**The Novel Psychoactive Substances in the UK Project: empirical and conceptual review work to produce research recommendations**

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**Abstract**

**Background:** Whilst illegal drug use has, largely, been declining in the UK over the past decade, this period has witnessed the emergence of a range of novel psychoactive substances (NPS), i.e. new, mostly synthetic substances that mimic the effects of existing drugs. Despite many causes for concern, there has been little prior study of the burden associated with NPS use in public health terms. Clarity is lacking on research priorities in this rapidly developing literature.

**Objectives:** To inform the development of public health intervention research on NPS through reviewing existing data on their use, associated problems and potential responses.

**Design:** A scoping review and narrative synthesis of selected bodies of evidence was undertaken to summarise and evaluate what is known about NPS use, related harms and responses. Relevant literature was identified from: electronic databases (covering January 2006 to June 2016 inclusive); google; relevant websites; online drug forums; and contacting experts. Articles were included if they were either primary studies, secondary studies involving the analysis and interpretation of primary research, or discussion papers. A conceptual framework postulating an evidence-informed public health approach to NPS use in the UK was developed through a pragmatic literature review, iterative development of concepts, and finalisation in light of the results from the empirical review work. The process also involved feedback from various stakeholders. Research recommendations were developed from both strands of work.

**Results:** 995 articles were included in the scoping review with the majority relating to individual level health related adverse effects due to NPS use. The prevalence of lifetime NPS use varied widely between (e.g. higher prevalence in young males) and within population subgroups. Adverse effects were psychiatric and other neurologic, cardiovascular, renal and gastrointestinal in nature, and there is limited evidence available on responses. In these and other respects, available evidence is at an early stage of development. Initial evidence challenges the view that NPS should be treated differently from other illicit drugs. The conceptual framework indicated that much of the evidence that would be useful to inform public health responses does not yet exist. We propose a systems-based prevention approach which develops existing responses, is multi-level and lifecourse-informed in character, and emphasises commonalities between NPS and other legal and illegal drug use. We make 20 recommendations for research, including nine key recommendations.

**Limitations:** Scoping reviews do not interrogate evidence in depth, and the disjunction between the scoping review and the conceptual framework findings is worthy of careful attention.

**Conclusions:** Key research recommendations build upon others that have previously been made, and offer more evidence-based justification and detail, as previous recommendations have not yet been acted upon. The case for decision-making on commissioning new research based on these recommendations is both strong and urgent.

**Future work:** The validity of recommendations generated through this project could be enhanced via further work with research commissioners, policy makers, researchers, and the public.

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**List of abbreviations**

|  |  |
| --- | --- |
| ACMD | Advisory Council on the Misuse of Drugs |
| A&E | Accident and emergency |
| AIPS | Ireland Prevalence Survey |
| BZP | Benzopirerazine |
| CDC | Centers for Disease Control and Prevention |
| CSEW | Crime Survey for England and Wales |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| ED | Emergency Department |
| EMCDDA | European Monitoring Centre for Drugs & Drug Addiction |
| EWS | Early warning systems |
| GBL | gamma-Butyrolactone |
| GHB | Gamma-hydroxybutyrate |
| HSCIC | Health and Social Care Information Centre |
| MDMA | 3,4-Methylenedioxymethamphetamine/ Ecstacy |
| MDPV | Methylenedioxypyrovalerone |
| MSM | Men who have sex with men |
| NDTMS | National Drug Treatment Monitoring System |
| NEPTUNE | Novel Psychoactive Treatment: UK network |
| NHS | National Health Service |
| NIDA | National Institute on Drug Abuse |
| NPS | Novel psychoactive substances |
| PI | Public Involvement |
| RCTs | Randomised controlled trials |
| SALSUS | Scottish Schools Adolescent Lifestyle and Substance Use Survey |
| SAMHSA | Substance Abuse and Mental Health Services Administration |
| SC | Synthetic cannabinoids |
| SCJS | Scottish Crime and Justice Survey |
| TCDO | Temporary Class Drug Order |
| QALYs | Quality Adjusted Life Years |
| WEDINOS | Welsh Emerging Drugs and Identification of Novel Substances |

**Scientific summary**

**Background**

The Advisory Council on the Misuse of Drugs (ACMD) defined novel psychoactive substances (NPS) as: *“psychoactive drugs which are not prohibited by the United Nations Single Convention on Narcotic Drugs or by the Misuse of Drugs Act 1971, and which people in the UK are seeking for intoxicant use‟.* NPS use provides grounds for concern including: technological advances that outstrip legal controls; cheap availability through the internet as well as from traditional drug dealers; high levels of cultural acceptability of NPS use in the UK by international standards; large uncertainties surrounding the identity of individual substances purchased online and on the streets. Even when a new substance is clearly and accurately identified, there may be very little information on effects, the risks posed by use, and how these may be reduced. There are systems in place for monitoring the emergence of new drugs nationally and internationally. The key UK policy development has been the implementation of the Psychoactive Substances Act in the spring of 2016. Although the research literature is developing rapidly, it is unclear how far the NPS phenomenon has been considered in explicitly public health terms, and therefore also unclear is the extent to which existing evidence is able to inform public health responses.

**Objectives**

Three specific objectives of the NPS-UK project were to:

1. Summarise and evaluate what is known about NPS use, related harms and responses.
2. Develop a dedicated conceptual framework for a public health approach to NPS use.
3. Make recommendations on key evidence gaps and priorities for future research.

**Methods**

The project comprised two main study components: a review of existing research (objective 1), and the development of a conceptual framework (objective 2). The conceptual framework was developed in part to assist with the narrative synthesis of the data from the empirical review. It was then used for the construction of a robust assessment of key evidence gaps and research priorities, and articulation of the key issues facing public health intervention research (objective 3).

***Evidence synthesis***

Electronic databases were searched between 1st January 2006 and 29th June 2016 inclusive: MEDLINE, Embase, PsycINFO and Science Citation Index. Searches for grey literature included a google search for “novel psychoactive substances”, “new psychoactive substances”, and “legal highs”; hand searching of relevant UK and US websites; and contacting experts. Primary studies, secondary studies involving the analysis and interpretation of primary research, and discussion papers with data on NPS use, problems or responses, and published in English language, were included.

We conducted a scoping review of all relevant material to map the available evidence. We used these data to conduct an evidence gap analysis based on a set of *a priori* research questions. The literature as a whole was judged to be at such an early stage of development that the benefits of conducting detailed risk of bias assessments were not justified. The evidence gap analysis informed decision-making on the selection of bodies of evidence for narrative synthesis. The four selected areas were those pragmatically judged most promising for syntheses (for example, in terms of UK relevance and sufficient depth of data) that would support the development of research recommendations.

***Conceptual framework development***

This work was done iteratively in two main stages. We began by examining the nature of contemporary evidence-informed public health, and possible similarities between NPS and other complex multi-sectoral public health challenges, as well as with tobacco, alcohol and illicit drug use. We then developed a preliminary hypothetical public health approach to NPS. We identified possible research data needs to complete the first stage of this work. We then utilised this Stage 1 version to interpret the data from the empirical review. Following the completion of the review work, we updated the conceptual framework in light of the empirical data in Stage 2. Because of the early stage of development of the empirical literature we made few substantive changes to the conceptual framework, and exercised caution in using it as a basis for research recommendations.

***Research recommendations & public involvement***

Research recommendations were developed from two distinct data sources. Firstly, research recommendations made by authors of primary studies in the existing literature selected for narrative synthesis were thematically coded. Secondly, we used the conceptual framework (developed prior to the review work and informed by wider public health sources of evidence) developed by the authors to identify what may be missing from this literature. Data from these two sources were then combined. Both earlier parts of the process and the research recommendations themselves were discussed in public engagement work involving policy makers, researchers and Novel psychoactive substance (NPS) users and user carers as stakeholders in informing the study design and processes, interpreting the findings, and validating the study recommendations.

**Results**

***Scoping review***

995 in total studies met the inclusion criteria. We mapped, and made extensive use of cross-tabulation to characterise the literature according to a set of analytic categories developed *a priori*. We also assessed evidence gaps in the literature according to *a priori* research questions to prioritize which research areas should be synthesised in more detail. We found little data on social and other risk factors, population-level risk factors, harms associated with long term NPS use, provision and effectiveness of prevention interventions, and treatment outcomes for NPS users. We undertook more detailed narrative syntheses as follows on: surveys on the prevalence and patterns of NPS use in the UK; UK qualitative studies on the patterns and harms associated with NPS use; systematic reviews (largely comprising data on harms associated with NPS use); and evaluations of policy responses to NPS use.

***Narrative synthesis***

*UK survey data*

We identified 29 studies. The most robust nationally representative data was for mephedrone (Crime Survey for England and Wales (CSEW) and the Scottish Crime and Justice Survey (SCJS) have been conducting national surveys since 2010-2011). Lifetime mephedrone use is uncommon in adults (approximately 1-2%) but is about two to three times more prevalent in men than women, and also young adults compared with older adults. Prevalence rates of recent mephedrone use are declining substantially. Nationally representative data on NPS use as a whole and on particular NPS other than mephedrone are less developed, and comparisons across years are not yet possible. Nationally representative surveys of school children have found similar low prevalence for mephedrone use and NPS as a whole. Data on particular sentinel populations likely to be at greater risk of NPS are growing, though remain quite limited. The key contributions are the collation of existing UK survey data from multiple sources on multiple substances, and drawing attention to the diversity of prevalence rates and issues in interpreting reported findings.

*Systematic reviews*

Systematic reviews (n=10) mainly comprised summaries of clinical presentation data. Side effects of NPS were wide ranging, with psychiatric, cardiovascular, renal and gastrointestinal symptoms being the most commonly reported. Treatment of these effects appears to mostly involve observation and supportive care, and in severe cases may require hospitalization. We did not find population-level data on acute health harms with dedicated attention to prevalence and policy issues, or data on chronic health or social harms in a longitudinal context.

*Qualitative studies of novel psychoactive substance in the UK*

Qualitative studies on NPS use in the UK (n=7) are at an early stage of development. Existing studies show potential to provide useful information on issues such as drug effects and reasons for, and patterns of, use. Qualitative studies may make useful contributions to behavioural epidemiological studies, and studies of drug market functioning and policy issues.

*Responses to novel psychoactive substance use and problems/harms*

Quantitative studies (n=17) evaluated the effects of legislative prohibitions of NPS use or supply on a number of outcomes including access, use, healthcare utilization and self-reported exposure and toxicity. Reductions in use, presentations or other outcomes were generally observed, though not always. Studies typically utilized simple counts of routinely collected data, particularly poison centre and hospital admissions data. Study designs were mainly before and after comparisons, without controls, which limits the basis for attribution of effects. Examination of the utility of routinely collected NPS data in different settings is needed and sources of information bias, and to evaluate pharmacovigilance and other data.

***Conceptual framework***

*Stage 1*

Our conceptual framework seeks to build upon concepts and approaches developed for drug use in general, as well as evidence-informed responses to other public health challenges which may be viewed as sharing similar features. Many contemporary public health challenges (such as health effects of climate change or obesity) are commonly conceptualised as requiring complex adaptive system changes that differ through the life-course. NPS may also be regarded in this way.

We provide a conceptual map of key individual-level risks and harms due to NPS adapted from those developed for other forms of drug use (*see Figure 1*). Apart from acute effects, most forms of risk of harm accumulate over time with continuing use. Harms to individuals, whether they are health-specific or wider harms, are strongly shaped by environmental and contextual influences, dynamically interacting with life-course stages. Intervention targets for prevention extend beyond those proximal to acts of drug use, as attention is warranted to social structural influences that shape individual risk. Other drug use, both licit and illicit, is expected to be implicated in production of harm where other drugs are being used, and it will be rare that none are.

Problems also manifest themselves at levels beyond the individual user, for example involving family members and local communities. Harms to society include the costs of health care, crime and law enforcement. Health impacts incurred by NPS users can be aggregated with measures of physical and/or mental health, lost Quality Adjusted Life Years (QALYs).

*Stage 2*

The empirical review findings indicated that the existing literature, although large, is at an early stage of development, and there is currently meagre data to inform directly what we hypothesised to be an evidence-informed public health strategic response to NPS. The hypothesised needs for research to inform public health responses have not yet been met. The conceptual framework itself was thus not significantly altered in Stage 2, as we found no reason to make major changes. We took account of the hypothesised nature of our conceptual data in making research recommendations.



***Public involvement***

Public involvement activities had demonstrable value in validating our study design, findings and research recommendations. The project was successful in engaging with policy makers and researchers at different stages of the research process. However, we were less successful with NPS user involvement, in part because the short term nature of the project offered restricted scope for investment in building relationships with NPS users over time.

**Conclusions**

There are 20 research recommendations presented as the principal conclusions of this study, of which there are 9 key recommendations as follows:

*Pharmacology related research*

1. Evaluate the effectiveness and sustainability of the existing pharmacovigilance system for NPS and the effects of planned innovations.
2. Evaluate the pharmacological, toxicological and related scientific base needed to inform the pharmacovigilance and public health surveillance systems.

*Epidemiology and related research*

1. Evaluate the effectiveness and sustainability of the existing public health surveillance system for monitoring NPS markets and other new online drug trends. This evaluation should cover monitoring actions, both quantitative and qualitative research, and associated commissioning arrangements, and be cognisant of opportunities for innovations such as test-purchasing new brands online as they become available.
2. Develop the behavioural epidemiology and related science of patterns and correlates of NPS use and problems in the context of alcohol, tobacco and other drug involvements.
3. Use cohort study designs to better understand the determinants of NPS use and related physical health, mental health and psychosocial problems, and how patterns of involvement and consequences change over time.

*Interventions*

1. Develop the science of prevention of NPS and other drug use. This should include evaluation of existing interventions and the development and evaluation of novel interventions addressing both proximal and distal determinants of NPS and related drug use, and how risks should be communicated to different groups.
2. Evaluate the public health impacts of legislative prohibitions of NPS use or supply, and other major policy initiatives.

