.05 (cutoff point for statistical significance). Implemented inferential statistics will include; student's test, and nonparametric inferential statistics particularly the Mann-Whitney U test and the Kruskal-Wallis H test. Statistical analyses will attempt to find a significant association between; gender versus age of psychedelic users (1), handedness versus age (2), age versus the most frequently used terms (3), handedness versus the most commonly used terms (4), Gender versus the most commonly used terms (5). The outcome can be considered by future studies to be incorporated as a representative of demographic parameters in psychedelic users.

- Integrative Analyses of Captagon, Octodrine, and NBOMe

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). Three chemical substances; captagon (fenethylline), Octodrine (DMHA), and nbome (n-bomb) were analysed in relation to their popularity, trends, and e-commerce. The analyses were done across a trend database (Google Trends), surface web, deep web and its Darknet, with a specific focus on AlphaBay market (Celestini et al., 2017). However, there were absolutely no data in relation to octodrine on the deep web. The analyses were comparative for the three substances, this was followed by an extensive in-depth analysis for each substance.

The implemented inferential statistical tests included t-test (independent and paired), ANOVA (single factor), and linear correlation (regression model). The significance of results was considered and an alpha value of 0.05 (95%) and a confidence interval (CI) of 95%. The initial (inceptive) analysis was done on Google Trends database; the aim was to reach a referential foundation by comparing the popularity of these substances among users of the surface web. The database was examined from the beginning of 2012 to the end of 2016 (retrospective, longitudinal analysis). Interpretation of the trends database was based on the use of a keywords pair for each substance, made of a generic name and chemical name; octodrine (DMHA), captagon (fenethylline), and n-bomb (NBOMe).

The examination of the deep web was carried out via the Tor browser and Grams search engine (Buxton and Bingham, 2002; Biddle et al., 2015; Mulazzani et al., 2013). Captagon was examined (snapshot, cross-sectional analysis) on the e-markets of the darknet, data were retrieved regarding the sold quantity, e-market, e-vendor, shipping country, the number of e-vendors per country, and e-vendor's power. The e-vendor's power is a manifestation based on the level of e-vendor (numerical), the number of positive feedbacks by e-customers, and the number of negative feedbacks. The shipping countries were examined for middle-eastern and Arabic countries.

In relation to nbome, data were more abundant on the darkest e-markets. Analyses were done in relation to three major e-markets; AlphaBay, HANSA, and Valhalla. Given the abundance of data, a more in-depth inferential conclusion was feasible. Retrieved data included the type of advertised nbome, e-market, e-vendor characteristics, and regional e-commerce data (shipping countries). A *power score* was calculated and assigned for each e-vendor, scoring was based on the e-vendor characteristics, these included; vendor level, trust level, the number of positive and negative feedback, the number of sold items, the number of subscribers, and antiquity of e-vendor's membership for each given e-market. Power score calculation was accurate and reliable to be later correlated with extrapolated data from regional data from shipping countries, specifically the population density per each country, this was followed by the application of a regression model to infer the direction of the association of power score versus population count (per country). The contribution of the Middle East was finally conveyed.

- Captagon

Ethical approval for this study was granted by the School of Pharmacy Ethics Committee, University of Hertfordshire, Hatfield, United Kingdom (November 2013; PHAEC/10-42). Four databases were searched: PubMed/Medline, the Cochrane Library, Scopus and Google Scholar. A list of pre-specified keywords was utilised across these databases to generate *Search Engine Results Pages* (SERPs). The literature searches were conducted in English, Arabic and Italian, Spanish, Portuguese from the 3rd of October 2015 to the 26th of May 2016 from Baghdad-Iraq via *Earthlink Telenet* Internet Service Provider (ISP) as well as from the UK and Italy.

Given the limited peer-reviewed literature available on the use of captagon, further exploratory qualitative searches were carried out by consulting a broad range of websites, drug fora and other online resources (e.g. e-commerce, e-newsgroups, chat-rooms, videos, e-newsletters, and bulletin boards) in both English and Arabic, using the keywords: *Captagon*, *01 pills*, *Fenethylline*, *Counterfeit Captagon*, *Counterfeit Amphetamine*, *Inferior Amphetamine*, and *Amphetamine*. These keywords were also applied on Google and AOL search engines, YouTube, Google Trends, three global e-commerce websites (Alibaba, Amazon, and eBay), and seven regional (Middle East) e-commerce websites.

The Dark web was also scrutinised for details concerning captagon electronic commerce (e-commerce) in Iraq, Syria, and the United Arab Emirates (UAE). Dark Web e-markets, including AlphaBay e-market, utilize technologies to provide anonymity for users when they purchase items, these technologies include: the use of specific or customized internet browsers, passwords specific to each e-market, secure routing protocols, virtual private networks (VPN), Internet Protocol Masking (IP masking), and Bitcoin payment system (Alphabaymarket.com, 2015a; Chen, 2007; Chen, 2012).

Additional media sources and the database of the *Global Public Health Intelligence Network* (GPHIN) were also consulted. This is a secure Internet-based early warning system that gathers preliminary reports of public health significance by monitoring global media sources near ‘real-time’, 24 hours a day, seven days a week basis. GPHIN is operated by the Public Health Agency of Canada and monitors news sources and websites across the globe in nine languages (i.e. English, French, Farsi, Portuguese, Arabic, Russian, Spanish and Chinese simplified/traditional) (Young, Dubeau, & Corazza, 2015). While a series of algorithms are used and adjusted to capture relevant data, the analysis of the data was carried out manually by a multidisciplinary and multilingual team of analysts. Data were analysed using thematic analysis focusing on users' experiences and qualitative appraisal tools, when appropriate. Data visualisation was carried out using *Microsoft Excel 2016*.

- Octodrine

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). The study was carried out from April-2016 to November-2016 by a team of interdisciplinary NPS researchers from four different locations worldwide: Iraq, Egypt, Italy, and the United Kingdom. A literature review was carried out across medical databases, paramedical databases, and unpublished data including the grey literature. All of these were scrutinised using pre-specified keywords and filters for each data bank.

A literature review on octodrine was carried out in the following databases; NCBI – PubMed, the Cochrane Library, Scopus, EBSCO – CINAHL, OpenGrey, and Google Scholar. These databases were searched using a keyword list, at the same time neither language nor time restrictions were applied. The keywords list (Table 1, Results Chapter) was compiled in accordance with a preliminary pilot study of literature and databases on the surface web and the deep web, and online e-commerce websites. The keywords were in compliance with *Medical Subject Headings* (MeSH) of PubMed-Medline (The National Center for Biotechnology Information, 2016). The keywords used were 34 in total, including single keywords (31) and the combination of these keywords (3) using the Boolean operator "AND" (Spink, 2003). The keywords also included synonyms of octodrine from other languages and names of chemical isomers.

Considering the lack of scientific investigations in the field and the absence of experimental and/or interventional studies in humans, an additional systematic search of the web, both surface web and the deep web, was carried out in order to investigate the extent of diffusion of octodrine, and the nature of the self-reported (subjective) experiences by users. The deep web was searched using the Deeperweb search engine (Deeper Web, 2016), while the online markets on the dark net were explored using the *Tor browser* and *Grams* search engine (TOR2WEB, 2016). Pre-determined inclusion-exclusion criteria (Table 2, Results Chapter) were used to filter throughout the retrieved scholarly peer-reviewed papers and other resources. A flow diagram of the literature review process following the application of the inclusion-exclusion criteria was implemented as a modification of the PRISMA flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), 2015).

Papers of the highest level-of-evidence in the literature were included for referencing this manuscript (Oxford Centre for Evidence-based Medicine, 2009). Papers of level-4 of evidence included one scholarly-published paper in relation to octodrine from 1947 (Fellows, 1947), and the 2nd paper from 1951 (Marsh & Hrring, 1951), and a 3rd paper also from 1951(Charlier, 1951). These three articles, in particular, provided the most valid published data in relation to the mechanism of action, pharmacodynamics, pharmacokinetics, and the adverse effects of octodrine. All of these documented data were purely based on experimental animal studies and were the cornerstone in writing this manuscript.

Other data were obtained from non-scholarly based articles available across the surface web and the deep web. These included bodybuilding websites, chemistry and chemists' websites, pharmaceutical companies, online e-commerce stores (Aegis Shield, 2016; Bodybuilding.com, 2016; Herbnutritionals, 2016; Mrsupplement, 2016; Price Plow, 2016; Suppversity, 2016; Yang, 2016). These resources were assessed using critical analysis and critical appraisal tools (Better Value Healthcare Ltd, 2016; Oxford Centre for Evidence-based Medicine 2009). However, the analysed data were not considered to be ranked anywhere at the pyramidal hierarchy of the level-of-evidence.

Additional data were also obtained by consulting Google Trends data (Google, Google Trends, 2016). Again, specific keywords were used, ten keywords in total. A subset of keywords was selected from the original keywords list based on the frequency of generated search engine result pages (SERPs) across the surface web and the deep web. However, not all of these keywords generated data from Google Trends. Successful keywords were "Octodrine"; "2-aminoisoheptane"; "Aminoisoheptane"; "DMHA", the first three keywords of these were used to create a trend line for the popularity of octodrine on the surface web back to the year 2004.

Data tabulation and graphic presentations were created using Microsoft Excel 2016. Statistical analyses were done using IBM's *Statistical Package for Social Science* version 20 (SPSS version 20), *Microsoft Excel 2016*, and a customised online statistics software (Alcula, 2016). The *Critical Appraisal Skills Programme* (CASP) appraisal tool was used to evaluate the retrieved literature (Better Value Healthcare Ltd., 2016). The appraisal was applied to the three papers published by Fellows (1947), Marsh and Herring (1951), and Charlier (1951). These papers were analysed using the CASP Cohort Study Checklist. The other two articles, written on ambredin, have been drafted in German language (Gode, 1958; Tschudin, 1950). Hence, they were analysed using the same CASP tool, after being translated into the English language, using Google Translate (Google, Google Translate, 2016). All of the referencing materials were analysed and categorised based on the classification system of level of evidence as proposed by the *Oxford Centre for Evidence-based Medicine* (CEBM) in 2009 (Oxford Centre for Evidence-based Medicine, 2009). The level-of-evidence of the appraised resources did not exceed level-4 for the best scholarly-published manuscripts.

- NBOMe

Ethical approval for this study has been granted by the University of Hertfordshire (November 2013; PHAEC/10-42). This is an analytic study of the surface web, cross-sectional and retrospective in nature; it was conducted from the 15th of October 2016 to the end of January 2017. The aim was to assess the data retrievable from Google Trends. This study will also review case reports of interest in relation to intoxications and mortalities caused by NBOMe compounds, and the popularity of these potent hallucinogens, and the change in these trends for the in the past years and since 2012.

The literature review was carried out only from Iraq using a pre-designed keywords' list (Table 1, Results Chapter), these keywords were allocated into four main themes including nomenclature and synonyms of NBOMe (1), intoxication and fatalities (2 and 3), and the geographical-regional distribution (4). The total number of individual keywords was 115, truncation and Boolean operators (AND, OR) were also implemented to either make the search more specific (narrow it down) or maximise (expand) the yield of the literature search process (Spink and Ozmultu, 2003). These keywords were highly relevant to *Medical Subject Headings* (MeSH) from the NCBI databases (The National Center for Biotechnology Information, 2016). This methodology was carried out in a systematic way across medical and paramedical databases including NCBI-PubMed/Medline, EMBASE, the Cochrane Library, Scopus, EBSCO – CINAHL, Web of Science (by Thompson Reuters), OpenGrey, and Google Scholar.

A preliminary (pilot) analysis of the published literature on PubMed-Medline has shown that the total number of published studies on NBOMe chemicals did barely exceed a hundred manuscripts (n=108, on the 1st of January-2017), besides there was a complete absence of manuscripts with high level-of-evidence including systematic reviews and meta-analyses, pragmatic randomized controlled trials (RCTs), and a total absence of experimental-physiologic trials and well-structured cohort studies in relation to NBOMe chemicals. Given this fact and the lack of published literature in relation incidents of intoxications and/or death from the developing world, additional data was consulted from unpublished (grey) literature and trends databases (Google, Google Trends, 2016). The explored grey databases also included the online drug fora (Bluelight.org, 2016; Drugs-forum.com, 2016; Erowid.org, 2016; Officialbenzofury.net, 2016; Reddit.com, 2016), social communication media, and media networks.

Google Trends engine was also searched using the three most important keywords "25b-nbome", "26c-nbome", and "25i-nbome" (Google trends, 2016). This design was used to retrieve data on the trends of NBOMe popularity worldwide and in three distinct geographic locations including the United Kingdom, the United States, and Australia. The aim was to create a digital database representative to the popularity of NBOMe products as searched by the internet (surface web) users; the purpose was to infer an estimate on the "electronic epidemiology" of the NBOMe phenomenon and the change in these trends for the past five years (2012-2017). Inferential statistics were deployed using the t-test, ANOVA test, and regression models. These tests were carried out using the statistical package for social science version 20 (SPSS v.20), Microsoft Excel 2016, and an online statistical solution software (Alcula, 2016). There were also arduous attempts to detect a pattern of correlation using data crunching and regression models, specifically linear regression, by correlating the reported cases of intoxications/fatalities with the data reclaimed from Google trends,

The critical appraisal of individual studies was done using the *CASP* appraisal tool (Better Value Healthcare Ltd, CASP-UK, 2016), and the *critical appraisal tools* of the *Oxford Centre for Evidence-based Medicine* (Oxford Centre for Evidence-based Medicine, 2009). Manuscripts and resources of the highest attainable level-of-evidence (Table 2, Results Chapter) were used to backup this study, although, the majority of these ranked as either level-4 or level-5 in accordance with classification system implied by the Oxford Centre for Evidence-based Medicine (Oxford Centre for Evidence-based Medicine, 2009). These studies were case reports (16.7%), case series (7.4%), and review articles (11.1%). There were no systematic reviews (0%), nor RCTs on NBOMe (0%). One experimental study was found (1.85%) which was the original study of Ralf Heim (Heim, 2014). Much of the data were retrieved from online drug fora (31.5%), high-quality and valuable data were also retrieved from trends' databases (3.7%). Data from systematic reviews and RCTs, written on topics pertinent to NBOMe, were also used in the citation of this manuscript (1.85%), and from observational studies including cross-sectional and cohort studies (7.4%). The majority of the bibliographic materials were published in the past five years (92.6%). The overall level-of-evidence of appraised resource materials was in the range of level-5 to level-1b, although the majority of these were either level-3b, 4, or 5. The level-of-evidence of this study itself is estimated to be of level-2b (Oxford Centre for Evidence-based Medicine, 2009).

- Critical Appraisal, Limitations Of Studies, Conclusion, and Recommendations

Each chapter will be evaluated in relation to its level-of-evidence, the analysis will be in compliance with level-of-evidence scheme implied by the *Oxford Center for Evidence Based Medicine* (CEBM, 2009; Better Value Healthcare Ltd, 2013). This brief chapter will represent self-criticism of pros and cons of the thesis, which will provide an insight into the limitations of the included studies, potential upgrades, its strengths, and weaknesses, and future recommendations.

IV. RESULTS AND DISCUSSION

Chapter 1. Extrapolations Based on Literature review – Evidence-Based Analysis of Literature

At the moment the snapshot was taken, the total number of hits (publications) was 587 (Appendix 1). The majority of authors were from the developed countries, particularly from Europe, the United States (US), and the United Kingdom (UK). Publications from the Middle East, including Arabic and Islamic countries, were scarce. The number of authors per a single publication ranged from one (minimum) to 29 (maximum), the average number of authors (per publication) was 4.75 (+/-) 2.99, both the median and the mode values for the number of authors (per publication) was four (4). The number of authors was analysed using a Q-Q plot and Box plot presentation; statistical outliers were evident in which the number of authors per a publication was more than 10, these outliers represent exceptional cases of the abundance of NPS researchers (per a particular published research). These outliers were; Corazza et al., 2013 (UK); Bade at al., 2017 (Spain); Deluca et al., 2012 (UK); Giese et al., 2015 (Sweden); Martinotti et al., 2014 (Italy); Cinosi et al., (UK, Italy); Brandt et al., 2014 (UK); Caloro et al., 2016 (Italy); Yun et al., 2016 (Republic of Korea); Acton et al., 2014 (Austria); McLaughlin et al., 2014 (Ireland); McLaughlin et al., 2017 (Ireland); Tanibuchi et al., 2017 (Japan); McLaughlin et al., 2016 (Ireland); Wohlfarth et al., 2016 (Sweden); Togari et al., 2016 (Japan); Vento et al., 2014 (Italy); Daveluy et al., 2016 (France); Brandt et al., 2017 (UK); Negishi et al., 2015 (Japan); McLaughlin et al., 2016 (Ireland); Lanza at al., 2015 (Austria); Simonsen et al., 2015 (Denmark); Parrott et al., 2013 (UK); Bersani et al., 2014 (UK); Lanza at al., 2013 (Austria); and Murray et al., 2012 (Ireland). Apparently, the majority of those authors are from Europe particularly from the UK and Italy; few are from Asia. [Please, refer to a particular reference section (Appendix 2); this appendix contains all the reference materials for all publication used to build the database for this chapter].

The research institutes at which these NPS studies took place were in Europe, particularly the UK and Italy and the US for the vast majority of the publications. A Box plot presentation of the number of publications per research institute shows that exceptional institutes (statistical outliers) had a minimum of four publications per Institute. The top 10 research institute (Figure 1 and 2), for research output (in an ascending order); King's College London (UK), Sapienza University of Rome (Italy), Liverpool John Moores University (UK), University of New South Wales (UK), University of Hertfordshire (UK), Massey University (New Zealand), Karolinska Institutet (Sweden), National Institutes of Health (US), Guy's and St Thomas' NHS Foundation Trust and King's Health Partners (UK), and Saarland University (Germany).

On the other hand, research output by country led to similar results; some countries had a profound research output (Figure 3), outstanding contributors (outlier) were observed strictly in countries from

Europe and North American, with a minimum of 31 publications per country, these countries are; UK (43%), US (19%), Italy (14%), Germany (14%), and Sweden (10%). It is striking that countries from the Middle East (Figure 4), including Iraq and Iran, contributed the least to the overall research output (less than 1%); this paucity in production is, of course, outpaced by the escalating NPS "industry" in the same geographic region (Middle East) (Al-Hemiary et al., 2014; Al-Imam et al., 2016). Contributing countries from the Middle East included; Israel, Iran, Cyprus, Iraq; Other contributing Arabic countries included Qatar and Algeria. Similarly, based on the sum of the number of authors (per publication), the developed countries contributed the most, this is contrary to countries from the developing countries, and especially Middle Eastern and Arabic countries (Figure 5). Furthermore, it has been hypothesised that the count of 1st authors and the sum of authors are positively correlated with each other, particularly in the developed countries. Hence, linear regression was carried out to test the hypothesis, which was confirmed to be very accurate (R^2 *score*=0.987).

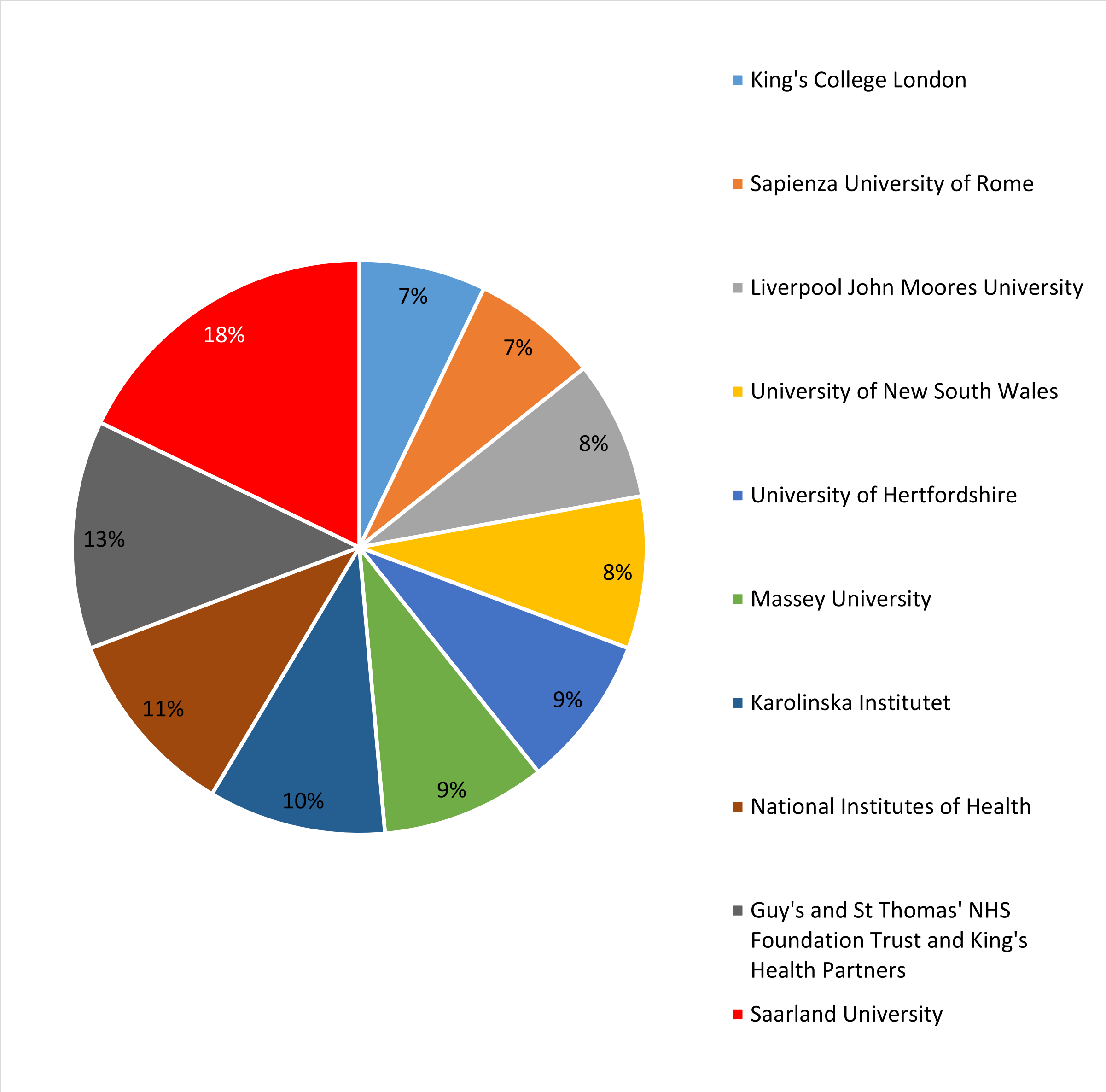
Analysis of the implemented Statistic and level-of-evidence (Figure 6 and 7) revealed that half of the NPS studies have only basic (descriptive) statistics, while almost one-third of the total research output (34%) had no statistics at all (None), and only 14% implemented advanced (inferential) statistics. Lack of application of inferential statistics is a critical defect in relation to original research activities of NPS; without these statistical inferences, valid and generalizable conclusions in relation to the studied population cannot be made. The level-of-evidence was also assessed in parallel to the assessment of the implemented statistics. The majority of studies in which either descriptive or inferential statistics were implemented, were mostly of level-3b or 2b. On the other hand, studies in which no statistic was implemented, were mostly of level-3a or 5. In relation to the level-of-evidence, the studies has contributed as follows; level-3b (50%), level-3a (19%), level-5 (17%), level-2b (12%), and other studies (level-1a, 1b, 1c, and 2a) contributed to no more than 2% of the total. Furthermore, linear regression analysis shows some degree of positive (+ve) correlation (R^2=0.047) between the type (quality) of statistical analysis and the overall level-of-evidence of publications indexed in PubMed.

Type of studies (Figure 8) included (in a descending order of frequency); analytic chemistry studies, reviews, observational cross-sectional, retrospective, case reports, case series, commentaries, molecular biology and analytic chemistry, editorials, policy analysis, perspectives, letters, systematic reviews, animal studies, book chapters, observational retrospective and cross-sectional, RCTs, short communications, hybrid studies, observational prospective studies, case-control studies, continuous professional development (CPDs), analytic chemistry and bacteriology, case registry, systematic review protocol, quasi-experimental studies, and communications. The top ten type of studies (Figure 9) in ascending order are: Policy analysis (2%), Editorial (3%), Molecular biology and analytic chemistry

(3%), Commentary (3%), Observational case series (4%), Case report (7%), Retrospective study (9%), Observational cross-sectional study (15%), Review (18%), and Analytic chemistry (36%).

NPS research output was also categorized into regions of the world (Figure 10); Africa (less than 1%), Middle East (1%), South America (2%), UK (5%), Australasia (6%), Asia (8%), North America (10%), and Europe excluding the UK (68%). Analysis of variance (one way-ANOVA) displayed a clear leverage of Europe over other regions (*p-value*<0.01). Apparently, the contribution of researchers from Middle East, Asia, and Africa is minimal. The frequency of usage of deep web and the e-markets on darknet seems to be compatible with the geographic distribution of researchers in the developed world, particularly in europe, North America, and Australia. However, that is not the case in the developing countries, especially in relation to the region of Middle East and Arabic Countries (Figure 11 and 12).

The outlet (Journal of publications) for NPS research were highly numerous and diverse (Figure 13 and 14). The top ten journals (in ascending order); *Journal of Psychopharmacology* (3%), *Current Neuropharmacology* (3%), *Drug and Alcohol Dependence* (3%), *Human Psychopharmacology* (7%), *Analytical and Bioanalytical Chemistry* (9%), *International Journal of Drug Policy* (9%), *Addiction* (10%), Clinical Toxicology (12%), *Forensic Science International* (13%), and *Drug Testing and Analysis* Journal (31%). *Drug Testing and Analysis* Journal publishes almost one-third of the total research output; this great publication percentage seems to be concordant with the fact that one-third (33%) of NPS research output is in relation to the discipline of the analytic chemistry (Ayres, 2012; Gibbons, 2012; Kinyua, 2015).



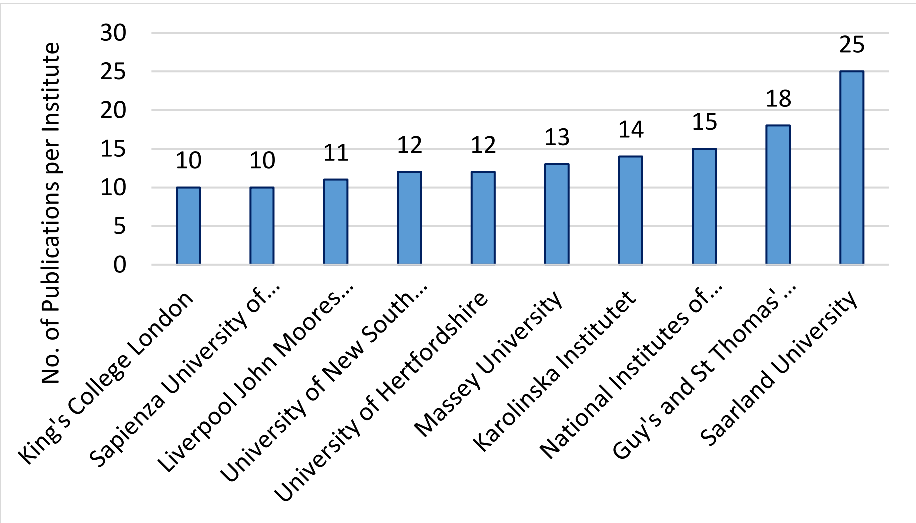


Figure 1. NPS Research Institutes: Top Ten Institutes (research output).

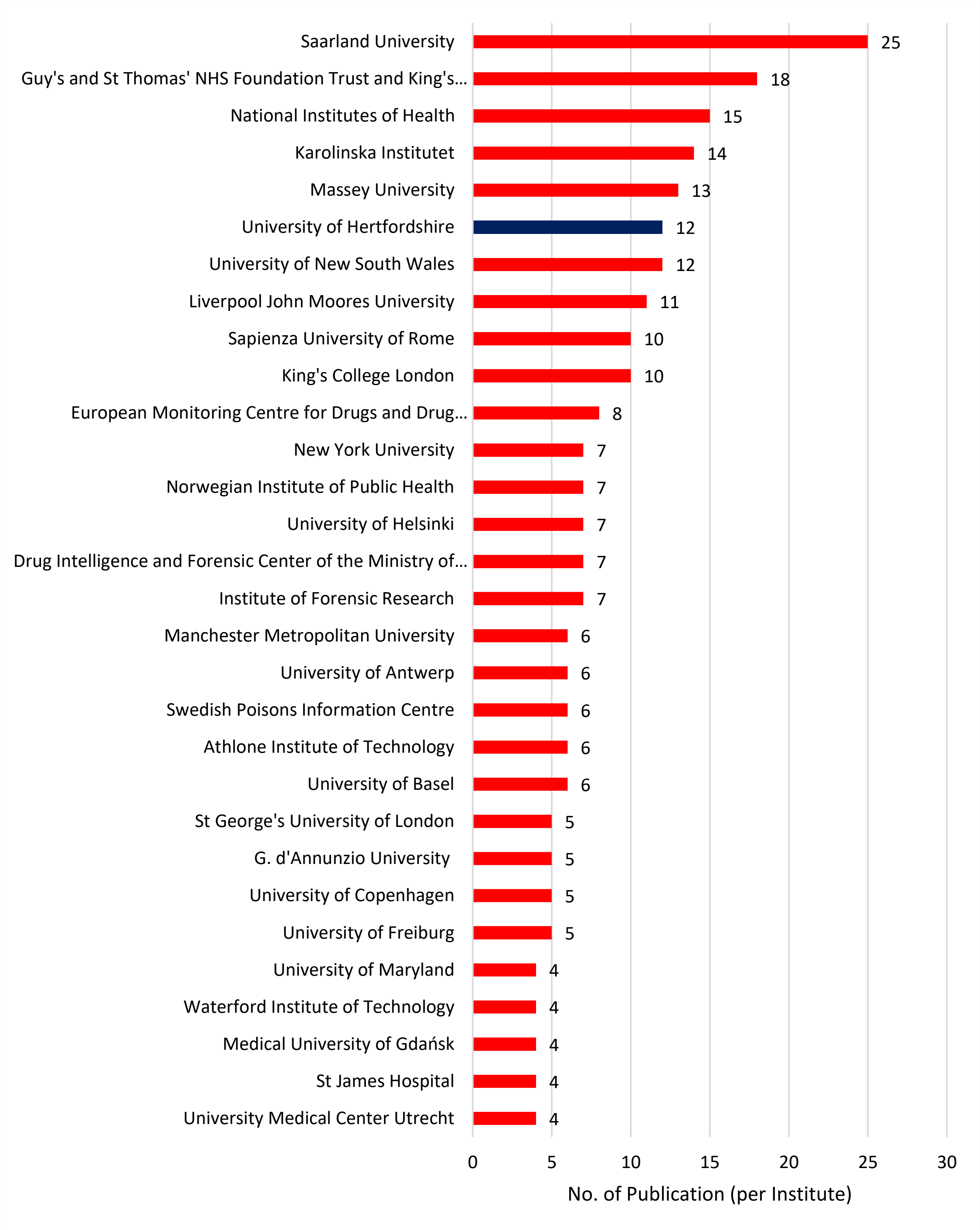
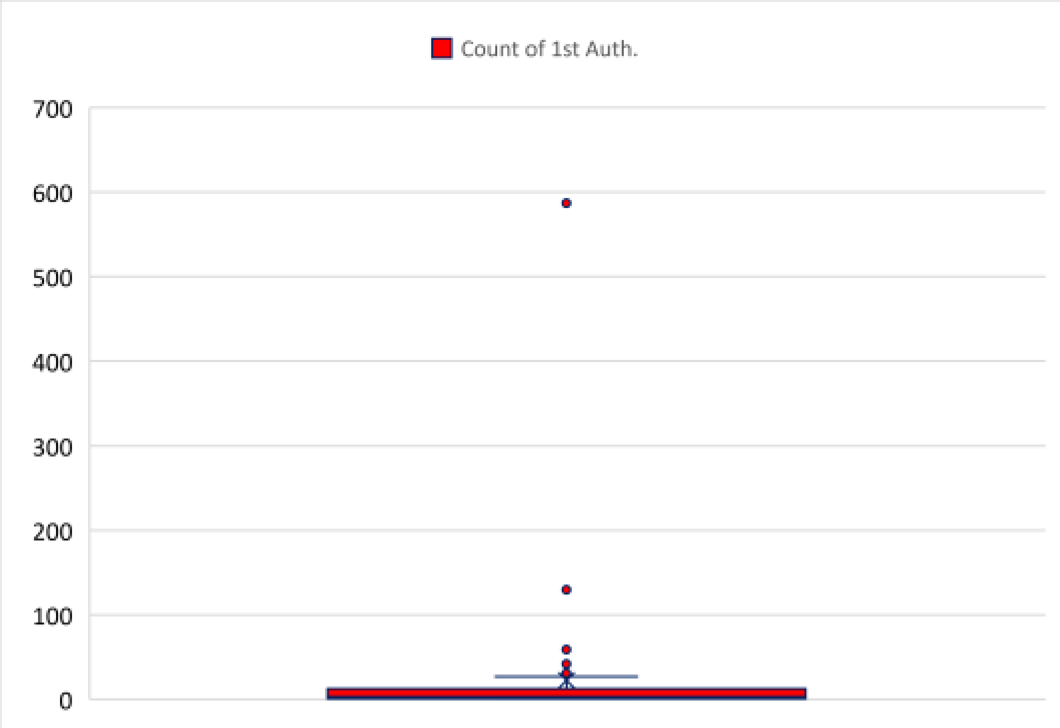


Figure 2. Top NPS Research Institutes.



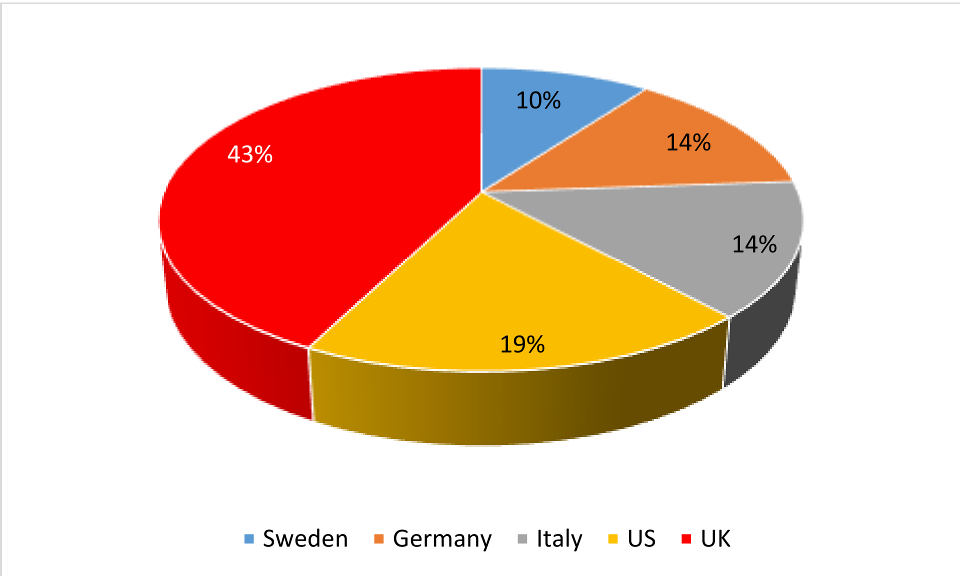


Figure 3. Research Output by Country (Boxplot, above), and Top Five Countries (Pie, below).

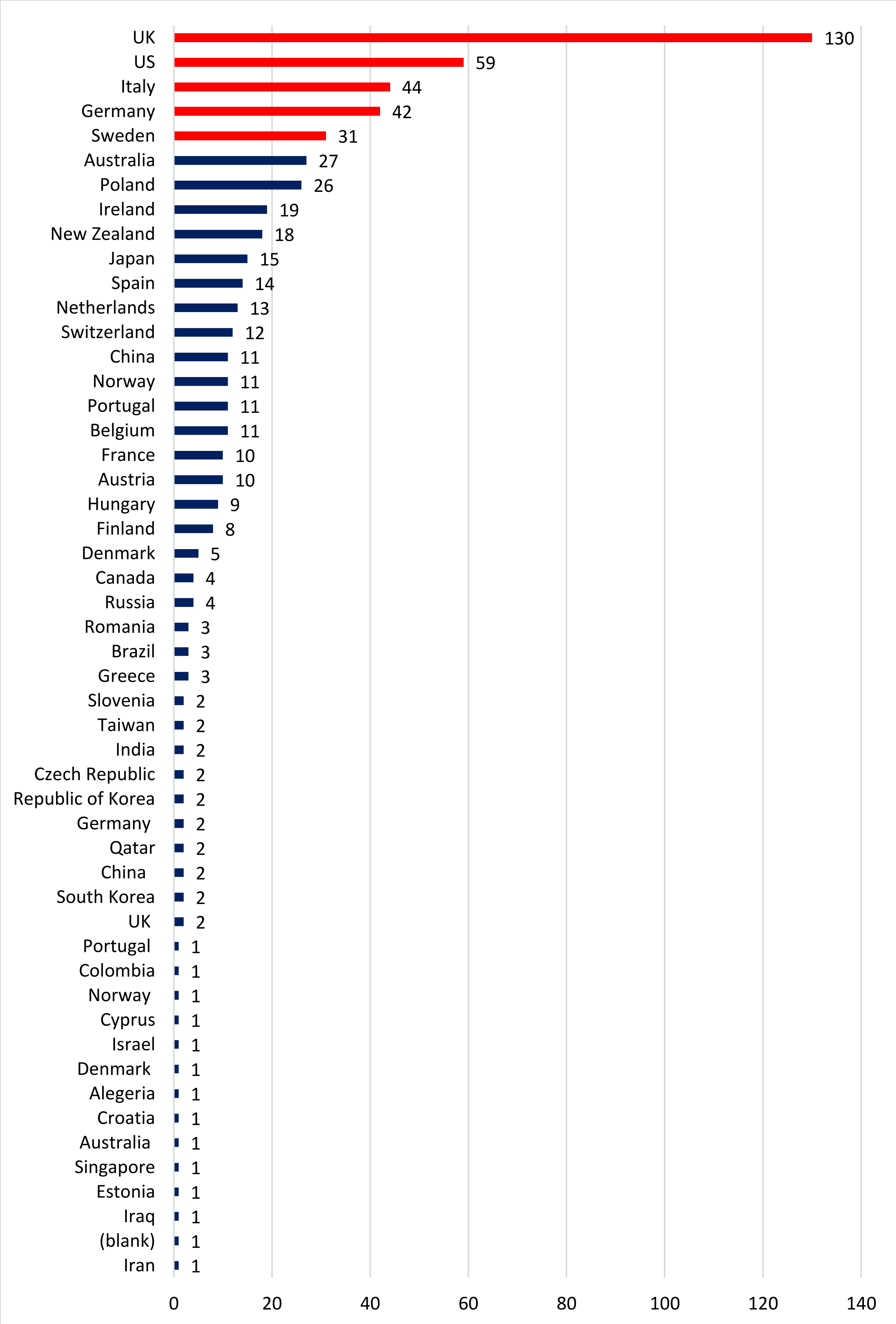


Figure 4. Research Output by Country: Exceptional Contributors are highlighted (red).

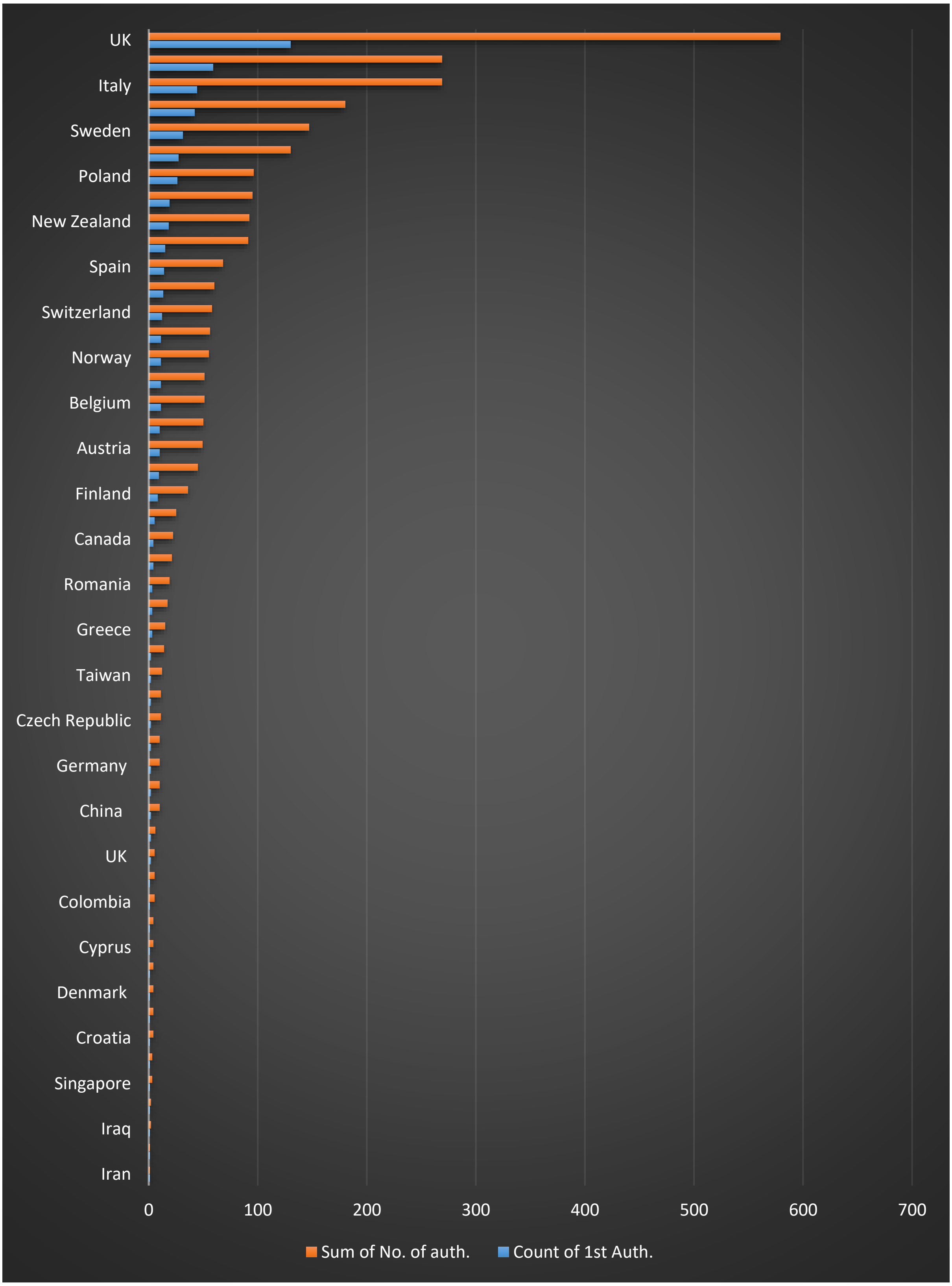


Figure 5. The International Contribution to the NPS Research Output.

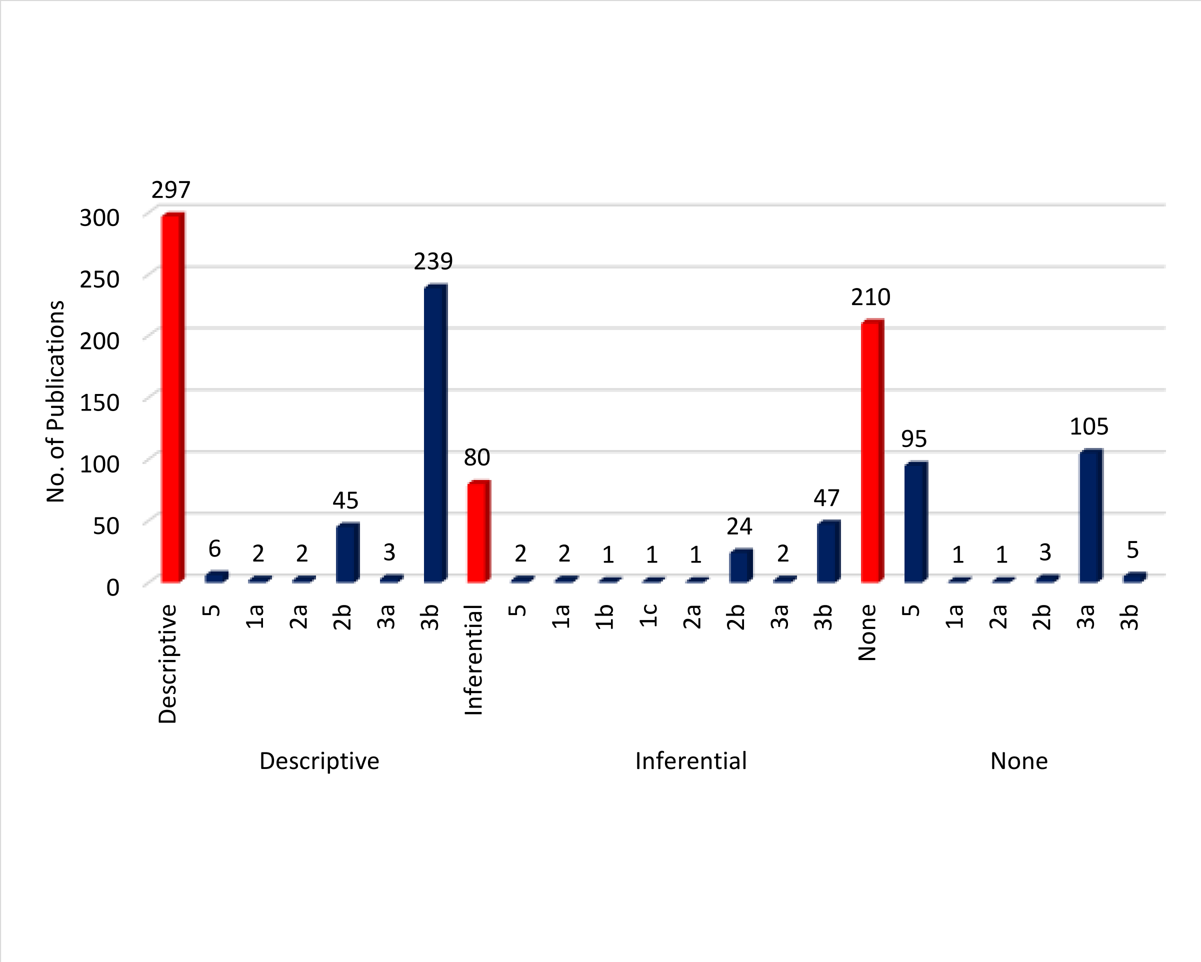
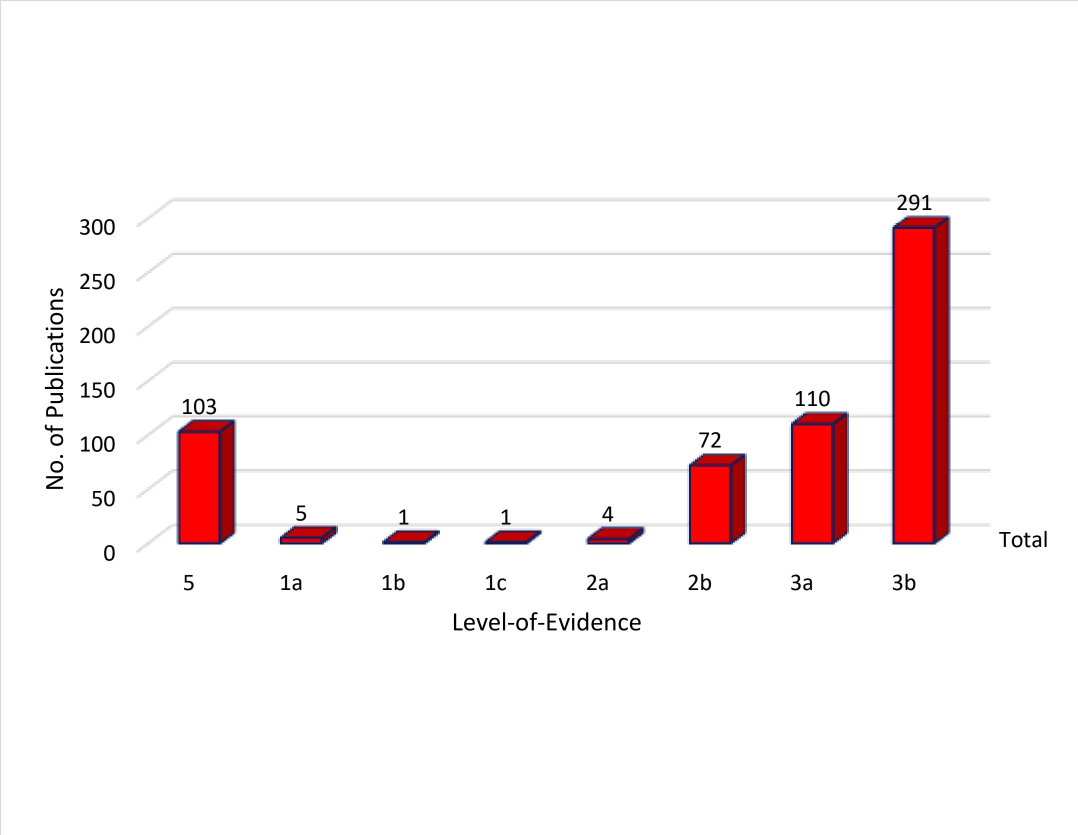


Figure 6. NPS Research Output (2010-2017): the Implementation of Statistic versus Level-of-Evidence.



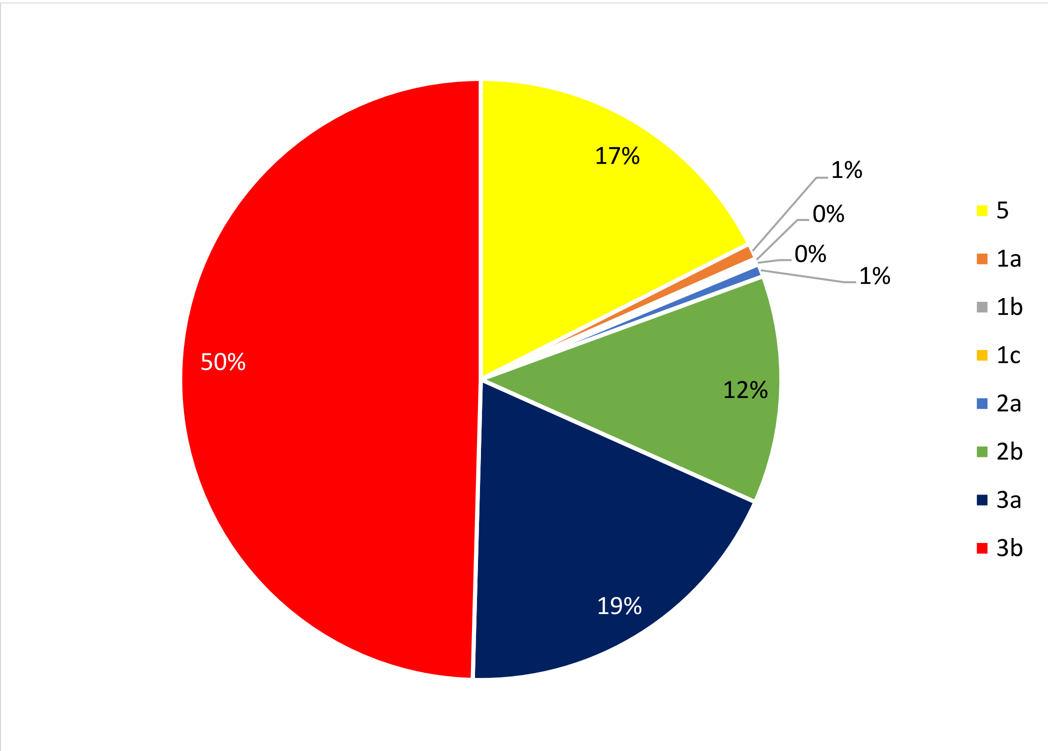


Figure 7. Level-of-Evidence: Retrospective Analysis of Literature (2010-2017).

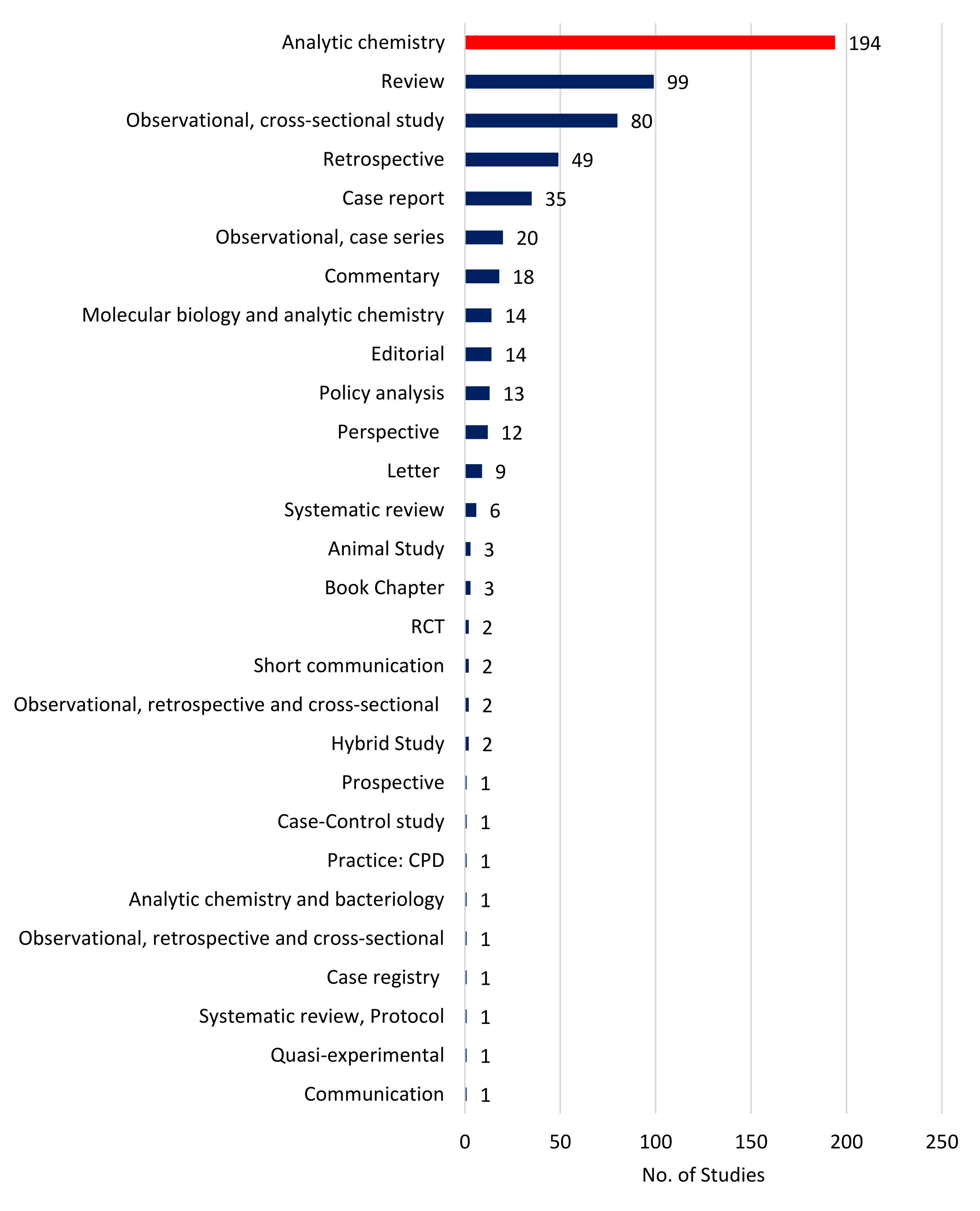
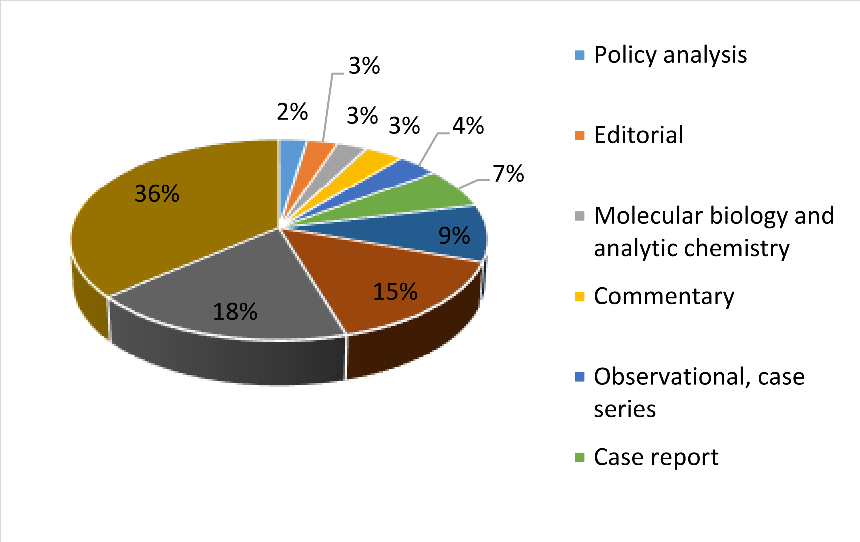


Figure 8. NPS Research Output (2010-2017): Type of Studies.



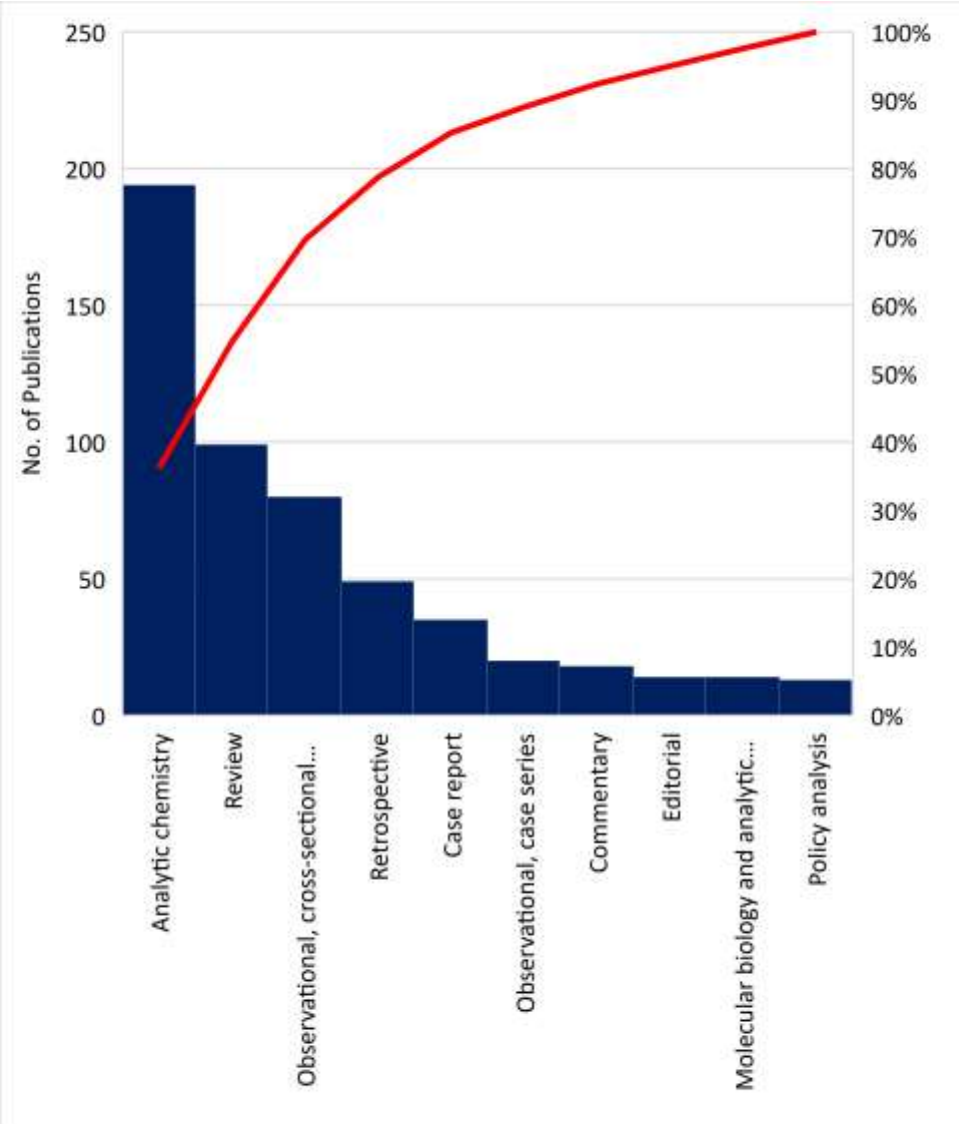
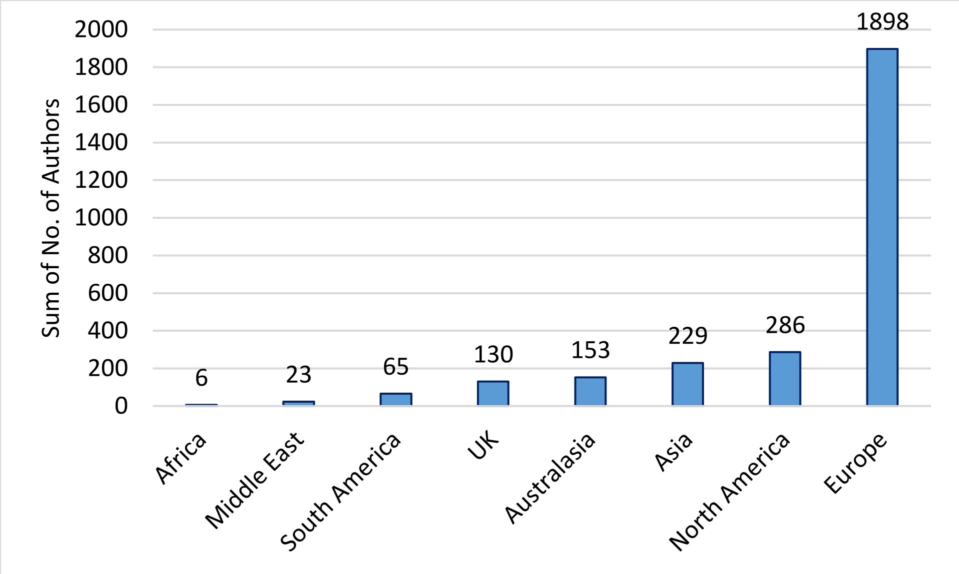


Figure 9. Top Ten Types of Studies in NPS Research (2010-2017): Percentages (above), and the Number of Publications (Below).



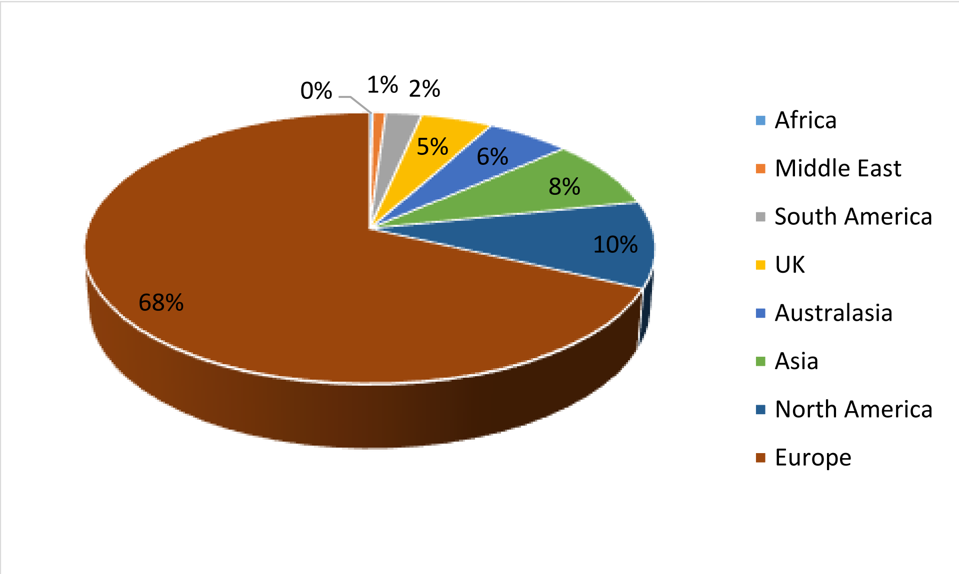


Figure 10. The Geographic Mapping of NPS Research.

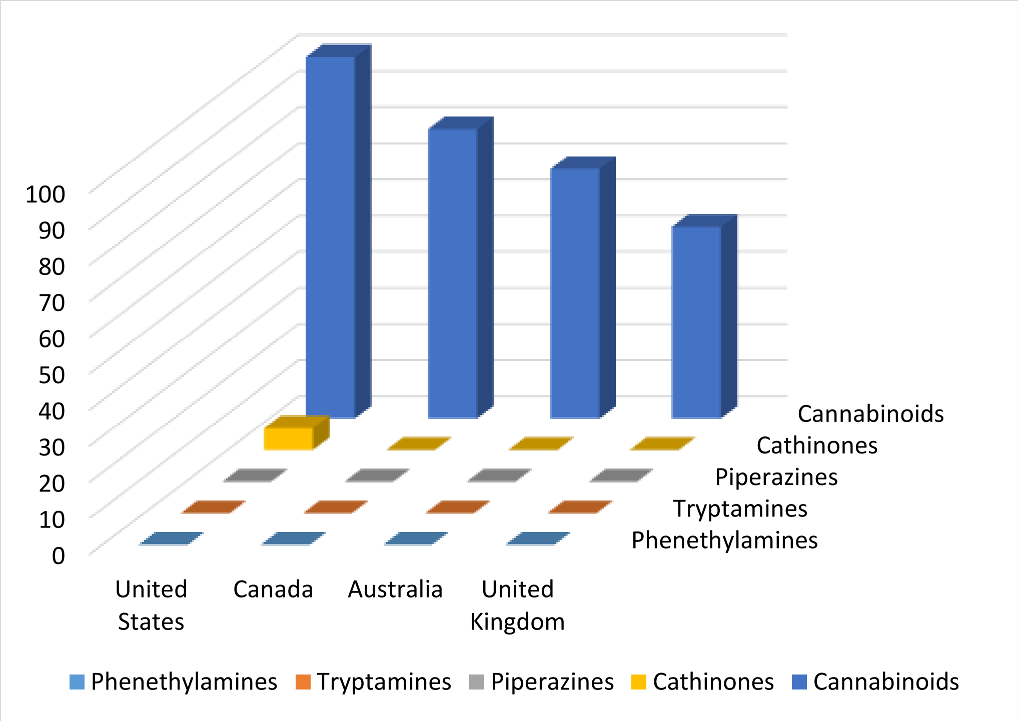


Figure 11. Google Trends (2012-2016): Cannabinoids are in the lead.

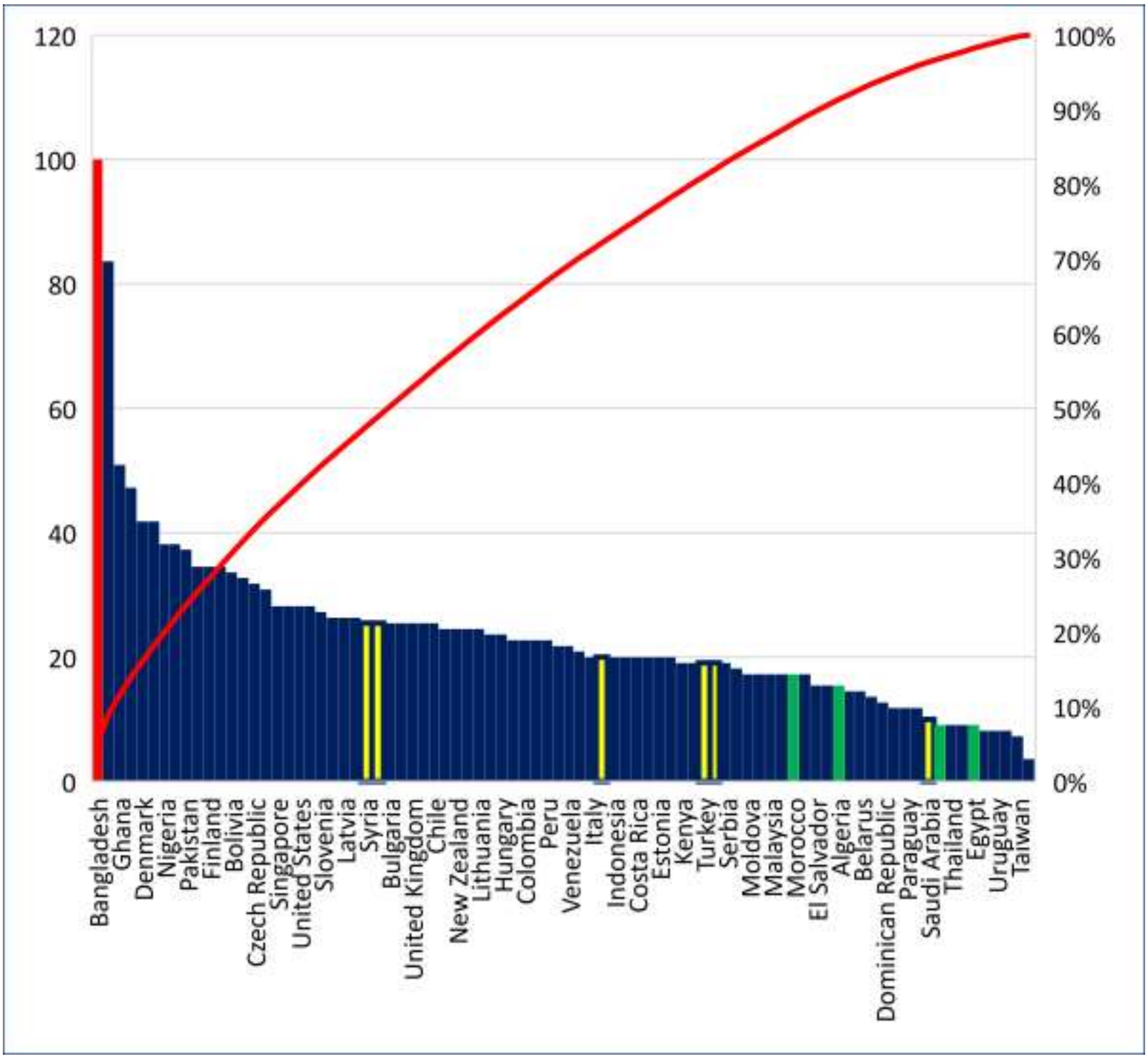


Figure 12. Deep Web Usage by Geographic Location (Country).

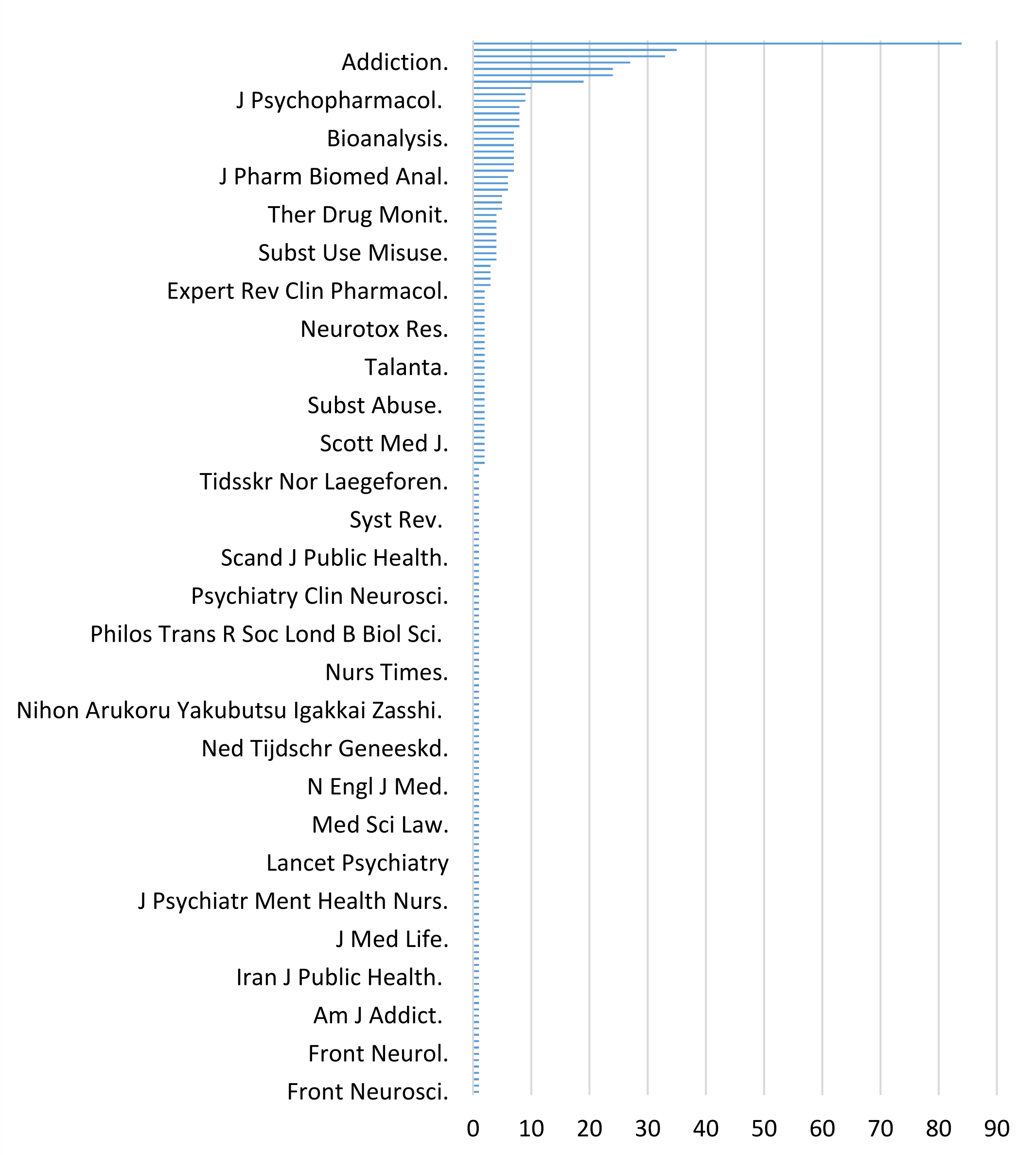
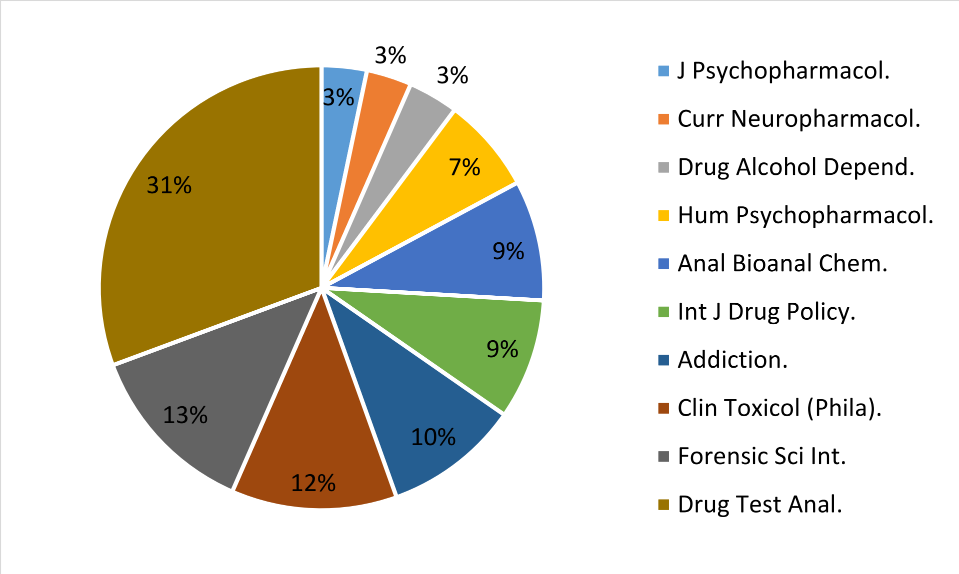


Figure 13. NPS Research Outlets: Journals of Publications.



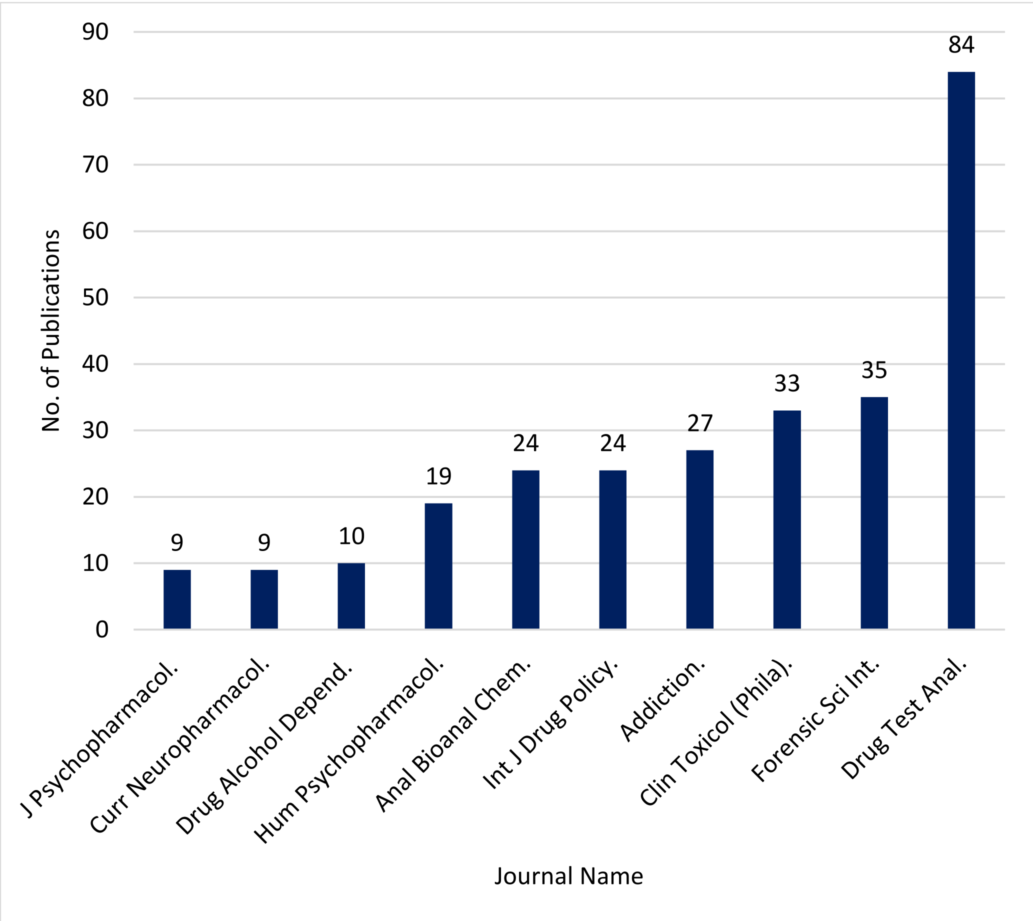


Figure 14. Most Popular Journal for Publication of NPS Research: Percentages (above), and the Number of Publication Per Journal (below).

A calculation of power scoring (Figure 1 and 2) revealed a shocking fact that summative power score of Pro-NPS (48+) is higher than that of Anti-NPS (21+). This may partially explain why the spread of NPS phenomenon, particularly its e-trade and e-commerce, is spreading at an exponential rate outpacing the efforts of NPS antagonists (anti-NPS) including; NPS researchers, policy makers, and legislators. However, these raw scores are not entirely accurate; some component of the basis of power cannot be estimated; these components are either unknown or anonymous. One of these is the cognitive foundation of the power of key players on the e-markets of the deep web. The anonymity of the deep web is the reason behind the lack of full accuracy of the tabulated power scoring (Conrad 2002; Mayer 2009; Phelps and Watt 2014, Van Hout et al., 2014). Pro-NPS seems to be ahead, i.e. more powerful, especially when it comes to terrorist; they can use illegal methods leading to an illegitimate power; including drug trafficking (trade and e-trade), illegal coercion and punishment, altogether with the lack of sense of morality, and the act of terror itself.

Power scores for NPS researchers were diverse (Figure 3). However, there were no exceptional cases (statistical outliers) for each of the power and the certainty score. Power scores and certainty scores seem to run in parallel with each other; their trends go up and down simultaneously. Hence, a positive linear correlation was hypothesised in between the two, and a linear regression was plotted accordingly; truly, there was a positive linear relationship (R^2 *score*=0.560). Consequently, it can be inferred that as the power of an NPS researcher increases, more data will be available on him (her) on the web, and his (her) corresponding anonymity will be varying accordingly. The number of publications indexed on PubMed was considered as an indicator of research output, and based on the Q-Q plot of research output, a cutoff limit of 40 articles per researcher was considered as the demarking point between low versus high output researchers. Accordingly, intergroup analysis (low versus high output), 25 researchers in each group, was constructed via the independent Student's t-test; there were significant differences for power score (8.07 versus 16.22, *p-value*=0.0001) and certainty score (9.48 versus 11.52 , *p*=0.0006) in between the two groups. Therefore, it can be inferred that the power and certainty scores were significantly bigger in high-output researchers. However, their anonymity on the web was lower than those of low research output.

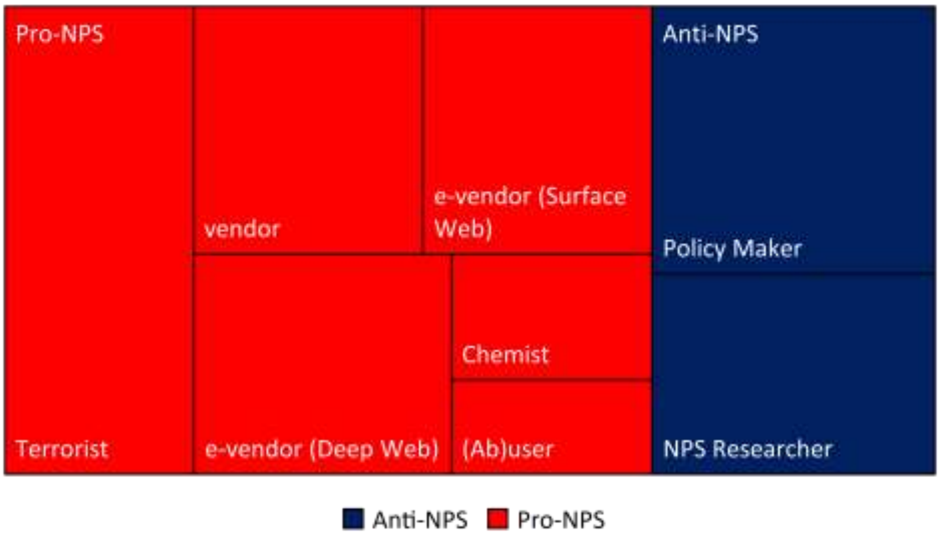
In relation to certainty scores, there were no statistical outliers; linear regression revealed a positive correlation (R^2 *score*=0.029) between the number of publications (PubMed/Medline) and certainty scores. The certainty scores for NPS researchers (n=50) were further analyzed by geographic location; There were significant difference between summative scores of; UK vs. Australia (*p-value*=0.029), Italy vs. Portugal (0.023), Italy vs. Australia (0.023), Germany vs. UK (0.001), Germany vs. Italy (0.027), Germany vs. Portugal (0.001), Portugal vs. Australia (0.019), US vs. UK (0.027), and US vs. Portugal (0.017). To be concluded, NPS researchers from UK, US, Germany have higher research output, higher power scores and certainty scores, and less anonymity on the web. A more integrated analysis (Figure 4) by continents (inter-continental) showed that the average certainty scores were higher in Europe (10.8) and North America (11) than in Australasia (9.8) and Asia (9.3). An inference could not be established due to the small sample size, although Europe is seen in the lead (Figure 5); it is also to be noticed that the random selection process yielded no researchers (0%) from the Middle East, while the UK, US, and Europe, were the top contributors in relation to the NPS research output.

AlphaBay e-market analysis was based on a snapshot taken on the 7th of February 2017. The e-market analysis relies on the number of items sold (Figure 6); Benzodiazepines (14646, 8%), Cannabis, Hashish, and cannabinoids (64903, 33%), Dissociatives (4303, 2%), Ecstasy and empathogens (30059, 15%), Opioids (16849, 9%), Paraphernalia (892, <1%), Prescription medications (8720, 4%), Psychedelics (13935, 7%), Stimulants (32494, 17%), and others. A parallel snapshot was taken for e-vendors on AlphaBay, e-vendors (n=40) were randomly picked using a *random number generator*. Each was scored for power; the scoring was based on; vendor level, trust level, membership length, and the percentage of positive feedbacks from e-customers. Power score and determinants of power score were plotted, and there were two phenomenal (outliers) e-vendors; these e-vendors were known by the usernames; *FrankMatthews* and *GreenLeafLabs*, both e-vendors shipped their items from Europe. Linear regression showed a linear correlation of e-vendor powers score with; e-vendor antiquity (R^2 *score*=0.302), and a stronger correlation with their trust level (0.812). There was also a positive linear correlation between e-vendor antiquity in the e-market and his (her) trust level (0.177). It is to be inferred that trust level for each e-vendor on AlphaBay e-market, is the most critical determinant of power score for a specific e-vendor on AlphaBay.

Valhalla e-market was also analysed in a similar fashion (Figure 7 and 8); the percentile contribution of a number of NPS items was very analogous to those on AlphaBay; Cannabis and Hashish, stimulants and empathogens were at the lead. Forty e-vendors were randomly picked (n=40); one outlier was detected, the e-vendor username was *DCdutchconnectionUK*, his (her) shipping countries included the UK and Netherlands. Power score analysis for Valhalla e-vendors was based strictly based on the number of positive and negative feedbacks from e-customers. Summative power scoring was calculated for geographic location (shipping country of e-vendor); UK, Finland, and the US are at the lead (Figure 9); other countries included Netherlands, Germany, Poland, Norway, Spain, India, and China; no countries from the Middle East appeared. The top three shipping countries (UK, Finland, and the US) were tested using the independent t-test. There was a statistically significant difference of UK over both; US (40 vs. 16, *p-value*=0.060) and Finland (40 vs. 20, p=0.030), while no difference was detected between US and Finland (16 vs. 20, p=0.260). It is to be inferred that e-vendors from the UK are of the highest power score on Valhalla e-market. The percentile distribution of NPS categories advertised was comparable on both e-markets (AlphaBay and Valhalla) (Figure 10). Additionally, power scoring for both e-markets seems to run also in parallel.