*Recommendations for research commissioners*

1. Consider using the research recommendations presented here as a possible basis for conducting a formal research priority setting exercise using consensus development methods (such as those developed by the James Lind Alliance).
2. Evaluate existing strategic provision for, and develop as necessary, a long term planning system for research on NPS and other drug use.

**Study registration**

The systematic review element of this study is registered as PROSPERO CRD42016026415.

**Funding**

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**Word count:** 2101

**Plain English summary**

**What was the question?**

Novel psychoactive substances (NPS) are new drugs, sometimes referred to as legal highs, that have recently received a lot of attention in the media, and from governments across the world. We aimed to look at research on: 1) what is known about who uses NPS, 2) what problems they experience, and 3) what might be the best ways to reduce these problems. We also aimed to offer advice on what new research studies might be done to better understand NPS in ways which help improve the health of the public.

**What did we do?**

Before looking at any studies, we developed ideas about what research we think might be useful to understand a new problem like this. We then looked at what studies have already been done on NPS. To advise on what new research was needed we tried to find gaps between what research has already been done and what we thought was needed to be done. We also recorded and used what researchers in this area had previously recommended.

**What did we find?**

We found many gaps in knowledge, and that available research is at an early stage in understanding NPS. Reported side effects after using NPS include mental health, heart, liver, and stomach problems. We made a number of recommendations on what new research we think should be done, and which of these we thought was most important.

**What does this mean?**

Much remains to be known about NPS. We suggest there is no justified reason for investigating NPS in isolation from other illicit drug. We have presented some options for what new research could be done in the future. We hope this will help experts on NPS to decide together what research would be most helpful in reducing harms for people who already use NPS, those who might be affected by NPS, and those who might use in the future, in the interests of better health across society as a whole.

**Word count:** 298

**Chapter 1: Introduction and background**

This report presents the findings from an NIHR PHR funded programme of work to inform the development of public health intervention research on novel psychoactive substances (NPS) through systematically reviewing existing data on their use in the UK, the associated problems and the potential responses.

This first chapter provides the background and rationale for conducting this research, and describes the research objectives. This chapter also provides content as it existed at the outset of this research i.e. prior to the implementation of the Psychoactive Substances Act in 2016. The remainder of the report is divided into the following chapters representing the phases of the study:

Chapter 2: Scoping review with narrative synthesis of selected bodies of evidence on what is known about NPS use, related harms and responses.

Chapter 3: What might an evidence-informed public health approach to novel psychoactive substance use in the UK look like? A conceptual framework

Chapter 4: Public involvement

Chapter 5: Research recommendations.

**Background**

While illegal drug use has, largely, been declining in the UK over the past decade,1 this period has witnessed the emergence of a range of new, mostly synthetic substances that mimic many of the effects of “traditional” drugs. These are known as “legal highs”, or new or novel psychoactive substances (NPS). The latter description refers to the fact that use of the substance(s) in question has not been specifically prohibited. The Advisory Council on the Misuse of Drugs (ACMD), the expert body that advises Government on drug policy and practice issues, has defined NPS as: *“psychoactive drugs which are not prohibited by the United Nations Single Convention on Narcotic Drugs or by the Misuse of Drugs Act 1971, and which people in the UK are seeking for intoxicant use”.*2

NPS use provides a number of grounds for concern. First, technological advances offer sources of supply with the capacity for continuous product innovations, leading to rapid increases in the numbers of different substances available, and despite speeding up the legal processes in the UK for controlling these substances,3 the rapidity of the technological developments outstrips legal controls. Second, they are readily and cheaply available through the internet and ‘headshop’ outlets as well as from traditional drug dealers (the Psychoactive Substances Act implemented during 2016 has since prohibited headshop supply).4 Third, by international standards, there are very high levels of cultural acceptability of NPS use in the UK.5 Fourth, they are perceived to be safe, or to pose little risk. Fifth, there are large uncertainties surrounding the identity of individual substances purchased online and on the streets. Even when a new substance is clearly and accurately identified, there may be very little information on effects, the risks posed by its use, and how these may be reduced.

Despite such causes for concern, there has been little consideration of the public health burden associated with NPS use, apart from investigations of acute problems presenting to health services, and fatalities.6-9 Also, whilst there has been valuable thinking done about the implications for the regulation of drug use,4, 10 dedicated attention to specifically public health responses has been limited.11 This project seeks to address these gaps.

UK general population surveys report past year use prevalence of mephedrone, which has attracted most concern, ranging from 1.1% to 1.8% among those aged 16 and older,12, 13 with prevalence largely stable in more recent years (up to the end of 2014 when these data were assembled).1 However, among those aged 16-24 years, last year use prevalence has been 3% or higher, similar to that of ecstasy.12, 13 The most recent national drug survey identified increases in the past year prevalence of nitrous oxide and salvia use, in both the younger 16-24 age group, and among all adults. Among the former, past year prevalence was 7.6%, approximately twice that of both ecstasy and powder cocaine.1 Moreover, a number of deaths have been associated with mephedrone use, both before and after it became controlled.14, 15

Monitoring of the emergence of new drugs through early warning systems, and of national policy responses in Europe, is undertaken by the European Monitoring Centre for Drugs & Drug Addiction (EMCDDA).16, 17 Very little work has been undertaken, however, on the problems associated with use. In addition there has been scant research consideration of the nature of the need to develop interventions that target NPS, whilst initiatives such as the Novel Psychoactive Treatment: UK network (NEPTUNE) project work to improve clinical practice in the management of harms resulting from NPS use.18 This is despite the strong focus on developing the evidence base to support responses to NPS in the UK Drug Strategy.19 These needs have also been emphasised for some years by the ACMD.2

**Rationale**

It is currently unclear how much dedicated targeting of the existing generation of NPS is needed, as the existing data suggest that NPS are rarely used by those who are not also involved in other forms of substance use.[12](#_ENREF_12) Even if the present generation of NPS are not very problematic, and it is very unclear whether this is so, there is a need to develop the capacity for public health NPS responses to new substances which may become problematic in the future. The longer term strategic need may be to develop the evidence base in such a way as to be able to identify and intervene early with some new drugs that appear likely to be particularly problematic, and by implication not others, in order to alter the course of possible future epidemics.20

There is therefore a pressing need to review what is known about NPS use in the UK, the extent and nature of problems associated with this use, and to consider potential public health responses. There have been no systematic reviews which evaluate what is currently known about NPS use in the UK. Moreover, given the continually changing nature of NPS use and the resulting uncertainty regarding their implications for public health and the NHS, it is important that strategic research efforts are not confined to the current generation of NPS, but are capable of adapting to new drugs that should be expected to emerge in the years to come.

**Research objectives**

The overall aim of the NPS-UK project was to inform the development of public health intervention research on NPS in the UK through systematically reviewing existing data on their use, the associated problems and the potential responses. The three specific objectives were as follows:

1. To summarise and evaluate what is known about NPS use, related harms and responses through the conduct of a review of peer-reviewed and grey literature.
2. To develop a dedicated conceptual framework for a public health approach to NPS use which identifies the scope for interventions based on approaches developed for the use of other legal and illegal drugs, and the concerns of public health and prevention more broadly.
3. To produce a statement of public health intervention research issues for NPS use in the UK that makes recommendations on key evidence gaps and priorities for future research.

The project comprised two main study components corresponding to the first two study objectives: a systematic mapping of available evidence and narrative synthesis of selected bodies of evidence (in relation to objective 1), and the development of a dedicated conceptual framework (in relation to objective 2). We concluded that a full systematic review was inappropriate for the size and nature of the available literature within the circumstances of this project (*see Chapter 2*). Synergies between the two study components are a key feature of this project. The conceptual framework was elaborated in part to assist with the narrative synthesis of the data from the empirical review work. It was then used also for the construction of a robust assessment of key evidence gaps and research priorities, and articulation of the key issues facing public health intervention research in the form of a series of research recommendations (objective 3).

**Chapter 2: Scoping review with narrative synthesis of selected bodies of evidence on what is known about novel psychoactive substance use, related harms and responses.**

**Background**

Novel psychoactive substance (NPS) use provides a number of grounds for concern as has already been elaborated in Chapter 1. These include technological advances that allow for rapid increases in the numbers of different substances available, in a way that outstrips the ability of legal processes for controlling these substances to cope,3 and easy accessibility via the internet.4 There has however been little consideration of the public health burden associated with NPS use,6-9 as well as public health responses to NPS use.11 It is unclear whether there is need for dedicated targeting of the existing generation of NPS, or to develop the capacity for public health NPS responses to new substances which may become problematic in the future. To be able to address this evidence gap, there is need to review what is known about NPS use, the extent and nature of problems associated with this use, and to consider potential effective public health responses.

**Aim**

This scoping review and narrative synthesis aimed to summarise and evaluate what is known about NPS use, and related problems/harms and responses in the international peer reviewed and grey literature. The core purpose in undertaking this study was to inform the development of public health intervention research in the UK.

**Research questions**

The broad ranging nature of this review posed significant challenges to the development of detailed research questions that could be answered in relation to the overarching research aim. We thus developed an initial set of research questions *a priori* that we hypothesised would be useful to the development of public health intervention research. These questions were organised in three preliminary concepts of use, problems and responses. In addition, a small number of more methodological questions to be considered were also identified. It was intended from the outset that the research questions for this study would be iteratively developed along with the corresponding content of the conceptual framework (*see Chapter 3*). The framework would be used to shape the interpretation of the data included in this study, and also guide decision-making about more advanced targets for study. The initial research questions were identified as follows:

***Novel psychoactive substance use***

1. What are the prevalence and patterns of NPS use in the UK general population and do they differ in particular subgroups of the population?
2. How do existing patterns of both legal and illegal drug use and social and other risk factors influence NPS use?
3. Which other population-level risk factors influence NPS use?

***Novel psychoactive substance related problems/ harm***

1. Which acute intoxication problems are associated with NPS use?
2. What problems are associated with long-term regular NPS use?
3. In addition to intoxication, long-term regular use and dependence problems, are there other types of NPS-specific problems or other problems associated with NPS use?

***Responses***

1. Are there dedicated primary or secondary prevention interventions in the UK, and if so what is known about their outcomes?
2. Which generic interventions (early in life and early in drug using careers) target NPS?
3. How extensively does current generic UK drug prevention practice cover NPS?
4. How good are treatment outcomes for NPS?
5. What promising approaches are currently available, or can be made available, in the UK for intervening with NPS use?
6. What are the population-level or social structural factors limiting the effects of individual-level interventions?

***Methodological questions***

1. What is the nature of the current early warning systems (EWS) provision?
2. Are there sentinel populations capable of being monitored to provide early warnings of new trends?
3. What are the issues raised by uncertainties about the identities of substances being used?

In each case, we endeavoured first to examine whether data were available to answer these questions, and if the data did not exist or were judged insufficient, we considered to what extent this constituted an important evidence gap, with assessment of importance shaped by the conceptual framework detailed in Chapter 3.

**Review methods**

The review was registered with international prospective register of systematic reviews (PROSPERO registration number CRD42016026415).21 Since we decided not to conduct a systematic review we did not use PRISMA reporting guidelines22 as many of the criteria were not applicable to our work. Instead we have endeavoured to provide a detailed and transparent account of the review methods and results that we judged appropriate for this evidence synthesis work.

***Literature searches***

Relevant literature was identified through performing a range of searches including the following: electronic database searches; google search; hand search of websites relating to the UK; identification of relevant online drug forums; and contacting experts. Details of these searches are described below.

*Electronic database searches*

The following electronic databases were searched via the OVID platform for articles published between 1st January 2006 and16th November 2015 inclusive: MEDLINE, Embase, PsycINFO and Science Citation Index (*see Appendix 1 for the search strategies used in each database*). The database searches were updated on 29 June 2016. The search strategies also included trade or brand names for a number of NPS products. These names were selected by perusing through the websites of three popular NPS online headshops (i.e. globalweekends.co.uk, [www.iceheadshop.co.uk](http://www.iceheadshop.co.uk), and [www.legalhighsworld.co.uk](http://www.legalhighsworld.co.uk)) and selecting those that appeared in all three for inclusion (Appendix 2).

*Google search for grey literature*

A google search was conducted using the following key phrases: “novel psychoactive substances”, “new psychoactive substances”, and “legal highs”. The file type was restricted to pdf, and the searches were conducted on 17th March 2016.

*Hand search of websites relating to the UK and USA*

Websites of the following institutions and organizations were hand searched on 13th May 2016 to identify national and international surveys, monitoring systems and early warning systems: gov.uk (which includes Department of Health, Home Office, Public Health England), NHS Evidence, Office of National Statistics, National Drug Treatment Monitoring System (NDTMS), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Scottish Government, National Assembly for Wales, Public Health Wales, Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS), Information Services Division Scotland, and the Department of Health Northern Ireland, Centers for Disease Control and Prevention (CDC), National Institute on Drug Abuse (NIDA), Substance Abuse and Mental Health Services Administration (SAMHSA).

*Search for relevant online drug forums*

Relevant online drug forums were identified from published literature as well as from contacting experts in the field.

*Contacting experts*

Calls for information were sent to Public Health England and forwarded to the NPS Clinical Network Working Group and the Novel Psychoactive Treatment UK Network (NEPTUNE). Nineteen researchers were also contacted for any unpublished relevant literature, or literature not identified by the searches.

***Inclusion/ Exclusion criteria***

*Type of article*

Articles were included if they were either primary studies (i.e. involving the collection of original primary data through directly measuring the outcome of interest within the relevant population), secondary studies involving the analysis and interpretation of primary research, or discussion papers. Commentaries and letters were only included if they presented new primary or secondary data. Non-English language publications were excluded.