On the 3rd e-market, HANSA, the type and percentile contribution of NPS items were also in harmony with the results from AlphaBay and Valhalla (Figure 11). Cannabis and Hashish were always the most advertised NPS item in all three e-markets; Cannabis and cannabimimetic represented almost one-third of the promoted NPS in each of the three e-markets. Moreover, NPS products sold under the category of cannabis and cannabinoids represented an obvious statistical outlier; no other outliers were detected. The other most popular sold NPS are stimulants and empathogens. Power scores for e-vendors (n=40) were based on a snapshot taken on the 8th of February 2017; power scoring was based on; trust level and vendor level, positive and negative feedbacks, e-vendor antiquity (days), the number of orders, and the number of subscribers. Power scoring of the e-vendors show two outliers; *Saint_Symbiosis* (UK) and *empathogens* (Canada). Based on visual data (Figure 12), it appears that the number of orders and the number of subscribers for e-vendors (HANSA) are much in line with each other (strong positive linear relationship), in contrary to the antiquity of e-vendors. Summative power score for shipping country of e-vendors, clearly shows that top shipping countries are; US (33%), Netherlands (24%), Canada (14%), and the UK (13%) (Figure 13). Other countries included Germany, Spain, Czech Republic, Philipines, and China. On the other hand, the highest number of orders and subscribers on HANSA was found in the Netherlands (Figure 14). However, the average power score for e-vendors from the Netherlands and the US was not significantly different (34.42 vs. 28, *p-value*=0.226). The strongest linear correlation for e-vendor power score was with; the number of orders (R^2 *score*=0.724), and the e-vendor level (0.715), while the weakest was with e-vendor antiquity (0.143). It can be concluded that the patterns of correlation of power scoring and its geographic mapping of HANSA e-vendors are unique from that of AlphaBay and Valhalla e-markets.

Though the sample of e-vendors on AlphaBay (n=40) and NPS researchers chosen from PubMed/Medline database (n=50) are not homogenous, corrective calculation (homogenization) of power scores was done, the aim is to infer if the power score is significantly higher for one of the two groups. Independent t-testing confirmed the that AlphaBay e-vendors possess higher mean of power scoring than researchers of NPS (61.52 vs. 48.68, *p-value*=0.01). The NPS researchers are still lagging behind.



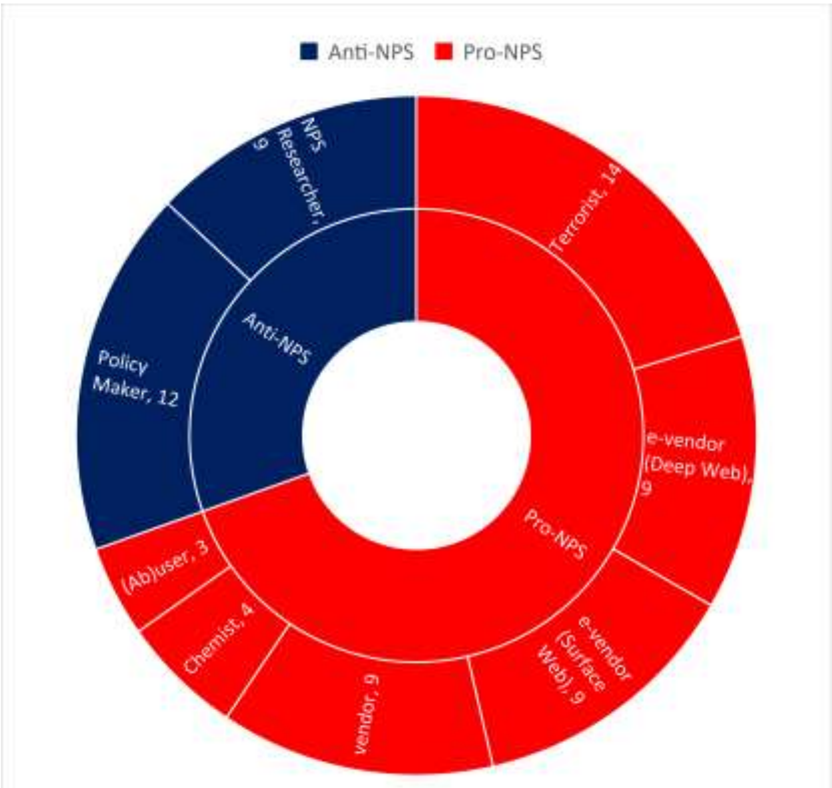
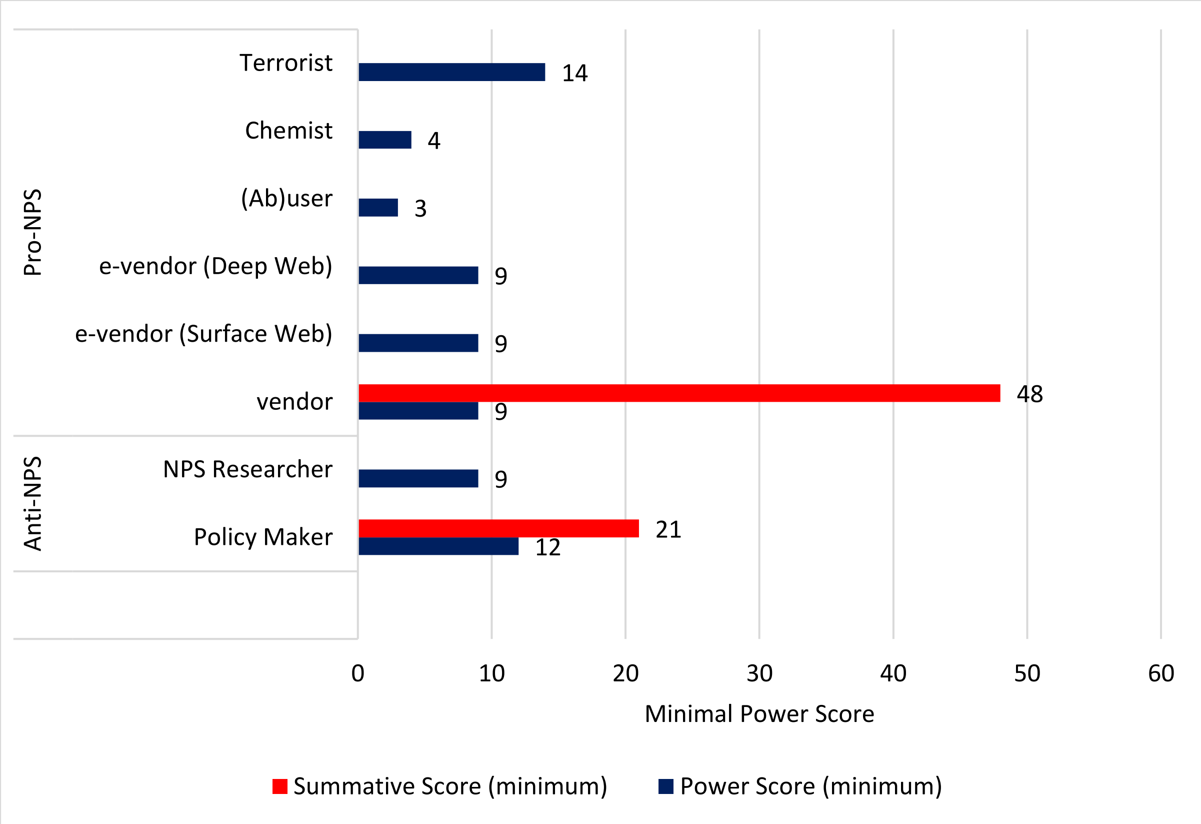


Figure 1. Components of Basis of Power for Key Players in the NPS Industry: Treemap (above) and Donut Presentation (below).



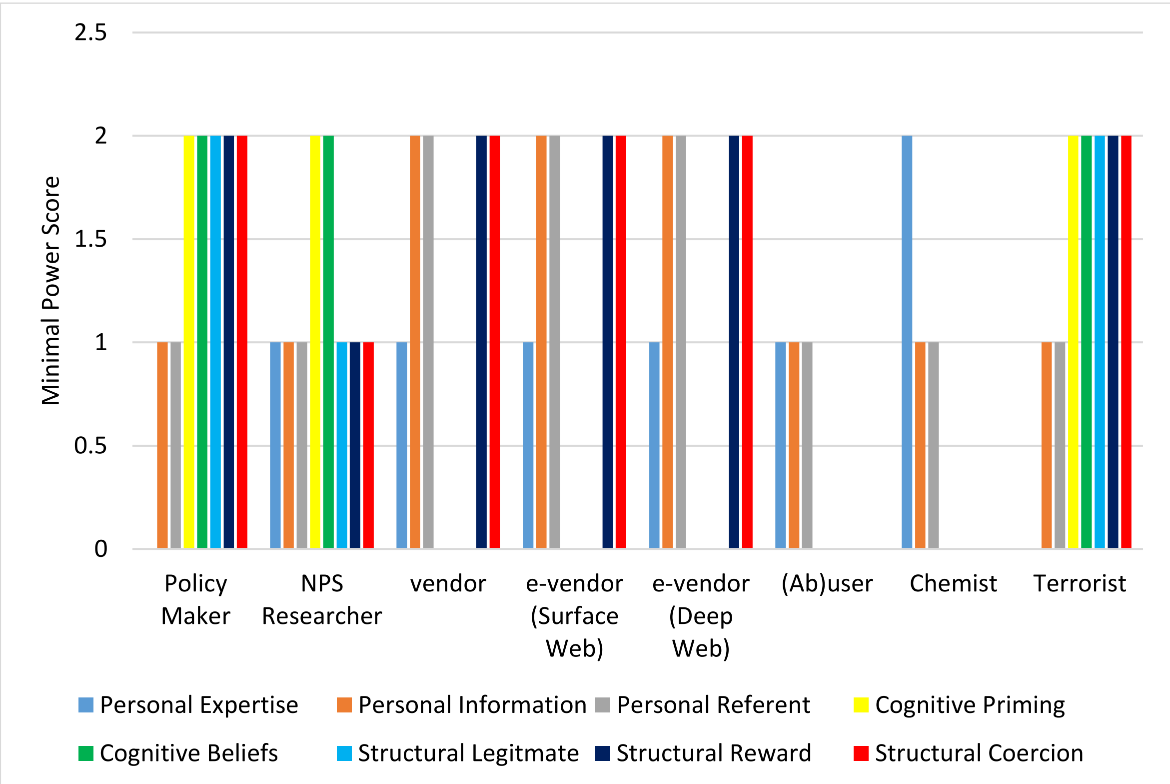
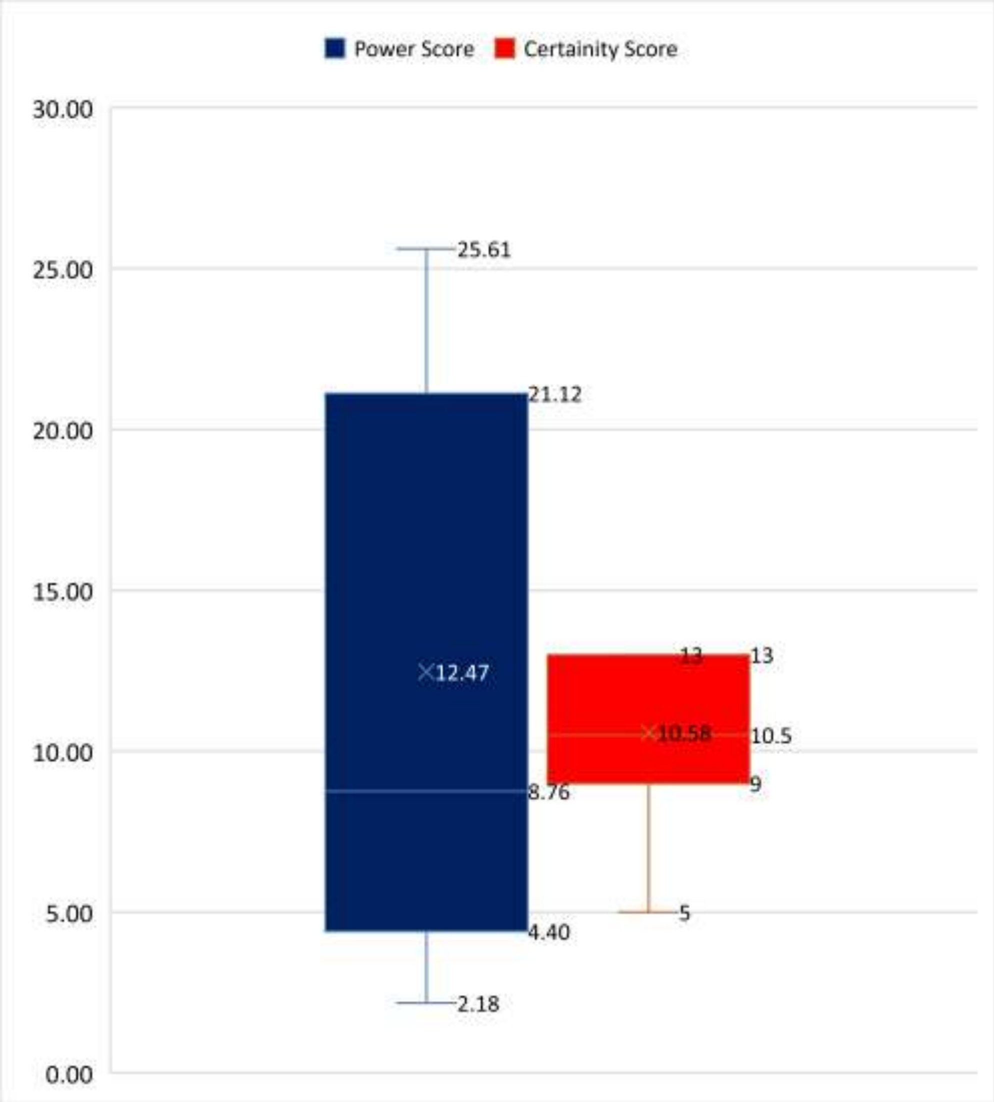


Figure 2. Individual and Summative Scoring of Power: Pro-NPS versus Anti-NPS.



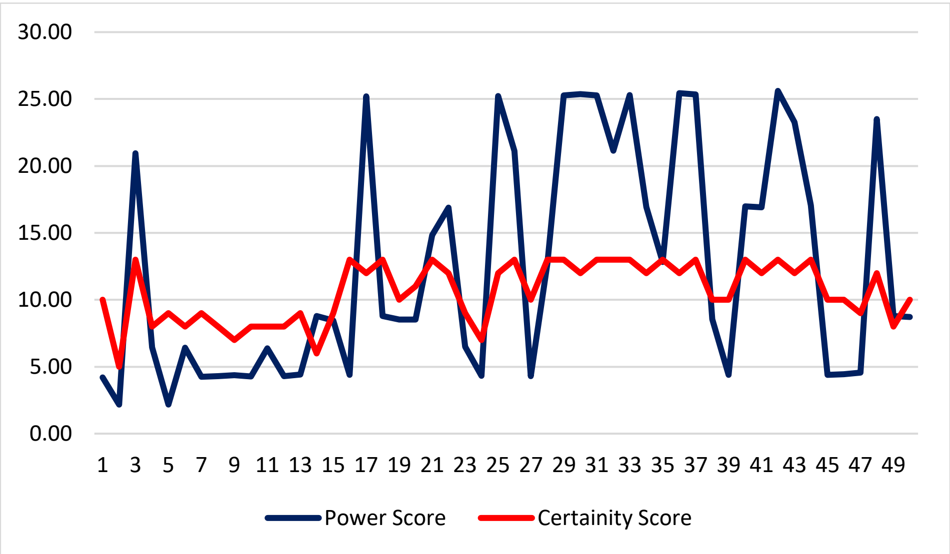


Figure 3. Power and Certainty Score: Boxplot Presentation (above), Comparative Line Graph (below).

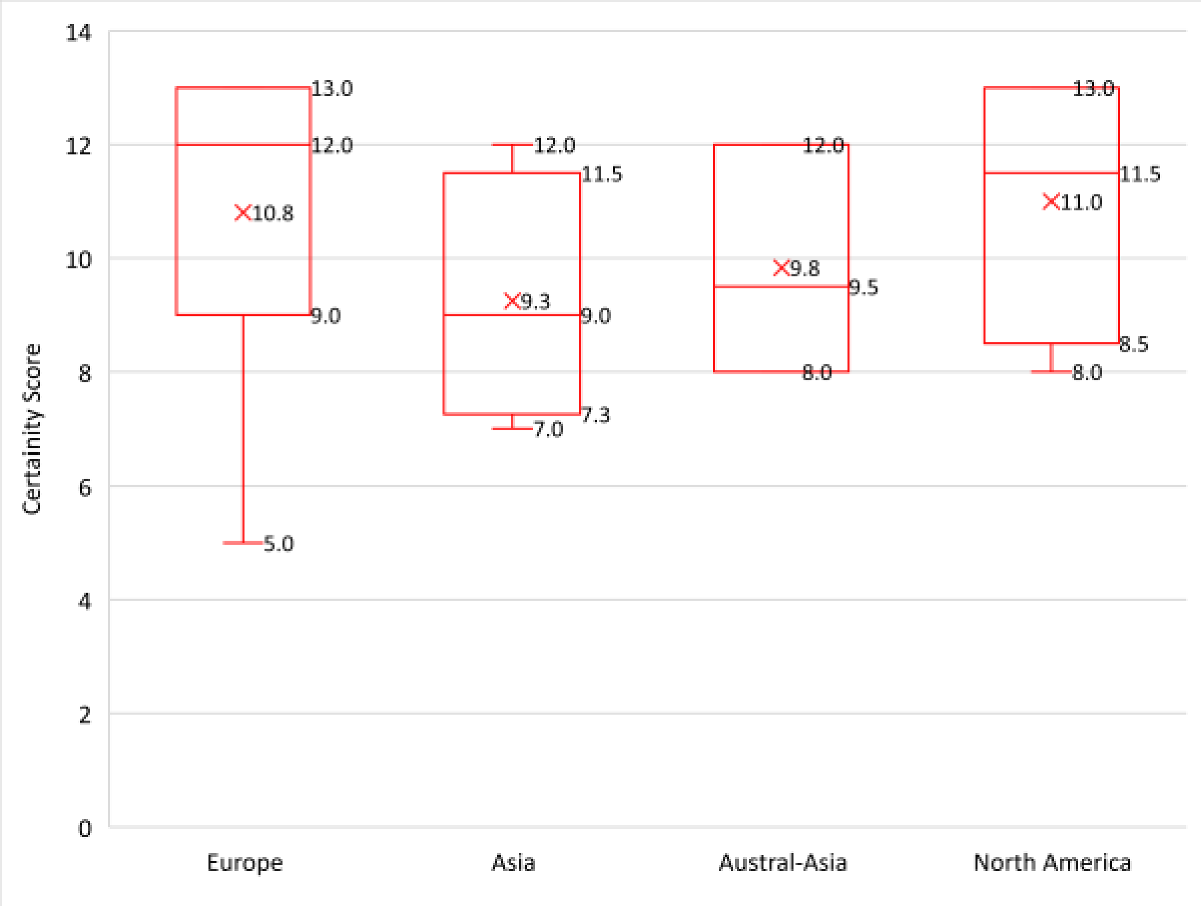


Figure 4. Continental Certainty Scores.

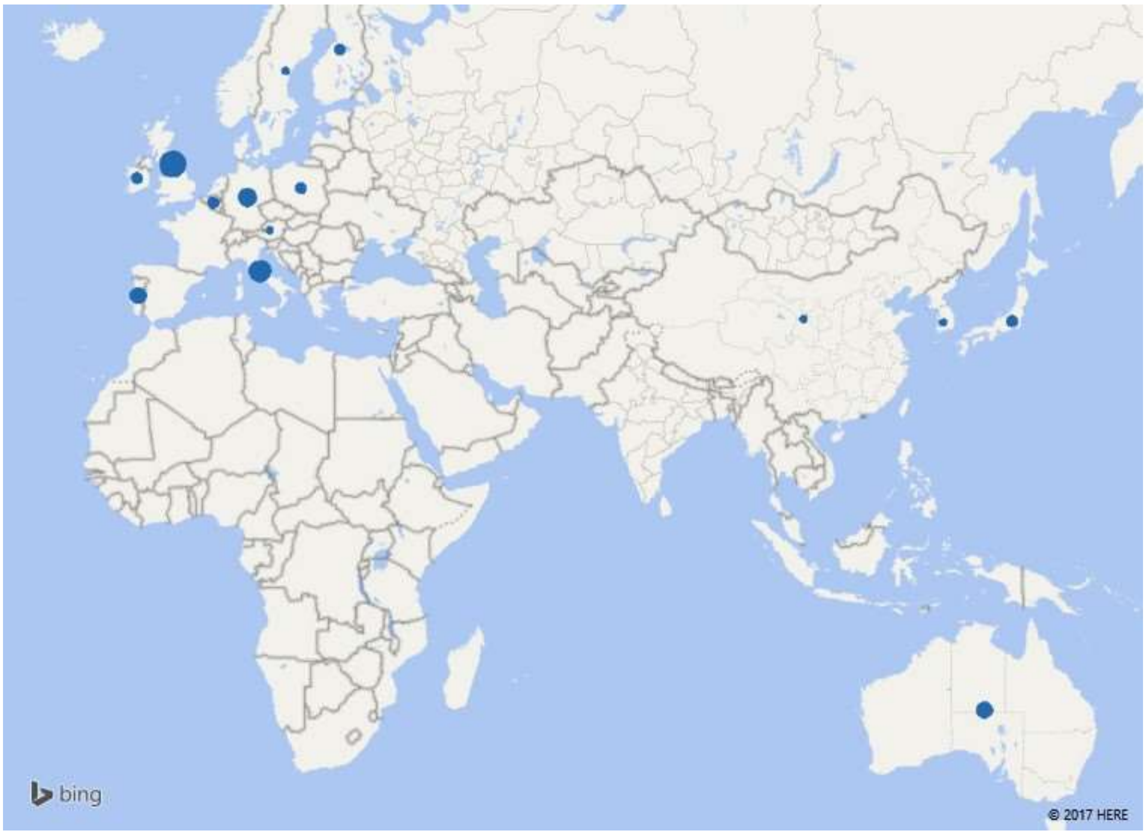
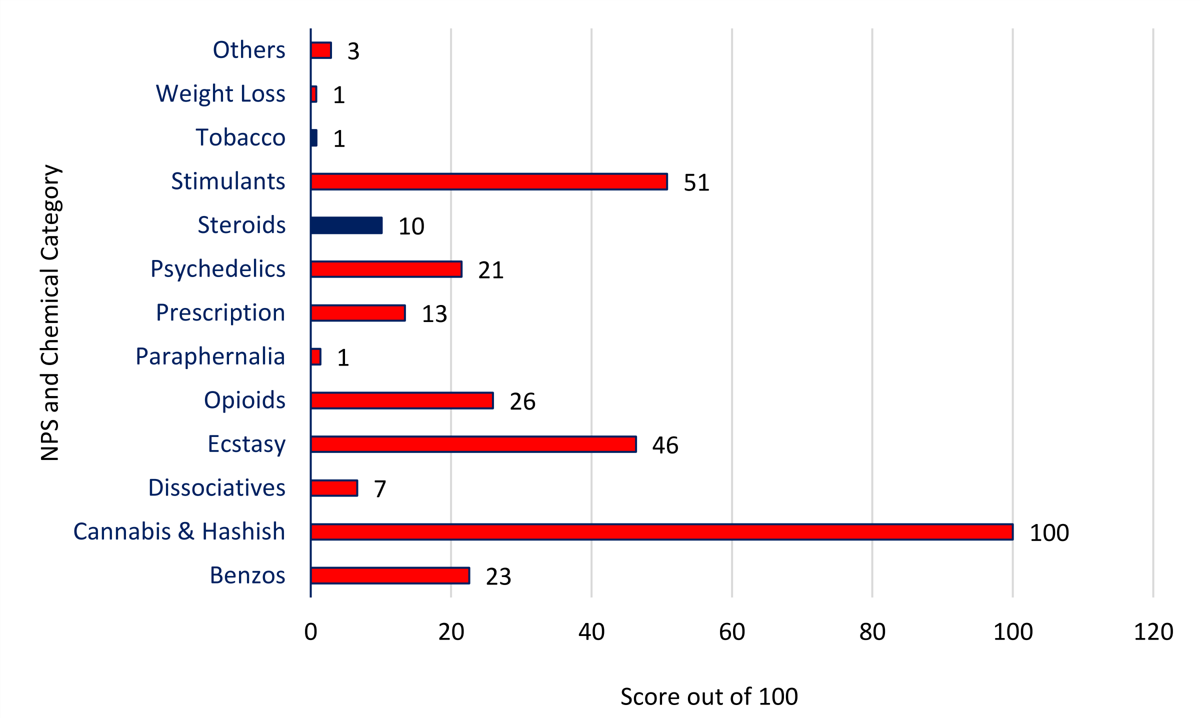


Figure 5. Geographical Presentation: Continental Certainity Scoring in Europe, Asia, and Australasia.



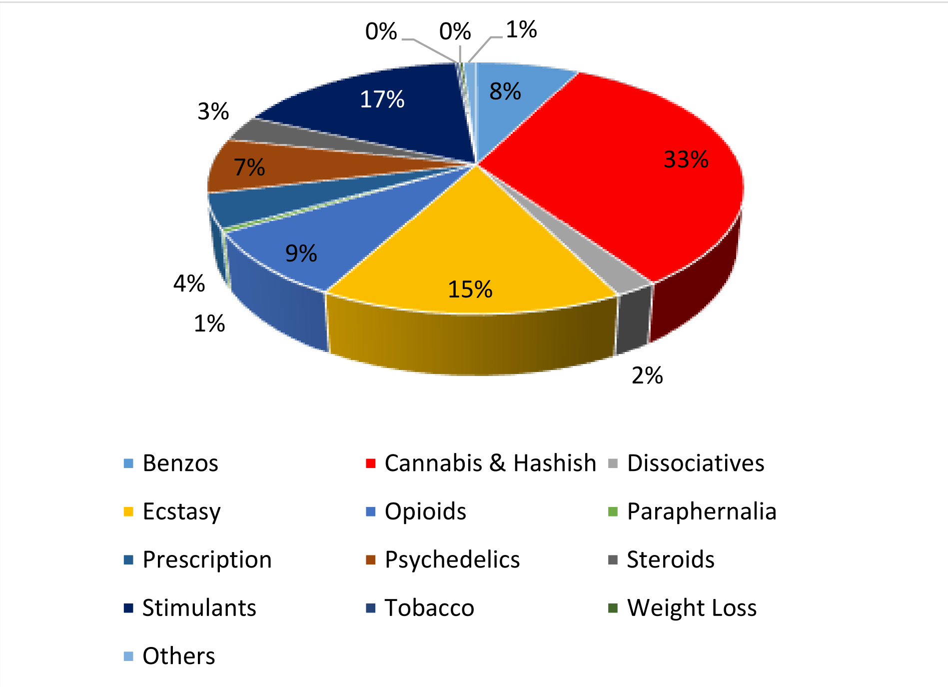


Figure 6. Psychoactive and Novel Psychoactive Substances Advertised on AlphaBay e-market.

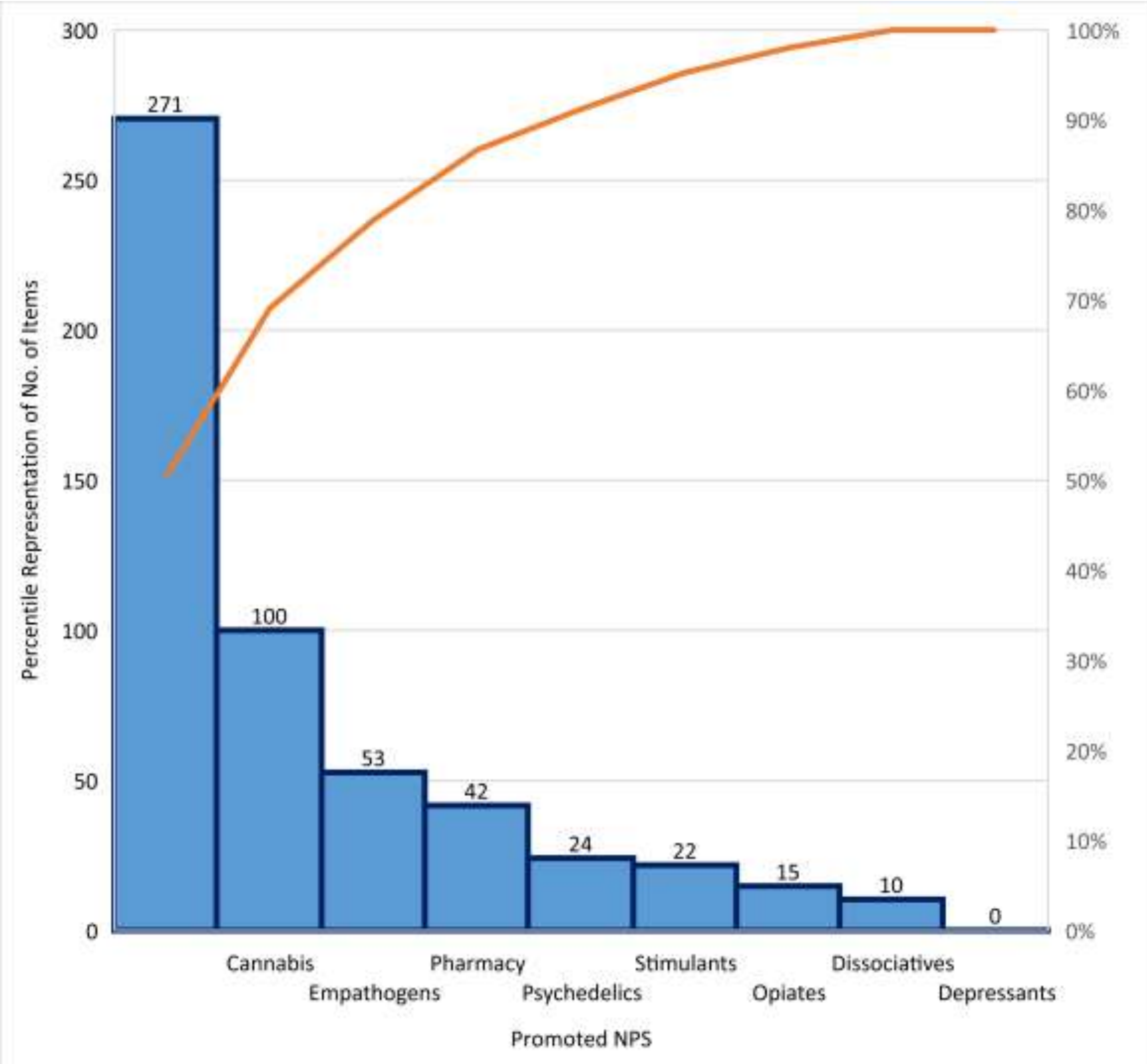


Figure 7. Psychoactive and Novel Psychoactive Substances Advertised by e-vendors on Valhalla.

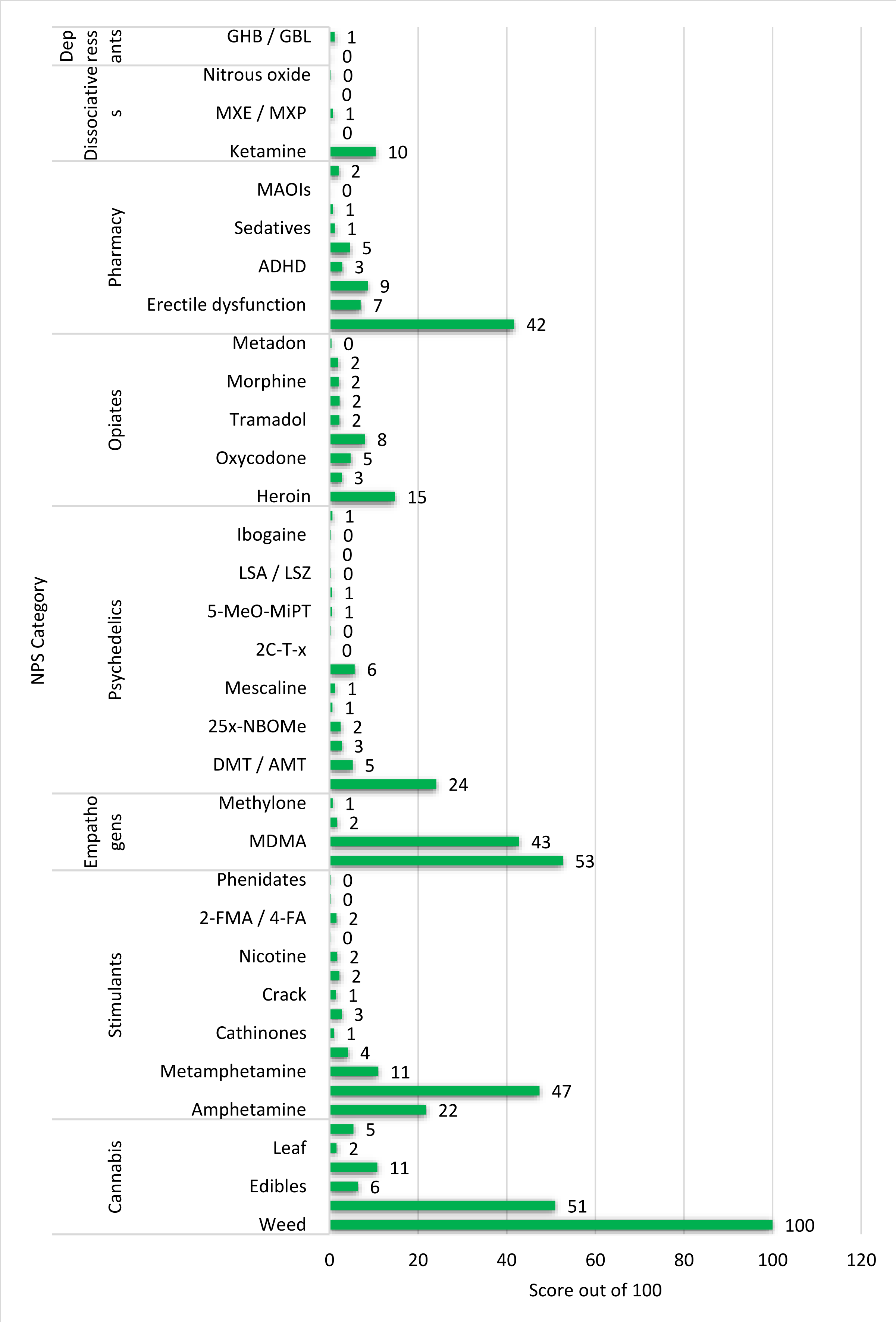
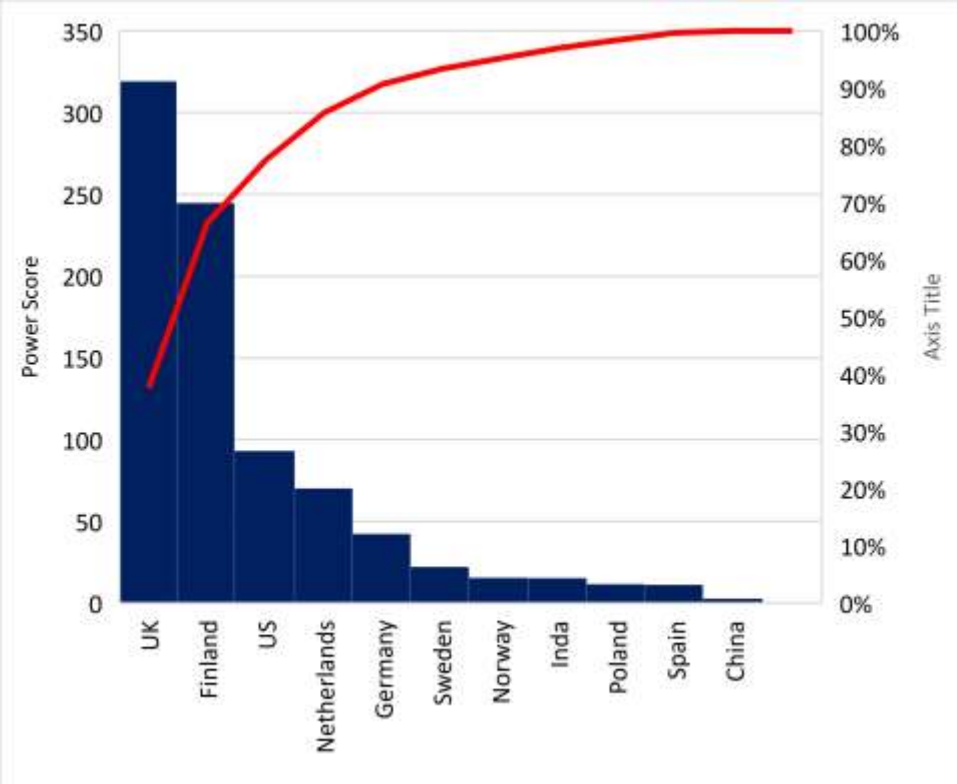


Figure 8. Psychoactive and Novel Psychoactive Substances Advertised on Valhalla.



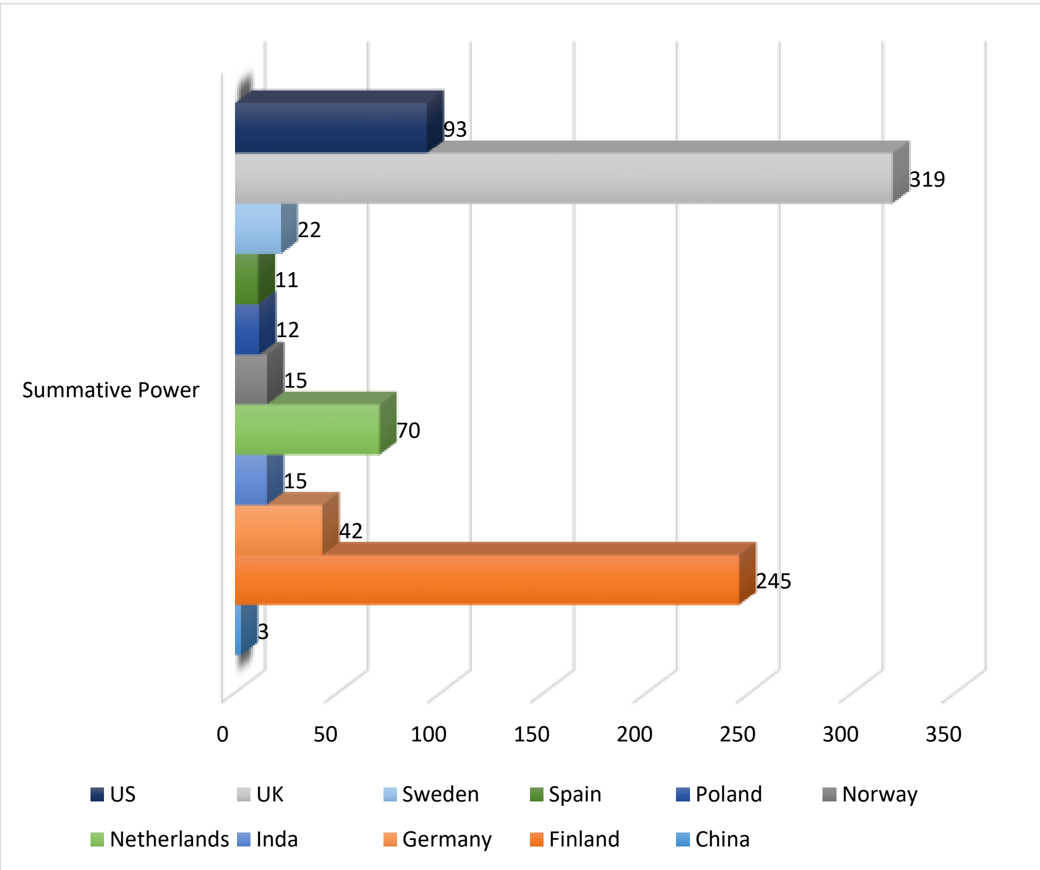


Figure 9. Summative Power Score of e-vendors on Valhalla by Geographic Location (Country).

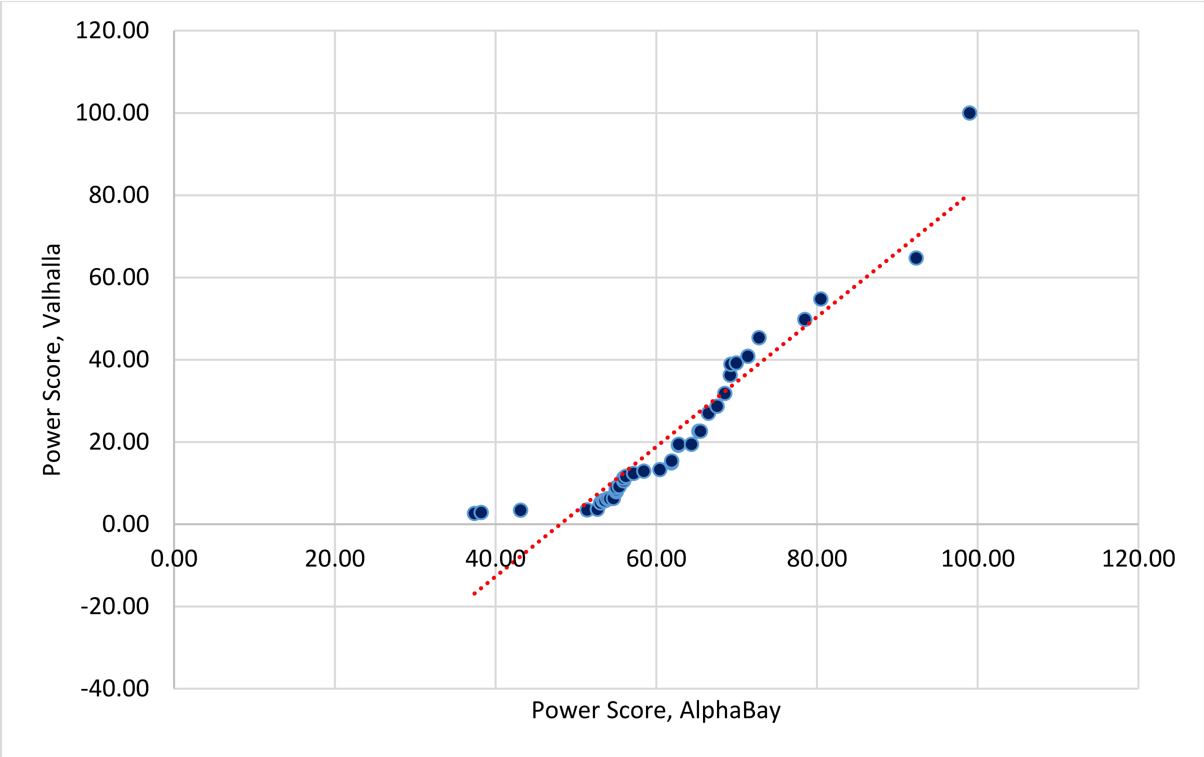
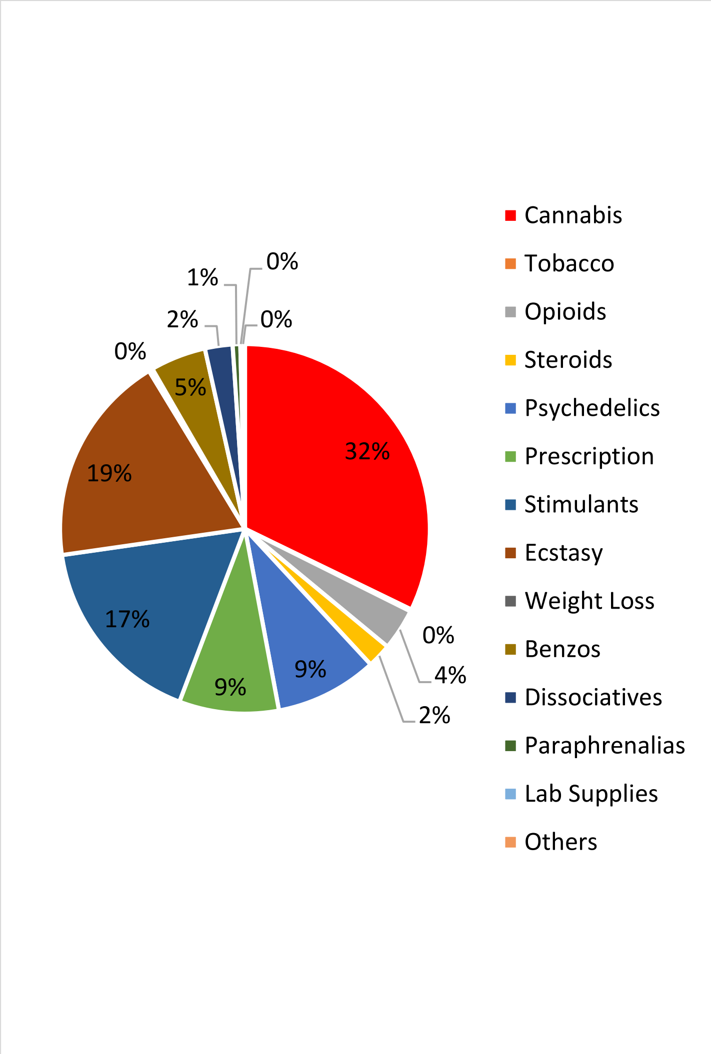


Figure 10. Power Score Correlation: AlphaBay versus Valhalla.



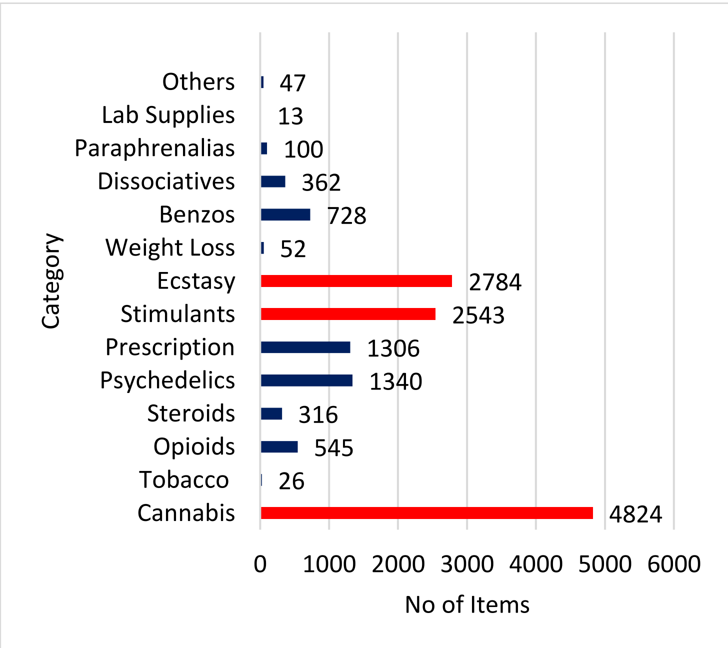


Figure 11. Psychoactive and Novel Psychoactive Substances Advertised on HANSA e-market.

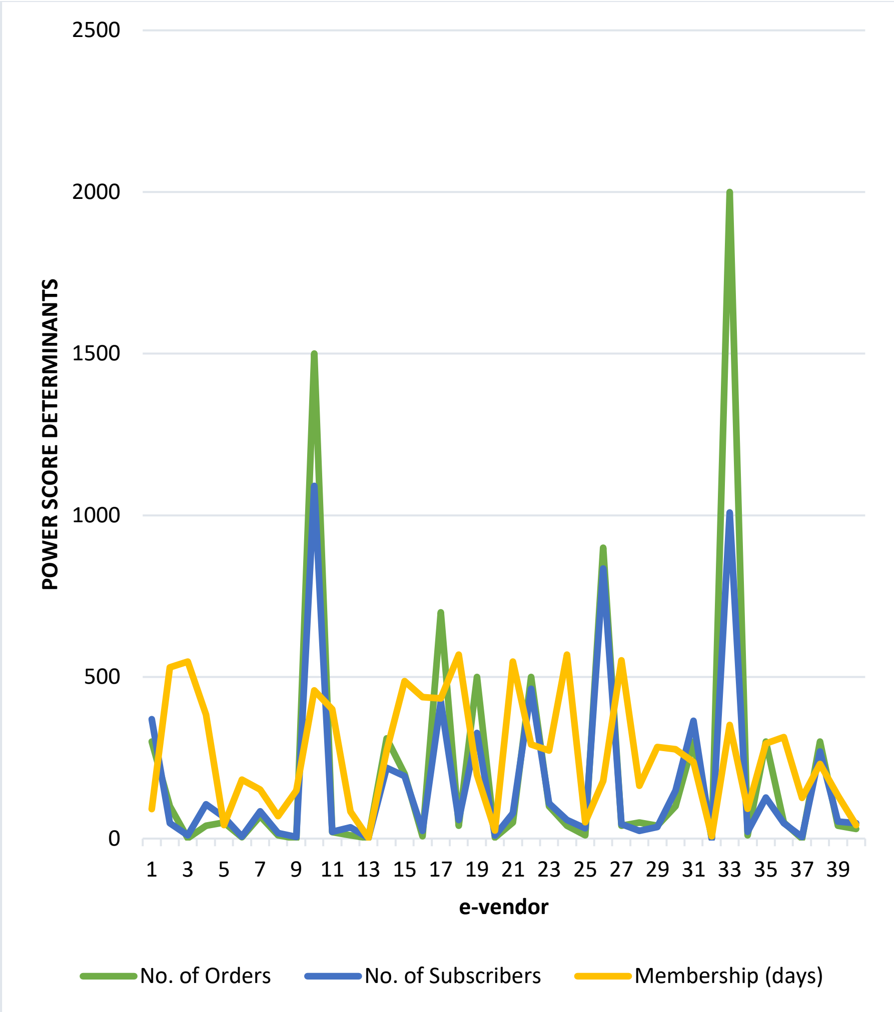
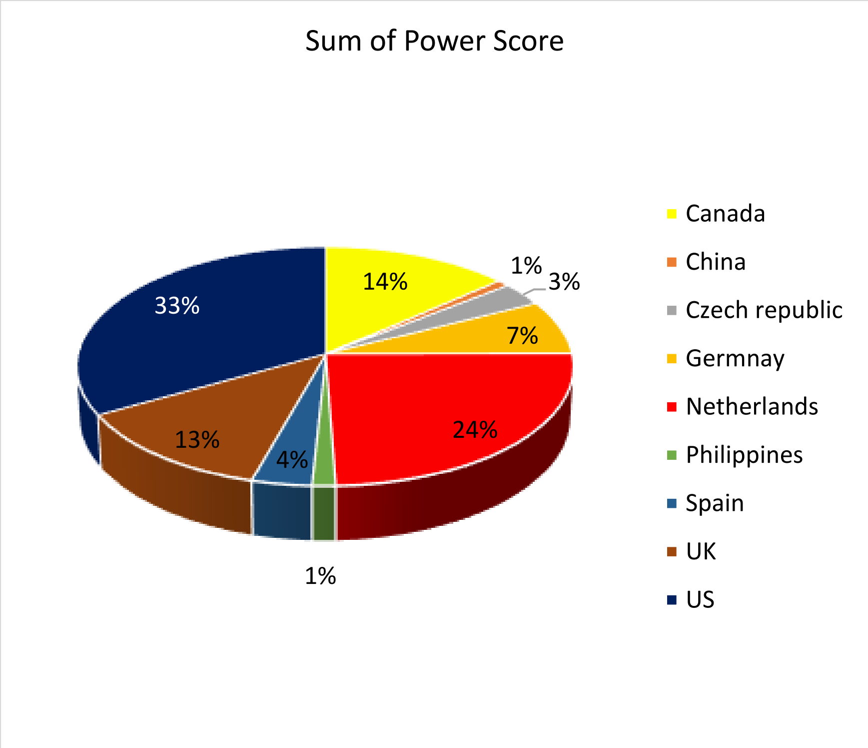


Figure 12. Power Score Determinant for e-vendors (n=40) on HANSA e-market



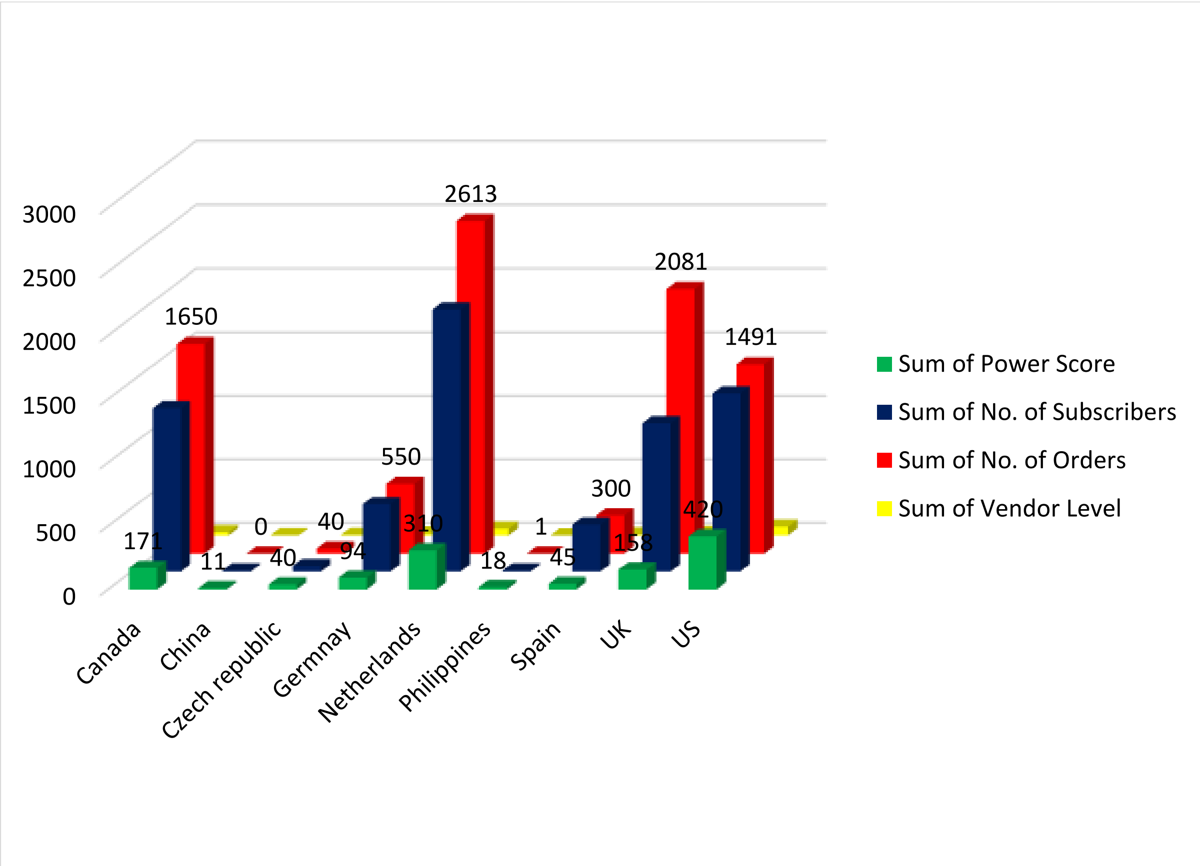


Figure 13. Top Shipping Countries of Psychoactive and Novel Psychoactive Substances in HANSA.

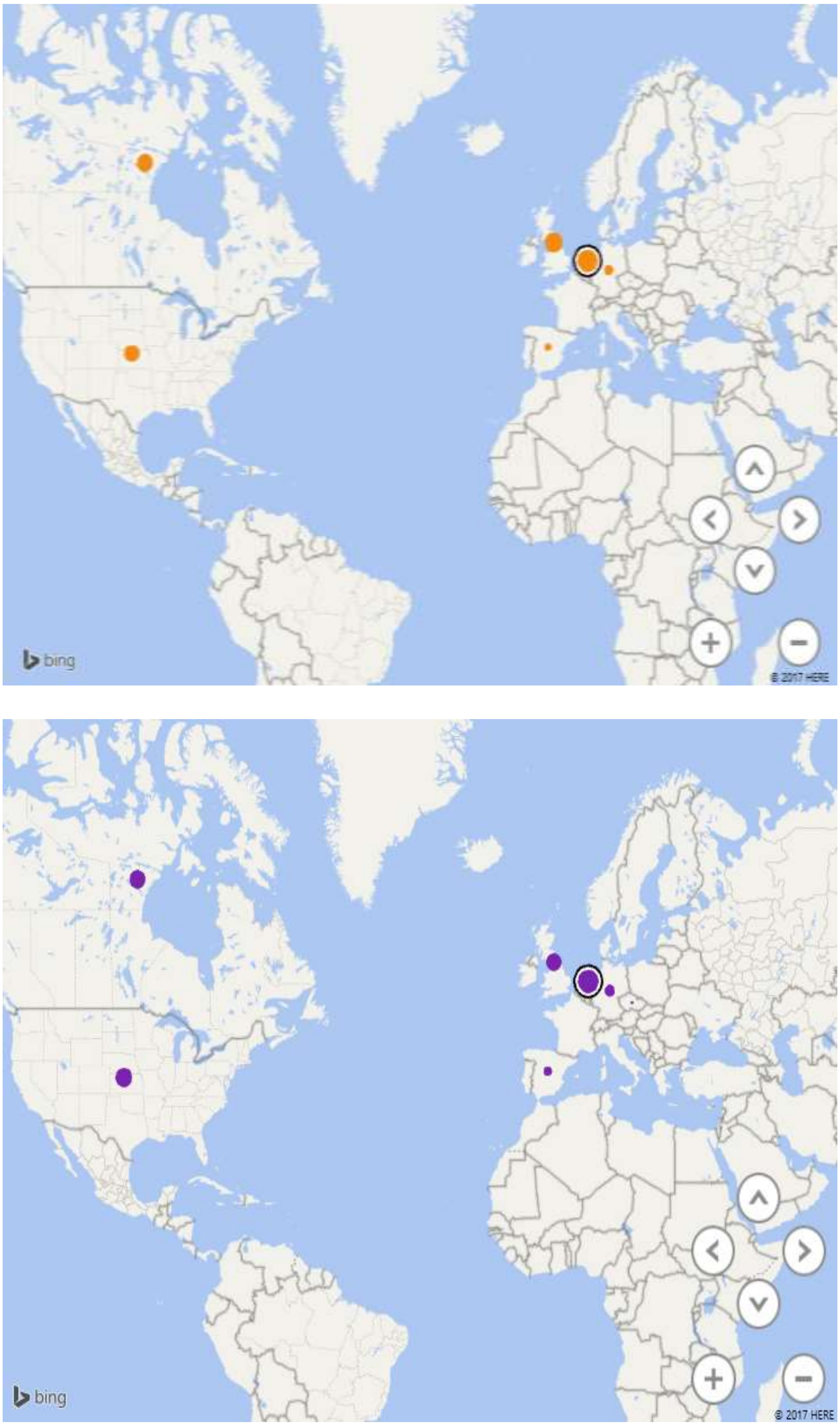


Figure 14. Geographic Mapping: Number of Orders (above), and Number of Subscribers (below).

Chapter 3. Extrapolations Based on Literature review – Most popular NPS

Google Trends database represents one of the major resources of data from the surface web; the trends database will always be approached first which will be followed by analyses of other components of the surface web including literature databases and online drug fora, then to be followed by analyses of the deep web and the darknet e-marketplace (Figure 1). In relation to Google Trends, there were no data accessible in connection with the Middle East or Arabic countries; Google Trends database enabled an option for geographic mapping (geo-mapping) which allowed a restricted access to data from four countries only; the US, UK, Canada, and Australia (Figure 2). Top *related queries* by surface web users in these countries were; *phenethylamine*, "*tryptamines I have known and loved"*, *synthetic cathinones*, and *bath salts*. Geo-mapping has shown that the US is in the lead in relation to the attentiveness of surface web users in categories of NPS; these countries contributed as follows; US (35%), UK (17%), Canada (26%), and Australia (22%). Interest in cannabinoids was the highest (98%), while all other classes of NPS summed up to a tiny fragment (2%), the majority of the latter fell into the chemical category of cathinones (Figure 3). In the global analysis, despite that synthetic cannabinoids seem to hold a high leverage against other classes of NPS, descriptive statistics are usually inconclusive for the purpose of inference. Hence, a statistical inference was established using ANOVA test. There was a significant difference (*p-value*<0.001), at an average (mean value) attentiveness of web users in; Cannabinoids (62.96), Phenethylamines (2.44), Cathinones (3.79), Tryptamines (2.93), Piperazines (1.91), and Pipradrol (1.12). The temporal change (2012-2016) in the trends was not conclusive (highly oscillating), though the highest attentiveness to cannabinoids was recorded on the March 2014 and April 2015 (Figure 4), while the highest interests in cathinones were recorded in May 2012, November 2012, and January 2013.

The temporal change (year by year) in the trends for each of the categories of NPS, appeared to be highly erratic and unsettled for the period 2012-2016 (Figure 5). Synthetic cannabinoids appears oscillating (saw-tooth patterns) with an exception for the transition from; 2012 to 2013 (*p-value*=0.254), 2013 to 2014 (p=0.265), and 2015 to 2016 (p=0.624). The trends for phenethylamines were also unstable except for the transition from; 2013 to 2014 (p=0.293), and 2015 to 2016 (p=0.241). On the other hand, both cathinones and tryptamines had more steady trends. Piperazine appeared to have oscillating trends for the period 2012 to 2015 with a subsequent steadiness till the end of 2016. Similarly, Pipradol oscillated up and down with an exception for the transition from; 2013 to 2014 (p= 0.083), 2013 to 2016 (p=0.412), and 2015 to 2016 (p=0.155).

The cannabinoids have been more popular than each of the other categories of NPS (Figure 6) for each year for the period from the beginning of 2012 to the definite end of 2016. Similarly, there were significant differences in between phenethylamines and other chemical categories of NPS (Figure 7) with an exception for; Phenethylamines versus Cathinones in 2012 (*p-value*=0.260), Phenethylamines versus Tryptamines in 2012 (p=0129) and 2013 (p=0.060), and Phenethylamines versus Piperazines in 2015 (p=0.098) and 2016 (p=0.279). Cathinones were also more popular than each of piperazine and pipradol groups for all the years (Figure 8) except for Cathinones versus Tryptamines in 2014 (p=0.283). The trends of all the remaining three classes of NPS, specifically tryptamines, piperazines, and pipradol were all significantly different from each other (2012-2016).

Trends in the United States (Figure 9) appeared to be consistent with the oscillating global patterns. Top related queries by web users were; *synthetic cathinones, cannabinoids breast milk, cannabinoids in breast milk, cbd, cannabinoids and cancer, synthetic marijuana, what is cannabis, what are cannabinoids, synthetic cannabinoids for sale, cannabinoids cancer, what is cannabinoids*, and *cannabis*. Interest in cannabinoids peaked in May 2012 and March 2014, while the highest interest in cathinones was recorded on; June 2012, April 2015, February 2016, and October 2016. Other patterns (inferential) were concordant to a high degree (Figure 10) with the global trends. ANOVA test confirmed that cannabis and cannabinoids are in the lead (*p-value*<0.001) over all other chemical categories of NPS.

In the United Kingdom (Figures 11 and 12), the temporal patterns seem to be different from that in the US. However, cannabinoids persist to be the most popular (*p-value*<0.001) while other categories of NPS were in close competition with each other. Interest in cannabinoids reached a maximum in December 2014 (different from the US patterns), while cathinones achieved the highest peaks in December 2013, and August 2015 (also distinct from the US). The only related query by web users was the term *synthetic cannabinoids*.

In Canada, the patterns (trends) were also novel from those seen in the US or the UK. However, both cannabinoids (rank 1st) and cathinones (rank 2nd) were the most popular. Top related queries were not accessible from the database. Interest in cannabinoids peaked in April-May 2012, January 2015, March 2015, and July 2016 (Figure 13), while interest in cathinones reached highest levels in May-June 2012, and June 2014. Furthermore, it seems that the Canadian citizens are not interested in other classes of NPS including phenethylamines, tryptamines, piperazines, and pipradrol. The inferential statistics also confirmed that cannabis and cannabinoids are more popular than cathinones for the entire period (2012-2016) at *p-value*<0.001.

In Australia, the trends of surface web users' interest seem to be somehow comparable to that of Canada, Australian citizens are highly interested in cannabinoids (rank 1st) and cathinones (rank 2nd), and they appear to be not interested in other categories of NPS (Figure 14). Attentiveness towards cannabinoids was maximum in February 2012, while cathinones peaked in April 2015. Top related queries on that database included only “synthetic cannabinoids”. Inferential statistics revealed that cannabis and cannabinoids were also the most popular at a $p<0.001$.

The repeated pattern in which cannabis and cannabinoids were ahead in the competition over all other types of NPS, was consistent with trending pattern on drug fora and the deep web (Figure 15). Based on cross-sectional and longitudinal analyses, cannabinoids and cannabimimetic were also of high prevalence in Iraq; (Al-Hemiary et al., 2014; Al-Hemiary et al., 2017). However, Middle Eastern and Arabic Countries did not contribute, by any means, to the e-trends on the surface web as observed via Google Trends database. Furthermore, geolocation confirmed the presence of only four countries; all of which are from the developed western world. This pattern was also in harmony in relation to the minor contribution of the Middle Eastern and Arabic countries on the deep web.

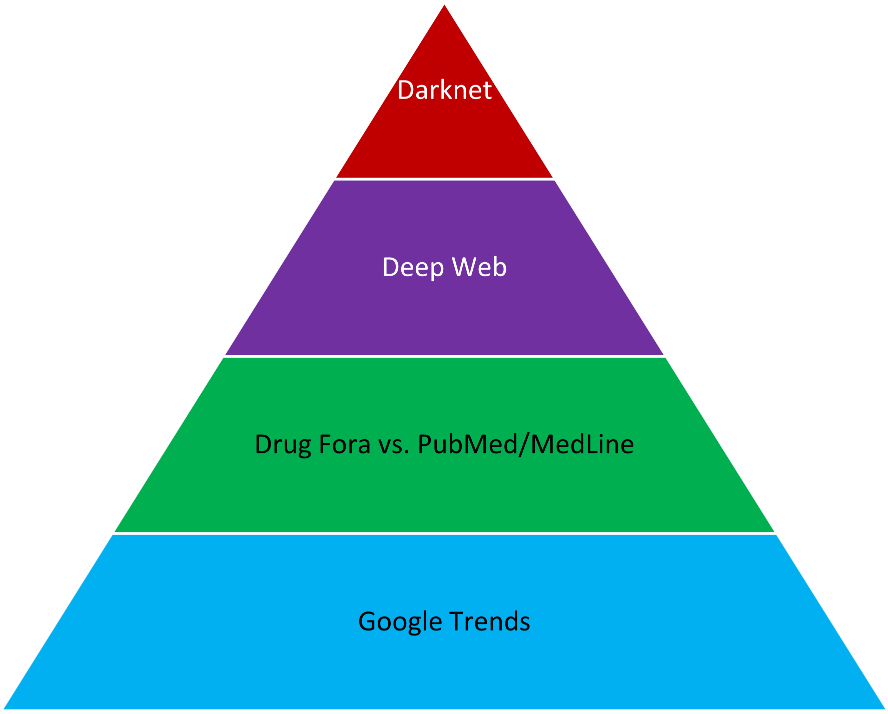
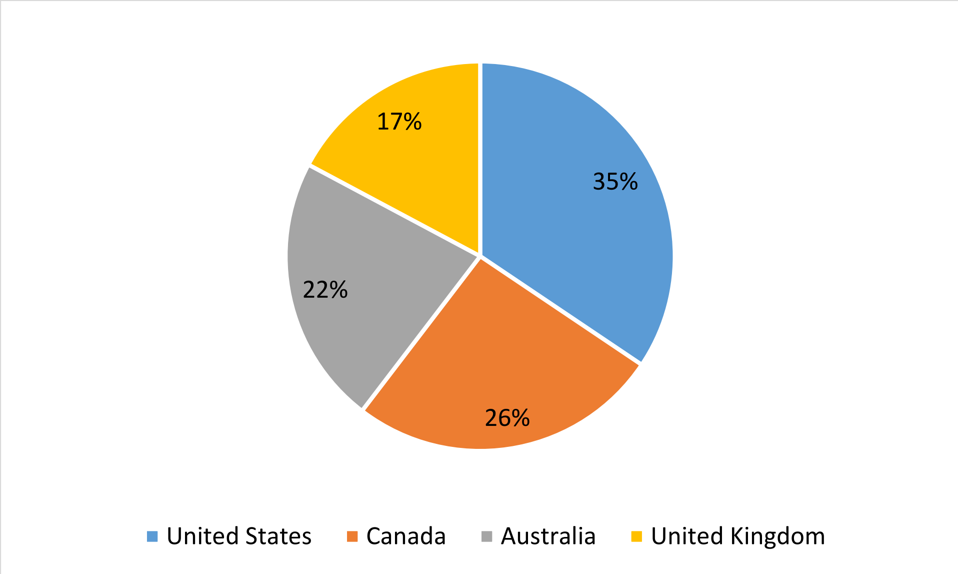


Figure 1. The hierarchical Analytic Approach for Studying the NPS e-phenomena on the Web.



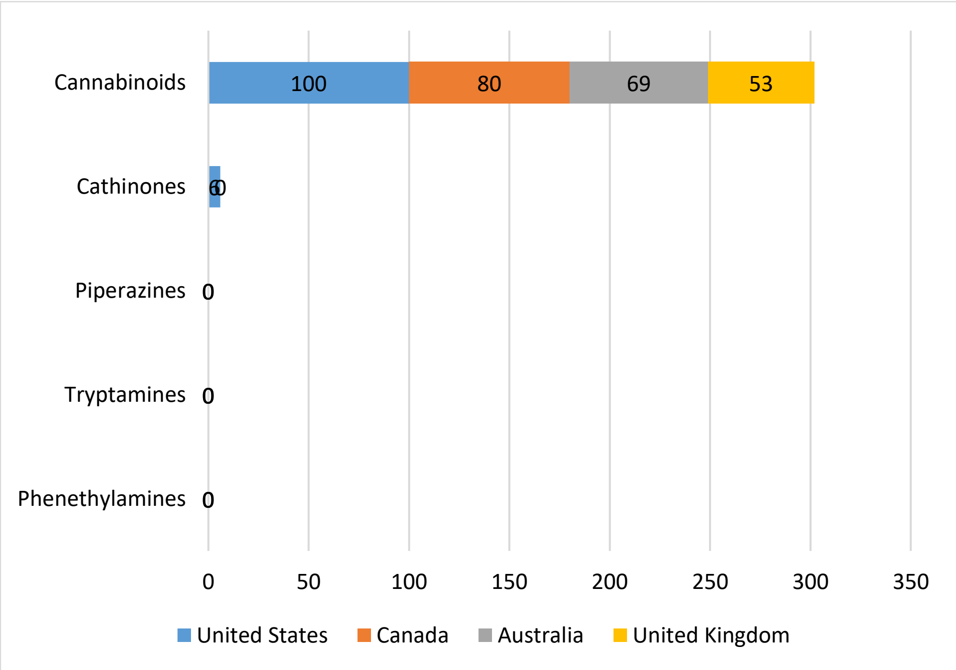
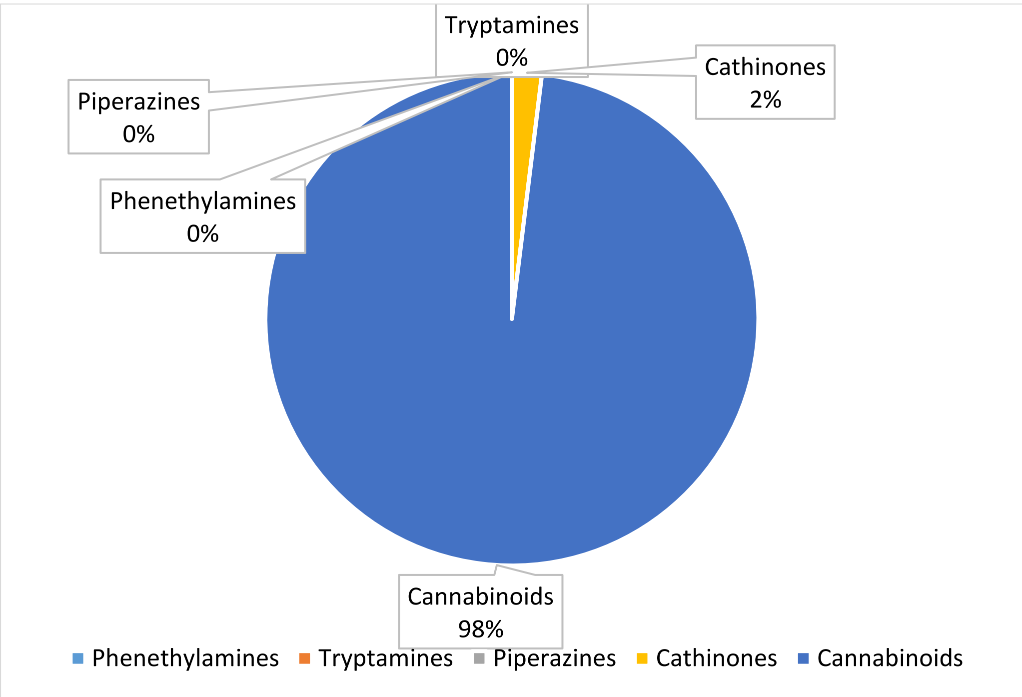


Figure 2. Google Trends (2012-2016) for Chemical Categories of NPS on the Surface Web.



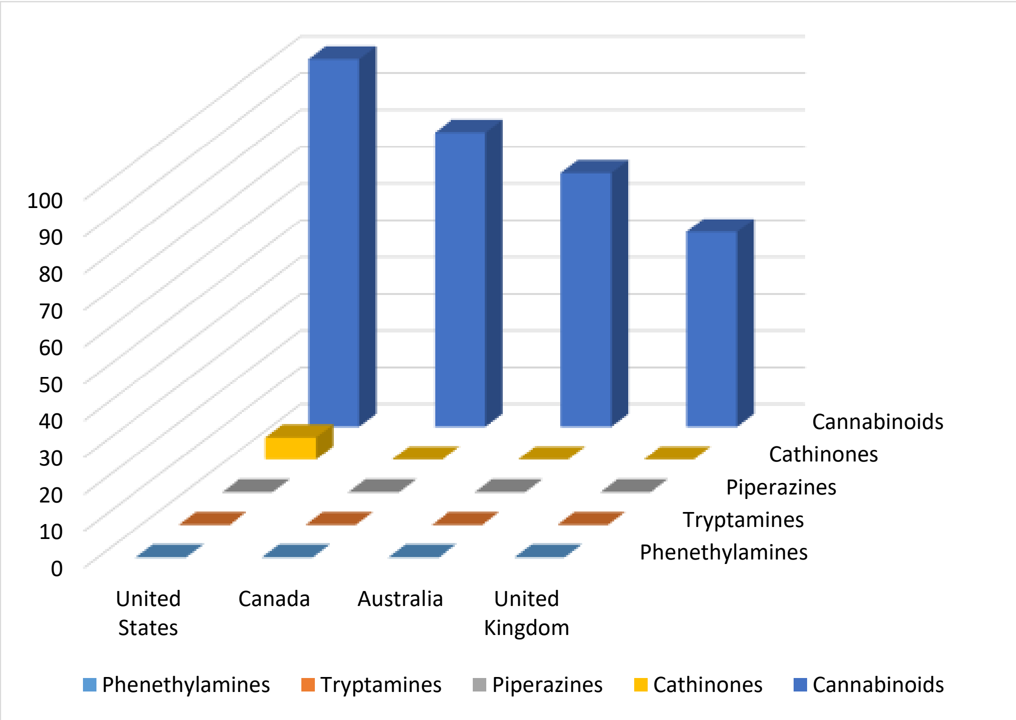


Figure 3. Google Trends (2012-2016) for Chemical Categories of NPS on the Surface Web.

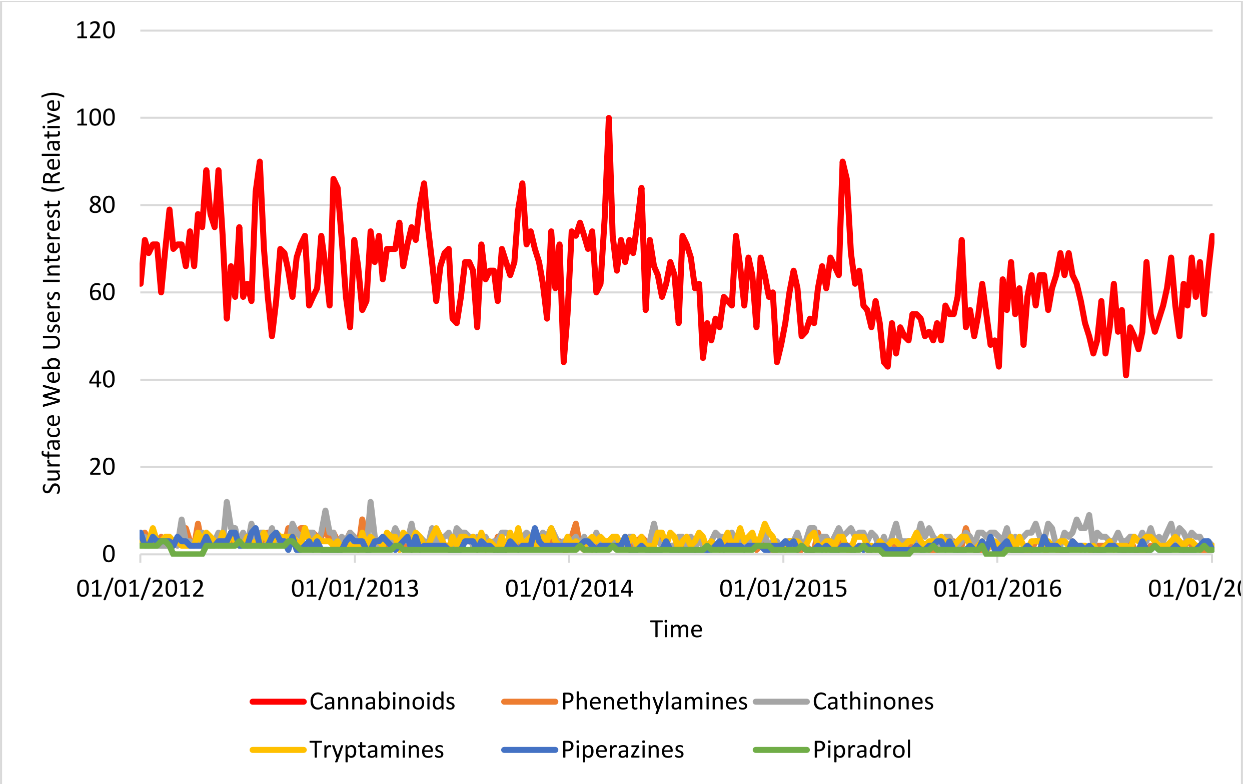


Figure 4. Google Trends (2012-2016): Major Chemical Categories of NPS (worldwide).

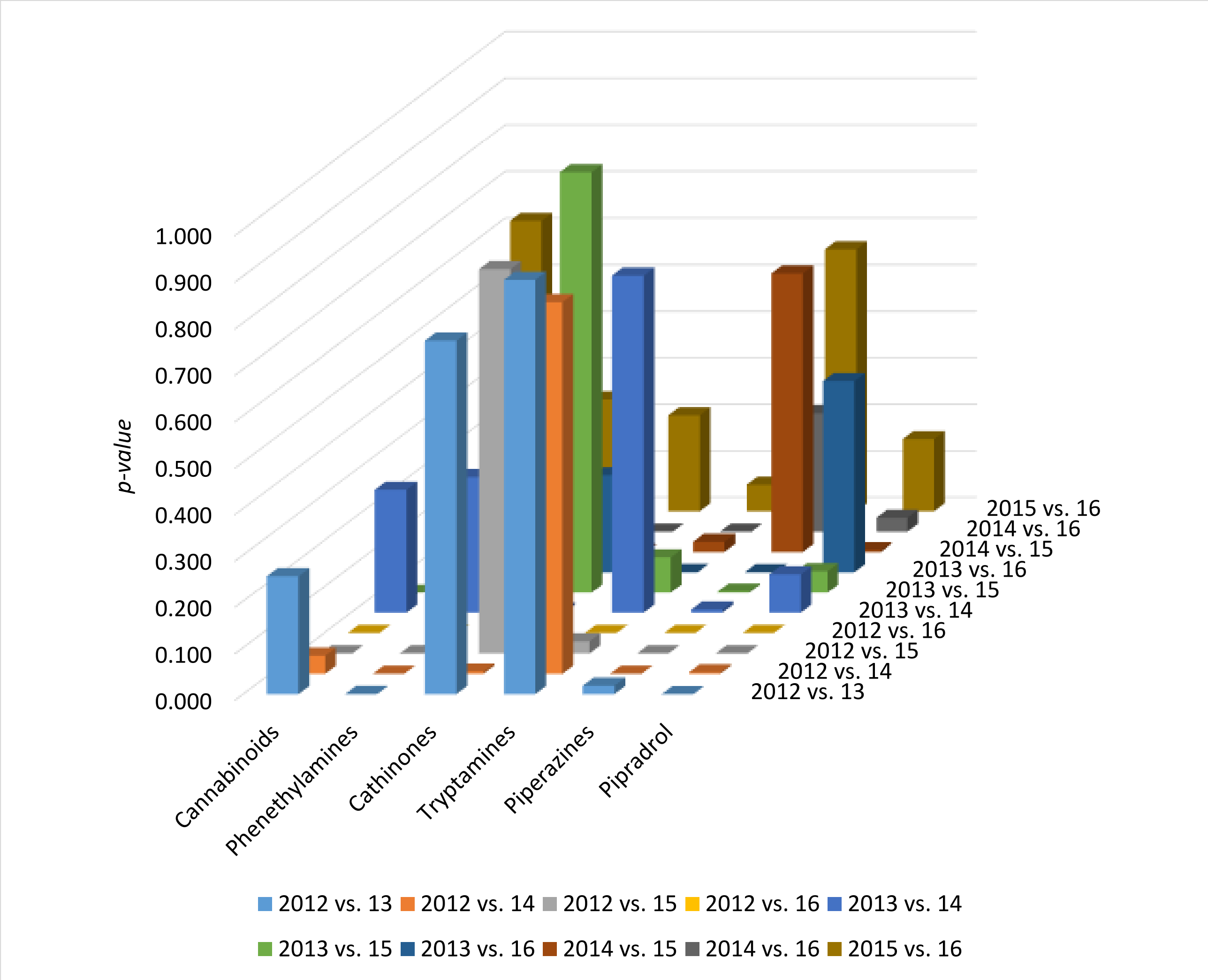


Figure 5. Change in Trends (2012-2016): Temporal Analysis for Major Chemical Categories (worldwide).

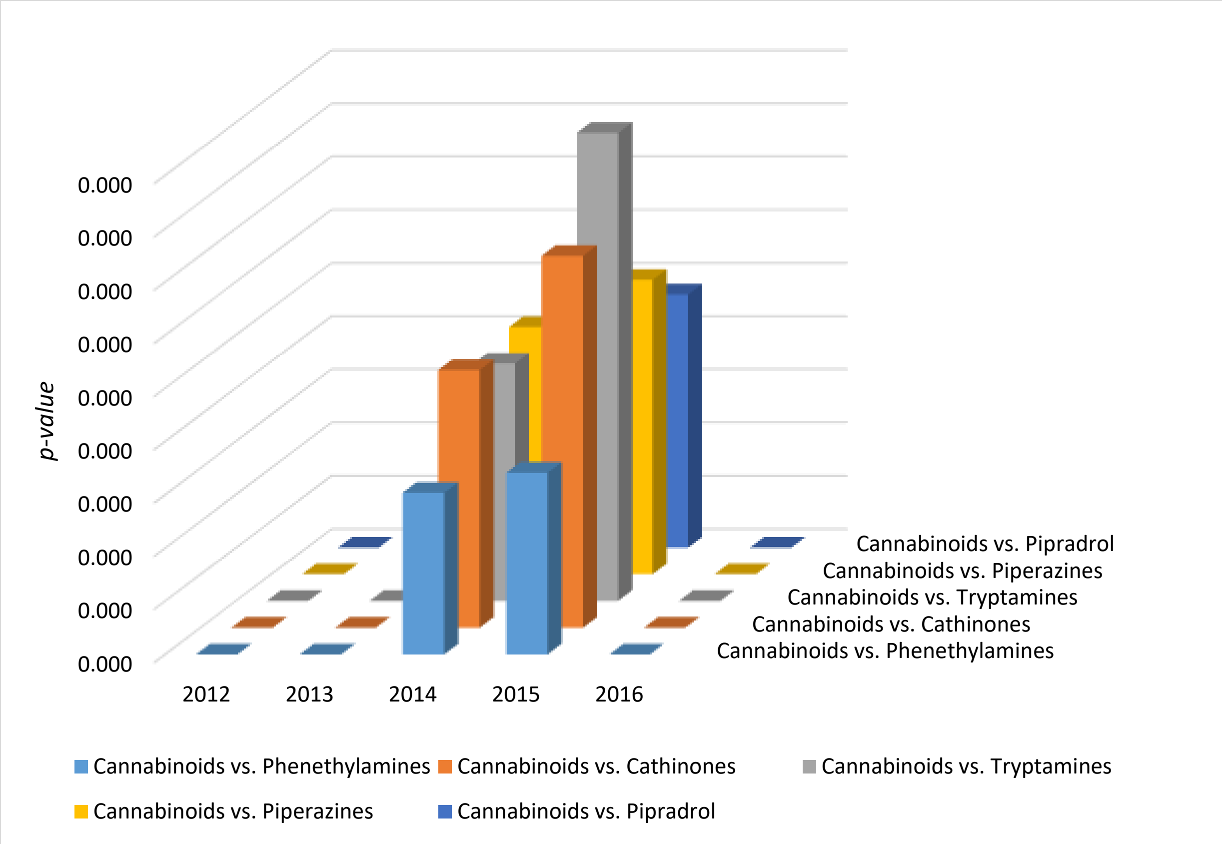


Figure 6. Inferential Statistics: Cannabinoids versus Other NPS Categories (worldwide).

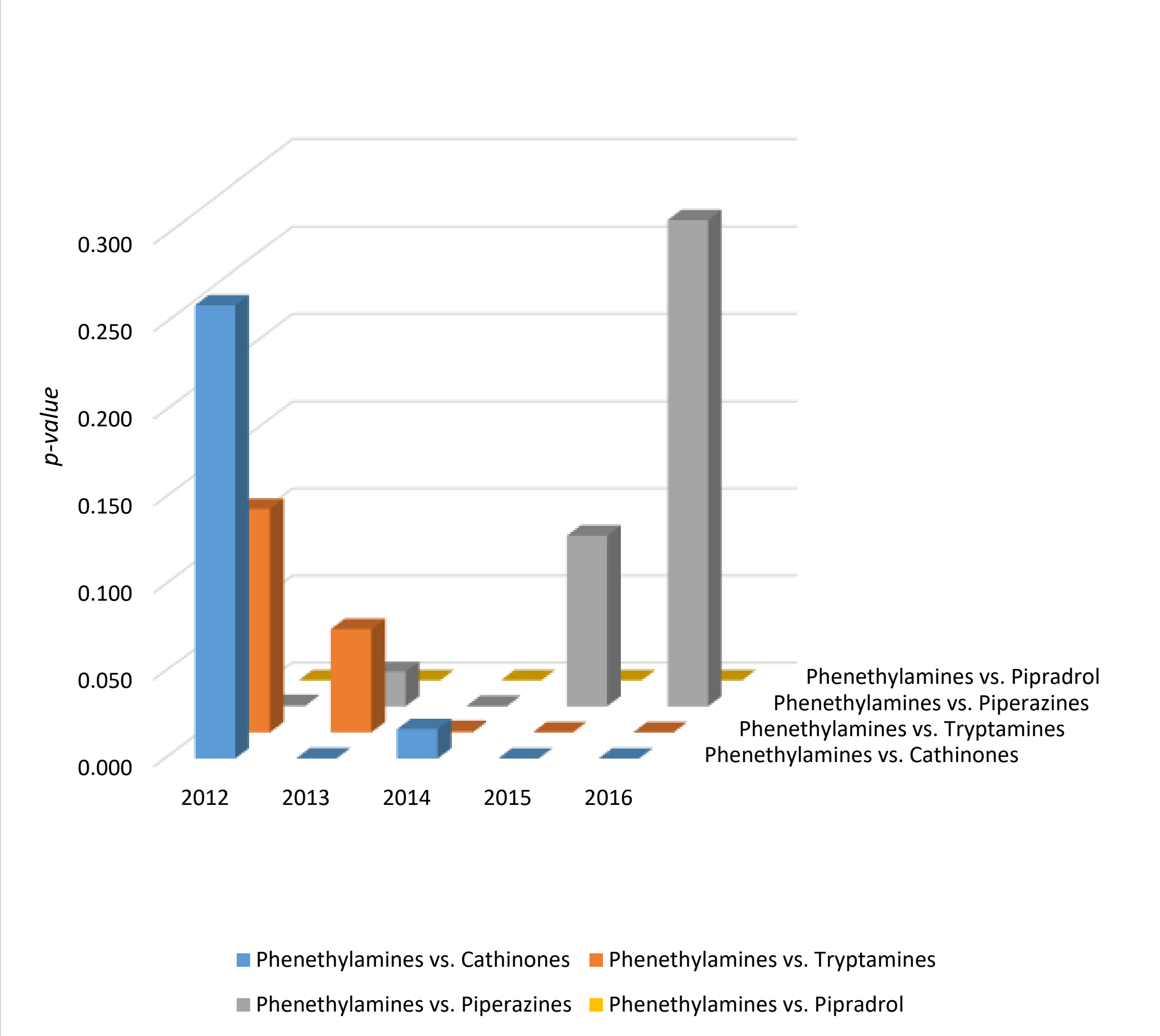


Figure 7. Inferential Statistics: Phenethylamines versus Other Categories of NPS (worldwide).

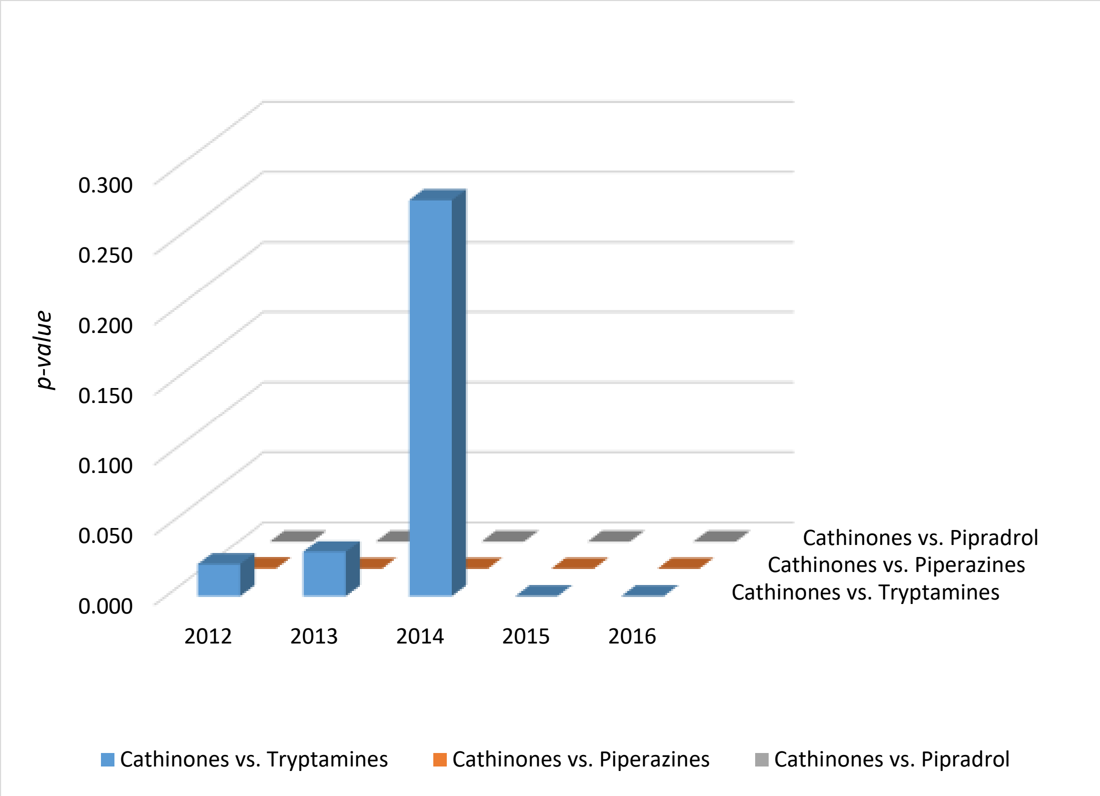


Figure 8. Inferential Statistics: Cathinones versus Other Categories of NPS (worldwide).

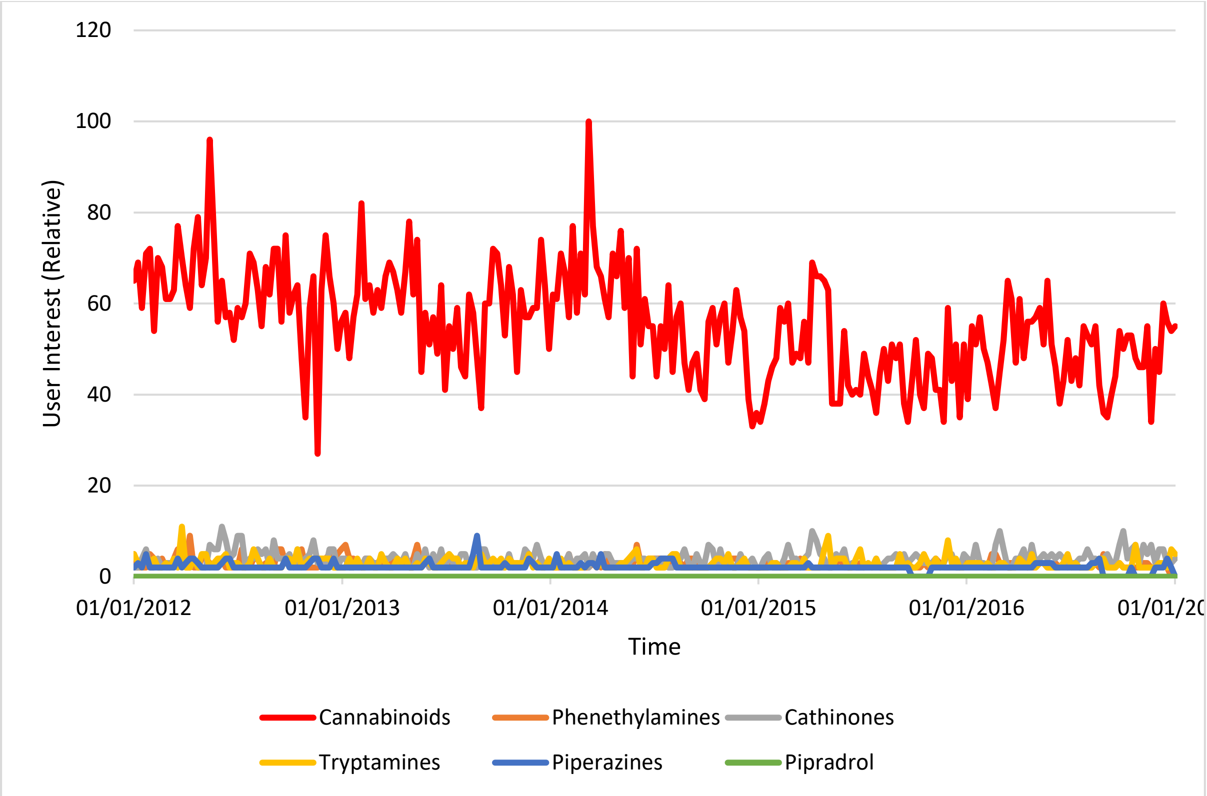


Figure 9. Google Trends (2012-2016): Major Chemical Categories of NPS (United States).

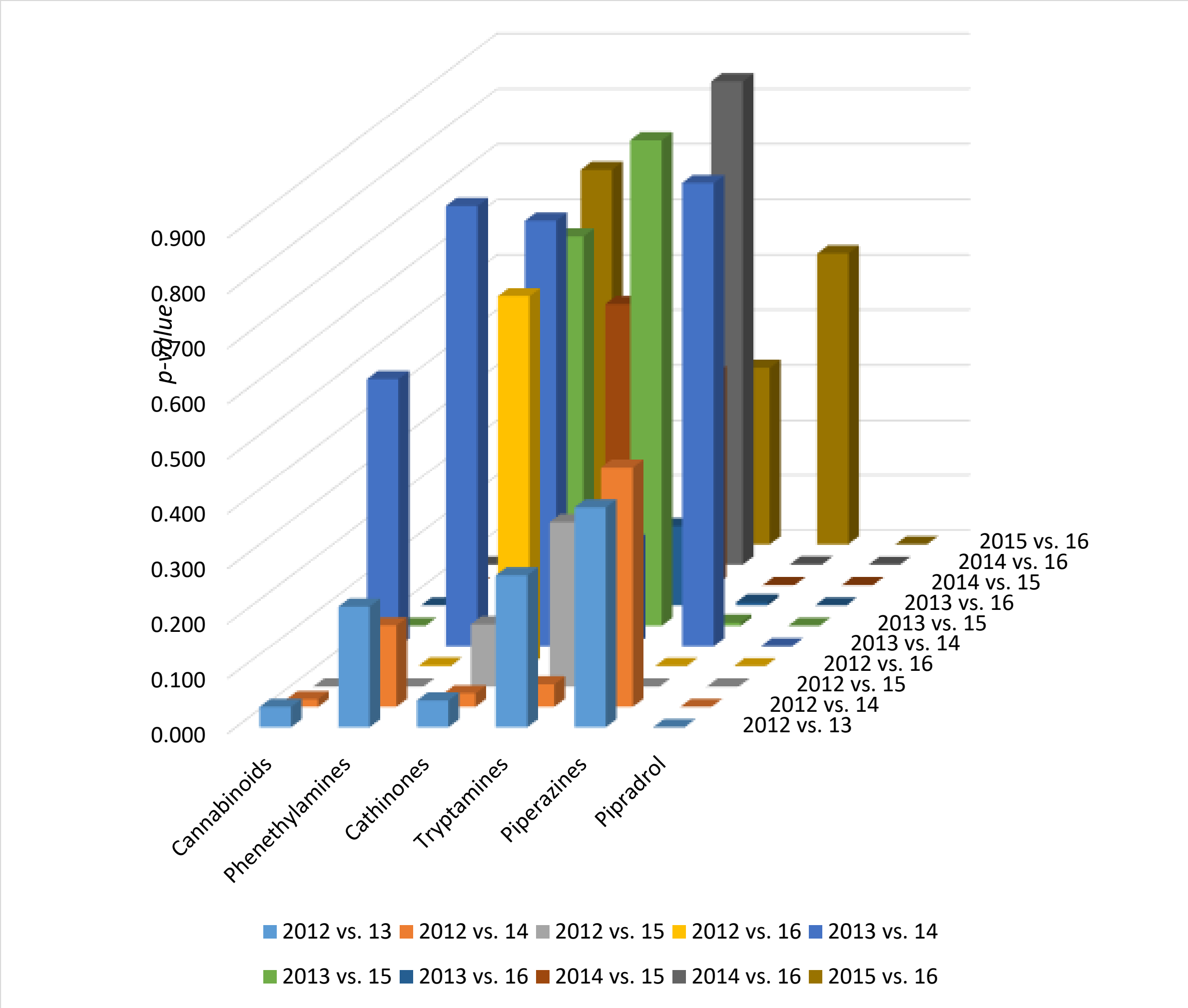


Figure 10. Inferential Statistics: Change in Trends (2012-2016) of the Major Chemical Categories of NPS (United States).

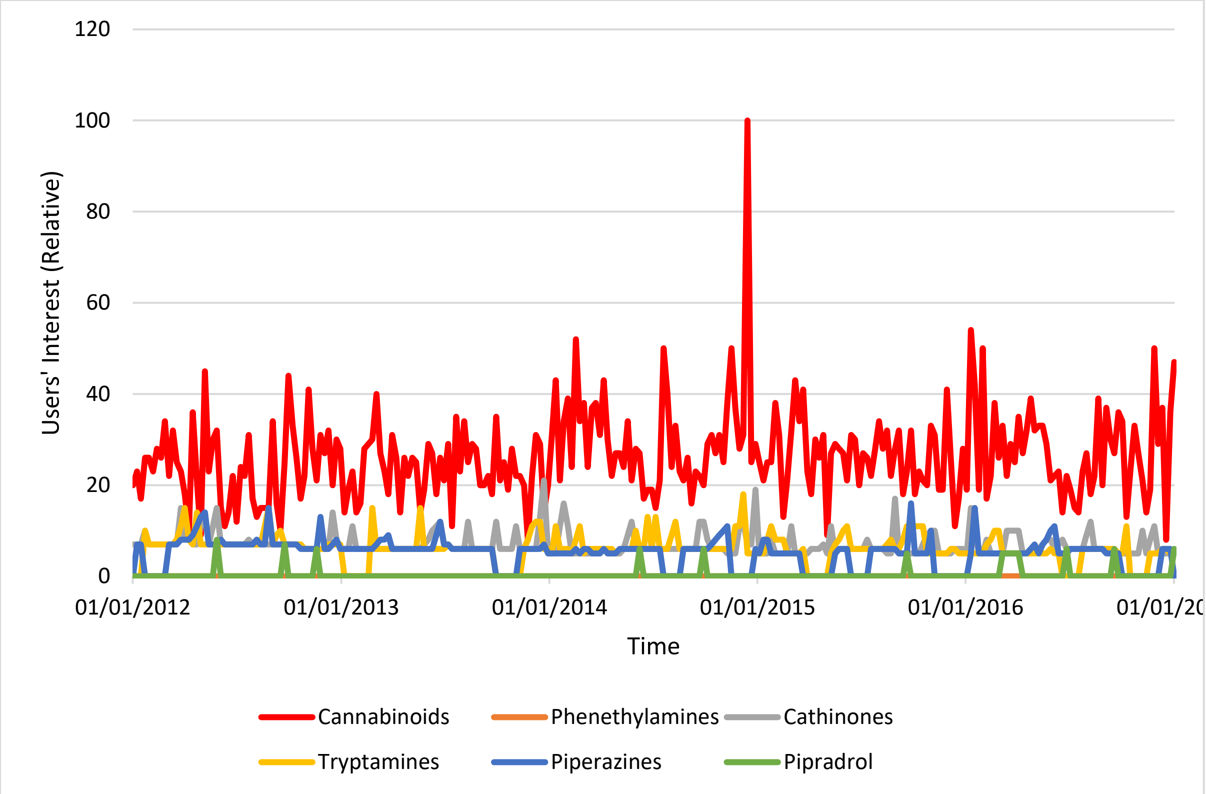


Figure 11. Google Trends (2012-2016): Interest in the Major Chemical Categories of NPS (United Kingdom).

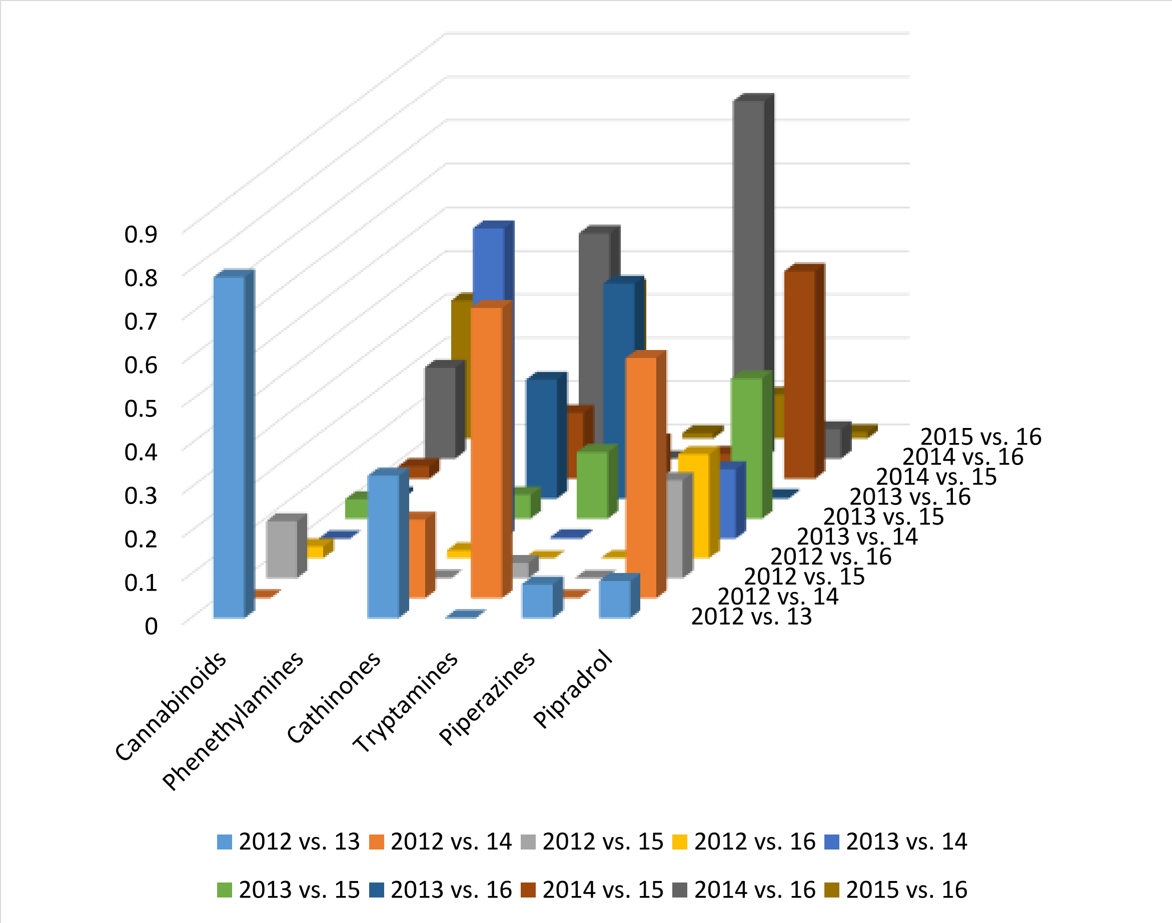


Figure 12: Inferential Statistics: Change in Trends (2012-2016) of the Major Chemical Categories of NPS (United Kingdom).

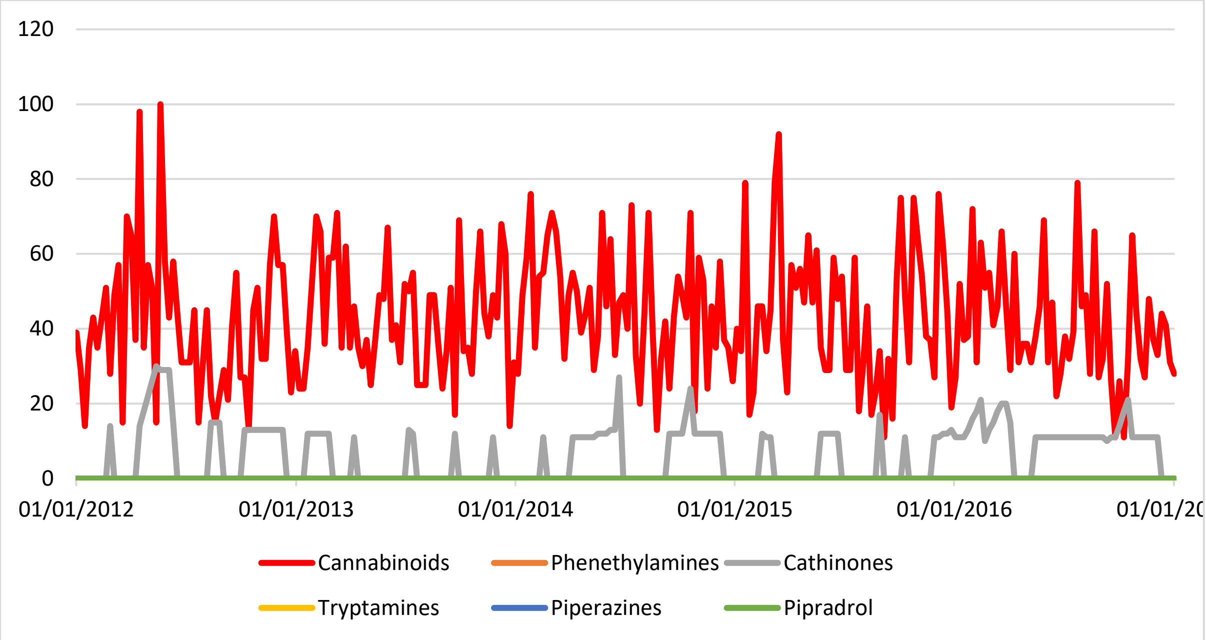


Figure 13. Google Trends (2012-2016): Interest in the Major Chemical Categories of NPS (Canada).

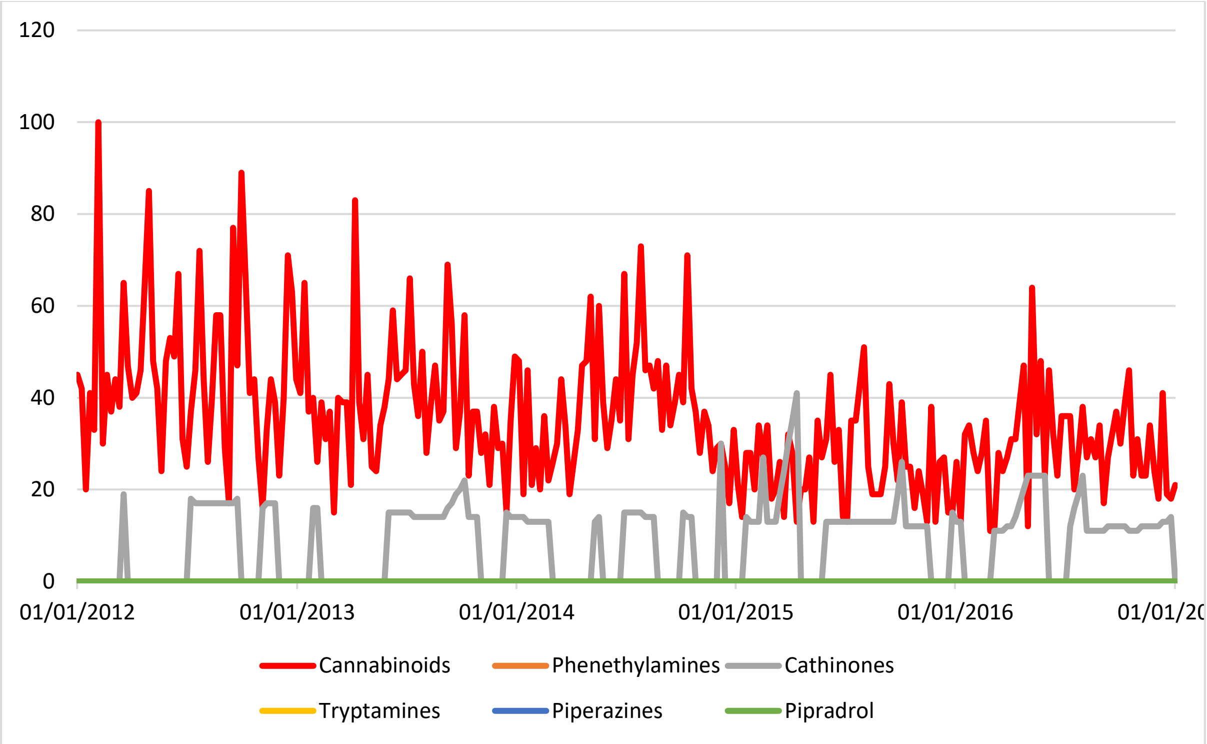


Figure 14. Google Trends (2012-2016): Interest in the Major Chemical Categories of NPS (Australia).

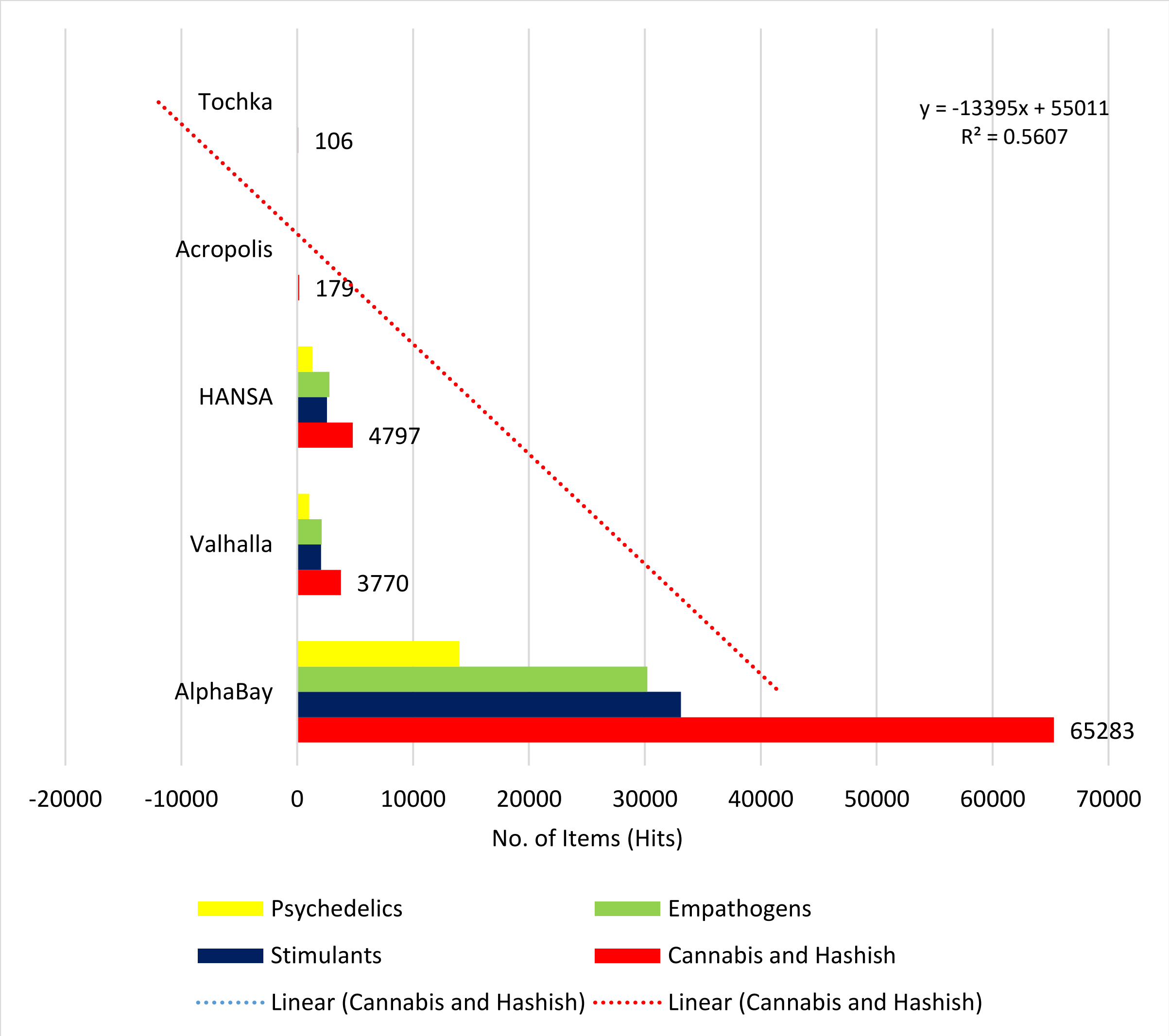


Figure 15. The Most Popular Chemical Categories of NPS on the e-marketplace of the Darknet.

The adopted classification system of NPS will be the same as found on the AlphaBay e-market, in which NPS are categorised into (Figure 1, Appendix 3); Dissociative substances (2%), Prescription-related and medicinal (5%), Psychedelics and Hallucinogens (7%), Benzodiazepines (8%), Opioids (9%), Empathogens (16%), Stimulants (18%), and Cannabis and Cannabinoids (35%). Apparently, cannabis and hashish, including cannabinoids and cannabimimetic, ranked 1st. The high popularity of cannabis and cannabinoids seems to be concordant with data already retrieved from Google Trends database. The internet (deep web) snapshot of AlphaBay e-market, made it possible to further analyse the advertised NPS in relation to risks and hazards which are represented by the incidents of intoxications and fatalities induced by NPS (ab)use all over the world. The majority of these incidents were found on in literature databases, including PubMed/Medline, and Erowid drug forum (Erowid, 2017). However, other drug fora have also contributed (Bluelight.org, 2016; Drugs-forum.com, 2016; Officialbenzofury.net, 2016; Reddit.com, 2016).

A total of 47 NPS substances were found to be advertised on AlphaBay (Figure 2 and 3), including; LSA, 2-FA, DMA/DOX, Topical and Others (of Cannabis and Hashish), Prerolls (of Cannabis and Hashish), MXE, Mescaline, MDA, Pressed Pills (Stimulants), Other RCs (Psychedelics), Methylone and BK, Synthetic (Cannabis and Hashish), Others (Dissociatives), Crack, Shakes (Cannabis and Hashish), GHB, RCs (Benzodiazepines), NBOMe, 2C-B, Seeds (Cannabis and Hashish), DMT, Powders (Benzodiazepines), Other RCs (Stimulants), Others (Psychedelics), Edibles (Cannabis and Hashish), Shrooms, Others (Benzodiazepines), Others (Empathogens), Ketamine (Dissociatives), Others (Opioids), Adderall and Vyvanse, Fentanyl and RCs (Opioids), Others (Stimulants), Heroin, Meth, Speed, Others (Cannabis and Hashish), Pills (Opioids), LSD, Concentrates (Cannabis and Hashish), Prescription, Pills (Empathogens), MDMA, Cocaine, Pills (Empathogens), and Buds and Flowers (Cannabis and Hashish).

Based on literature review and data retrieved from the drug fora, risky substances included nearly three dozens of NPS, including (ascending order of popularity); DMA/DOX, MXE, Mescaline, Methylone, Synthetic Cannabinoids, GHB, Benzodiazepines, NBOMe, 2C-B, DMT, Stimulants research chemicals (RCs), Shrooms, Ketamine, Opioids, Adderall and Vyvanse, Heroin, Meth, Speed, LSD, MDMA, and Cocaine and crack. Out of these, only 14 NPS will be analysed, via literature review and drug fora, for incidents of intoxications and deaths. It was found that these events can be categorised into; intoxication, chronic morbidity, near-death event, pharmacological fatality, behavioural fatality, suicide, automutilation, and homicide. Incidents reported from the region of the Middle East were absent except for; MDMA (Iran, Turkey, and Israel), DMT and Ayahuasca (Iran, and Turkey), and PCP

(Israel). The lack of reporting of incidents from the Middle East, represents either real (true positive) lack of incidents or under-reporting of incidents (false negative); it is very likely that the 2nd reason is the most plausible due to the lack of; professional training in the field of NPS and addictions, research facilities, diagnostic and therapeutic procedures relevant to the discipline of NPS (Al-Imam et al., 2016; Bigdeli et al., 2013; Wood et al., 2014). In fact, the level of reporting from Israel goes in compliance with this justification, as Israel is the most developed and technologically advanced country in the entire region of the Mediterranean sea.

The majority of the incidents took place in the developed world, particularly in the US, UK, Western Europe and Scandinavia including Germany and the Netherlands, Poland, Australia, Canada, and Japan. This goes in compliance with data extracted from Google Trends. There were also fewer reports from Latin (South) American and East Asia, including; MDMA (China), Psilocybin (Japan), Ketamine (China, Republic of Korea), DMT and Ayahuasca (Brazil, Colombia, and Peru), NBOMe (China), Methylone (Japan), 2C-B (Japan), and Adderall-Vyvanse (China). However, it seems that Meth-Speed (methamphetamine), is an NPS unique for East Asia; incidents were highly reported in China, Japan, Malaysia, and Thailand.

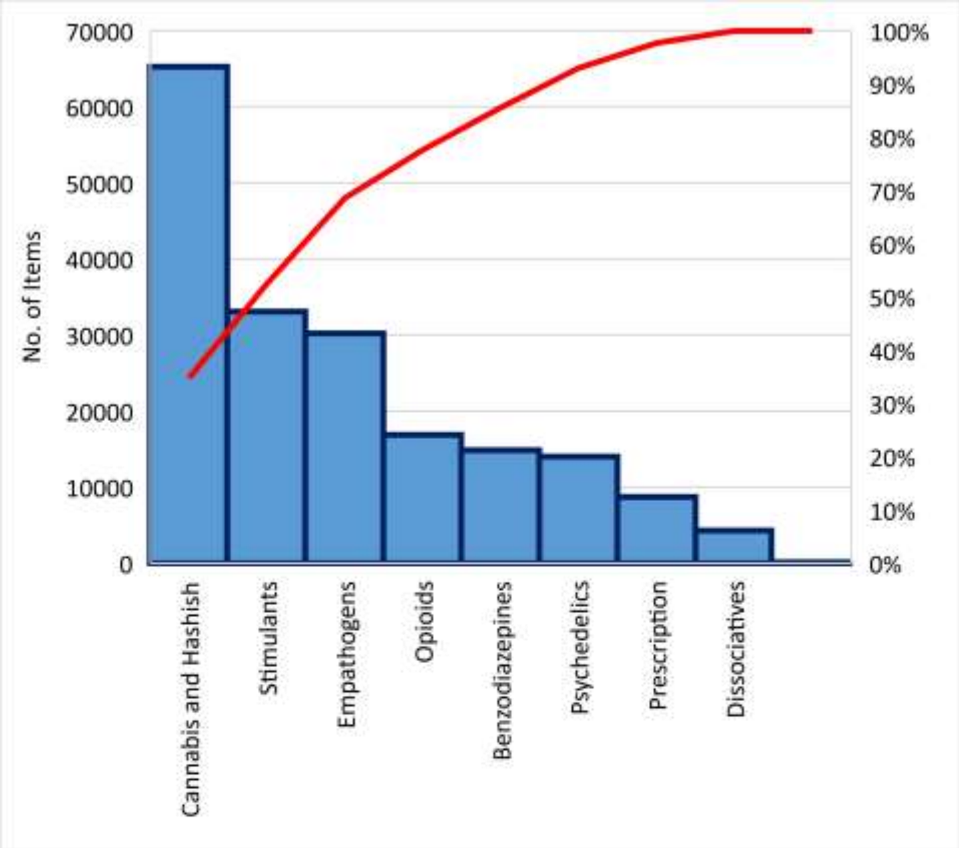
It is also apparent that the majority of these events were reported in male victims rather than females. In fact, almost two-thirds of incidents were reported in men; Most of the incidents were reported in the past ten years although some documented incidents may go back in time as far as the 1950s, as in the case of LSD (Table 1). In relation to age, the majority of victims were adults in the 2nd, 3rd, and 4th decades of life. However, exceptional case of extremes of age, pediatric or advanced age groups, also occurred in; LSD (US), MDMA (Iran, Slovenia, and Australia), Ketamine (US and UK), DMT and Ayahuasca (UK, Turkey, Netherlands, Czech Republic, and Peru), PCP (US and Israel), MXE (UK), GHB (France, Switzerland, US, and Italy), 2C-B (US), Adderall-Vyvanse (Japan), Meth-Speed (China, US, and Japan), and Mescaline-Peyote (US and Germany). These unique age groups of NPS incidents were also evident as statistical outliers on box plot presentation (Figure 4). Descriptive statistics were implemented to conclude the age groups (mean +/- standard deviation) for those risky NPS, these were; 25.3 +/- 3.2 (LSD), 23.8 +/-7.6 (MDMA), 22.7 +/- 6.9 (Psilocybin), 29.4 +/- 9.8 (Ketamine), 33 +/- 14.2 (DMT and Ayahuasca), 31.8 +/- 10.1 (PCP), 18.3 +/- 3.6 (NBOMe), 26.7 +/- 6.3 (DMA-DOB), 27.2 +/- 7.2 (Methylone), 28.6 +/- 15.3 (GHB), 27.5 +/- 8.7 (2C-B), 23.4 +/- 11.5 (Adderall-Vyvanse), 35.8 +/- 11.2 (Meth-Speed), and 24.4 +/- 10.7 (Mescaline-Peyote).

The descriptive statistics for age grouping are discrete enough to show substance-to-substance uniqueness in relation to incidents of intoxication and deaths. However, further inferential statistics were also applied using ANOVA test and t-test (Figure 5). The analysis of variance (ANOVA) revealed a significant difference at a *p-value*<0.001 among high-risk NPS. There seems to be a unique age group of incidents due to some high-risk NPS, these include; LSD, MDMA, Psilocybin, DMT, PCP, NBOMe, and Adderal. Analysis with Student's t-test (independent) showed a significant difference between; LSD and DMT (p-value=0.029), LSD and PCP (0.016), LSD and NBOMe (0.001), LSD and Meth (<0.001), MDMA and Ketamine (0.026), MDMA and DMT (0.008), MDMA and PCP (0.001), MDMA and NBOMe (<0.001), MDMA and MXE (0.032), MDMA and Meth (<0.001), Psilocybin and Ketamine (0.015), Psilocybin and DMT (0.005), Psilocybin and PCP (0.001), Psilocybin and NBOMe (0.012), Psilocybin and MXE (0.020), Psilocybin and Meth (<0.001), Ketamine and NBOMe (<0.001), Ketamine and Methylone (0.032), Ketamine and Meth (0.021), DMT and NBOMe (<0.001), DMT and Methylone (0.009), DMT and Adderal (0.047), PCP and NBOMe (<0.001), PCP and DMA (0.075), PCP and MXE (0.041), PCP and Methylone (0.005), PCP and Adderal (0.005), NBOMe and DMA (0.010), NBOMe and MXE (<0.001), NBOMe and Methylone (0.002), NBOMe and GHB (0.003), NBOMe and 2C-B (0.024), NBOMe and Meth (<0.001), DMA and Meth (0.001), MXE and Meth (<0.001), Methylone and Meth (<0.001), GHB and Meth (0.033), 2C-B and Meth (0.036), Adderal and Meth (0.010).

It seems that these incidents of intoxications and death were highly reported in relation to psychedelics (Hallucinogens). Therefore, additional analyses were implemented based on data retrieved from Google Trends (Figure 6 to 8) for the period from the beginning of 2012 to the end of 2016. The analysis included the most popular psychedelics including; Lysergic acid diethylamide (LSD), MDMA, Psilocybin, Phencyclidine (PCP), Ketamine, N,N-Dimethyltryptamine, Dextromethorphan, Peyote, Ayahuasca, Salvia divinorum, Ergine, NBOMe, AL-LAD, alpha-Methyltryptamine, 2,5-Dimethoxy-4-bromoamphetamine, and TMA-6 (Dargan, 2013; Psychedelic.com, 2017). Based on ANOVA test, there has been a significant difference (*p-value*<0.001) in relation to the popularity of all these psychedelics among users of the surface web. Hence, statistical testing with Student's t-test (paired) was implemented. The trends were highly oscillating, there was no specific pattern, apart from increments in the trends during the holidays in developed countries, specifically; Christmas and the New Year (Bellis et al., 2007; Halpern and Mechem, 2001; Lai et al., 2013). LSD (1st rank) and MDMA (2nd rank) appeared to be the most popular psychedelics on the surface web, while Psilocybin, Phencyclidine, Ketamine, and N,N-Dimethyltryptamine seemed to be of equal popularity. Geographic mapping (Figure 9) as accessible from Trends database, it revealed that these substances were highly sought out by developed countries. Top ten countries were; Australia (1st), Canada (2nd), United States, (3rd), United Kingdom, New Zealand, Ireland, Norway, Netherlands, Switzerland, and Estonia. The Middle East accounted for a minute fragment of 3% only. Middle Eastern countries and Arabic countries included (descending order); Israel (1st), Iran (2nd), Morocco, UAE, Turkey, Egypt, and Saudi Arabia.

Table 1. A Summary of LSD Incidents of Intoxications and Deaths (1956-2017).

<table>
<tr><th></th><th>Date</th><th>Gender</th><th>Age</th><th>Location</th><th>Number of Death</th><th>Outcome</th></tr>
<tr><td>1</td><td>1985</td><td>M</td><td>25</td><td>UK</td><td>1</td><td>Pharmacological?</td></tr>
<tr><td>2</td><td>1977</td><td>M</td><td>34</td><td>US</td><td>1</td><td>Pharmacological?</td></tr>
<tr><td rowspan="8">3</td><td rowspan="8">1972</td><td rowspan="4">F</td><td>20</td><td rowspan="8">US</td><td rowspan="8">8</td><td rowspan="8">Near-death, Pharmacological</td></tr>
<tr><td>19</td></tr>
<tr><td>28</td></tr>
<tr><td>33</td></tr>
<tr><td rowspan="4">M</td><td>39</td></tr>
<tr><td>29</td></tr>
<tr><td>28</td></tr>
<tr><td>28</td></tr>
<tr><td>4</td><td>1969</td><td>F</td><td>20</td><td>US</td><td>1</td><td>Suicide?</td></tr>
<tr><td>5</td><td>1953</td><td>M</td><td>43</td><td>US</td><td>1</td><td>Homicide (CIA assassination), suicide?</td></tr>
<tr><td rowspan="5">6</td><td rowspan="5">-1967</td><td rowspan="5">M, F</td><td rowspan="5">Not documented (ND)</td><td rowspan="5">US and Canada</td><td>19</td><td>Attempted suicide</td></tr>
<tr><td>4</td><td>Attempted homicide</td></tr>
<tr><td>11</td><td>Successful suicide</td></tr>
<tr><td>1</td><td>Successful homicide</td></tr>
<tr><td>9</td><td>Suicidal intentions</td></tr>
<tr><td rowspan="2">7</td><td>1956</td><td rowspan="2">ND</td><td rowspan="2">ND</td><td rowspan="2">US</td><td rowspan="2">2</td><td rowspan="2">Psychotherapy-induced suicide</td></tr>
<tr><td>1957</td></tr>
<tr><td>8</td><td>1988</td><td>M</td><td>14</td><td>Canada</td><td>1</td><td rowspan="6">Behavioural fatality</td></tr>
<tr><td>9</td><td>1989</td><td>M</td><td>18</td><td>US</td><td>1</td></tr>
<tr><td>10</td><td>2002</td><td>M</td><td>16</td><td>UK</td><td>1</td></tr>
<tr><td>11</td><td>2008</td><td>M</td><td>17</td><td>US</td><td>1</td></tr>
<tr><td>12</td><td>2007</td><td>M</td><td>26</td><td>US</td><td>1</td></tr>
<tr><td>13</td><td>2007</td><td>M</td><td>19</td><td>US</td><td>1</td></tr>
</table>



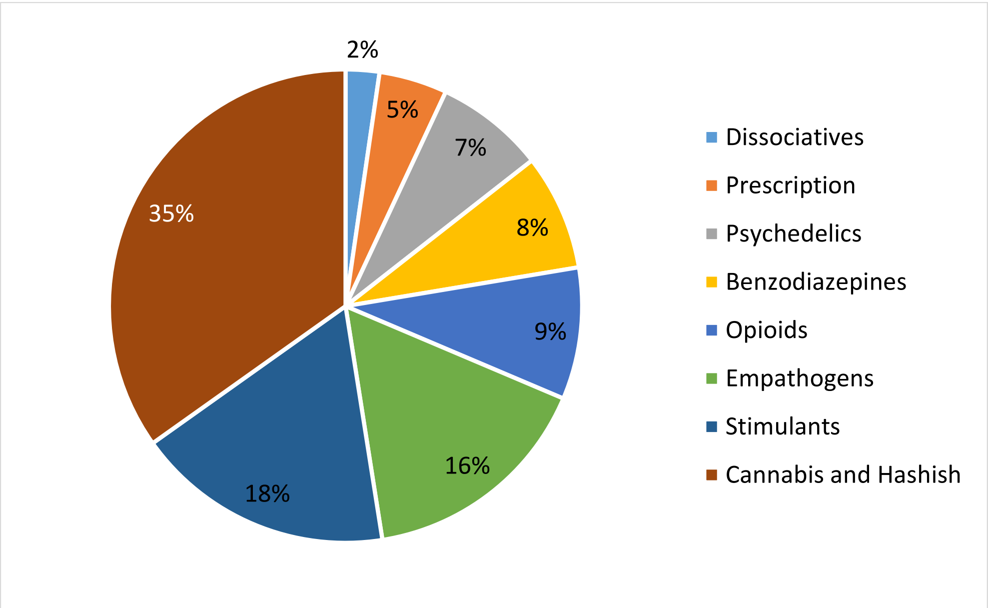


Figure 1. The Most Popular Categories of NPS on AlphaBay e-market on the Deep Web.

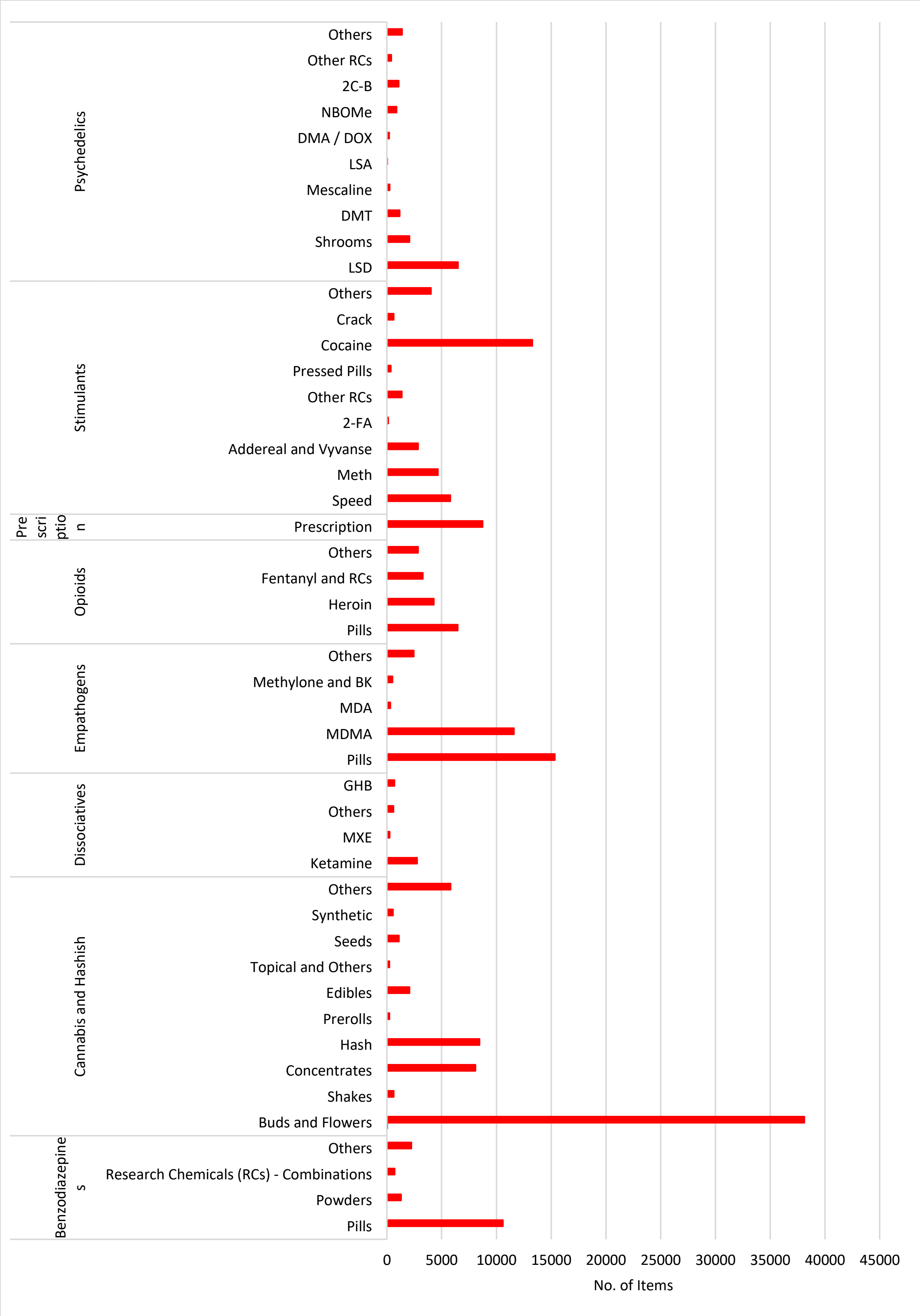


Figure 2. The Most Popular Psychoactive and Novel Psychoactive Substances on AlphaBay e-market.

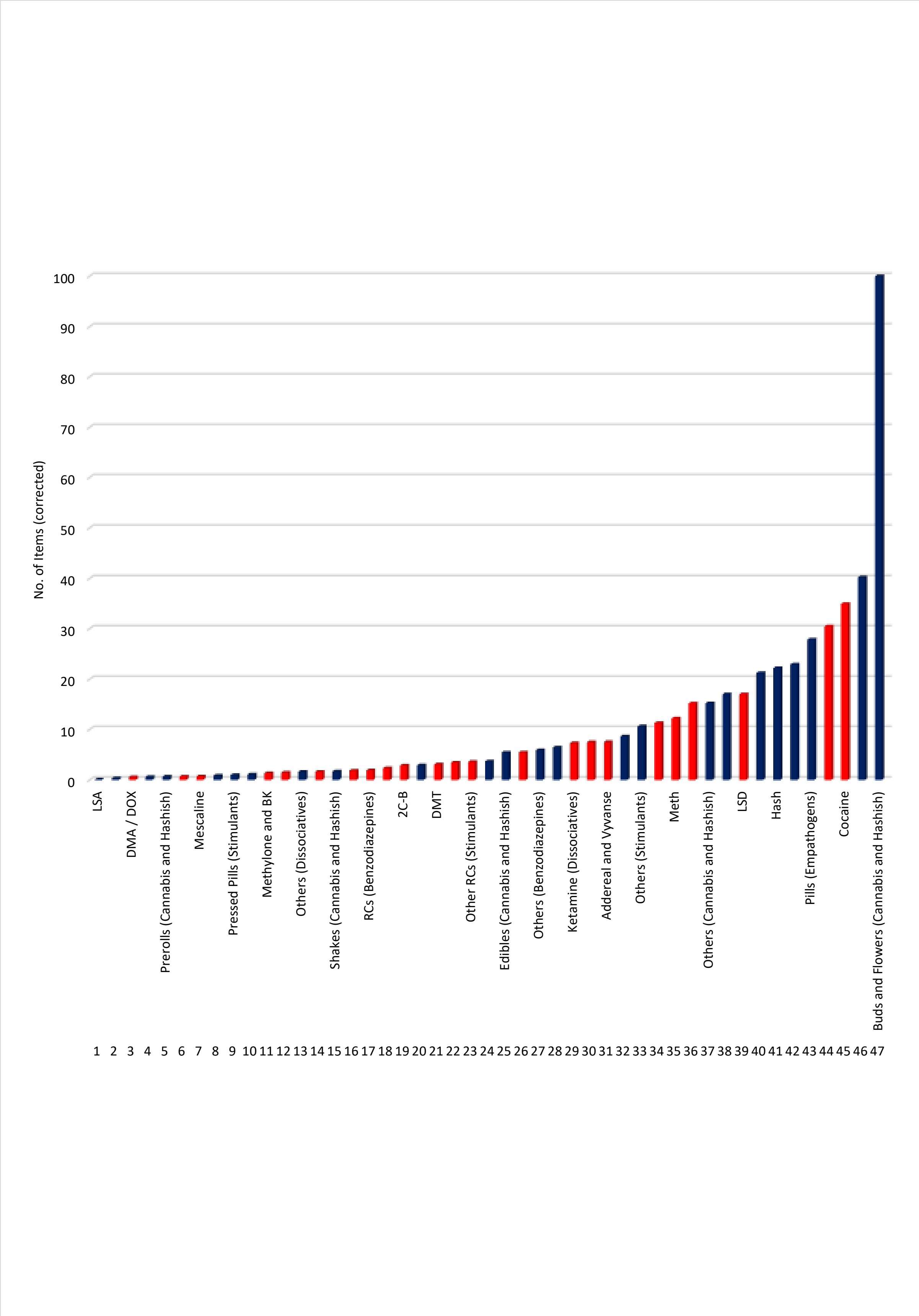


Figure 3. The Most Popular Psychoactive and Novel Psychoactive Substances on AlphaBay: High-risk Substances are Color-coded as Red.

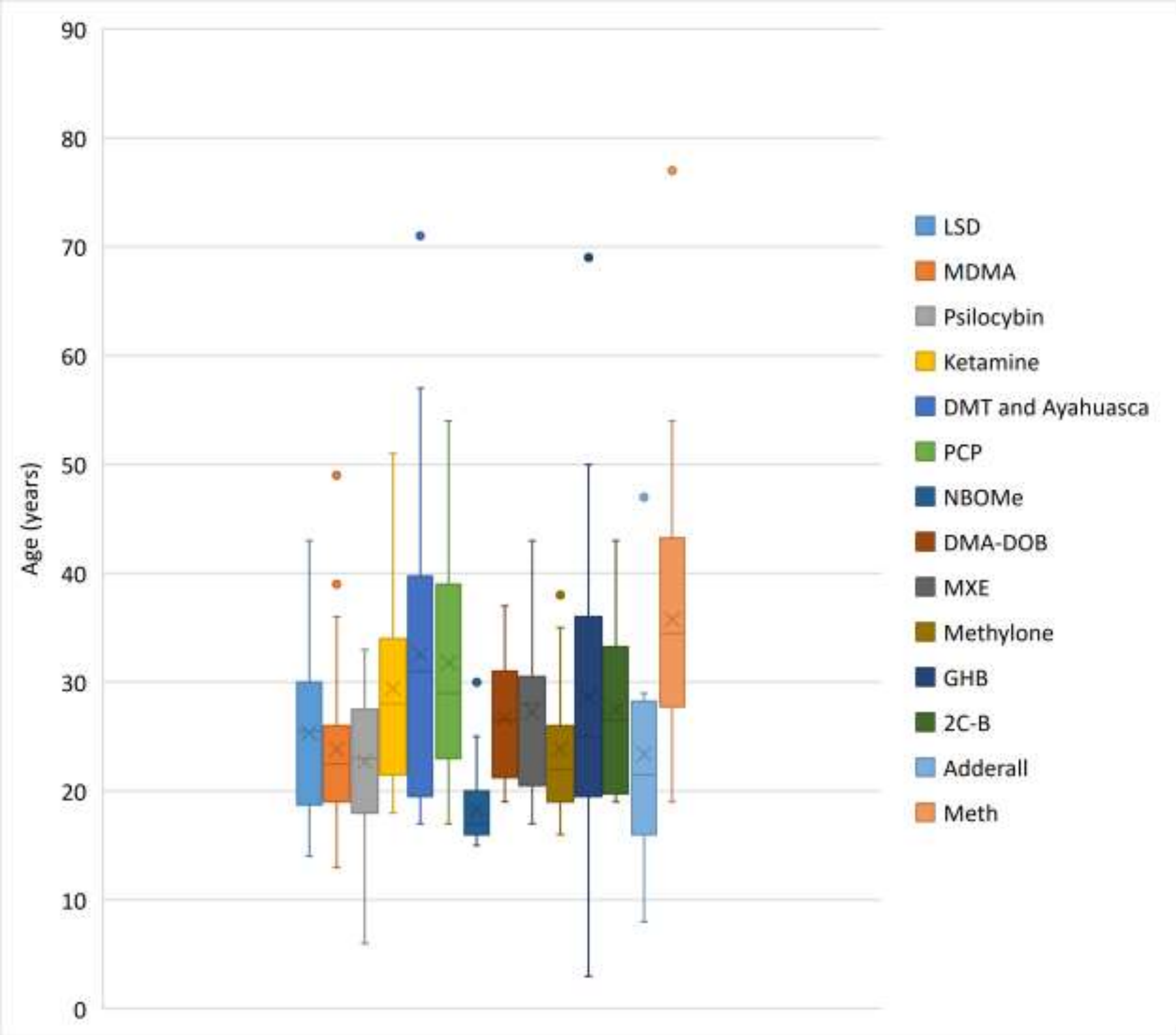


Figure 4. Boxplot Presentation: Age of Victims of Incidents in Connection with 14 NPS Substances of High-risk of Intoxication and Death.

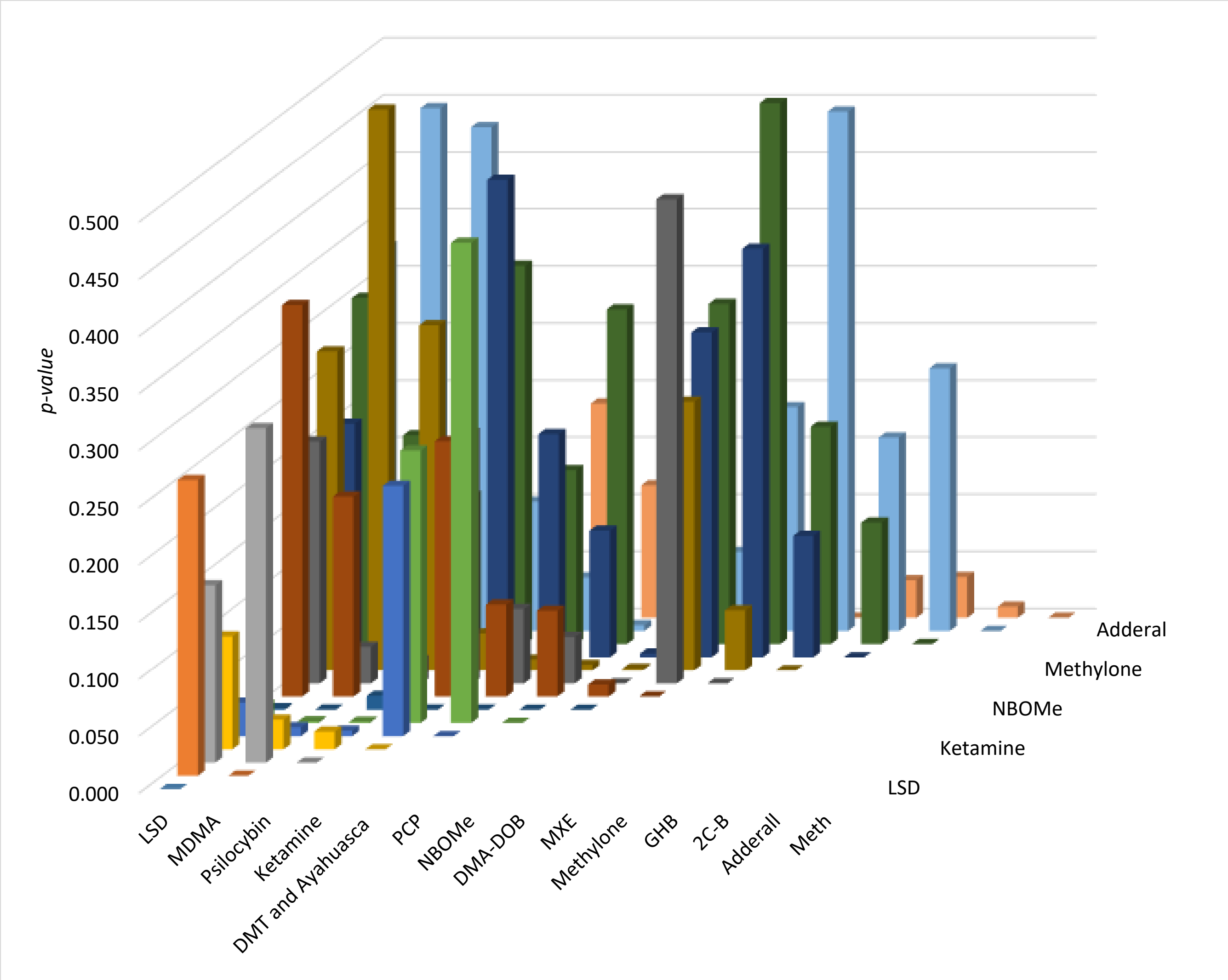


Figure 5. Inferential Statistics (Independent t-test): Age of Victims of Incidents in Connection with 14 NPS Substances of High-risk of Intoxication and Death.

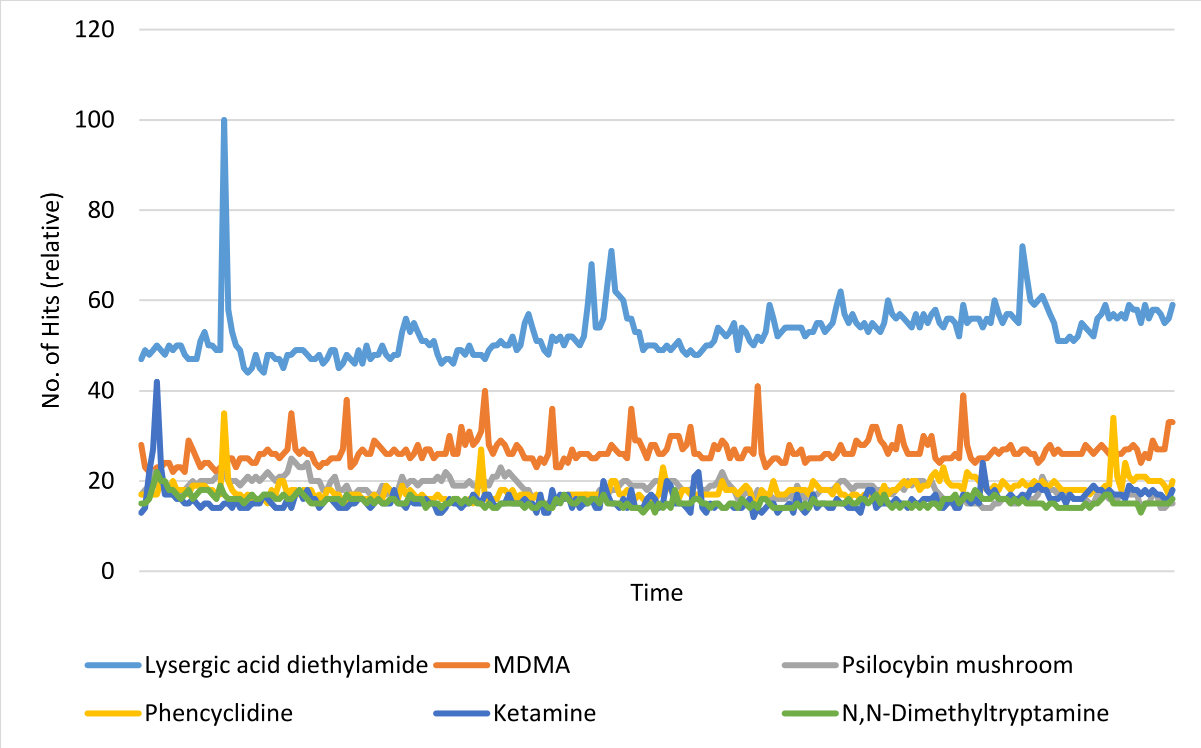


Figure 6. Google Trends of Psychedelics (2012-2016): Lysergic acid diethylamide, MDMA, Psilocybin, Phencyclidine, Ketamine, and N,N-Dimethyltryptamine.

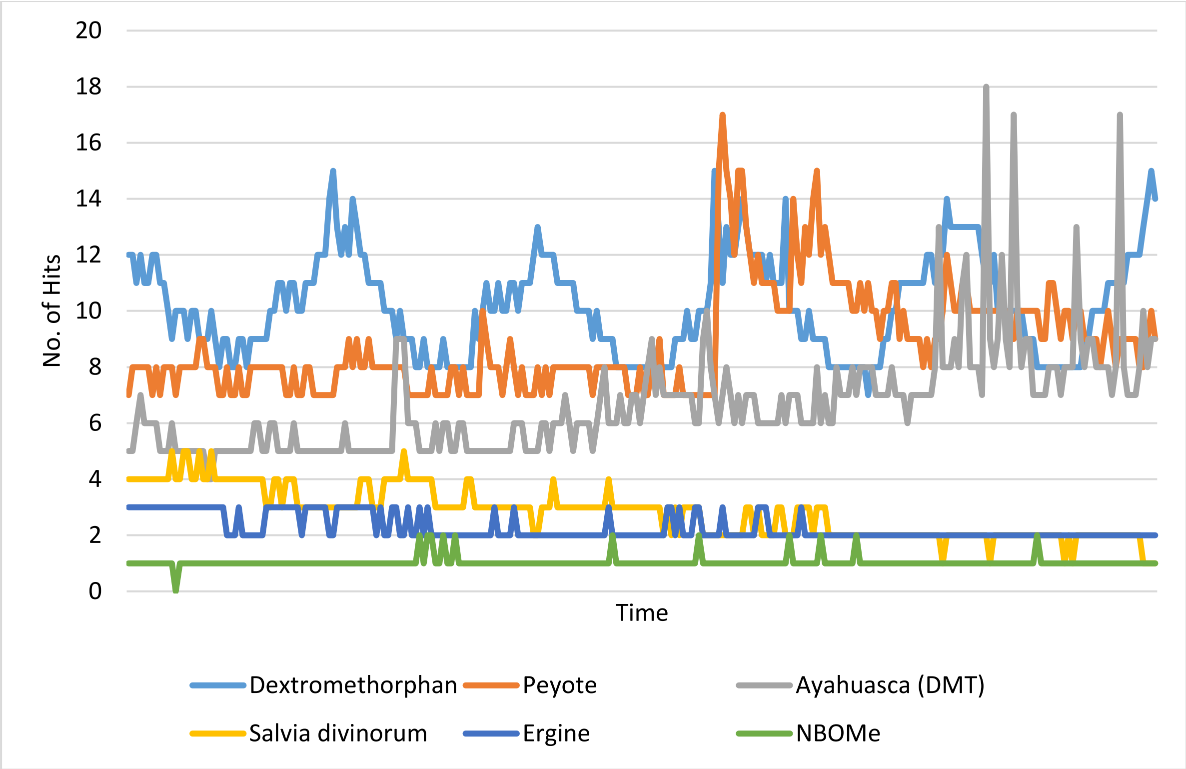


Figure 7. Google Trends of Psychedelics (2012-2016): Dextromethorphan, Peyote, Ayahuasca, Salvia divinorum, Ergine, and NBOMe.

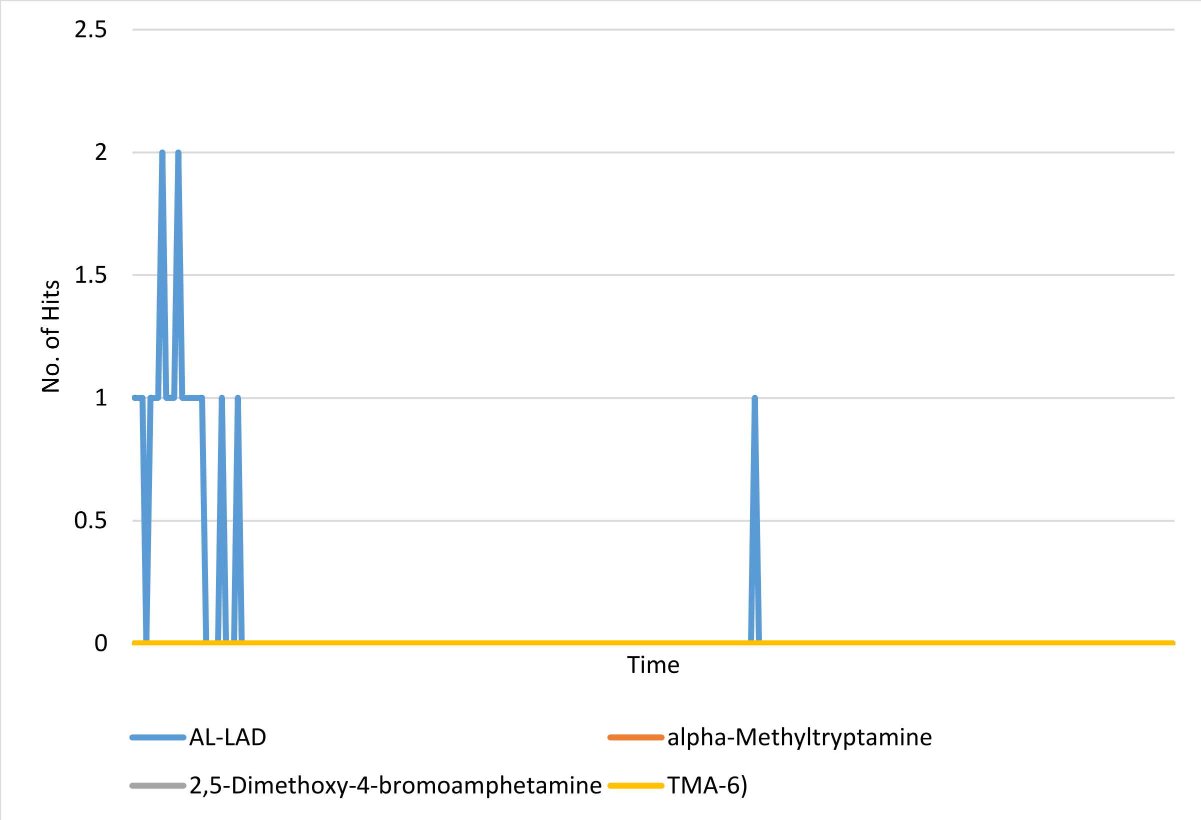


Figure 8. Google Trends of Psychedelics (2012-2016): AL-LAD, alpha-Methyltryptamine, 2,5-Dimethoxy-4-bromoamphetamine, and TMA-6.

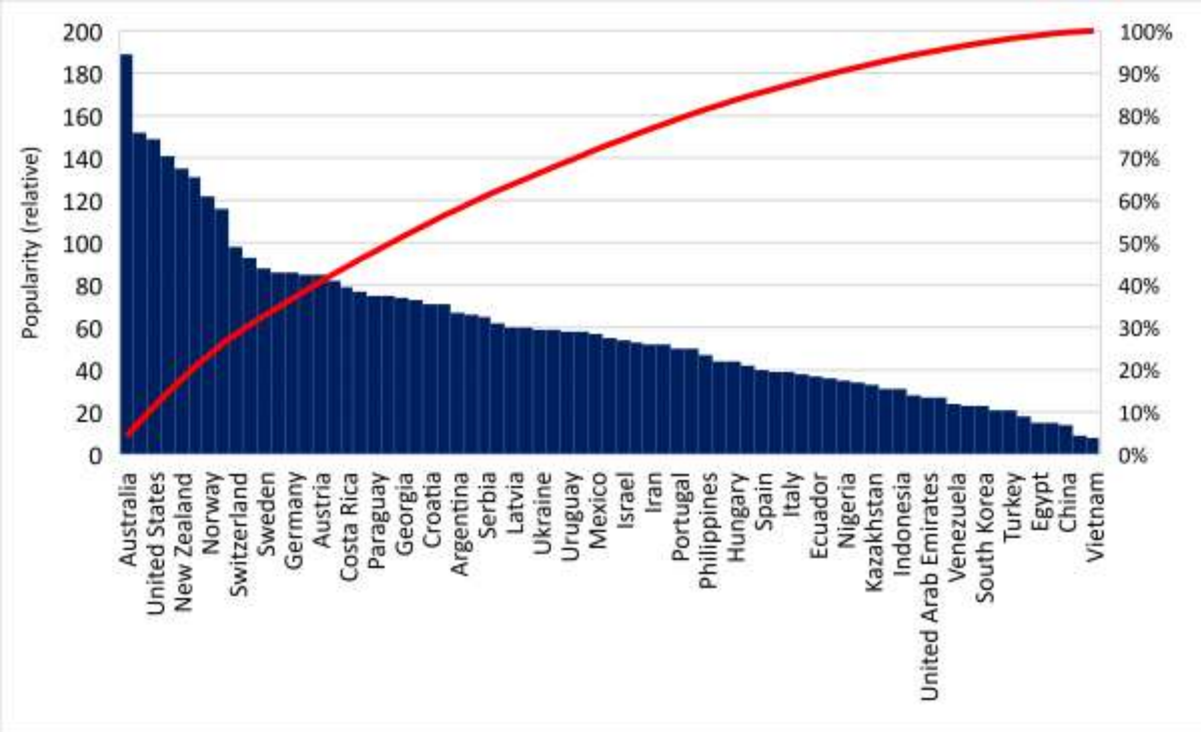


Figure 9. Google Trends: International Geo-mapping of the Most Popular Psychedelics (2012-2016).

Analyses of Google Trends database appears to be steady to some degree (Figure 1) with an exception for the keyword *Bitcoin*; attentiveness to this keyword seems to escalate during 2013-2014, it was noticed specifically in; March-April 2013, October 2013-March 2014, and December 2016-January 2017. The highest peak for *Bitcoin* was reached in November 2013 (Figure 1). Descriptive statistics (Table 1, Figure 2) clearly shows that the surface web users are highly interested in two main keywords; *Tor* (17.7 +/- 2.1) and *Bitcoin* (17.5 +/- 14.9), while the other keywords averaged; *Deep web* (5.9 +/- 2.7), *Darknet* (0.9 +/- 1), and *Bitcoin network* (1.3 +/- 1.5).

The attentiveness towards the keyword *Bitcoin network* was noticed to be synchronised with the attentiveness towards *Bitcoin* keyword; both keywords peaked at the end of November 2013. It is important to know that In October 2013, the Chinese *Baidu* search engine allowed its users to implement the *Bitcoin payment system*. Furthermore, in November, it was estimated that approximately 12 million bitcoins were mined in e-payments, and remarkably by the 23rd of November 2013, the total market of bitcoins in the United States has exceeded 10 billion US dollars (Chang G, 2013; Fensch J, 2014; Hendrickson et al., 2015). On the other hand, attentiveness towards the keyword *Deep web* escalated from May till November 2015; it reached a peak in August 2015. The other two keywords, *Darknet* and *Tor*, appears to more steady; the keyword *Darknet* was found to be of the least importance for surface web users. The soaring attentiveness of surface web users in particular keywords (*Tor*, *Bitcoin*, and *Deep web*) was also validated (confirmed) via Boxplot presentation (Figure 2); statistical outliers are also evident in relation to the keyword *Bitcoin*.

ANOVA test showed a significant difference (*p-value*<0.001) in relation to the attentiveness of surface web users for the five keywords for the period 2012-2016. Independent t-test (Figure 3) showed that both *Tor* and *Bitcoin* Keywords were of comparable popularity (17.7 versus 17.5, p=0.419) for the period 2012-2016. However, the attentiveness of surface web users to the keyword *Deep web w*as significantly less than that of; *Tor* (5.9 versus 17.7, p<0.001) and *Bitcoin* (5.9 versus 17.5, p<0.001). On the other hand the chronological (historical) analysis of the mapped keywords, confirmed the presence of significant changes in 2013 and 2015 (p<0.001) as seen in Figure 3, while no major shifts in the trends for the keywords between; 2013 and 2014 (0.158), 2013 and 2015 (0.422), and 2014 and 2016 (0.274).

Geo-mapping of the keywords showed the contribution of five countries was phenomenal (statistical outliers), these countries are (descending order); Bangladesh, Norway, Germany, Denmark, and Ghana (Figure 4). Other top contributing countries included; Austria, Nigeria, Sweden, Pakistan, Switzerland, Finland, Netherlands, Bolivia, Poland, the Czech Republic, US, UK, and Canada.

Apparently, Bangladesh and some African countries are in the top of the list; this has been attributed to the ban of social media networks in those countries leading to the use of the anonymous web as an alternative “hacking” solution to gain access to the social communication media, including Facebook and Twitter (Aliens, 2017).

Middle Eastern and Arabic countries included (descending order); Syria, Iran, UAE, Israel, Algeria, Morocco, Saudi Arabia, and Egypt (Figure 4). This contribution represented a tiny fragment (7.1%) of the global geo-mapping. Concerning the geo-mapped countries, linear regression (Figure 5) showed a positive linear correlation between two keywords *Tor* and *Bitcoin* (R^2 *score*=0.044), which has further confirmed that the trends of these two keywords are synchronised and in harmony for the period 2012-2016. On the other hand, there has been some degree of negative correlation between *Tor* keyword and; *Bitcoin* network (0.016) and *Darknet* (0.044).

A comparison was also set between countries from the European Union to infer the presence of significant differences, and Norway was an apparent statistical outlier. Student’s t-test (independent) was used for statistical inference (Figure 6). Accordingly, there were obvious (significant) differences, the Middle East contributed much less (*p-value*<0.001) than countries from the EU. Hence, the attentiveness of EU surface web users was the highest in relation to the mapped keywords for the period 2012-2016. Norway (rank 1st) and Germany (2nd rank) were the top contributing country from the EU (Figure 7).

On the darknet, fifteen (n=15) main e-markets have been identified; AlphaBay, Agora, Nucleus Market, Abraxas, HANSA, Middle Earth, Darknet Hero League, Outlaw Market, Majestic Garden, Silkkitie, Oasis, Real Deal Market, Tochka Market, Oxygen, and Arsenal (Google, 2017). The power score analysis (Appendix 4) showed two outliers (exceptionally popular) e-markets; AlphaBay and Agora (Figure 8). It seems that AlphaBay is the principal market on the darknet. Descriptive Statistics (Table 2, Figure 9) obviously visualise that the top three e-markets (AlphaBay, Agora, and Nucleus Market) are in the lead with a big gap over other e-markets.

Inferential analysis, using linear regression, shows a positive linear correlation between; power score and the number of votes (R^2 *score*=0.961), overall rating and support rating for each e-market (R^2 *score*=0.549). Furthermore, the *power score* was rearranged in descending order to allow the analysis (independent t-test) of high versus low-power e-markets. Initially, a comparison was made between the top seven markets and the remaining eight e-markets (Figure 10), which showed a clear leverage of the top seven e-markets (p-*value*=0.006). Even when comparing the 1st two e-markets versus the remaining thirteen e-markets, AlphaBay and Agora were still proven superior (p=0.018).

The final analytic step is to pick five e-markets from the darknet and perform an observational analysis of the advertised NPS (Figure 11 and 12). A *random number generator* was used, the five e-markets were; AlphaBay, Valhalla, HANSA, Acropolis and Tochka. The randomization in selection aims to prevent selection biases and to assess the heterogeneity of advertised NPS at e-markets of different power-scoring. The Internet snapshot was taken on the 25th of February 2017. Categories of NPS found on AlphaBay were; Benzodiazepine (14860 items), Cannabis and Hashish (65275), Dissociatives (4319), Ecstasy (30207), Opioids (16889), Prescription (8736), Stimulants (33098), and Psychedelics (14007). Valhalla categorised the NPS as; Cannabis and Hashish (3917), Stimulants (2266), Empathogens (2108), Psychedelics (1065), Opioids (944), Prescription (1766), Dissociatives (258), and Depressants (53). HANSA e-market advertised NPS as; Cannabis and Hashish (4796), Opioids (535), Psychedelics (1313), Prescription (1345), Stimulants (2582), Ecstasy (2780), Benzodiazepine (730), and Dissociatives (360). On the other hand Acropolis e-market adopted a bit different categorization system; Benzodiazepine (3), Cannabis and Hashish (186), Dissociatives (6), Ecstasy (52), Opioids (34), Prescription-related (12), Psychedelics (59), Stimulants (52), Research Chemicals (3), and Barbiturates (1). The 5th e-market, Tochka, categorise NPS in a classical way; Cannabis (108), Stimulants (53), Psychedelics (21), Empathogens (17), Opioids (7), Dissociatives (6), Prescription (44), and Others (20).

It seems that four NPS categories of NPS dominate (Table 3, Figure 12, Appendix 5) each of these five e-markets, these were; cannabis-hashish and cannabinoids (rank 1st), Stimulants (rank 2nd), empathogens (rank 3rd), and psychedelics (rank 4th). Furthermore, the number of items, under the category of cannabis and cannabinoids, behaved as a statistical outlier in Acropolis e-market; cannabis and cannabinoids have contributed to 45.6% of the total number of NPS on the e-market Acropolis. However, inferential statistics revealed that there was no statistically significant difference in the number of items which were sold under each of the top four NPS categories (Figure 13). On the other hand, there was a significant difference in relation to the number of items sold on all of the randomly selected e-markets (Figure 14), with an exception for the number of articles sold on Acropolis and Tochka e-markets (*p-value*=0.09). It is to be deducted that AlphaBay e-market is always in the lead, while cannabis and cannabimimetic represent the most popular category of NPS on the darknet e-marketplace.

A thorough, systematic analysis was finally done for the NPS items sold under each category of NPS in AlphaBay e-market (Figure 15), these included: LSD, shrooms, DMT, Mescaline, LSA, DMA / DOX, NBOMe, 2C-B, and other research chemicals/RCs (Psychedelics); Speed, Meth, Adderall and Vyvanse, 2-FA, Pressed Pills, Cocaine, Crack, RCs, and others (Stimulants); Prescription, Fentanyl and RCs, Heroin, Pills, Prescription-related, and others (Opioids); MDMA, MDA, Methylone, and others (Empathogens); Ketamine, MXE, GHB, and others (Dissociatives); RCs and combinations, Pills, Powder, and others (Benzodiazepines). Cannabis and Hashish included diverse items classified as; buds and flowers (38122), shakes (635), Concentrates (8081), Hash (8455), Prerolls (243), Edibles (2059), Topical and others (228), Seeds (1098), Synthetic Cannabinoids and Cannabimimetics (551), and others (5811). In summary, the top sold psychoactive substances on AlphaBay were; Cannabis and Hashish (65283), Cocaine (13291), MDMA (11599), methamphetamine (5791), and LSD (6489); these substances alone accounted for 54.7% of the total output of AlphaBay e-trade events.

Table 1. Descriptive Statistics of Five Keywords' Mapping on Google Trends (2012-2016).

	Deep web	Darknet	Tor	Bitcoin network	Bitcoin	Mean
Min.	1.00	0.00	14.00	0.00	2.00	3.40
Max.	12.00	11.00	26.00	11.00	100.00	27.00
Range	11.00	11.00	12.00	11.00	98.00	23.60
Mode	8.00	1.00	18.00	1.00	17.00	3.80
Median	6.00	1.00	18.00	1.00	16.00	8.90
Mean	5.94	0.91	17.68	1.28	17.48	8.66
Var.	7.01	1.05	4.28	2.22	221.82	13.78
St. Dev.	2.65	1.02	2.07	1.49	14.89	3.71

Table 2. Power Scoring of e-markets (n=14) on the Darknet e-marketplace.

No.	Darknet Market	Overall Rating	Support Rating	Votes	Power Score (Corrected)	Sum
1	AlphaBay	4	4	243	225.49	417.65
2	Agora	4	4	192	192.16	
3	Nucleus Market	4	4	152	166.01	1091.99
4	Abraxas	4	3	82	111.93	
5	Hansa	4	4	51	100.00	
6	Middle Earth	4	3	55	94.28	
7	Darknet Hero League	4	4	34	88.89	
8	Outlaw Market	4	4	27	84.31	
9	Majestic Garden	4	4	14	75.82	
10	Silkkitie	4	3	26	75.33	
11	Oasis	4	4	11	73.86	
12	Real Deal Market	4	4	7	71.24	
13	Tochka Market	3	4	8	63.56	
14	Oxygen	3	3	8	55.23	
15	Arsenal	2	1	10	31.54	

Table 3. The Most Popular Categories on Darknet e-marketplace.