*Condition or domain being studied or discussed*

Articles were included if they were on novel psychoactive substance use, problems and responses.

*Participants/ population*

Articles were included if reporting on humans. No other limits were set on the population.

*Response(s), exposure(s)*

The exposure of interest was novel psychoactive substance use, and we were interested in any associated problems. Any intervention or response aimed at addressing novel psychoactive substance use and related problems was eligible and we were particularly interested in population-level data.

*Comparator(s)/ control*

Not applicable.

*Context*

There were no restrictions on context or location.

*Primary outcomes*

The primary outcomes were: prevalence of NPS use, prevalence of problems associated with NPS use, and responses to NPS use.

*Secondary outcomes*

None

***Article selection***

The screening of titles and abstracts and the selection of articles from retrieved potentially relevant full manuscripts was conducted by two reviewers (NM and NDM) using the selection criteria described above. The reviewers independently classified the articles as “include”, “unclear”, or “exclude”, with discrepancies being resolved by discussion or referral to a third reviewer (JM). Full manuscripts that did not fulfil all of the criteria were excluded with documented reasons for their exclusion.

***Data extraction***

Data extraction was performed using EPPI-Reviewer 4 software. The data extraction form was designed by two researchers (NM and NDM), piloted on a small selection of articles and adjusted as necessary. The following data was extracted:

* Include/exclude decision, with reasons for exclusion where applicable.
* General characteristics for included studies: author, year, location, setting, study design, publication type.
* Population characteristics: age, gender, ethnicity, sample size, novel psychoactive use status.
* Novel psychoactive substance type:
* Principal focus (use, problems, responses)
* Research recommendations in the case of reviews, systematic reviews, qualitative studies, surveys and articles on responses.

Data from each article were extracted by one researcher and checked by another, with discrepancies being resolved by consensus or recourse to a third researcher if necessary. Where necessary, authors were contacted for missing or unclear data.

***Definitions***

This section focuses on key definitions of categories used in this study as follows:

*Principal focus*

The following definitions were used for use, problems and responses:

Use: Any use of a novel psychoactive substance.

Problems: Any acute or chronic health-specific, social or wider harm due to NPS use, experienced by the user or others.

Responses: Any intervention at policy, health or other service, or clinical levels, aimed at addressing novel psychoactive substance use and/or related problems

*Study designs*

For study designs, a distinction had to be made between generic literature reviews and systematic reviews. To be included as a systematic review the paper had to meet the following criteria:

* Search of at least two electronic databases, or one electronic database and reference checking of included studies or some other source of obtaining further studies
* Explicitly stated inclusion/exclusion criteria
* List of included studies
* Risk of bias assessment of included studies conducted by authors or sufficiently reported study characteristics of included studies that would enable others to make judgements on risk of bias of individual studies
* Narrative or quantitative synthesis of data from included studies

Any review that did not meet these criteria was classified as a literature review.

***Risk of bias (quality) assessment***

No risk of bias assessment was conducted.

***Strategy for data synthesis***

The framework for data synthesis was the conceptual framework specifically designed for use in data analysis and interpretation for the current scoping review and narrative synthesis, to which the research questions listed above contribute. Data synthesis was done in three stages: evidence mapping, identification of evidence gaps, and then a narrative synthesis of selected research areas.

*Evidence map*

For reviews addressing complex topic areas, evidence mapping is a well-established tool to explore relevant literature before progressing to more advanced research design decision making.23 The extracted data was utilized by one researcher to map the literature according to principal focus (use, problems/harms or responses), NPS type, study design, region, setting, year of publication and publication type. This was checked by another researcher. The aim of the map was to provide a comprehensive yet concise descriptive map of the nature and breadth of research on NPS, and identify obvious research gaps.

The evidence map also included the analysis of the following subgroups:

* Number of records by year of publication and: principal focus (use, problems/harms, responses), NPS type, study design and publication type.
* Number of studies by geographic region.
* Percentage of records by NPS type and: publication type, study design, geographic region and setting.

*Identification and evaluation of evidence gaps*

After the mapping, the research questions listed above were then utilised to identify and evaluate evidence gaps, and to make decisions about narrative syntheses. In addition, the conceptual framework (*see Chapter 3*) guided our evaluation of what was missing from the literature.

This process, based on the evidence map, facilitated discussions about categories of evidence where it was feasible to conduct narrative syntheses (in consultation with the project steering group). We initially considered whether it would be possible to restrict the inclusion criteria to a small number of narrowly focused research questions for the purposes of conducting a full systematic review (i.e. including detailed risk of bias assessment).

However, in discussion with the project steering group, we concluded that given the early stage of development for all areas of the literature this would not be the best use of the time and resources of the project. Therefore, we developed broader inclusion criteria that enabled us to conduct narrative syntheses where there was judged to be a sufficient evidence base.

The steering group supported this decision. We were also necessarily pragmatic in our decision-making addressing questions of primary relevance to the UK as the data allowed, in ways which were manageable within the time and resources allocated to the project, bearing in mind the large size of the literature included in the scoping review and the short duration of the project (14 months).

*Narrative synthesis*

In addition to the evidence map, and evidence gap analysis, a narrative descriptive synthesis was conducted for the following categories of articles and data:

* Systematic reviews
* UK survey data on NPS use
* UK based qualitative studies
* Articles on responses, including policy evaluation studies and studies of individual level interventions

***Changes to the review protocol***

This review was originally designed as a systematic review of what is known about novel psychoactive substance use, related problems and responses from a public health perspective (PROSPERO registration number CRD42016026415).21 However, after identification of 995 eligible studies and the mapping of these, it was decided that all areas represented by this literature that were not already adequately covered by systematic reviews were not mature enough in terms of study numbers and quality to warrant a full systematic review. A decision was then made on this basis to conduct narrative syntheses in the areas indicated above, in addition to updating the evidence map until the end of June 2016 (with a view to project completion at the end of October 2016). This decision was influenced by the time available for this project and was discussed and approved by the project steering group committee as the best way to proceed.

**Results**

**Evidence Map**

***Literature searches***

A total of 13772 records were identified through electronic databases searches. A further 3260 were obtained through other sources including contacting key researchers and policy experts (Figure 2). Of the 19 key researchers contacted, six responded, with four providing further records of published literature, and one stating that the full results of one study had not yet been published. Policy experts provided four further records. 995 articles were eligible for inclusion in the review after removing duplicates and screening titles, abstracts and, where necessary, full texts. 6,10,14,24-1015

Of the 542 records excluded after reviewing the full texts, the main reasons for exclusion were: 211 were not specific to NPS (e.g. recreational drug use, club drug use, substance use/abuse, psychoactive substance use without presenting data on NPS use separately); 107 on drugs that are not included in the review as NPS (e.g. specific to illicit drug use, alcohol, tobacco, ketamine, khat, GHB or GBL); 69 on detection, identification and quantification on NPS including methods validation; 65 were comments, editorial or letters to editor within new primary or secondary data; 56 were in non-English language. Most of the remaining 34 were either, Acts, regulations or drug schedules; or descriptions of surveillance and pharmacovigilance systems.

Additional records identified through other sources

(n= 3260)

Google search= 3130; Hand search of relevant websites= 87; Online drug forums= 4; Policy experts= 4; Contact authors = 35

Records identified through database searching  
(n = 13772)

## Identification

Records after duplicates removed  
(n = 10625)

## Screening

Records excluded  
(n = 9088)

Records screened  
(n = 10625)

Full-text articles assessed for eligibility  
(n = 1537)

Full-text articles excluded (n = 542)

## Eligibility

Studies included in evidence mapping  
(n = 995)

## Included

**Figure 2: Flow of articles for the evidence mapping**

***Characteristics of included articles***

General characteristics of the 995 included articles in terms of the principal focus, setting, NPS type, study design and publication type are briefly summarized in Table 1. The majority of articles reported on problems or harms due to the use of NPS. Many of the articles focused on multiple issues as represented in Figure 3. Synthetic cannabinoids and synthetic cathinones were the NPS that were most reported on, with case report/series being be most popular study design followed by non-systematic literature reviews. Most articles were for general hospital settings, followed by specialist settings. Within hospital settings, most articles were for emergency departments (236 reports), whilst for specialist settings most articles were for poison centres (65 reports). 252 of the included reports were not specific to a particular setting.

**Table 1: General characteristics of included articles**

| **Characteristics** |  | **Distribution (n)** |
| --- | --- | --- |
| *Principal focus* | | |
|  | Use | 385 |
|  | Problems/ Harms | 773 |
|  | Responses | 148 |
| *Novel Psychoactive Substance (NPS) type* | | |
|  | All NPS | 259 |
|  | Synthetic cannabinoids | 310 |
|  | Synthetic cathinones | 271 |
|  | Phenethylamines | 69 |
|  | Piperazines | 29 |
|  | Other | 114 |
| *Setting* | | |
|  | Specialist settings (addiction treatment, psychiatric treatment, forensic and rehabilitation, poison centres, needle exchange, other similar settings) | 134 |
|  | General Hospital (inpatient, emergency department, outpatient settings) | 294 |
|  | Primary care setting | 3 |
|  | Educational Setting (school, higher educational institutions- University/ College) | 32 |
|  | Criminal justice | 9 |
|  | Police | 27 |
|  | Defence forces (Airforce, Army, Navy) | 9 |
|  | Community setting | 64 |
|  | Home | 27 |
|  | Club/ disco/ dance scene | 14 |
|  | Internet | 59 |
|  | Data registry | 13 |
|  | Early warning systems | 9 |
|  | Research setting | 22 |
|  | Other | 21 |
|  | Not applicable | 252 |
|  | Nor reported | 24 |
| *Study design* | | |
|  | Systematic review | 10 |
|  | Literature review | 243 |
|  | Randomised controlled trial | 13 |
|  | Survey | 130 |
|  | Laboratory sample analysis | 58 |
|  | Secondary quantitative data analysis | 99 |
|  | Prospective cohort studies | 6 |
|  | Case-control | 1 |
|  | Qualitative study | 47 |
|  | Case series/ reports | 367 |
|  | Other | 64 |
| *Publication type* | | |
|  | Peer reviewed journal article | 654 |
|  | Peer reviewed report | 1 |
|  | Non-peer reviewed article/ report | 119 |
|  | Conference abstracts | 205 |
|  | Book | 4 |
|  | Dissertation | 1 |
|  | Online discussion forum | 4 |
|  |  |  |

Most of the categories above are not mutually exclusive. For example, on study design some articles use multiple study designs. Another example is presented in Figure 3 below for principal focus.

***Principal focus***

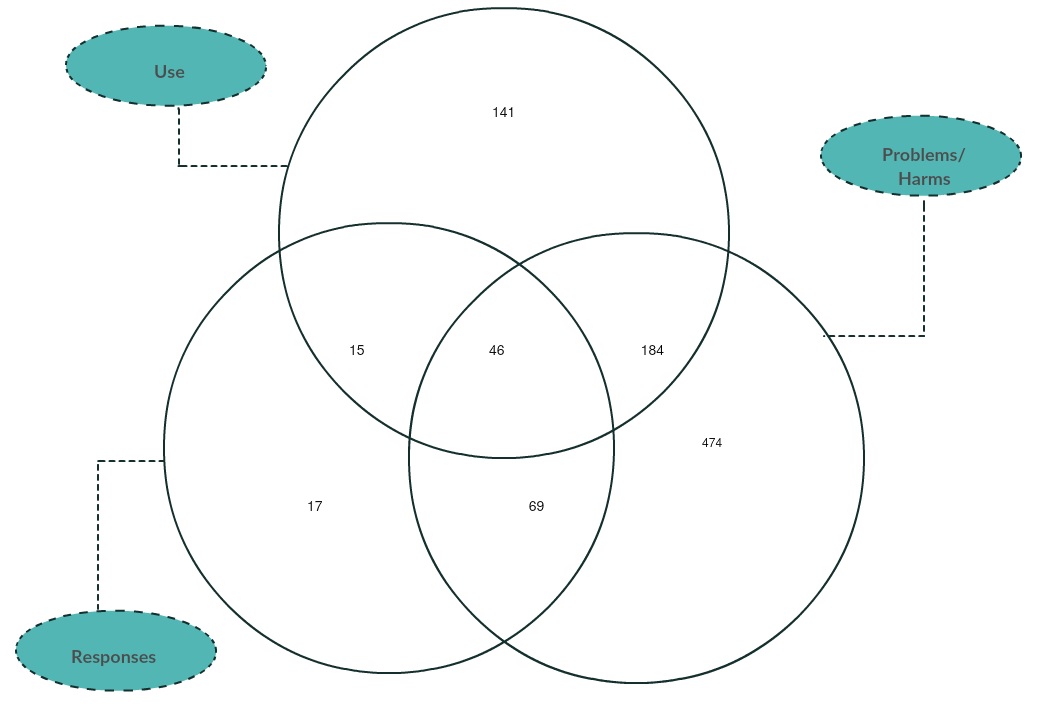
For principal focus, the majority of reports were on problems/ harms to individual NPS users. It is however important to note that many articles had more than one focus as demonstrated in Figure 3 below.

*Use*

Of the 385 reports on NPS use, 117 presented survey data. The remaining 268 articles presenting NPS use data were as follows: case reports/ series (20 articles); laboratory sample analysis (39 articles); qualitative studies (39 articles), RCTs (one article); review (124 articles); secondary qualitative data analysis (49 articles); systematic reviews (one article); prospective cohort studies (two articles);214, 1016 other designs (21 articles).

The 117 NPS use articles based on survey data comprise 13 national surveys and 104 surveys of sub-populations or convenience samples. Of the 13 national surveys, there are seven conducted among adults of which three were conducted in the UK, two in the USA, with one each for Canada and New Zealand. Two were conducted among young people (one covering Europe and the other in Poland), and four were in schools (two in the UK, and one each for the USA and Romania). In terms of NPS type, of the 117 surveys presenting NPS use data, 54 provided data on all NPS, 28 on synthetic cathinones, 25 on synthetic cannabinoids, four on piperazines, one on phenethylamines and 19 were on other NPS.