	AlphaBay	Valhalla	HANSA	Acropolis	Tochka	Sum	Corrected Mean
Cannabis and Hashish	65283	3770	4797	179	106	74135	14827
Stimulants	33099	2064	2576	40	51	37830	7566
Empathogens	30220	2101	2780	49	17	35167	7033.4
Psychedelics	14007	1030	1313	45	20	16415	3283

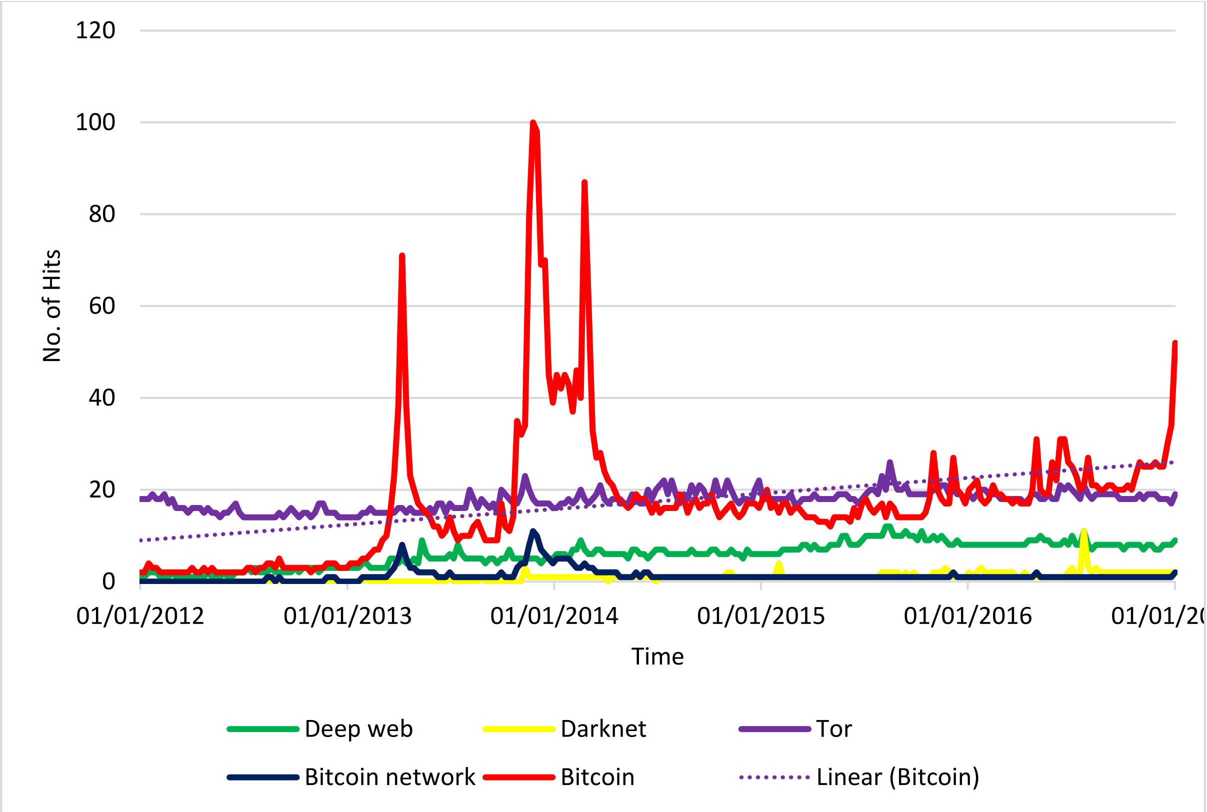
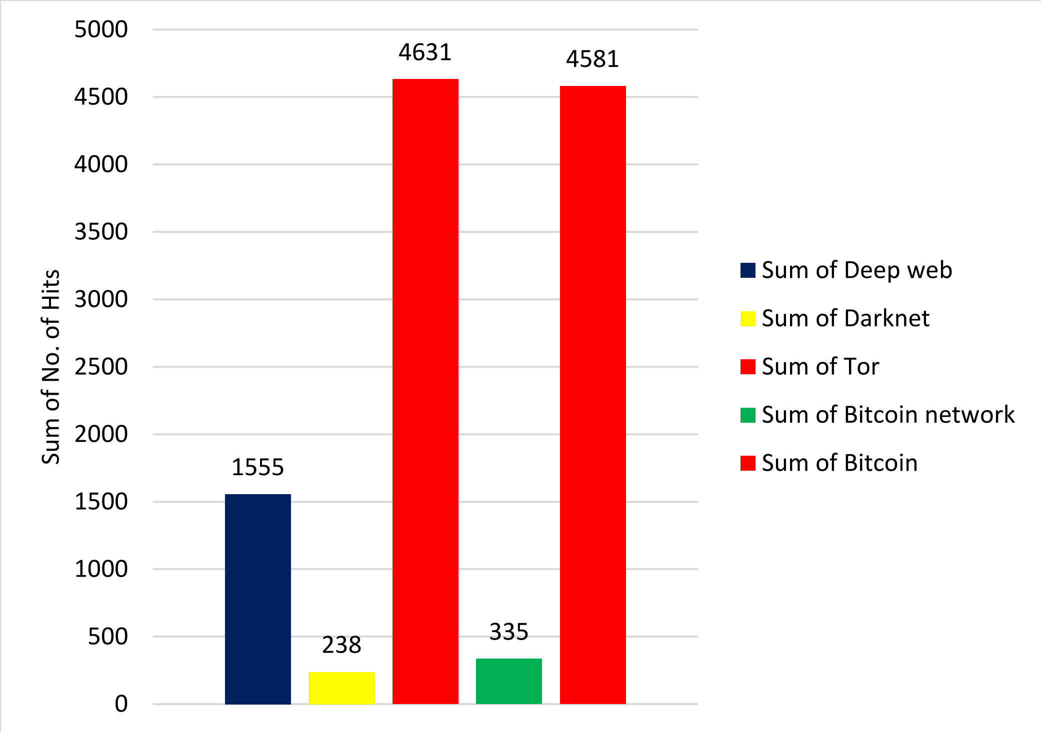


Figure 1. Google Trends: Five Keywords of Relevance to the Deep Web (2012-2016).



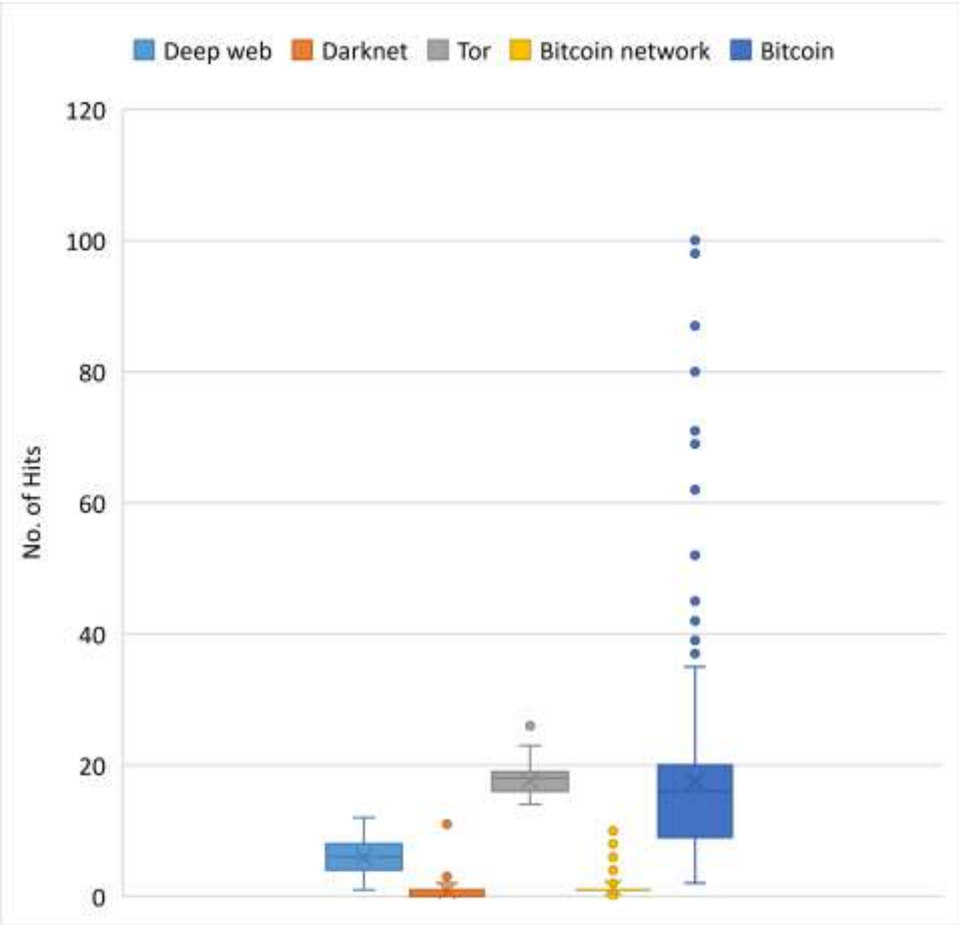


Figure 2. Keywords of Relevance to the Deep Web as Mapped on Google Trends: Sum of Number of Hits (above), Boxplot Presentation (below).

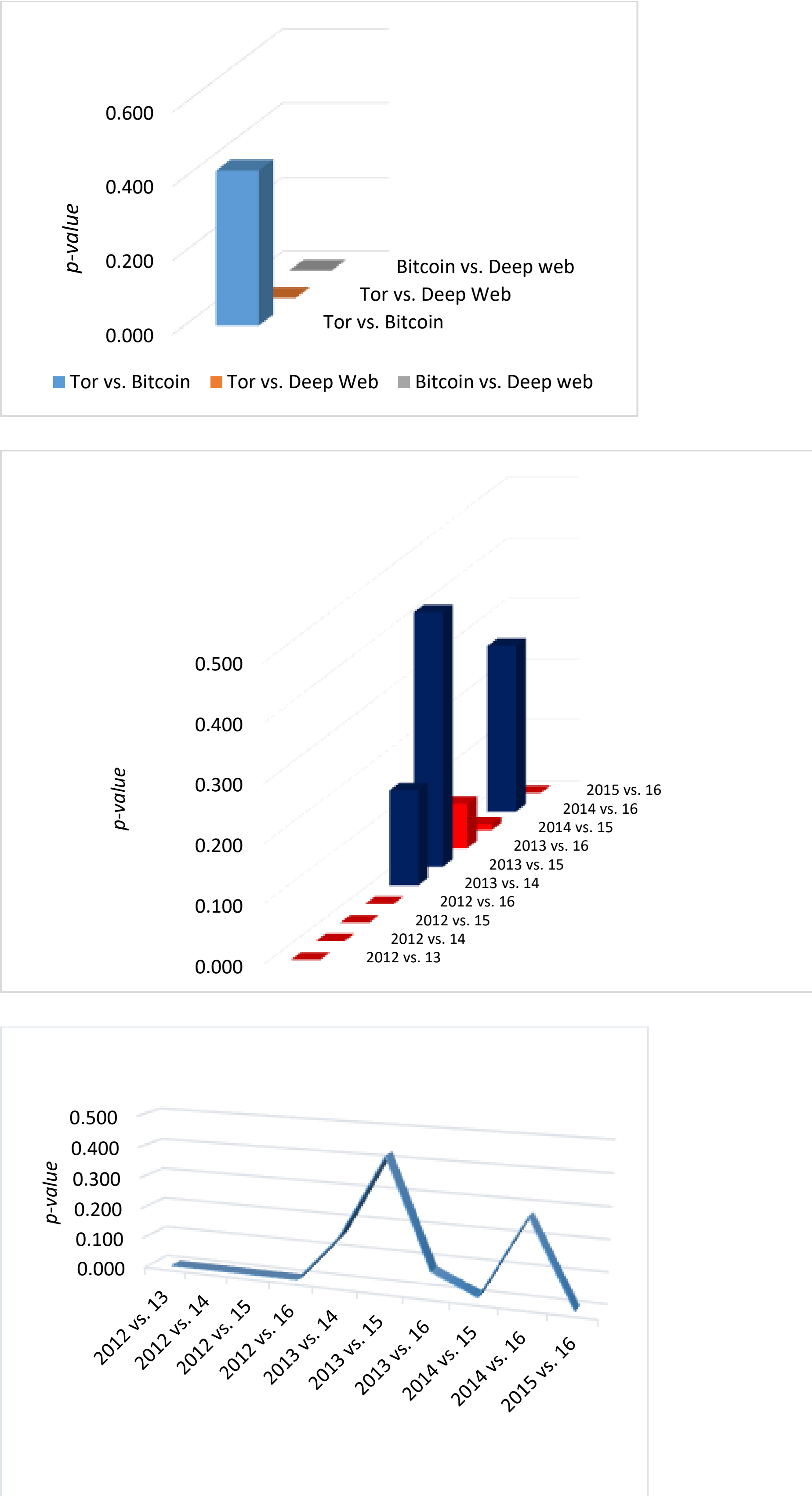
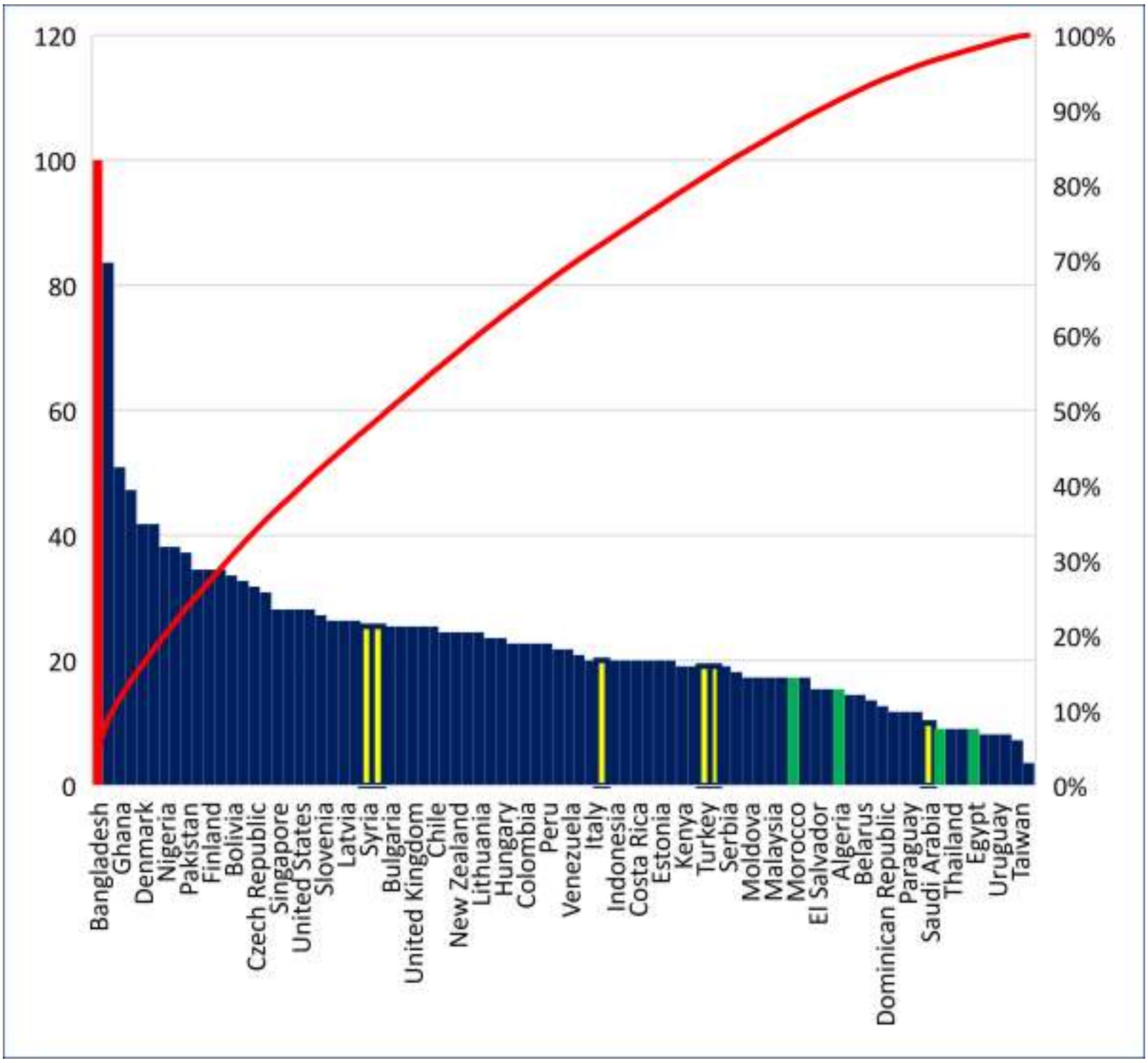


Figure 3. Inferential Statistics: t-test for Keywords of Relevance to the Deep Web: Mapping on Google Trends.



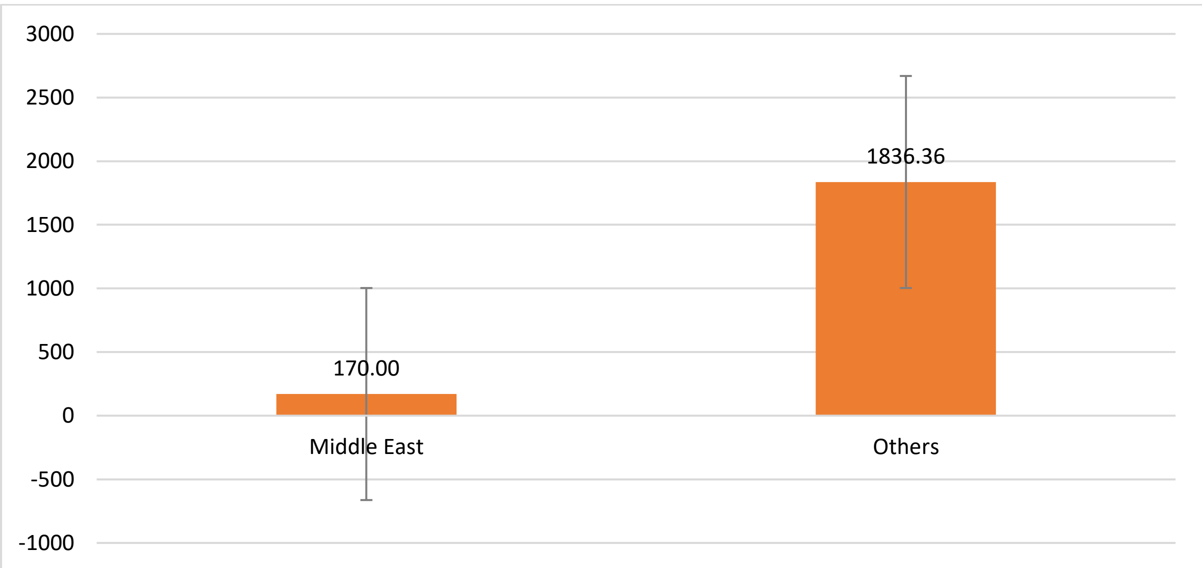
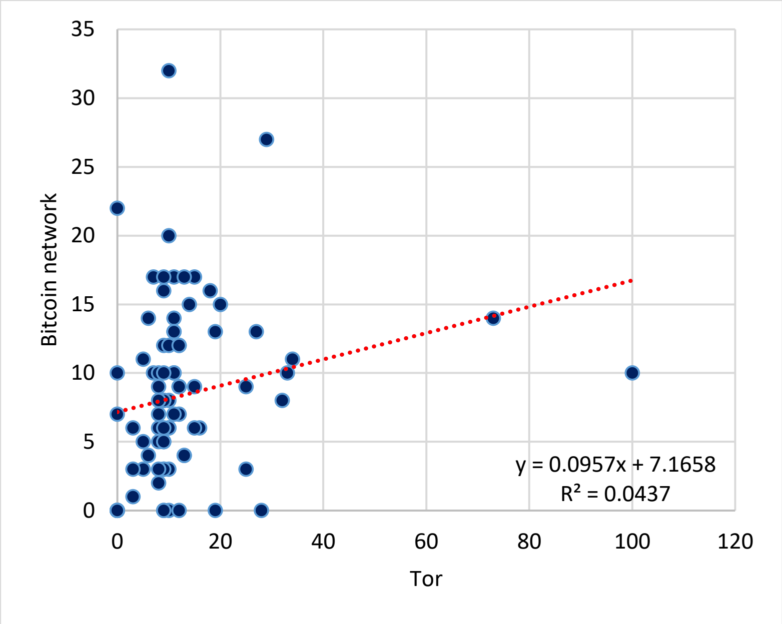
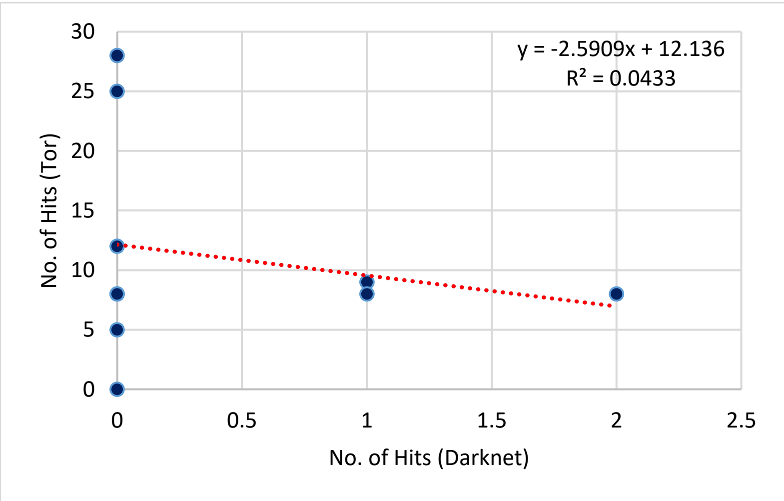


Figure 4. Geo-mapping of the Keywords on Google Trends (2012-2016): Contributing Countries in (above), and Juxtaposition of the Middle Eastern Contribution (below).





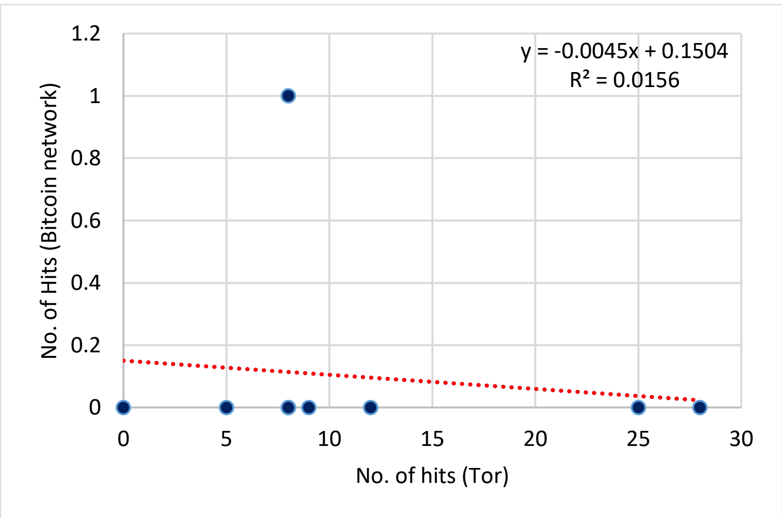


Figure 5. Linear Regression: Correlations of Keywords of Relevance to the Deep Web.

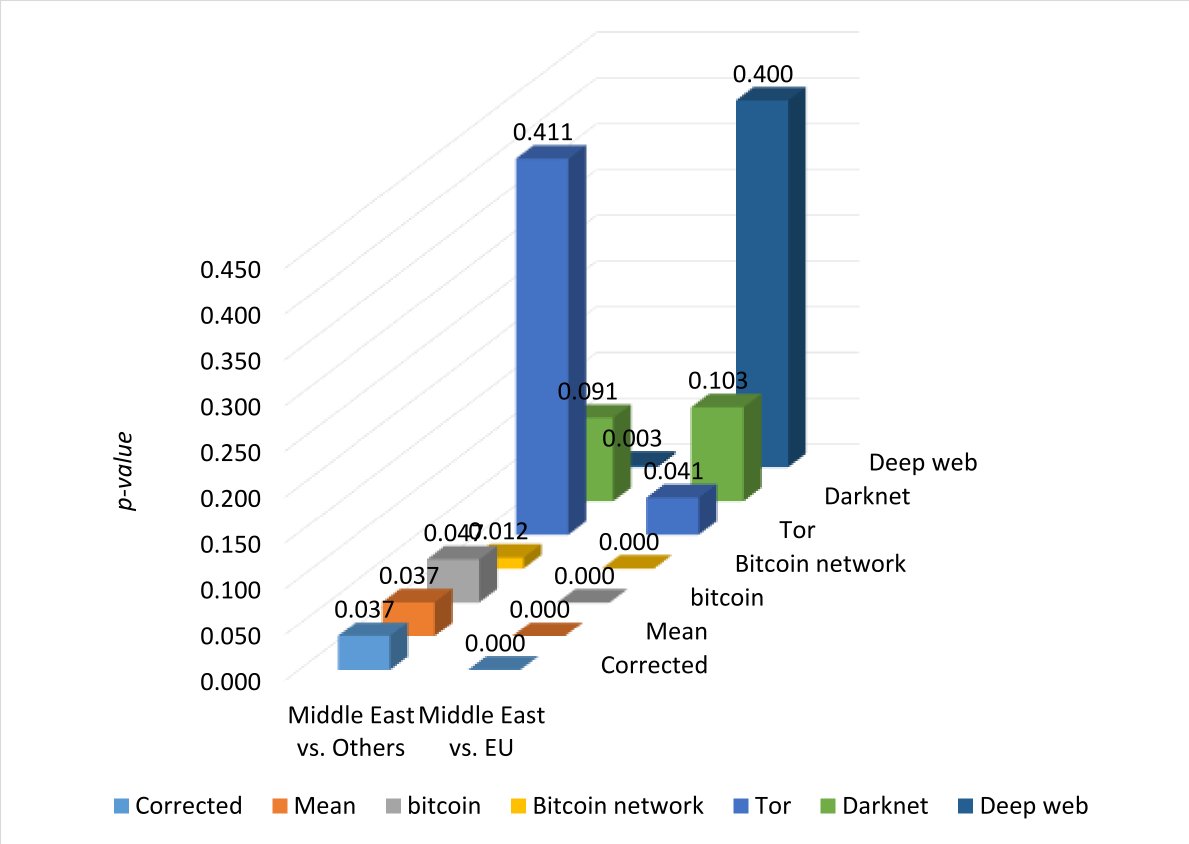
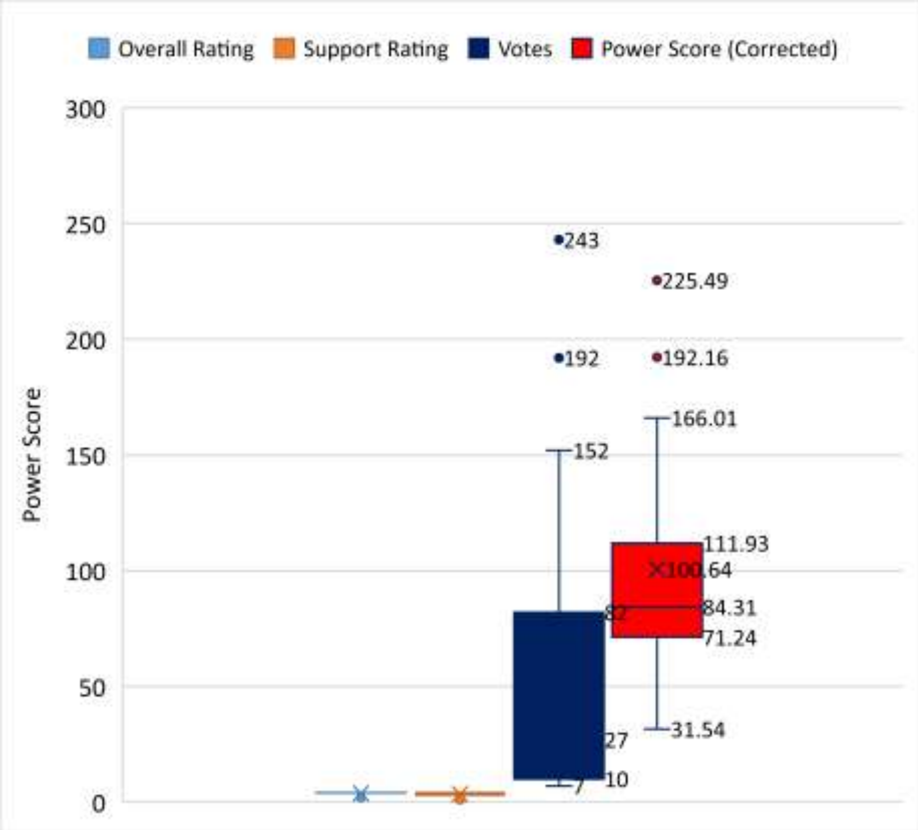


Figure 6. Inferential Statistics on the Regional Geo-mapping of the Keywords.

Figure 7. Interest by Region (Geo-mapping) of Keywords on Google Trends: Countries Shown are from the Middle East, Arabic World, and the European Union.



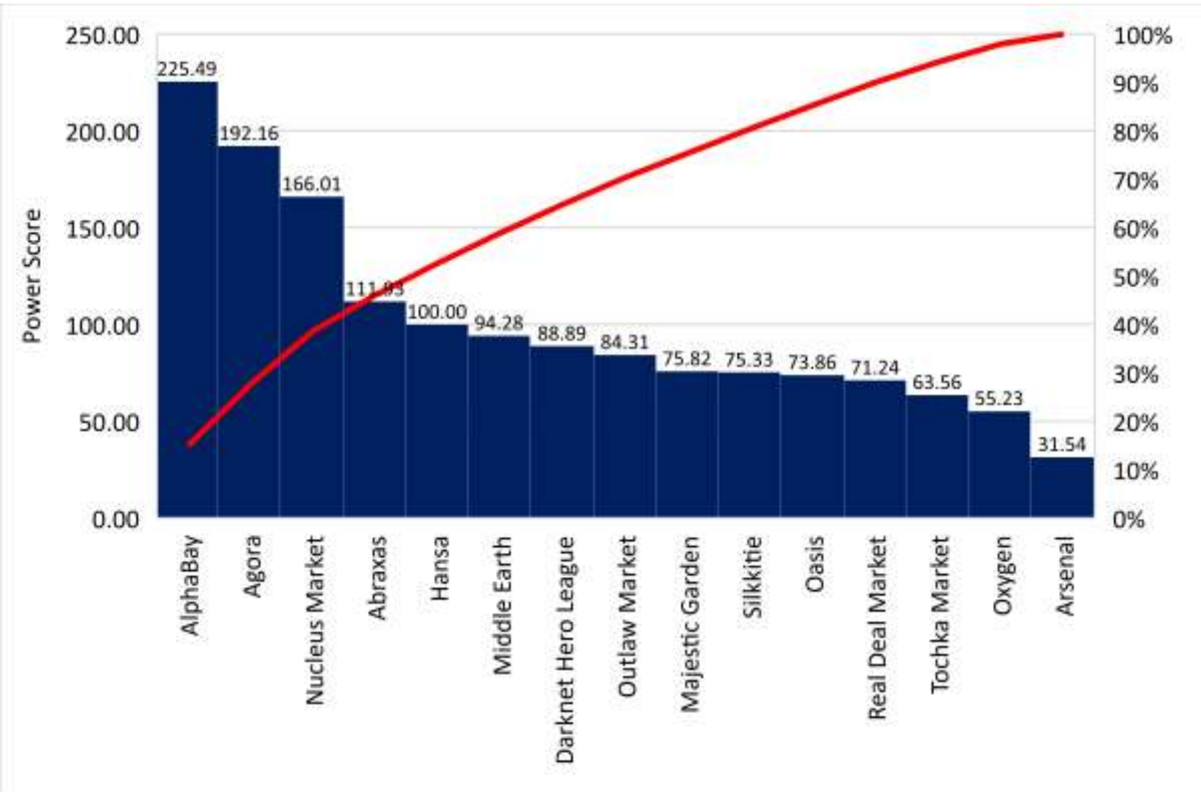
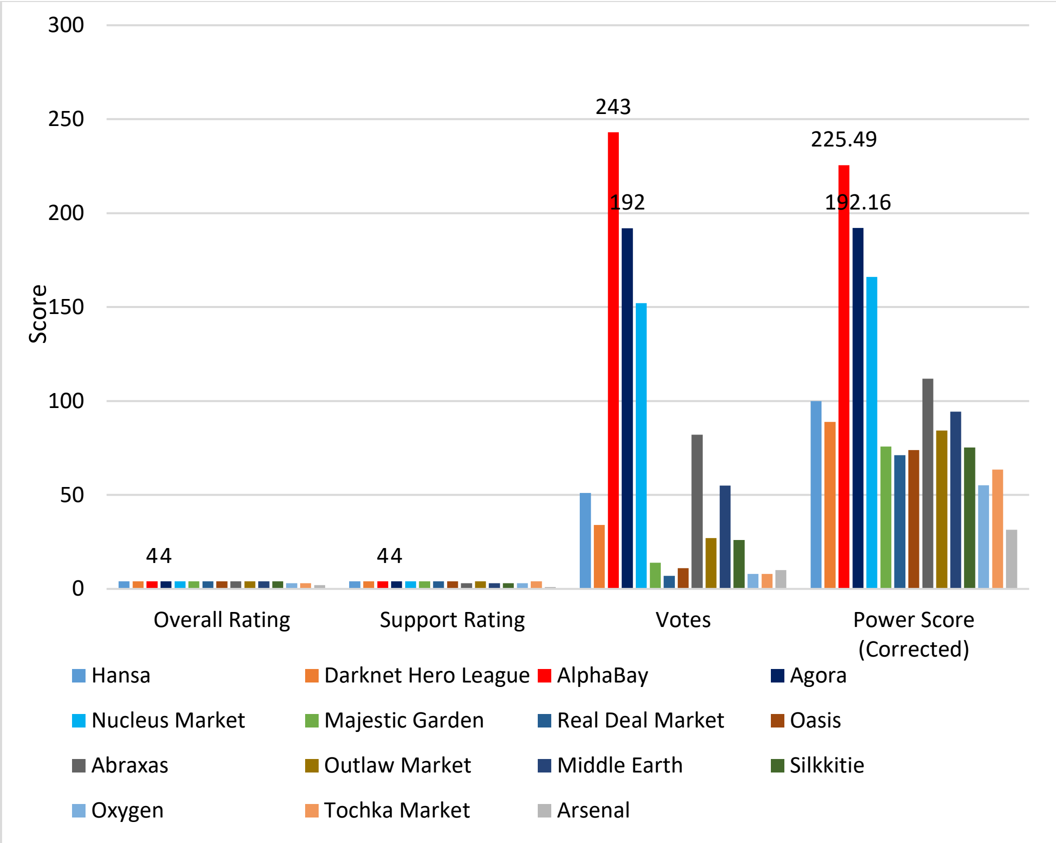


Figure 8. Power Score of e-markets on the Darknet: Pareto Chart (above) and Boxplot Presentation (below).



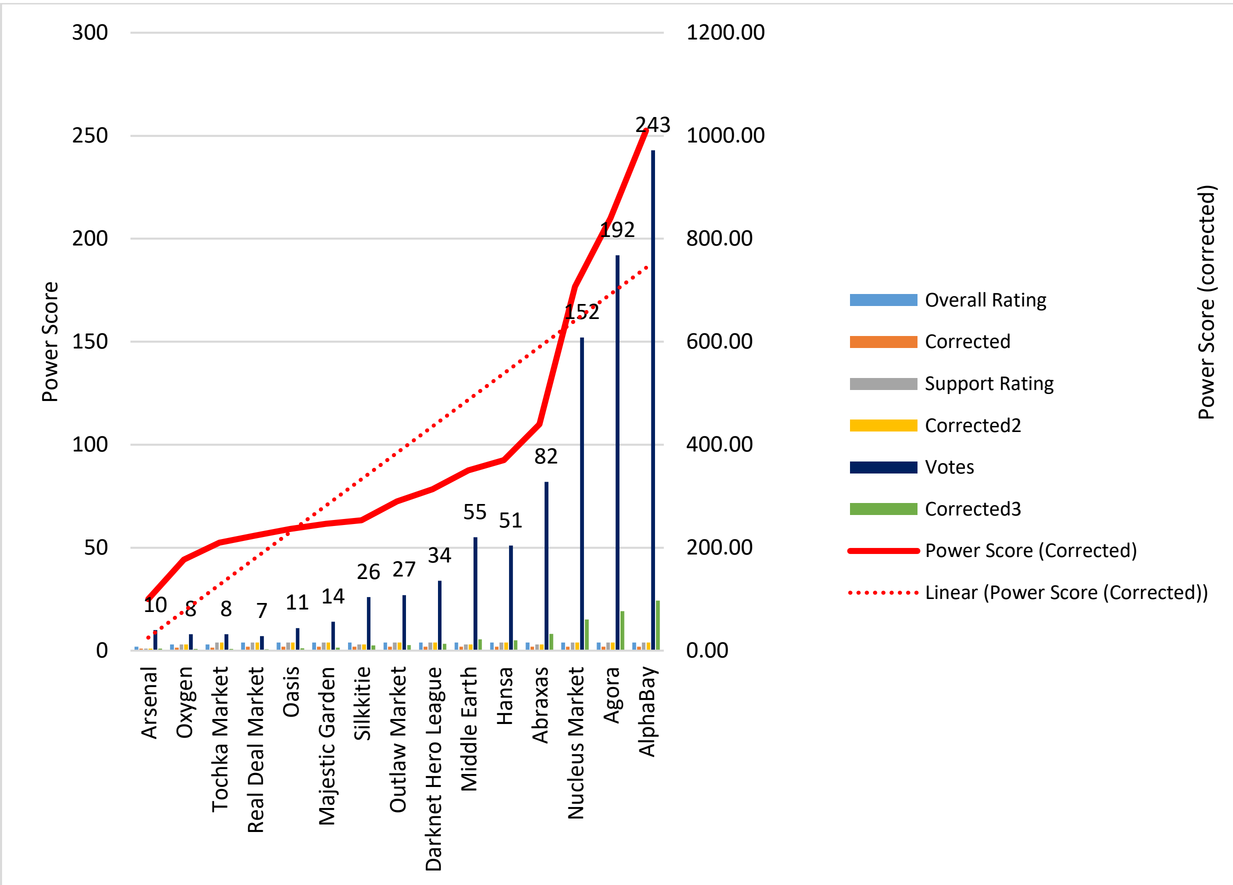


Figure 9. Power Scoring of the e-markets on the Darknet.

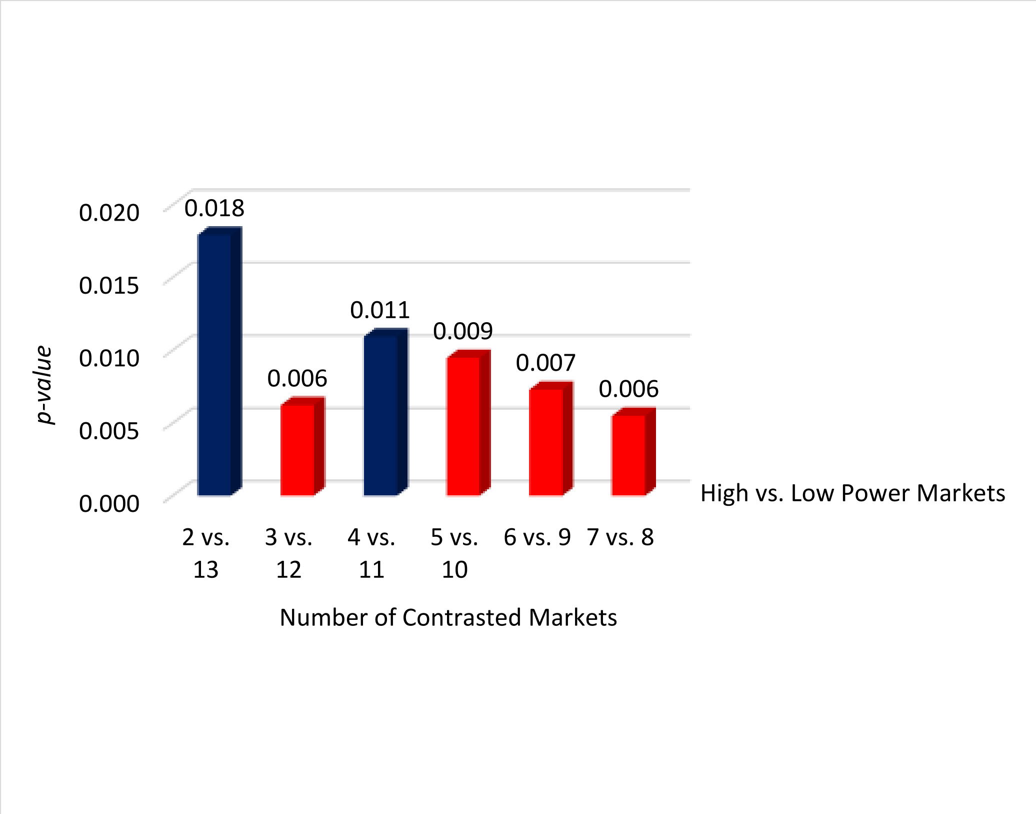


Figure 10. Inferential Statistics and Analyses of Power: High-power versus Low-power e-markets on the Darknet.

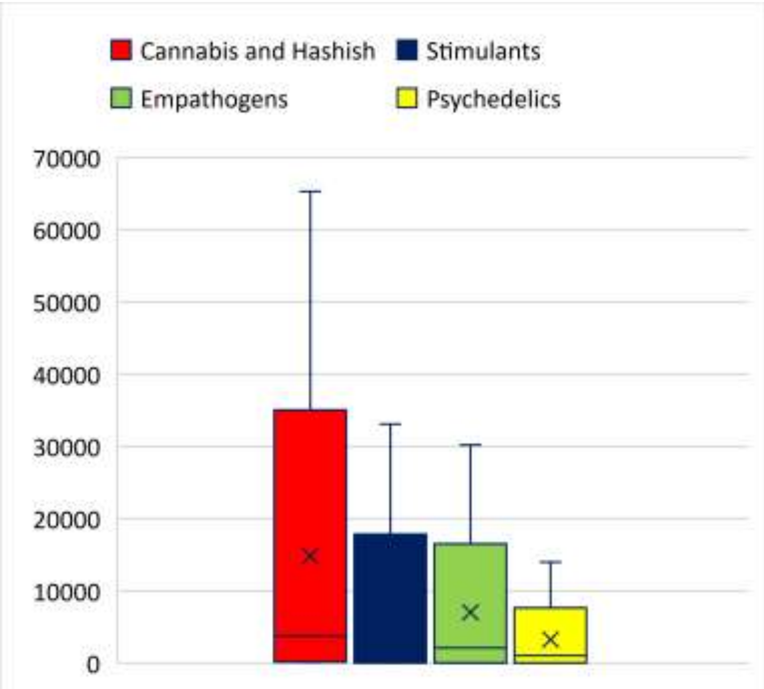


Figure 11. Most Popular Categories of NPS on the Darknet.

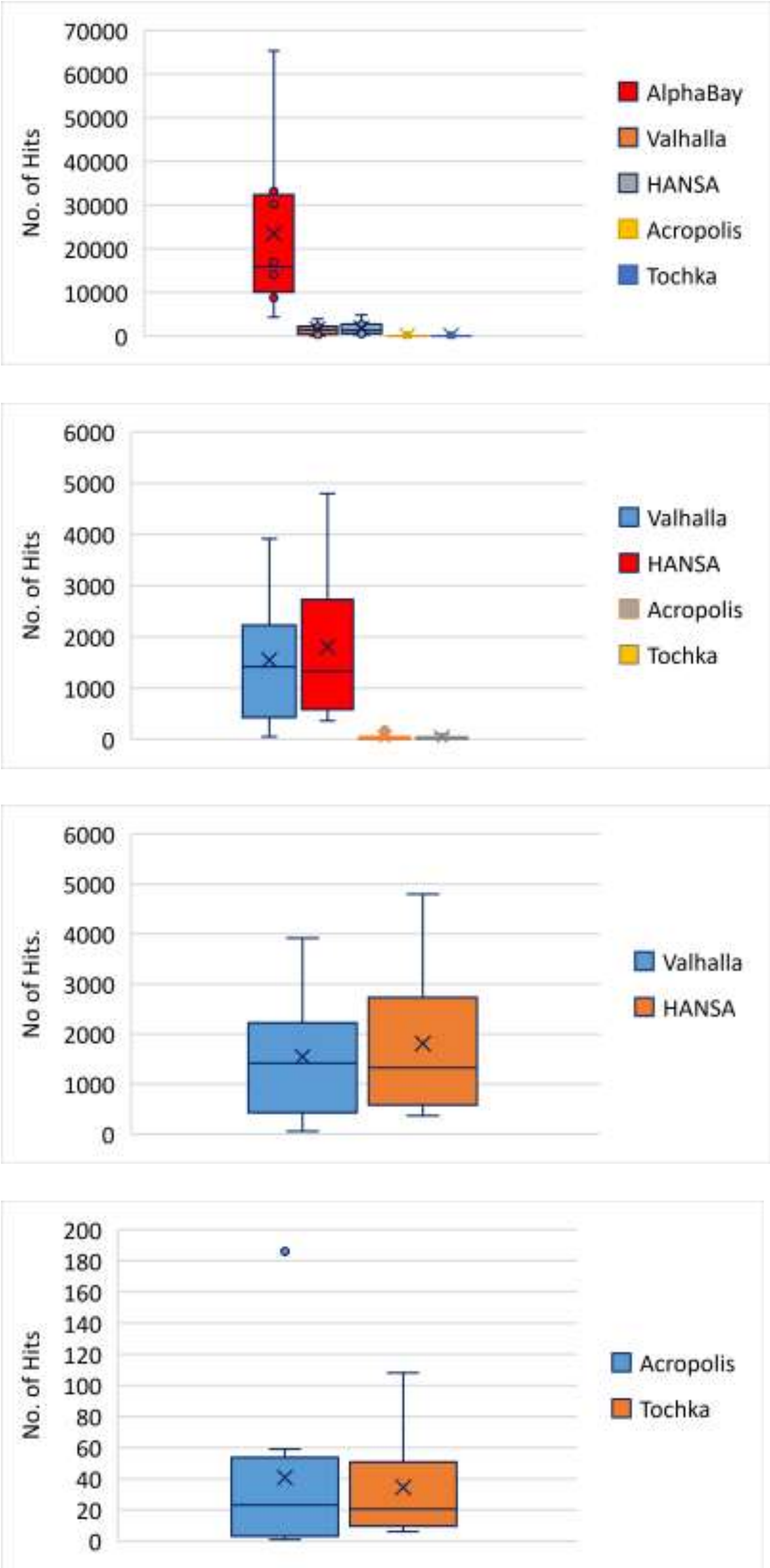
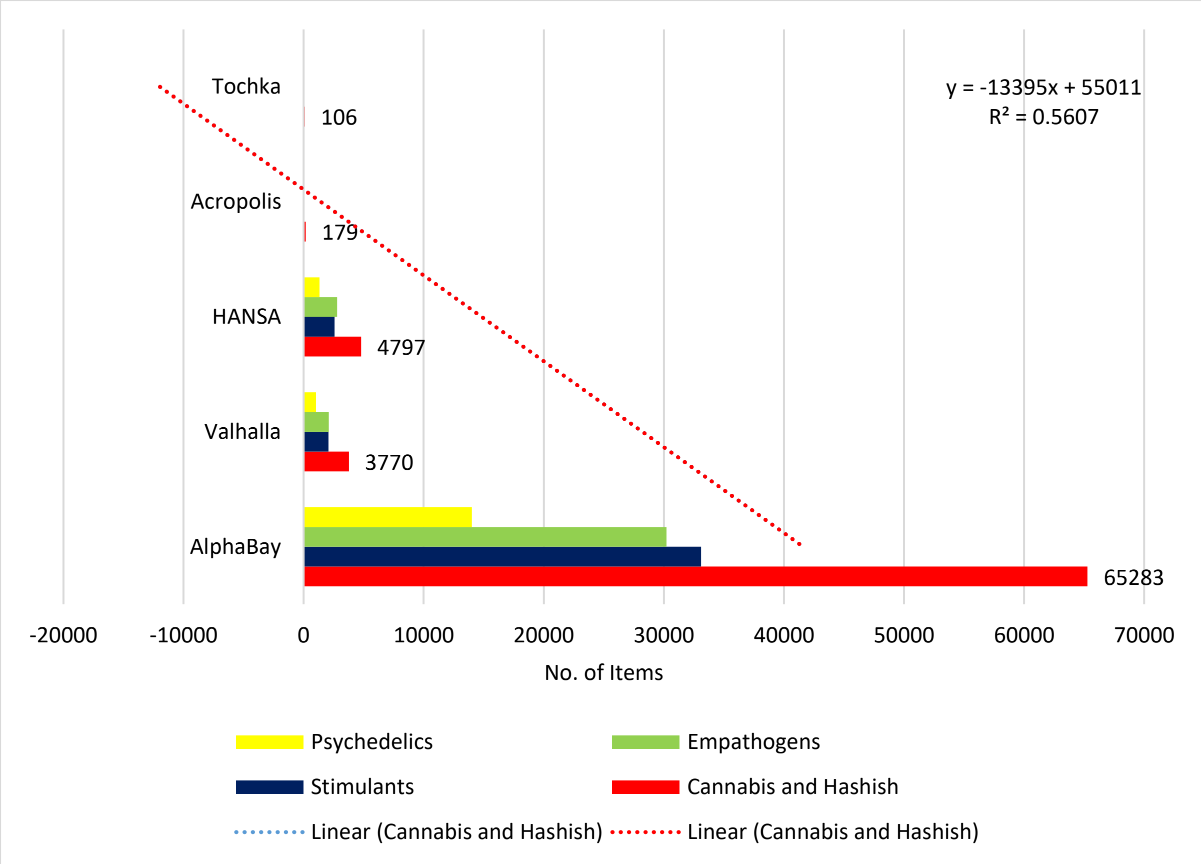


Figure 12. Boxplot Presentation of Number of NPS Substances Advertised on Selected e-markets from the Darknet.



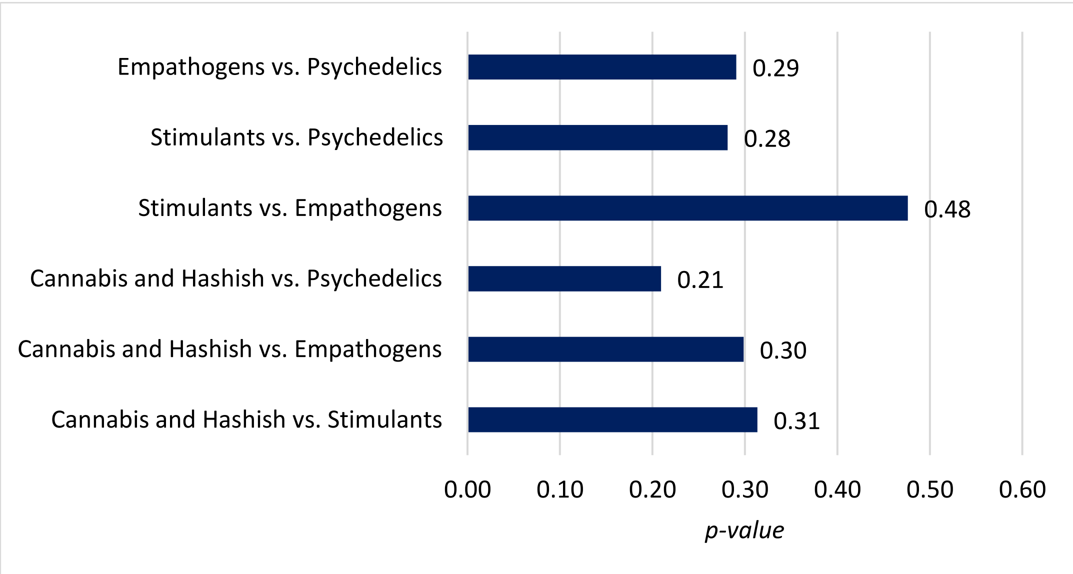


Figure 13. The Most Popular Categories of NPS on the Darknet e-markets (above), and Inferential Statistics (below).

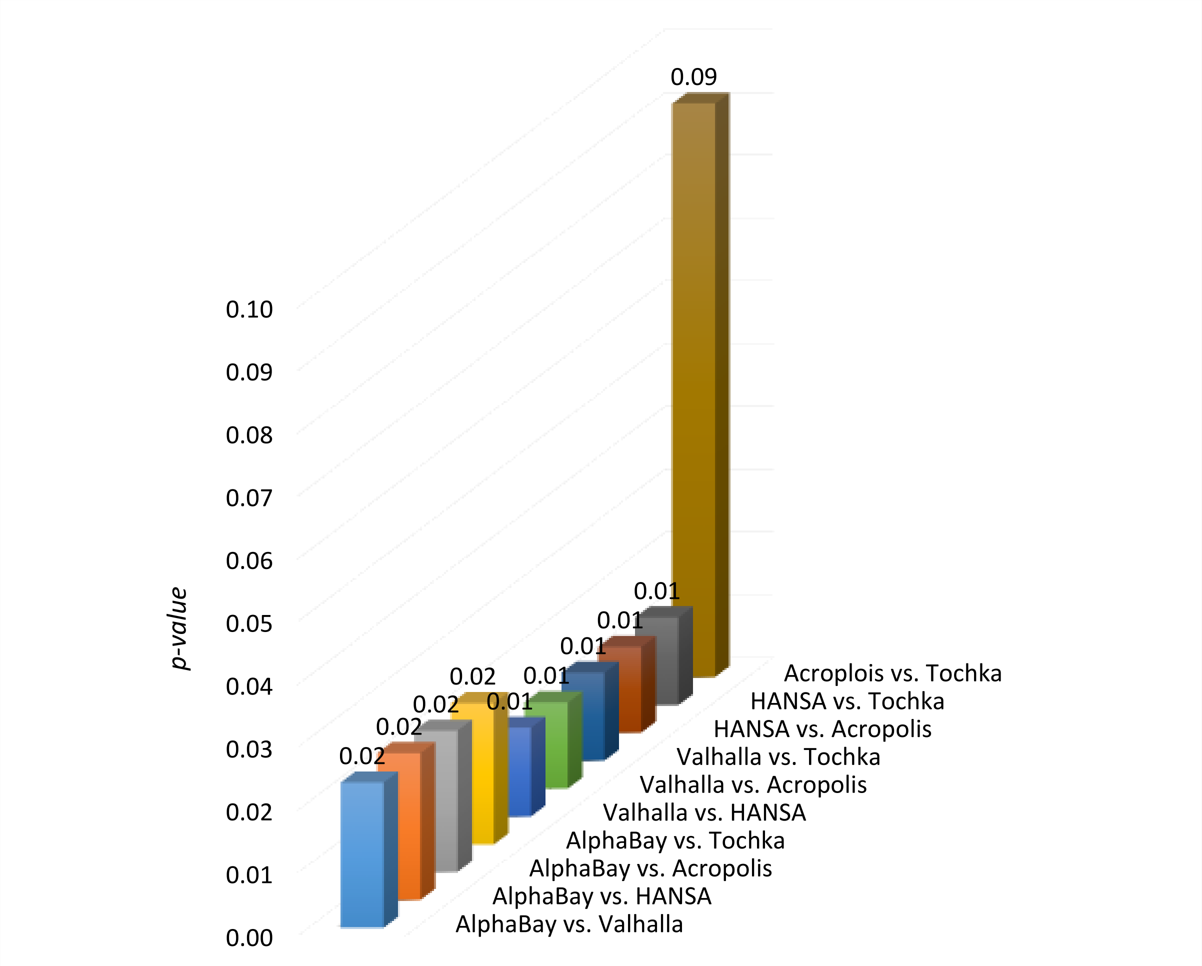


Figure 14. Inferential statistics: the Most Dominant e-markets on the Darknet.

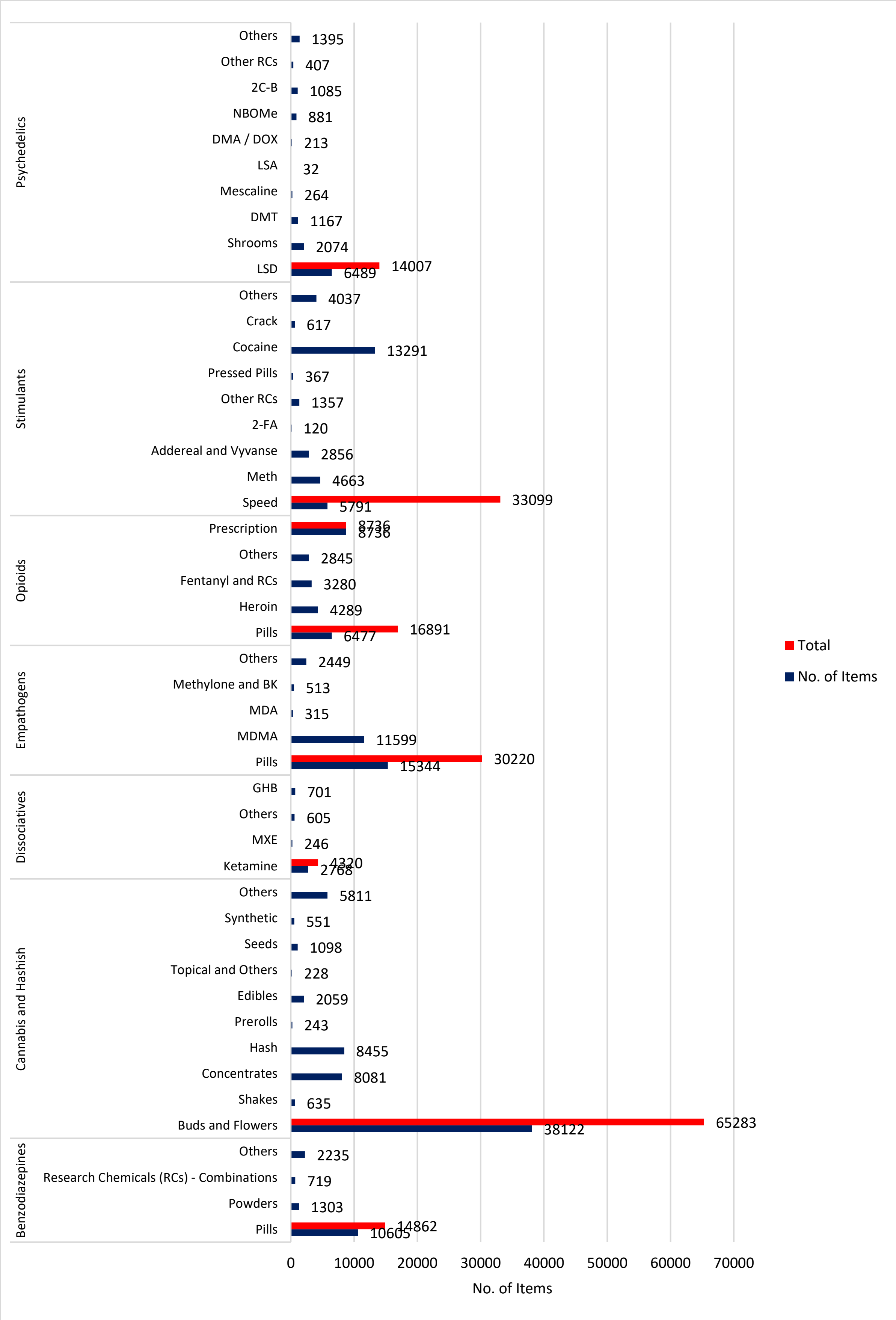


Figure 15. The Most Popular Psychoactive and Novel Psychoactive Substances Advertised AlphaBay.

The major categories of NPS in e-commerce were mapped on the darknet; benzodiazepines (1023 items), cannabis and cannabinoids (19768), dissociative substances (923), empathogens (3821), opioids (943), prescription-related NPS (1728), stimulants (5623), and psychedelics (3127). It is evident that cannabis-hashish and cannabinoids are the most common on the darknet. Accordingly, each of these categories was numerically "corrected" to be compared with cannabis and cannabinoid. This comparative analysis of NPS categories will make statistical analyses more plausible. Descriptive statistics of the number of hits (Figure 1), showed that each category of NPS averaged a "corrected" number of hits of; 0.8 +/- 1.2 (benzodiazepines), 9.2 +/- 19.6 (cannabis and cannabinoids), 0.9 +/- 1.7 (dissociatives), 2.8 +/- 6 (empathogens), 1.1 +/- 2.3 (opioids), 1.3 +/- 2.2 (prescription-related), 2.8 +/- 4.9 (stimulants), and 2.1 +/- 3.5 (psychedelics). It is to be concluded that the top four categories of NPS on darknet were; Cannabis and cannabinoids (rank 1st), stimulants (2nd), empathogens (3rd), and psychedelics (4th). Geo-mapping showed that the main shipping countries (regions) for benzodiazepines were; US, Phillippines, India, Germany, Denmark, UK, Canada, Netherlands, European Union, and China; there were no shipping countries from the Middle East or the Arab world.

For cannabis-hashish and cannabinoids; US, UK, Germany, Netherlands, Canada, Spain, Finland, Belgium, Australia, and France; Shipping countries from Arabic world included only Morocco and Oman; both summed to 0.04% of the total e-trade. For dissociative substances; Netherlands, UK, Germany, US, Finland, Canada, China, Norway, Spain, and Australia; there was no contribution from the Middle East or the Arab world. For empathogens; Netherlands, Germany, UK, Finland, US, Australia, Belgium, Spain, Norway, and Canada; Oman was the only contributing country from the Arabic world accounting for 0.04% of the total e-trade of dissociatives. For opioids; Germany, US, India, Netherlands, Australia, Spain, France, UK, Italy, and Canada; there was no contribution from the Middle East and the Arab world. For prescription-related NPS; US, Germany, Netherlands, Belgium, India, UK, Australia, Denmark, and Japan; there was no contribution from the Middle East and the Arab world. For stimulants; Netherlands, Germany, US, UK, Finland, Australia, Spain, China, Norway, and Belgium; Oman was the only contributing country from the Arab world accounting for 0.05% of the total e-trade of stimulants. For psychedelics; Netherlands, UK, Germany, US, Canada, Finland, Australia, Ireland, and France; there was no contribution from the Middle East or Arabic countries.

The analyses of the high-risk and popular NPS on darknet showed the number of hits as follows; LSA (3378), 2-FA (134), DMA / DOX (108), MXE (366), Mescaline (801), MDA (972), Methylone and BK (442), crack (18904), GHB (3850), NBOMe (2560), 2C-B (1383), DMT (1499), Ketamine (4331), Adderall and Vyvanse (2179), Fentanyl (3202), Heroin (5843), Meth (12867), LSD (10709), Cannabis and Hashish

(19768), and MDMA (28446). The most popular substance per geographic location (Appendix 6 and 7) was MDMA (7949, Netherlands). The other most popular substances were; cannabis and cannabinoids (primarily sold in the US), Crack (Netherlands), Meth (Netherlands), and LSD (Netherlands). The contribution of US, UK, Western Europe, and Canada is evident and undeniable for the e-trade phenomenon on the darknet. MDMA was in the lead over all other substances, while cannabis and cannabinoid represented the leading NPS category. Holistic geographic analyses (Geo-mapping) of the shipping countries of these NPS (Figure 2) revealed that the top shipping locations were; the Netherlands, US, UK, Australia, Canada, France, Germany, and Spain. In relation to these top contributing countries, it was inferred; crack was more advertised for e-trade than Meth (*p-value*=0.005), LSD was more advertised than crack (0.002), MDMA was more advertised than crack (0.041), while Meth and LSD were advertised significantly less than MDMA (0.013, 0.009 respectively). Furthermore, linear regression in these locations confirmed a positive linear correlation between; crack versus cannabis and cannabinoids (R^2 score=0.410), MDMA versus crack (R^2 score=0.151), and MDMA versus cannabis and cannabinoids (R^2 score=0.151).

In relation to these five popular substances, Google Trends analyses for the period from the start of 2012 to the end of 2016 (Figure 3) showed that surface web users of highest attentiveness (interest) were from (descending order); US, Chile, Canada, Australia, Costa Rica, Uruguay, Puerto Rico, New Zealand, Argentina, and the UK. Apparently, several countries are from Latin and Central America; these were not compatible with the data retrieved from the darknet snapshot; it may be attributed to the traditional trade rather than e-trade of NPS in south and central America (Atkinson et al., 2017; Duddley, 2010; Scott and Marshall, 1998; and Wolf, 2016). Additionally, high attentiveness (outliers) were found in; Chile, US, Australia, New Zealand, and the Czech Republic. These outliers were in relation to; methamphetamine, MDMA, and cannabis; no outliers were found in relation to cocaine (Figure 3: Boxplot). Inferential statistics, using the paired Student's t-test, was implemented to conclude inferences on the most popular NPS for surface web users (Figure 4). There was a significant difference between all five substances with an exception for; MDMA vs. Meth (0.164) and MDMA vs. LSD (0.246).

Contributing countries from the Middle East and the Arab world (Figure 5) included; Israel, Iran, Turkey, UAE, Morocco, Saudi Arabia, and Egypt; all these countries contributed to a fragment of 3% of the total (global) attentiveness of surface web users. MDMA, cocaine, and cannabis contributed the most primarily in Israel, Iran, and Turkey. Inferential statistics shows that the users' attentiveness towards LSD was significantly more than methamphetamine. Furthermore, the e-trade of these substances was synchronised (positive linear correlation) in between; UAE and Morocco (R^2 *score*= 0.5404), and in between Iran and Turkey (R^2=0.8731); no other inferences could be reached. No discrepancy was noticed departing from the darknet results; the surface web users from the Middle East were also most interested in cannabis and cocaine (Figure 6). Attentiveness to cannabis and cannabimimetic was highly oscillating through time, unlike all the remaining four substances which had more steady trends. Interest in cannabis and cannabinoids has two main peaks which took place during November 2012 and November 2016, obviously in the holiday seasons.

The AlphaBay e-market is a dominant one on the darknet. However, it is still to be inferred if AlphaBay is a representative to the darknet e-marketplace. This hypothetical assumption has been tested by mapping the number of items under each category of NPS on both AlphaBay and Grams engine (Figure 7), these were; benzodiazepines (1023, 14860 items), cannabis, hashish, and cannabinoids (19768, 65275), dissociative substances (923, 4319), empathogens (3821, 30207), opioids related substances (943, 16889), prescription-related NPS (1728, 8736), stimulants (5623, 14007), and psychedelics (3127, 33098). The AlphaBay-to-Grams ratio of the number of hits was ranging from 3.3% to 17.9% while averaging 8.3%. The average of the number of hits (per each category of NPS) on AlphaBay was 4620, while the average on Grams was 23424 hits; the number of items on AlphaBay was significantly less than Grams engine (4620 vs. 23424, *p-value*=0.004). However, an Inference via linear regression shows a positive linear correlation between the number of items on AlphaBay and Grams engine (R^2 *score*=0.791). It is to be concluded that AlphaBay is not only the most dominant e-market on the darknet but also represents a proper representative for the entire e-trade phenomenon on the e-marketplace of the darknet.

Countries from the Middle East region and the Arabic world contributed the least to the global e-trade on the deep web. Here, the contribution will be assessed for NPS categories via using specific keywords for each category on Grams search engine; the top contributing countries were; Afghanistan (64%), Oman (29%), and Morocco (7%). Another way of mapping the darknet was done via using keywords specific to high-risk and popular NPS. The mapped NPS substances included; LSA, 2-FA, DMA, MXE, Mescaline, MDA, Methylone, Crack, GHB, NBOMe, 2C-B, DMT, Ketamine, Adderall, Fentanyl, Heroin, Meth, LSD, Cannabis and Cannabinoids, and MDMA. The contributing countries (Figure 8) included; Afghanistan (77%), UAE (12%), Oman (4%), Morocco (2%), Egypt (3%), and Cyprus (2%). Some of these substances were not in circulation on darknet at the time the snapshot was taken; these substances included; LSA, 2-FA, MXE, 2C-B, DMT, Ketamine, and Adderall; it seems that these substances are exclusive to other regions of the world including; Western Europe, US, UK, Canada, and Australasia. On the other hand (Figure 9), trending NPS included; Heroin, Meth, Crack, Cannabis and Hashish, MDMA, GHB, NBOMe, LSD, DMA, Mescaline, MDA, Methylone, and Fentanyl. Afghanistan appears to be in the lead, possibly due to its high population count. Accordingly, an assumption (hypothesis) that the number of items in each country is proportional directly with its population count; this was tested via linear regression, and it was proven to be true (R^2 *score*=0.137). Other factors may also be contributing to this phenomenon may include political instability as in Afghanistan.

Analyses in relation to the characteristics of e-vendors from the Middle East and the Arabic World produced a more accurate and wider mapping of the region; the characteristics included; e-markets of NPS (1), location or shipping country (2), number of advertised item (hits) per location (3); promoted NPS in the Middle East and Arabic countries (4), Grams rating (5); and power scoring (6). Power score for each e-vendor was assessed primarily on AlphaBay e-market based on; vendor level, trust level, the percentage of positive feedbacks from e-customers, AlphaBay score index, and e-vendor antiquity in the e-market. The e-markets included; AlphaBay, HANSA, Oasis, Valhalla, Agora, Evolution, Abraxas, and Middle Earth. Nineteen e-vendors were identified, they did e-trade not only in the Middle East but also in other regions of the world; this observation was found to be suspicious and worthy of deeper investigation. The e-vendors (Figure 10) included; eztest (Benzodiazepines and GHB), MagicCarpetUk (Hashish), TripleDutchDelivery (Hashish and MDMA), stiffstyle (Hashish), MrNatural (MDMA, Mescaline, NBOMe, and LSD), mikehamer (Stimulants), alterEgo (Lorazepam), fake (DMA, MDA, Crack, GHB, Fentanyl, Meth, and MDMA), chris03 (MDMA and Methylone), koplak12 (crack), TheCocaHero (crack), DrRelax (crack), hcb965 (NBOMe), AlCaponeA1 (Heroin), dawoud522 (Heroin), dutchdream (Meth), zeroz (Meth), ThinkingForward (Meth), and Dogkingdom (LSD). The mapped e-markets and shipping countries were diverse. An e-vendor with the highest power score, *ThinkingForward*, has e-trade activity in three e-markets; AlphaBay, Evolution, and HANSA. His (her) shipping locations included; UK, Afghanistan, and others (mapped as *unknown* on darknet). His (her) most popular NPS of e-commerce was methamphetamine. This e-vendor must have the ability to move freely between Afghanistan and the UK; he (she) could be either a UK national or had a network of accomplices (other e-vendors) operating under the same username from these countries.

Boxplot presentation of e-vendors (Figure 11) revealed the most powerful e-vendors (statistical outliers), these were; ThinkingForward, MrNatural, eztest. The e-vendors contributed to the e-trade as follows; ThinkingForward (23%), MrNatural (23%), eztest (13%), TheCocaHero (8%), DrRelax (7%), dutchdream (6%), MagicCarpetUk (6%), stiffstyle (6%), chris03 (5%), fake (2%), mikehamer (2%), alterEgo (2%), hcb965 (1%), TripleDutchDelivery (1%), AlCaponeA1 (1%), Dogkingdom (<1%), koplak12 (<1%), zeroz (<1%), and dawoud522 (<1%). A Combo plot (Figure 12) of the power score and the total number of items for each e-vendor, clearly shows there is a positive linear correlation. Accordingly, linear regression was done, and it was inferred that a positive linear correlation was found between; total number of hits/e-vendor vs. Power score (R^2 *score*=0.216), e-vendor's antiquity vs. Power score (0.610), and total number of hits/e-vendor vs. e-vendor's antiquity (0.028); the strongest correlation was found between e-vendor's antiquity and power scoring. The Middle Eastern and Arabic countries involved in the e-trade on darknet included; Israel, Turkey, Cyprus, UAE, Afghanistan, Egypt, Oman, and Morocco.

Special correlations were done, the Middle East and Arabic countries contribution to the e-trade on darknet was far less than the of the European Union. It has also been known that GHB is used to sedate victims during sexual assault incidents and rape, a linear regression (Table 1) found a positive linear relationship (R^2 score= 0.0389) between the number of GHB hits on Grams engine and the incidence of sexual assaults in these locations (Elsohly and Salamone, 1999; Mehling and Johansen,2016; Schwartz et al., 2000; Varela et al., 2004). Finally, a correlation was done in relation to the total number of hits (Grams) for nine geolocations known of high NPS e-prevalence; Australia, Canada, European Union, France, Germany, Netherlands, Spain, United Kingdom, and the United States. These countries were chosen as they represented the top contributors for e-trade phenomenon on darknet for specific high-risk and popular NPS including; LSA, 2-FA, DMA/DOX, MXE, Mescaline, MDA, Methylone and BK, Crack, GHB, NBOMe, 2C-B, DMT, Ketamine, Adderall, Fentanyl, Heroin, Meth, LSD, Cannabis and Hashish, and MDMA. The correlation was done between the total number of hits (per location) and the religious affiliation percentages for each country (Figure 13). It was found that one religious affiliation in these countries, Christianity to be specific, was negatively correlated with the number of hits on Grams engine, at an R^2 *score* of 0.426. On the other hand, Islam and Judaism had almost no correlation with the number of hits (0.0002, 0.0005 respectively) neither positively nor negatively. However, atheism was found to be positively correlated with the number of hits (0.399). Therefore, it can be assumed that countries with high population of atheist are expected to have more advanced levels of NPS e-trade on the darknet; it seems that Christianity was *protective* against this phenomenon in the selected countries.

Table 1. GHB on the Darknet: the Number of Hits per Location (Grams Search Engine), and the Incidence of Sexual Assaults.

NPS Substance	Location	No. of Hits/Location	Sexual Assault in 2010 (per 100,000 population)
GHB	Netherlands	647	9.2
	United States	505	27.3
	Germany	355	9.4
	United Kingdom	308	17
	Australia	128	28.6
	Canada	63	1.7
	China	44	2.3
	Norway	41	19.2
	Poland	40	4.1
	Finland	39	15.2
	Philippines	29	6.3
	Belgium	27	27.9
	India	14	0.4
	Italy	13	7.6
	Czech Republic	12	4.6
	Spain	9	3.4
	France	8	16.2
	Switzerland	5	7.1
	Denmark	4	6.4
	New Zealand	4	25.8
	Ireland	4	10.7
	Japan	3	1
	Brazil	2	36.9
	Afghanistan	2	1.2
	Austria	2	10.4
	Bulgaria	1	2.8
	Estonia	1	6
	Mexico	1	13.2

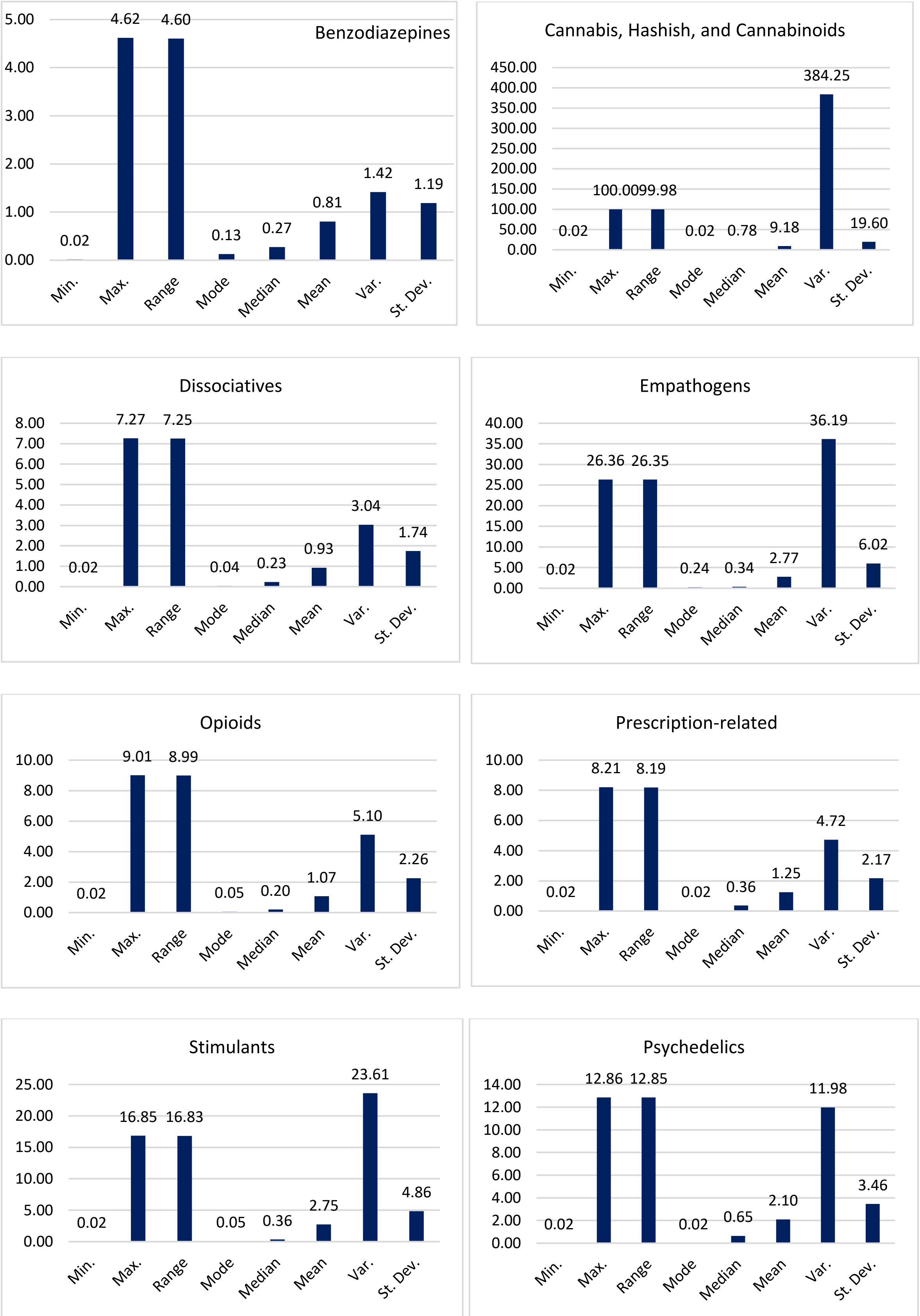


Figure 1. Descriptive Statistics in Relation to Number of Hits (Grams Search Engine): the Major Categories of NPS Advertised on the Darknet.

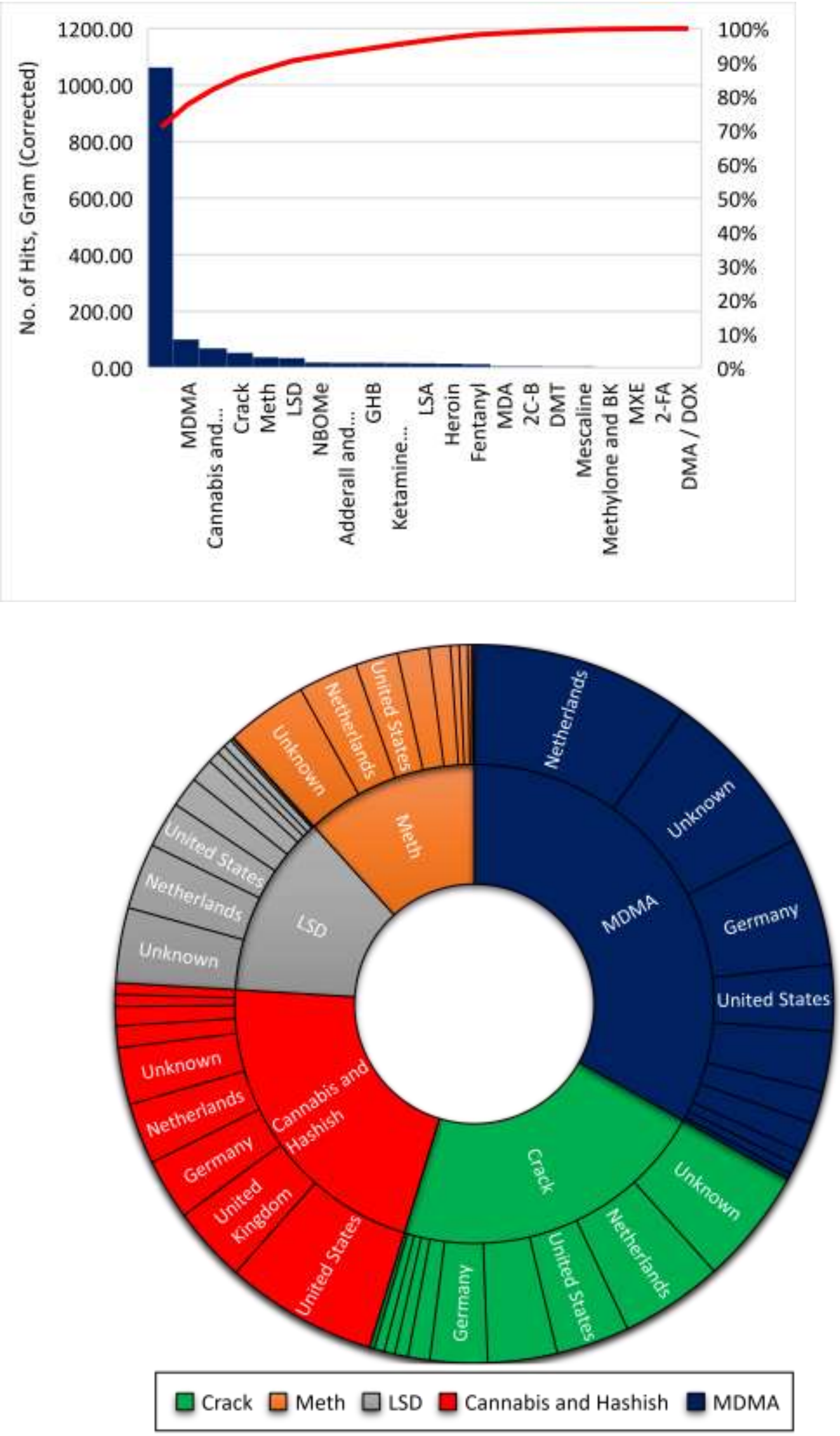
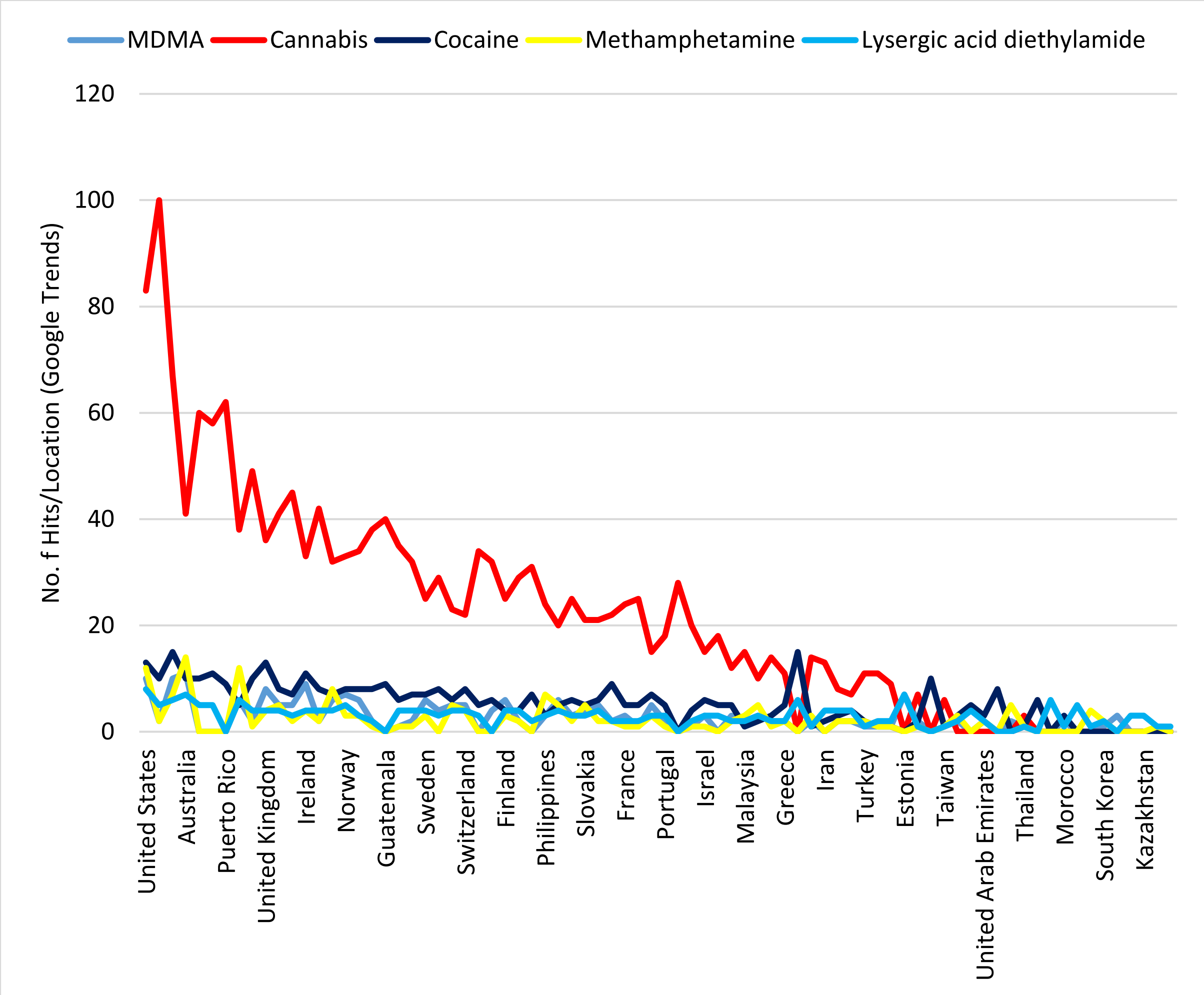


Figure 2. The Main Shipping Countries of the Most Popular NPS and NPS-related Substances on the Darknet.



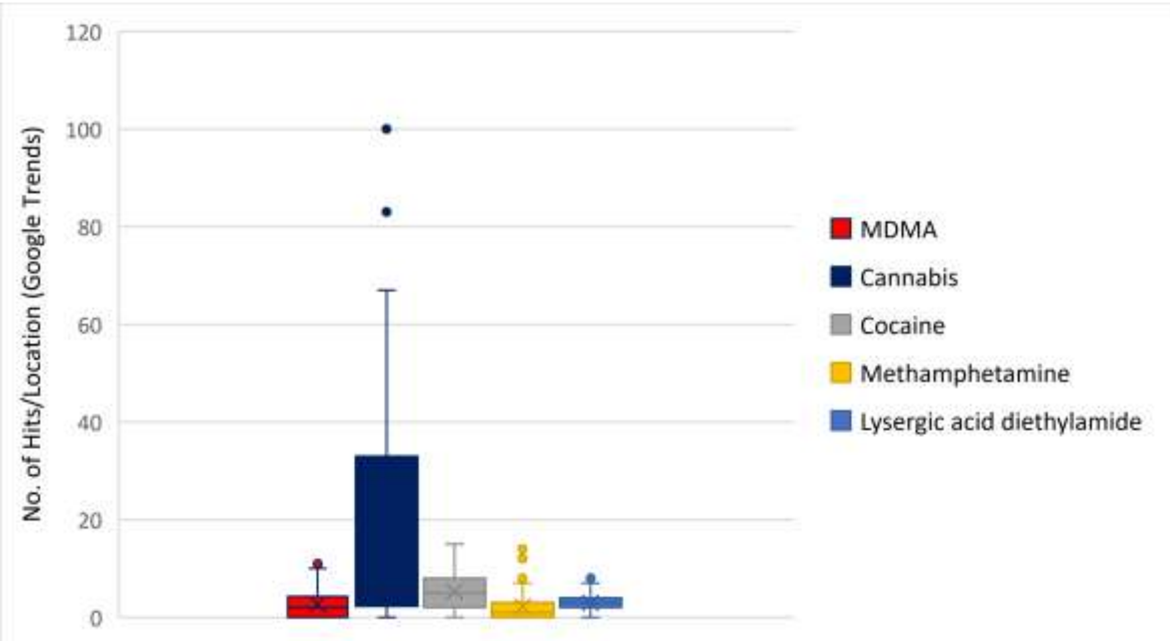


Figure 3. Geo-mapping of the Surface Web Users Attentiveness towards the Most Popular Psychoactive and Novel Psychoactive Substances on the Darknet.

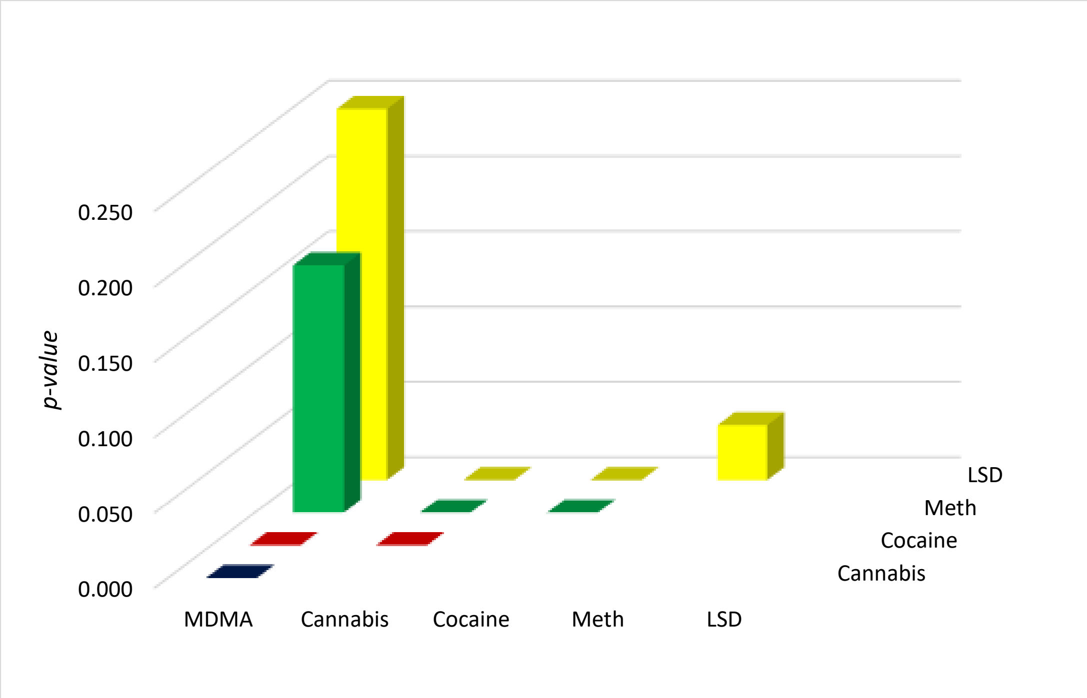


Figure 4. Google Trends: Inferential Statistics of the Most Popular Psychoactive and Novel Psychoactive Substances.