UK survey data is presented in detail in the section entitled ‘*UK survey data*’.



**Figure 3: Principal focus**

*Problems*

The 773 articles on problems due to NPS comprised at least 566 primary studies or secondary quantitative data analysis and 211 evidence syntheses; among these 4 included both a primary study and evidence synthesis (Table 2).

**Table 2: Study design of reports on problems/ harms due to NPS**

| **Study design** | **Frequency** |
| --- | --- |
| *Primary studies and secondary quantitative data analyses (n=566)* | |
| Randomised controlled trials | 12 |
| Surveys | 44 |
| Prospective cohort studies | 4 |
| Case-control | 1 |
| Secondary quantitative data analyses | 78 |
| Laboratory analysis | 27 |
| Qualitative studies | 33 |
| Case reports/ series | 367 |
| *Evidence syntheses (211)* | |
| Systematic reviews | 10 |
| Reviews | 201 |

Of the 10 systematic reviews, one was on all NPS, five on synthetic cannabinoids, two on synthetic cathinones and two on phenethylamines. More details of these 10 systematic reviews are provided within the narrative synthesis results section under *‘Systematic reviews’*

*Responses*

Of the 148 reports on responses to NPS use, 17 were quantitative policy evaluation reports mainly evaluating legislative policy responses utilizing before and after comparisons. Six reports were qualitative studies of legislative policy responses. 84 were policy discussion papers, whilst 34 reports were on clinical management of NPS users, 13 on interventions to increase awareness and understanding of NPS among clinicians and members of the public, five on harm reduction. The two reports were quantitative surveys of opinions on policy responses, and another two classified under ‘other’ were on forensic science and research responses.

The quantitative policy evaluation studies are presented in more detail under the ‘*Responses to NPS use and problems/harms*’ section.

***Year of publication***

The number of records by year of publication is shown in Figure 4 below.



**Figure 4: Number of records by year of publication for 2006-2015**

There has been a year on year increase in the number of publications on NPS between 2009 and 2014. Although there is a slight dip in 2015 this may reflect that at the time of searching not all studies published in 2015 had yet been added to the bibliographic databases. Therefore we cannot yet confirm whether this trend continued into 2015.This general trend is also observed for principal focus (Figure 5), NPS type except for synthetic cathinones and piperazines (Figure 6) and for peer reviewed journal articles and non-peer reviewed journal articles and reports (Figure 7). Our search also identified 198 records from 2016 and nine that did not have a publication date.

**Figure 5: Number of records by year of publication and principal focus for 2006-2015**

There were 85 records on use, 143 on problems/harms and 26 on responses from 2016 also identified, and six records on use, eight on problems/harms and two on responses that did not have a publication year.

**Figure 6: Number of records by year of publication and NPS type for 2006-2015**

The number of records identified for 2016 (upto 29 June 2016) were: 71 for synthetic cannabinoids, 34 for synthetic cathinones, six each for phenethylamines and piperazines, 24 for other NPS and 72 on all NPS. Of the nine records with no publication year one was on synthetic cathinones, one on other NPS and seven on all NPS types.

**Figure 7: Number of records by year of publication and publication type for 2006-2015**

For 2016, 114 peer reviewed journal articles, 13 non-peer reviewed journal articles/reports and 63 conference abstracts were identified. Peer reviewed reports, books, dissertations and online discussion forums have not been included in the graph as the numbers are too low.

Figure 8 below represents the number of records by year of publication and study design. The general trend for case reports/ series, reviews, systematic reviews, surveys, and qualitative studies was an increase up to 2013/14 and then a decrease. On the other hand there is a general increase in the number of qualitative studies, RCTs and other research designs. The 9 records with no publication year include qualitative studies (two records), reviews (two records), a survey, a case report and four records in the ‘other’ category. There were also one prospective cohort study each for 2013 and 2015, and one case-control study in 2015. Of the identified 2016 records, two were systematic reviews, 40 reviews, 34 surveys, 53 case reports/ series, 20 laboratory sample analyses, 12 qualitative studies, five RCTs, 26 secondary qualitative data analyses, and four prospective cohort studies. 15 fell into the ‘other’ category and there were no case control studies identified for 2016.

****

**Figure 8: Number of records by year of publication and study design for 2006-2015**

***Geographical location***

Table 3 below shows the number of articles included by geographic region where the study was conducted. 19 of the 185 articles reporting on the United Kingdom also reported on at least one other country in Europe (this figure is also included in the 200 under the ‘Rest of Europe’ category but excluded from the ‘Multi-regional’ category). The ‘not applicable’ category comprises reviews and systematic reviews that are international in nature, summarizing data from different regions.

**Table 3: Number of studies by geographic region**

| **Region** | **Distribution (n)** |
| --- | --- |
| United Kingdom | 185 |
| Rest of Europe | 200 |
| North America | 294 |
| Australia/ New Zealand | 58 |
| Africa | 0 |
| Asia | 29 |
| Middle East | 7 |
| Multi-regional | 22 |
| Not applicable | 216 |

***Novel psychoactive substance type***

The figures below show percentage of records by NPS type and study design (Figure 9), region (Figure 10), setting (Figure 11) and publication type (Figure 12).



**Figure 9: Percentage of records by NPS type and study design**

For most NPS types, the majority of studies were case reports/ series, reviews or surveys. Prospective cohort and case-control studies are not represented here because of very low numbers.



**Figure 10: Percentage of records by NPS type and study region**

The majority of synthetic cannabinoids, synthetic cathinones and phenethylamines studies were conducted in North America, whilst this was Australia/ New Zealand for piperazines. Articles that looked NPS in general were mostly from the UK and the Rest of Europe.



**Figure 11: Percentage of records by NPS type and study setting**

The majority of studies on synthetic cannabinoids, synthetic cathinones and phenethylamines were conducted in general hospital settings. On the other hand the majority of studies on piperazines are either in research settings or not specific to any setting.



**Figure 12: The percentage of records by publication type for each NPS category**

Most articles were peer reviewed journal articles for each of the NPS category.

***Study design***

Figure 13 summarises the percentage of records by publication type for each study design category.



**Figure 13: The percentage of records by publication type for each study design category**

Most types of study designs were published as peer reviewed journal articles. There were also three peer reviewed articles and three conference abstracts on prospective cohort studies; one peer reviewed article for a case-control study; there online drug forums; and one dissertation that conducted secondary quantitative data analyses.

***Summary of the evidence mapping***

We identified a very large number of relevant reports (n=995). However, despite the large size of the literature in this area there still remain large gaps in the evidence base, presumably due to the recency of its development. It is therefore challenging to both summarise this literature and also prioritise areas of the evidence base that require more detailed evidence synthesis.

In order to structure this summary and make decisions about further synthesis we return to the *a priori* research questions on NPS use, NPS related problems/harms, and responses introduced at the beginning of this chapter. We briefly summarise the data available in relation to each initial question, as the basis for an assessment of whether there was sufficient data to conduct more detailed syntheses.

*Novel psychoactive substance use*

1. What are the prevalence and patterns of NPS use in the UK general population and do they differ in particular subgroups of the population?

We identified studies on prevalence and patterns of NPS use in the UK (*see Table 4*). These comprised nationally representative surveys in adults (such as the Crime Survey for England and Wales and the Scottish Crime and Justice Survey) and school children (such as Health and Social Care Information Centre, 2015) which indicate NPS use is relatively rare at the population level (between 1-2%). Population prevalence rates for mephedrone use are declining however it is not yet possible to assess trends over time for NPS use as a whole. Surveys in targeted subgroups thought to be more likely to engage in NPS use have been conducted. Most data are in attendees of gay friendly night clubs where a similar pattern of decline in mephedrone has been identified. Therefore, the prevalence and patterns of NPS use in the UK is a promising area of research that suggests more detailed synthesis of these data will be informative.

1. How do existing patterns of both legal and illegal drug use and social and other risk factors influence NPS use?

There is limited preliminary evidence as this research question does not appear to have been investigated in a dedicated manner. It would be challenging to provide even basic information on this subject. Therefore there does not appear to be sufficient data available to conduct a more detailed synthesis.

1. Which other population-level risk factors influence NPS use?

There are nationally representative survey data suggesting males compared with females and younger adults compared with adults as a whole are more likely to engage in NPS use. However, we identified very little data on other population-level risk factors that influence NPS use. Given the limited exploration of these risk factors we concluded that there was insufficient data to conduct further evidence syntheses. However we decided that data on age and gender should be considered in the context of the national survey data on prevalence above (*see section on narrative syntheses of UK surveys*).

*Novel psychoactive substance related problems/ harm*

1. Which acute intoxication problems are associated with NPS use?

There were a large number of case reports and case series on intoxication problems associated with NPS (such as attending access and emergency services after NPS use). However, there was little or no population-level data other than registries of drug related deaths. These data have begun to be synthesised, we identified 10 published systematic reviews (*see Table 5 for further details*). Given the size of the literature and the limited quality of the primary studies, the priority for synthesis appears to be summarising the findings of systematic reviews in this area, including assessment of the extent to which this large literature on case reports and registry data has been covered by these reviews.

1. What problems are associated with long-term regular NPS use?

We identified very limited epidemiological data on problems associated with regular NPS (such as symptoms of dependence, physical health problems, and enduring mental health problems). However, this has begun to be explored in qualitative studies in NPS using populations. We identified seven qualitative studies in nine papers and therefore we will synthesise these studies in more detail in subsequent sections of the report.

1. In addition to intoxication, long-term regular use and dependence problems, are there other types of NPS-specific problems or other problems associated with NPS use?

Social and health harms associated with NPS use other than the types described above do not appear to have been investigated. Therefore we concluded it would be premature to conduct further syntheses, and indeed it may be better to pursue such questions in future research in the first instance in relation to specific NPS drugs or drug types rather than for NPS as a whole.

*Responses*

1. Are there dedicated primary or secondary prevention interventions in the UK, and if so what is known about their outcomes?

We did not identify evidence on primary or secondary prevention interventions in the UK therefore further syntheses are not currently possible.

1. Which generic interventions (early in life and early in drug using careers) target NPS?

We did identify some treatment audit data that shows proportions of people who use NPS receiving drug treatment services. However, no specific data exists on the content of these interventions and therefore there are very limited opportunities to conduct further syntheses.

1. How extensively does current generic UK drug prevention practice cover NPS?

We did not find any data to inform a response to this question therefore no further evidence synthesis was conducted. Although there are policies such as the Psychoactive Substances Act 2016 and publicly available educational resources such as Talk to Frank that incorporate NPS there were no data available for inclusion.

1. How good are treatment outcomes for NPS?

We did not find any studies to inform a response to this question therefore no further synthesis was conducted.

1. What promising approaches are currently available, or can be made available, in the UK for intervening with NPS use?

Although limited, there are data on NPS responses that suggest the need for further exploration. For example, key policy responses at present in many countries around the world involve prohibition of NPS possession or supply. We have identified studies that have begun to evaluate the effectiveness of such responses, which we will therefore further examine in the narrative synthesis (*see Table 6 for further details*).

1. What are the population-level or social structural factors limiting the effects of individual-level interventions?

We did not find any data to inform a response to this question. Therefore we did not conduct further evidence syntheses.

There were also three methodological questions as follows:

What is the nature of the current early warning systems (EWS) provision?

Are there sentinel populations capable of being monitored to provide early warnings of new trends?

What are the issues raised by uncertainties about the identities of substances being used?

We did identify some data that was relevant to all three questions, though this related to the substantive areas such as: descriptions of EWS, sentinel population studies and detection, identification and quantification of substances (including waste water analysis, use of the World Wide Web and validation of analytical methods). Such topics are already covered elsewhere in the evidence mapping, and as the studies are not methodological in nature, it would be impractical to identify methodological issues across the literature as a whole. We therefore have no basis for any further methodological syntheses within this study.

*Interim conclusions*

We have identified a number of areas of the NPS evidence base where there is very limited research. For example, there is very limited data on epidemiological studies of the long term harms of NPS, outcomes associated with current UK prevention provision for NPS use, and outcomes associated with the effectiveness of psychosocial interventions for NPS use.

We identified UK prevalence data on NPS use both at a general population level and in potential sentinel populations. Initial scoping suggests this is an area that requires more detailed synthesis to assess current findings and future research needs. Similarly, given the importance of legislation and other policy initiatives on NPS use, synthesising studies evaluating the effectiveness of these types of responses should be useful. There is also a need to explore further the qualitative studies we identified on long term harms and other subjects to inform future research. Finally, there is a relatively large literature on harms and problems associated with NPS use although mainly consisting of case reports and case series. In addition we identified systematic reviews on harms and problems that seek to synthesise some of this literature. We judged that detailed synthesis of the primary literature may be useful, though the existence of the systematic reviews may merit earlier attention. Therefore we made a pragmatic decision to summarise these reviews, judging this to be of greater priority given the size and scope of our project.

**Narrative synthesis**

As indicated in earlier sections, the narrative synthesis will focus on UK survey data which includes general population surveys, as well as particular targeted subgroup studies; data from the 10 identified systematic reviews; qualitative studies of NPS use in the UK; and responses to NPS use and problems/harms

***UK survey data***

We identified 29 studies assessing prevalence of NPS use in the UK (Table 4). These surveys varied in focus with some examining NPS prevalence in general populations (including some nationally representative surveys of adults and school children in the UK).920, 965, 968, 1017-1019 Other focused on specific sentinel populations such as attendees of night clubs, people attending mental health services, homeless populations and prisoners.158, 169, 454, 744, 877, 936, 948, 1020-1030 Finally, other surveys particularly targeted NPS users to investigate patterns of use.888, 923, 964, 1031-1034

**Table 4 Summary study characteristics of surveys of NPS use in the UK**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author** | **Population** | **Drug** | **Sampling** | **Participant characteristics** |
| **Nationally representative** | | | | |
| Department of Health, Northern Ireland1017 | General population | NPS | Nationally representative sample of Ireland | N=2,535  Reflective of the general population |
| European Commission920 | European Youth (15-24 years) | NPS | Nationally representative samples for member states | N=13,128  (UK: N=501)  Reflective of the general population |
| Health and Social Care Information Centre1018 | 11-15 year olds | NPS | Nationally representative sample of schools in England | N=6,173  Reflective of the general population |
| NHS National Services Scotland965 | 13 and 15 year olds | NPS | Nationally representative sample of schools in Scotland | N=33,685  Reflective of the general population |
| Office for National Statistics968 | General population | NPS | Nationally representative sample of England and Wales (Crime Survey for England and Wales) | N=35,000  Reflective of the general population |
| Robertson1019 | General population | NPS | Nationally representative sample of Scotland (Scottish Crime and Justice Survey) | N=12,035  Reflective of the general population |
| **Community sample – not nationally representative** | | | | |
| Corazza *et al*.169 | Pupils and students | NPS | Online (The Study Room forum) | N=446  Gender: 50% male  Mean age: 19 years (range 13-30) |
| Dargan *et al*.1021 | Pupils and students | Mephedrone | Tayside area | N=1,006  Gender: 50% male  Mean age school children: 14 years  Mean age university students: 21 years |
| Penney *et al*.1027 | School children (15-18 years) | NPS | Greater London | N=533  Gender:55% male  Age: range 15-18 years  Ethnicity: 14% White, 26% Black, 9% Mixed, 23% Asian |
| Mounsey *et al*.1026 | School children (15-18 years) | NPS | Greater London (four private schools, and four state schools) | N=917  Gender: not reported  Age: range 15-18 years  Ethnicity: not reported |
| **Sentinel populations/Subgroups** | | | | |
| Baker1020 | Prisoners | Synthetic cannabinoids | Prison in Rochester | N=101  Gender: 100% male  Mean age: 32 years (range 18-59)  Ethnicity: 72% white, 12% black, 6% Asian, 6% mixed ethnicity  Offences convicted for: 30% violent offences, 21% robbery, 26% drugs, 5% motoring related, 9% acquisitive |
| Homeless Link936 | Homeless people | NPS | Clients of day centres for homeless people | N=56  Gender: 59% male  Mean age: 29 years |
| Chung *et al*.158 | HIV positive MSM | NPS | HIV outpatient clinic | N=223  Gender: 100% male  Sexuality: 100% MSM |
| Daskalopoulou *et al*.1022 | HIV positive MSM | Mephedrone | HIV outpatient clinic | N=2,248  Gender: 100% male  Median age: 46 years  Ethnicity: 89% White  Sexuality: 100% MSM |
| Thurtle *et al*.744 | Attenders of Sexual health clinics | NPS | 2 clinics in London | N=1,472  Gender: 53% male  Mean age: 30 years |
| Lovett *et al.*454 | Attenders of gay friendly night clubs | Mephedrone, Methiopropamine | Gay friendly night clubs | N=397  Gender: 89%  Mean age:30 years |
| Measham *et al*.1023  Moore *et al*.1025 | Attenders of gay night clubs | NPS, mephedrone | Gay friendly night club (2010) | N=308  Gender: 82% male, 17% female, 1% trans-gender 1%  Mean age: 30 years  Ethnicity: 75% White, 10% Black, 10% Mixed race, 4% Asian  Sexuality: Homosexual 70%, Bisexual 9%, Heterosexual 17% |
| Measham *et al*.948 | Attenders of night clubs | NPS | Night clubs in Lancashire | N=343  Gender: 48% male  Mean age: 23 years (range 17-55)  Ethnicity: 96% White |
| Wood *et al.*1030  Wood *et al*.1029 | Attenders of night clubs | NPS, mephedrone | Gay friendly night clubs in London (2011) | N=315  Gender: 82% male, 15% female, 1% transgender  Mean age:30 years |
| Roche and Huke877 | Psychiatric populations | NPS | Eating Disorders outpatients | N=72  No further data on study characteristics reported |
| Moore and Lesser1024 | Psychiatric populations | NPS | Acute mental health services in Devon | N=100  No further data on study characteristics reported |
| Stanley *et al.*1028 | Psychiatric populations | NPS | General adult psychiatric wards in a Scottish city | N=388  Gender: 49% male  Mean age: NPS users 36 years, non-NPS users 43 years  Ethnicity: not reported |
| Winstock *et al*.1034 | NPS users | Mephedrone | Recruited through dance music and clubbing website | N=947  Gender: 60% male  Mean age: 24 years. |
| Winstock *et al*.1033 | NPS users | Mephedrone | Recruited through involvement in the dance music scene (subsample of Winstock 2011a) | N=100  Gender: 77% male  Mean age: 25 years |
| Winstock *et al.*1032 | Poly-drug users | Methoxetamine | Online survey of UK-based polydrug users | N=5,367  Gender: 82% were male  Mean age: 25 years  Ethnicity: 91% white  Sexuality: 78% were heterosexual, 9% homosexual, 7% bisexual |
| Fletcher *et al*.923 | NPS users | NPS | Tayside area | N=687  Gender: ratio of female to male participants was approx. 5:2  Age: most respondents were 20-64 years |
| O’Brien *et al.*1031 | NPS users | NPS | Online survey | N=183  Gender: 78% men, Age: majority aged 16-29 years |
| NHS Lothian Substance Misuse Directorate964 | NPS users | NPS | Opportunistic sampling by outreach workers | N=100  Gender: 77% male  age range: 21-59 years  approximately half were homeless , 76% been in prison, almost all unemployed |
| Brookman888 | Various at risk groups | Mephedrone | Agencies in South Wales: Criminal justice, charities working with offenders, drug users or those with broad range of needs` | N=67  Gender: 73% male  Age: range (15-55 years)  12% under 18 years,  48% were aged 18-29, 40% were over 30 years |

*Nationally representative prevalence studies*

Adults

Data on adult NPS use is available from nationally representative surveys conducted by government agencies. The most extensive data is on mephedrone use which has been collected since 2010/2011 (questions on lifetime use of mephedrone were included later from 2012/2013) annually in the Crime Survey England and Wales (CSEW) 968 and the Scottish Crime and Justice Survey (SCJS).1019 Data on mephedrone use is also available from the All Ireland Prevalence Survey (AIPS) collected in 2010/2011 and 2014/2015.1017

Data on generic NPS use from nationally representative surveys are more limited. The CSEW968 and the AIPS1017 only began collecting data on generic NPS use in 2014/2015. The SCJS has been collecting data on generic NPS use since 2010/2011.1019 However comparisons of prevalence over time are difficult since specific substances included in this category have changed. Of particular note, the 2014/2015 SCJS no longer categorised mephedrone as a ‘new drug’ which has a substantial impact on prevalence estimates of NPS use.1019 However, the advantage is that this is comparable with the CSEW968 and AIPS making comparisons across surveys possible in 2014/2015 and potentially in the future. European Commission920 also conducted a nationally representative survey of NPS use in member states that included the UK.

*Mephedrone use:* The lifetime prevalence for all adults (16 years and over) of mephedrone use has remained relatively constant in the past three to five years of surveys. Estimates were similar in the CSEW968 and the AIPS1017 with 2% of the population using mephedrone, compared with 1% in the SCJS.1019 Past year prevalence declined in both the CSEW968 (2010-2011: 1.3% to 2014-2015: 0.5%) and the SCJS (2010-2011: 0.7% to 2014-2015: 0.3%)1019 we could not find data to assess this on the AIPS.

Estimates for younger adults (16-24 years) were two to three times higher compared with all adults. Mephedrone lifetime use was 5-6% across years (2012-2013, 2013-2014, 2014-2015) in the CSEW,968 and 4% in the SCJS (2012-2013)1019 and AIPS (2010-2011).1017 Past year use declined from 4.4% in 2010-2011 to 1.9% in 2014-2015 in the CSEW,968 we could not assess whether there was a similar decline in SCJS1019 or AIPS.1017 Together these data suggest that the peak incidence of mephedrone has passed.

*Generic NPS use:* As discussed above, comparisons across surveys are not possible nor are comparisons across years in the SCJS, therefore we will focus only on the 2014/2015 data.

For all adults, the prevalence of lifetime NPS use (excluding mephedrone) was 2% in the AIPS and SCJS1019 and slightly higher (3%) in the CSEW. 968 NPS use was approximately two to three times higher in younger adults: 4% (SCJS – 16-24 years),1019 6% (CSEW – 16-24 years),968 7% (AIPS - 15-34 years).1017 The UK prevalence estimate of lifetime NPS use from the European Commission (2014) survey was higher (10%) than the other UK national surveys, and was higher than the average prevalence across European countries (8%).

All three UK national surveys found that men were approximately two to three times as likely to engage in NPS use compared with women. However, the European Commission920 did not find that NPS use differed by gender.

Young people (11-15 years)

*NPS use:* HSCIC survey in England of 11-15 year olds found lifetime prevalence of NPS use was 2.5%.1018 This was similar to the Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS) which found a prevalence of 2%.965Both surveys found older children were more likely to use NPS. In England NPS prevalence was 0.5% for 11 year olds but 5% for 15 year olds.1018 In Scotland 1% of 13 year olds and 4% of 15 year olds reported NPS use.965NPS use was slightly higher for boys in the SALSUS survey (2% boys and 1% girls)965 but there was no evidence of gender differences in the HSCIC survey.1018

*Mephedrone and other individual NPS:* Mephedrone use was low in both the HSCIC (0.5%)1018 and SALSUS (1%) surveys.965 In England the prevalence remained relatively constant across years 2012-2014.1018 In Scotland there was a reduction from 2% in 2010 to 1% in 2013.965

SALSUS provided more data on individual NPS.965 Prevalence of synthetic cannabinoids increased from 1% in 2010 to 2% in 2013. Salvia use was recorded for the first time in that survey in 2013 with 1% reported prevalence.

*Sub-population studies*

School children and university students

Four further studies169, 1021, 1026, 1027 were identified that conducted surveys of schools or university students. However, like all studies included in this section, these surveys are not designed to provide nationally representative samples of this population.

*NPS use:* Prevalence estimates differed substantially between studies. Corazza *et al.*169 conducted an online survey using the Study Room website. Participants’ ages ranged from 13-30 years with a mean of 19 years. They reported the highest lifetime prevalence estimate (31%) of NPS use for any sub-population in this group of website users. This was much higher than national surveys looking at a similar age group where lifetime prevalence of NPS use ranged from 4-10%. Corazza *et al.*169 found that the most commonly reported NPS used were mephedrone (41%), salvia (20%) and synthetic cannabinoids (11%).Mounsey *et al*.1026 in a questionnaire survey of the schools population of eight schools (four private and four state schools) of 15-18 year olds in Greater London found a lifetime prevalence rate of 8% for NPS use. In contrast, Penney *et al*.1027 had a much lower estimate (1.1%) of NPS use in a similar study in three schools in London (see above for national prevalence data among 11-15 year olds).

*Mephedrone and other individual NPS use:* Estimates of mephedrone use differed widely in sub-population surveys. The highest estimate (20%) was found by Dargan *et al*.1021 in a survey of schools, colleges and universities in Tayside. Corazza *et al*.169 also found a relatively high rate of 13% for mephedrone use. This contrasted with Penney *et al*’s1027 survey of school children with a much lower prevalence (0.5%). All data reported here refer to lifetime prevalence.

Data on other individual NPS were limited. Corazza *et al*.169 reported prevalence rates of 6% for salvia and 3% for synthetic cannabinoid use. Penney *et al*.1027 provided prevalence data on synthetic cannabinoids (0.7%) and methoxetamine (0.2%).

Attenders of night clubs

Surveys were conducted by the same research team in gay-friendly night clubs in South East London in 2010, 2011, 2012 and 2013. Lifetime use of mephedrone was high: 54% in 20111023 and up to 72% in 2013.454 However, past month use and use on the night of survey declined steeply in these surveys: Past month use was 41% and use that night 21% in 2010.1023 In 2011 this increased to 53% past month use and 41% use that night.1029 However, in 2013 past month use had declined to only 6%.454 Other NPS use was much less frequent across all years of their surveys including MDAI, BZP, methiopropramine, and methoxetamine.

Measham *et al.*948 also conducted surveys of drug use in 10 night clubs in Lancashire (2010-2011) which did not focus on gay-friendly clubs. Prevalence of NPS use was much lower with lifetime reported use of mephedrone 13%, past year use 7% and past month use 2%. The lifetime prevalence of ‘Bubble’ was 18%, 11% past year use and 3% within past month. Methoxetamine past 12 month use was only 3% but this was before it had been banned which may impact on future use.

Cybernauts

O’Brien *et al*.1031 conducted an online survey of ‘cybernauts’ (n=183). Frequency of NPS use was high with 32% reported using in the past week. Participants identified themselves as knowledgeable consumers, using the internet to accumulate information about NPS as well as sharing their own experiences and informing fellow users of potential harms.

Psychiatric populations

Two eating disorders clinics in Leeds and London were surveyed for NPS use based on case notes.877 A total of 22% reported lifetime use (14% ketamine and 13% mephedrone). NPS use was higher in people with binge-purging behaviours and a history of self-harm.

Stanley *et al*.1028 in a larger retrospective case notes review (N=388) of adult inpatients in general psychiatric wards found the same prevalence rate (22%) of lifetime NPS use. NPS use was thought to contribute to psychiatric symptoms in 59% of these participants. NPS users were more likely to be younger, male and to have a forensic history, compared with non-NPS users.