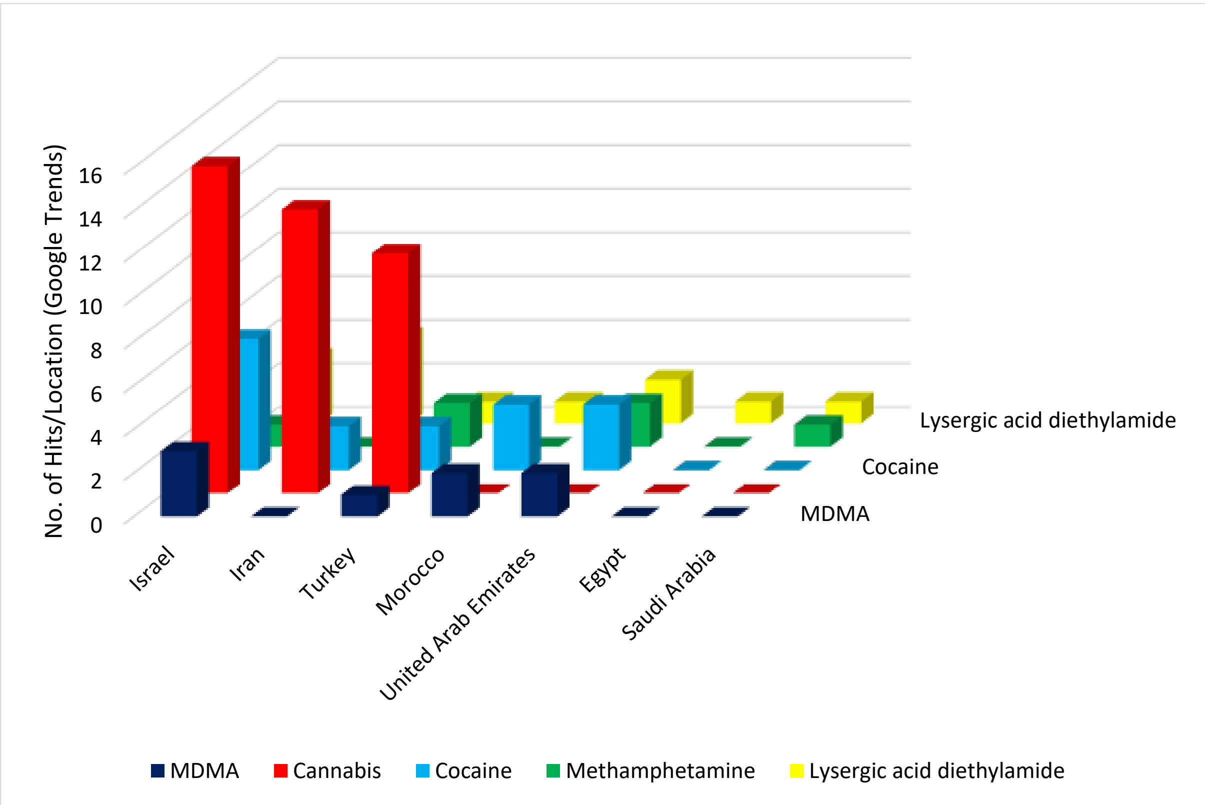
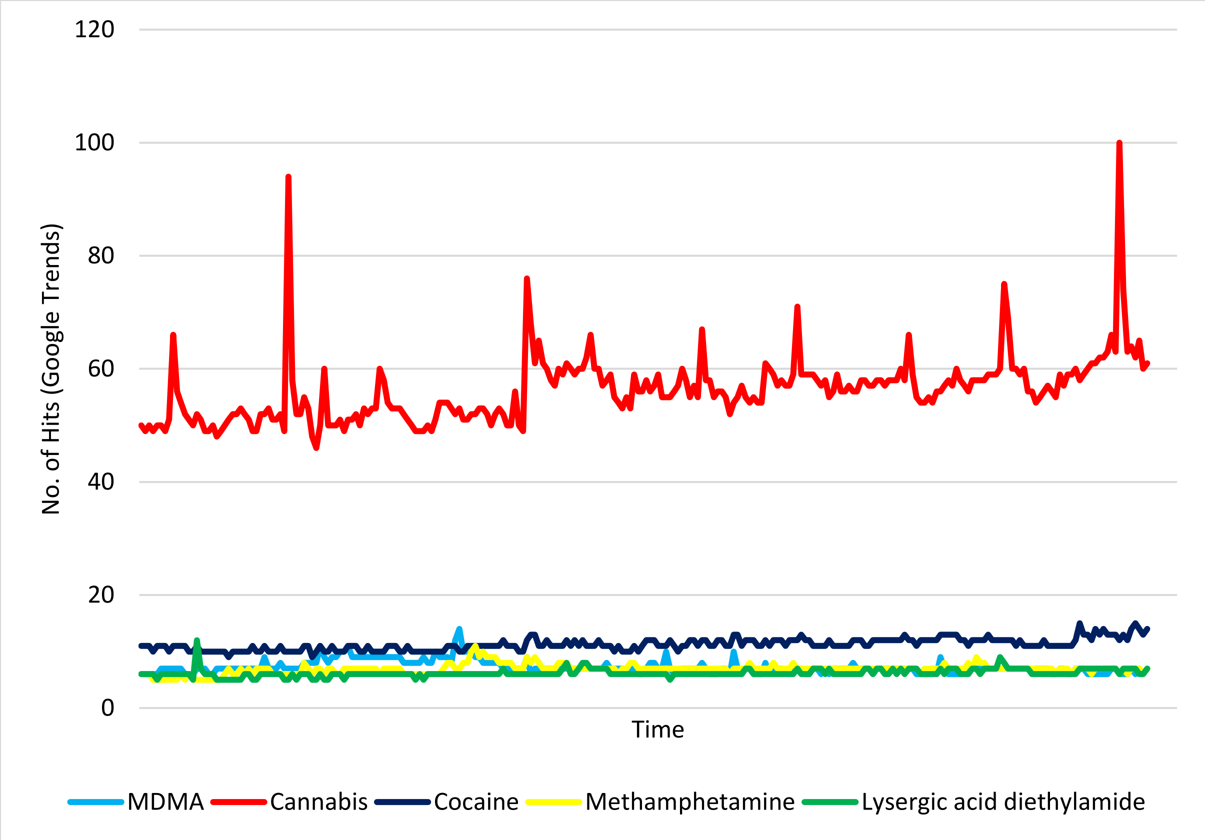


Figure 5. Geo-mapping on Google Trends: Contribution of the Middle East and the Arab World for High-risk and Popular NPS.



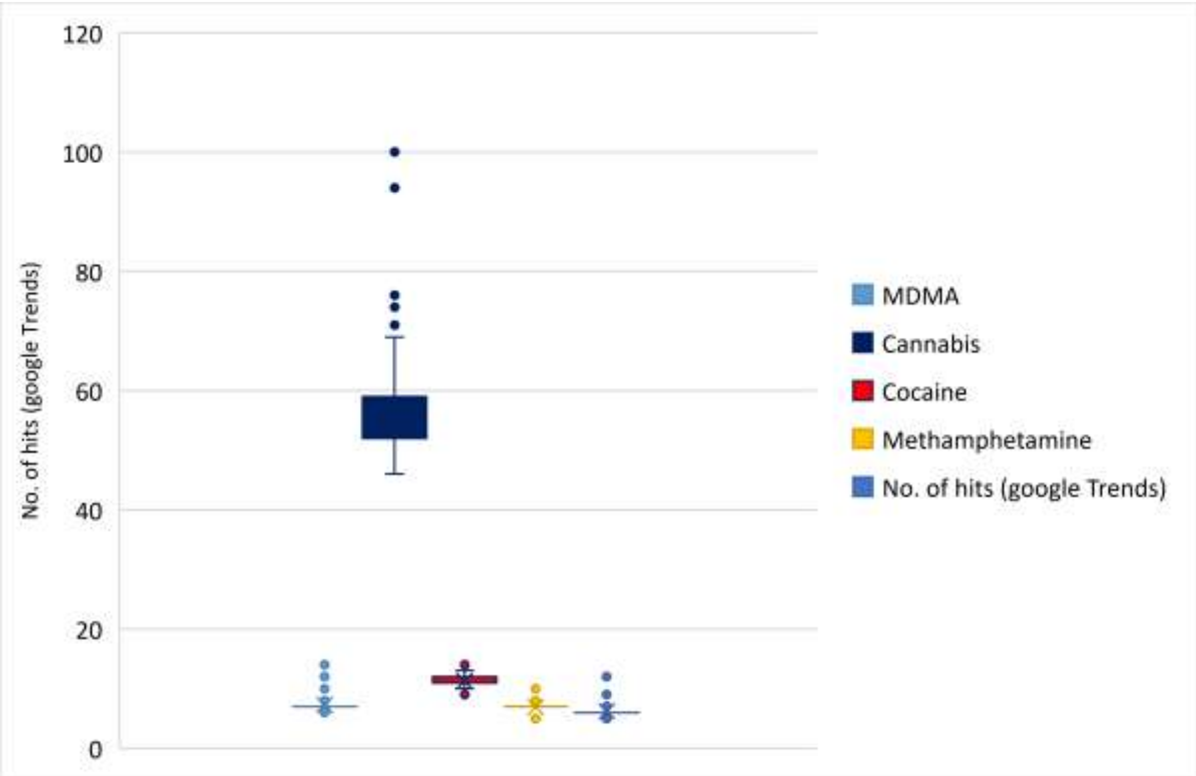


Figure 6. Google Trends: Historical Changes in the Trends for 2012-2016 (above), Boxplot Presentation (below).

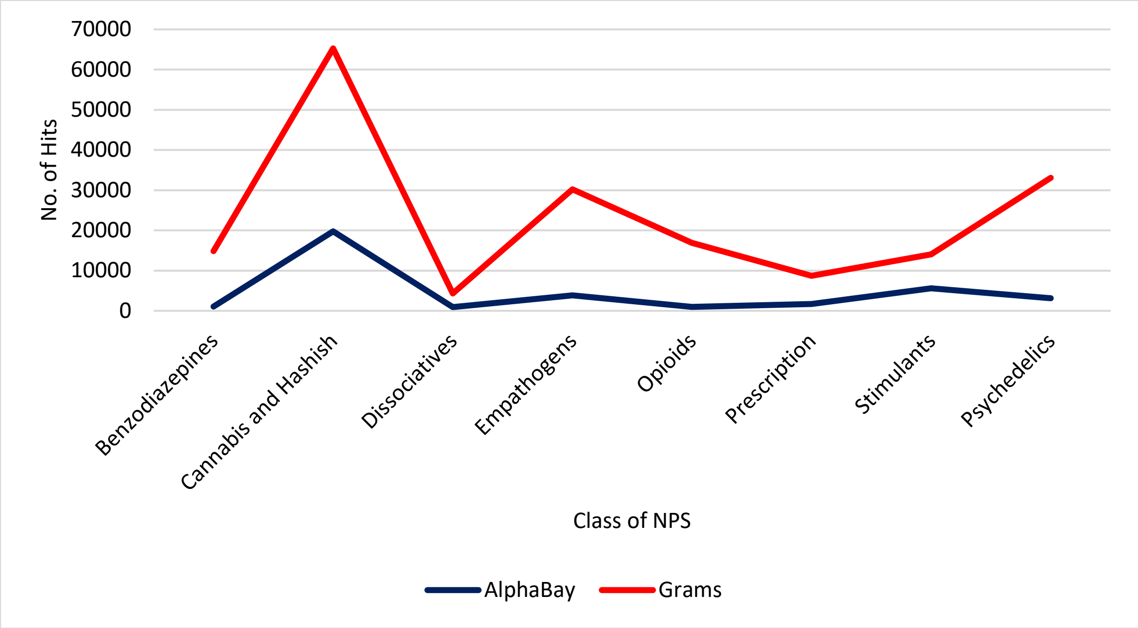


Figure Categoris of Psychoactive and Novel Psychoactive Substances on Grams Engine and AlphaBay.

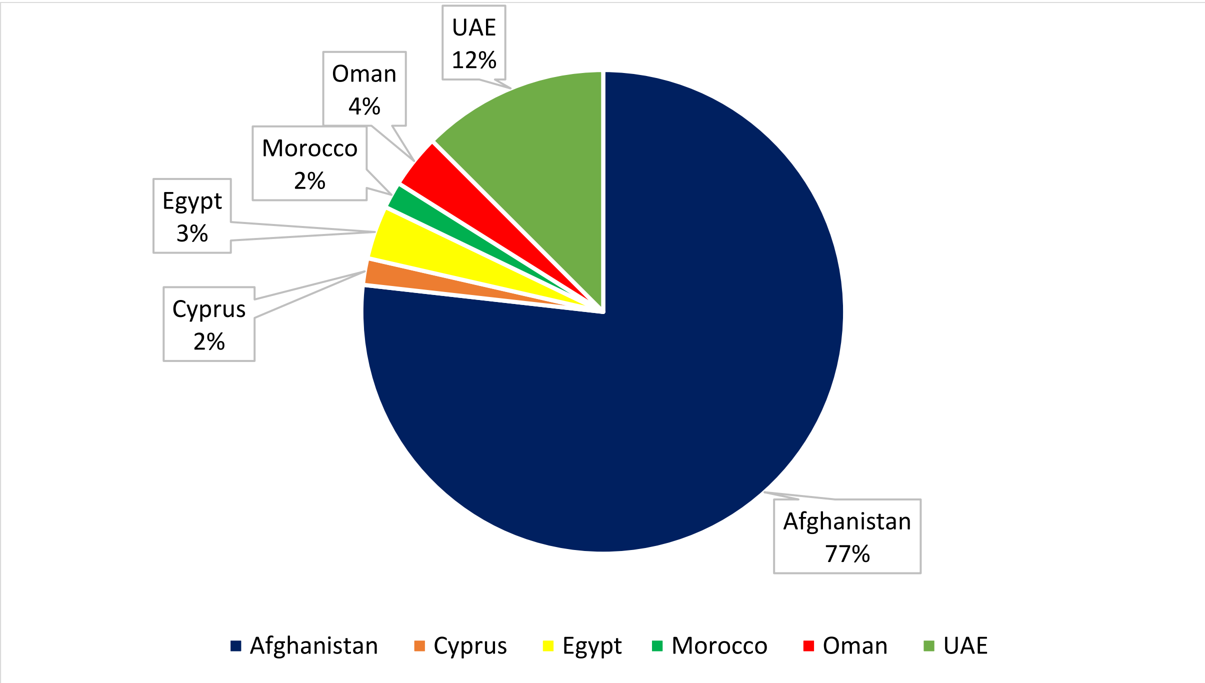


Figure 8. Geo-mapping within the Darknet: High-risk and Popular NPS in the Middle East and the Arabic World.

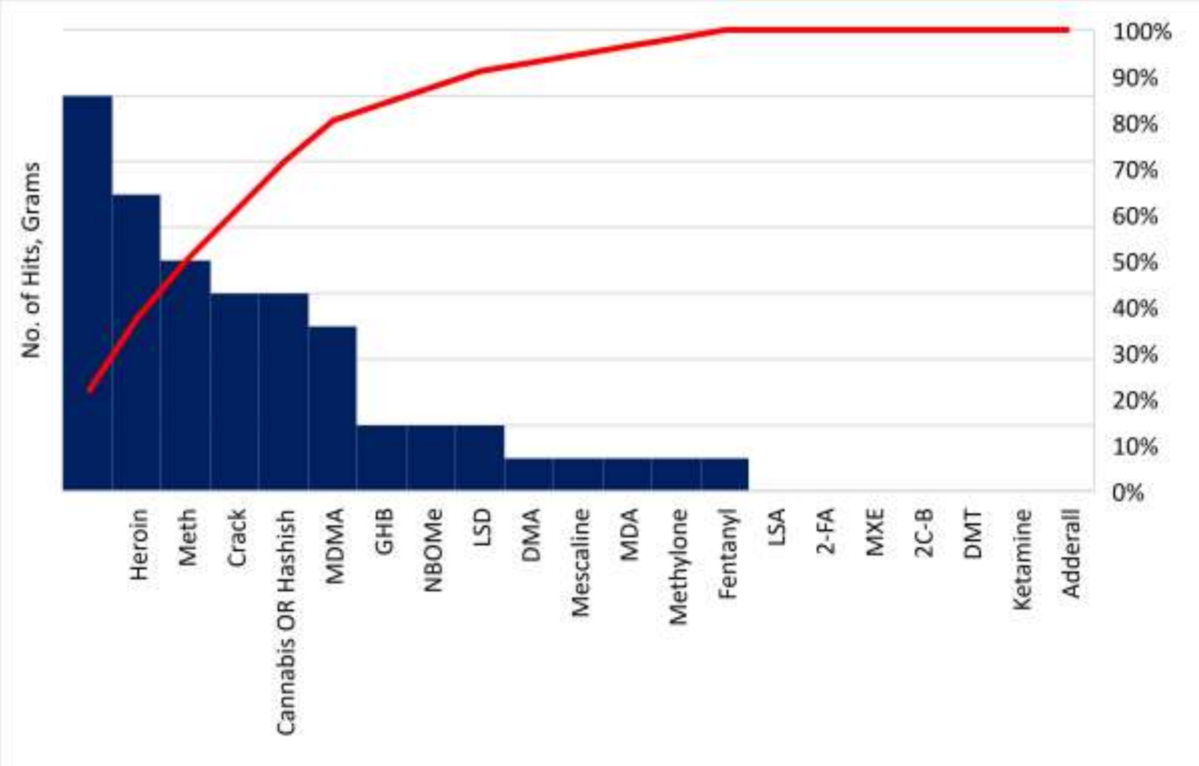


Figure 9. Geo-mapping of High-risk and Popular Psychoactive and Novel Psychoactive Substances in the Middle East and Arabic Countries.

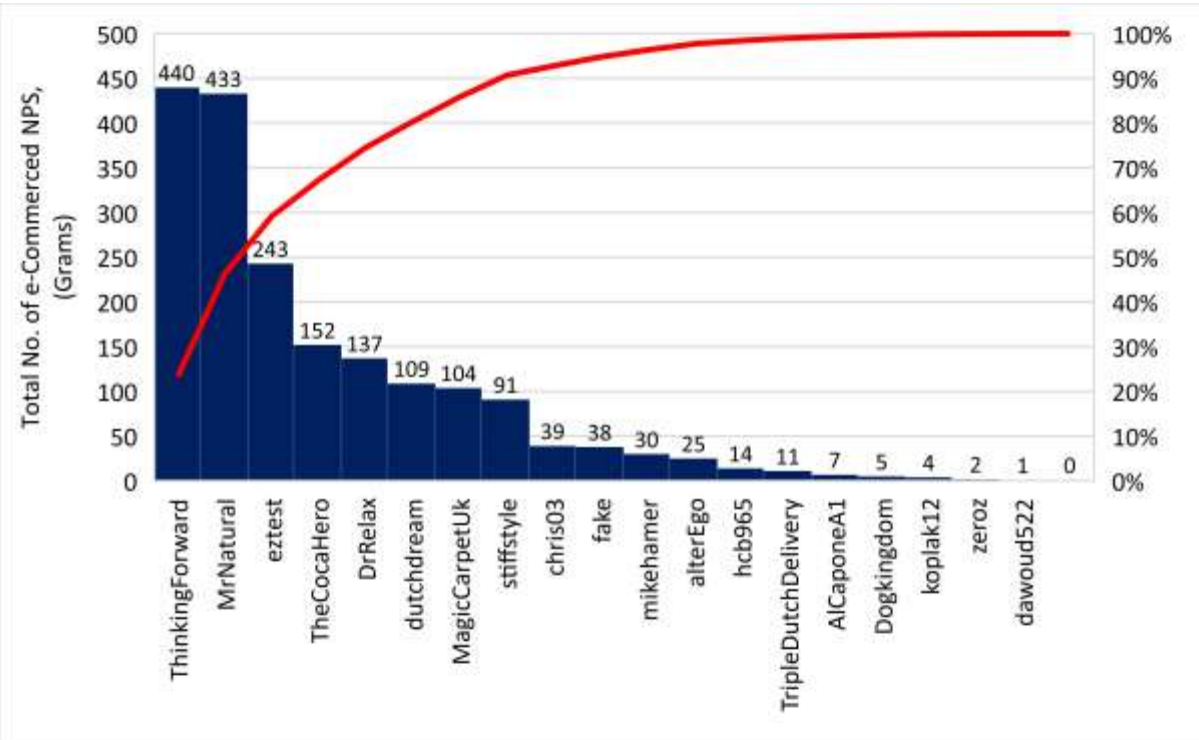
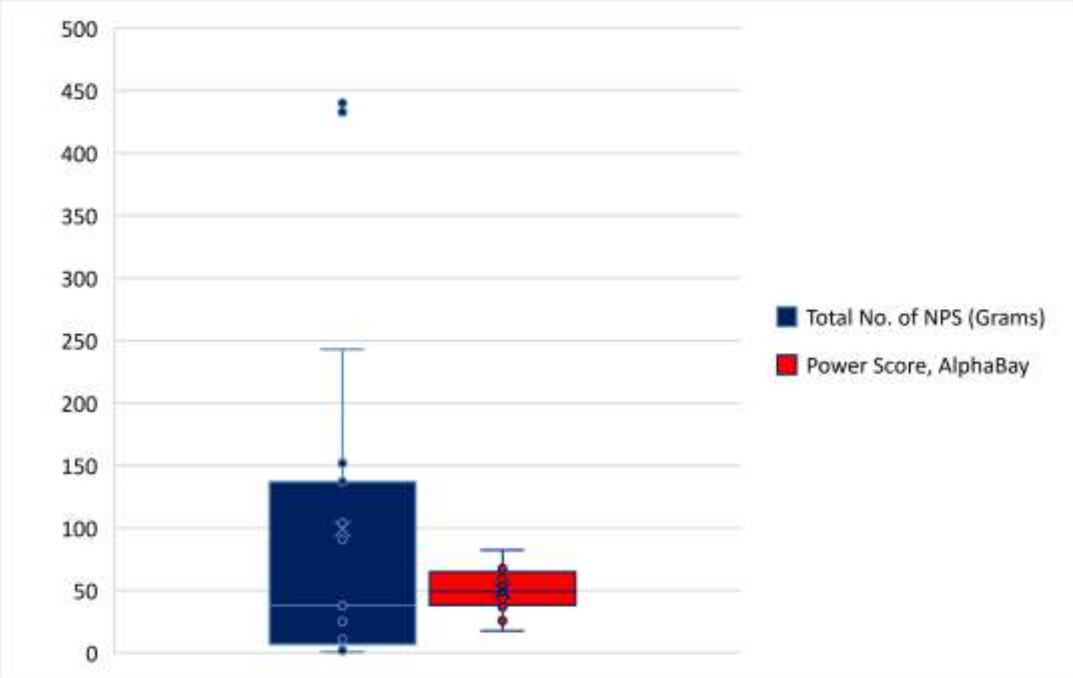


Figure 10. Geo-mapping of e-vendors from the Middle East and Arabic Countries: the Total Number of Hits on Grams Search Engine.



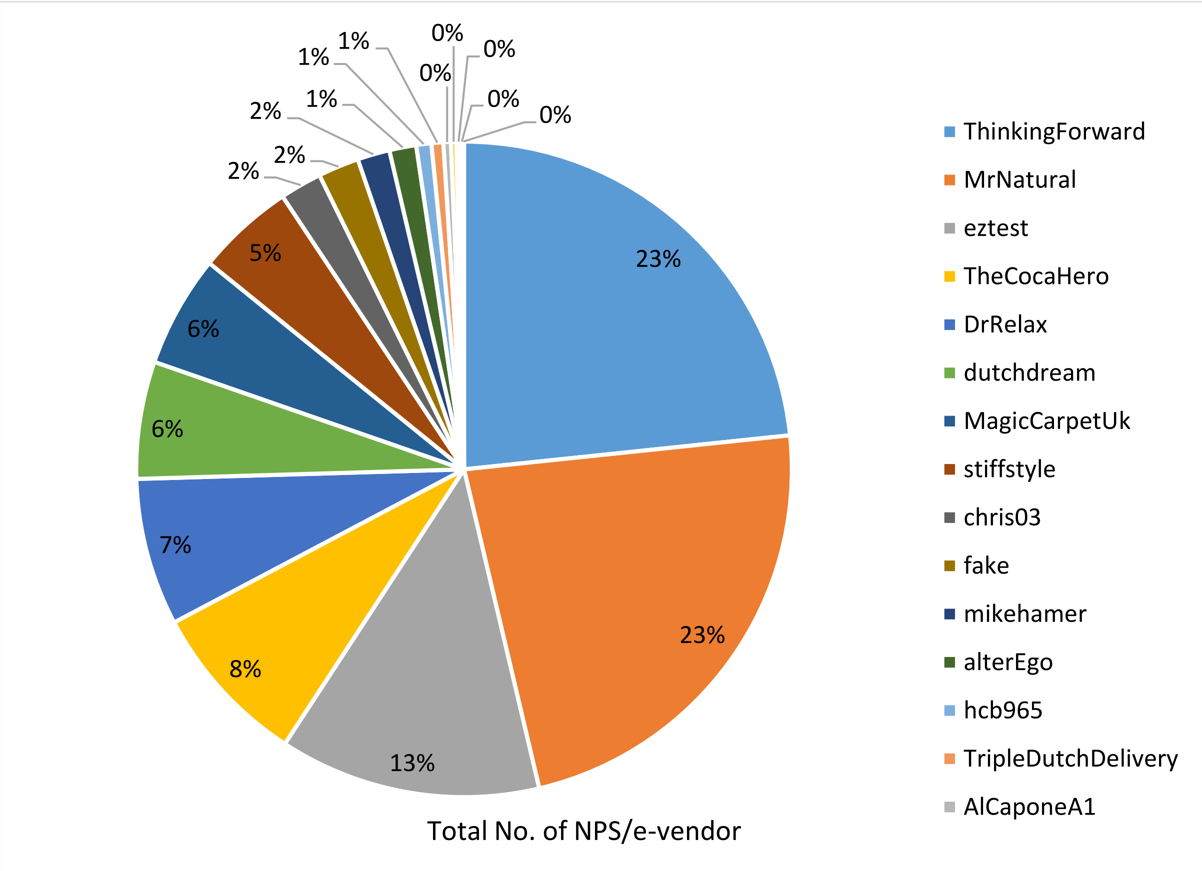


Figure 11. e-vendors operating in the Middle East: Boxplot Presentation (above), Number of Items Advertised on Grams Search Engine (below).

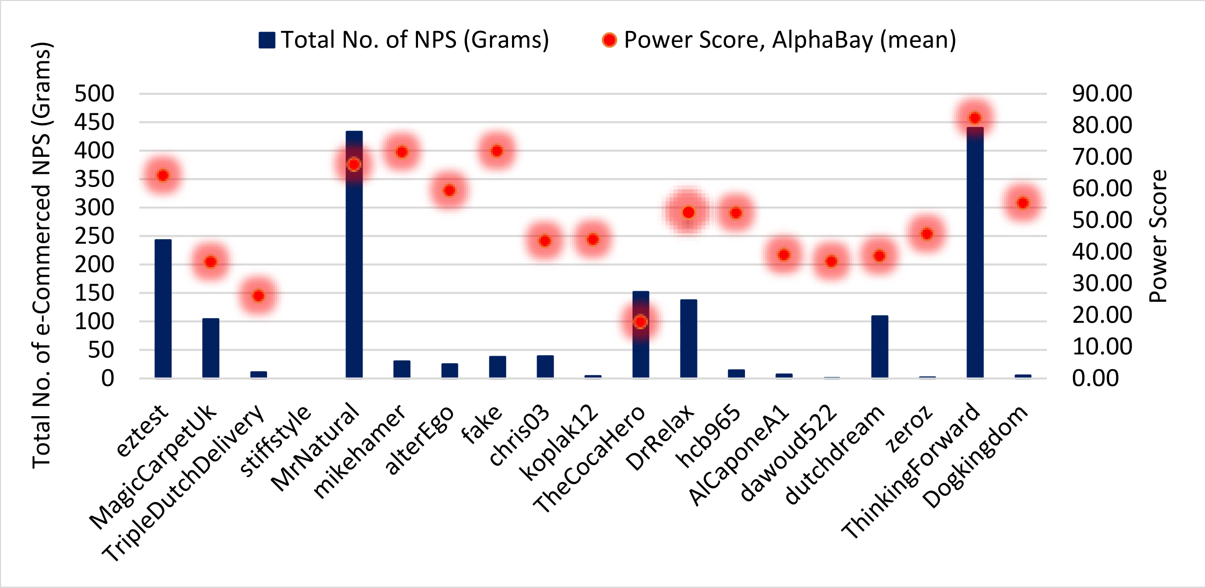


Figure 12. Total Number of Items (Grams Search Engine) and Power Score for e-vendors in the Middle East and Arabia.

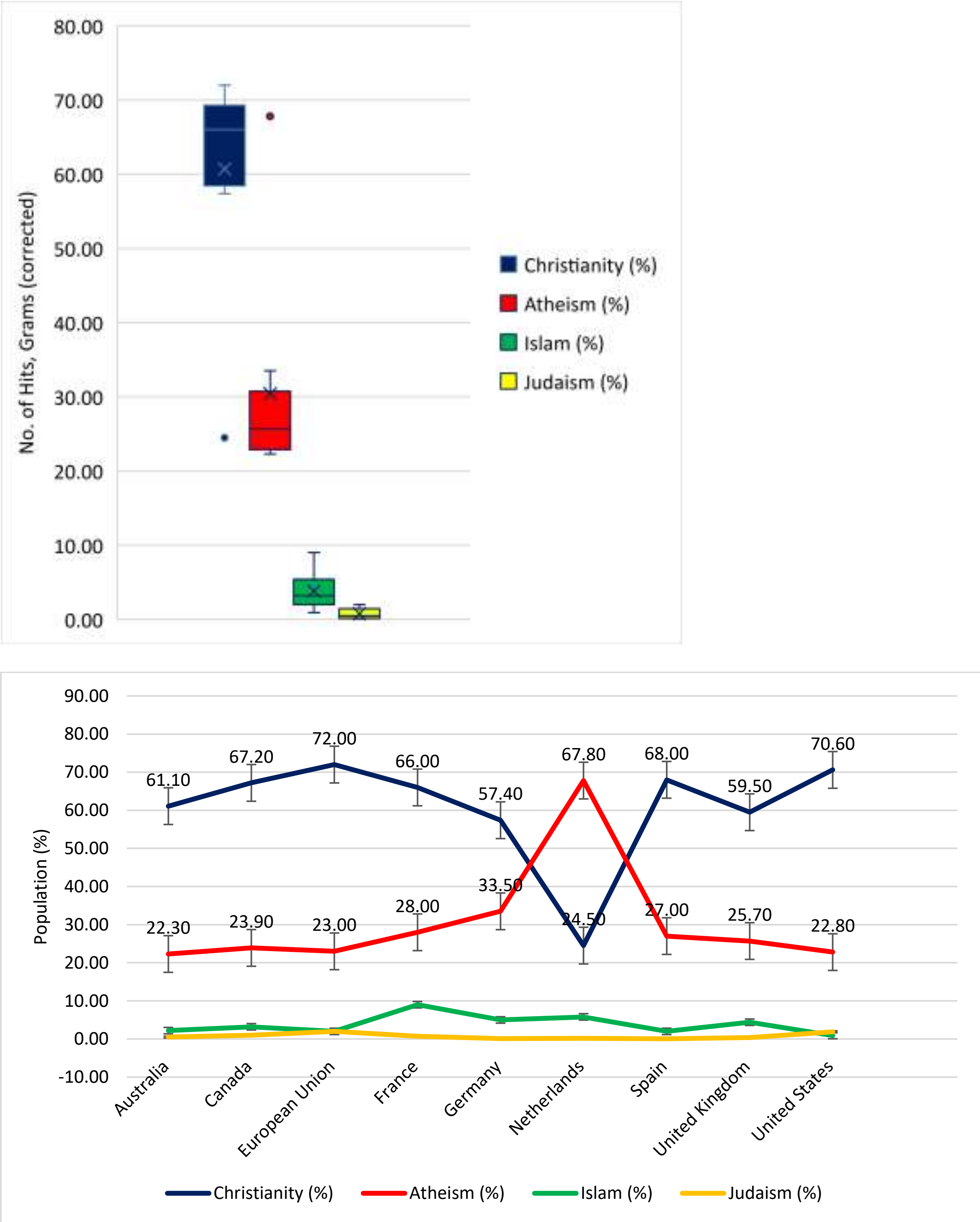


Figure 13. Descriptive Analysis: Religious Affiliation versus the Total Number of Hits (Grams) in Nine Countries of High NPS Prevalence.

I. NPS Prevalence in a Population of Iraqi Medical Students (Survey)

The e-form of the survey was *pilot-tested* by a group of 20 students; the average duration of time required to complete the questionnaire was 5.3 (+/- 1.2) minutes. The total number of participants was 458, including participants from year-1 students (n=157), year-2 to year-6 (n=301) (Appendix 8 and 9). This 1:2 ratio will enable and intergroup group analyses to be carried out in between students of years-1 versus students from year-2 to year-6, the aim of this intergroup correlation is to test the hypothesis if NPS awareness and prevalence of (ab)use will significantly vary as the students progress in the medical college.

In relation to year-1 students, the age of the participants was from 17-20 years with an average of 18.39 (+/- 0.65) years (Figure 1.1); the vast majority of year-1 participants were aged 18 (58%) and 19 years (33.1%). Females were the majority (58.6%). The majority were right-handed while left-handed were a minority (3.8%) as expected. Arabs were the most common ethnic group 96.8%, while Turkish and Kurdish people accounted for 3.1% and 0.6% respectively. The majority were Muslims 96.8%, while atheists and Mandaists accounted for 2.5% and 0.6% respectively. Most were residents of urban areas while rural area residents accounted for 7.6%; the majority of year-1 students lived with their parents (91.7%), few of them lived either with friends (6.4%) or a male/female partner (1.9%). Few of these students were employed (7.6%), and none of them was married (0%). Only 11.4% were diagnosed with either neurological or psychiatric condition, all of the psychiatric conditions were related to the neurotic spectrum including; generalised anxiety disorder (50%), personality disorders, social anxiety, panic attacks, phobias, tension headache ,and migraine headache; participants with psychotic disorders were not detected. On the other hand, 26.8% of the total year-1 population has disclosed their need to be evaluated by a psychiatrist either for social support or to treat an existing psychiatric condition. Only 15.3% used to regularly drink caffeinated beverages (Pepsi, Coca cola, etc.), while others were habituated to energy drinks (15.9%) or smoking (6.4%), but none of them (0%) used to drink alcohol or had an *alcohol use disorder* (AUD).

In relation to NPS awareness, year-1 students had some level of knowledge (24.2%), the rest of them (75.8%) never heard of any of the terms; *novel psychoactive substances*, *NPS*, *research chemicals*, *legal highs*, *designer drugs* or *street drugs*. Specific terms in the Arabic language were also screened for; these include; حشيش, قات, أفيون, أرتين, كبسله, نركيله, أركيله, مخدرات, كبتاغون, أوكتودرين, أولان, هالوبريدول, زولوفت, فاليوم, ليبريوم, كريستال, أكستاسي, ماجنوليا, الخ. In relation to those who were aware of NPS, the level-of-knowledge was; negligible (33.8%), beginner (35%), intermediate (26.8%), or advanced (4.5%). Students have also identified their source of knowledge on NPS from; Internet (45.2%), lectures

(36.3%), friends and family (24.2%), textbooks (14%), newspapers and media (4.5%), online drug fora (0.6%), and other undesignated resources (1.3%). The top known traditional psychoactive and novel psychoactive substances were (Figure 1.2); valium (50.3%), opium and opioid-related substances (20.4%), Xanax (14.6%), cannabis, hashish, and synthetic cannabinoids (10.8%), amphetamines and amphetamine-type stimulants (8.9%), Crystal Meth (8.3%), Krokodil (7.6%), Khat (6.4%), Salvia Divinorum (4.5%), captagon (4.5%), Haldol (4.5%), Olan (2.5%), octodrine (2.5%), Ayahuasca (1.9%), and NBOMe (0.6%). Less than one-tenth (9.6%) of the year-1 population used one or more of these substance; the (ab)use was categorized based on the frequency of use into; few occasions per year (52.6%), on monthly basis (31.6%), and on weekly basis (15.8%), while none has used NPS on a daily basis. In relation to the chronicity of (ab)use, these were categorised into; few months (26.3%), 1-5 year (36.8%), more than 5 years (26.3%), and more than 10 years (10.5%). The (ab)users used to purchase their substances from; friends and family members (40%), from local pharmacies and ”chemists” shops (40%), or from the internet via e-commerce (20%). Additionally, 15.3% of the year-1 population were aware of the presence of e-commerce activity in relation to these substances. Only 42.1% of NPS (ab)users admitted to being taken to the hospital due to some serious adverse reactions or intoxication (Figure 1.3), these included; loss of consciousness (3.8%), hypersensitivity and allergic reactions (3.8%), delusions (3.2%), cardiac and vascular problems (2.5%), respiratory problems including asthma and suffocation (2.5%), hallucinations (1.3%), musculoskeletal problems (1.3%), aggression and violent behaviour (1.3%), and blood-transmitted diseases including hepatitis and HIV (AIDS) (0.6%).

In relation to year-2 up to year-6 students, the age of the participants was from 18-24 years with an average of 20.36 (+/- 1.15) years (Figure 1.4); the vast majority of participants were aged 20 (33.6%) 21 (24.9%), and 19 (24.3%). Females were the majority (69.4%). The majority were right-handed while left-handed contributed to 8%. The most common ethnic group (Figure 1.5) were Arabs (88.7%) and Christian ethnicities (5.6%), while Kurdish and Turkish people accounted for 3.3% and 1.3% respectively, other ethnicities contributed modestly (1%). The majority were Muslims (92%), Christians (5.6%), Mandaists (2%), and atheists (0.3%). Most were residents of urban areas (96.7%) while rural area residents accounted for 3.3%; the majority of year-2 to year-6 students lived with their parents (95%), few of them lived either with friends (2.7%) or a male/female partner (0.3%), and only 2% lived alone. Few were employed (7%), while the rest were unemployed. Those who were married accounted for 1.7%. Only 16.9% were diagnosed with either neurological or psychiatric condition; all of the psychiatric conditions were related to the neurotic spectrum including; generalized anxiety disorder (27.5%), depression, personality disorders, irritable bowel syndrome (IBS), social anxiety, panic attacks, phobias, tension headache ,and migraine headache; participants with psychotic disorders were not detected. On the other hand, 39.2% of the total year-2 to year-6 population has disclosed their need to be evaluated by psychiatrists, which is significantly higher than in year-1 participants (26.8%); most of those declared their need to see a psychiatrist either for social support or to treat an existing psychiatric condition. Only 15.6% used to regularly drink caffeinated beverages (Pepsi, Coca cola, etc.), while others were habituated to energy drinks (12%) or smoking (11.3%). Alcohol intake prevalence was found to be 1.3%, while AUD was estimated to be a bit less (0.7%). Alcohol consumption seems to be increasing as the students progress in the medical college.

In relation to NPS awareness, year-2 to year-6 students had some level of knowledge (27.6%), the rest of them (72.4%) never heard of any of the terms; *novel psychoactive substances*, *NPS*, *research chemicals*, *legal highs*, *designer drugs* or *street drugs*; the level of awareness was not significantly greater than in year-1 students (*p-value*=0.77). Of those who are aware of NPS, the level-of-knowledge was categorised as; negligible (26.9%), beginner (44.5%), intermediate (23.9%), or advanced (4.7%); these were also not significantly different from year-1 participants (p=0.41). Students have also identified their source of knowledge on NPS from; Internet (41.5%), lectures (38.2%), friends and family (18.6%), textbooks (9%), newspapers and media (3.3%), online drug fora (1%), and other undesignated resources (9.3%). The top known traditional psychoactive and novel psychoactive substances were (Figure 1.6); valium (67.8%), opium and opioid-related substances (51.5%), Xanax (17.9%), cannabis, hashish, and synthetic cannabinoids (25.9%), amphetamines and amphetamine-type stimulants (65.1%), Crystal Meth (9.3%), Krokodil (6.3%), Khat (17.3%), Salvia Divinorum (2%), captagon (10.6%), Haldol (8.6%), Olan (8.6%), octodrine (3.7%), Ayahuasca (0.7%), and NBOMe (0.3%). More than one-tenth (15%) used one or more of these substances and these were significantly higher than in year-1 students (*p-value*<0.001); the (ab)use was categorized based on frequency of use into; few occasions per year (84.6%), monthly-basis (3.8%), weekly basis (3.8%), while those who (ab)used substances on a daily basis were a bit higher (7.7%). In relation to chronicity of (ab)use, these were categorised into; few months (28.6%), 1-5 year (28.6%), more than 5 years (39.3%), and more than 10 years (10.7%). The (ab)users used to purchase their substances from; friends and family members (26.2%), from local pharmacies and "chemists" shops (67.4%), or from the internet via e-commerce (6.4%). Additionally, only 15% of the year-2 to year-6 population were aware of the presence of e-commerce activity in relation to pschoactive substances. Only 42.1% of NPS (ab)users admitted to being taken to the hospital due to some serious side effect or adverse reactions (Figure 1.7), these included; loss of consciousness (1.7%), hypersensitivity and allergic reactions (3%), cardiac and vascular problems (2%), respiratory problems including asthma and suffocation (1.7%), hallucinations (3.3%), musculoskeletal problems (3.7%), aggression and violent behaviour (1.3%).

II. Psychedelic User and the Abuse of Power (Internet Snapshot no.1)

The number of words per comment (WPC) averaged 14.6 words. Exceptional (statistical outliers) included comments with 31 to 224 words per comment (Figure 2.1). The majority of commenting psychedelics users were males (85.2%) versus females (14.8%). Positive (optimistic) and negative (pessimistic) ideas were diverse; examples of these comments; *Destroy the universe*, *Create another reality where evil doesn't exist*, *Suicide*, *Kill myself*, *Destroy all humans*. The overall theme of comments (Figure 2.2) was either positive (27.3), negative (57.6%), or uncategorizable-unspecific (15.2%), the contribution of males and females to each thematic category appeared to be proportional.

The geo-mapping was consistent with data from the previous chapters; the highest proportion of users was from developed countries and the western world (Figure 2.3 to 2.5) especially from the US, UK, Canada, and Western Europe. On the other hand, the Middle East and Arabic countries contributed the least to this online community. The top contributing countries to negative comments, included (descending order); US, UK, Canada, Germany, Netherlands, Australia, Bulgaria, Croatia, Russia, and Sweden. Middle Eastern and Arabic countries included; Iran, Morocco, and Turkey. Top contributing countries to positive comments, included; US, UK, Canada, Netherlands, Australia, Belgium, Denmark, Italy, Sweden, and the Czech Republic. Middle Eastern and Arabic countries included; Israel, Turkey, and Iraq. Top contributing countries to uncategorizable comments, included; US, UK, Mexico, Germany, Sweden, Romania, Malaysia, Lithuania, Israel, Denmark, and China. Israel was the only contributing country from the Middle East. Exceptional (outliers) contributing countries included three countries; US, UK, and Canada.

The number of words per comment was analysed using ANOVA test in relation to the nature-theme of comments (positive, negative, and uncategorizable), for which there was a statistically significant difference (*p-value*<0.001). The number words per comment (Figure 2.6) averaged; 10.8 (N), 24.4 (P), and 11.6 (U). Additional inferential statistics were done using t-test (Figure 2.7); there was no significant difference in length of negative and uncategorizable comments (p=0.404). On the other hand, psychedelic users with positive theme (optimistic users) commented significantly more than users of; negative comments (p=0.001), and uncategorizable comments (p=0.005). It means that psychedelic users with positive ideas tend to speak and elaborate, while other users (negative and uncategorizable) tend to be brief in their commentaries. Student’s t-test was also used to detect any significant difference in the length of comments between males and females; males appeared to comment more (more words per comment) than females regardless of the theme (positivity-negativity) of the commentary (15.7 versus 8.2, *p-value*=0.012).

Linear regression (Figure 2.8) was constructed for correlation of; gender versus nature (theme) of comment (1), words per comment versus theme of comment (2), gender versus words per comment (3). Each of the *gender* and *theme* of comments were encoded to enable this parametric analysis. It appears that gender and themes of comments were not correlated (R^2 *score* of 0.0003), males and females contributed similarly (proportionally) to all themes of comments (P,N, and U). Females tend to comment with fewer words (R^2=0.0102) unless their comments are positive. The conclusion (inferred via t-test) that positive comments tend to be more detailed and elaborate (more words per comments) was also confirmed via linear regression (R^2=0.057).

III. The Preferred Terminology Implemented by Psychedelic Users (Internet Snapshot no.2)

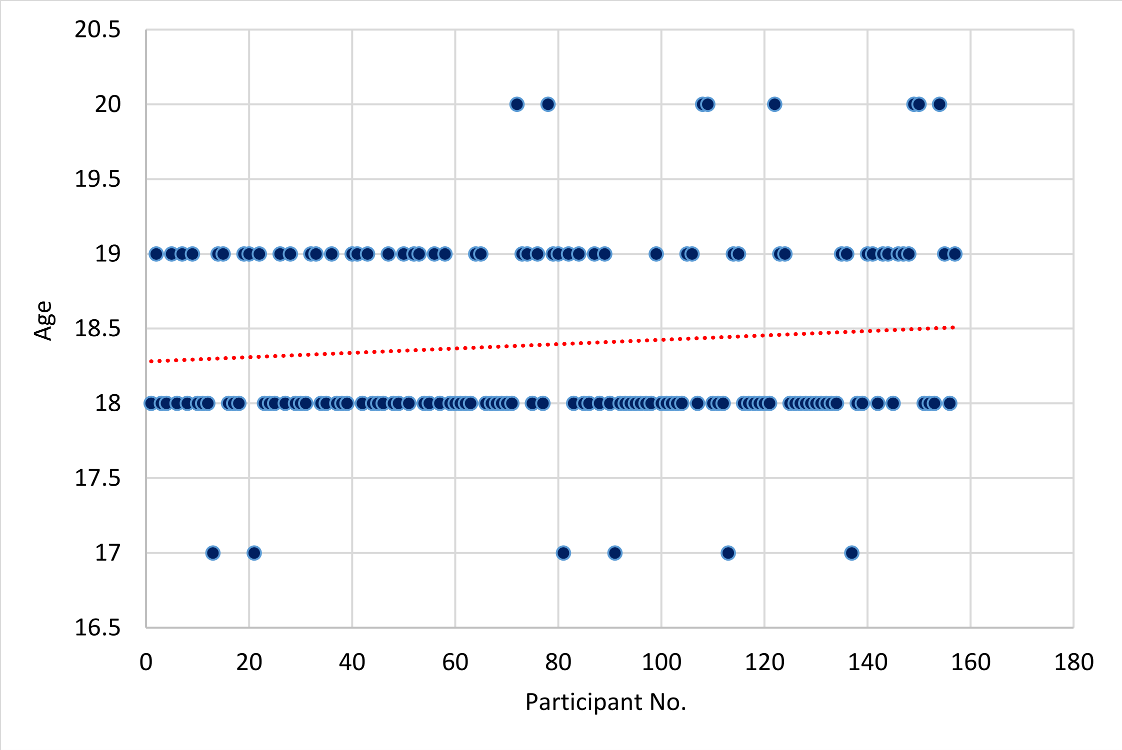
The discovered terms during the initial screening were; *Psychedelic*, *Entheogen* (generating the divine within), *Hallucinogen*, *mysticomimetic* (mimicking mystical state), *Oneirogen* (creating dreams), *Psychotomimetic* (mimicking psychosis), *Psychotogen* (Producing psychosis), *Spiritual Aids*, and *trip*. Accordingly, the most used term for each user was tabulated together with his (her) demographics (Appendix 10); age, gender, handedness, and sexual orientation (whenever known) in a database of 239 entries (Figure 3.1). Their age was ranging from 14 to 70 years; median age was 25, the mean age was 30.7 (+/- 14.4) years, while the most common age (mode) was 22 years. Exceptional age (statistical outliers) for users was at least 61 years old; exceptional age groups for psychedelic users should be investigated in future studies and beyond the scope of this dissertation. Males predominated the studied population at 74%, while females represented 24%, the rest of the population (2%) identified themselves as transgender individuals (Figure 3.2). The majority of the users were right-handed (92.1%), while left-handed individuals represented the remaining population (7.9%), and no ambidextrous individuals were detected. The handedness of this population of psychedelic e-users is in harmony with that of the normal population (Corballis, 2014; Costanzo et al., 2015). Apparently, there are no indicators of a particular correlation between cerebral dominance (represented by handedness) and the tendency to (ab)use psychedelic substances. Similarly, most of the users were heterosexual (85.5%), bisexual individuals were relatively high (13.9%), while homosexual individuals (gays and lesbians) were a minority (0.6%). Accordingly, it is possible that sexual orientation to be correlated with the tendency to (ab)use hallucinogenic substances or other NPS, larger samples are required to be studied for this purpose.

The majority of males and females were right handed (Figure 3.3), left-handed men and women represented 5% and 2% respectively, while transgender individuals were exclusively right-handed. The most frequently used terms (Figure 3.4) were; psychedelic (73%), entheogen (12%), hallucinogen (11%), spiritual aids (3%), mysticomimetic (1%), psychotomimetic (<1%), medicines (<1%), and trip

(<1%). Further descriptive analysis (Figure 3.5) showed that right-handed users who used the term *psychedelics* were a majority (53%), while right-handed individuals using the terms entheogen and hallucinogen represented 8% for each.

Student's t-test (unpaired) found no difference in age of males and females (30.9 +/- 14.4 versus 30.6 +/- 14.7, *p-value*=0.44). However, there was there was a significant difference in relation to handedness; right-handed psychedelic users were significantly older than left-handed (31.2 +/- 14.8 versus 25.8 +/- 7.7, p=0.013). The top three used terms were; *psychedelic* (rank 1st), *entheogen* (2nd), and *hallucinogen* (3rd). These were further analysed for differences in age (Figure 3.6); Individuals who used the term *psychedelic* were significantly younger than those who used the term *hallucinogen* (29.1 +/- 14.5 versus 35.8 +/- 15.2, *p-value*=0.025), the same individuals were also significantly younger than the ones who frequently used the term *entheogen* (29.1 +/- 14.5 versus 33.2 +/- 11.5, p=0.049). On the other hand, there was no significant difference in age in between individuals who used the terms *entheogen* and *hallucinogen* (p=0.248).

There was also significant difference (Figure 3.7) in the age in between right-handed and left-handed people who preferred to use the term *psychedelics*, right-handed individuals were older (29.9 +/- 15.5 versus 24 +/- 5.3, *p-value*=0.006), while there was no significant difference in age in between right and left-handed individuals in relation to the other two frequently used terms; *hallucinogen* (p=0.333) and *entheogen* (p=0.312). Inferences were different when it came to the analysis of terms versus gender and handedness (Figure 3.8); right-handed females who used the term *entheogen* were significantly older than right-handed males who used the same term (41.1 +/- 10.2 versus 30.4 +/- 10.9, p=0.012). On the other hand, there were no significant differences in age between right-handed males and right-handed females who used the terms; *hallucinogen* (p=0.236) and psychedelic (p=0.119).



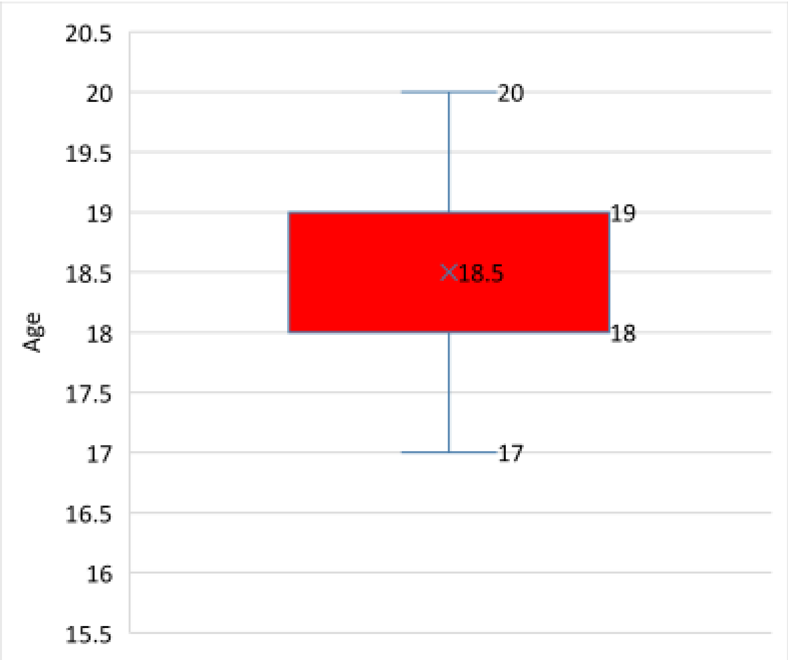


Figure 1.1. The Age of Participants from Year-1: Scattered Diagram (above), Boxplot Presentation (below).

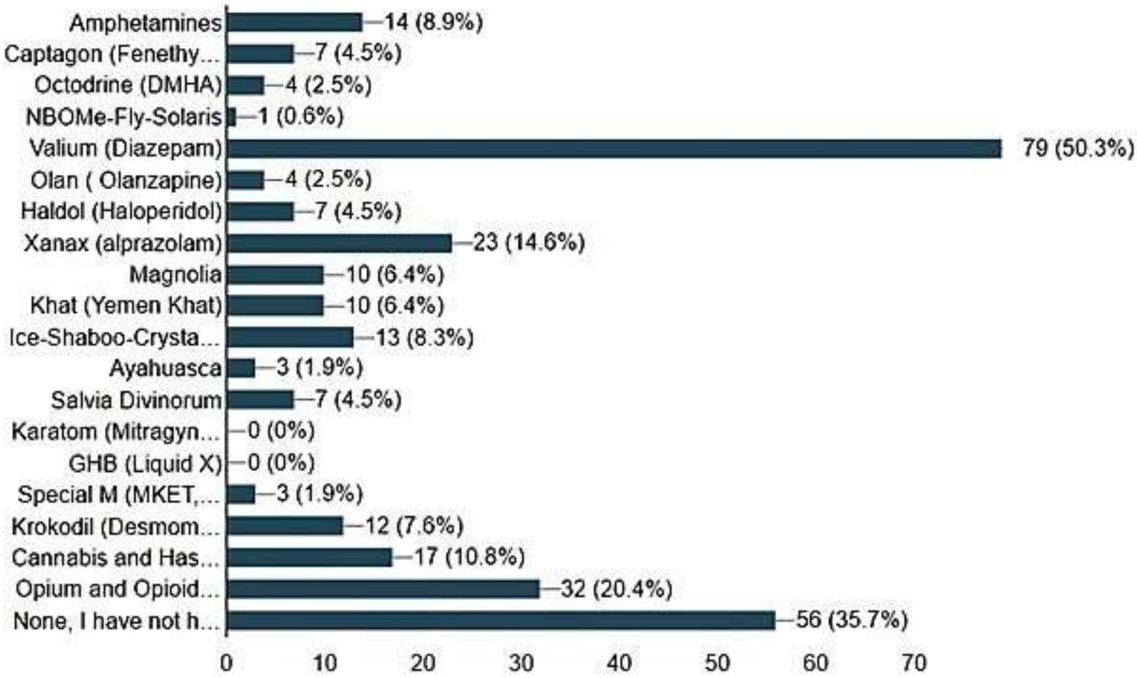


Figure 1.2. The Awareness of Year-1 Students Towards Selected Psychoactive and Novel Psychoactive Substances.

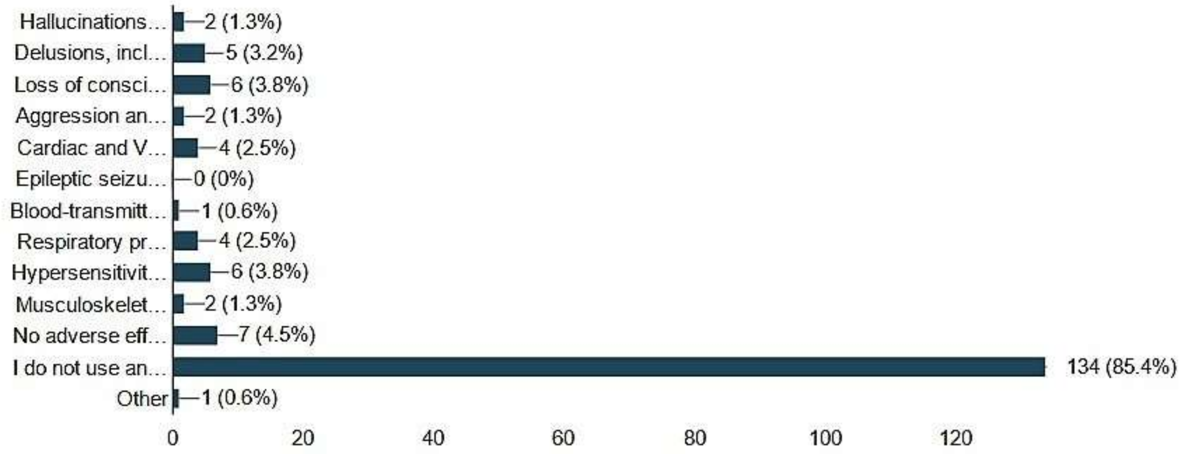
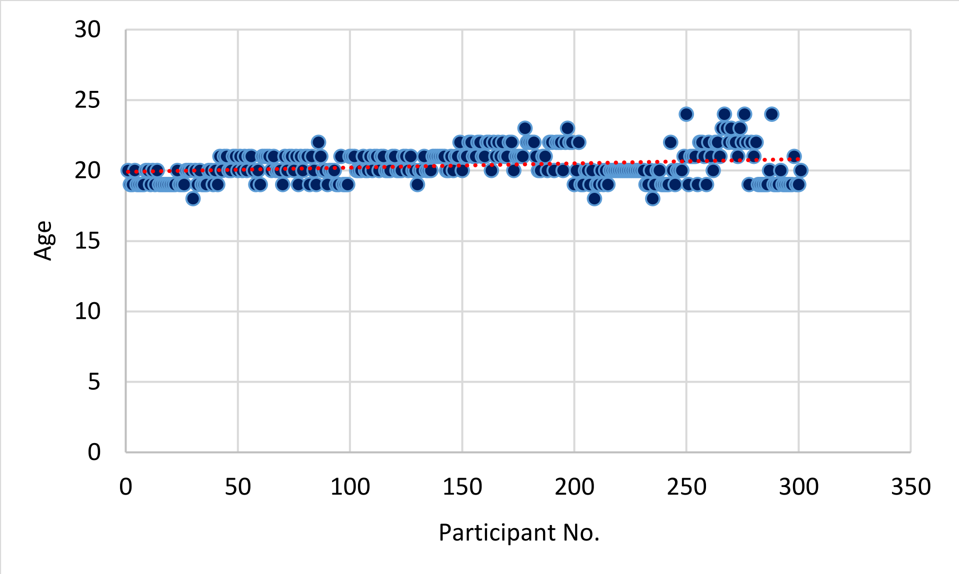


Figure 1.3. The Most Commonly Encountered Adverse Reactions in Year-1 Students.



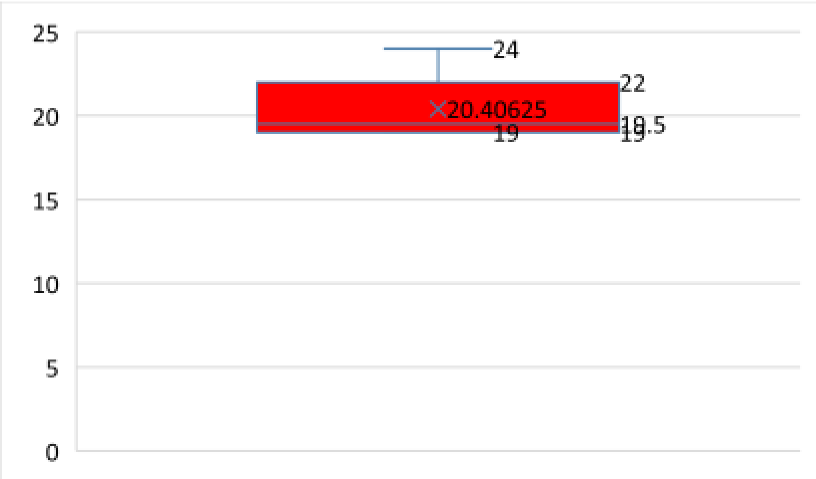


Figure 1.4. Age of Participants from Year-2 to Year-6: Scattered Diagram (above), Boxplot Presentation (below).

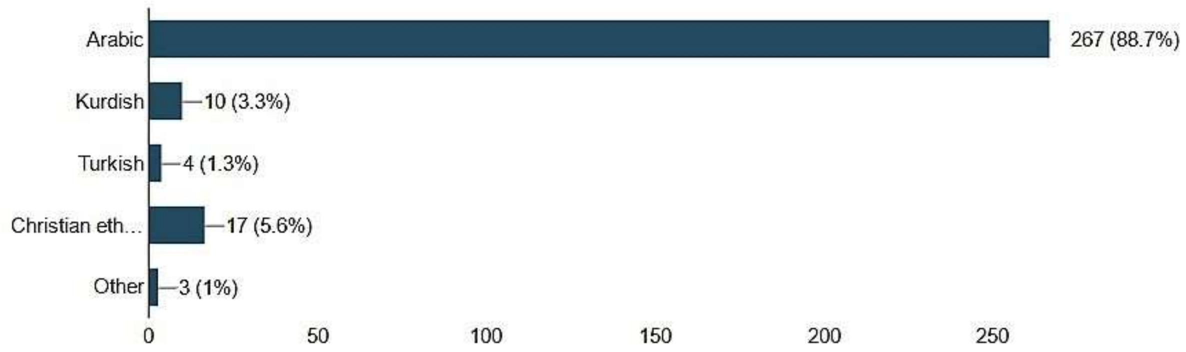


Figure 1.5. Ethnic Distribution of Survey's Participants, Year-2 to Year-6.

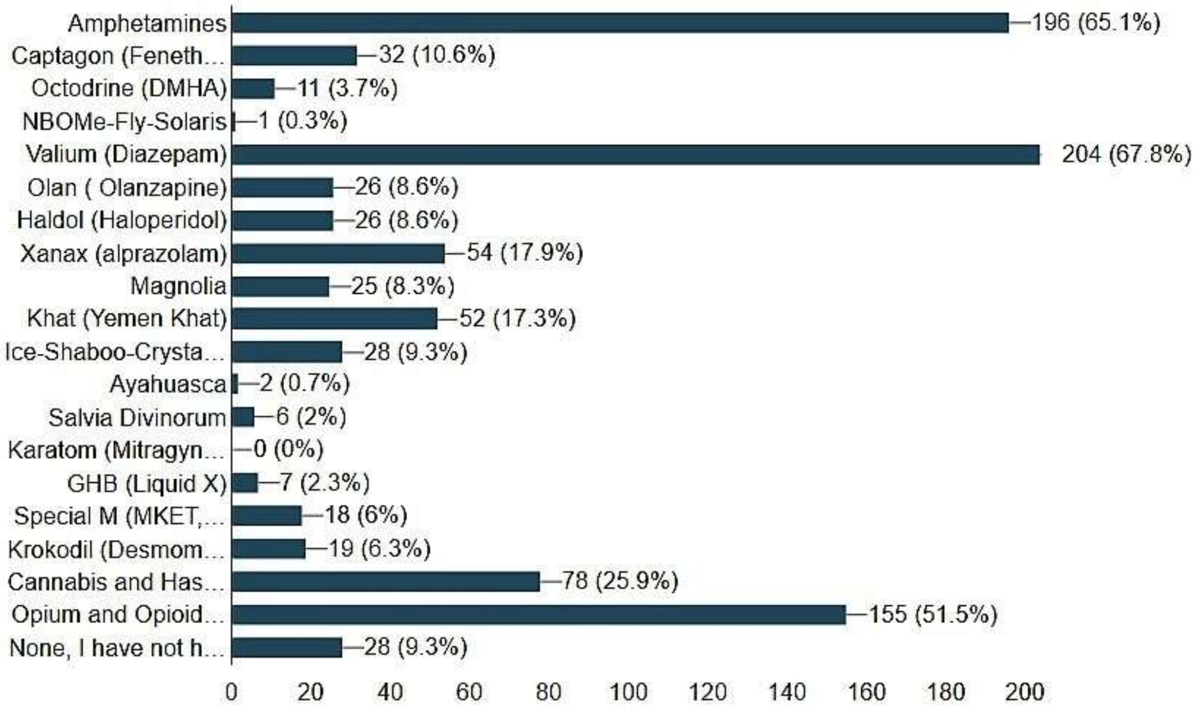


Figure 1.6. The Awareness of Year-2 to Year-6 Students Towards Selected Psychoactive and Novel Psychoactive Substances.

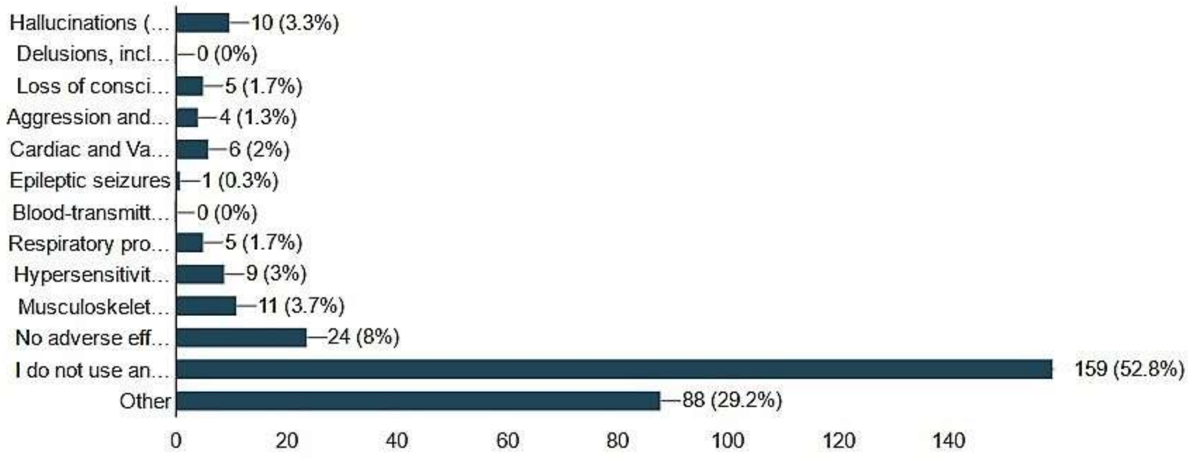
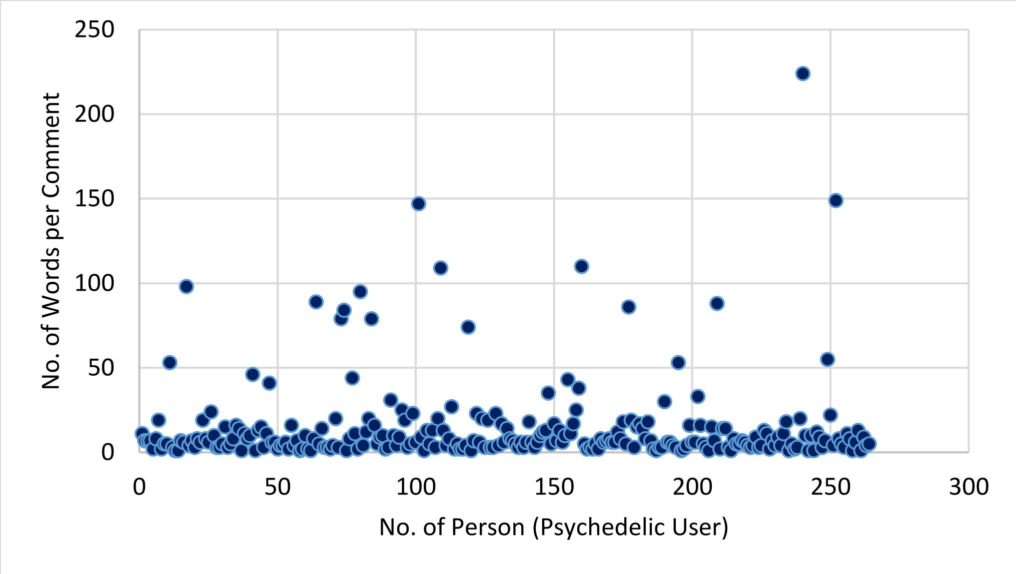


Figure 1.7. The Most Commonly Encountered Adverse Reactions in Year-2 to Year-6 Students.



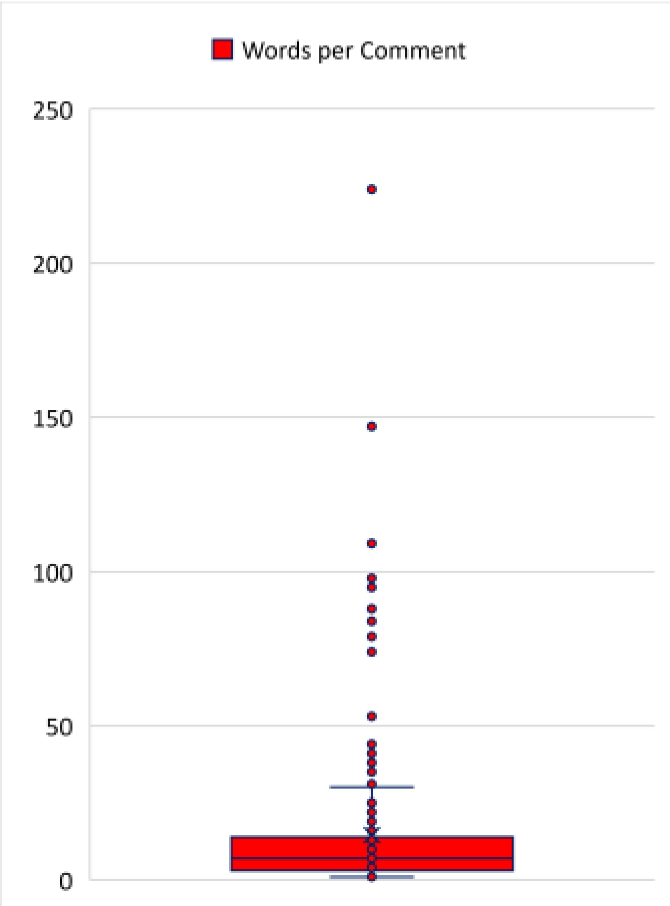


Figure 2.1. The Number of Words per Comments: Scattered Graph (above) and Boxplot Presentation (below).

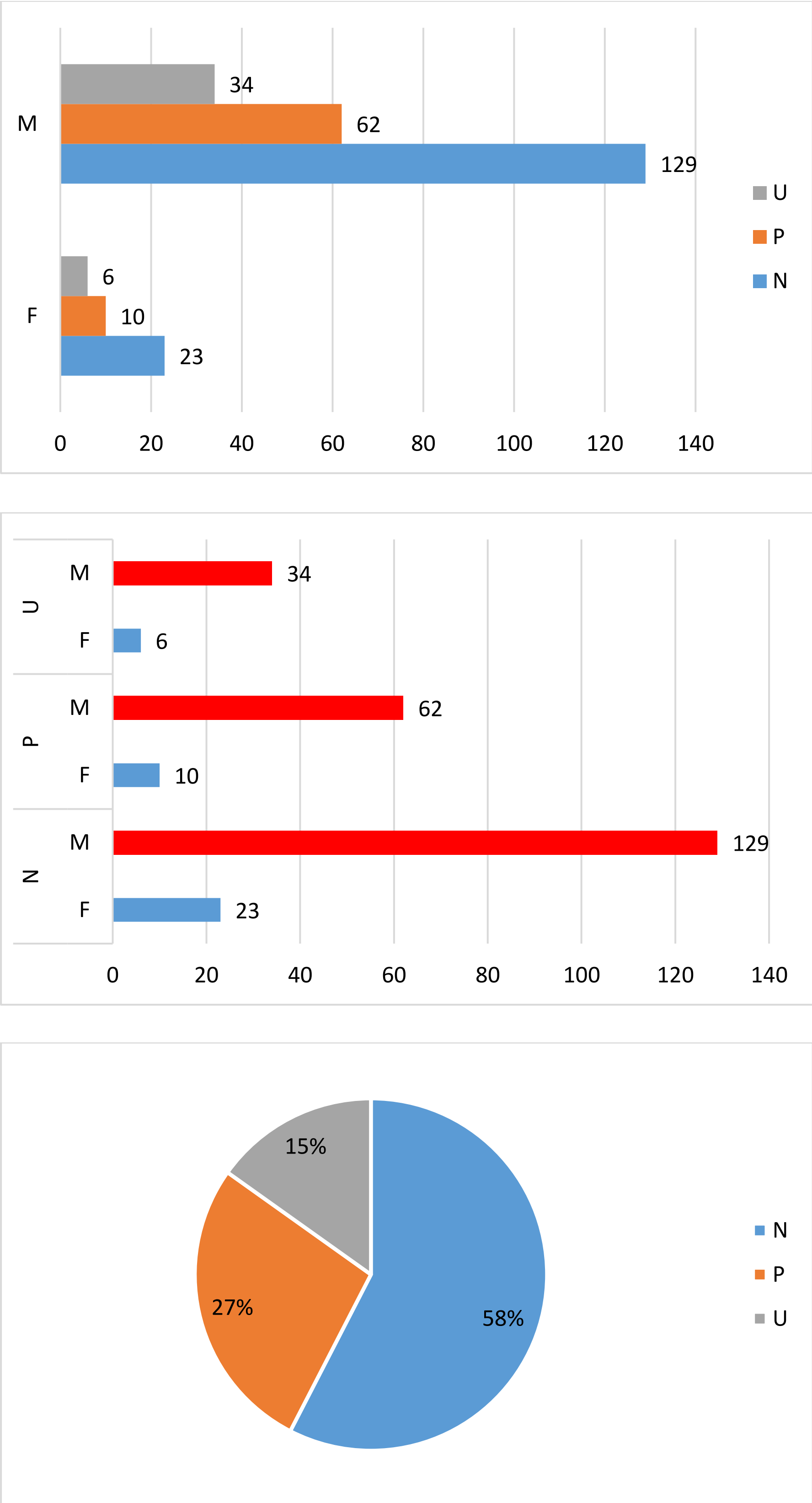


Figure 2.2. The Contribution of Psychedelic Users by Gender versus the Nature of the Comments.

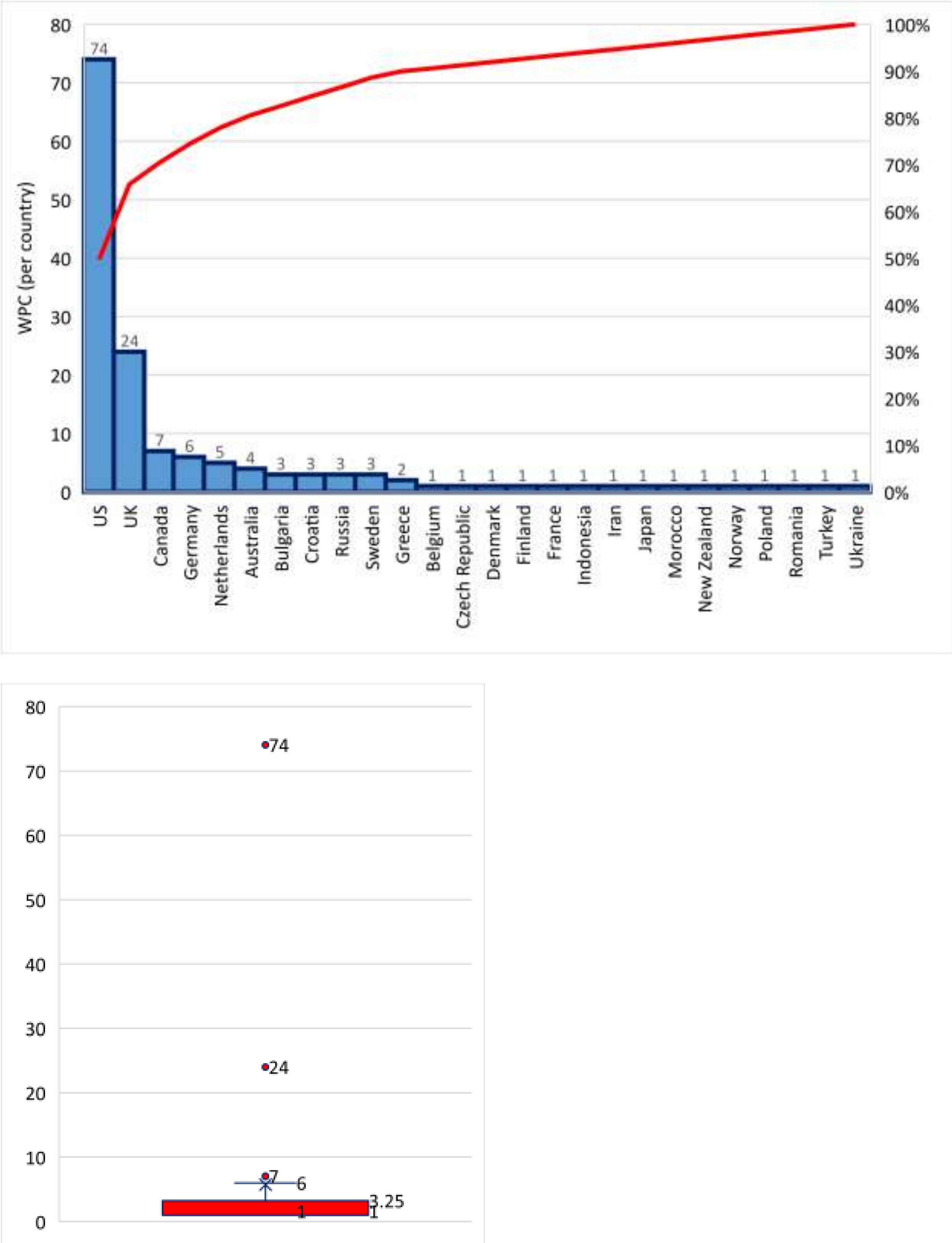


Figure 2.3. Geo-mapping for Negative (N) Comments.

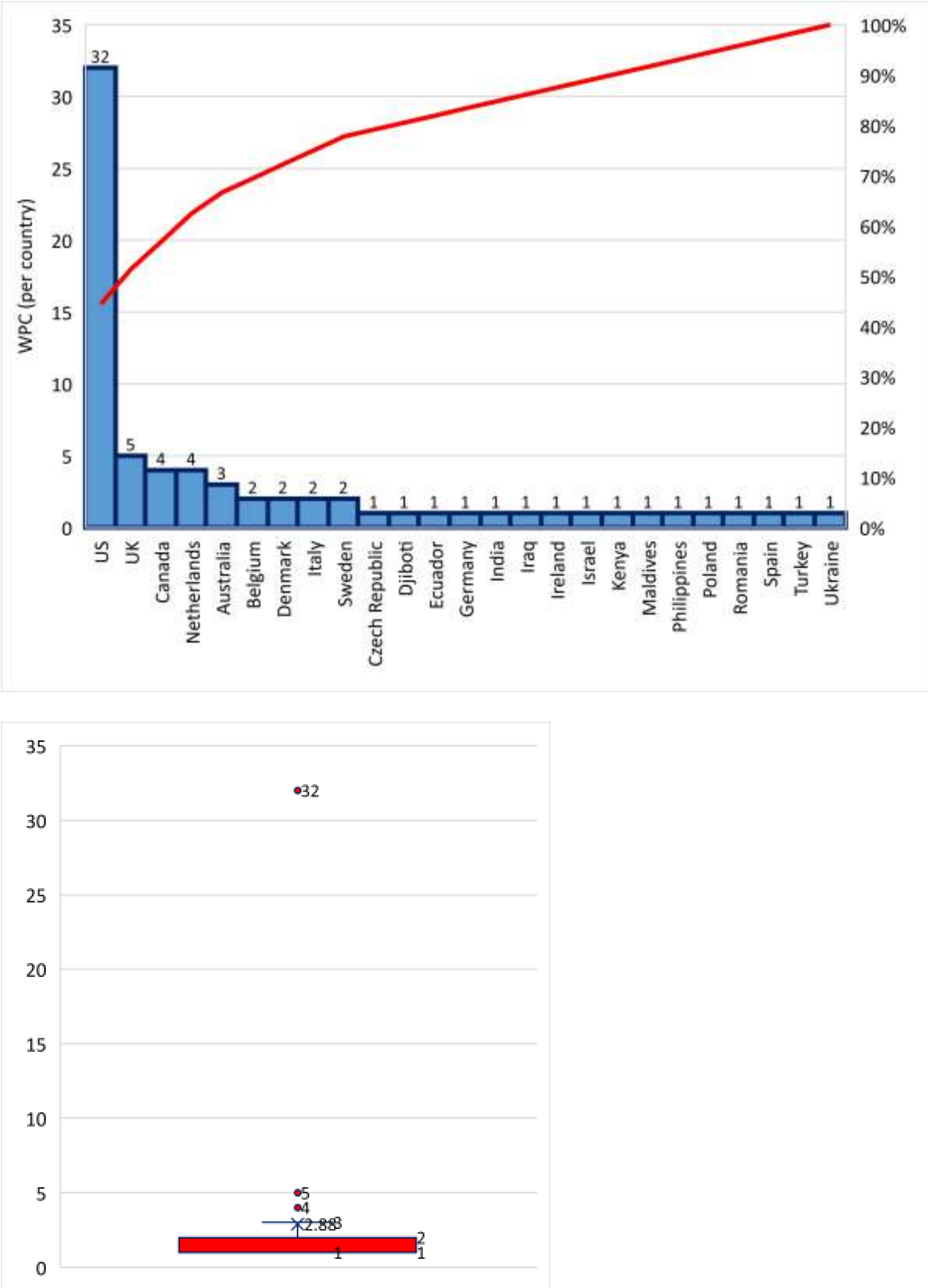
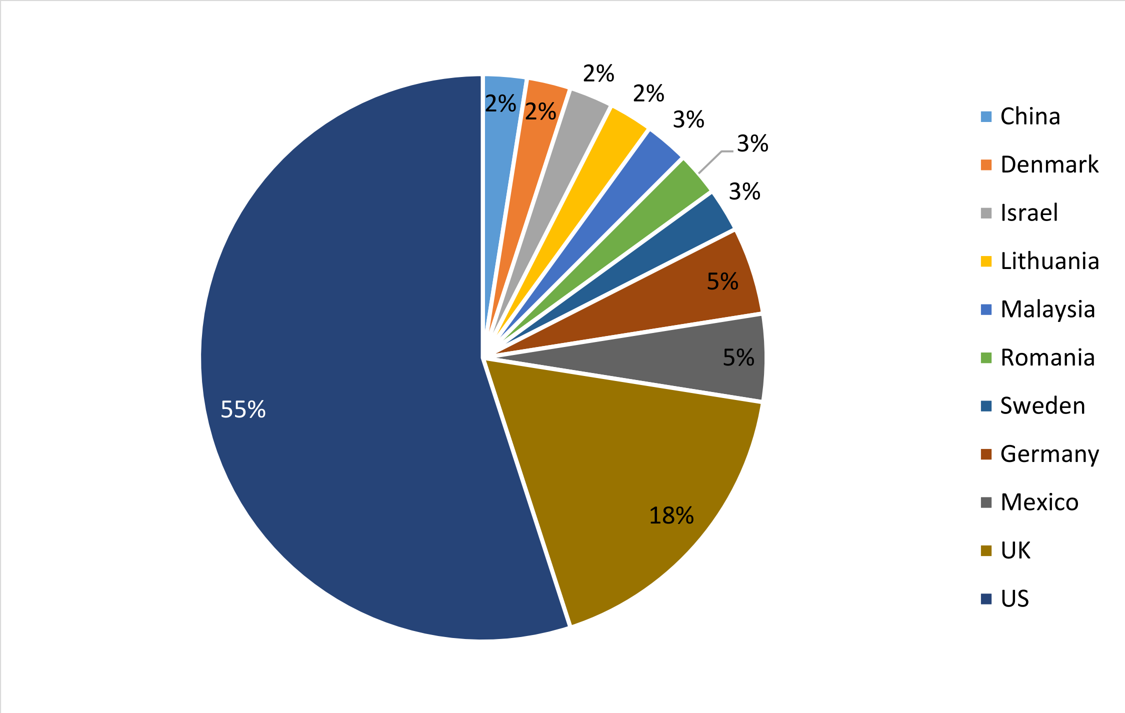


Figure 2.4. Geo-mapping for Positive (P) Comments.



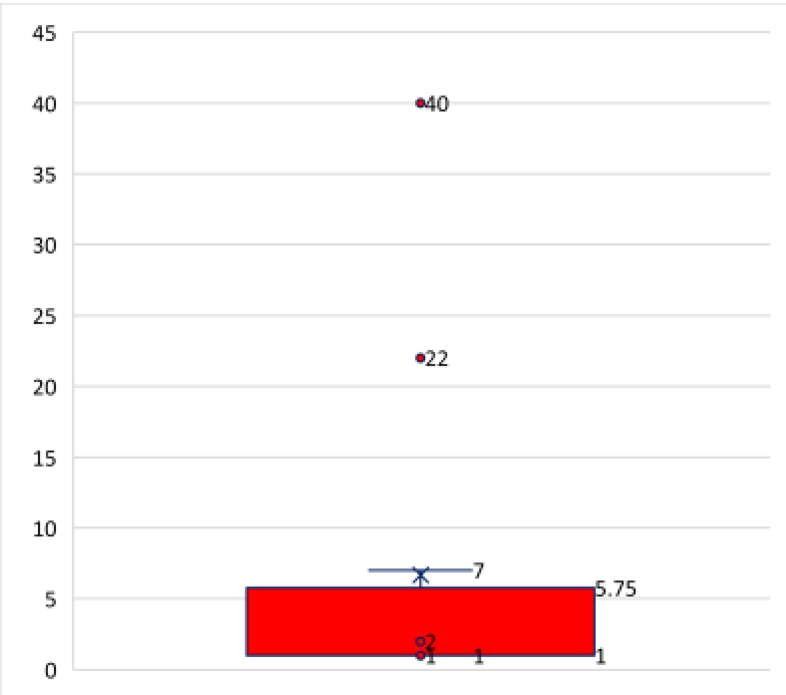


Figure 2.5. Geo-mapping for Uncategorizable (U) Comments.