Moore and Lesser1024 also conducted a retrospective review on case notes of 100 patients presenting to acute mental health services in Devon. They found an overall prevalence rate of 8% for lifetime NPS use, with higher rates of use in inpatients (12%) than those seen by the crisis team (4%). In seven out of eight NPS users in the sample it was judged their use was associated with their clinical presentation.

Attendees of STI clinics

Chung *et al*.158 conducted a retrospective case review of 431 STI screens in 223 HIV positive men who have sex with men (MSM). Prevalence was high, with 24% reporting lifetime mephedrone use. However, a larger study (N=2,248) of HIV positive MSM attending 10 HIV clinics1022 found a much lower prevalence estimate for mephedrone use (7%).

Thurtle *et al.*744 surveyed attendees of two sexual health clinics in central London (N=1626), 44% were MSM. Regular monthly use was relatively low (1.6%) in the total sample and lower in 16-24 year olds (0.3%). Prevalence for other NPS such as ivory wave, spice, naphyrone, methylone was even lower.

Prisoners

Baker1020 conducted a non-randomly sampled survey in a Prison in Rochester. Questionnaires were provided in classrooms and activity areas within prison, and also to prisoners employed as cleaners. 66% reported it was fairly easy or very easy to buy Spice but was higher for those who reported using Spice (88%). 43% reported any use of synthetic cannabinoids (‘Spice’), 39% reported use in prison, 22% reported being a current user. Of those using Spice in prison, 21% said they would still use Spice outside, 39% said they would use an alternative drug, 23% they would not have used anything. The most important reasons for using Spice were making time pass quicker (37%), relaxation (22%) and not being detected in mandatory drug testing (22%). Most (71%) did not think that Spice was safer because it was legal outside prison. Most also thought Spice was more dangerous than cannabis (56%), 13% thought Spice was as safe as cannabis. 57% of those that used Spice viewed it as fairly or very addictive.

Homeless populations

Homeless Link936 conducted a small survey among homeless clients (n=56) of four day centres in Manchester. Lifetime prevalence was strikingly high in this study (80%) and the majority of those that reported using NPS did so on a daily basis (66%). A further 14% engaged in NPS use five or six days a week. Most NPS users also used a variety of other substances, most commonly crack cocaine and cannabis In terms of the most commonly consumed individual NPS, most users simply reported ‘any’ or ‘all’, followed by a range of different synthetic cannabinoids (such as Pandora’s Box, Hipster, Spice). Most used at least three types of NPS (84%).

Most common reasons for use were convenient and easy access (38%), legality of substances (31%), substitute for other substances (e.g. alcohol or illegal drugs, 26%), cheaper than other substances (21%). NPS use was reported to have a negative impact on their relationships (27%), physical health (27%), and homelessness (21%). 57% reported having a drug problem, 3% reported they were in recovery, there rest did not think they had a drug problem.

*Targeted studies of novel psychoactive substance users*

General NPS use

All studies described here do not employ random or other formal sampling methods. Fletcher *et al.*923 conducted a survey in Tayside recruiting 120 people who had used NPS (as well as those who knew of people who had used NPS and those who had not used NPS).

Over half of those who reported lifetime NPS use had last used more than one year previously and were thus no longer users. Additionally, 10% had used in the past week, 20% past month, and 20% between six months to a year ago. Mephedrone was the most common drug reported. NPS was most commonly used as tablets, powder, snorted or smoked. NPS was most commonly first tried at ages 16-19 years. 19% reported that NPS was the first drug they had ever taken. Cannabis was much more common as the first drug taken (51%), and cocaine slightly less common than NPS (14%). Of those who ceased using NPS, 91% found it either easy or very easy to stop. Most commonly cessation was due to side effects of NPS.

Mephedrone

Winstock *et al.*1034 examined data on 947 (41%) people in the UK who reported lifetime mephedrone use as part of a larger online survey of club drug use. Reported mephedrone use was much higher in the larger online survey than lifetime methylone (11%) and MDPV (2%) use. Among participants who had reported lifetime mephedrone use, 94% reported past year use and 80% past month use. The most common route of administration was by snorting (66%). Those who snorted mephedrone rated it as more addictive than cocaine and carrying more risk.

Winstock *et al*.1033 conducted a more detailed telephone survey on 100 participants of this sample of mephedrone users. Use of other drugs with mephedrone was very common. Participants reported high lifetime prevalence rates for ecstasy (96%) and cocaine use (92%). In a typical mephedrone session, 82% drank alcohol, 36% used cannabis, 35% used ketamine, 26% used cocaine, and 23% ecstasy. Possible stimulant dependence (three or more dependence symptoms) was reported in 30% of participants.

Brookman888 investigated violence and other harms in mephedrone users (N=67). She provided questionnaires designed for young people and adults to 14 agencies across South Wales (including criminal justice organisations and charitable agencies working with offenders or drug users). 46% used mephedrone on a daily basis, 15% every other day, a further 19% used mephedrone once a week, 6% every other week and 13% once a month. Almost two-thirds (63%) snorted the drug, 56% injected and 45% by oral injestion. Just over 80% used mephedrone with another drug, most commonly alcohol (N=29), cannabis (N=23) or heroin (N=19). Diazepam was most frequently used to reduce effects of comedown (N=37), followed by cannabis (N=7). Violence was fairly frequent with 42% reporting becoming violent when using mephedrone. Females were more likely (50%) than males (40%) to report violence as a result of mephedrone use.

Methoxetamine

Winstock *et al.*1032 reported on a subsample (N=326) of past year users of methoxetamine from a larger online survey (Global Drug Survey) of 7700 UK-based poly drug users (other material from this survey is reported only as news items in mass media, and are thus not eligible for inclusion as there were no reports of study findings available). This comprised 4% of the overall survey population. 25% of last month methoxetamine users reported use on four or five days of that month. Motivations for use in comparison with ketamine were: easier to get hold of, less damaging to their kidneys or bladder, preferred the effects. 89% reported first use via intranasal route.

Injection drug users

A harm reduction service in Lothian conducted a survey of their NPS using clients (N=100).964 The majority of participants were existing injectors (92%), and the most common reported reason for using NPS was that their friends were taking them (approximately 70%). Of those injecting NPS, the majority injected multiple times a day. The most commonly used NPS were ethylphenidate, synthetic analogues of methamphetamine (e.g. methiopropramine), and mephedrone. Heroin (73%), methadone (49%) and benzodiazepines (51%) were also commonly used in this sample. 20% reported sharing needles, approximately half shared injecting equipment. 22% of participants had stopped using NPS. The most common reason was due to the physical or mental health impact with 54% receiving medical treatment as a result of NPS use

*Summary*

The most robust nationally representative data on NPS use is for mephedrone where CSEW and SCJS have been conducting national surveys since 2010-2011. However, we acknowledge there are a number of limitations to the data on mephedrone use and NPS use in general. For example, though participants may report using a substance (such as mephedrone), names of NPS are used interchangeably with a number of other types of drug therefore there is inherent uncertainty about reported usage of a particular NPS.

Lifetime mephedrone use is relatively uncommon in adults as a whole (approximately 1-2%) but is about two to three times more prevalent in men than women, and also young adults compared with older adults. It appears that prevalence rates of recent mephedrone use are declining substantially, for example the CSEW found a halving of prevalence from 2010-2011 to 2014-2015 in both general adults and young adult samples. Nationally representative data on NPS use as a whole, and on particular NPS other than mephedrone are much less developed, and comparisons across years are not yet possible. Considerable uncertainties thus persist about basic data for monitoring this issue.

Surveys of school children have also found low prevalence for mephedrone use and NPS as a whole. Prevalence rate are higher in older children and in boys compared with girls. Other surveys focusing on a small number of schools in a particular area of the UK differ widely and it is impossible to conclude whether observed variations reflect the particular characteristics of the schools studied, or is reflective of differences in prevalence among particular subgroups of school children, or due to methodological issues.

Data on particular sentinel populations likely to be at greater risk of NPS are growing though remain limited. At present, there are some data on attendees of gay-friendly night clubs where trends in mephedrone use can be assessed. However, the main limitations of such studies regard their generalisability across the UK, and possible impacts on levels of problems. NPS use has also been examined in a variety of other potential sentinel populations such as broader populations of night club attendees, prisoners, homeless people, Psychiatric populations. However, at present, the small number of studies for each population limits the conclusions that can be drawn.

There are also a small number of surveys examining in more detail patterns of NPS use. However, further work is needed to draw firmer conclusions, and for such work to contribute substantially to decision-making.

***Systematic reviews***

The 10 included systematic reviews1035-1044 (as defined under ‘definitions’ within the methods section) are summarized below by NPS type, and in Table 5. The majority address clinical problems/harms due to NPS, with one also including data on clinical management. One was on all NPS, five on synthetic cannabinoids, two on synthetic cathinones and two on phenethylamines.

*All novel psychoactive substances*

Gray *et al.*1038 focused on mental and physical health effects and fatalities due to NPS use among adults with a diagnosis of severe mental illness. 14 studies representing a total of 648 individuals (19 individuals from 12 case studies, 608 from one questionnaire study and 21 from one qualitative study) were included. Participants were mostly males aged between 20 and 35 years. The most commonly reported effects of NPS were on psychotic symptoms (in some cases they were novel in form and content to the patients’ usual symptoms) and on significant changes relating to behaviour, including agitation, aggression and violence. Patients’ vital signs, such as blood pressure, pulse rate and temperature, were also reported to be commonly affected. Gray *et al*.1038 reported one death from the case reports.

**Table 5: Systematic reviews**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Principal Focus** | **Population** | **NPS type** | **Types of included studies** |
| Brewer and Collins1035 | Problems/ harms: Clinical manifestations | Adolescents and adults: age range 12-67 years | Synthetic cannabinoids | Case reports |
| Busardo *et al*.1036 | Problems/ harms: Fatalities | Cases with analytically confirmed presence of  mephedrone | Synthetic cathinone: mephedrone | Case reports |
| Castaneto *et al*.1037 | Use  Problems/ harms: Clinical manifestations | Not specified | Synthetic cannabinoids | Wide ranging including surveys, case reports, series and retrospective case reviews. |
| Gray *et al*.1038 | Problems/ harms: Mental and physical health effects and fatalities | Adults (aged 18 years or over) with a diagnosis of SMI and a history of NPS use. | All NPS | Case reports/ series, qualitative interviews,  explorative questionnaire study |
| Gunderson *et al*.1039 | Problems/ harms: Clinical manifestations | Not specified | Synthetic cannabinoids | Case reports; semi-structures interviews; toxicology laboratory studies |
| Kyriakou *et al*.1040 | Problems/ harms: Clinical manifestations and fatalities | Not specified | Phenethylamines: NBOMe | Not specified |
| Miotto *et al*.1041 | Problems/ harms: physical and neuropsychiatric adverse effects; withdrawal | Not specified | Synthetic cathinones: bath salts | Retrospective studies, toxicology data, chemical analyses studies, and case reports |
| Papanti *et al*.1042 | Problems/ harms: Clinical manifestations (psychosis) | Psychiatric treatment patients; accident and emergency patients; general public calls  toxicology/ poison centres | Synthetic cannabinoids | Retrospective toxicology surveys; case reports/ series; human laboratory studies; interviews/ surveys with synthetic cannabinoids users |
| Suzuki *et al*.1043 | Problems/ harms: Clinical manifestations and fatalities | Not specified | Phenethylamines: NBOMe | Case reports |
| Tait *et al.*1044 | Problems/ harms: Adverse events  Responses: Clinical management (associated treatment of adverse events) | Hospital presentations and poison centre data | Synthetic cannabinoids | Case series (≥10 cases)  Case reports (≤10 cases) |

*Synthetic cannabinoids*

User groups

Castaneto and colleagues1037 included nine surveys on synthetic cannabinoid (SC) use. One study was a world-wide online survey, whilst another was an online survey of online drug forum users. The rest were single country surveys of self-selected individuals (five in the US, including two among military personnel and one among high school students; one in Australia, one in the UK). They reported that the majority of SC users are young adults who perceive SC as safer than non-cannabinoid illicit drugs and a favourable cannabis alternative eliciting a cannabis-like “high” while avoiding detection by standard drug screens. Most SC smokers are men from 13 to 59 years old, many with a history of poly drug use such as cannabis, alcohol, and nicotine.

Side effects

Brewer and Collins1035 summarised 24 case reports (settings and study regions were not specified in the report) with more than 550 cases included. Varied presentations of psychological and physiological manifestations were reported including vague symptoms such as glassy/red eyes, mild diarrhoea, abdominal pain, loss of motivation, insomnia, or difficulty concentrating; and more distinct signs such as agitation, anxiety, nausea and vomiting, hallucinations, paranoia, and profound tachycardia.

Gunderson *et al*.1039 reported on nine studies (five case reports of toxicity, three human toxicology studies evaluating synthetic cannabinoid detection in serum and urine samples, and one semi-structure interview qualitative study among inpatients on a forensic and rehabilitative psychiatric unit) with a total of 28 cases. They reported side effects including alteration in mood, perception, conjunctival injection, xerostomia, increased pulse, hypertension, hyperventilation, diaphoresis, numbness and tingling, nausea, vomiting, tremors, muscle twitching and seizures; and more severe adverse effects including acute anxiety and psychotic reactions, particularly in those with an underlying biologic vulnerability.

Papanti *et al*.1042 reported on 41 studies with more than 2200 individuals with an average age of 23 years and a male/female ratio of more than 3:1. The studies included retrospective toxicology surveys (nine); case reports/case series (25); human laboratory studies assessing the potential acute toxicological effects (four); and interviews/ surveys focusing on self-reported harms/unwanted effects identified in users (three). 11 were carried out in psychiatric treatment settings, five in consultation/liaison psychiatry settings following presentation to the accident and emergency (A&E) departments, two in substance abuse services, and one in a forensic setting. Further, 15 studies were carried out in A&E settings, whereas nine included retrospective toxicology/Poison Centres’ studies analyzing calls concerning a suspected exposure. Reported adverse effects included florid/acute transient psychosis (six studies), persistent psychotic disorder (four studies), and relapse/worsening of a pre-existing psychosis (four studies). Two studies based on exposure calls reported psychotic disturbances in 9.4–11% of the cases, and two studies involving emergency department (ED) patients with analytical confirmation of SC recorded psychotic disturbances in 19–41% of cases. Other psychopathological issues reported in association with SC intake included: paranoid thoughts/combativeness/irritability (nine studies), altered perceptions/mental status (six studies), thought disorganization (four studies), confusion (three studies), agitation/anxiety/ panic attacks/restlessness (nine studies), and depression/ suicidal thoughts (three studies).