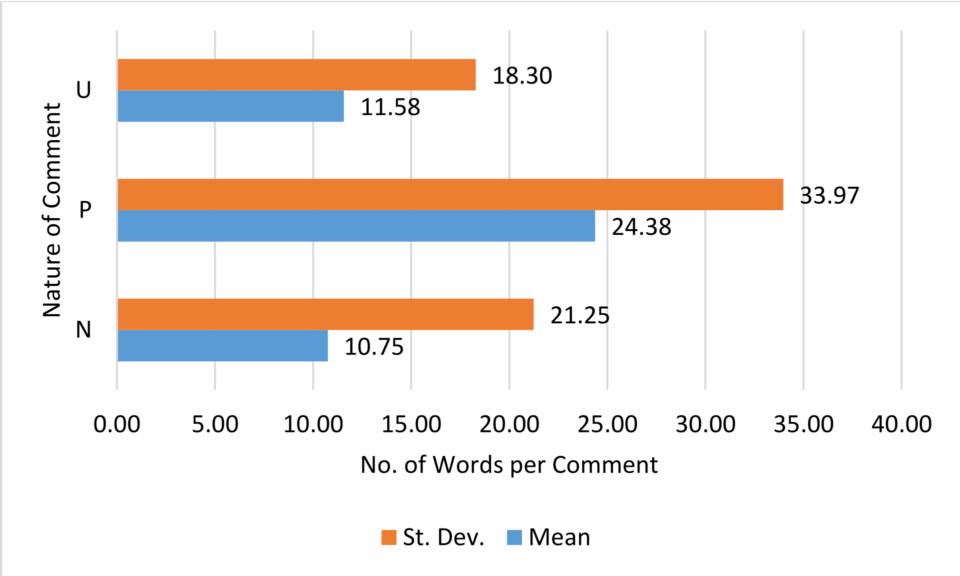


Figure 2.6. Descriptive Statistics: the Number of Words per Comment for the Three Themes of Comments.

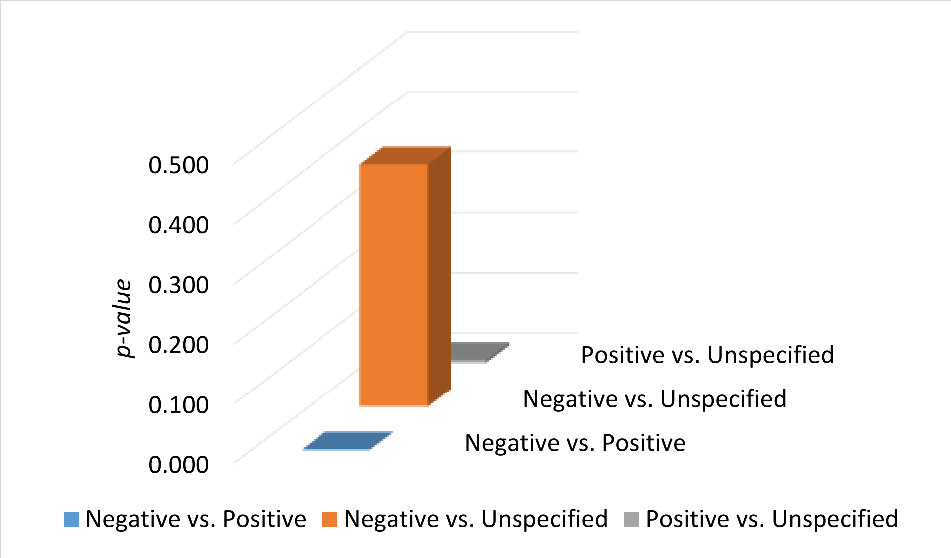


Figure 2.7. Inferential Statistics: Student’s t-test for the Number of Words per Comment versus the Theme of Comments.

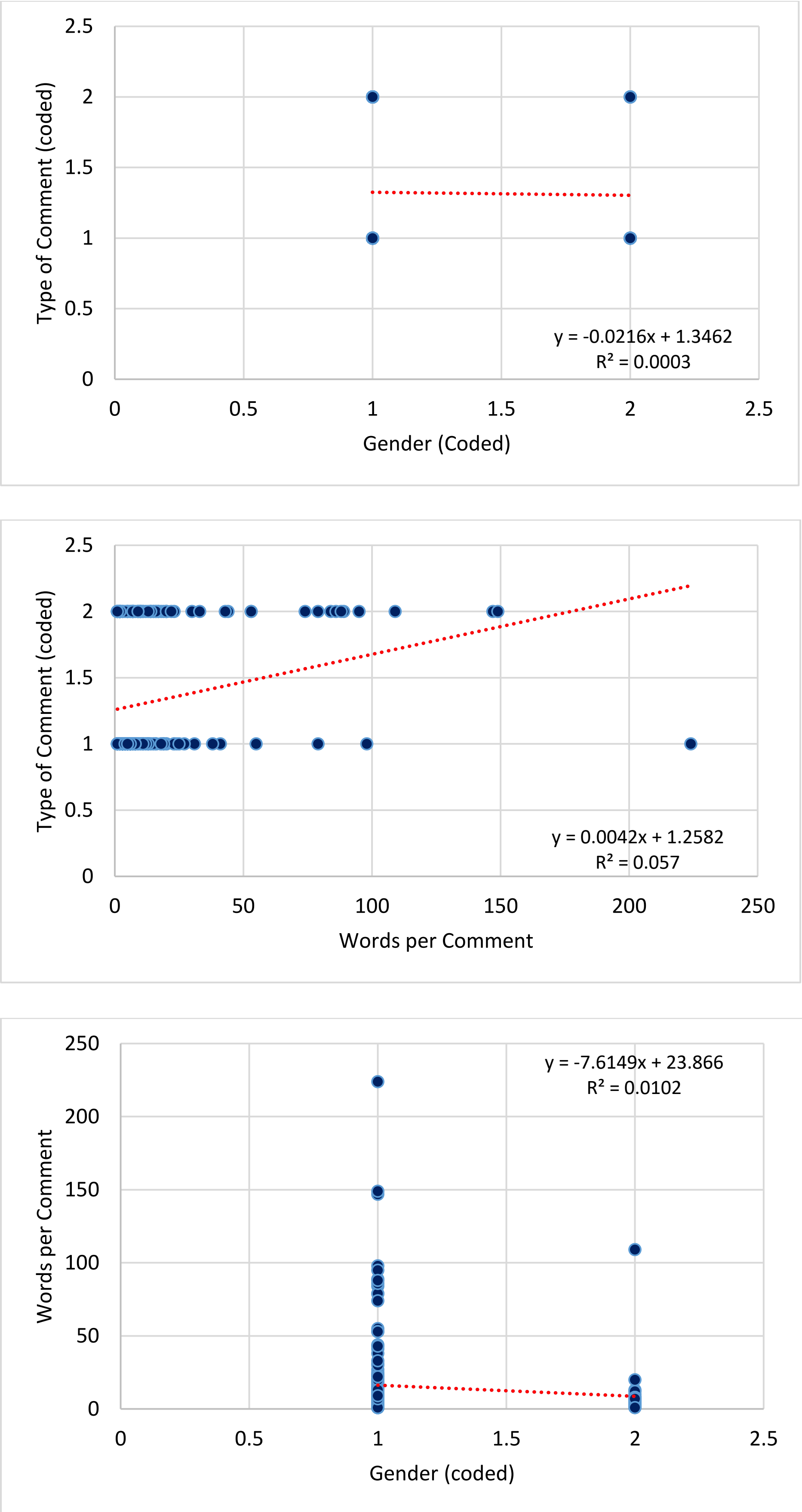
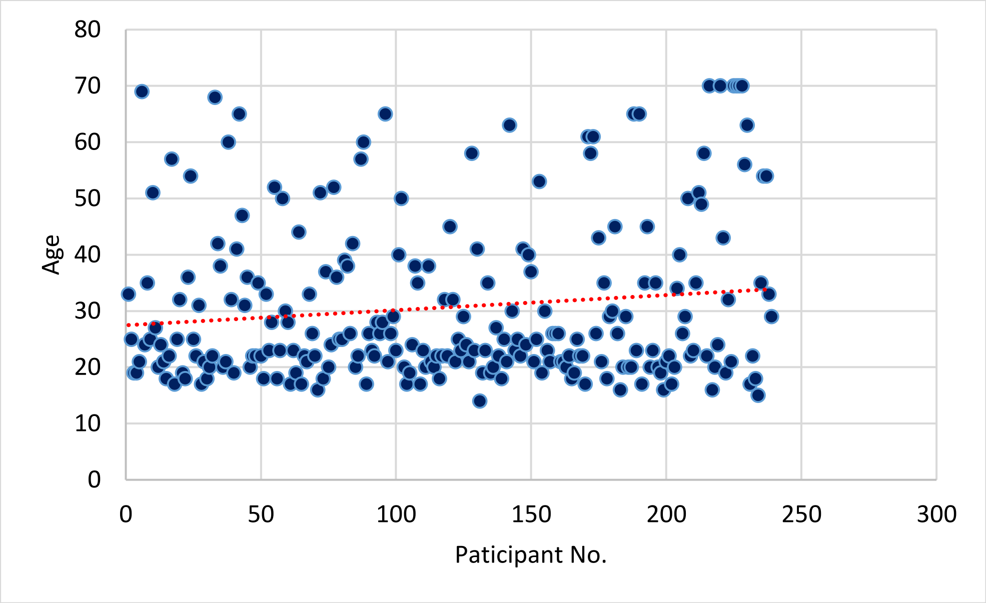


Figure 2.8. Inferential Statistics: Linear Regression of Relevance to the Nature of Comments.



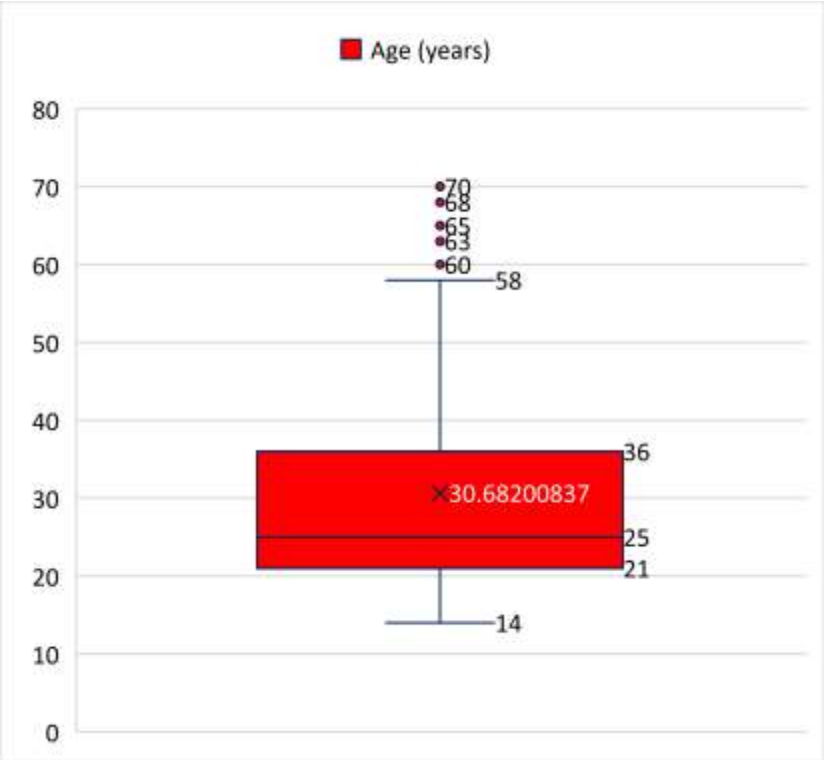


Figure 3.1 The Age of Psychedelic User: Scattered Digram (above) and Boxplot Presentation (below).

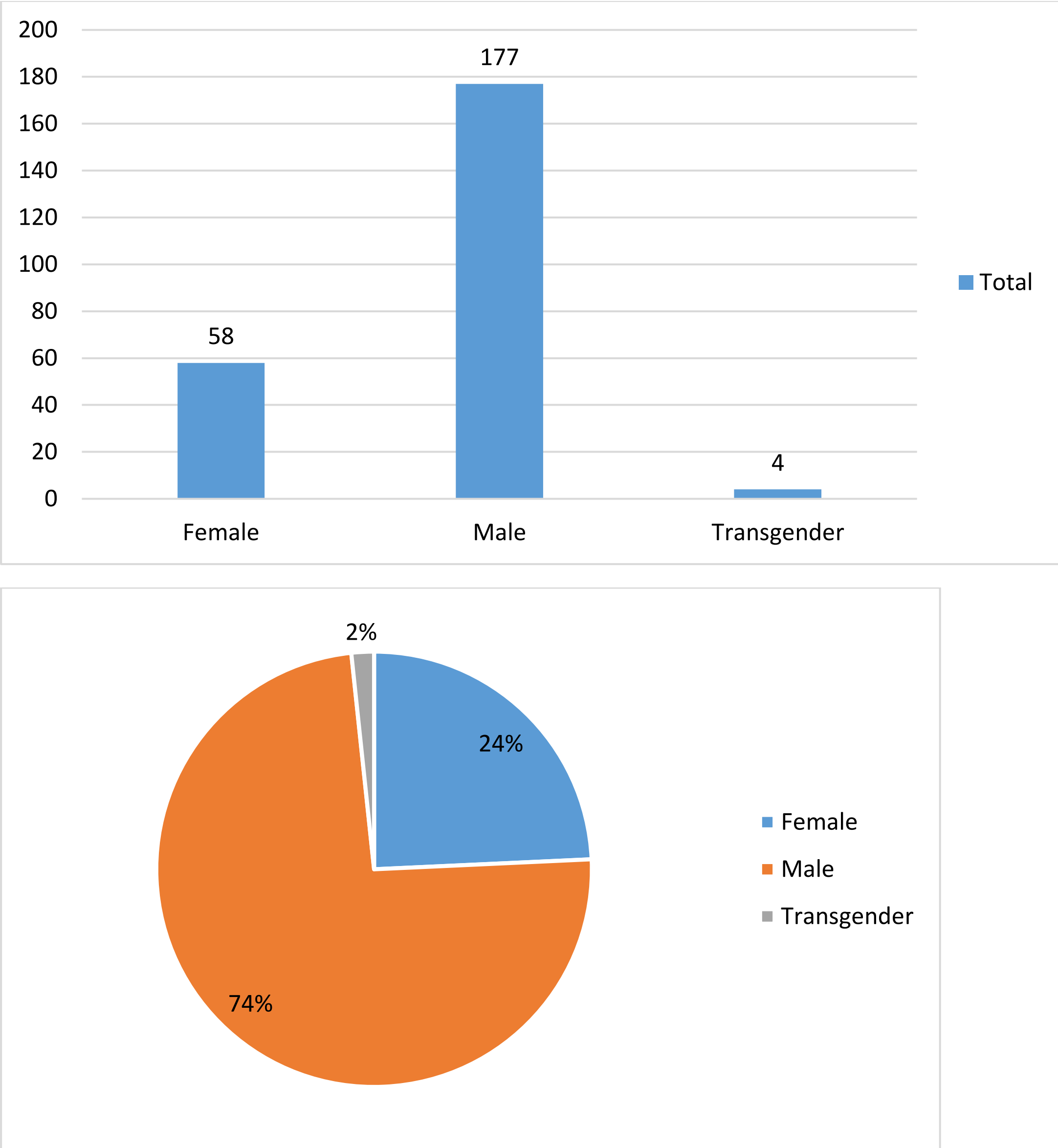
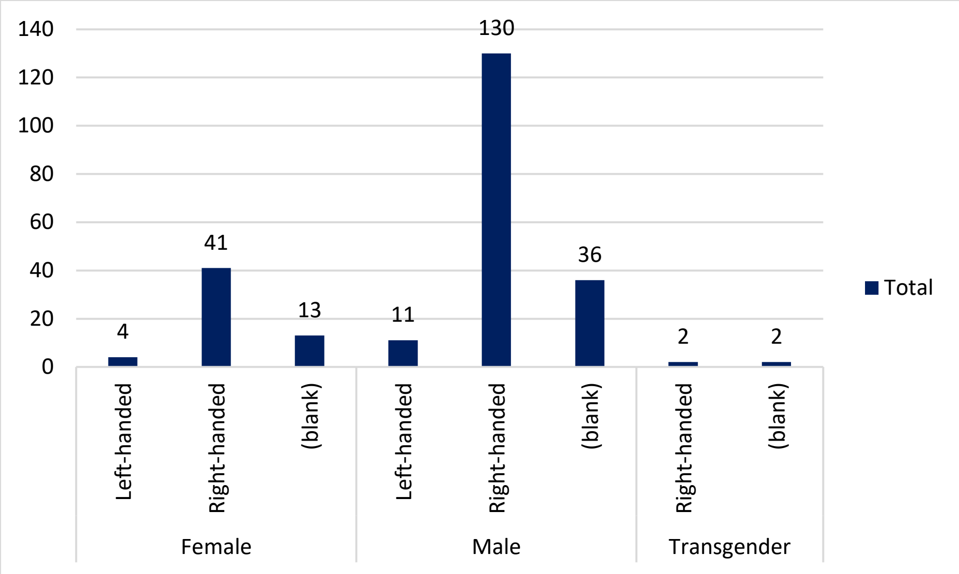


Figure 3.2. The Gender of the Studied Population of Psychedelic Users.



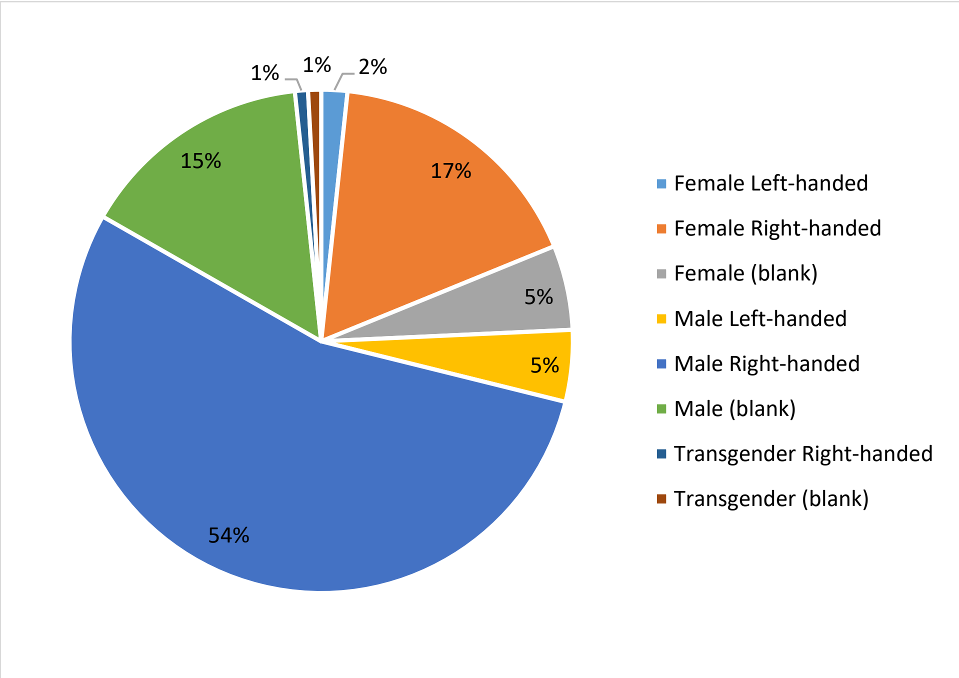


Figure 3.3. Handedness versus Gender in the Selected Population of Psychedelic Users.

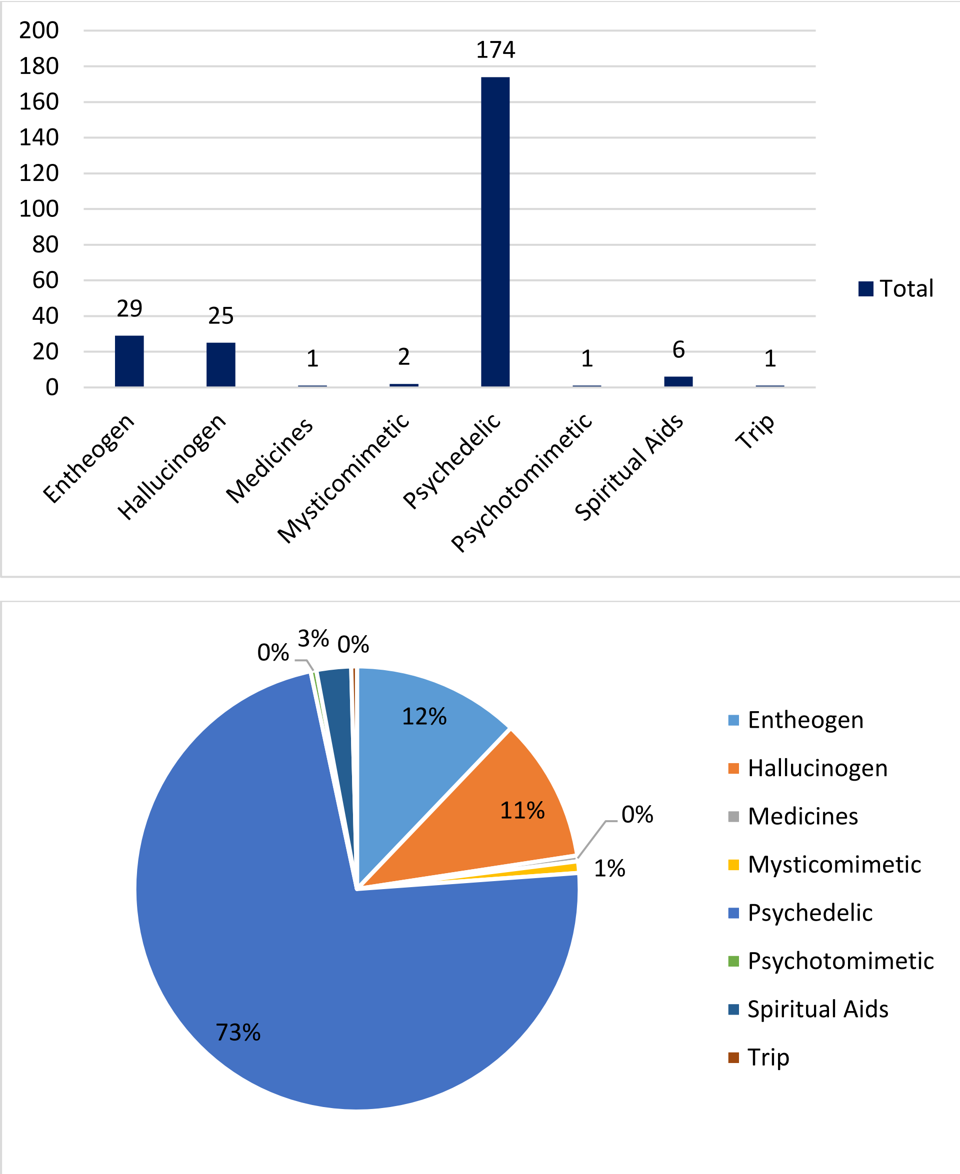
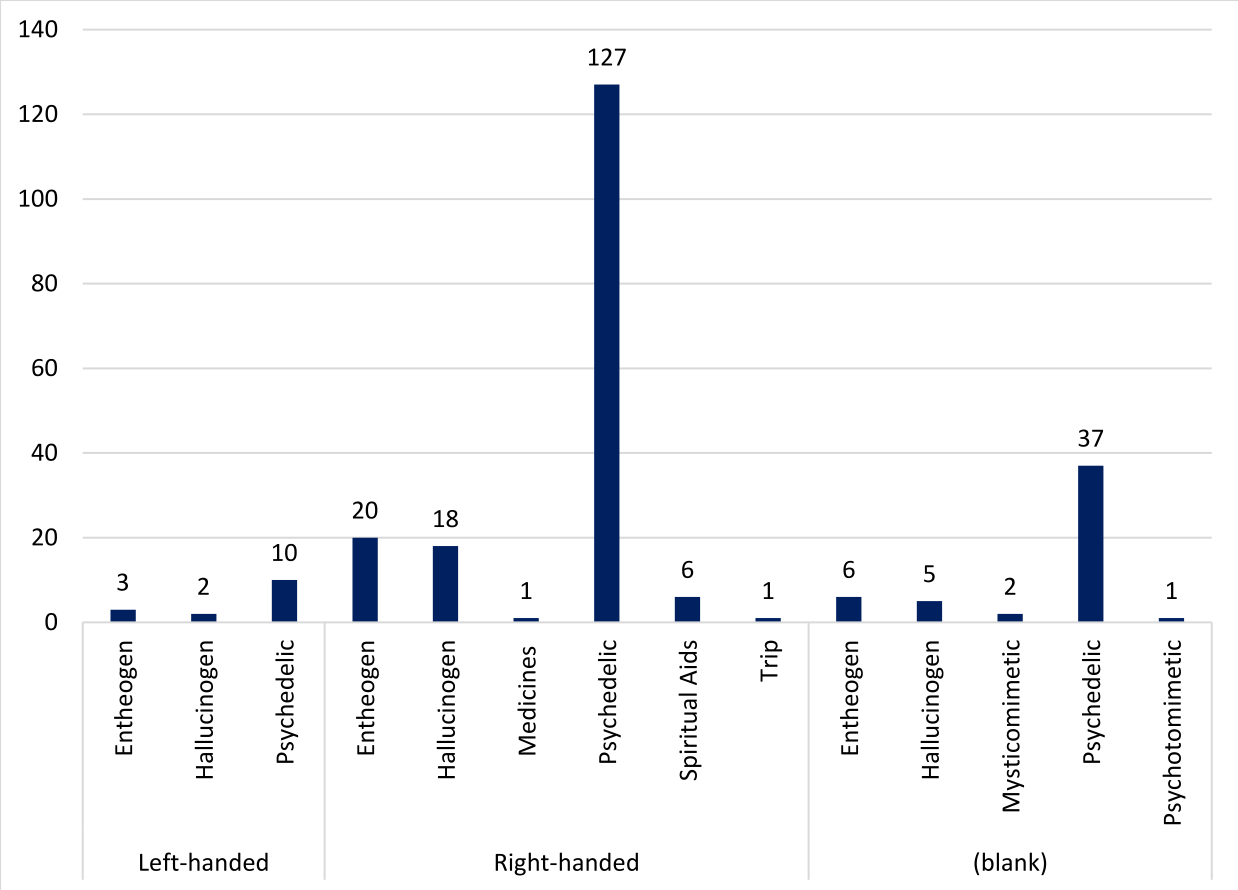


Figure 3.4. The Most Frequently Used Terms for *Psychedelics*.



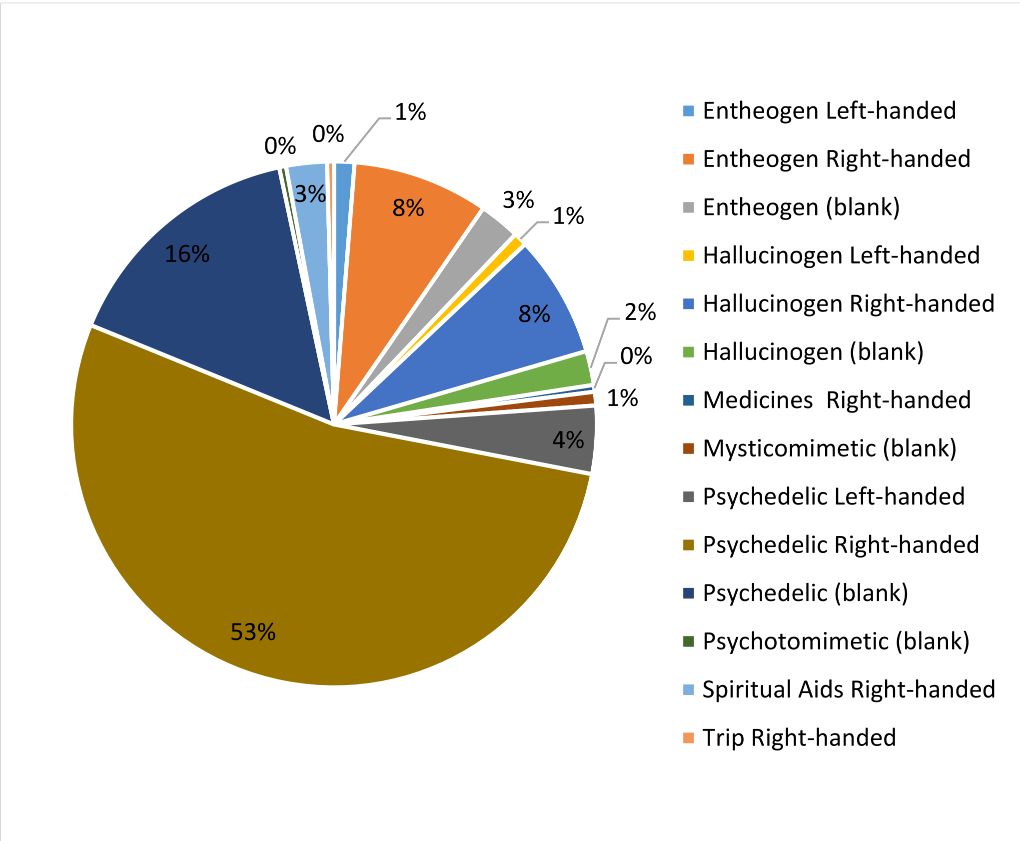


Figure 3.5. Descriptive Analyses: Handedness versus Terminology.

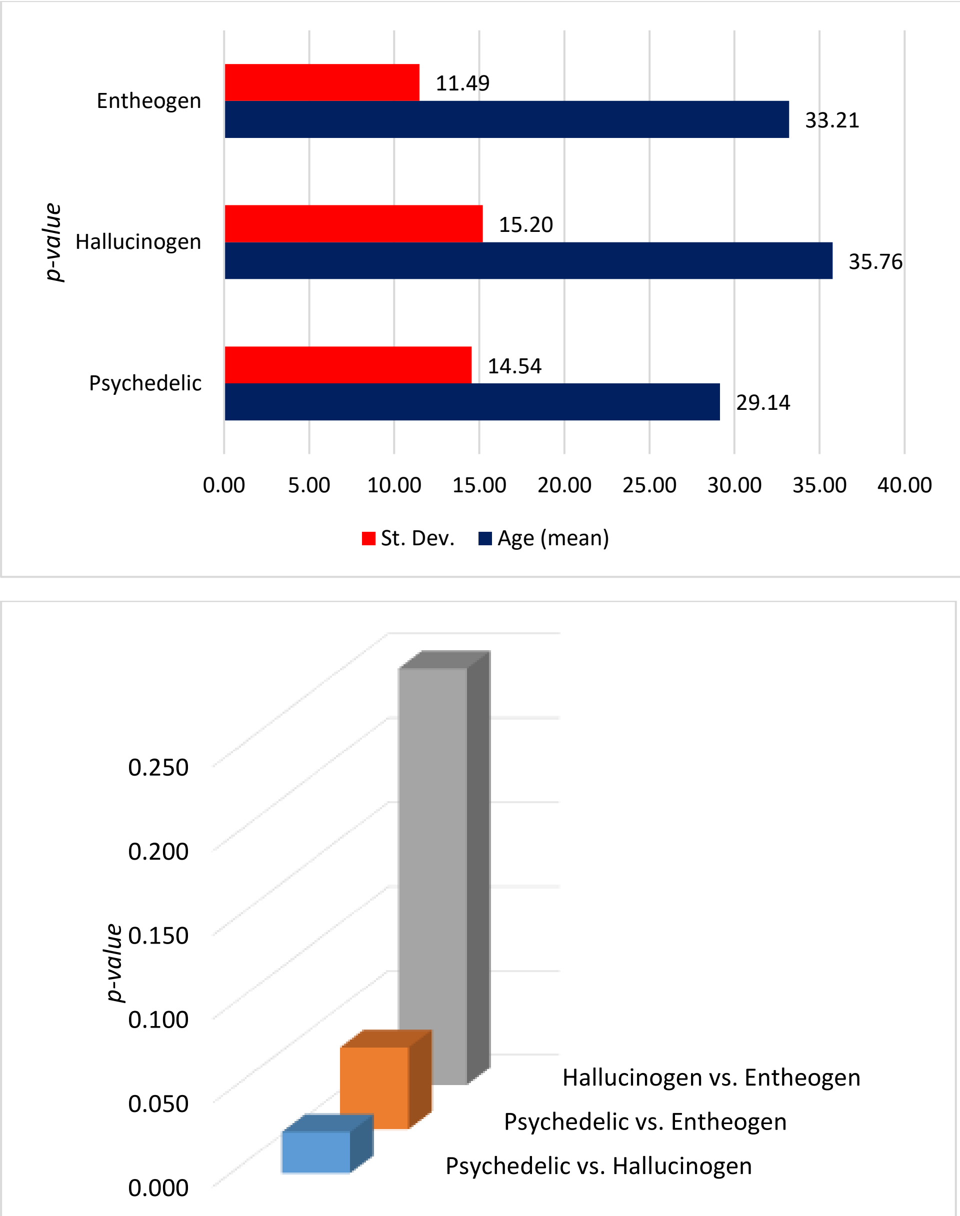


Figure 3.6. Descriptive and Non-parametric Statisitc: Terms versus Age.

		Age vs. Handedness		
Non-parametric	Entheogen	0.312		
	Hallucinogen	0.333		
	Psychedelic	0.006		
	Age (mean)		St. Deviation	
	Rt. Handed	Lt. Handed	Rt. Handed	Lt. Handed
Entheogen	34.10	30.33	12.10	13.05
Hallucinogen	32.61	28.00	11.82	11.31
Psychedelic	29.94	24.00	15.51	5.29

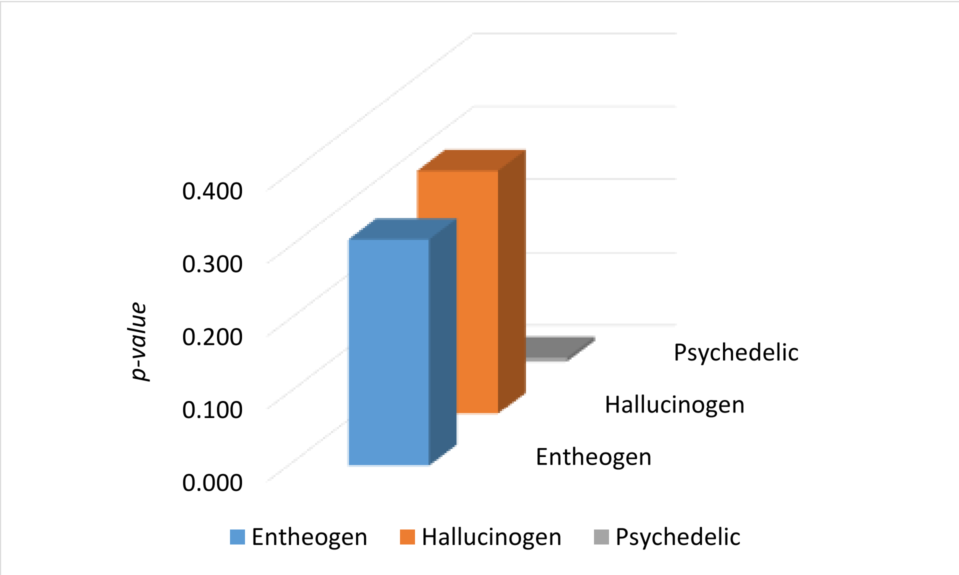
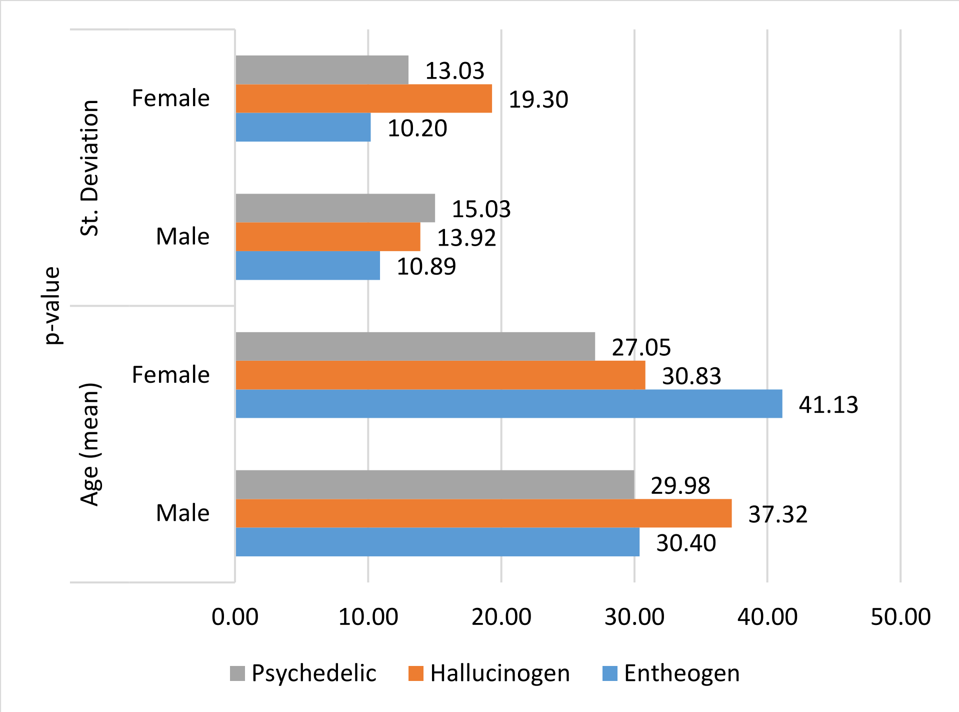


Figure 3.7. Descriptive and Non-parametric Statisitc: Terms versus Age and Handedness.



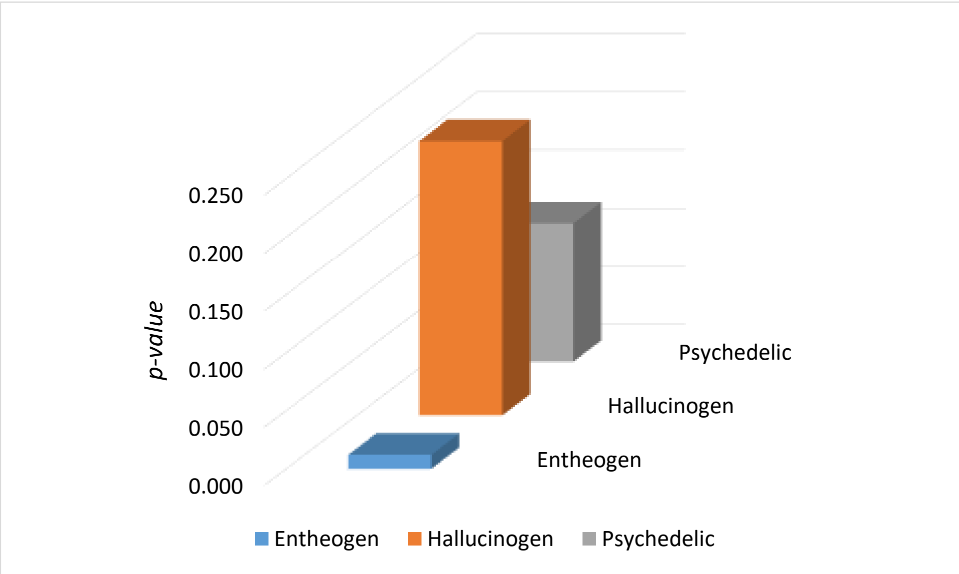


Figure 3.8. Descriptive and Non-parametric Statisitc: Terms versus Gender and Handedness.

Chapter 8. Integrative Analyses of Captagon, Octodrine, and NBOMe

BACKGROUND

The situation on NPS has been escalating to an unprecedented level, the “explosion” and abundance of these substances particularly on the darknet poses an economic, public, health, and security threats on a global scale (Corazza et al., 2013; Krabseth et al., 2016; Orsolini et al., 2016). In this chapter and the subsequent three chapters, three types of NPS will be explored; captagon (fenethylline), octodrine (DMHA), AND NBOMe (n-bomb or smiles). Each one of these substances represents a unique class of its own and having its unique pharmacodynamics and pharmacological effects; captagon (amphetamine-type stimulant), octodrine (sympathomimetics), and NBOMe (hallucinogenic-psychedelic) (Ling et al., 2013; Nichols 2016; Rao and Hoffman, 2014). In relation to the mechanism of actions, the final common pathway shared by the three substances is the central monoamines (dopamine, serotonin, and catecholamines), and to a lesser extent peripheral monoamines as in the case of octodrine. The main action of these substances is exerted via monoamine transporters (MATs) (Mayer et al., 2016; Simmler et al., 2014).

Fenethylline, a psychostimulant drug that is often branded as *captagon*, is a combination of amphetamine and theophylline. Since the cessation of its licit production in 1986, counterfeited products have been produced illicitly in the southern-eastern Europe and far-east Asia; its profitable trade has been linked to terrorist organisations, including ISIL. Octodrine, also known as dimethyl hexylamine (DMHA), is a sympathomimetic agent; there is an evidence of growing use of it as a pre-workout stimulant and a weight-reducing agent. There is a significant paucity of scientific literature, despite the various and unregulated use of octodrine. Finally, NBOMe(s), also known by the street name N-Bomb, are potent serotoninergic and sympathomimetic agents, hallucinogens, and psychedelics.

Captagon has been linked to terror attack in western Europe in the past years, it is an amphetamine-type stimulant (ATS) which enhance the physical abilities by reducing the need for sleep or rest, it is typical for use in conflict zones by militias and terrorist organizations, and in planning for terror attacks (Al-Imam et al., 2016; Kravitz et al., 2016). On the other hand, NBOMe is a hallucinogenic substance and an entheogen (psychedelic), which is used to reach an “advanced” state of spiritual existence and cognitive awareness (Dos Santos et al., 2016). There are several variants of NBOMe; the most popular are the 25c, 25b, and 25i (Kyriakou et al., 2015). The 25i variant is the most fatal, even in microgram doses, which put NBOMe on the list of most fatal NPS (Chung et al., 2016; Shanks et al., 2014). On the other hand, octodrine appears to be a drug of mild physiologic effects; it has been long forgotten after its discovery, it has re-emerged as a physiological-psychological stimulant to be used as pre-workout regiments by athletes and allied users (Charlier, 1951 ; Fellows, 1947). To date, there are no human studies, and very few animal studies on both octodrine and NBOMe, their pharmacodynamics and pharmacokinetic properties are far from being understood.

This chapter will explore each substance in a comparative and an integrative approach, via analysis of the surface web and the deep web, and a trends database. The aim is to; visualise the extent (web prevalence) for each substance (1), perform a geo-mapping for the spread of each substance (2), to see if the patterns are compatible on both divisions of the web (3), and to infer data on the basis of the power in relation to the e-vendors of these substances on the darknet e-markets (4). The analysis will be based on cross-sectional (internet snapshots) and longitudinal analysis (mainly retrospective). Data mining will embody the ultimate application of this approach; this technique has never been applied before by NPS researchers (Fayyad et al., 1996; Han et al., 2011).

RESULTS AND DISCUSSION

Based on Google Trends analyses, users of the surface web were more interested in captagon than in either nbome or octodrine (Figure 1). Users were aware of both the generic name and the chemical name of captagon. On the other hand, the use of the chemical name was more popular than the generic name for nbome. Both names, generic and chemical, of octodrine were unpopular. The graphical presentation concludes the popularity of in ascending order; octodrine (dmha), nbome (n-bomb), and captagon (fenethylline).

Retrospective analysis shows a steady trends for octodrine over a duration of five years, an almost steady trends for nbome, and unstable (erratic) trends for captagon. The popularity for nbome increased in an episodic fashion by 200-250% over the baseline at specific dates; June (2013), July (2013), August (2013), October (2014), may (2015), June (2016). On the other hand, captagon has been steady over the years (2012-2017) except in late 2015 in October and November (highest peak), and the middle of 2016 (July). There was also a relatively small rise in the trends in June (2015) with reference to both the generic name (captagon) and the chemical name (fenethylline). Most of these increments were sudden and spiky (Figure 1) and in correlation with terror attacks, particularly in Europe (Al-Imam et al., 2016). It is very evident that trends databases, including Google Trends, can give a clear insight and should be integrated into early warning systems in anticipation of a terror attack or incidents of intoxications and fatalities induced by NPS. The highest rise in captagon trends was exactly around the middle of November (2015) to the 1st week of December (2015), the increment in the trends peaked at 100x above the baseline, which is an obvious statistical outlier; it coexisted in correlation with the terror attacks. The potentials of data mining exist here to anticipate and prevent terror attacks; data mining relies on database analysss using inferential statistics with some degree of automation (artificial intelligence), the reward from such application will be remarkable to enhance security, preserve human lives, and reduce the burden of financial and collateral damage (Kohavi and Provost, 2001).

Though it was apparent that captagon was taking the lead all over the years, particularly in 2015 and 2016, inferential statistics were done. Analysis of Variance (single factor, ANOVA) confirmed the presence of statistically discernable trends (p-value<0.001) among the three substances. The unpaired t-test shows that captagon is taking the lead ahead of both octodrine ($p<0.001$) and nbome ($p<0.001$). On the other hand, there was no statistical difference between nbome and octodrine ($p=0.079$) at 95% CI.

Retrospective inference (2012-2017) indicated that there was no significant change in the individual trends for each substance, neither for octodrine nor for nbome. However, change of captagon trends over time (Figure 1), show a steady trends over the years with an exception for; 2012 versus 2015 (p=0.009), 2013 versus 2015 (p=0.013), 2014 versus 2015 (p=0.019), and to a less extent for 2015 versus 2016 (p=0.059), the latter is significant at 90% CI. It is to be concluded that the attentiveness of surface web users towards captagon has significantly increased in 2015.

Regional interest (trends geo-mapping) shows the top countries in which surface web users are surfing for data about captagon, the percentage of contribution of these countries are; France (34%), Turkey and Germany (each at 15%), Italy (11%), Canada and Spain (each at 10%), and the US (5%). Using the chemical names (dmha, fenethylline, nbome) to retrieve the geo-map of the trends (Figure 2) showed a comparable pattern for captagon, revealed that top countries interested in fenethylline are; France (35%), Germany (15%), Turkey (15%), Canada (10%), Spain (10%), Italy (10%), and the US (5%); there was also a minor contribution from Australia, Russia, Brazil, and the UK. It is to be concluded that attentiveness of surface web users towards both names of captagon, generic and chemical, are well established. However, this is not the case for octodrine and nbome, in which the generic name is more popular than the chemical name. Geomapping of nbome trends revealed five leading countries of interest; US (30%), Australia (27%), Russia (18%), Brazil (15%), and the UK (10%). It seems that the pattern is differentiated from that of captagon. Captagon is popular in West European countries and North America, while nbome appears to be popular in the US, Asia, Australia, Latin America, and England. Furthermore, Middle Eastern and Arabic countries did not contribute by any means to the geo-map of the overall trends. This e-trade of NPS seems to be of a high affinity in relation to western countries, and more of an issue for developed countries rather than for developing countries with the exception of Brazil and in connection with nbome.

The top related queries were (Google, 2017); *captago isis, isis, captagon daesh, captagon efectos, captagon syria, captagon ingredients, droga isis, isis drug, drogue daesh, captagon drog, dmha booster, dmha stimulant, n-bomb drug, 25b nbome, 25i erowid, nbome droga, 251 nbome, 25i nbome buy, nbome vs acid, nbome efeitos, nbom, 2cc nbome, 2c-b*. Apparently, all these terms are used by a diverse array of surface web users of different languages, cultures, and countries. Most of these terms were related to captagon and nbome, and to a less extent in relation to octodrine. Octodrine is still ambiguous to the majority of surface web users.

In relation to the darknet e-markets on the deep web, it was explored via Grams search engine using two keywords in combination with a boolean operator “captagon OR fenethylline”, the snapshot was taken on the 10th of February 2017. Captagon was e-commerce in five regions, distributed as; Germany (52%), European Union (20%), worldwide (15%), Netherlands (10%), and the UAE (3%). Captagon e-commerce in the darknet seems to be restricted to developed western European countries and developed Arabic countries from the Arabian Gulf region, specifically the United Arab Emirates.

It was observed that captagon was strictly sold in the form of tablets in highly different quantities, captagon was only found in three e-markets; AlphaBay, HANSA, and Dream. Only Four e-vendors were e-commercing with captagon; those are nicknamed; GoldenCamel, Infinity-Drugs.to, DoctorMario, and DSQ. The last two nicknames were found to be an alias of the same e-vendor, he (she) is likely to have a European nationality, as he (she) was also involved in the e-commerce of captagon in Netherlands, UAE, EU, and worldwide. The basis of power for each e-vendor has been explored. The geo-mapping, e-vendors, and the number of hits were presented (Figure 3).

NBOMe seems to be more abundant in the e-commerce markets of the darknet; the snapshot was taken on the 10th of February 2017 using the keyword *"nbome" OR "NBOME" OR "NBOMe"*. Three major markets were explored AlphaBay, HANSA, and Valhalla. The Power scores for e-vendors within each e-market was estimated with a high degree of accuracy. On Alphabay, the shipping countries (Figure 4) were ; the UK (rank 1st), US (2nd), Spain, Slovakia, Portugal, Poland, New Zealand, Germany, China, Canada, Belgium, Australia, and Argentina. It seems that e-vendors from the UK and the US are controlling the AlphaBay market in relation to NBOMe e-commerce. There were no statistical outliers in connection with e-vendors' power score; the socres were in the range of from 167.48 to 393.08; the scoring calculation was based on the e-vendor's related parameters, the number of feedbacks, and the membership duration (e-vendor's antiquity). Three main types (Figure 5) of NBOMe were sold; 25b-, 25c-, and the 25i- variants. The 25i-NBOMe was the most popular, followed by 25b-NBOMe. Over two dozens of e-vendors were identified (Figure 6); alquimia2017, Baron-JOY, bornagain, Chemical_Express, Dahbome, DailyFix, Electricpower, EuroLivery, Fentastic_UK, FRENCHCONNECTION, GoodzUK, Keys3r_Soze, littlegoblin, LoveIsTheKey, mr.pills, MrNatural, NBFriend, ososo12345, Psychonauta01, SoulDark, theRoadLessToxic. These nicknames (usernames) can give an insight on the geo-mapping (location), and occasionally the gender of the e-vendor.

The power scores appear to be correlated in a linear fashion with the length of e-vendor's membership within the specified e-market. Accordingly, a regression model was used to analyse the pattern of correlation (Figures 7). Consequently, it is to be concluded that the power score for each e-vendor is correlated (positive, linear) to some degree with e-vendor's level, trust level, the number of positive feedbacks, and the membership duration. The strongest correlation was found with e-vendor's trust level at an R^2 score of 0.782, and his (her) membership duration at (R^2=0.798). A hypothesis was also assumed; it states that the e-vendor power score increases in parallel with the population count of the shipping country (Worldometer, 2017). This hypothesis was rejected (proven wrong) after being tested using another regression model; it seems that the population count was not correlated with e-vendor power score at (R^2=0.003).

The number of e-vendors within HANSA e-market appears to be less than that in AlphaBay, nine e-vendors were identified; smart666tiger, GodsGarden, HUEHUEBRASIL, Baron-JOY, mrnatural, mrsunshine, DmanT, ChemicalAllstars, and ElDorado. The 25i and 25c were the most sold NBOMe variants (Figure 8), these were sold in the US (34%), Brazil (11%), Germany (11%), Slovakia (11%), Spain (11%), UK (11%), US (11%), and Worldwide/unspecified (11%). Power scores were also calculated based on e-vendor's level, the number of positive feedbacks, the number of subscribers, and membership duration. The scoring range was 17 to 346; there was one statistical outlier, it belonged to e-vendor from the US, known by the alias *smart666tiger* (username). Linear regression was done for power score versus number of subscribers (*R^2 score*=0.871), membership duration (0.075), vendor level (0.830), the number of positive feedbacks (0.899), population count per shipping country (0.180). The correlation was positive for all the regression relations with an exception for population count; it appears to be that e-vendor's power score increases a bit as the population count decreases.

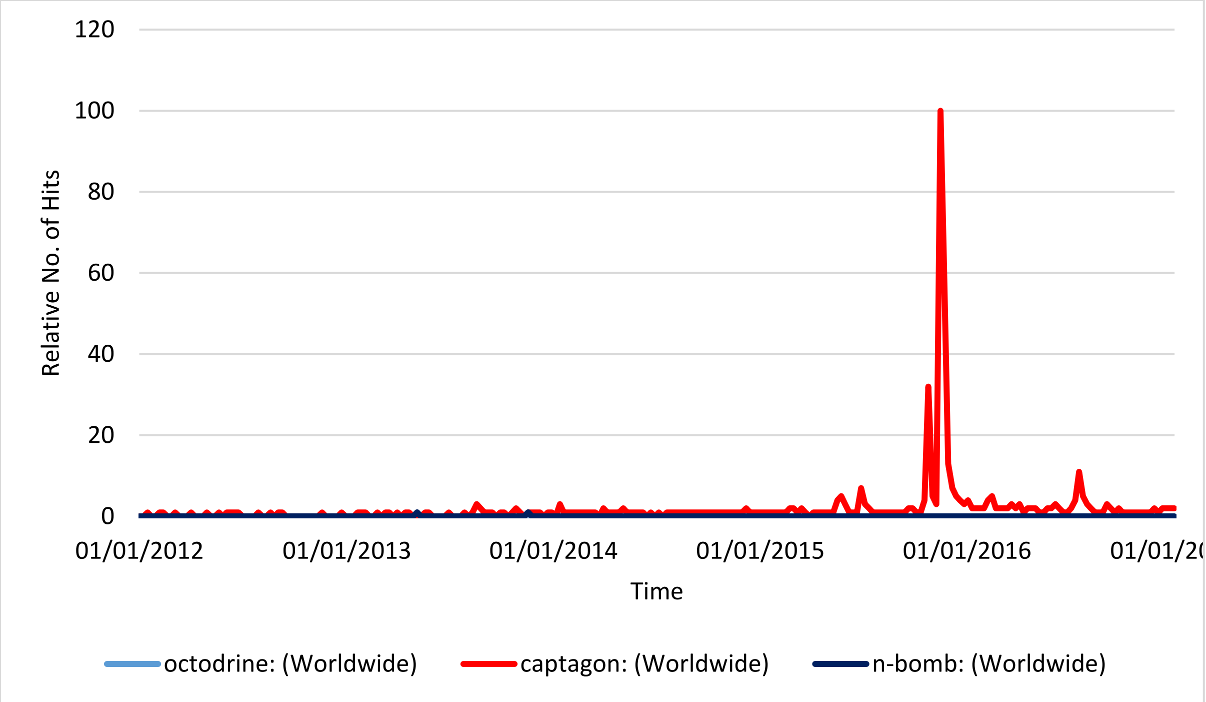
The number of e-vendors in Valhalla market was even less (n=5), their usernames; LoveIsTheKey, MrSunshine, domesticdoode1, Citra, and ROCKETCHEM. Similarly, to the other two e-markets, 25I-NBOMe was the most sold variant. The main shipping countries were the US, UK, and Spain (Figure 9). Power scores calculation were based on the number of positive and negative feedbacks (Figure 10); no statistical outlier was present. The number of e-vendors was not enough to infer a strong regression correlation (Figure 11). However, the raw power score seems to be correlated with the population count. There were also alternative shipping countries for e-vendors, at which substances other than NBOMe are traded, these countries include; France, Belgium, Netherlands, Portugal, Czech Republic, Germany, Australia, Sweden, and China. These locations seem to be concordant with data retrieved from Google Trends. An inter-market inference was made using t-test (independent) in relation to e-vendors' power score. At 95% CI, there was no significant difference between AlphaBay versus Valhalla, HANSA versus Valhalla. However, there was a significant difference in power scoring of AlphaBay versus HANSA (*p-value*<0.001). At 90% CI, there was a significant difference in the authority (power) score of AlphaBay versus Valhalla (p= 0.092). ANOVA test provided concordant data (p<0.001) in favour of AlphaBay e-vendors. To conclude, power scoring of e-vendors from AlphaBay appears to be significantly higher than those from Valhalla and HANSA e-markets.

Conclusive graphical presentation of the three e-markets and power score determinants are visually presented in a combo graph (Figure 12). Two e-vendors brings particular attention MrNatural, and MrSunshine, each seems to have access to multiple key e-markets on the darknet (Table 1) including;

AlphaBay, Valhalla, HANSA, Oasis, Agora, and Dream. Furthermore, each e-vendor sells similar types of NPS including psychedelics, ecstasy, Stimulants, and Opioids. MrNatural seems to be localised mainly to the US and Romania, while MrSunshine operates in US, Belgium, Netherlands, Portugal, Czech Republic, and Switzerland. The power score for each e-vendor was calculated based on Grams rating and the number of hits on Grams search engine (Figure 13). This snapshot was taken on the 11th of February 2017. MrNatural appears to be the most potent on the darknet.

Table 1. Exceptional e-vendors of Captagon on the Darknet.

	e-vendor Name	Garms' Rating	No. of Hits (Grams)	Alias Names	Market	Positive Feedbacks	Negative Feedbacks	Power Score (Grams')
1	MrNatural	5	433	MrNatural	AlphaBay	95	5	100
				MrNatural	Valhalla	7	0	
				mrnatural	HANSA	2	0	
				mrnatural	Oasis	Inaccessible		
2	MrSunshine	5	179	Mr_Sunshine	AlphaBay	100	0	71
				MrSunshine	Valhalla	2023	-1	
				mrSunshine	HANSA	7	0	
				MrSunshine	Agora	Inaccessible		
				mrsunshine	Dream			



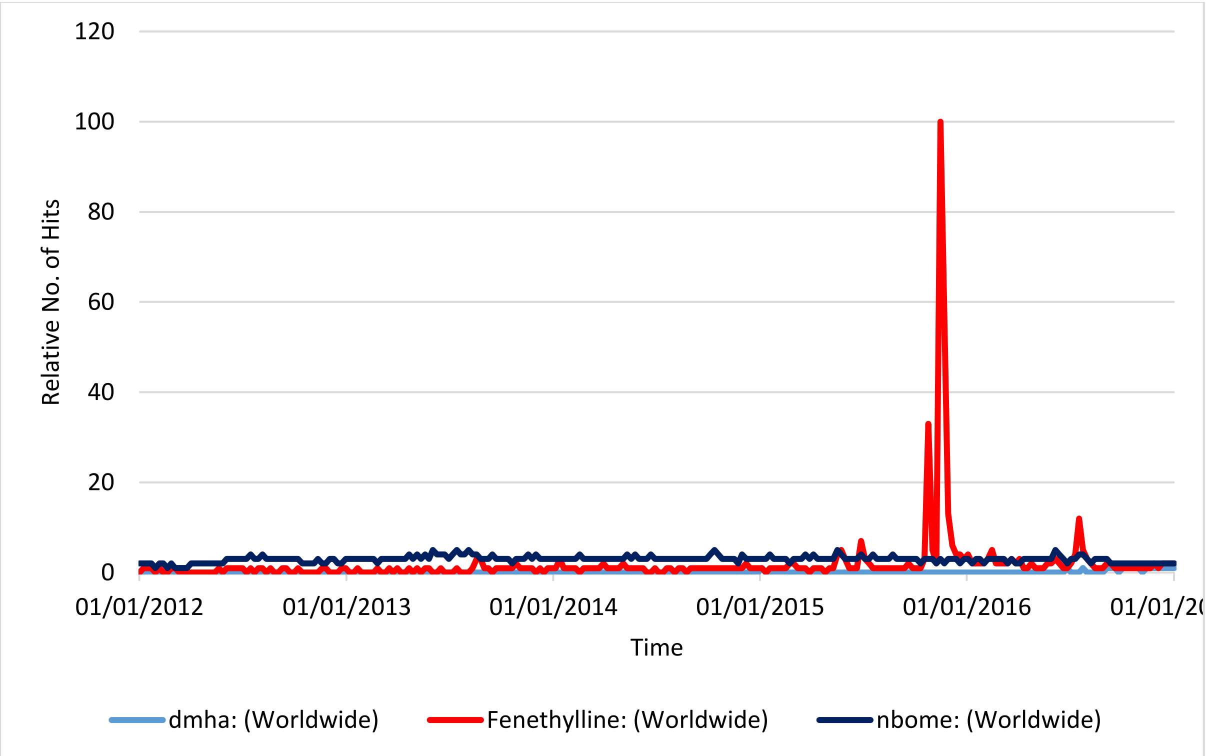


Figure 1. Google Trends (2012-2016): Octodrine, Captagon, and NBOMe: Two Different Sets of Keywords Used in the Two Line Graphs.

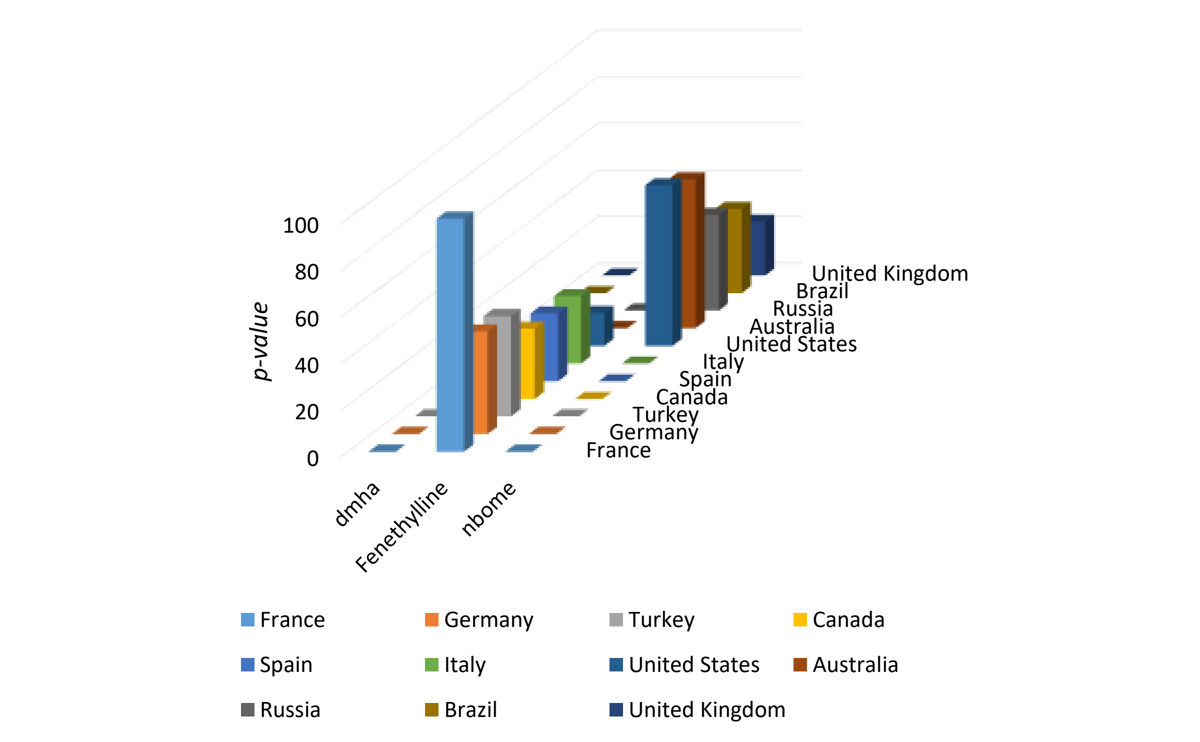


Figure 2. Geo-mapping of dmha, Fenethylline, nbome (keywords) on Google Trends.

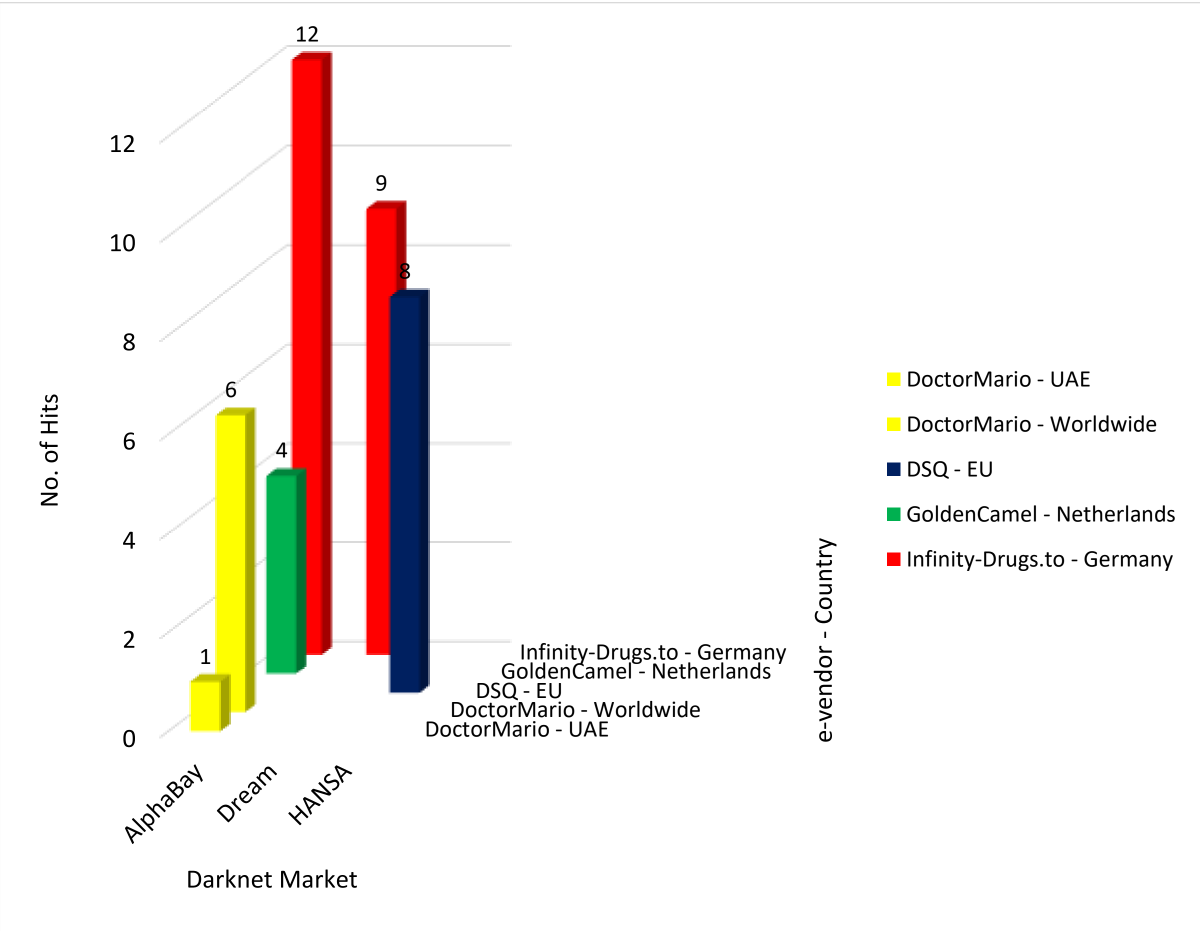
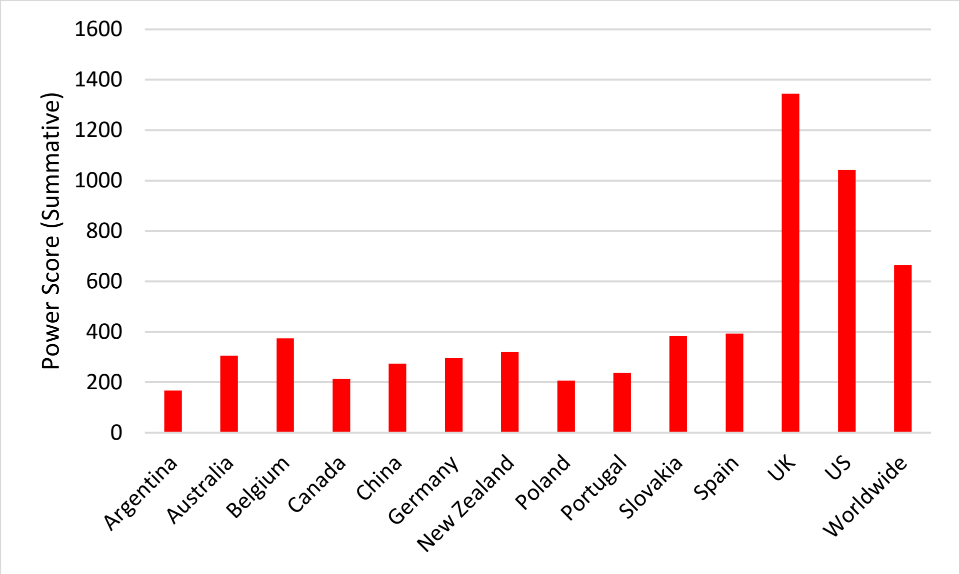


Figure 3. Captagon e-vendors on Darknet: Geographic Location, e-vendors, and the Number of Hits.



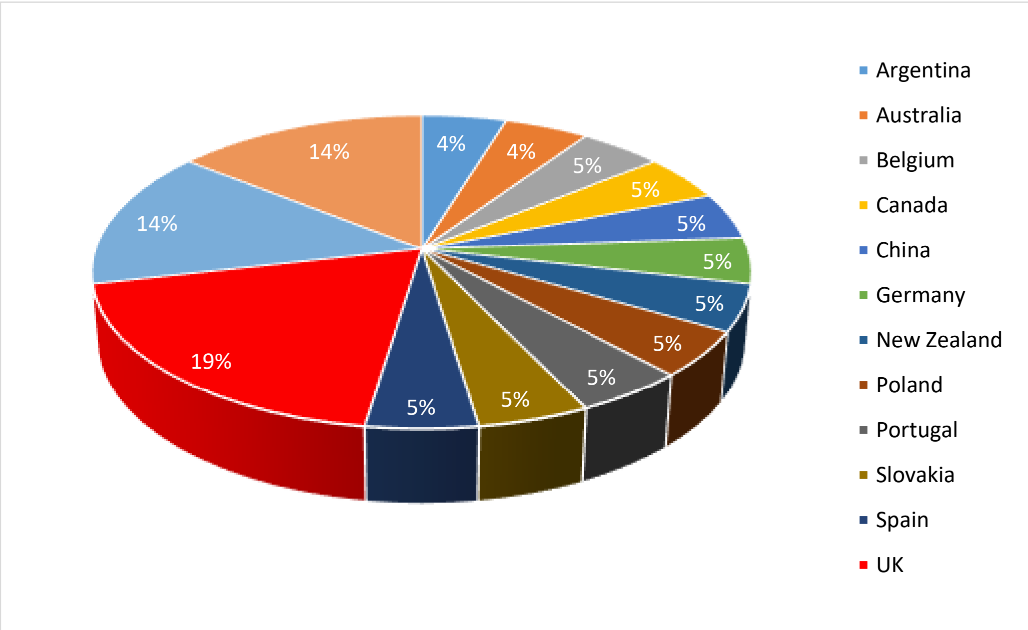


Figure 4. Geo-mapping of the Summative Power Score for e-vendors of NBOMe on AlphaBay.

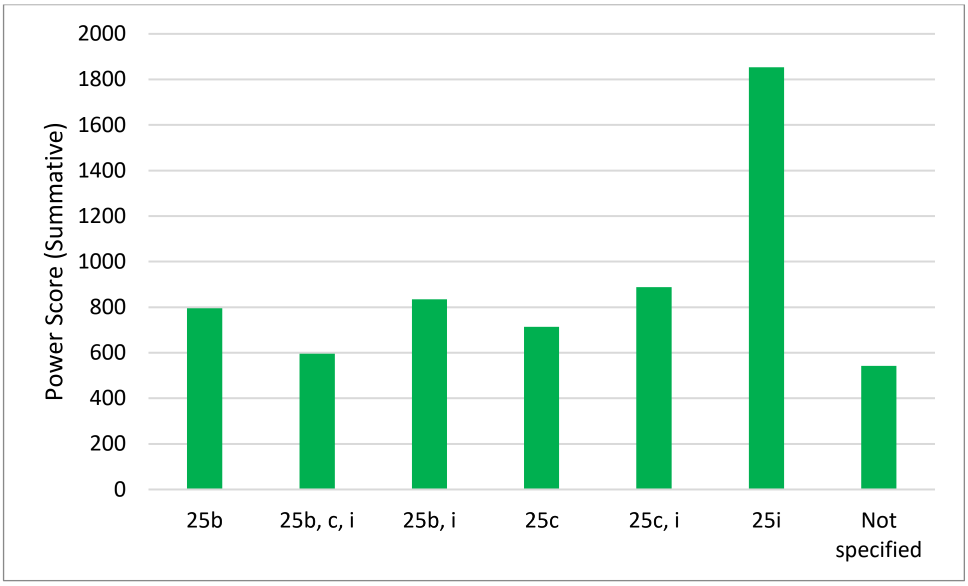


Figure 5. The Main Advertised Variants (Types) of NBOMe on AlphaBay.

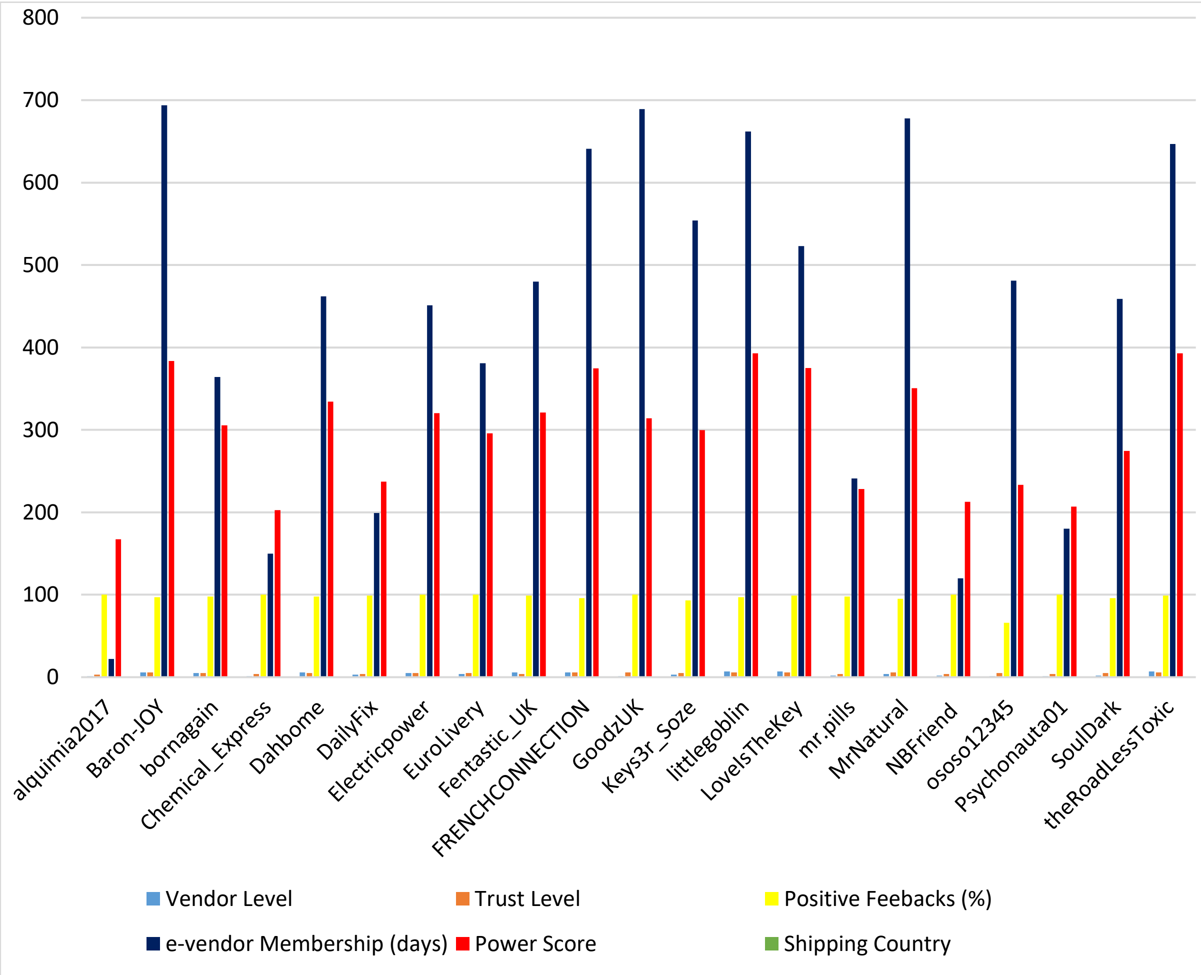


Figure 6. Analyses of the Characteristics of NBOMe e-vendors on AlphaBay.

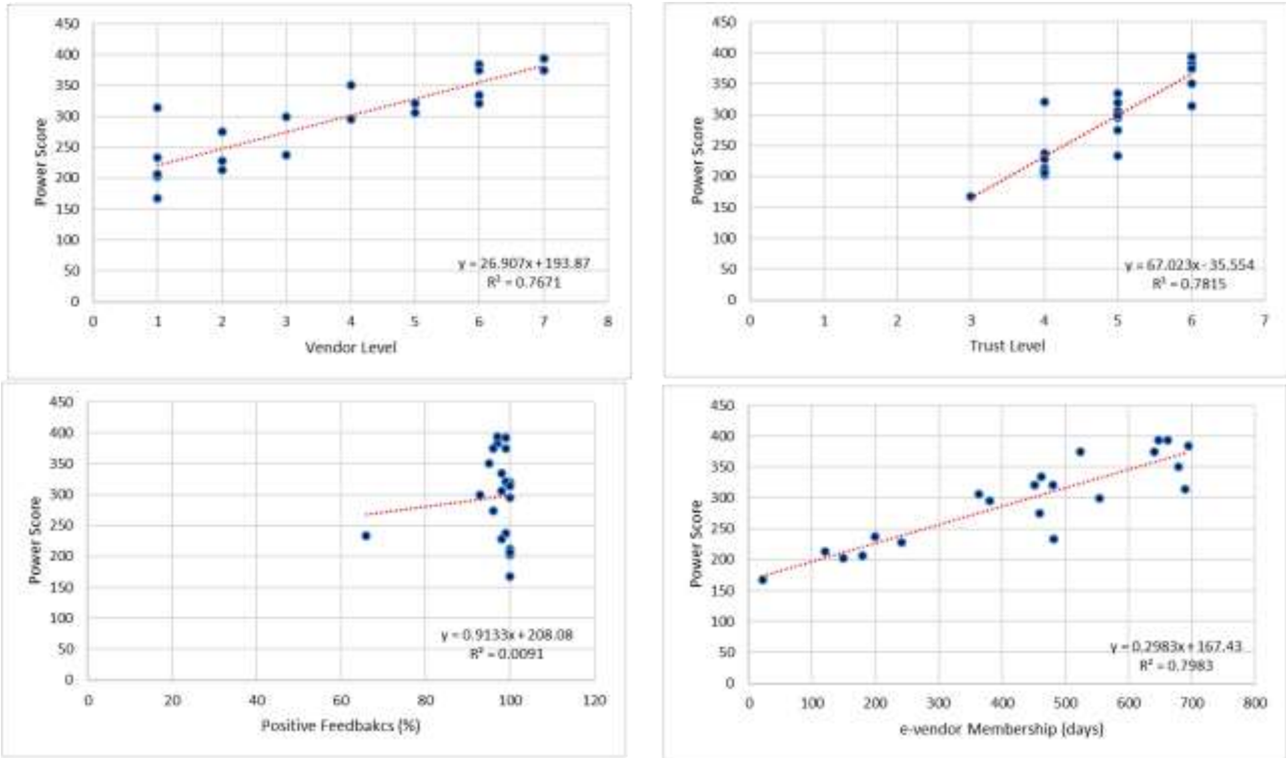
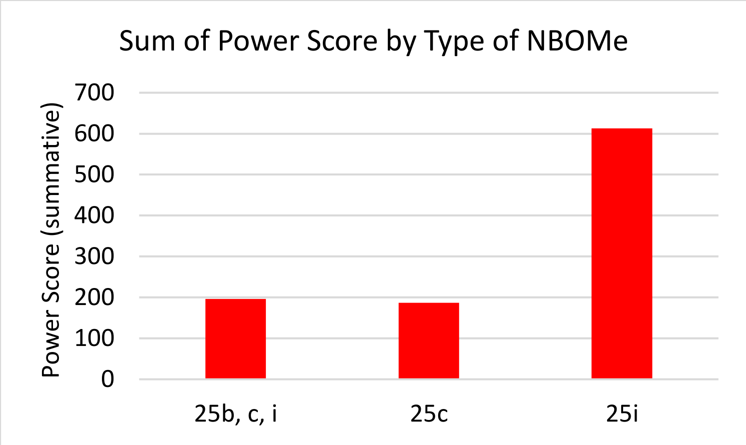
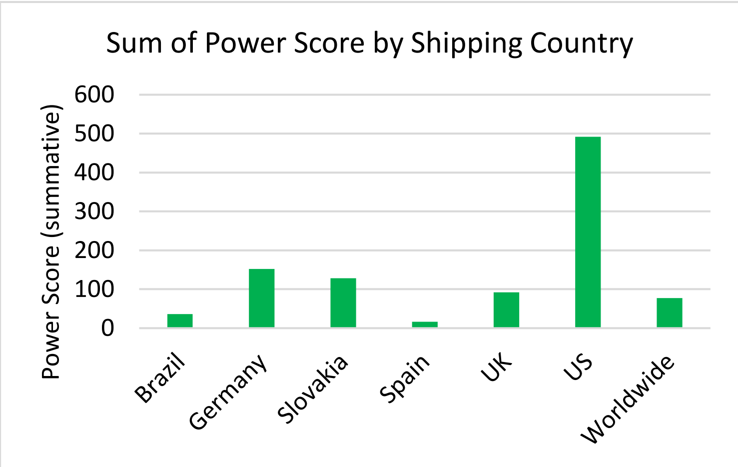


Figure 7. Linear Regression: Power Score of NBOMe e-vendors on AlphaBay





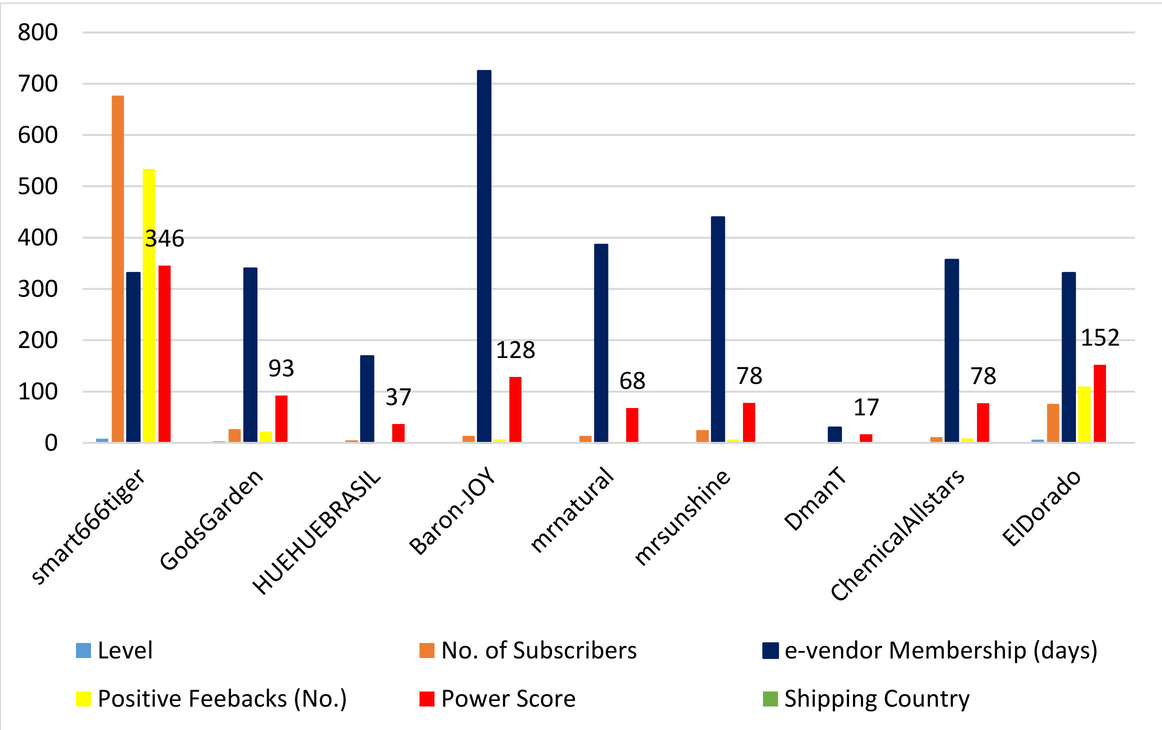
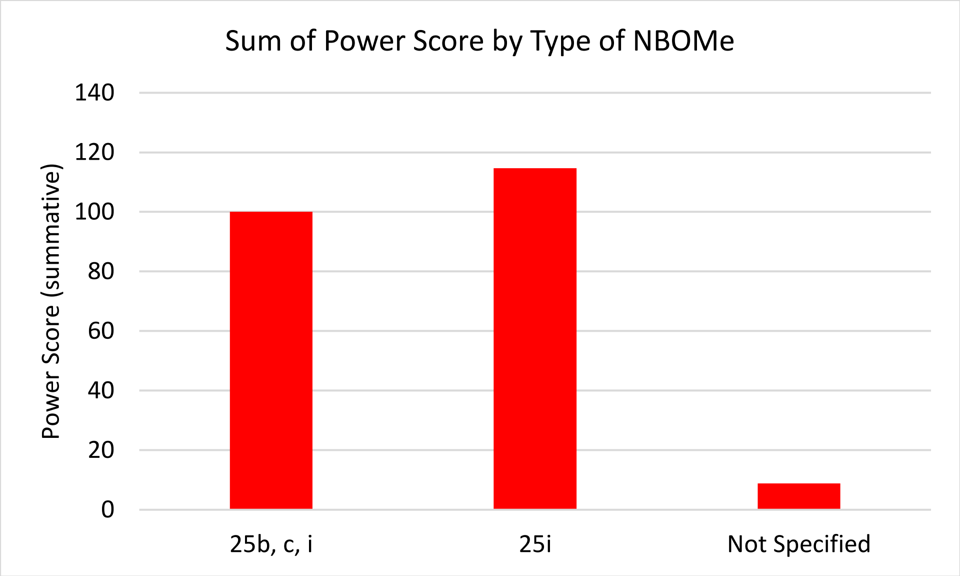


Figure 8. NBOMe on HANSA Market: Advertised Variants (above), Geo-mapping (below), and e-vendor’s Power Score (below).



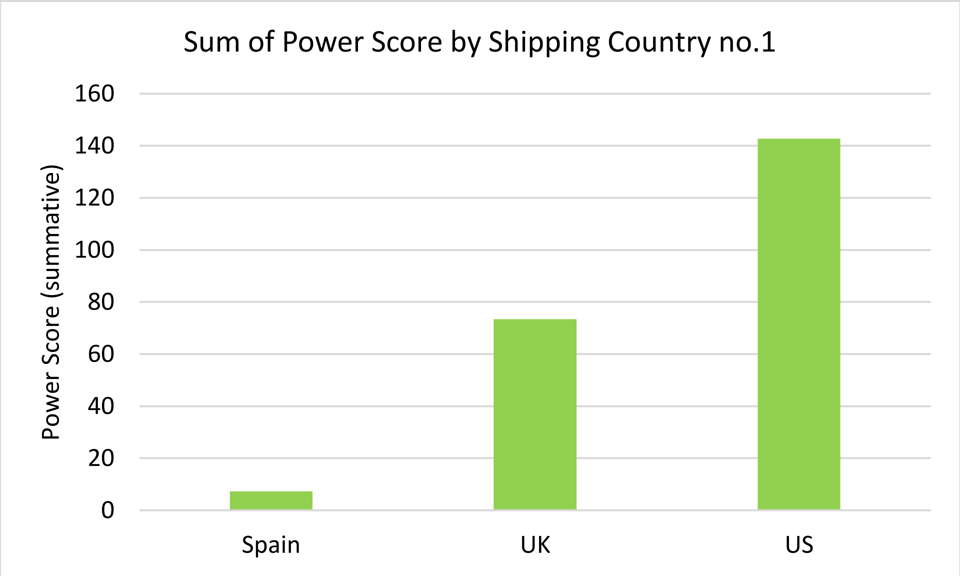


Figure 9. NBOMe on Valhalla e-Market: the Most Popular Variants of NBOMe (above) and their Geo-mapping (below).

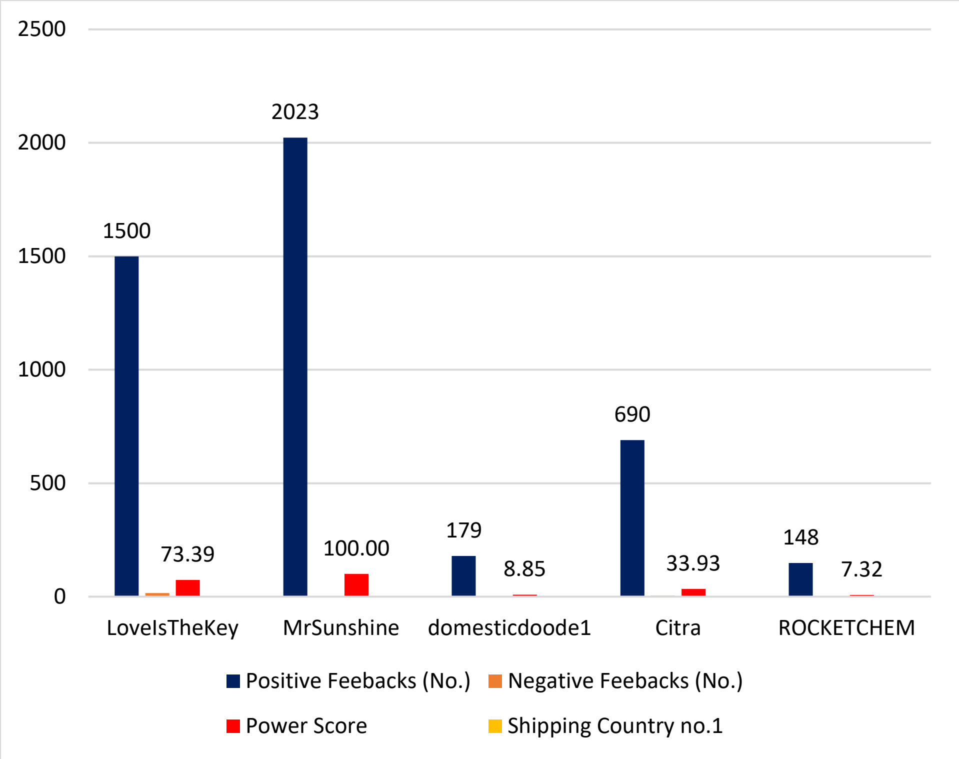
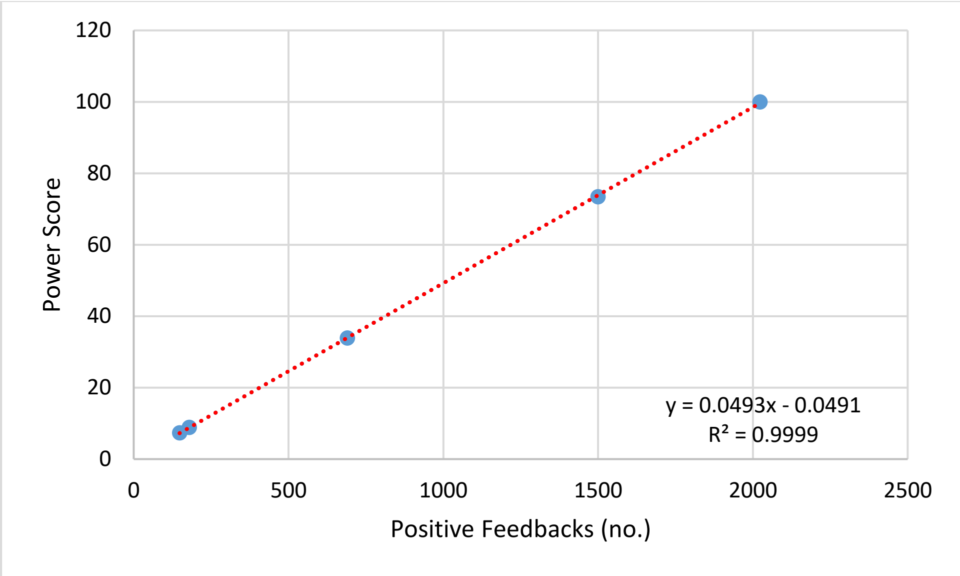


Figure 10. The Power Score Characteristics for NBOMe e-vendors on Valhalla e-market.



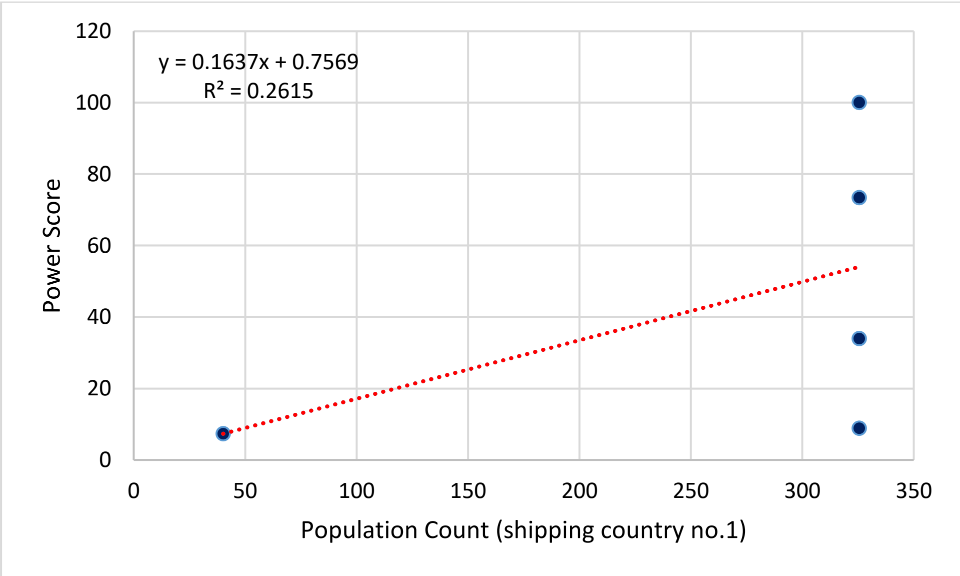


Figure 11. Linear Regression: Power Score versus; Positive Feedbacks (above) and Population Count (below).

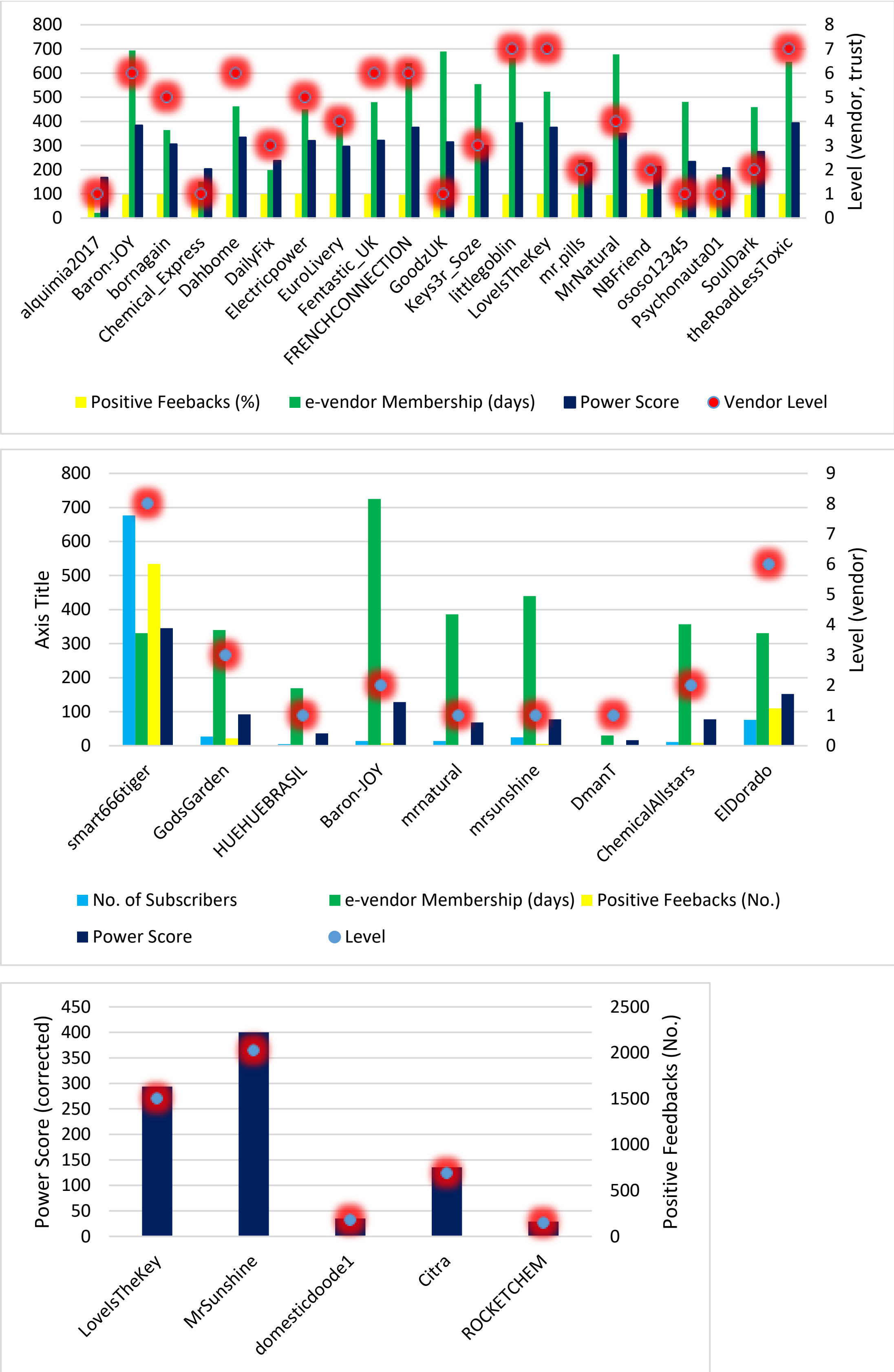


Figure 12. Power Score of e-vendors: AlphaBay (above), HANSA (middle), and Valhalla (Below).

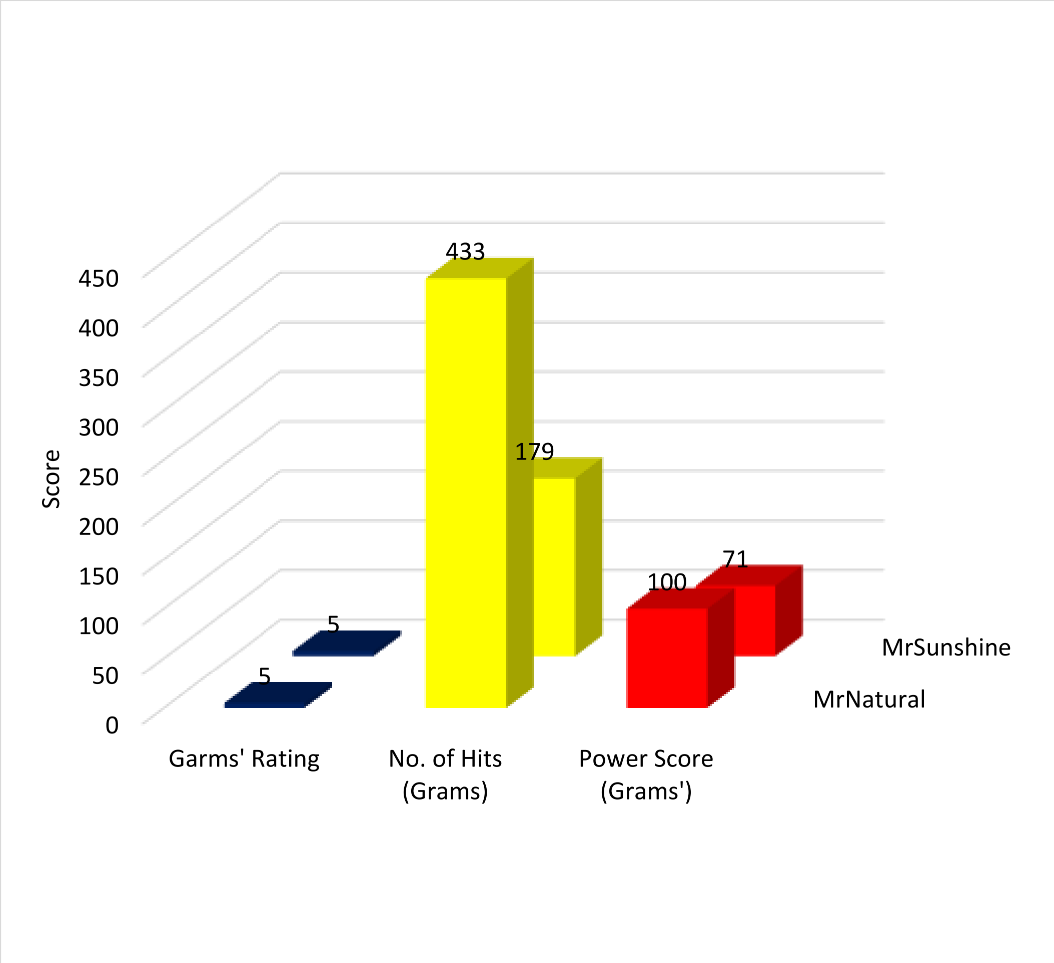


Figure 13. Power Characteristics for Two Unique e-vendors of NBOMe on the Darknet.

Chapter 9. Captagon

BACKGROUND

Fenethylline, also known as *amphetaminoethyltheophylline* and *amfetyline*, is a codrug of *amphetamine* and *theophylline* which behaves as a prodrug to both of the aforementioned drugs. It is marketed for use as a psychostimulant under the brand names *Captagon*, *Biocapton*, and *Fitton*. Fenethylline was first synthesized by the German Degussa AG in 1961 as a part of an investigational programme on side effects of theophylline derivatives and particularly on cardiovascular, pulmonary and central nervous system and a strict prescription status only under medical supervision was requested three years later (Kristen, Schaefer, & Von Schlichtegroll, 1986; Katselou et al 2016).

The chemical structure (Figure 1 and 2) of fenethylline is 7-(2-a-methylphenyl-aminoethyl)-theophylline. Although there are no current FDA-approved indications for fenethylline, it was mainly used as a medicament, primarily during the 1960s and 1970s, for the treatment of children with Attention Deficit Disorder (ADHD), narcolepsy, and depression. One of the main advantages of fenethylline is that, unlike other amphetamines, it does not significantly elevate blood pressure (Kikura & Nakahara, 1997). On the other hand, theophylline is a member of the xanthine family; it bears structural and pharmacological similarity to theobromine and caffeine, it is used mainly for the treatment of pulmonary conditions, including apnea (Barnes, 2003). Theophylline also increases cardiac contractility and heart rate; as a positive inotropic and chronotropic agent, increasing blood pressure, increasing renal and cerebral blood flow. Fenethylline is metabolised by the body to its constituent drugs: amphetamine (24.5% of oral dose) and theophylline (13.7% of oral dose) (Ellison, Levy, Bolger, & Okun, 1970). However, fenethylline was never approved for the medical uses in the United States due to the mere fact that no new investigational drug application was submitted to the Food and Drug Administration (Katselou et al., 2016). It was later listed as a Schedule I controlled substance in the United States and became illegal in most countries in 1986 (United Nations Office on Drugs and Crime, 2016).

Although illegal, captagon is now a primary substance of misuse in Saudi Arabia, where it is used by a high majority (40%) of the overall substance users in the country, mainly by young men aged 12-22 (Arab News, 2015). Additionally, captagon is essentially used by militant groups, to increase fighting aggression, alertness and performance, similarly to amphetamines and methamphetamines (Defalque, & Wright, 2011; Van Hout & Wells, 2016). Further, because of its psychostimulant and cognitive-enhancing properties, captagon is also used by fighters of the Islamic State of Iraq and the Levant (ISIL, formerly known as ISIS) and other militant groups in Syria and Iraq (Shahrour, 2013). It is important to mention that Al-Qaeda strictly adheres to Islamic law in terms of substance use and abuse (Van Hout & Wells, 2016). In Islamic law, otherwise known as Sharia, Muslims should abstain, under any condition, from drinking alcohol and drug abuse with the exception for the therapeutic use of medicines (Sattari, Mashayekhi, & Mashayekhi, 2012). Therefore, ISIL, unlike Al-Qaeda in relation to drug use and abuse, is being selective when it comes to Sharia law to justify its means. A similar example is the use of Khat in Yemen. The use of Khat in Yemen pre-date Islam itself (Nichols, Khondkar, & Gibbons, 2015). Preliminary forensic reports from the famous Paris attacks, which took place in November 2015, indicates that captagon might also have been used by the incriminated ISIL State fighters (Barker, 2015). Although still not confirmed by forensic tests (Lines, 2015). It is known that ISIL attackers are supplied by a black-market of *amphetamine* supplements (McConnell & Todd, 2015). In an interview with the CNN, a 19-year-old ISIL fighter said: *They gave us drugs; hallucinogenic pills that would make you go to battle not caring if you live or die* (McConnell & Todd, 2015).

The side effects are similar to other types of amphetamine-type stimulants (ATS). However, dangerous side effects, that are also incompatible with a war zone requirement include; psychosis, visual distortions and hallucinations, acute heart failure, acute myocardial infarction (AMI), and epileptic fits (Shufman & Dickman, 1999). AMI has been increasingly reported since the beginning of the civil war in Syria (2011), Turkey, and the Middle East (Arslan, Zeren, Çelikel, Ortanca, & Demirkiran, 2015). The first case of AMI in association with captagon was documented in a 21-year old man (Ulucay, Kargı, & Aksoy, 2012).

Nearly a decade ago, data from the International Narcotics Control Board (INCB) and the Interpol, revealed that the drug has been produced illicitly in illegal laboratories mainly based in south-eastern Europe, specifically in Turkey, Bulgaria, Slovenia, Serbia, and Montenegro (Drug Enforcement Admin, US Department of Justice, and United States of America, 2003). From here it has been trafficked to its main consumer markets on the Arabian Peninsula, primarily in Saudi Arabia, for later consumption in the Middle East (Drug Enforcement Admin, US Department of Justice, and United States of America, 2003). However, in recent years, there has been strong indicators based on statistical data, that captagon illicit production has shifted to the region of the Middle East and the north of Africa, primarily Syria, Iraq, and Saudi Arabia (Europol, 2011).

Overall, in 2002, more than 1.4 million tablets were seized in Syria, and 107.5 kilogrammes of the drug were seized in Turkey (Drug Enforcement Admin, US Department of Justice, and United States of America, 2003; Herbert, 2014). The illicit trade is rapidly increasing and more recently in 2016, 8.8 million pills, mainly containing captagon, were found in Egypt (GPHIN, 2016a), while 11,000 captagon tablets were seized in the city of Al-Nasiriya (January 2016), a city to the south-east of the Iraqi capital Baghdad.

Toxicological tests revealed the presence of contaminants such as amphetamine, methamphetamine, procaine, caffeine, quinine, metronidazole, theophylline, among others, besides the absence of fenethylline, as seen in Table 1 (Alabdalla, 2005; Al-Hussaini, 1996). As the current civil war and terrorism in Syria continue, the demand for illicit drugs, including captagon is very high. This substance is also diffused in Iraq, Jordan, Kuwait, and Qatar (Herbert, 2014). However, the content of products sold illicitly as captagon still needs to be determined. Alabdalla (2005) who carried out chemical analysis of counterfeit captagon tablets from 124 seized batches across Jordan, confirmed the absence of fenethylline. The analysis was done via Gas Chromatography–Mass Spectrometry (GC–MS). The counterfeited nature of the captagon tablets seized in Europe was also confirmed by the analysis of seized captagon tablets between 2008 and 2011, which indicated that it no longer contained fenethylline, but amphetamine in combination with caffeine and other substances (Europol, 2011).

Overall the captagon trade in the Middle East, Arabian Gulf region, and the north of Africa, is currently a prolific illegal trade with a high profit margin (Al-hemiary, Al-diwan, Hasson, & Rawson, 2014; Barker, 2015; Herbert, 2014;) as it can be clandestinely synthesized, using straightforward and inexpensive chemistry techniques and raw materials (Barker, 2015; Katselou et al., 2016) and its illicit market contributes in funding global terroristic organizations, including ISIL (GPHIN, 2016b).

RESULTS AND DISCUSSION

A total of 38 studies emerged from the literature search were considered relevant and consulted for further investigation. Among these, five were found to be of low scientific evidence and therefore excluded. Additional data was also carefully selected from the analysis of over hundreds of online media networks and other online resources. A wide range of information on captagon could openly be retrieved from Google and AOL search engines, YouTube, and Amazon, where the substance was illicitly advertised and sold as a powerful psychostimulant in the form of tablets, pills and powder (Arab News, 2015; Freeman, 2014; Herbert, 2014; Kalin, 2014; McConnell & Todd, 2015; United Nations Office on Drugs and Crime (UNODC), 2010). Retrieved data were heterogeneous, which included: drug purchase materials, books, documentaries, chemical analysis data, and other irrelevant results.

The deep web and its darknet, mainly AlphaBay, generated most of the original data in relation to the region of the Middle East, specifically Syria, Iraq, and UAE. In these countries, amphetamine-type stimulants (ATS) are not accessible from pharmacies without an official medical prescription. Therefore, in such regions, the e-commerce is even more crucial in the search, distribution, and acquisition of these products in an illegal way. Additionally, it must also be noted that in regions of conflicts and civil war as in Syria and Iraq, the e-commerce is either highly restricted or disabled because of the fragile Internet-infrastructure. Therefore, in areas of conflict, traditional trading of captagon is the most prominent method. On the contrary, e-commerce plays a major role in more stable areas within the conflict zone, in which the Internet and e-commerce websites are still accessible and operational. This has been confirmed by the fact that most of the relevant data emerged from seven popular e-commerce websites in the Middle East and the North of Africa (Souq.com, Souqelkhaleej.com, Kingsouq.com, Halalat.com, Aliexpress.com, Araboo.com, and Sa.pricena.com).

Concerning the global e-commerce websites (Table 2, Figure 3), both Alibaba and eBay were implementing effective control policies to prevent e-commerce of *captagon.* For instance, *Alibaba* website displayed an automatic message, when prompted with certain keywords in relation to *captagon*; the message declared that the sought keywords and related search are prohibited under Alibaba's website control policies. On the contrary, Amazon, allowed easy access to *amphetamines* and ATS, although sometimes the keywords yielded SERPs, most of these were irrelevant to neither *captagon* nor ATS.

Concerning the local (Arabic) e-commerce website in the Middle East, Persian Gulf, and the North of Africa (Table 3, Fig. 4), most websites yielded no SERPs or very few and non-relevant SERPs. (Liginlal, Gopinath, Ahmad, & Meeds, 2014; Liginlal, Rushdi, Amhad, & Meeds, 2013). It was observed in previous studies that drug related information on portals in Arabic and Farsi tend to be more hidden and disguised (Corazza et al., 2014; Bigdeli et al., 2013).

Relevant results emerged from the Dark web searches on the darknet, which have an increased role in drug trafficking (Chen, 2011; Chen et al., 2008; Cuthbertson, 2015; Gabriel, 2016). AlphaBay Market, based in Russia, is one of the darknet e-markets operating in the sectors, which permits the sale of many illegal items. (Alphabaymarket.com, 2015a; Chen, 2007; Chen, 2012). The keywords used by the researchers across the deep web resulted in data from only two countries in the Middle East; UAE and Syria (Table 4, Figure 5). All results were found on AlphaBay market and traced back to the same vendor (Alphabaymarket.com, 2015b, 2015c). This e-vender has specialised in selling captagon tablets only, and the supply manufactured in Dubai is listed as *unlimited*. The price range was from 16.30 to 217.28 USD, depending on the quantity of sought captagon tablets. Concerning captagon for Intravenous use, there was no relevant data on the deep web and the darknet. AlphaBay seems to be the largest e-market for the region of the Middle East, concerning the captagon e-commerce, while Valhalla market appears to be the largest e-market for Europe, including the Netherlands (Table 5).

An illicit online pharmacy, located in India, also provided access for captagon e-commerce (captagon 50 mg pills (rather than tablets), without the need for a prescription and the price was variable based on the quantity of purchased pills, and up to 360 pills at the cost of 144 USD (Anonymous Pharmacy, 2015). This online pharmacy can be reached on the surface web (Liginlal et al., 2014). In comparison with AlphaBay e-market, both use the same payment system on AlphaBay, known as *Bitcoin Payments*, which make the payment untraceable and anonymous. The price is 20-24 times less costly than in the AlphaBay e-market.

Google Trends also confirmed a very significant increased interest in captagon with a pick in late 2015, compared to previous years (2006-2014). Geo-mapping revealed that the contributing countries were mainly from the EU including; Belgium, France, Germany, Turkey, and Italy (Table 6, Figure 6). This shows an indicative correlation with the Paris terror attack, captagon and ISIL while excluding Al-Qaeda.

Described effects from users include a sense of bravery (lack of fear), feelings of pleasure, increased energy and alertness as well as a reduced need for sleep and food (Drug Enforcement Admin, US Department of Justice, and United States of America, 2003). Overall, captagon users reported feelings; of well-being, increased productivity, alertness, an intense appreciation of the ambient environment, surrounding sounds and colours, visual distortions; its effects are reportedly fierce, long lasting and slowly released (Bluelight.org, 2014). In order to moderate (dampen) the euphorigenic and activating effects of the drug, captagon is also taken in combination with cannabis and alcohol. Withdrawal symptoms may include depression and headache (Bluelight.org, 2004).

A number of side effects have also been identified .These include an increase in heart rate, body temperature, respiration, blood pressure as well as extreme depression, neurological excitation, lethargy, sleep deprivation, heart and blood vessel toxicity, and malnutrition on the long term (Drug Enforcement Admin, US Department of Justice, and United States of America, 2003). Hazardous side effects included: psychosis, visual distortions, visual and auditory hallucinations, acute heart failure, acute myocardial infarction, and epileptic fits (Shufman & Dickman, 1999; Ulucay, Kargı, & Aksoy, 2012).

Oral tablets and pills can be used intravenously for an intense and immediate effect; this can usually be done by crushing the tablets or pills and heating them up (Drugs-Forum, 2013). Similarly, the pills might be converted into a syrup, although side-effects may include gastric-duodenal peptic ulcers and intestinal disturbances. Crushing and injecting pills is hazardous as may lead to seizures and cardiac arrhythmias as well as other adverse effects in the presence of unknown adulterants and contaminants.

Table 1. Chemical Ingredients of Counterfeit-Captagon (Alabdalla, 2005).

Substance	Pharmacology
Amphetamine	Stimulant
Methamphetamine	Stimulant
Ephedrine	Sympathomimetic
Metronidazole	Anti-amebic
Caffeine	Stimulant
Theophylline	Vasodilator
Chlorphenamine	Anti-Histamine
Procaine	Local anesthetic
Trimethoprim	Antibiotic
Chloroquine	Anti-malarial
Quinine	Anti-malarial

Table 2. SERPs Results in Relation to the Major Controllers of Captagon e-commerce.

Source	Keywords	SERPs	Total
Google	Captagon	691,000	8,486,936
	01 pills	10,300	
	Fenethylline	44,000	
	Counterfeit Captagon	1,270	
	Counterfeit Amphetamine	249	
	Inferior Amphetamine	117	
	Amphetamine	7,740,000	
AOL	Captagon	378,000	2,029,988
	01 pills	3,090	
	Fenethylline	8,430	
	Counterfeit Captagon	353	
	Counterfeit Amphetamine	109	
	Inferior Amphetamine	6	
	Amphetamine	1,640,000	
YouTube	Captagon	4,320	83,351
	01 pills	5	
	Fenethylline	126	
	Counterfeit Captagon	165	
	Counterfeit Amphetamine	111	
	Inferior Amphetamine	24	
	Amphetamine	78,600	
Alibaba.com	Captagon	3,042*	27,938
	01 pills	1,834*	
	Fenethylline	0**	
	Counterfeit Captagon	22,137*	
	Counterfeit Amphetamine	0**	
	Inferior Amphetamine	0**	
	Amphetamine	925***	
Amazon.com	Captagon	5*	873,317
	01 pills	1,125	
	Fenethylline	0	
	Counterfeit Captagon	865,160	
	Counterfeit Amphetamine	0	
	Inferior Amphetamine	3,518	
	Amphetamine	3,509	
Ebay.com	Captagon	244,887*	245,321
	01 pills	120*	
	Fenethylline	0	
	Counterfeit Captagon	0	
	Counterfeit Amphetamine	0	
	Inferior Amphetamine	0	
	Amphetamine	314*	

*Irrelevant SERPs results. **Anti-PIEDs policy ***SERPs generated were for medical devices/kits for measurement of body levels of *amphetamine(s)*.

Table 3. SERPs Results for Regional Controllers of Captagon e-commerce.

Regional & Arabic e-commerce websites	Keywords	SERPs	Total
Souq.com	Captagon	13*	19
	01 pills	6*	
	Fenethylline	0	
	Counterfeit Captagon	0	
	Counterfeit Amphetamine	0	
	Inferior Amphetamine	0	
	Amphetamine	0	
Souqelkhaleej.com	Captagon	0	0
	01 pills	0	
	Fenethylline	0	
	Counterfeit Captagon	0	
	Counterfeit Amphetamine	0	
	Inferior Amphetamine	0	
	Amphetamine	0	
Kingsouq.com	Captagon	0	0
	01 pills	0	
	Fenethylline	0	
	Counterfeit Captagon	0	
	Counterfeit Amphetamine	0	
	Inferior Amphetamine	0	
	Amphetamine	0	
Halalat.com	Captagon	0	0
	01 pills	0	
	Fenethylline	0	
	Counterfeit Captagon	0	
	Counterfeit Amphetamine	0	
	Inferior Amphetamine	0	
	Amphetamine	0	
Aliexpress.com	Captagon	0	85
	01 pills	84**	
	Fenethylline	0	
	Counterfeit Captagon	0	
	Counterfeit Amphetamine	0	
	Inferior Amphetamine	0	
	Amphetamine	1*	
Araboo.com	Captagon	0	1
	01 pills	0	
	Fenethylline	0	
	Counterfeit Captagon	0	
	Counterfeit Amphetamine	0	
	Inferior Amphetamine	0	
	Amphetamine	1***	
Sa.pricena.com	Captagon	0	0
	01 pills	0	
	Fenethylline	0	
	Counterfeit Captagon	0	
	Counterfeit Amphetamine	0	
	Inferior Amphetamine	0	
	Amphetamine	0	

*Irrelevant SERPs. **Some SERPs were irrelevant. ***A generated SERP for an article related to a foreign language on the topic of *Amphetamine(s)*.

Table 4. SERPs versus Keywords on AlphaBay e-market.

Source	Keywords	SERPs	SERPs In Arabic Countries			Total SERPs for Arabic Countries	Other Countries
Grams	Captagon	9	4	Syria	1	24	UK Philippines China Poland Canada Australia Finland Sweden Portugal Spain Switzerland Hungary Latvia Afghanistan Austria Czech Republic Luxembourg Norway
				UAE	3		
	01 pills	4934	0	Syria	0		
				UAE			
	Fenethylline	9	4	Syria	1		
				UAE	3		
	Counterfeit Captagon	333	4	Syria	1		
				UAE	3		
	Counterfeit Amphetamine	1294	4	Syria	1		
				UAE	3		
	Inferior Amphetamine	974	4	Syria	1		
				UAE	3		
	Amphetamine	962	4	Syria	1		
				UAE	3		

Table 5. Online e-markets for Captagon e-commerce on the Deep Web.

Dark web market	Number of results	Shipping Country	
Valhalla	5	Netherlands	5
AlphaBay	4	UAE	3
		Syria	1
Hansa Market	4	Europe	4

Table 6. Average Interest for Years 2006-2015 (Google Trends, 2015).

Keyword	Year									
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Captagon	2.58	3.09	1.58	1.92	1.58	1.08	1	1.58	2	13.92
Fenethylline	0	0	0	0	0	0	0	0	14	21.33
ISIS	0	0	0	0	0	0	0	2.17	28.59	10.42
Al-Qaeda	9.45	7.5	5.92	4.92	4.75	6.33	4.33	4.67	4.42	4.42

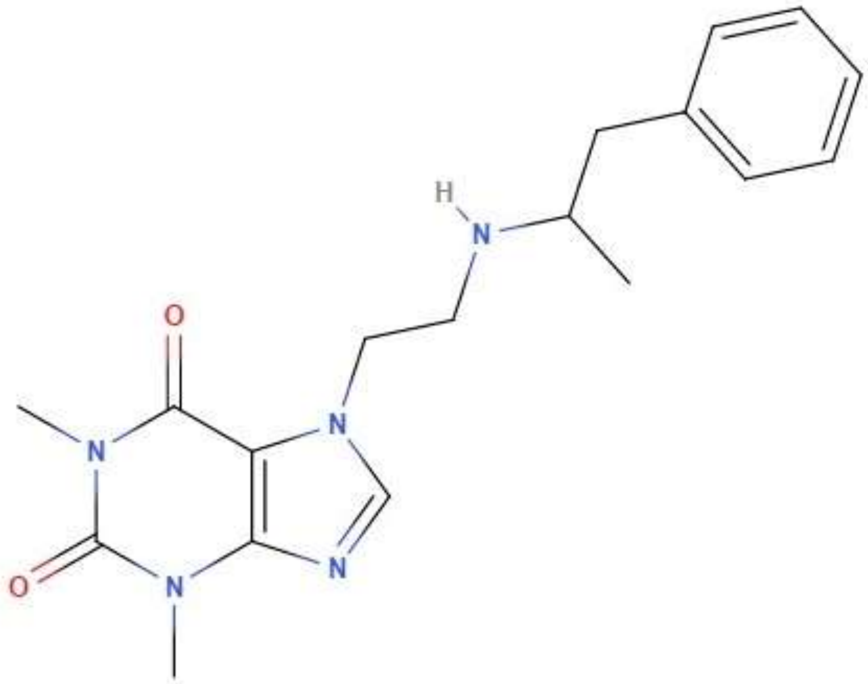


Figure 1. The Molecular Structure of Fenethylline.

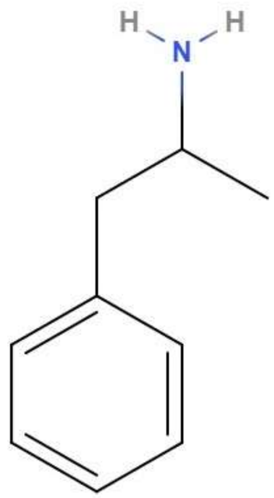
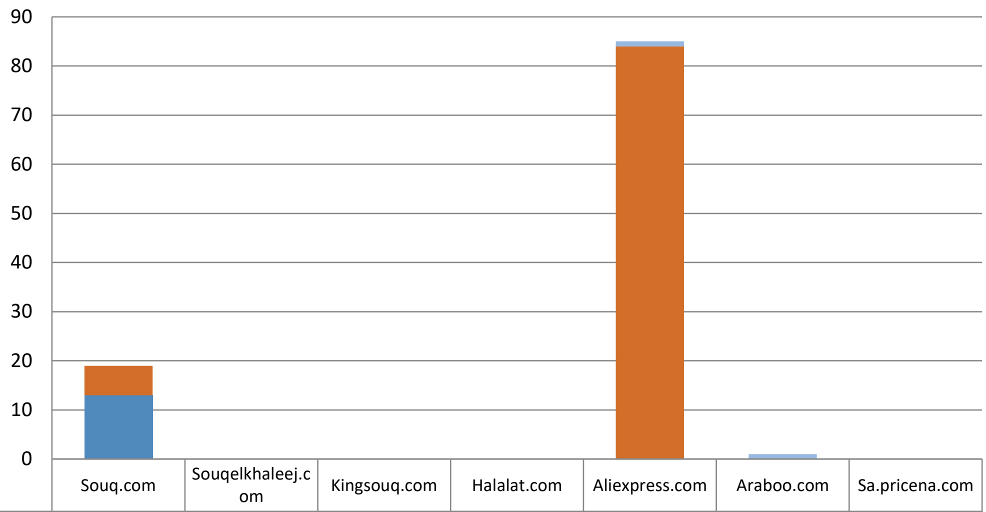


Figure 2. The Molecular Structure of Amphetamine.

	Captagon	"01 pills"	Fenethylline	"Counterfeit Captagon"	"Counterfeit Amphetamine"	"Inferior Amphetamine"	Amphetamine
Ebay	244,887	120	0	0	0	0	314
Amazon	5	1,125	0	865,160	0	3,518	3,509
Alibaba	3,042	1,834	0	22,137	0	0	925
Youtube	4,320	5	126	165	111	24	78,600
AOL	378,000	3,090	8,430	353	109	6	1,640,000
Google	691,000	10,300	44,000	1,270	249	117	7,740,000

Figure 3. Component Bar Chart for the Major Controllers of Captagon e-commerce



	Souq.com	Souqelkhaleej.com	Kingsouq.com	Halalat.com	Aliexpress.com	Araboo.com	Sa.pricena.com
Amphetamine	0	0	0	0	1	1	0
“Inferior Amphetamine”	0	0	0	0	0	0	0
“Counterfeit Amphetamine”	0	0	0	0	0	0	0
“Counterfeit Captagon”	0	0	0	0	0	0	0
Fenethylline	0	0	0	0	0	0	0
“01 pills”	6	0	0	0	84	0	0
Captagon	13	0	0	0	0	0	0

Figure 4. SERPs Results for *C*aptagon Local e-commerce Websites.

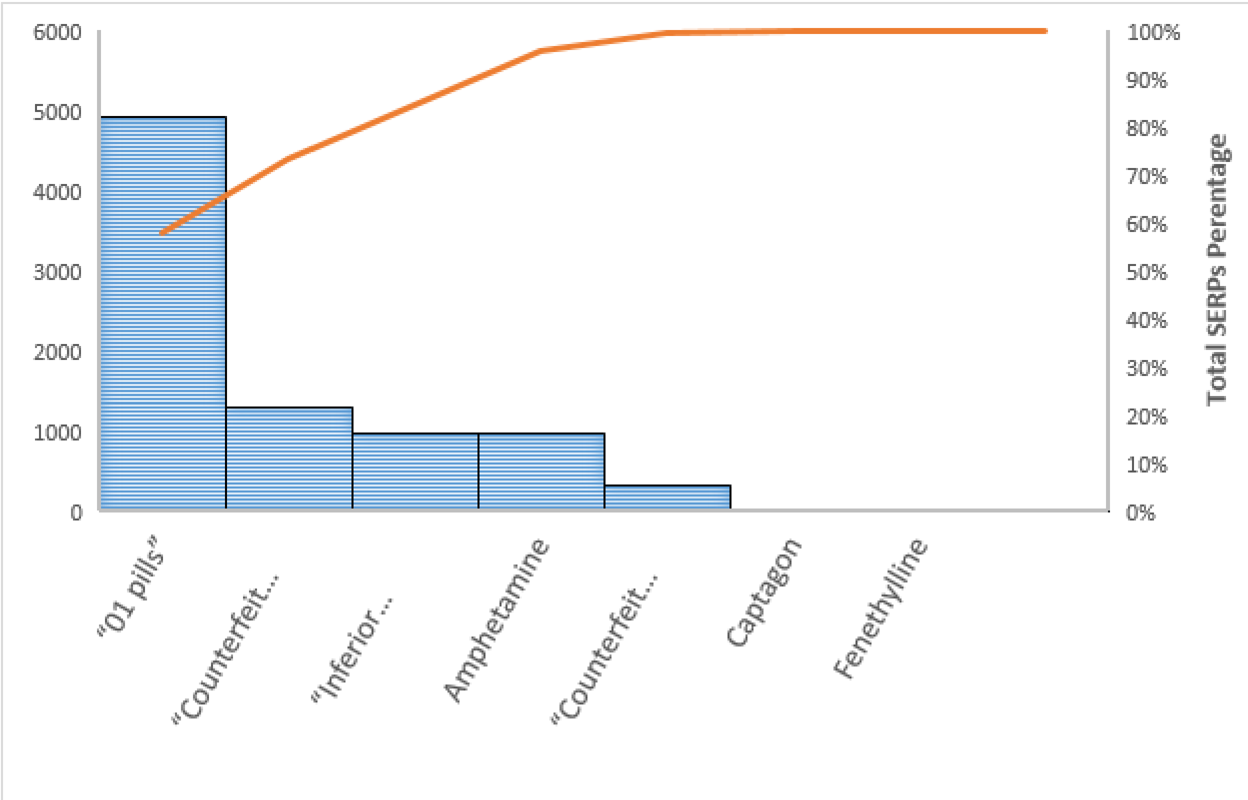


Figure 5. SERPs versus Keywords on AlphaBay e-market (Deep web).

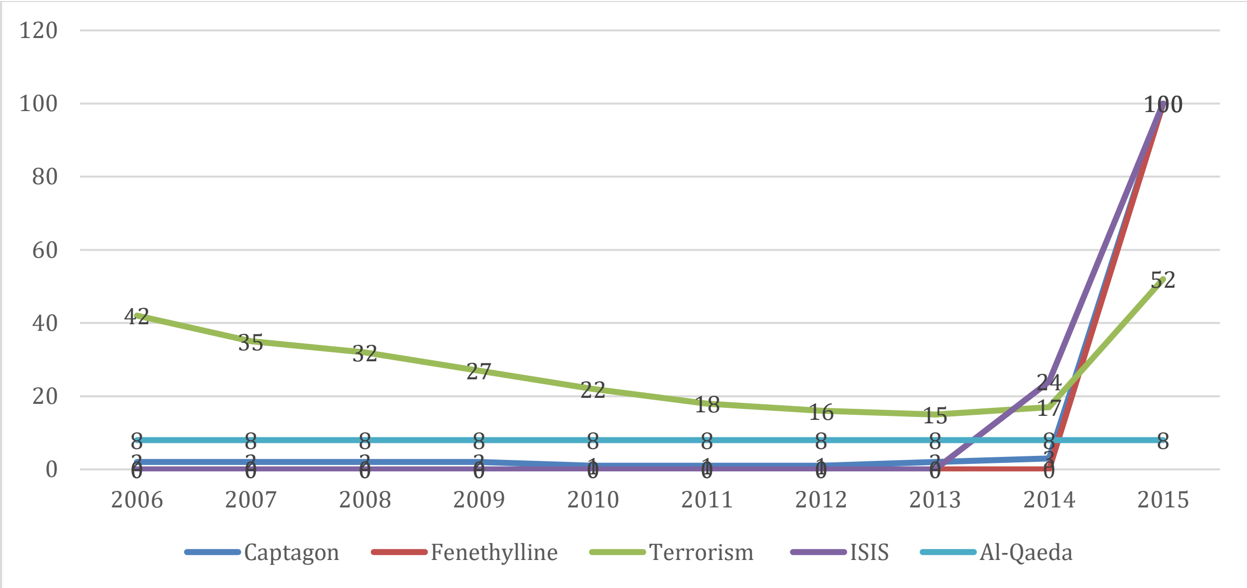


Figure 6. Google Trends for Captagon and Captagon-related queries (Google Trends, 2015).

Chapter 10. Octodrine

BACKGROUND

Octodrine is an amphipathic primary amine (Figure 1) known under many names including dimethyl hexylamine (DMHA) and 6-methylheptan-2-amine. This molecule contains the structural features present in 1,3-dimethylamylamine (1,3-DMAA), a neural stimulant with a structure similar to ephedrine and adrenaline; DMAA is banned by many sports and government agencies. Octodrine discovery was reported in the late 1940s and reappeared recently as part of a new generation of stimulants that claim to boost energy levels, attention and concentration, and to maintain intense workout. Octodrine can be related to the rapid emergence of the market of over 540 NPS reported in 102 countries (UNODC, 2016). Octodrine, chemically known as the 2-amino 6-methyl heptylamine, has been previously studied in 1947 (Fellows, 1947) and 1951 (Marsh and Hrring, 1951) strictly using animal models. To date, there has been no experimental studies or interventional trials towards humans. Octodrine is rapidly spreading nowadays between athletes for being consumed as a pre-workout formula to increase fitness and as an agent to facilitate weight loss. There were some reports of octodrine substance abuse during the Rio Olympics in 2016 (World Anti-Doping Agency, 2016). The substance has already spread in online commerce websites and can be easily purchased without any medicinal prescription. All these justify the need for a prompt action to investigate octodrine in relation to; the reason behind its reemergence and spread in different communities (1), availability via electronic commerce (2), and its threats to health (3). This study will compare the magnitude of octodrine diffusion on the surface web versus deep web, to reach a definitive conclusion on the main division of the internet promoting it.

No systematic scientific investigations have been undertaken since octodrine reemerged as a possible substance of abuse. Sympathomimetic effects of octodrine were explained as an alpha adrenergic agonist-mediated via G-protein-coupled receptors (GPCRs) stimulating the sympathetic component of the autonomic nervous system (ANS). It is similar in structure to tuaminoheptane, a drug used as a nasal decongestant, which is in turn similar to norepinephrine and considered to be of a mild-to-moderate sympathomimetic (Kuo et al., 2004). Octodrine itself was available as a decongestant named *vaporpac* with an alpha agonist action; vaporpac is not available anymore in the markets (National Institutes of Health, 2016). In animals, including several mammal species, octodrine was found to increase; the pain threshold, cardiac rate (positive chronotropic effect) and myocardial contractility (positive inotropic effect). There was no significant detectable effect on the intestine, urine secretion, and respiration (Fellows, 1947). However, respiration of dogs under anaesthesia was found to be stimulated by 2-amino 6-methyl heptane and lasted for more than 60 minutes (Charlier, 1951). The motor stimulatory effect was shown to be far less than amphetamine which makes octodrine milder in action; however, data for acute toxicity was collected from experimental animal models (Fellows, 1947). Octodrine as a parent compound has a vasopressor activity that clearly diminishes after the introduction of hydroxy or methoxy group to position-6 leading to a decrease of hypertensive side effect while sparing the other cardiovascular effect (Marsh & Hrring 1951). Gas and liquid chromatography analytical methods were used in the drug screening for octodrine in urine samples (Broecker, Herre, and Pragst, 2012; Dugal et al., 1980).

Octodrine has been related to a poisonous plant *Aconitum kusnezoffii* and shown to be of a similar structure to dimethyl amyl amine (DMAA), a dietary supplement that was previously available on the market that exerts amphetamine-like effects (Aegis Shield, 2016). Octodrine is increasingly available for sale in a powder form to be consumed prior workouts and athletic activities (a pre-workout formula) without evidence-based recommended doses. Octodrine was listed in products under different names such as DHMA, and 2- amino isoheptane (Aegis Shield, 2016; Bodybuilding.com, 2016; Herbnutritionals, 2016; Mrsupplement, 2016; Price Plow, 2016; Suppversity, 2016; Yang, 2016).

According to the systematic review of the evidence-based and scholarly published literature, octodrine is considered as a mild stimulant (Charlier, 1951; Fellows, 1947; Marsh & Hrring 1951). It has a positive inotropic and chronotropic effect; it increases the respiratory rate and blood flow to muscles and brain. It causes excessive sweating and decreases pain during the workout and intense physical activities (Charlier, 1951; Fellows, 1947; Marsh & Hrring 1951). These pharmacodynamics properties make octodrine favourable for many athletes. Octodrine was also found to have antimicrobial and antifungal properties with the potential to be one of the safest drugs discovered as an antifungal agent for the treatment of candidiasis (Kim, 2015)

The fact that Octodrine has not been studied in human is a cause for concern. Although octodrine appears to be safe as a mild sympathomimetic agent, the full pharmacodynamic properties were never fully explored; there are no reported interventional studies in humans, and all data are based on animal models from early studies back in the 1940s and 1950s. Furthermore, the chemical and comparative chemical signature and the full pharmacodynamics of the commercially available octodrine-containing products have not been systematically studied. Therefore, octodrine is critically understudied, and it is vital to draw the attention to whether or not it should be added to the world anti-doping agency (WADA) prohibited list of drugs to ensure fair and safe competition among athletes.

Data presented in this study was based on a systematic review of the literature and a systematic observational analysis of the web content, both surface and deep. These analyses were fully exploited via descriptive and inferential statistics. To the best of the authors' knowledge of the available literature on the topic, this is the first reported observational cross-sectional analytic study of the content of the web, in relation to octodrine. The level-of-evidence of this paper is estimated to be of level-2b, in accordance with the classification system adopted by the Oxford Centre for Evidence-based Medicine (Oxford Centre for Evidence-based Medicine, 2009).

RESULTS AND DISCUSSION

Based on a preliminary screening of literature databases and a cross-sectional analysis of the content of the web, both surface and deep, it is to be inferred that octodrine (DMHA) is an under-researched chemical substance which possesses multiple medicinal properties. Octodrine can exert sympathomimetic and broncho-spasmolytic effects, with a possibility to act as a stimulant, an anti-obesity and an appetite suppressant agent. It was reported that this molecule has also shown broad-spectrum antimicrobial effects and specific antifungal properties. It has been reported to be used a nasal decongestant as well as pre-workout additive (Aegis Shield, 2016; Bodybuilding.com, 2016; Charlier, 1951; Fellows, 1947; Herbnutritionals, 2016; Marsh and Herring, 1951; Mrsupplement, 2016; Price Plow, 2016; Suppversity, 2016; Yang, 2016). There were only five papers in the entire body of literature in relation to octodrine, octodrine derivatives, and octodrine-related compounds (Fellows, 1947; Marsh and Herring, 1951; Charlier, 1951; Gode, 1958; Tschudin, 1950). Other scholarly written papers, a total of seven, covered octodrine only marginally, these papers dealt with the chemical properties of several chemicals including octodrine, while others paper provided data on its antimicrobial effects (Kim et al., 2015; Niu et al., 2015).

There are also scattered documentation of data in few other articles, including an invention patent from 2012 (portal, 2012). Furthermore, the lack of experimental studies including the randomised controlled trials (RCTs) and other interventional studies on humans led to the complete absence of systematic reviews and meta-analytic studies in relation to octodrine. Secondly, the chemical analysis of octodrine and ambredin (octodrine is an active ingredient of ambredin) is mandatory for the purpose of national and international comparative chemical analysis and future receptor-ligand studies. These studies are vital to comprehensively explore the mechanism of action and the pharmacodynamics of this long-forgotten, but re-emerging substance.

Other databases provided results, but they were either marginally related to octodrine or octodrine-related chemicals (Broecker, Herre, and Pragst, 2012; Dugal et al., 1980; Kim et al., 2015; Niu et al., 2015), or completely unrelated to octodrine (Table 1 and 2). Graphically plotted data of results retrieved from Google search engine (Figure 2), showed the keywords of highest yielding SERPs. The top keywords were: “DMHA”, “5-methyl-2-heptylamine”, “hexylamine, 1, 5-dimethyl-“, “2-amino-5-methylheptane”, “Octodrine”, “6-methylheptan-2-amine”, and “C8H19N”. Furthermore, retrieved hits and results pages from the surface and deep web, indicate that both Google and Google Scholar behave as statistical outliers. Other data on octodrine were documented at bodybuilding and fitness websites, bio(chemistry) and bio(chemists) websites, toxicology websites, pharmacy and pharmaceutical websites, online e-commerce websites, medical and paramedical literature databases. However, these were neither scholarly-written nor of a recognised level-of-evidence.

MEDICAL, PARAMEDICAL DATABASES, AND GREY LITERATURE

Based on searching NCBI – PubMed, The Cochrane Library, Scopus, EBSCO – CINAHL, OpenGrey, and Google Scholar (Table 1 and 2, Figure 2 to 5). The Majority of Search Engine Result Pages (SERPs), were retrieved from Google Scholar (7,825) and PubMed-Medline (106). Obviously, there is a relatively large number of published manuscripts found in PubMed, a total of 106 papers. However, most of these papers were not related to octodrine. In fact, only three papers were found to be pertinent to the topic. These papers were found using two keywords: *2-amino-6-methylheptane* and *6-methyl-2-heptylamine*. The Cochrane Library generated fewer results (2), using the keyword *DMHA*. However, both papers dealt with topics other than octodrine. On the other hand, Scopus generated more results (242), while EBSCO – CINAHL database generated (6). Similarly, the vast majority of these papers were found to be irrelevant to octodrine or octodrine-related compounds.

Two of the three papers found on PubMed were published in the *Journal of Pharmacology and Experimental Therapeutics* in 1947 and 1951 respectively (Fellows, 1947; Marsh & Hrring 1951), while the 3rd paper (Charlier, 1951) was published at the *Archives internationales de pharmacodynamie et de thérapie*. These particular papers were also indexed in Google Scholar database. Since the 1950s and for the next seven decades, there were no other scholarly-published data specific for octodrine in peer-reviewed journals, neither observational nor experimental studies could be found on the entire web including medical and paramedical databases, and the unpublished literature.

There was also a complete absence of papers, in relation to octodrine, in the grey (unpublished literature). Based on the search of OpenGrey (Open Grey, 2016), the list of keywords failed to generate any results. To re-encapsulate, there was no RCTs, quasi-experiments, or any other interventional studies apart from cohort studies on animals done in 1947 and 1951. Additionally, there were no systematic reviews; the lack of adequate experimental studies and the total absence of RCTs, lead to the complete absence of meta-analytic studies. There were no other observational studies other than animal studies, no review articles, including systematic reviews, and no case reports or case series.

DATA REPORTED MARGINALLY IN SCHOLARLY PEER-REVIEWED PAPERS AND INVENTION PATENTS

Octodrine has been reported marginally in several papers, including an invention patent from 2012, the invention patent is in relation to a novel stable anaesthetic for reducing skin reactions (Portal, 2012). Octodrine was also reported in two papers that are pertinent to the discipline of toxicology and chemical chromatography, in which the octodrine physiochemical properties including relative retention time (RTT), and its identification in hair samples were documented (Dugal et al., 1980; Broecker, Herre and Pragst, 2012). Furthermore, Niu et al. (2015) and Kim et al. (2015), discussed the broad-spectrum antimicrobial effect, antifungal effect, the anti-persister activity of octodrine, and its use in the treatment of *Candida albicans* and uropathogenic strains of *Escherichia coli*. These two papers also discussed octodrine properties from a microbiological perspective, and in relation to the emergence of microbial resistance towards octodrine. Additionally, Kuo et al. (2004) and Schlessinger et al. (2011), documented the sympathomimetic properties of octodrine, and the effect in relation to norepinephrine transporter (NET) and G-protein-coupled receptors (GPCRs); these studies provided results that are in harmony with the results back from 1947 and 1951 animal studies (Fellows, 1947; Marsh & Hrring 1951).

ANALYSES OF GOOGLE TRENDS DATABASE

Google Trends (table 3A AND 3B) provided valuable data in relation to the surface web users interest (attentiveness) towards octodrine. Four keywords provided real insight on the trend as far back as the year 2004. These keywords are *octodrine*; 2-*aminoisoheptane*; *aminoisoheptane*; and *DMHA*. There was an obvious incremental increase of interest in octodrine starting in the year 2012. This interest had a plateau for the period in between 2013 and 2014 and was followed by a steep rise in 2014-2015, followed by a further elevation in the trends starting in 2015 (Table 3A and 3B, Figure 5). In a prior study, it was emphasised that a collaboration with search engine authorities, including Google search engine, is essential for controlling the electronic commerce (e-commerce) of these NPS on the surface web and in order to provide factual data of high statistical power (Al-Imam et al., 2016).

BODY BUILDING WEBSITES, (BIO)CHEMISTRY WEBSITES, BLOGS AND ONLINE FORUMS, AND PHARMACEUTICAL WEBSITES

These websites provided a major quota of data across the web. However, they were neither scholarly-written-peer-reviewed nor published by official journals or scientific bodies. Data included details on the chemical and molecular structure, dosage, route of administration, octodrine-related compounds and derivatives, extraction from a botanical species, mechanism of action, data from unpublished experimental studies using animals, and details on pharmacodynamics and pharmacokinetics (Aegis Shield, 2016; Bodybuilding.com, 2016; Herbnutritionals, 2016; Mrsupplement, 2016; Price Plow, 2016; Suppversity, 2016; Yang, 2016). Overall, these data rank at the bottom of the hierarchy of retrieved literature, they are merely anecdotal opinions to be either categorised as level-5 or for which categorization was not applicable (Oxford Centre for Evidence-based Medicine, 2009). Therefore, the majority of these data are of no value for subsequent meta-analytic studies or systematic reviews.

Nevertheless, some of these reported "facts" are interesting and yet to be proven with tangible evidence.

THE DEEP WEB AND THE DARKNET

In relation to the e-commerce of NPS Substances, these substances were almost always predominantly existing on the deep web and its darknet e-marketplace; the deep web was proven more valuable than the surface web in relation to the e-commerce and diffusion of knowledge on these substances (Corazza et al., 2014; Van Hout, 2013; Al-Imam et al., 2016). However, that is not the case with octodrine; it was found that the deep web and its illicit e-markets on the darknet failed to generate data of significant relevance to octodrine comparable to the data generated from the surface web. This fact is also apparent numerically, the total number of hits were 48,725 (deep Web) and 5,894 (darknet) which is significantly lower than that of the surface web.

The total number of hits retrieved from the surface web was 750,657 (Table 1), these were distributed as follows: Google Search Engine (742,476), Google Scholar (7,825,) PubMed (106), The Cochrane Library (2), Scopus (242), EBSCO – CINAHL (6), and OpenGrey (0). PubMed-Medline yielded three scholarly papers on octodrine (Charlier, 1951; Fellows, 1947; Marsh and Hrring 1951), and two other papers related to the medicinal substance known as ambredin, which has octodrine as one of its three active ingredients (Gode, 1958; Tschudin, 1950). Non-parametric Inferential statistics were applied, using the 2-tailed chi-square test at an alpha value of 0.05 and 95% CI, the test was implemented by contrasting the observed values and expected values in relation to the number of hits on both divisions of the web, surface and deep. The corresponding *p-value* was 0.001 which denote a significant level of difference. Hence, it is to be concluded that the surface web is the prime source data in relation to the e-commerce of octodrine and its diffusion on the internet.

Additionally, the vast majority of data found on the darknet were not related to octodrine, and those of the deep web had a very high similarity or shared the same results pages and web addresses of those retrieved from the surface web. Therefore, the quantity and quality of the data found on the deep web were inferior in comparison to data from the surface web. The quality of data on the surface and deep web were evaluated via the appropriate appraisal tool (Table 4 and 5, Figure 6) and inferential statistics (Table 6, Figure 4) using the 2-tailed chi-square test (Better Value Healthcare Ltd, 2016; Oxford Centre for Evidence-based Medicine 2009).

ONLINE DRUG FORA

Octodrine is mostly mentioned in fitness and body-building online fora; it is considered as the *heir* of DMAA, banned by both the United States Food and Drug Administration (FDA) and WADA. The blog priceplow.com defined the molecule as *the next big thing* in 2016 (Priceplow.com, 2016). According to the same blog, 100-150mg of octodrine orally seem to be comparable to 35-50mg DMAA, but still a little weaker. Other users reported having experimented adding octodrine at low doses (60 mg) to caffeine (300 mg), in order to obtain energy and *a kind of aggression*. Higher doses, at 75 mg or above, may cause adverse effects such as eyes twitching, pulsing sinus area (carotid sinus), and absent-mindedness; some customers reported a rise in blood pressure after the intake of supplements containing octodrine (Anabolicminds.com, 2016). Octodrine was also reported to be effective in increasing the cognitive abilities and modifying the pain threshold without central nervous system side effects (Project Bodybuilding, 2016). Some bodybuilders identify octodrine-containing products as *the best pre-workout stimulant* (Bodybuilding.com, 2016). Appetite suppression is another desired effect of octodrine: according to users, 25 mg twice a day are enough to *keep one's mind off food* (Prohormoneforum.com, 2016).

The major limitations of this study are;

1. The paucity of the available literature, total absence of review articles, systematic reviews, and meta-analytic studies. Similarly, there is a lack of case reports in relation to octodrine-related incidents of intoxications and death.
2. Lack of sufficient experimental data required for creating systematic reviews and meta-analytic studies. Similarly, lack of observational data including both retrospective, prospective cohorts, and cross-sectional studies.
3. Only five peer-reviewed papers were found to be directly pertinent to octodrine; these were used for the purpose of the literature review. Further, these papers were published approximately 6-7 decades ago. Other scholarly-published studies dealt with octodrine in a limited way (i.e. octodrine was not the main focus of these studies).
4. Lack of peer-reviewed and scholarly published articles on the chemical analysis of octodrine. A comprehensive chemical analysis is mandatory to be carried out in future research. The aim is to establish and compare the chemical signature of octodrine, both nationally and internationally, and identify potential contaminants and other active ingredients in the currently promoted products under the name octodrine or DMHA.
5. Lack of data on the mechanism of action by which octodrine may induce appetite suppression and weight reduction (anti-obesity agent).
6. The sympathomimetic effect of octodrine is well-understood. However, the central effect including the psychostimulant effect was not fully explored. Future studies can also assess the central effect of octodrine and its correlation with patterns of cerebral dominance and the lateralization of brain functions (Al-Hadithi et al., 2016).

7. Inability to access the original raw data upon which the Google Trends data was constructed. Besides, there is an inadequate provision of data in relation to the geographic mapping of the trends worldwide, particularly in comparing the developing world, including the middle east and the north of Africa, versus the developed countries.

Table 1. The Number of Hits per Keywords for Octodrine.

	Keyword	Database/Source								
		Surface Web							Deep Web	
		Google	Google Scholar	NCBI - PubMed	The Cochrane Library	Scopus	EBSCO - CINAHL	OpenGrey	Deep Web [*]	Dark Net [#]
1.	Octodrine	29,000	237	3	0	11	0	0	2640	0
2.	Octodrinum	826	3	3	0	0	0	0	2660	0
3.	Octodrina	790	4	3	0	0	0	0	57	0
4.	Ottodrina	247	0	30 [#]	0	0	0	0	8	0
5.	Ambredin [&]	636	18	2	0	2[#]	0	0	19	0
6.	Vaporpac	1,370	37	1 [#]	0	0	0	0	297	0
7.	2-aminoisoheptane	8,090	1	0	0	0	0	0	995	0
8.	Aminoisoheptane	8,070	1	0	0	0	0	0	1,010	0
9.	Dimethylhexylamine	11,400	1,140	14	0	0	0	0	670	0
10	Dimetylhexylamine	11,400	1	1	0	0	0	0	687	0
11	DMHA	323,000	2,210	45 [#]	2	227	5 [#]	0	11,100	0
12	2-amino-6-methylheptane	11,900	82	1 [**]	0	0	0	0	1,480	152
13	2-metil-6-amino-eptano	5,210	0	0	0	0	0	0	1,620	152
14	6-methylheptan-2-amine	19,300	3	0	0	0	0	0	1,560	152
15	6-methyl-2-heptylamine	42,800	15	1 [**]	0	0	0	0	2,050	281
16	6-methyl-2-heptanamine	5,260	6	0	0	0	0	0	1,660	281
17	2-amino-5-methylheptane	32,200	2	0	0	0	0	0	1,550	152
18	2-metil-5-amino-eptano	11,700	0	0	0	0	1 [#]	0	1,720	152
19	5-methylheptan-2-amine	5,650	1	0	0	0	0	0	1,570	277
20	5-methyl-2-heptylamine	88,700	2	0	0	0	0	0	2,110	281
21	5-methyl-2-heptanamine	5,320	5 [#]	0	0	0	0	0	1,680	281
22	1,5-Dimethylhexylamine	11,100	189	1 [#]	0	0	0	0	830	0
23	alpha,epsilon-dimethylhexylamine	584	0	0	0	0	0	0	4	1,729
24	hexylamine, 1, 5-dimethyl-	69,100	3,560	0	0	0	0	0	6,650	55
25	2-heptylamine, 6-methyl-	10,600	34	2	0	2	0	0	2,060	281
26	S-51	[#]								
27	SKF-51									
28	S-51 AND Octodrine	2,360	0	0	0	0	0	0	840	0
29	SKF-51 AND Octodrine	15,300	0	0	0	0	0	0	536	6
30	C8H19N	18,940	302	0	0	0	0	0	1202	0
31	$C_8H_{19}N$									
32	Aconitum kusnezoffii AND Octodrine	43	0	0	0	0	0	0	26	0
33	Aconite extract AND Octodrine	1,050	28	0	0	0	0	0	35	1,662
34	Other Keywords Combinations + Boolean Operators	[#]								
	Total	742,476	7,825	106	2	242	6	0	48,725	5,894
	Total of Surface vs. Deep Web	750,657							54,619	

[#] Displayed SERPs were NOT relevant to Octodrine and/or related chemicals.

[*] Search Engine used is Deeperweb.com

[&] A compound with three active ingredients, including Aceverine Hydrochloride, Octodrine Phosphate, and Theophylline

[@] A plant from which Octodrine is presumably extracted

[**] The only published one-of-two scientific papers on Octodrine. Both papers were published in the Journal of Pharmacology and Experimental Therapeutics, in 1947 and 1951 respectively.

Table 2. Descriptive statistics based on the number of hits that are found by searching for sources relevant to octodrine in various search engines and databases (data from Table 1).

	Google	Google Scholar	NCBI - PubMed	The Cochrane Library	Scopus	EBSCO - CINAHL	OpenGrey	Deep Web *	Markets on Dark Net #
Minimum	43	0	0	0	0	0	0	4	0
Maximum	323,000	3,560	45	2	227	5	0	11,100	1,729
Range	322,957	3,560	45	2	227	5	0	11,096	1,729

Table 3A. Data retrieved from Google trends in relation to the popularity of octodrine in the past decade.

Keyword versus year	Yes/No	Trends (2004-)	Spikes in Time
Octodrine	Yes	Intermittent Interest July 2004-	Two Spikes: Aug-2004, Mar-2015
Octodrinum	No		
Octodrina	No		
Ottodrina	No		
Ambredin	No		
2-aminoisoheptane	Yes	Interest from July 2013-	No Interest May-Sep 2014
Aminoisoheptane	Yes	Incremental Jul-2015-	Spike on Aug-2013
Dimethylhexylamine	No		
Dimetylhexylamine	No		
DMHA	Yes	Persistent-Oscillating Interest Jan-2004-	2 Prominent Spikes: MAR-204, Aug-2004
Yes/No Ratio	4/6		

Table 3B. Data retrieved from Google trends based on keywords relevant to octodrine with highest number of hits for the past decade

Keyword versus year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Octodrine	100	67	0	26	17	53	0	47	48	36	50	50	104
2-aminoisoheptane	0	0	0	0	0	0	0	0	0	154	166	424	673
Aminoisoheptane	0	0	0	0	0	0	0	0	0	28	0	146	459

Table 4. Inclusion and exclusion criteria for selection of articles and the web to be analysed in this study.

Inclusion Criteria
1. Studies and publication related to octodrine
2. Studies and publication of octodrine-related compounds and chemicals, in which octodrine is an ingredient
3. Studies and publication in which octodrine is marginally included
4. All languages, including German and French
5. All years of publication (no date restriction)
6. Surface web and deep web, and the dark net
7. Grey (unpublished) literature, including master's and doctorate theses
8. Data from Google Trends
9. Fitness and body building websites
10. (Bio)chemistry, pharmacy and pharmaceutical websites
11. Online drug fora
12. Human and animal studies
13. Observational and experimental studies
Exclusion Criteria
1. Duplicate Articles
2. Initial screening for relevance (reading the title and abstract)
3. Articles found to be irrelevant by analysing the full article
4. Low scoring for an article on CASP critical appraisal tool (poor quality of appraised manuscript)

Table 5. Analysis of bibliographic materials that mention the relevant keywords.

		Web	Retrospective and Cohort Studies	Invention Patent	Cross-Sectional	Total
Reference Date	Before 2012	1	7	0	0	8
	After 2012	23	4	1	5	33
Number of Manuscripts/Resources		24	11	1	5	41
Level of Evidence		N/A	Level 4 to Level 5	N/A	Level 5	N/A
Total Number of Reference Materials is 41						

Appraisal of level-of-evidence and classification of bibliography and reference materials used for the literature review.

Table 6. Expected values (chi-square test related function) of the number of hits per keyword relevant to octodrine, in correspondence with the actual value of the number of hits (observed values) in Table 1.

Keyword	Database/Source					Total SERPs
	Surface Web			Deep Web		
	Google	Google Scholar	NCBI - PubMed	Deep Web *	Markets on Dark Net #	
Octodrine	29,408	308	4	1,929	231	31,880
Octodrinum	3221.23	33.76	0.45	211.31	25.25	3,492
Octodrina	787.78	8.26	0.11	51.68	6.18	854
Ottodrina	262.90	2.76	0.04	17.26	2.06	285
Ambredin	622.66	6.53	0.09	40.85	4.88	675
Vaporpac	1,573	16	0	103	12	1,705
2-aminoisoheptane	8,381	88	1	550	66	9,086
Aminoisoheptane	8,377	88	1	550	66	9,081
Dimethylhexylamine	12,199	128	2	800	96	13,224
Dimetylhexylamine	11,152	117	2	732	87	12,089
DMHA	310,274	3,252	44	20,353	2,432	336,355
2-amino-6-methylheptane	12,559	132	2	824	98	13,615
2-metil-6-amino-eptano	6,441	68	1	422	50	6,982
6-methylheptan-2-amine	19,385	203	3	1,272	152	21,015
6-methyl-2-heptylamine	41,646	436	6	2,732	326	45,147
6-methyl-2-heptanamine	6,648	70	1	436	52	7,207
2-amino-5-methylheptane	31,275	328	4	2,052	245	33,904
2-metil-5-amino-eptano	12,520	131	2	821	98	13,572
5-methylheptan-2-amine	6,917	72	1	454	54	7,498
5-methyl-2-heptylamine	84,030	881	12	5,512	659	91,093
5-methyl-2-heptanamine	6,721	70	1	441	53	7,286
1,5-Dimethylhexylamine	11,180	117	2	733	88	12,120
alpha,epsilon-dimethylhexylamine	2137.34	22.40	0.30	140.21	16.75	2,317
hexylamine, 1, 5-dimethyl-	73,211	767	10	4,802	574	79,365
2-heptylamine, 6-methyl-	11,971	125	2	785	94	12,977
S-51 AND Octodrine	2,952	31	0	194	23	3,200
SKF-51 AND Octodrine	14,614	153	2	959	115	15,842
C8H19N	18,859	198	3	1,237	148	10,222
$C_8H_{19}N$						10,222
Aconitum kusnezoffii AND Octodrine	63.65	0.67	0.01	4.18	0.50	69
Aconite extract AND Octodrine	2,560	27	0	168	20	2,775
Total SERPs	751,946	7,881	107	49,326	5,894	815,154
Inferential Non-Parametric Test	chi-square test					
Chi-square p-value (2-tailed)	0.0001					

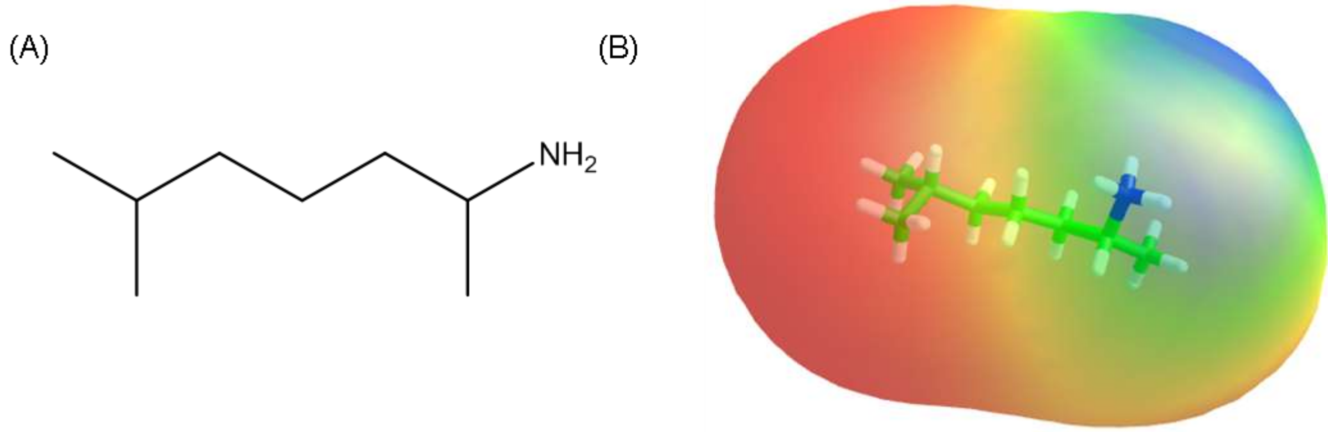


Figure 1. Chemical structure (A) and molecular lipophilicity potential (MLP) surface (B) of octodrine molecule (hydrophobic surfaces are depicted in red and polar surfaces are in blue).

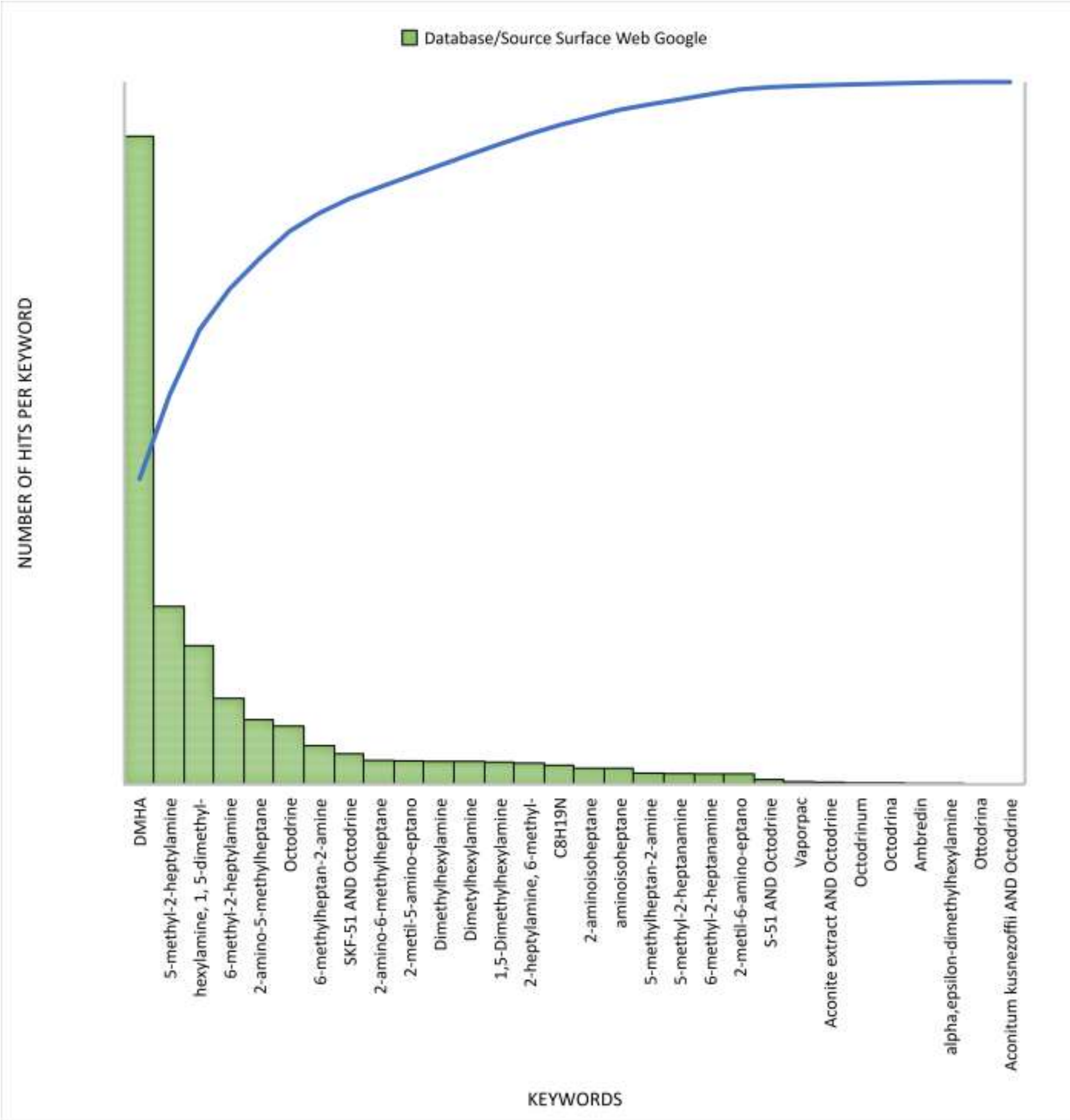


Figure 2. Results from Google search engine database.

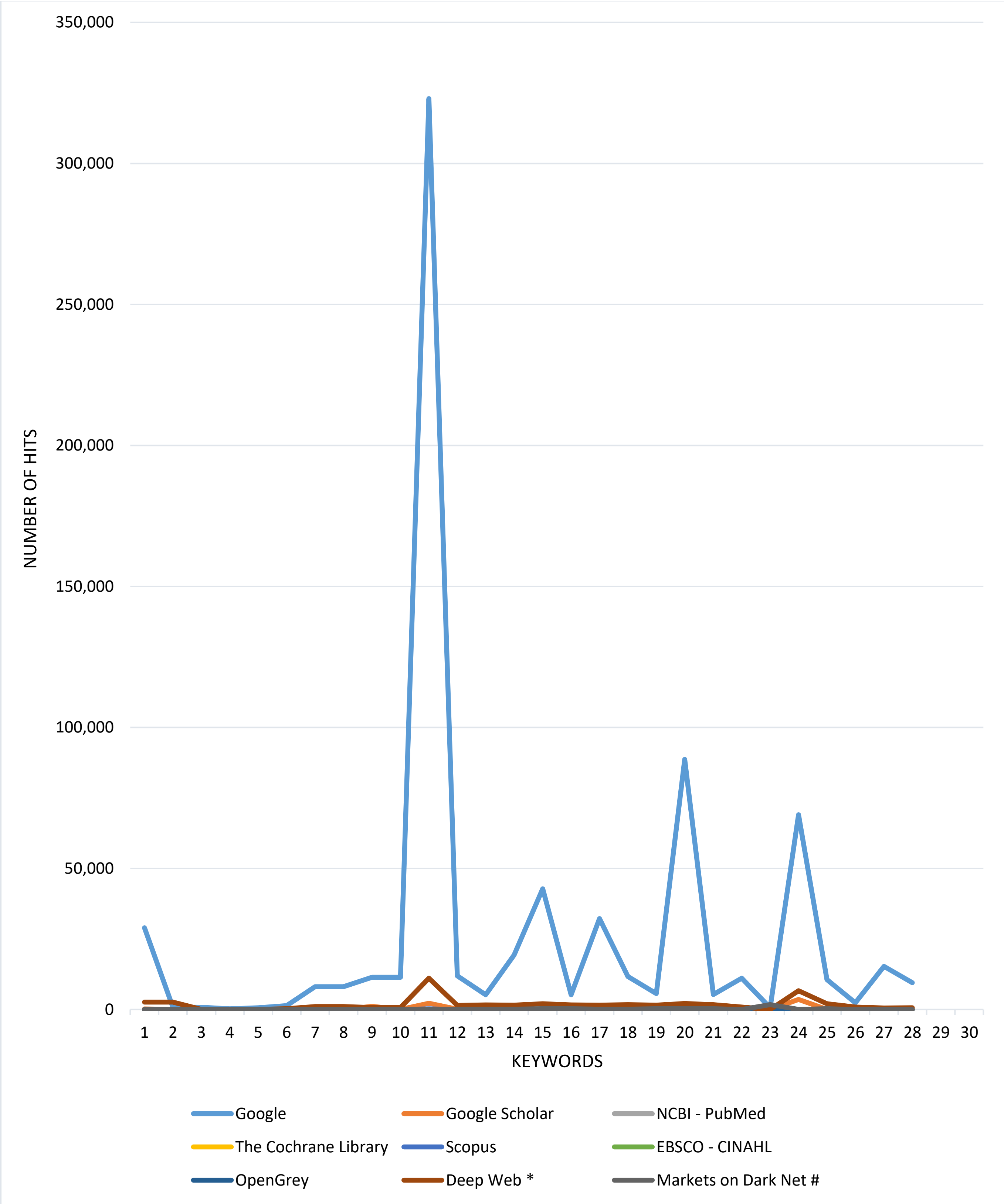
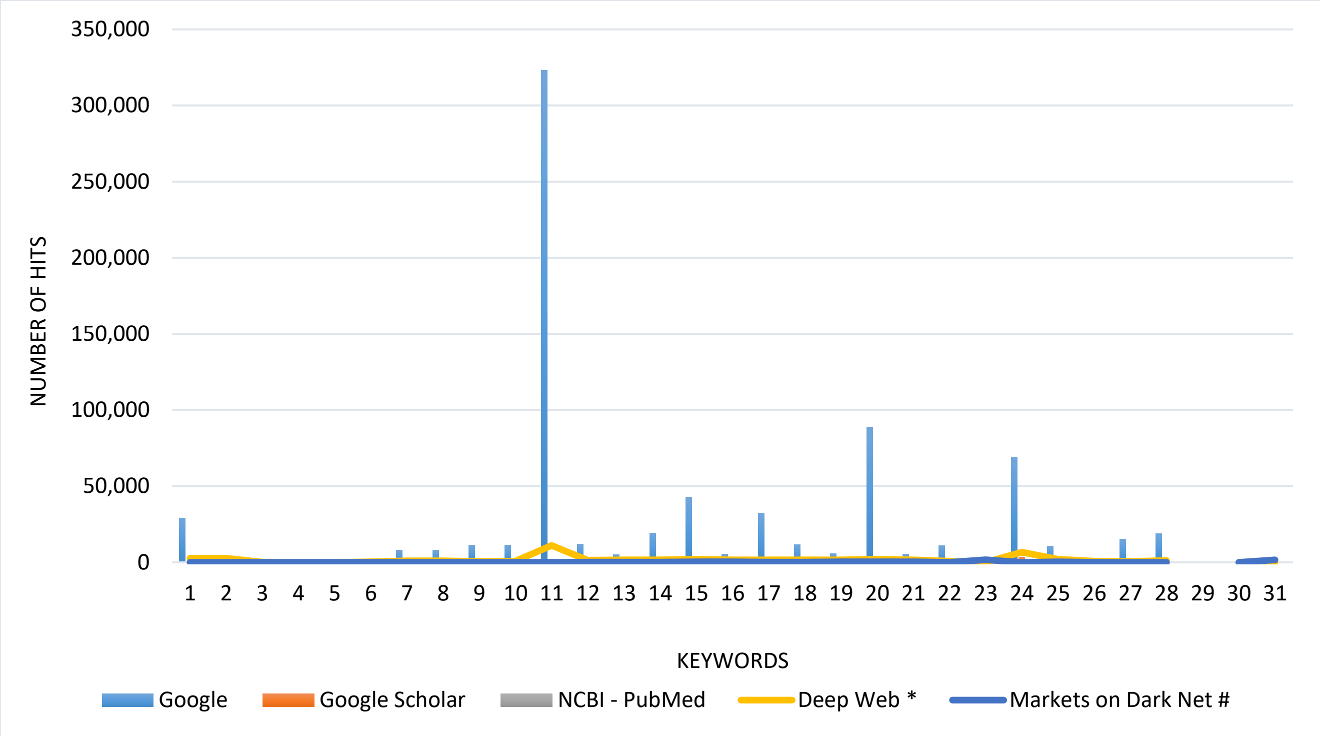


Figure 3. The contribution of search engines and databases to search results.