Tait and colleagues1044 reported on 106 papers, letters and conference abstracts representing over 4000 cases. They also included ~1900 cases from the USA National Poison Data System for nine months in 2010 in their report. They reported a prototypical presentation ED of a young male (59-100%) with tachycardia (37-77%), agitation (16-41%) and nausea (13-94%). The most frequent cardiovascular symptom was tachycardia; with some cases presenting with chest pain, more severe outcomes including peri-mesencephalic subarachnoid haemorrhage, middle cerebral artery occlusion, myocardial infarction in adolescent males, cardiac arrest. Acute kidney injury was reported in 29 cases in total and all required hospitalization. Generalised tonic-clonic seizures were reported in 4% poison centre SC reports, 14% of ED SC presentations, and 15% of paediatric (0-19 years) poison centre SC reports. Gastrointestinal side effects included nausea and vomiting (13-94% of presentations), and abdominal pain relieved by hot showers similar to the hyperemesis syndromes seen with cannabis abuse. Psychiatric presentation features such as agitation, panic attacks, paranoia and hallucinations were also reported. More severe cases included new onset of psychosis (10 cases reported), in many cases with concurrent use of other substances. These needed hospitalization and symptoms persisted for up to five months, and potentially included affective, suicidal or psychotic symptoms, significant self-injury, catatonic features, and Capgras delusion. SC was reported to potentially worsen existing psychosis due to other causes. Withdrawal symptoms were also reported in two cases. Treatment of adverse effects was reported to be mostly observation and supportive care (intravenous fluids, benzodiazepines, oxygen) with discharge within eight hours.

Castaneto *et al*.1037 reported acute SC intoxication that could lead to ED presentation and hospitalization, requiring supportive care, benzodiazepines, and fluids. While most such patients got released within 24 hours of admission, severe adverse effects such as cardiotoxicity, acute kidney injury, and psychosis resulted in hospitalization for as long as two weeks. Some chronic SC users experienced withdrawal symptoms when they stopped drug intake.

Fatalities

Castaneto *et al*.1037 reported that deaths directly linked to SC use were quite rare (only 4 fatalities identified). Tait and colleagues1044 reported at least 26 SC deaths: 22 (maximum 27) in the USA, three from Europe and one in Japan.

*Synthetic cathinones*

Side effects

The systematic review by Miotto *et al*.1041 included 29 case reports and 11 surveys (the settings and study regions were not clearly identified in the report). They reported the following physical adverse effects: cerebral edema, diaphoresis, hyperreflexia, hypertension, hyperthermia, jaw tension, muscle spasms, mydriasis, myocardial infarction, respiratory distress, seizures, tachycardia, palpitations, chest pain, tremors, nausea, headaches, infections, sweating with distinct acidic odour and negative comedowns symptomatologies. A number of neuropsychiatric adverse effects were also reported including aggression, agitation, combative behaviour, dysphoria, hallucinations, insomnia, paranoia, anxiety, psychosis and suicidal thoughts. Withdrawal has also been reported among bath salt binge users and described as similar to, or more intense than, the withdrawal from other stimulants.1041 Surveyed mephedrone users identify withdrawal symptoms similar to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for stimulant withdrawal.1041

Fatalities

Busardo *et al*’s review1036 of fatalities due to mephedrone included 10 case reports representing 18 fatal cases with analytically confirmed mephedrone in biological sample/s of the deceased. 14 of these fatalities were male, two were female, the gender was unknown in two cases and the average age was 28 years (range: 17-55). Death was attributed to mephedrone intoxication for nine cases (range of post-mortem blood mephedrone concentration: 1.33-22 mg/L). Six cases were deaths due to multiple drug toxicity involving mephedrone (range of post-mortem blood mephedrone concentration: 0.04-1.3 mg/L). Three deaths were attributed to other causes to which mephedrone could have contributed (i.e. vehicular collision; severe self-inflicted injury; adverse effects of this drug, with cardiac fibrosis and atherosclerotic coronary artery disease as a contributing factor).

*Phenethylamines*

Side effects

Kyriakou *et al*.1040 included 14 case reports in total, of which nine reported 17 cases of intoxication (including one case of attempted suicide) due to NBOMe. Only one of these studies had a clearly identified study region/ country which was the United Kingdom. Clinical manifestations of intoxication included serotonergic and sympathomimetic symptoms.

The review by Suzuki *et al*.1043 included 10 case reports, representing 20 individual patients (85% male, average age of 20.3 (range 15 to 31)). The most common adverse effects included: agitation (85.0%), tachycardia (85.0%), hypertension (65.0%), dilated pupils (55.0%), delirium (40%), hallucinations (40%), seizures (40.0%), tachypnea (25.0%) and fever (25.0%). The most common laboratory abnormalities were : elevated creatine kinase (45.0%), leukocytosis (25.0%), hyperglycemia (20.0%), transaminitis (15.0%), and elevated creatinine (10.0%). identified in only three (15.0%) cases. Seven cases were discharged after a short period (<15 hours) of observation, while eight (40.0%) required admission to an intensive care unit. One (5%) required surgery for self-inflicted stab wound.

Fatalities

From the 14 case reports in Kyriakou *et al*’s review,1040 four reported on five deaths. Suzuki *et al*.1043 reported three fatalities.

*Summary*

The literature here categorised as systematic reviews mainly comprises summaries of clinical presentation data. Reported side effects of NPS are wide ranging and include psychological and physiological manifestations, with psychiatric and other neurologic manifestations, and cardiovascular, renal and gastrointestinal being the most reported among cases reported. Treatment of these effects appears to mostly involve observation and supportive care, and in severe cases may involve hospitalization.

An important limitation to the current data is the difficulty of recording hospital admissions that are due to NPS because of a lack of relevant or specific ICD-10 codes to identify these. Further methodological development is needed to improve the monitoring of harms associated with NPS. There are no previous systematic reviews that are concerned with acute health harms in either a population context, including dedicated attention to use prevalence and policy issues, or to or chronic health or social harms in a longitudinal context.

***Qualitative studies of novel psychoactive substance in the UK***

We identified seven qualitative studies (reported in nine papers).888, 945, 1020, 1031, 1045-1049

*Effects of particular novel psychoactive substance*

Mephedrone

Two studies (reported in four papers) focused on the effects and side effects of mephedrone.888, 945, 1047, 1048 Participants were recruited through personal contacts of the researchers and internet forums. The findings from O’Neill1048 combine data from McElrath and Van Hout945 and McElrath and O'Neill1047 therefore the focus will be on the O’Neill1048 paper for this study. They interviewed two samples of mephedrone users in Northern Ireland (study one: n=23 and study two: n=45) with a similar age range (19-51 years and19-49 years respectively). Study two had a higher proportion of males (62%) than study one (48%). Brookman888 interviewed a sample of 12 mephedrone users in Wales with a mean age of 28 years and 75% were male.

Both studies888, 1048 reported similar findings both in terms of subjective effects such as positive feelings (e.g. euphoria and well-being) and physical side effects (e.g. damage to nose from snorting, unpleasant ‘come downs’). Brookman was particularly interested in the effects of mephedrone on crime and violence and therefore reported more data on this subject.888 Just over half of their participants had engaged in acquisitive crime to fund their use and described mephedrone as highly addictive. Violence was also commonly reported: for some this was associated with the ‘buzz’ phase, for others violence was more likely as a result of the ‘come down’ phase, or associated with acquisitive crime needed to fund the drug habit.

Salvia

Dalgarno1046 conducted email interviews with 10 Salvia users recruited from internet forums, 70% were male and aged ranged from 23-38 years. Experiences varied widely, some participants reported no or limited effects of salvia. There are various potential explanations for the unpredictable effects of salvia including its short half-life. Others reported more unpredictable effects, and sometimes they experienced pleasant hallucinogenic effects although not every time they used salvia. Two participants reported some similarities with ketamine although the effects were less predictable.

*Subgroups*

Chemsex

One study1045 conducted interviews of 30 gay men in London in which most (27/30) used mephedrone, typically in combination with GHB/GBL. Their mean age was 36 years, just under half (13/30) were HIV positive. Frequency of use during sex differed among participants; some only used chemsex drugs infrequently with a regular partner, and some only with casual partners. Others engaged in chemsex on almost a daily basis and this had a substantial negative effect on their relationships.

Most commonly, chemsex involved group sexual activity and a majority engaged in more adventurous sexual activity (e.g. ano-brachial intercourse and being anally receptive to multiple men in quick succession) than when they were not using drugs. However, it is unclear whether this led to greater risk of health harm. Although a third reported injecting, all reported the use of clean needles and using safe injection practices.

The most commonly reported harm was risk of overdose, particularly in relation to GHB/GBL use. Many reported dissatisfaction with chemsex in that it led to sexual selfishness. Other social harms were the effect on their employment (missing work due to withdrawal effects and a lack of career development associated with apathy and depression).

Prisoners

There was also one small study of prisoners (four males in a young offenders’ prison) focused on ‘Spice’ (synthetic cannabinoid) use.1020 All four had tried Spice first in prison, after having used illegal drugs outside prison. The main reasons reported for use were not being detected in mandatory drug testing, and also that it made time go quicker. The most common side effects were paranoia, heart racing, and blackouts. All participants reported perceptions of addictiveness of this drug, and that high prices in prison had led to debt.

*Macro-factors influencing novel psychoactive substance use*

O’Brien *et al*.1031 conducted a qualitative analysis based on online interactions with NPS users (N=9) and their responses to open-ended questions (n=93) on an internet forum. NPS users were critical of drug policy, particularly the Temporary Class Drug Order (TCDOs) that were being employed at that time.

O’Neill1048 conducted two qualitative studies of mephedrone users (n=23) and recreational drug users (n=45) in Northern Ireland. Of these samples, five mephedrone users reported lower levels of drug purity and continued availability after legislation prohibiting mephedrone use and supply.

Wallis1049 conducted interviews with retailers and early innovators in NPS use, and also with enforcement professionals, policy makers and Early Warning System representatives (sample size not reported).Participants expected that supply of NPS were unlikely to be affected by the most recent UK legislation (Psychoactive Substances Act 2016) designed to prohibit all NPS. They thought such legislation would be unlikely to effect access through the internet or the fast courier system. Participants also noted a more professional approach to marketing NPS than for traditional illegal drugs including a focus on attractive packaging and branding, with long term demand for particular NPS depending on competition with existing drugs in terms of price and effects.

Internet forums were considered an important channel for communicating information on new drugs, and retailers reported monitoring forums to determine which drugs to stock in their store. Mass media reports were also thought to influence NPS use, with spikes in use of particular NPS receiving attention in the mass media, even when reported negatively as a dangerous drug.

*Summary*

Qualitative studies on NPS use in the UK are at an early stage of development. Existing studies show some potential to provide useful information on issues such as drug effects and reasons for, and patterns of, use. Such data may inform targets for behavioural epidemiological studies. Qualitative studies more generally may also make useful contributions to the study of drug market functioning and policy issues.

***Responses to novel psychoactive substance use and problems/harms***

This section will summarize data from quantitative policy evaluation studies by country. Seven of these studies were conducted in the UK,1010, 1050-1055 five in the USA,1055-1059 two in New Zealand,1016, 1060 one each for Australia,118 Finland1061 and the Republic of Ireland.1062 The study characteristics including country, intervention/ response, study setting, publication type, NPS type and study design are summarized in Table 6 below. There was also one study where the country was not specified. Sixteen of these studies were on legislative control, and one was on a multi-pronged approach that included surveillance and reporting, in addition to law enforcement and legislative changes.1059