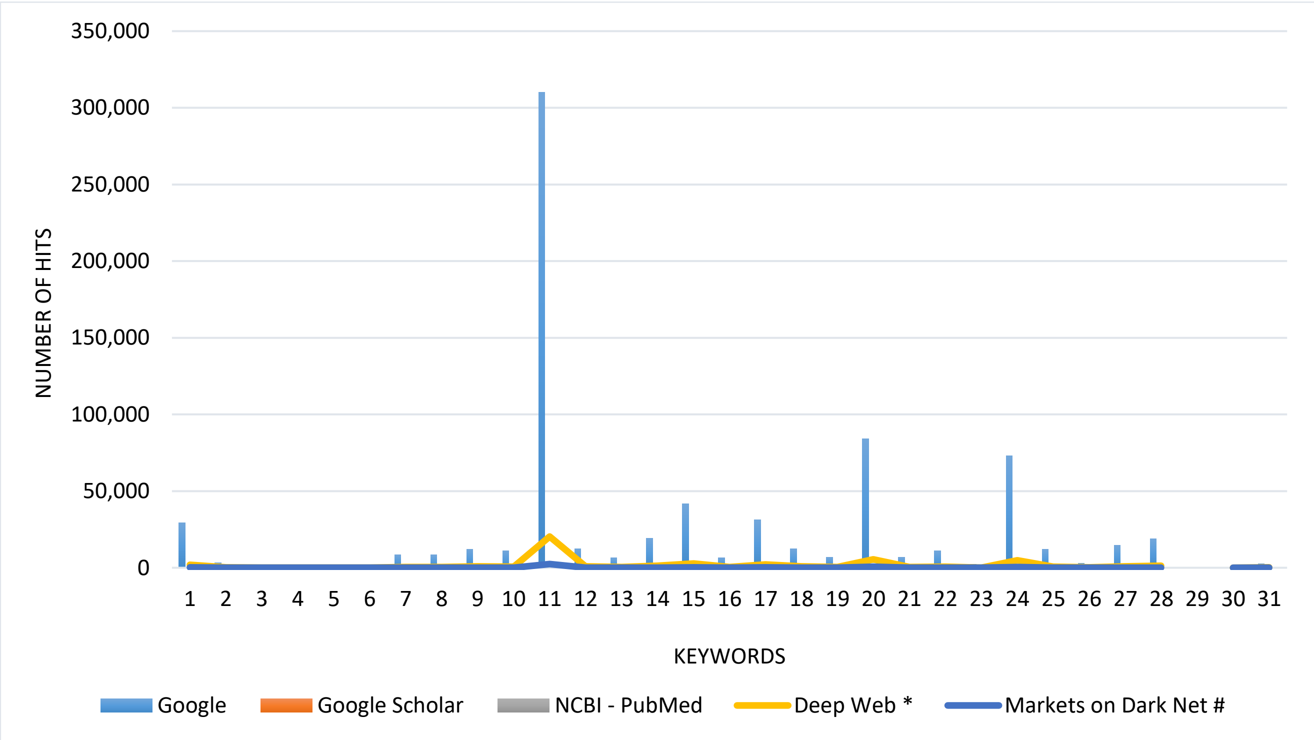
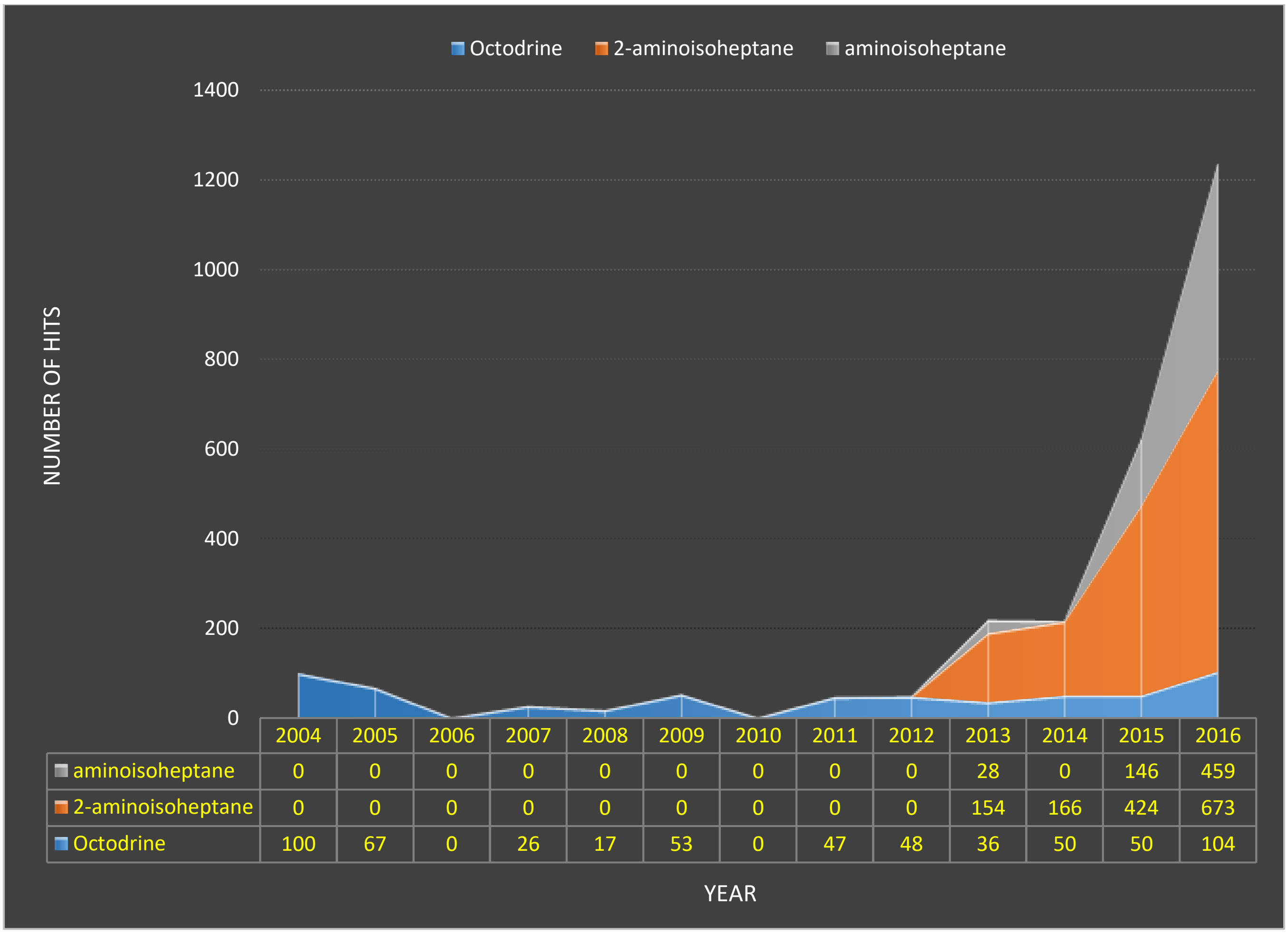


Figure 4. Inferential Statistics, Chi-square Test: a p-value of 0.0001 was found for the observed value (top graph) and the expected value (bottom graph) for the number of hits per keywords in the surface web versus the deep web.



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
aminoisoheptane	0	0	0	0	0	0	0	0	0	28	0	146	459
2-aminoisoheptane	0	0	0	0	0	0	0	0	0	154	166	424	673
Octodrine	100	67	0	26	17	53	0	47	48	36	50	50	104

Figure 5. Trend line and area-under-curve, based on data from Google Trends: number of hits (y-axis) per keyword across the years (x-axis).

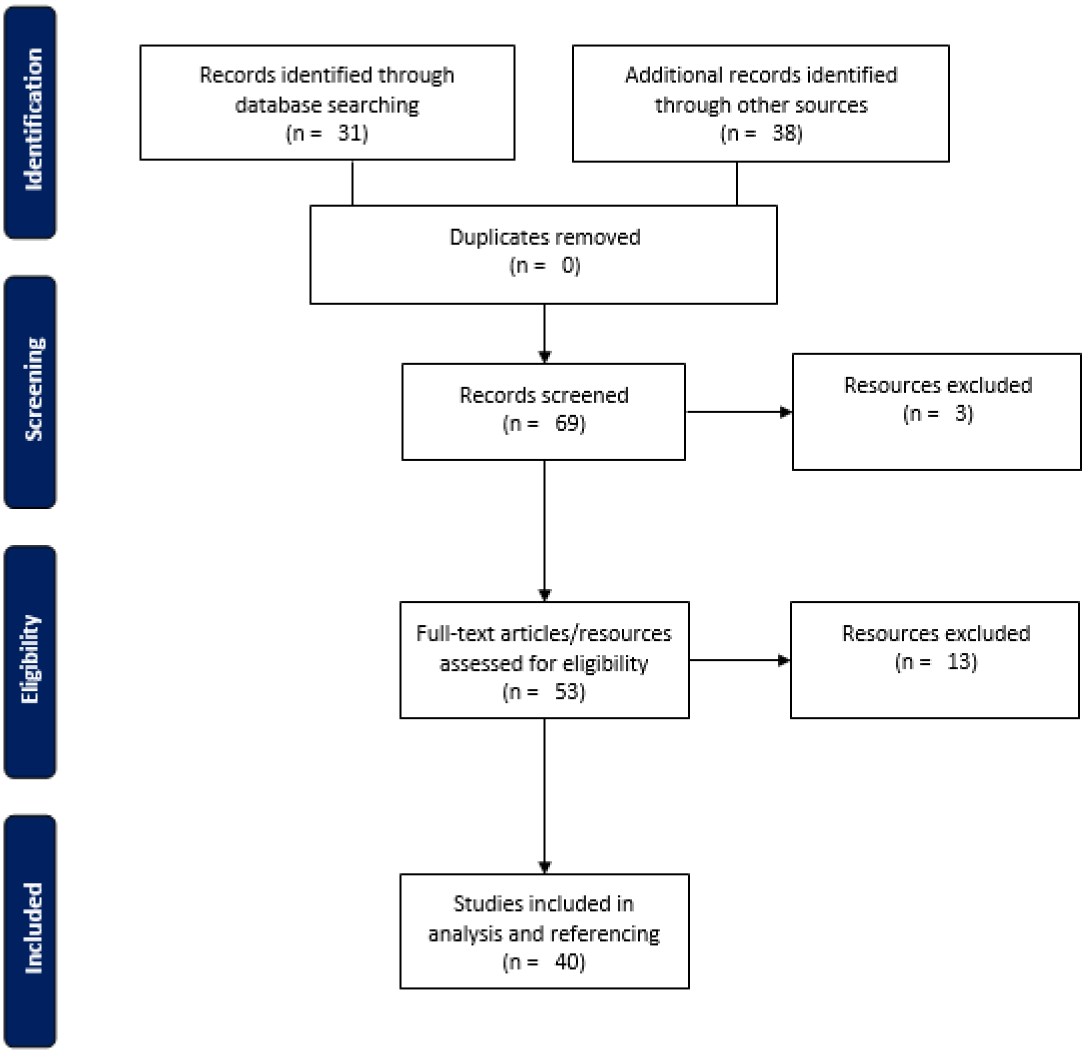


Figure 6. Flow diagram of the search and review of information in relation to octodrine. Both surface web and deep web were searched. A literature review on octodrine was also carried out in the following databases; PubMed-Medline, the Cochrane Library, Scopus, EBSCO – CINAHL, OpenGrey, and Google Scholar.

Chapter 11. NBOMe(s)

BACKGROUND

NBOMe compounds, commercially known as “N-Bomb” or “Smiles” signifying their potency, are a uniquely potent group of phenethylamine derivatives. These have been recently used in the past decade for their potent hallucinogenic effects to induce a “psychedelic trip”, these chemicals belong to a different category of NPS known as hallucinogens (Drugfreeworld.org, 2016; UNODC, 2016; Wood et al., 2015). NBOMe chemicals were discovered by Ralf Heim in 2003 while he was researching for a pharmacological tool to study the 5-HT_{2A} receptors. Therefore, these drugs had no history of human use prior to that point in time, besides there are no medical applications for NBOMe at the moment (Heim, 2004; Wood et al., 2015). The 25X-NBOMe series are substituted phenethylamine compounds, the most common 25b-NBOMe, 25c-NBOMe, and 25i-NBOMe (Figure 1), all have been detected in Europe since 2011 (Wood et al., 2015).

The current published data on NBOMe compounds are non-representative from an epidemiologic perspective. However, in 2013 the Global Drugs Survey has shown that 25i-NBOMe was the most commonly (ab)used, it also represents the most potent NBOMe. Hence the name “N-Bomb”, these data were concordant with what was retrieved from trends databases (Google Trends, 2016; Wood et al., 2015). In September 2014, the United Nations Office on Drugs and Crime reported that 25i-NBOMe was the most frequently reported NPS, accounting for 43% of all cases reported to them worldwide (Wood et al., 2015).

This study aims to infer an estimation for the epidemiologic magnitude of the N-Bomb phenomenon using data retrieved from trends databases, case series, case reports, review articles, and online drug fora. To date, there have been no studies to deploy the use of inferential statistics to describe these trends or the shift in trends of N-Bombs across the years from 2012 to the current date.

All N-bombs, particularly 25i-NBOMe, are super-potent 5-HT type-2A receptor agonist. Therefore, a typical (ab)user can experience a psychedelic effect in the sub-milligramme dose (Andreasen et al., 2015; Byard et al., 2016; Kueppers and Cooke, 2015; Lowe et al., 2015; Poklis et al., 2014), making it almost as potent as another potent hallucinogenic compound known as lysergic acid diethylamide (LSD). In fact, NBOMe products are promoted as a “legal alternative of LSD” (Bersani et al., 2014; Nikolaou et al., 2015; Wood et al., 2015), although NBOMe blotters taste distinct from LSD blotters (Psychonautwiki.org, 2016; Reddit.com, DrugsAMA, 2016). It is sold to users in the form of blotting papers (blotters), powder, and liquid form (Bluelight.org, 2016; Wood et al., 2015). These are most commonly administered via oral, buccal or sublingual ingestion, nasal insufflation, intravenous and intramuscular injections, per vaginal and per rectal administration, and freebase smoking (Bersani, 2014; Bluelight.org, 2016; Forrester, 2014; Wood et al., 2015).

The pharmacodynamics are very similar between the three forms of NBOMe; the main difference is the potency which is determined by the affinity towards the 5HT receptors. The most commonly reported features of intoxication are induced by the activation of the serotoninergic pathway and the sympathetic nervous system, resulting in a status of hyper stimulation of all body systems specifically the cardiopulmonary and nervous system. Hence users are frequently apprehended in a state of agitation, aggression, hyperventilation, increased physical strength, and clouded consciousness or a psychotic-like state (Bersani et al., 2014; Forrester, 2014; Gee, 2015; Hill et al., 2014; Nikolaou et al., 2015; Rose, et al., 2015; Suzuki et al., 2014; Wood et al., 2015).

There have been some sporadically reported cases of intoxication, suicidal attempts, and fatalities. These possibly represent the “tip of the iceberg”. Almost all were attributed to the most potent form (the 25i variant). These catastrophic incidents have been reported highly in the developed world including the United States, United Kingdom, Australia, Canada, China, Denmark, Netherlands, other European countries, and other regions of the world (Andreasen et al., 2015; Byard et al., 2016; Kueppers and Cooke, 2015; Lowe et al., 2015; Poklis et al., 2014; Rose et al., 2013; Shanks et al., 2015; Suzuki et al., 2014; Tang et al., 2014; Walterscheid et al., 2014). In the published literature, there are no verifiable reports of intoxication or fatality from the developing world including the Middle East.

RESULTS AND DISCUSSION

CRITICAL APPRAISAL AND EVIDENCE-BASED ANALYSIS OF BIBLIOGRAPHY

The critical appraisal of individual studies was done using the *CASP* appraisal tool (Better Value Healthcare Ltd, CASP-UK, 2016), and the critical appraisal tools of the Oxford Centre for Evidence-based Medicine (Oxford Centre for Evidence-based Medicine, 2009). Manuscripts and resources of the highest attainable level-of-evidence (Table 1) were used to backup this study, although, the majority of these ranked as either level-4 or level-5 in accordance with classification system implied by the Oxford Centre for Evidence-based Medicine. These studies were case reports (16.7%), case series (7.4%), and review articles (11.1%). There were no systematic reviews (0%), nor RCTs on NBOMe (0%). One experimental study was found (1.85%) which was the original study of Ralf Heim (Heim, 2014). Much of the data were retrieved from online drug fora (31.5%), high-quality and valuable data were also retrieved from trends' databases (3.7%). Data from systematic reviews and RCTs, written on topics pertinent to NBOMe, were also used in the citation of this manuscript (1.85%), and from observational studies including cross-sectional and cohort studies (7.4%). Most of the bibliographic materials were published in the past five years (92.6%). The overall level-of-evidence of appraised resource materials was in the range of level-5 to level-1b, although the majority of these were either level-3b, 4, or 5. The level-of-evidence of this study itself is estimated to be of level-2b (Oxford Centre for Evidence-based Medicine, 2009).

TRENDS IN NBOME USER INTEREST

Valuable data were retrieved from Google trends database (Google, Google Trends, 2016), filters were used for search terms ("25b-nbome", "25c-nbome", and "25i-nbome"), time (1st of January-2012 to 31st of December-2016), and geographic locations including worldwide, United States (US), United Kingdom (UK), Australia. Interestingly, data were not available neither from the developing world nor from China or India. These data show the extent of internet users' interest in these "research chemicals", in other words, the "electronic popularity" of these chemicals, presented in the form of a percentile (0-100) scale.

The popularity worldwide (Figure 1) found that 25b (least popular), 25c, and 25i (most popular). Boxplot presentation indicated that 25i popularity is several folds more searched (popular) than the other two NBOMe(s); are people attracted to what can kill them! Furthermore, there are discernible statistical outliers in each one of the three, these represent a sharp increment in the searched NBOMe over time; the most prominent of these are seen in June-2013 and October-2014, and there has been a rise in NBOMe-related in intoxications and fatalities soon after each of these as seen in the combo graph (Figure 1). To be concluded, there is a rise in the popularity for the period from January-2012 to June-2013, with a subsequent decline for the period that follows. Nevertheless, the popularity of 25b seems to be almost constant over time, unlike that of 25c and 25i. These data (worldwide popularity of NBOMe) were also correlated with cases of intoxications and deaths (Figure 1), these cases were verified from drug fora and PubMed-Medline database (Figure 1 and 2). It was unforeseen that these incidents (of intoxications and death) run almost in parallel with the NBOMe temporal trends of popularity.

The popularity in of NBOMe in the US seems to follow a very similar pattern to that pattern seen in the global (worldwide) analysis. There has been a sharp increment rise in popularity in September-2012, April-2013, and May-2014. Similarly, the intoxication-death incidents also follow the historical (chronological) change in NBOMe popularity. It seems that the US has the greatest effect (rank 1st) on the worldwide NBOMe popularity, In fact, it appears that the US determine the overall pattern of searched NBOMe over the internet (surface web), while the UK rank 2nd and Australia rank 3rd. Possibly, there are several factors behind this pattern, including demographics, cultural, and social-economics, but principally it seems that the population count in these three nations is the most critical factor in influencing this effect, the US population (325 million), UK (65 million), and Australia (24 million).

The searched NBOMe in the UK seems to follow a more erratic pattern, although 25i is apparently the most popular while 25b is the least popular (same as the US). However, the 25i popularity is slightly higher than that of 25c and 25b. The sharp incremental rise occurred in for the period June to August-2012, January-2013, March-2013, June-2013, August-2013, then there is a significant decline for the period that follows and to this current date. In Australia, the pattern seems to be more consistent than that of the UK, 25i is also the most popular while 25b and 25c are of inferior and comparable popularity (to each other). This pattern is almost consistent from the entire period of 2012 to 2016, although a significant (very sharp) sharp rise occurred in May and June-2016.

Auxiliary individual analyses for each of the three NBOMe variants were also done. The 25b popularity seems to be most popular in the UK (almost 2-3 folds more than that of the US), and the least popular was in Australia. Statistical outliers can be easily visualised in a boxplot, an incremental rise in NBOMe popularity in September-2012, May and June-2013, August-2013, this appears to be followed by a subsequent abrupt decline in an almost persistent pattern to this current date. The 25c analyses have shown that it is most popular in the US, and least popular in Australia, although the popularity is comparable (very close to each other) in both quantity and direction over time. There has been a sharp incremental rise in popularity in July-2012, August-2012, April-2013, Septembre-2013, August-2014, and June and July-2014. The 25i analyses have shown that it is most popular in the US and least popular in Australia, the popularity of 25i in Australia was much less than that of the UK as seen in the Boxplot, statistical outliers are also seen, and these correspond to incremental rise in popularity specifically in April-2012, May-2013, July-2013, September-2015, and then the popularity sharply decline afterwards until the current date. There is also some more significant (remarkable) rise in popularity of 25i in September and October-2012, April-2013, June-2013, and May-2014. Additionally, it has been mentioned formerly that the 25i-NBOMe is responsible for the vast majority of cases of intoxications and fatalities. When these catastrophes are correlated with the 25i popularity, it is conspicuous that there is a pattern of correlation in between the two trends.

CHANGES IN TRENDS

The inferential statistics (t-test and ANOVA test) for the popularity of NBOMe for the period 2012-2016, do not show any statistically significant change in trend (popularity of NBOMe on the surface web) between any given year and the year next to it (Figure 3). However, there has been some degree of difference (as indicated by the *p-values*) across a longer time span, for example in the UK and for the period 2013-2016 (0.079), and for the period 2012-2016 (0.066). Similarly, in Australia for the period 2013-2015 (0.089), and for the period 2013-2016 (0.055). These values are considered significant at an *α value* of 0.10 (90% CI) and should be analysed in the context of the overall NBOMe trends (Figure 2 and 3). Besides, there has also been less pronounced "significant" change in the trends, these changes existed: worldwide and for the periods 2012-2016 (0.27) and 2013-2016 (0.24), in the US for the periods 2012-2016 (0.22), 2012-2015 (0.29), 2013-2015 (0.25), 2013-2016 (0.17), and 2014-2016 (0.20), in the UK for the periods 2012-2014 (0.23), 2012-2015 (0.13), 2013-2014 (0.22), and 2013-2015 (0.13), and in Australia for the periods 2012-2016 (0.20), 2013-2014 (0.18), and 2014-2016 (0.11). However, all these *p-values* are not significant, unless an α value of 0.20 or 0.30 is considered (70% and 80% CI), which indicates an unreliable confidence interval for a precise statistical inference. To summarise, there has an incremented public interest in NBOMe from 2012 to 2013-2015; this was later followed by an overall decline towards our current day. These changes were not homogeneous worldwide. It is also enthralling to denote that this pattern of change in trends has been almost simultaneous to the reported cases of intoxications and death (Table 2, Figure 1 and 2). The cases of the correlated morbidities and mortalities have been analysed from the published literature and were indexed in PubMed-Medline database and the online drug fora.

NBOME-RELATED MORTALITIES

According to the reports of NBOMe-related fatalities (Erowid.org, 2016), there have been 24 documented incidents of death, the majority of substance users were males (79.2%) from the United

States (87.5%) at an age ranging from 15 to 25 years, while one decedent was aged 30 representing a statistical outlier. These incidents occurred from March-2012 to January-2016, the majority were attributed to the most potent 25i-NBOMe variant (75%), other NBOMe (25c, 25b) were also incriminated (25%), while the nature of the detected NBOMe was unknown/uncharacterized in 12.5% of cases (Erowid.org, 25C-NBOMe (2C-C-NBOMe) Fatalities / Deaths; Erowid.org, 25I-NBOMe (2C-I-NBOMe) Fatalities / Deaths; Erowid.org, Other or Unknown NBOMe Compound Fatalities / Deaths). The lethal dose (LD-50) is unknown for all NBOMe compounds due to the lack of animal studies. These fatalities were attributed to pharmacological-induced death (87.5%) and behavioural-induced death (12.5%), while the suicidal and homicidal potentials are described as unknown or yet to be confirmed (Erowid.org, 2016; Tang et al., 2014). These decedents were from multinational backgrounds including individuals from the United States, Australia, and Ireland (Erowid.org, 2016). These data are also concordant with the case series presented in this study (Andreasen et al., 2015; Byard et al., 2016; Kueppers and Cooke, 2015; Lowe et al., 2015; Poklis et al., 2014; Rose et al., 2013; Shanks et al., 2015; Suzuki et al., 2014; Tang et al., 2014; Walterscheid et al., 2014). Linear regression models (Figure 2 and 3) for these incidents (intoxications and deaths) were plotted in correlation with the trends' data (Google, Google Trends, 2016) in section 3.3 in an aim to reach a potential pattern of interrelationship in between the two phenomena Moreover, the clustered-death analysis via linear regression shows an overall negative curvilinear trend for the fatalities in the period 2012-2016, an R^2 value of 0.77 and a statistically significant difference (decline) in NBOMe-related deaths in 2014-2016 (*p-valu*e of 0.088), this is considered to be statistically significant at an alpha (α) value and a 90% confidence interval (90% CI).

USER REPORTING ABOUT NBOME

The majority of users describe the NBOMe experience as a fascinating experience; one enthusiastic user described his trip as "*Such Beauty. Fuck.' These three words were all I could conjure to explain what I was experiencing with the new and yet-to-be fully understood 2C-I-NBOME aka 25-I. Those three words do not even present the tip of the iceberg that is this wonderful experience from such an interesting and inspiring molecule.*" (Erowid.org, NBOMe Series Reports, 2016). NBOMe is not used as an ingredient in a pre-workout formula for gym users/athletes. It has not displaced into the world of sports performance (Erowid.org, 25I-NBOMe (2C-I-NBOMe) Fatalities / Deaths; PHF Supplements Forum, 2016). NBOMe has been reported to be taken to enhance sexual experiences and as a potential entactogen (empathogen), although at higher doses itis difficult for males to have or maintain an erection, as one user described "*it gets difficult to get a boner*".

Some drug fora (Quora.com, 2016; Psychonautwiki.org, 2016) provide instruction on how to use NBOMe, saying it is “not advised” to insufflate large amounts of NBOMe or to be taken in combination with selective serotonin reuptake inhibitors (SSRIs) and/or tricyclic antidepressants (TCAs), otherwise an inevitable serotonin toxidrome/syndrome will be imminent (Boyer and Shannon, 2005; Haberzettl et al., 2013; Psychonautwiki.org, 2016). Besides, NBOMe (particularly the 25i-NBOMe) can significantly elevate the blood pressure and exceptionally in individuals with already-established hypertension (Quora.com, 2016; Hare Krishna, 2016; Wood et al., 2015).

NBOMe Powders are considered to be more dangerous (compared to blotters) as they are not “well-calibrated”, while NBOMe blotters are known to induce “psychedelic trip” at doses as low as 300 µg (0.3gm), and seizures and/or other features of intoxication at 1.5gm, in addition, idiosyncratic reactions can occur at any dose, some (ab)users advise against the 25i variant and to try the least potent 25b (Erowid.org, NBOMe Series Reports, 2016; Officialbenzofury.net, 2016; Reddit.com, DrugsAMA, 2016). Additionally, there have been few contradictory (negative) opinions of NBOMe as reported by some users, “*I have used several times LSD, Mushrooms, 2cb, Nbome and the experience was always the same with only negative aspects. The discomfort is such that prevents me from having any focus*”; another user described a near-death experience (Bluelight.org, Hasnamus, 2016).

CASE REPORTING AROUND INTOXICATION AND MORBIDITIES

The signs and symptoms of reported intoxications with N-Bombs are merely the result of the combined features of hyperactivation of the serotonergic pathway, both centrally and peripherally, and the sympathetic autonomic nervous system, hence the most commonly reported features of intoxication are manifestations of both sympathomimetic and serotoninergic effects, these include tachycardia, hypertension, agitation and aggression, seizures and status epilepticus, hyperthermia, progressive dissociation, and drug-induced psychosis (Bersani et al., 2014; Forrester, 2014; Gee, 2015; Hill et al., 2014; Nikolaou et al., 2015; Quora.com, Hare Krishna, 2016; Rose, et al., 2015; Suzuki et al., 2014; Wood et al., 2015). The more severe cases frequently develop acute renal and liver injury and/or failure, rhabdomyolysis, serotoninergic syndrome (serotonin toxidrome), and sympathomimetic toxicities, multiple discrete intraparenchymal haemorrhages, cardiac failure, pulmonary oedema, and eventually death. (Andreasen et al., 2015; Byard et al., 2016; Kueppers and Cooke, 2015; Lowe et al., 2015; Poklis et al., 2014; Rose et al., 2013; Shanks et al., 2015; Suzuki et al., 2014; Tang et al., 2014; Walterscheid et al., 2014). Serotonin toxidrome by itself can potentially produce acute toxicity involving metabolic acidosis, rhabdomyolysis, seizures, renal and liver failure, and disseminated intravascular coagulation (Bersani et al, 2014; Boyer and Shannon, 2005; Forrester, 2014; Haberzettl et al., 2013; Nikolaou et al., 2015; Wood et al., 2015).

These cases (Table 2) represent case reports of interest, while case series and review papers were excluded to avoid an overlap or duplication of reported cases. The toxicological and postmortem investigations, for the presence of an incriminated NBOMe, unveil that the almost all cases of death are caused by the 25i variant, although 25b and 25c were also reported (Andreasen et al., 2015; Byard et al., 2016; Tang et al., 2014). These NBOMe psychedelics were highly potent that the detected serum/blood concentration was in microgram per millilitre (µg/ml), nanogram per millilitre (ng/ml), and astonishingly even in picogram per millilitre (pg/ml) (Poklis et al., 2014; Suzuki et al., 2014).

These substances were either used for recreational purposes, psychedelic/hallucinogenic experiences, and suicidal intentions (Suzuki et al., 2014), a couple of male-female ended in death (Walterscheid et al., 2014). Most of the (ab)users were males (84.6%), aged 15 to 23, although one victim of intoxication was a Chinese individual at the age of 31 years, representing a statistical outlier (Tang et al., 2014). The majority of NBOMe ab(users) were Caucasians from the United States (61.5%), polypharmacy (poly-substance use) was calculated to be quite high (69.3%), and most cases ended in death (69.3%) despite receiving medical intervention; these fatalities were reported in 2013, 2014, 2015, and 2016. Most of these cases required admittance to emergency unit and intensive care unit for life support, hydration, intubation and assisted ventilation. The less severe cases of intoxication were effectively managed using intravenous hydration, sedation with benzodiazepines (intravenous), the use of anticholinergic agents, and other symptomatic and supportive measures (Gee et al., 2016; Hill et al., 2016; Rose et al., 2012; Suzuki et al., 2015). The onset and duration of the NBOMe-induced effects largely depend on the doses and the routes of administration. Insufflation of NBOMe seems to produce more rapid and severe intoxication. Hence it is the most dangerous mode of drug administration. It is also reported that to get the full effects of an NBOMe blotter paper, it is required to be lightly chewed for at least 20 minutes (Psychonautwiki.org, 2016), while the long-lasting residual symptoms may last for several months after the substance use (Bersani et al., 2014; Bluelight.org, 2016).

Table 1. Critical Analysis of the Bibliographic Resources.

References	Systematic Reviews and RCTs	Cross-Sectional and Cohorts	Reviews	Case Series	Case Reports	Drug Fora	Trends' Databases	Web	Others
Before 2012	0	0	1	0	0	0	0	2	1 *
After 2012	1	4	5	4	9	17	2	8	0
Total	1	4	6	4	9	17	2	10	1
Percentage (%)	1.85	7.4	11.1	7.4	16.7	31.5	3.7	18.5	1.85
Cumulative %	1.85	9.25	20.35	27.74	44.45	75.95	79.65	98.15	100
Grand Total	54								
Level-of-Evidence Ω	1b	3b to 4	2b	4	5	N/A	N/A	N/A	5
Overall Evidence	Level-5 to Level-1b								

* Doctorate thesis by Ralf Heim (Heim,2014)

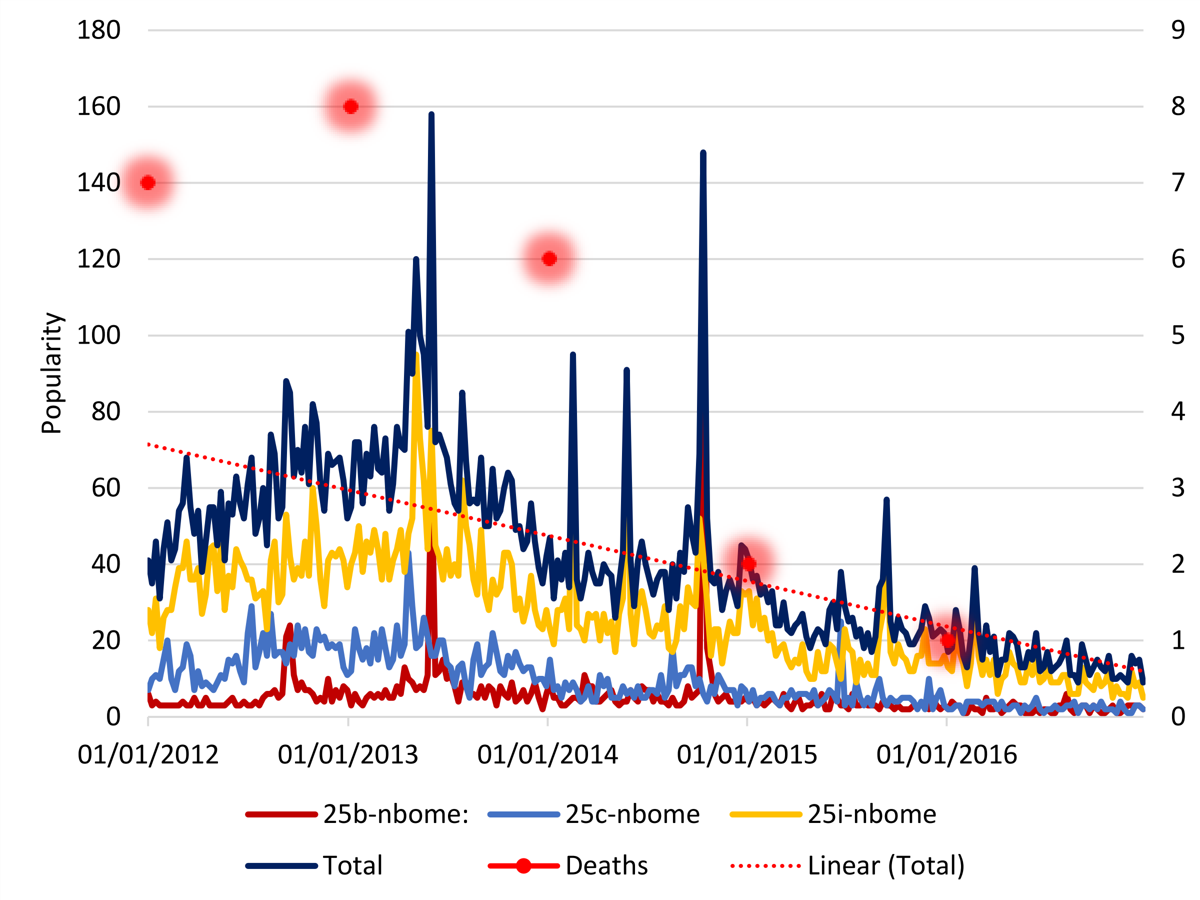
Ω According to the system imposed by the Oxford Centre for Evidence-based Medicine (Oxford Centre for Evidence-based Medicine, 2009).

Table 2. NBOMe-related Cases of Intoxications and Fatalities: Summary of Case Reports of Interest.

Paper	Date of Submission	Individual's Age and Gender	Country	Type of NBOMe	Serum/Blood Concentration	Polypharmacy	Life Status
Kueppers and Cooke, 2015	11-2014	23 F	Australia	25I	28 µg/l	Yes	Death
Rose et al., 2013	03-2013*	18 M	US	25I	0.76 ng/ml	Yes	Intoxication
Lowe et al., 2015	10-2015*	15 M	US	25I	0.76 ng/ml	Yes	Death
Suzuki et al., 2014	11-2014*	18 M	US	25I	34 pcg/ml	Yes	Intoxication/ Suicidal Attempt?
Byard et al., 2016	11-2016*	19 M	Australia	25B	6 µg/l	Yes	Death
Andreasen et al., 2015	12-2014	22 M	Denmark	25C	0.60 µg /kg	Yes	Death
Shanks et al., 2015	11-2015*	18 M	US	25B	1.59 ng/ml	Yes	Death
		16 M	US	25I	19.8 ng/ml	No	
Walterscheid et al., 2014	03-2014*	21 M	US	25I	Not Declared	Yes	Death
		15 F	US	25I	Not Declared	Yes	
Poklis et al., 2014	07-2013	19 M	US	25I	405 pcg/ml	No	Death
Tang et al., 2014	06-2014*	17 M	China	25B	0.18 to 2.78 ng/ml	Not Declared	Intoxication
		31 M		25B, 25C		Not Declared	Intoxication

* Date of paper (manuscript) submission is unknown; the tabulated date is the date of publication.

Ω Reviews and case series have been excluded to avoid duplicates and data overlap.



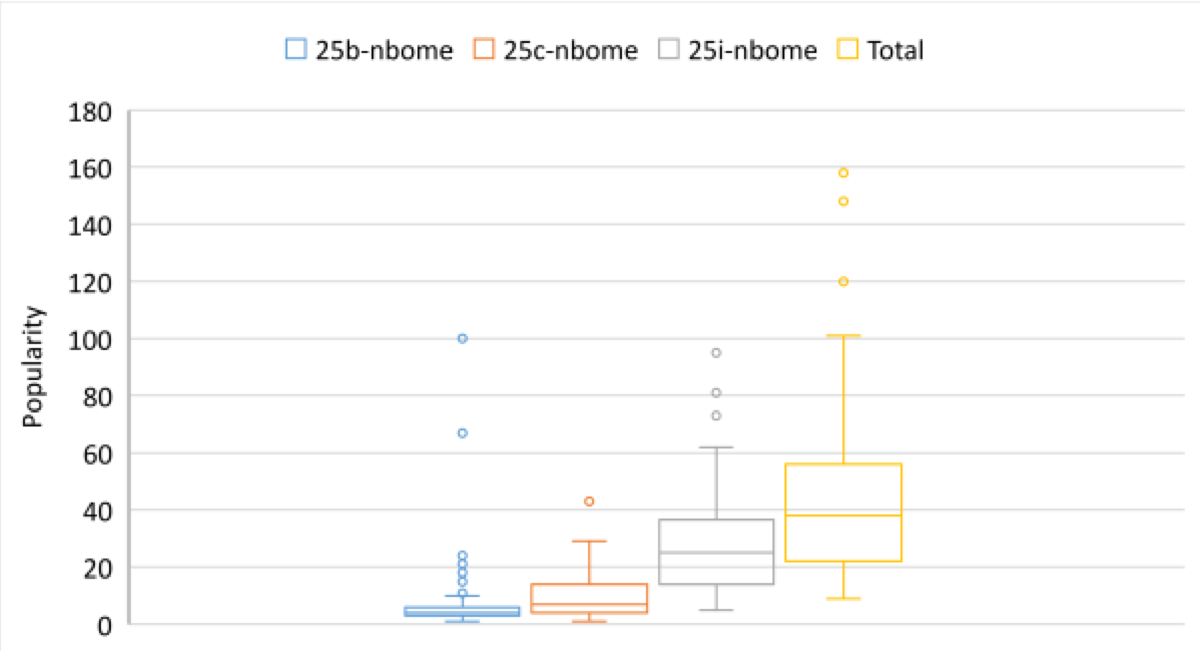
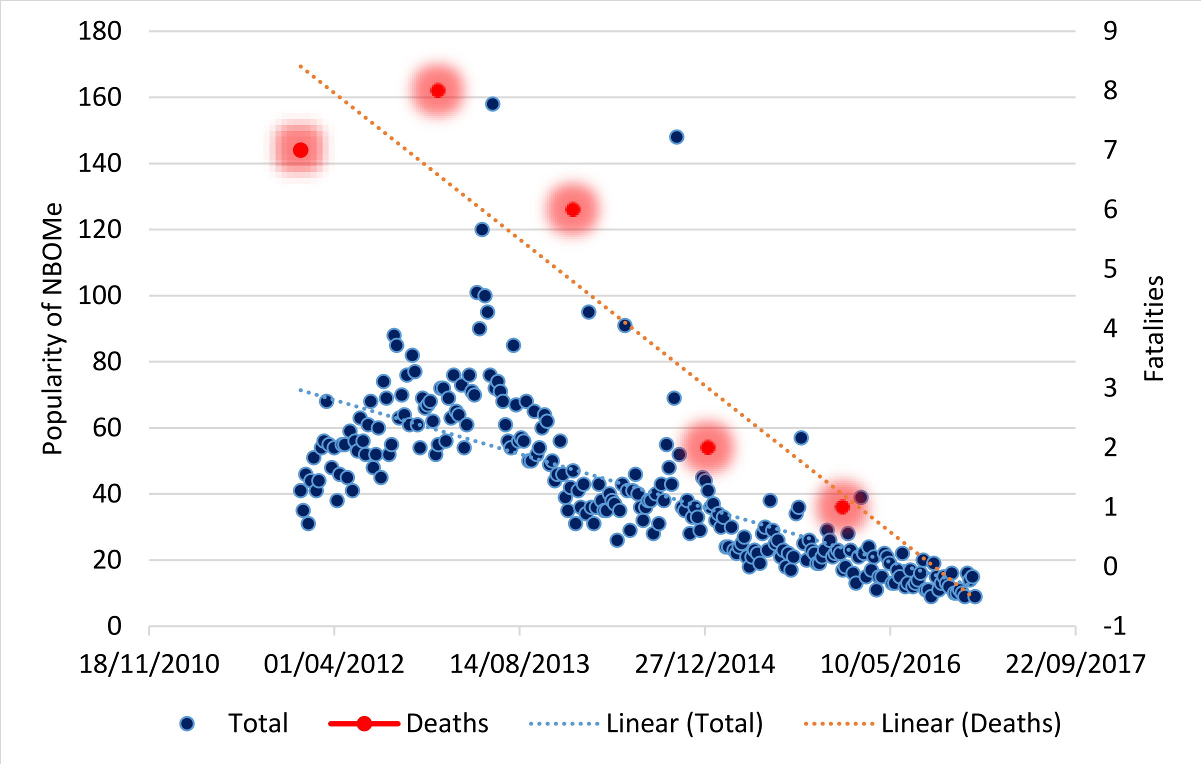


Figure 1. The Popularity on the Surface Web: Combo graph of Intoxications-Deaths and Google Trends Data (above), and box plot presentation (below)



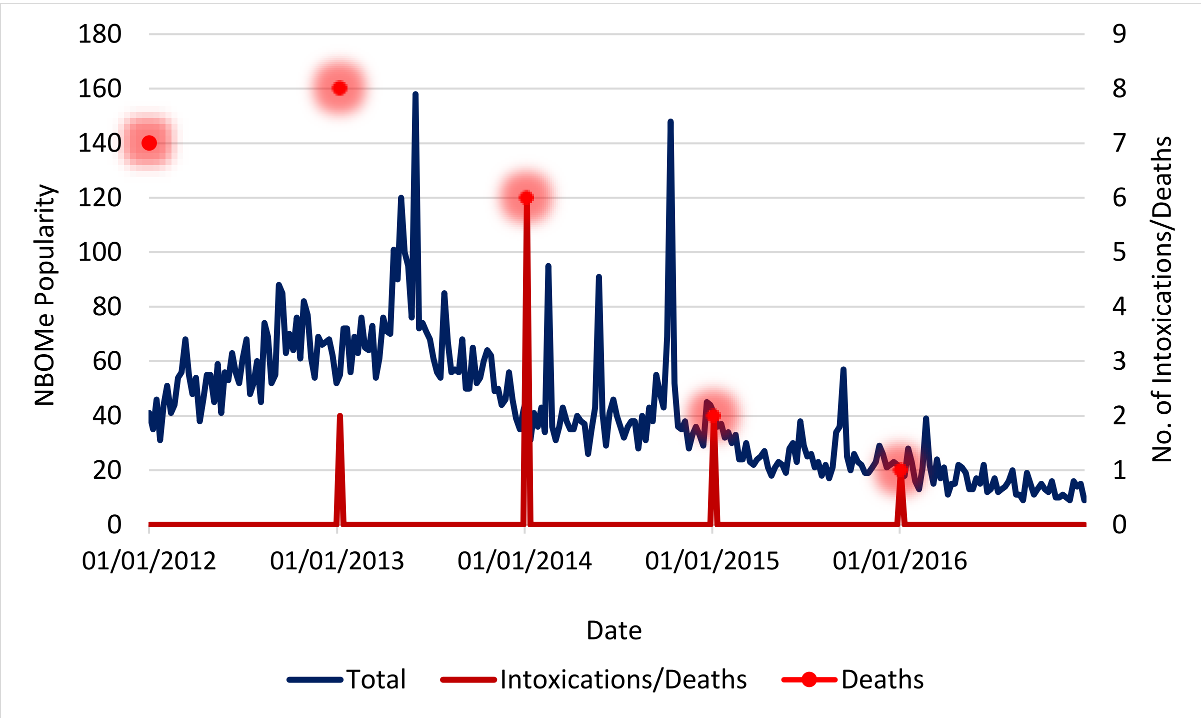


Figure 2. Combo Graphical Presentation: NBOMe Popularity versus Fatalities Reported via Drug Fora (above), and NBOMe Popularity versus Fatalities Reported via PubMed/Medline Database (below).

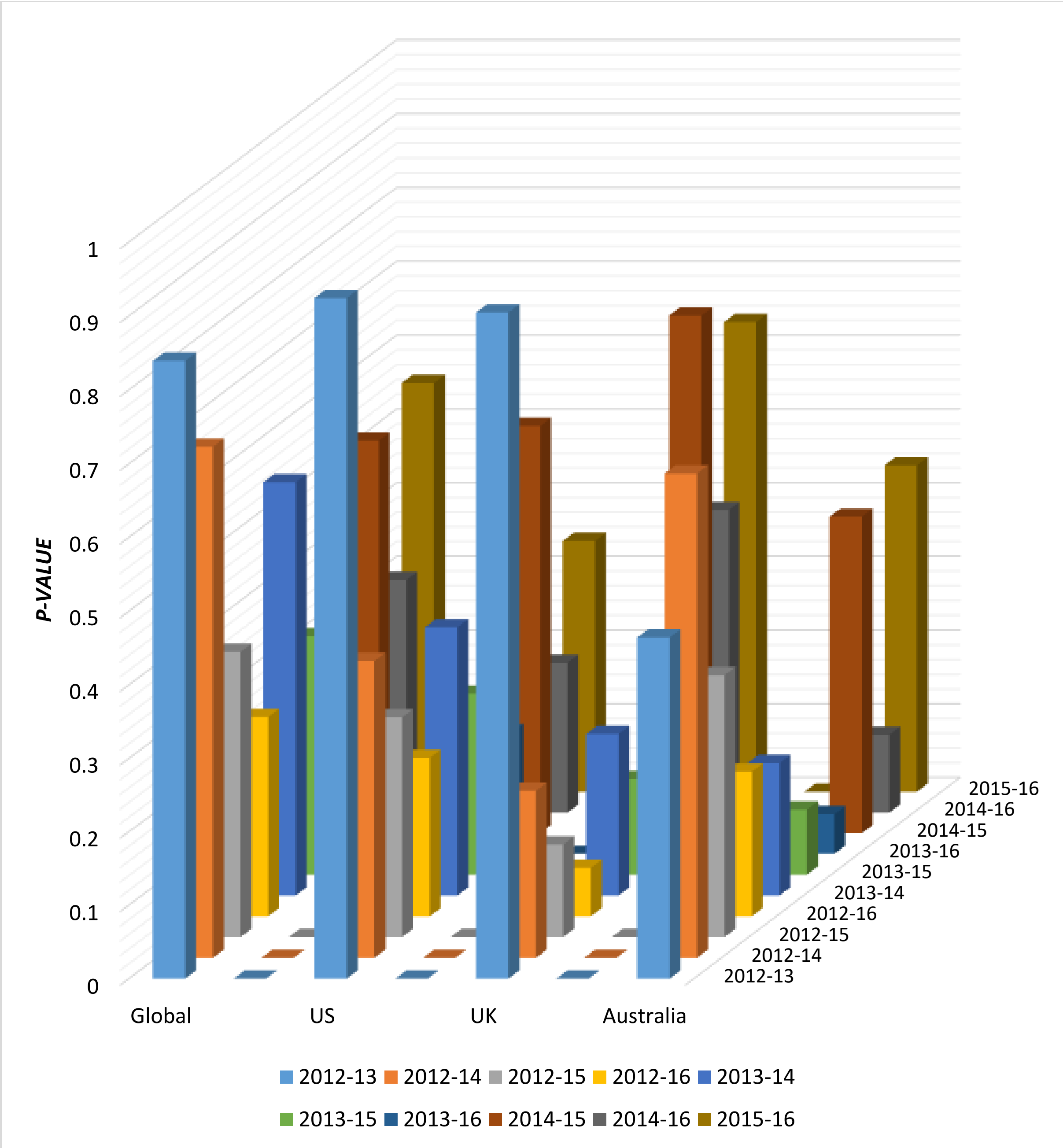


Figure 3. Three-dimensional Presentation of *p-values* for Change in NBOMe Popularity (2012-2016).

V. DISCUSSION

NPS researchers are densely populated in the developed parts of the world, namely in western Europe, the UK, North America, and Australasia. Europe is in the lead. Among all countries, the United Kingdom appears to have the biggest contribution in relation to the number of; NPS researchers, publications, and research institutes. Unfortunately, the region of the Middle East and other Arabic-Islamic countries, the level of NPS research is still primitive and constitute no more than few hundredth of the total (global) research output and publications. Furthermore, regulating bodies are still lacking in the Middle East; the legal status and legislative actions are often blurred. The research output from the Middle East was found to be very humble. The level-of-evidence of the analysed body of literature was not satisfactory, and on top; the implementation of inferential statistics was not always applicable. Future research efforts should focus on effective integration of data science methods, with an aim to upgrade the level-of-evidence. Training of researchers from the Middle East and other developing countries will be fruitful to fight the NPS phenomenon and its e-trade. It will also fortify the public health and the economy from the daring threats of the NPS industry. Potentials for data mining are also indispensable; these can be deployed in real-time for careful analysis of all sorts of databases including databases of the published literature.

The principles of social science were found to be indispensable and complementary for a holistic explanation of the; NPS phenomenon, its rapid growth and the inequitable balance of opposers and protagonists of the NPS industry. The principles of sociology were applied to explore the basis of power from a quantifying analytical perspective. Perhaps, one limitation of the study is that it did not explore the basis of power (authority) of whole units, including; regulating bodies or terrorist organisations. However, the same principles of social science can also be applied, quantified, and statistically analysed in future studies. Similar ventures of social science in relation to NPS discipline were never attempted before in connection to the discpline of NPS research. The analysis of the individual basis of power showed that NPS researchers, legislators, and policymakers are still lagging behind, whereas terrorist possesses a supreme power score. The analysis of the basis of power of e-markets on darknet showed comparable results on three major e-markets on the darknet; AlphaBay, Valhalla, and Hansa. Power scores of e-vendors were geographically mapped to high concentration zones in the UK, US, Finland, the Netherlands, and other countries from Western Europe. Based on the random selection process, the presentation of e-vendors from the Middle East was concluded to be completely absent from this map. This negligible presentation sounds in consonance with the small representation by NPS researchers from the Middle East; they account closely to few hundredths of the global NPS research output. Furthermore, all exceptional e-vendors trading in the region of the

Middle East were found to be originally either shipping or trading from Europe, none of them was from the Middle East.

Data describing the attentiveness (interest) of surface web users towards a specific category of NPS appears to be restrictively originating from four countries; the US, the UK, Canada, Australia. In each of these developed countries, the user attentiveness was found to be highly oscillating for the period from 2012 to 2016. However, there are some fixed norms; cannabinoids seem to be the most popular category of NPS, while cathinones were the second most common, particularly in the US. Meanwhile, other categories of NPS are in fierce competition with each other. In Canada and Australia, the pattern is very similar with the exception that nothing can be inferred about categories of NPS other than cannabinoids (rank 1st) and cathinones (rank 2nd). It has been inferred that the trends in the US are steering the global NPS trends. The trends were found to be in disharmony as an observer goes from the US to the UK, and from the UK to each of Australia and Canada. Data from Google Trends database gave a predictive inference to the parallel patterns on the deep web. One limitation of this study is the absence of data from other regions of the world including the Middle East, Arabic countries, or the densely populated parts of the world including China and India; it is a limitation of the database itself. A critical application of supreme value is the implementation of data mining techniques and knowledge discovery in databases to attain real-time inferences on changes of the trends.

The explosive nature of the spread of NPS on the web is unparalleled, particularly on the deep web, due to the factor of anonymity and the theoretically untraceable *Bitcoin payment system*. An efficient way to augment the efficacy of observational web analytics, including internet snapshots, is to categorise these advertised NPS substances by their popularity. Most popular NPS will be easier to follow, observe, and analyse. The method is economical in order to achieve the best results in the case of limited human and financial resources. It was found that three categories of NPS are always in the lead; cannabis and cannabimimetic (1), stimulants (2), and empathogens (3). However, it is critical to know that the attractiveness of these chemicals to customers can be changeable through time. This has been confirmed by the oscillating nature of the trends (Google Trends database) as observed in the past decade. Therefore, the NPS databases should be upgraded on a regular basis. Data mining techniques offer a logical and an economical solution for this problem; these can be deployed to provide automatic updates and real-time analyses on the most popular NPS in the e-commerce. Furthermore, to date, the e-trade activities were found to be almost exclusive to the developed countries; the Middle East and Arabic countries are contributing microscopically, even on the deep web. However, Israel, Iran, and Turkey were found to be contributing the most within the region of the Middle East. Additionally, data from the surface web, Google Trends database, and deep web were found to be in harmony. In summary, it is recommended that the internet analytic methods to keep the focus on the e-markets from the developed world, in addition to some of the East Asian countries including Japan, China, Thailand, and Malaysia.

The deep web is an anonymous and a colossal virtual place in which an observer can easily be "lost" while conducting observational analyses or taking snapshots. However, this obstacle was overcome by implementing a different tactic to rendering the task; easier, more focused, and made of as minimum observations as possible. The tactic was made of three overlapping steps, the 1st one relies on Google trends analyses to estimate the interest (attentiveness) of surface web users in relation to the deep web, and the geo-mapping of the contributing countries including the Middle East and the Arab World. The 2nd and 3rd steps are carried out on the deep web itself to infer; the basis of power for the e-markets on darknet (1), and the most popular NPS on the e-marketplace (2). AlphaBay and Agora were found to be dominating the e-marketplace, while the most frequently advertised NPS (in descending order of frequency; cannabis and cannabimimetic (cannabinoids), stimulants, empathogens, and psychedelics. This simplified yet *systematic snapshot technique* can be repeated at any given moment of time. Besides. It is recommended that this technique is to be combined with the powerful tools for data mining, the data output should be highly accurate and in real-time leading to remarkable results.

The anonymous darknet was also thoroughly explored, and primarily in relation to the contribution of countries from the regions of the Middle East. Despite, the several implemented techniques to analyse the darknet e-marketplace, the Middle-Eastern contribution seems to be negligible and even statistically insignificant when compared to other regions of the world, for example, the European Union. Accordingly, it can be surmised that the global e-trade is highly dependent on the developed countries particularly; Western Europe, UK, US, Canada, and Australasia. Power scoring of e-vendors whom activities are carried out in the Middle East and Arabic countries gave an insight that these individuals (e-vendors) are either not of Middle Eastern nationality or at least hold dual citizenship from the Middle East and other nations. The reason behind this assumption is the presence of multiple shipping countries for each e-vendor, some countries are Middle Eastern, while the majority of the rest were from the developed world. Furthermore, the usernames (nicknames) of e-vendors gave an impression that they were foreign rather than domestic to the Middle East. It is possible that several e-vendors operate in networks from different countries. Geo-mapping of Google Trends yielded additional data from countries in south and central America including; Chile, Costa Rica, Uruguay, Puerto Rico, and Argentina. These countries did not contribute significantly on the darknet e-marketplace; it can be assumed that the NPS commerce in the south and central America is not entirely dependent on the electronic commerce; other resources might be involved including the traditional ways of drugs' trade and trafficking. Special statistical correlations were proven to be indispensable; an interrelationship was inferred between the NPS e-prevalence on the darknet and certain social and demographic parameters. These parameters included religious affiliations and atheism, population count and density, and sexual assaults. To be concluded, the deep web is a massive cyberspace, most of which is ambiguous and nondescript. The internet snapshot method used to observe and analyse a minimal contribution, as in the case of the Middle East, is highly time-consuming and efforts-depleting. Furthermore, the snapshot will get obsolete as time passes by. Hence, an innovative mixed-breed of snapshot method and data mining technique can solve the problem; this combined methodology will serve to provide real-time analyses and build accurate databases based on cross-sectional and prospective analyses of the e-trade on the darknet. Additionally, combining this hybrid technique with Google Trends' analyses will further augment the accuracy and enhance the geo-mapping of NPS e-prevalence to unprecedented levels.

In relation to the studied population of undergraduate Iraqi medical students, the level of awareness on NPS did not differ on the transitions of students from year-1 to other years; the level-of-knowledge was also not significantly different. However, the knowledge about traditional psychoactive and novel psychoactive substances increased substantially. Similarly, the chronicity of use was significantly different in between year-1 students versus year-2 to year-6 students. The encountered side effects and adverse reactions were not significantly different; the most frequently reported adverse effects included; loss of consciousness, musculoskeletal-related, and hallucinations. There seems to be some degree of knowledge on NPS derived from prototypical (archetype) medicines including cannabinoids, opioids, benzodiazepines, phenothiazines, and other antipsychotic medications. Data from the internet snapshots revealed that in a population of psychedelic users, there was a preference for selected terms of hallucinogenic substances; top terms included; *psychedelic*, *entheogen*, and *hallucinogen*. There was also some significant difference in between the psychedelic users based on; age, gender, and patterns of handedness. Furthermore, those (ab)users of NPS tend to abuse the use of power. The vast majority of (ab)users were; young, predominantly males, and from the western developed countries, the Middle East contribution was *infinitesimal*. However, males and females seem to contribute equally (proportionally) in relation to positive (optimistic) and negative (pessimistic) comments in relation to a fictional granted supreme (divine) power. Those who contributed with positive (or optimistic) comments appear to elaborate and discuss their ideas; they were talkative and passionate of how they wanted to *change the world to be a better place*. However, these optimistic psychedelic users represented a minority of the studied population. The aetiology behind the phenomenon of power abuse towards coercion and punishment is yet to be explored in future studies.

Analyses of Google Trends showed the advanced popularity of captagon over both NBOMe and octodrine; captagon popularity increments were correlated with terror attacks in the developed world, particularly in Eastern European countries including France and Belgium. On the other hand, NBOMe seems to be most popular in Europe, Russia, North American, and Australia. Data from Google Trends can serve as a strong foundation for data mining techniques for an efficient peremptory warning system against an anticipated terror attack or a swarm of intoxications and fatalities due to substance (ab)use. Surface web analysis gave a compatible insight in relation to patterns detected on the darknet e-markets. Both divisions of the internet were concordant with regards to the geo-mapping of substances' diffusion with an exception for octodrine; octodrine appears to be more prevalent among users of the surface web. It also seems that the Middle East contributes the least to the e-trade of these three substances. It is likely that these substances are diffused in Middle Eastern countries by other modalities, independent from the use of the web. Further, this study proposes a novel method to analyse the e-markets on the darknet via the use of; analysis of the basis of power of e-vendors, inferential statistics, geo-mapping in parallel with data from Google Trends database, and the implementation of linear regression models to provide correlations with the population count of e-vendors' shipping countries. The integrated analysis eventually brought the attention to the exceptional cases represented as statistical outliers including e-vendors of highly active (suspicious) activities within the darknet e-marketplace.

The study of captagon e-commerce shed light on the critical phenomenon of using NPS under terrorists' settings; additional investigations are needed on the use of psychoactive drugs (traditional and novel) used by terrorist organizations primarily within the zones of conflict and civil unrest. Data are essential to influence a prompt policy response. Interventions cannot be limited to the Middle East and cannot be confined to the Syrian war. Its dimensions are much wider, and it has already reached the EU. Captagon was found to be advertised and sold online with no need for a medicinal prescription; captagon is sold at illicit online pharmacies and websites internationally; it is used to feel fearless and increase aggressiveness, alertness, and enhance other cognitive functions. While the demand is expanding in the conflict zones, its trade and e-trade are becoming a profitable market for ISIL and other criminal organisations. Overall, captagon is a dangerous psychostimulant; novel strategies should be implemented to design an efficient and strict policy to fight its national and international spread.

In relation to octodrine, there was no RCTs, quasi-experiments, or any other interventional studies apart from cohort studies on animals done in 1947 and 1951. Additionally, there were no systematic reviews; the lack of adequate experimental studies and the total absence of RCTs and pragmatic RCTs have led to the complete absence of meta-analytic studies. There were no other observational studies other than animal studies, no review articles, including systematic reviews, and no case reports or case series. Octodrine is a long-forgotten chemical substance since the late 1940s; it had re-emerged in 2012. The pharmacodynamics and pharmacokinetics of octodrine have not been fully explored, neither the chemical profile of the commercially-available octodrine products. The psychoactive properties of this substance on humans were neither described in the literature nor studied. The metabolic pathway and the adverse reactions were not studied in humans. Hence, it is mandatory to put this substance *under the microscope*; octodrine is a potential candidate to be included on WADA's and FDA's controlled or prohibited list of drugs. This study is the first to be carried out in seven decades to implement a systematic review of the literature and cross-sectional analysis of the content of the web in relation to the diffusion and e-commerce of octodrine. It is also critical to bring to the spotlight the noteworthiness of subsequent studies on octodrine, specifically chemical analysis and receptor-ligand studies.

NBOMe(s) are potent, dangerous, and psychologically active substances. It belongs to a family of complex chemical compounds; their potency and popularity are interlinked worldwide. Data from online drug fora and the appraised case series and case reports gave an insight towards the demographics of victims and decedents. (Ab)users appeared to be predominantly males from the developed world, primarily from the United States, and in their 2^{nd} or 3^{rd} decades of life. The majority of NBOMe (ab)users are attracted to using the most potent and a lethal form of NBOMe, the 25i variant. There is also a lack of systematic reviews, randomised controlled trials, and experimental studies on this NPS. This is due to the fact that these chemicals have been recently discovered in 2003-2004, and were recently promoted worldwide for use as NPS chemicals in 2011. Needless to say, data from Google trends can serve as an indicator of when to predict high incidence of "waves" of intoxication or fatalities, for example in association with holidays, public celebrations, carnivals and rave events, and the street availability of NBOMe. These analyses can serve as an efficient early warning system to provide insightful orientation to the emergency units and intensive care units at hospitals in anticipation of such catastrophic events. The purpose is to initiate or maintain pre-specified protocols to keep the casualties to a minimum. Such protocols can be developed in collaboration with local health authorities and international organisations including the world anti-doping agency (WADA), the UNODC, and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Prior studies on NPS compounds (NBOMe and others) have highlighted that noteworthiness of the chemical characterization, and the vitality to conclude the comparative chemical profile both nationally and internationally for scientific and medico-legal attributes. Other studies have also highlighted the significance of patterns of cerebral dominance (lateralization of brain functions) in connection with the (ab)use of NPS and traditional psychoactive substances (Al-Hadithi et al., 2016; Al-Imam et al., 2016). The spread of NBOMe on the deep web was not assessed, and it is beyond the scope of this study. Nevertheless, the role of the deep web in the diffusion and e-commerce of these NPS is never to be ignored (Google, Deeperweb.com, 2016; TOR2WEB, 2016; Van Hout and Hearne, 2017).

There are also some limitations to this study on NBOMe(s). In relation to NBOMe popularity and interest over time, data were only collected from Google trends. However, these data are highly specific as they reflect the use of specific and scientific search terms by a range of millions (if not billions) of internet users and customers including users/patients, abusers (addicts), chemists, researchers, and scientists. Data collected from Google trends can be erroneous in case of people using virtual private networks (VPN) and internet protocol masking (IP mask) while surfing the surface web. Further, not all the cases of morbidities and mortalities have been (can be) reported in the literature, many cases were either documented in grey literature databases or not reported at all. Additionally, there could be some overlap between case series and case reports of morbidities and mortalities, and especially for review articles. Furthermore, the exact date of the published case reports of intoxication and death can be either inaccurately reported or not reported at all; this will have some effect the statistical analyses for correlation with trends databases. However, these dates can be roughly estimated from date of manuscript submission to each journal. Therefore, direct communication with the authors is necessary to collect missing data (dates) whenever feasible. Some cases of individuals with morbidities and mortalities had more than one psychoactive or novel psychoactive substances (polypharmacy) in their biological fluids. Accordingly, NBOMe may not be the direct cause of intoxication and/or death.

VI. CONCLUSION

1) CRITICAL APPRAISAL AND LIMITATIONS OF STUDIES

The dissertation is made of 11 results chapters; each chapter is made of individual studies (Table 1). Critical appraisal and evaluation of the level-of-evidence for each chapter and its individual studies was carried out. The appraisal relied on the level-of-evidence categorization system of the *Oxford Center for Evidence-Based Medicine* (CEBM), and the CASP appraisal tools (Better Value Healthcare Ltd, 2013; Davidoff et al., 1995; Oxford Centre for Evidence-based Medicine (CEBM, 2009). The overall level-of-evidence of the dissertation was estimated to be of level-2b, which fits under the category of *outcomes research*. The individual studies were entirely observational; there were no experimental studies. The absence of experimental designs, including quasi-experimental studies and randomised controlled trials (RCTs), is considered as one of the limitations of this dissertation (Christensen et al., 2004; Harris et al., 2006; Van der Worp et al., 2010). The implemented observational studies included; reviews, retrospective analyses, cross-sectional analyses, and Internet snapshots. Retrospective observational analyses and Internet snapshots were the most common modalities. Statistical analyses were carried out in all chapters, both descriptive and inferential.

Regarding the individual studies, the level-of-evidence was (Figure 1 and 2); level-5 (12%), level-2b (57%), and level-3b (31%). The implemented statistics were; combined descriptive and inferential (88%), Inferential alone (5%), Descriptive alone (2%), None (5%). The vast majority of the studies were a hybrid of descriptive and inferential studies of level-2b (57%). Therefore, the overall level-of-evidence of the dissertation is estimated to be of level-2b, which fits into the category of *outcomes research*. The major limitations can be summarised in; lack of experimental studies, toxicology and chemical analyses, and physiological animal studies (1), exclusive reliance on Google Trends as a representative for trends databases (2), absence of prospective observational analyses (3), and restriction of the surveys and internet snapshots to selected populations of relatively small sample size (4).

2) CONCLUSION

The systematic review and critical appraisal of PubMed-indexed articles of the published NPS literature showed that; attempts of NPS research started to evolve in 2010, NPS researchers are densely populated in the developed parts of the world, namely in western Europe and the UK, North America, and Australasia. Among all countries, the United Kingdom appears to have the biggest contribution in relation to the number of; NPS researchers, publications, and research institutes. Almost one-third of the research output (36%) was in connection to toxicology and analytic chemistry, while reviews and cross-sectional studies were less common (15%, 18%). The principles of social science were found to be indispensable and complementary for a holistic explanation of the NPS phenomenon. Similar ventures of social science in relation to NPS discipline was never explored before. Power scores of e-vendors from the darknet were geographically mapped to high concentration zones in UK, US, Finland, the Netherlands, and Western Europe.

Google Trends analyses showed that data describing the attentiveness (interest) of surface web users towards a specific category of NPS appears to be restrictively originating from four countries; the US, the UK, Canada, Australia. The trends were highly oscillating although cannabinoids seem to be the most popular category of NPS, while cathinones were ranked 2nd. Apparently, the US is in the lead steering the global trends. Data from Google Trends database gave a predictive inference to the collateral patterns on the deep web. A critical application of supreme value is the implementation of data mining techniques and knowledge discovery in databases to attain real-time inferences on changes of the trends. Data retrieved from Google trends database can serve as an indicator of when to predict “waves” of intoxication or fatalities, for example in association with holidays, public celebrations, carnivals and rave events, e-commerce and street availability of NPS. These analyses can serve as an efficient early warning system to provide insightful orientation to the emergency units and intensive care units at hospitals in anticipation of such catastrophic events; protocols can be developed in collaboration with local health authorities and international regulating bodies including WADA, UNODC, and EMCDDA.

The complimentary usage of PubMed, drug fora, and Google Trends was successful in extrapolating the most trending and high-risk NPS; the contribution from the Middle East to incidents of intoxications and fatalities was absent except for Israel. Within the deep web, It was found that four categories of NPS are always in the lead; cannabis and cannabimimetic (1st), stimulants (2nd), and empathogens (3rd), and psychedelics (4th). Data mining techniques can be deployed to provide automatic updates and real-time analyses on popular and high-risk NPS in the e-commerce. It is recommended that the internet analytic methods and snapshots to keep maintaining focus on the e-markets from the developed world, in addition to some of the East Asian countries including Japan, China, Thailand, and Malaysia. Further, deep web analyses including the darknet e-marketplace have shown that the contribution of the Middle East never exceeded 7% of the total e-trade, data were limited to; Iran, Israel, Turkey, Afghanistan, Oman, United Arab Emirates, and Saudi Arabia. Other Arabic countries included; Egypt, Morocco, and Algeria. In relation to the observational internet snapshots of the darknet, it was confirmed that the Middle-Eastern contribution was negligible and statistically insignificant when compared to other regions of the world including the EU. Power scoring of e-vendors whom activities are carried out in the Middle East and Arabic countries gave an insight that these individuals (e-vendors) are mostly not of Middle Eastern nationality. It was interesting to observe the e-vendors of NPS operating in the Middle East were highly involved in e-trade activities in other countries; the UK, Western Europe and Scandinavia, US, Canada, Australia, and New Zealand.

Surveys and internet snapshots confirmed the lack of awareness and the very low prevalence of (ab)use of NPS among the selected Iraqi population of undergraduate medical students. Data on the awareness and knowledge of NPS seems to be either completely lacking or basic. Similarly, the (ab)use and prevalence of NPS in the studied population of Iraqi students were also minimal, unlike those of the western societies in developed countries. However, there seems to be some degree of knowledge on NPS derived from prototypical (archetype) medicines and traditional psychoactive substances including cannabinoids, opioids, benzodiazepines, phenothiazines, and other antipsychotic medications. Data from the internet snapshots revealed that in a population of psychedelic users, there was a preference for selected terms of hallucinogenic substances; top terms included; *psychedelic*, *entheogen*, and *hallucinogen*. There was also some significant difference in between the psychedelic users based on; age, gender, and patterns of handedness. Furthermore, those (ab)users of NPS tend to abuse the use of power. The vast majority of (ab)users were; young, predominantly males, and from the developed countries, the Middle East contribution was *infinitesimal*. However, males and females seem to contribute equally (proportionally) in relation to positive (optimistic) and negative (pessimistic) comments in relation to a fictional granted supreme (divine) power. Those who contributed with optimistic comments appear to elaborate and passionate to discuss their ideas.

Captagon was found to be highly prevalent in the Middle East, unlike NBOMe and octodrine; relevant data were available in both divisions of the web, unlike octodrine for which almost no data existed on the deep web. The study of captagon e-commerce shed light on the critical phenomenon of using NPS under terrorists' settings. Octodrine is a long-forgotten chemical substance since the late 1940s; it had re-emerged in 2012. The pharmacodynamics and pharmacokinetics of octodrine have not been fully explored, neither the chemical profile of the commercially-available octodrine products. Further, the psychoactive properties of this substance were neither described in the literature nor studied. The metabolic pathway and the adverse reactions were not studied in humans. Hence, octodrine is a potential candidate to be included on WADA's and FDA's controlled or prohibited list of drugs. On the other hand, NBOMe(s) are potent psychologically active substances. (Ab)users appeared to be predominantly males from the developed world, primarily from the United States, and in their 2nd or 3rd decades of life. There is also a lack of systematic reviews, randomised controlled trials, and experimental studies on this NPS. Additionally, prior studies on NPS compounds (NBOMe and others) have highlighted that noteworthiness of the chemical characterization nationally and internationally for scientific and medico-legal attributes. Other studies have also emphasized the significance of patterns of cerebral dominance (lateralization of brain functions) in connection with the (ab)use of NPS and traditional psychoactive substances (Al-Hadithi et al., 2016; Al-Imam et al., 2016).

To summarize, the growth of NPS industry, including the e-commerce, and its links to terrorism, are reaching unprecedented levels. The contribution of the Middle East and Arabic country to the e-trade phenomenon was found to be minimal; it can be even described as *infinitesimal* especially when juxtaposed to developed countries from the European Union, the United States, Canada, and Australasia. Unless some ingenious upgrades of the current research methodologies and its tools are applied, the NPS trade and e-trade will ever continue to prevail rendering all its counter-attempts fade into dust, these attempts should not be limited to NPS research, but should also include the legislative actions, policy planning, management of the immigrants' crisis, and counter-terrorism. In summary, the contribution from the Middle East to the NPS e-phenomena was *microscopic*; it did not exceed 3-7% of the entire NPS phenomenon e-trade. Similarly, the NPS research in the region of the Middle East can be described to be in its infancy. The overall level-of-evidence of this dissertation is assumed to be of level-2b in compliance with the Oxford Center for Evidence-Based Medicine (2009).

Within the discipline of NPS research, upgrades and enhancements should be deployed at these front lines; augmenting the quality and quantity of studies especially in the poorly-mapped and developing countries including Middle Eastern (1), incorporation of efficient use of data science and advanced web analytics (2), compulsory training in information science, biostatistics, and basic neuroscience for all NPS researchers (3), integration of social science methodologies (4), validation and incorporation of data mining technologies and real-time analyses (5), inclusion of the rarely-used experimental studies including quasi-experiments, RCTs, pragmatic RCTs, and animal modelling (6), enhancement and potentiation of internet snapshot techniques (7), implementation of comparative chemical analyses and characterization of the trending NPS (8), and the full exploitation of trends databases of the surface web (9). Perhaps, the integration of real-time data mining and data crunching will represent the climax armament to antagonise the alarming e-trade phenomenon effectively.

3) FUTURE RECOMMENDATIONS

1. In relation to the diffusion of NPS in the Middle East, surface web analyses gave a compatible insight with patterns detected on the darknet e-markets. Both surface and deep web were concordant with regards to the geo-mapping of the Middle-Eastern NPS e-commerce. At the moment, it appears that the Middle East contributes minimally within the darknet e-markets. It is likely that these substances are diffused in the Middle-Eastern countries via other modalities, independent from the use of the web; those are worthy of investigation.
2. The interdisciplinary structure of this dissertation brings to the spotlight the noteworthiness of subsequent studies in relation to NPS of interest. For instance, captagon, octodrine, and NBOMe. Data on octodrine are still considerably lacking in the scholarly-published literature.
3. Studies in relation to any particular NPS should be integrated with inclusion of several disciplines of research methodologies including; Evidence-based Medicine and critical analysis and appraisal tools, social science, counter-terrorism studies, chemical characterization and comparative chemical characterization of substance of interest, receptor-ligand binding studies, physiologic animal models, and experimental studies including quasi-experiments and RCTs. All should be integrated together to be interpreted by means data science tools and statistical models for the purpose of inference in relation to the general population.
4. Experimental trials on humans are considerablly lacking especially in relation to potent NPS including stimulants and hallucinogens. Ethics might interfere with the majority of these studies. However, these studies are critical. Few experimental trials studies were found in the published literature from the past century; these produced some impressive results that are still unparalleled even by today standards of research. Recent studies have replaced humans with animal models. Nevertheless, the human body physiology can vary considerably from that of an animal.
5. Data retrieved from Google Trends database can be of great value to predict imminent threats including “waves” of intoxication or fatalities due to NPS (ab)use. For example, in association with major holidays, public events, mass gatherings, rave events, and carnivals. Accordingly, a warning system protocol can be activated to provide orientation to; health care sectors, emergency and intensive care units at hospitals, counter-terrorism units, and even military forces in anticipation of NPS-related catastrophic events. These

protocols can be developed in collaboration with NPS-regulating bodies including the UNODC, EMCDDA, and WADA.

6. Data mining, also known as knowledge discovery in databases, is an interdisciplinary division of computer science. It lies at the intersect of; data science and statistics, machine learning, databases systems, and artificial intelligence. The application of data mining is vital for the discovery of patterns within large sets of data. Unfortunately, mining techniques were not seriously considered for the discipline of NPS research. Data from Google Trends can serve as one of the cornerstones for data mining techniques. The mining technologies can act as a *formidable* peremptory warning system against an anticipated terror attack or a swarm of intoxications/fatalities due to an emerging NPS. For a supreme effectively, data mining can be effectively integrated with an already existing early warning system, for example, the *EU Early Warning System* and *the Global SMART Program*.

4) CONTRIBUTION TO SCIENCE

The researcher, Dr Ahmed Al-Imam has been publishing his research output in scholarly international journals, and actively participating as an oral speaker at national and international conferences. Below, is a summary of his contribution in relation to the discipline of NPS research, including publications and participation in conferences .

A. CONFERENCE PARTICIPATIONS – ORAL PRESENTATIONS

- The *9th Scientific Conference of Al-Nahrain College of Medicine* – Iraq 2015
- *The 4th International Conference of NPS* – Hungary 2016
- *The 64th National Conference of Anatomical Society of India* – India 2016

B. PUBLICATION OF RELEVANCE TO THE DISPLINE OF NPS

1. Al-Imam A, “Pseudohypertension-Like Presentation: An Exceptionally Rare Presentation in an Athletic Female Patient with Morphea,” Case Reports in Dermatological Medicine, vol. 2016, Article ID 7027352, 3 pages, 2016. doi:10.1155/2016/7027352. Available at https://www.hindawi.com/journals/cridm/2016/7027352/
2. AL-Imam, A., Santacroce, R., Roman-Urrestarazu, A., Chilcott, R., Bersani, G., Martinotti, G., and Corazza, O. (2016), Captagon: Use and trade in the Middle East, Hum. Psychopharmacol Clin Exp, doi: 10.1002/hup.2548
3. Al-Imam A, Corazza O, Roman-Urrestarazu A, Sanatcroce R, Botre' F, Bersani G, Martinotti G. Pharma-terrorism: The Use of Captagon During Civil Conflict and Terrorist Attacks, IV International Conference on Novel Psychoactive Substances. Research and Advances in Psychiatry. 2016; 2(3): 89. Available at http://www.novelpsychoactivesubstances.org/keynotespeakers/
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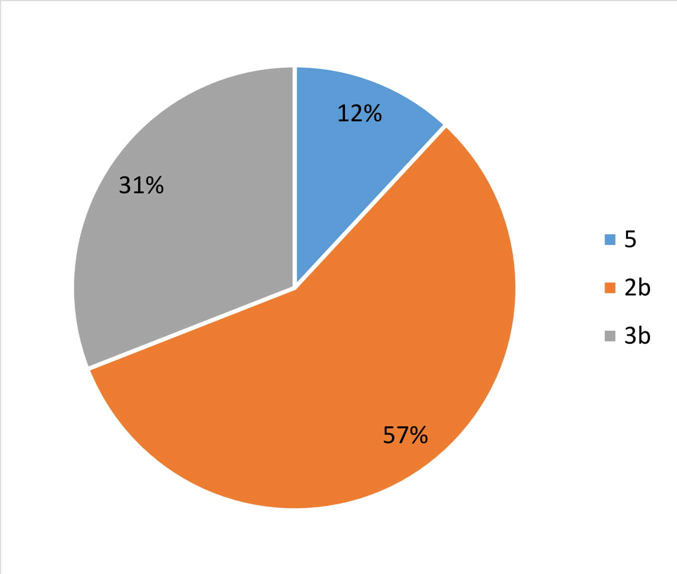
Table 1.Critical Analysis of the Level-of-Evidence.

Title	Study	Type of Study	Subtype of Study	Level-of-Evidence	Cumulative Level-of-Evidence
Evidence-Based Analysis of Literature	Literature review	Observational	Retrospective	2b	2b
Analysis of Bases of Power	Power scoring	Observational	Retrospective and cross-sectional	2b	2c
	Certainty scoring	Observational	Retrospective and cross-sectional	2b	
	Geo-mapping	Observational	Cross-sectional	3b	
Most popular NPS	Google Trends	Observational	Retrospective	2b	2c
	Geo-mapping	Observational	Retrospective	2b	
	Darknet	Observational	Internet snapshot	3b	
Drug Fora and Complementary PubMed Analyses	PubMed/Medline	Observational	Retrospective	2b	2b
	Drug Fora	Observational	Retrospective	2b	
	News and Social e-media	Observational	Retrospective	2b	
	Google Trends	Observational	Retrospective	2b	
Darknet – Part 1	Google Trends	Observational	Retrospective	2b	3a
	Grams Engine	Observational	Internet snapshot	3b	
	e-markets	Observational	Internet snapshot	3b	
Darknet – Part 2	Google Trends	Observational	Retrospective	2b	3a
	Grams Engine	Observational	Internet snapshot	3b	
	e-markets	Observational	Internet snapshot	3b	
Surveys and Internet Snap Shots	Survey	Observational	Cross-sectional	2b	2b
	Internet snapshot-1	Observational	Cross-sectional	2b	
	Internet snapshot-2	Observational	Cross-sectional	2b	
Analyses of Captagon, Octodrine, and NBOMe	Google Trends database	Observational	Retrospective	2b	2c
	Deep web and darknet	Observational	Cross-sectional and Internet snapshot	3b	

Captagon	Literature databases	Observational	Retrospective	2b	2c
	News and social e-media	Observational	Cross-sectional	3b	
	Google Trends	Observational	Retrospective	2b	
	Darknet e-markets	Observational	Internet snapshot	3b	
Octodrine	Literature databases	Observational	Retrospective	2b	2c
	Drug fora	Observational	Retrospective	2b	
	Google Trends	Observational	Retrospective	2b	
	News and social e-media	Observational	Cross-sectional	3b	
NBOMe	Literature databases	Observational	Retrospective	3b	2c
	Drug fora	Observational	Retrospective	2b	
	Google Trends	Observational	Retrospective	2b	
	News and social e-media	Observational	Cross-sectional	3b	
	Darknet e-markets	Observational	Internet snapshot	3b	
Participation In Conferences and Publications	The 4th International NPS Conference	Observational	Anecdotal	5	5
	NATCON64	Observational	Anecdotal	5	
Critical Appraisal, Limitations, and Conclusion	Critical Appraisal and Limitations	Observational	Retrospective	2b	2b



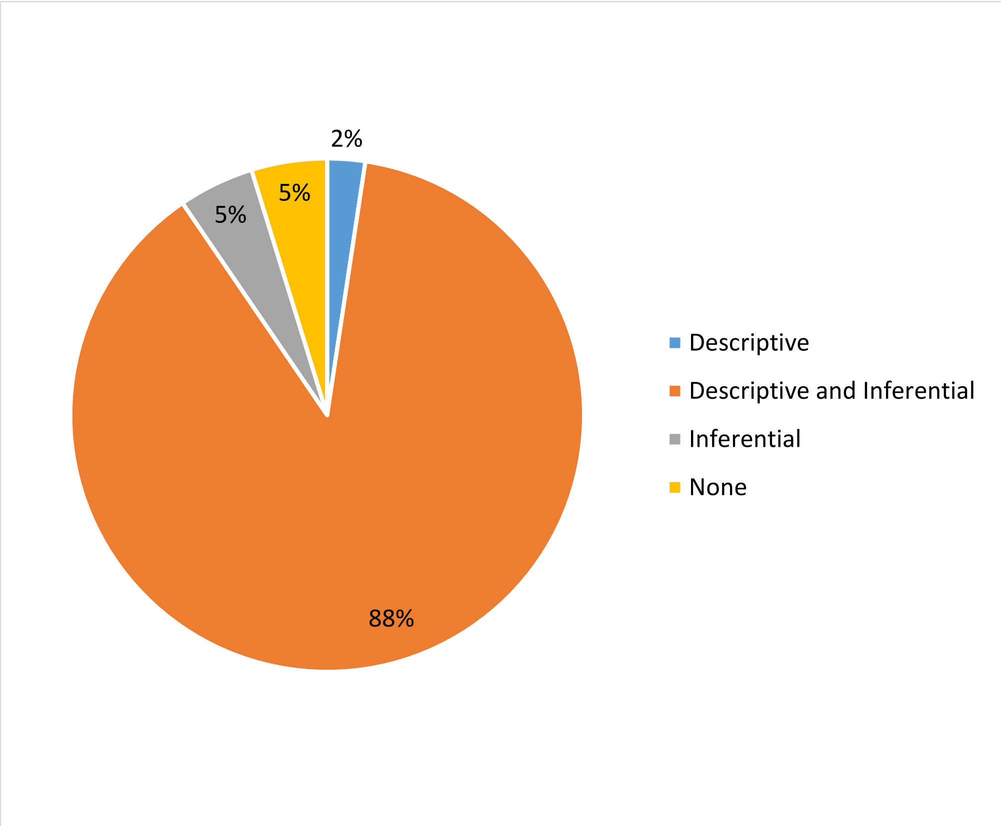


Figure 1. Percentile Contribution of Studies by: the Level-of-evidence (above) and the Type of Statistical Analysis (below).

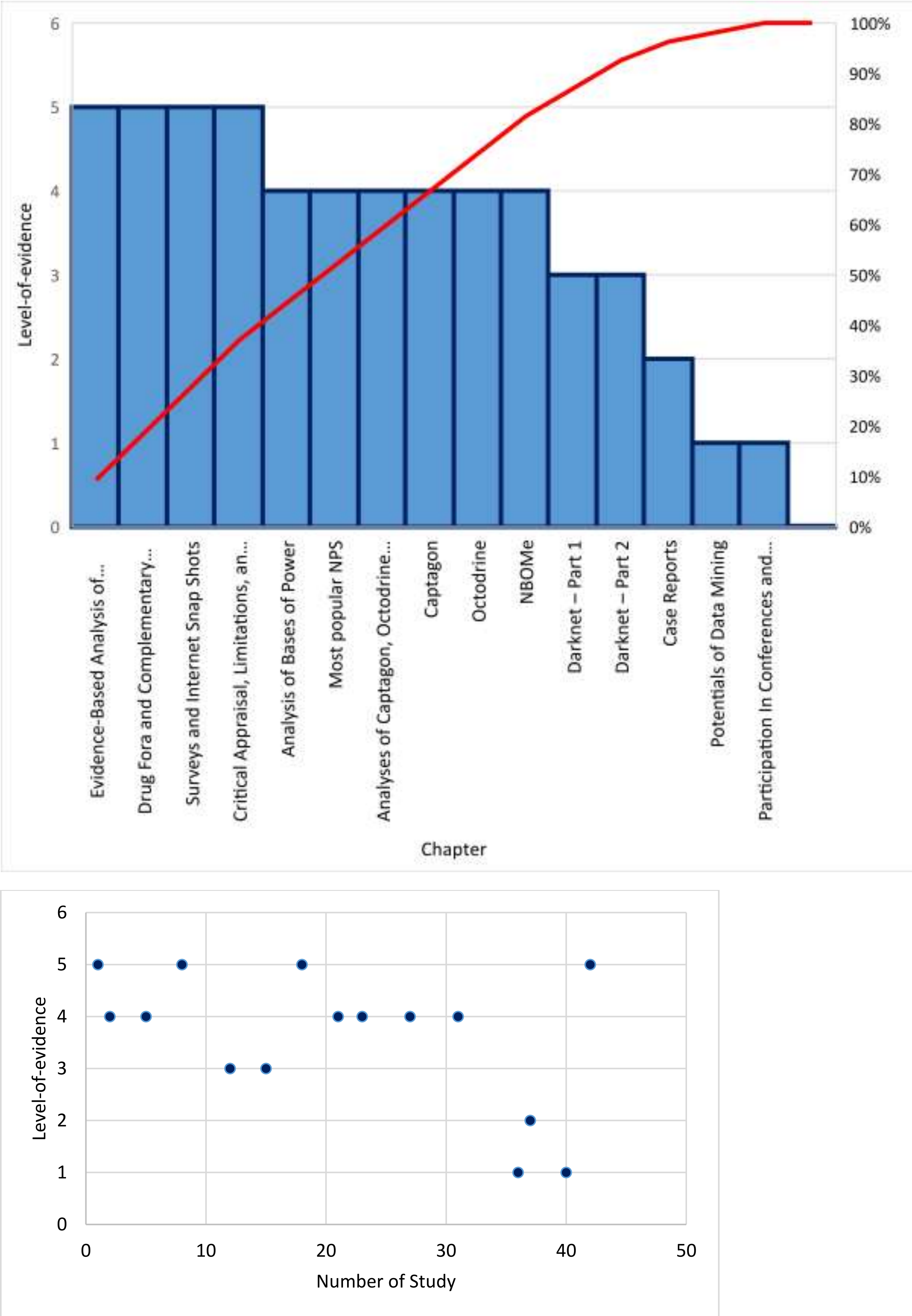


Figure 2. Thw Cumulative Level-of-evidence: Pareto Chart (above) and Scattered Diagram (below).

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APPENDICES

Refer to the appendices in the compressed file (.RAR).