**Table 6: Characteristics of and results from quantitative policy evaluation studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study**  **Country** | **Setting**  **Publication type** | **Intervention** | **NPS type** | **Study design** |
| Brown *et al*.118  Australia | Poisons Centre  Conference abstract | 9 June 2013 legislation and enforcement by state and federal governments to restrict the sale of synthetic cannabinoids. | Cannabinoids | Before and after comparison through retrospective review of Poisons Information Centre Data (5 months prior and five months after ban) |
| Christie and MacFarlane1060  New Zealand | Addiction treatment setting  Letter to Editor | May 2014: Ban of NPS under the Psychoactive Substances Act | Cannabinoids | Before and after comparisons (12 month before and 12 months after) |
| Dargan *et al*.1050  UK | Community setting  Peer reviewed journal article | December 2009: The classification of synthetic cannabinoid receptor agonist constituents of Spice were as Class B in the UK | Cannabinoids | Before and after comparison using product purchased from legal high websites |
| Kriikku *et al.*1061  Finland | Police custody: driving under the influence of drugs; toxicology unit: autopsy cases  Peer reviewed journal article | Ban of 3,4-methylenedioxypyrovalerone (MDPV) in June 2010 | Cathinone: MDPV | Before and after comparison |
| Loeffler *et al*.1055  USA and UK | Poison centre  Letter to the Editor | The 21 October 2011 temporary federal  ban on a number of bath salt compounds-USA  April 2010 mephedrone ban in the UK  April 2012 ban on methoxetamine in the UK | Cathinones: bath salts; mephedrone  Methoxetamine | Before and after comparison using data from national poison  control centers (PCC) |
| Pettie *et al*.1051  UK | General hospital inpatient setting  Conference abstract | 10 April 2015 control of methylphenidate-based NPS by the UK government under the Misuse of Drugs Act 1971 (Temporary Class Drug) Order | methylphenidate-based NPS | Before and after comparison using hospital admissions data |
| Plumb *et al*.1056  USA | Poison centre  Conference abstract | A state law making spice illegal | Cannabinoids | A retrospective chart review: Before and after comparison |
| Reuter1057  USA | Setting: not applicable  PhD thesis | 2011 legislation criminalising the possession of ingredients used in the production of synthetic drugs | Cathinones: bath salts | Before and after comparison. |
| Ryan and Arnold1058  USA | Poison centre  Conference abstract | Control of six cathinones under Schedule I in Louisiana on January 6, 2011 | Cathinones | Before and after comparison through secondary analysis of the National Poison Data System (December 2010 - month prior; and February 2011- month after ban) |
| Sheridan *et al*.1016  New Zealand | Internet  Peer reviewed journal article | Prohibition of BZP-containing  party pills and related substances from 1st April 2008  (provided for a six-month  amnesty period in which possession of small quantities for personal use was permitted) | Piperazines: Benzylpiperazine (BZP) and related substances | Before and after comparison through an internet based survey among adults aged 18–30 years |
| Smyth *et al*.1062  Republic of Ireland | Specialist alcohol treatment service: Youth Drug and Alcohol service  Peer reviewed journal article | 2010 legislative changes in Ireland- adding over 100 NPS onto the Misuse of Drugs Act, and restrictions on sell of psychoactive substances. | All NPS | Before and after comparisons (before: six months prior 10 May 2010; after: six months prior 10 May 2011) using data from the National Drug Treatment Report System |
| Wahl and Theobold1059  USA | Poison centre  Conference abstract | A multi-pronged approach of surveillance, reporting, law enforcement partnership and legislative changes | All NPS | Before and after comparison with national averages |
| Winstock *et al.*1052  UK | Internet survey  Letter to editor | April 2010 classification of mephedrone and similar compounds as Class B substances in the UK under the Misuse of Drugs Act | Cathinone: Mephedrone | Before and after comparison: Findings from an online survey conducted in June 2010 compared with those from one in November,  2009, and another telephone survey in 2010 before the legislation |
| Wood *et al*.1053  UK | Emergency Department (ED)  Conference abstract | Control of cathinones under the UK Misuse of Drugs Act, 1971 on the 16th April 2010 | Cathinones: mephedrone | Before and after comparison through secondary analysis of ED data. (eight months each side) |
| Wood *et al.*1054  UK | ED  Peer reviewed journal article | Control of cathinones under the UK Misuse of Drugs Act, 1971 on the 16th April 2010 | Cathinones: mephedrone | Before and after comparison through secondary analysis of ED data. (12 months each side) |
| Wood *et al*.1010  UK | Nightclubs (gay-friendly)  Conference abstract | Control of methoxetamine under the Temporary Class Drug Order (TCDO) legislation in March 2012. | Methoxetamine | Before and after survey comparison (July 2011 and July 2012) |

*United Kingdom*

Dargan *et al*.1050 evaluated the impact of the December 2009 classification of synthetic cannabinoid constituents of spice as Class B on the components in ‘Spice’ products. They purchased 16 and 20 spice products from online sources before and after the classification respectively. They found that classified synthetic cannabinoid receptor agonists continued to be supplied over the internet to UK users. The proportion of spice products that were purchased online containing at least one classified synthetic cannabinoid fell to 85% of all pre-classification sources. Furthermore, new synthetic cannabinoid receptor agonists not covered by the legislation appeared after legislative controls.

In April 2010 cathinones such as mephedrone and similar compounds were classified as class B substances under the UK Misuse of Drugs Act, 1971. In their online survey of 150 mephedrone users, Winstock *et al*.1052 found a decrease in the number that continued to use mephedrone after classification. There were also changes in access to, and sources of mephedrone, with a 40% increase in purchases from dealers and a significant increase in the mean price per gram of mephedrone from £10 to £16. Loeffler and colleagues1055 reported a decrease in the number of poison control centre contacts regarding mephedrone. Wood *et al*.1053 reported a reduction in the levels of presentations to the emergency department with toxicity associated with self-reported mephedrone use from 57 in the eight months before the reclassification to 47 in the eight months after. In another study, the level of presentations fell significantly in the first six months following reclassification to a steady level of three to five presentations every two months in months 7-12 following reclassification.1054

Loeffler and colleagues1055 reported a decrease in the number of poison control centre contacts regarding methoxetamine after its ban in the UK in April 2012. On the other hand Wood *et al*.1010 reported a significant increase in life-time, last year and last month use of methoxetamine from 2011 to 2012 among emergency department attendees (Life-time 2011: 6.1% vs 2012: 21.0%, p < 0.001; Last year 2011: 4.8% vs 2012: 19.2%, p < 0.001; Last month 2011: 1.9% vs 2012 10.1%, p < 0.0001) after its control under the Temporary Class Drug Order (TCDO) legislation in March 2012. Data was collected via two non-randomly sampled surveys, with 315 respondents in July 2011 and 330 respondents in July 2012 respectively.

A study by Pettie and colleagues1051 evaluated the impact of the 10 April 2015 control of methylphenidate-based NPS by the UK government under the Misuse of Drugs Act 1971 TCDO. They found 290 drug-related admissions in the six months before and 263 in the six months after control for all substances. Admissions associated with NPS decreased from 192 (66% of total admissions) pre-control to 135 (52%) post-control. Methylphenidate-NPS related admissions reduced significantly from 88 pre-control compared to 8 post-control. However, synthetic cannabinoid admissions increased from 22 patients beforehand, to 60 patients after the legislation, as did stimulant NPS admissions (methiopropamine and cathinones), from 12 to 27. Hospital admissions associated with opioid (heroin, dihydrocodeine, methadone) toxicity increased from 83 (29%) to 109 (41%) after control. Benzodiazepine admissions also increased from 17 to 37 cases in the two months before and after legislation.

*USA*

In their study evaluating the impact of the October 2011 temporary federal ban on a number of bath salts (synthetic cathinones) in the USA, Loeffler *et al*.1055 found that the ban resulted in a decrease in the number of poison centre contacts regarding mephedrone and bath salt compounds. Reuter1057 examined the 2011 legislation criminalising the possession of ingredients used in the production of synthetic drugs using Arizona poison control data and found that bath salt use decreased following criminalization. Control of six cathinones under Schedule I in Lousiana on January 6, 2011 was reported to have resulted in a 94.5% decrease in the number of synthetic cathinone calls to the Louisiana Poison Center from 110 to 6.1058

A conference abstract by Wahl and Theobold1059 reported that a state-based multi-pronged approach of surveillance, reporting, law enforcement partnership and legislative changes for all NPS resulted in a decrease in cathinone derivative exposure from 11% higher to 59% below the national average during a 25 month surveillance period. Exposure to cannabinoids also decreased from 30% higher to 78% lower than the national average during the same period.

Plumb *et al*.1056 reported on a state law making spice illegal that resulted in significant decrease in the rates of synthetic cannabinoids exposures reported to the poison centre from 16 months before to 13 months after the legislation.

*New Zealand*

On the 1st of April 2008 benzopiperazine (BZP) containing party pills and related substances were prohibited in New Zealand. The prohibition provided for a six month amnesty period in which possession of small quantities for personal use was permitted. A study by Sheridan *et al*.1016 examined longitudinally the effect of prohibition on use in 273 participants. They found that overall the use of BZP party pills significantly decreased over time. However, both time points of the survey were after the ban (the first survey included retrospective questions for use 6 months previously). Christie and MacFarlane1060 reported a reduction in presentations for clinical management of synthetic cannabinoid effects in an addiction treatment setting from 47 in the 12 months before the May 2014 ban of NPS under the Psychoactive Substances Act, to 24 in the following 12 months.

*Australia*

In Australia Brown *et al*.118 reported a reduction in the number of synthetic cannabinoid cases reported to the poison information centre from 70 in the five months prior to June 2013 legislation and enforcement by state and federal governments to restrict their sale to 20 cases in the following five months.

*Finland*

Kriikku *et al*.1061 reported that the number of 3,4-methylenedioxypyrovalerone related driving under the influence of drugs and autopsy cases decreased markedly after its ban in June 2010.

*Republic of Ireland*

In 2010 legislative changes in the Republic of Ireland resulted in over 100 NPS being added onto the Misuse of Drugs Act, and restrictions on the sale of psychoactive substances. Smyth *et al*.1062 conducted a before and after comparison (before: 6 months prior 10 May 2010; after: 6 months prior 10 May 2011) using data from the National Drug Treatment Report System. They reported a range of reductions in presenting substance use with the exception of NPS oral pills. Lifetime rates of use were similar between the two periods.

*Summary of findings*

Most studies presented here evaluated the effects of legislative prohibitions of NPS use or supply on a wide range of outcomes including access, use, healthcare utilization and self-reported exposure and toxicity. Positive outcomes are generally observed, though studies typically utilized simple counts of routinely collected data, particularly poison centre and hospital admissions data. The study designs were mainly before and after comparisons without any controls which makes attribution of effects difficult. There is a need to examine the utility of routinely collected NPS data in different settings and sources of information bias, and to evaluate pharmacovigilance and other data. This will allow more rigorous study designs capable of assessing major policy changes.

**Conclusions**

***Main findings***

The main finding is that the literature on NPS use, problems and responses is currently at a very early stage of development in being capable of informing public health decision-making. Nationally representative surveys on prevalence are available for the UK. However, the most comprehensive data is on mephedrone, with data on NPS use as a whole, and on particular NPS other than mephedrone being much less developed, and comparisons across years not yet possible. Data on reasons for, and patterns of, use is largely limited to a small number of qualitative studies.

For problems or harms due to NPS use we identified a large number of case reports/case series of acute intoxication, toxicity, emergency presentation or similar data. There were also 10 systematic reviews of this literature which mostly reported psychiatric and other neurologic, cardiovascular, renal, and gastrointestinal adverse effects whose treatment was mostly observation and supportive care. There are also limited data on subjective adverse effects of NPS use from few qualitative studies. Literature on acute health harms in a population context is also limited, as is literature on adverse effects due to long term regular NPS use and chronic health or social harms in a longitudinal context.

We identified studies evaluating the effectiveness of regulation or prohibition of NPS possession or supply. 17 of these studies were quantitative evaluation studies: 16 of which evaluated the effects of legislative prohibitions of NPS use or supply, whilst one evaluated a multi-component intervention comprising surveillance, reporting, law enforcement partnership and legislative changes. Overall the studies reported generally favourable effects on a number of outcome including access, use, healthcare utilization and self-reported exposure and toxicity. However, most outcomes were simple counts of routinely collected data (poison centre/ hospital admissions data) and all studies were before and after comparisons without any controls, which makes rigorous attribution of changes to intervention effects challenging.

***Strengths and limitations of the study***

*Strengths*

This study utilized a multi-staged multipronged analytical approach summarized in Figure 14 below. This involved the development of a conceptual framework hypothesising an evidence-informed public health approach to novel psychoactive substance use in the UK (*see Chapter 3*); and systematic review work which comprised a scoping review evidence mapping stage, evidence gap analysis in relation to *a priori* research questions and a narrative presentation/synthesis of four selected bodies of literature. Two researchers independently selected articles and extracted data in-order to minimize selection bias and errors in data extraction. The findings of the scoping review were interpreted in light of the conceptual framework. Together these strands of conceptual and empirical research were used as the basis for a set of research recommendations. Although the review and conceptual framework findings were quite distinct, the analytical approach afforded high level integration of findings, with the main observation being that the existing literature does not resemble what we think may be needed for an evidence-informed public health strategic approach, and there is a reasonable level of support for our view in the research recommendations made in the existing studies themselves. In addition to what is presented in Figure 14, the findings of the review work, conceptual framework and the draft research recommendations derived from these were shared and discussed with one NPS user and five user carers (who attended a group discussion at a face-to-face user carer forum), four policy makers and five researchers (who constituted the project steering group *(see Chapter 4)*). The feedback from these three groups were utilised to refine and finalize the research recommendations (*see Chapter 5*). It is intended that this analytical approach, and the transparency with which it is presented, has enhanced the validity and rigour of the research recommendations drawn from this work, as well as their relevance to the UK context.

**Scoping review and narrative synthesis**

Evidence map

Evidence gap analysis

Narrative synthesis

**Conceptual framework development**

1

2

**Research recommendations development**

Development of empirical research recommendations based on scoping review and narrative synthesis

Development of conceptual framework based research recommendation

1 = Interpretation of scoping review and narrative synthesis findings in light of conceptual framework

2 = Planned revision of conceptual framework in light of the systematic review findings

**Figure 14: Overarching analytical approach**

*Limitations*

Risk of bias assessment was not conducted because of the large number of articles identified. Besides the size of this literature however, the areas covered by this review that were not already covered by systematic reviews were judged not to have adequate study numbers and/or study quality and/or study findings sufficient to warrant a systematic review. The study designs, in most cases, were such that it is difficult to establish the nature of relationships between NPS use and problems/ harms, or responses to NPS use and outcomes. This was also a pragmatic decision, made whilst being mindful of time pressures, and in light of the need to undertake this work quickly in order to be as useful as possible.

***Possible implications for research recommendations***

There are a number of evidence gaps identified in the scoping review and narrative synthesis. First, there are a number of areas where literature is scarce (*a priori* research questions 2, 3, 5-10 and 12). Second, even in those areas where some literature was identified, at a high level of generality, existing studies are not sufficiently well advanced to be able to meaningfully inform public health approaches to NPS use. For example, there is need for epidemiological research on acute health harms (i.e. undertaken in a population-at-risk context), as well as on chronic health and other health and social harms due to regular NPS use. There is an obvious need for more rigorous study designs capable of assessing major policy changes. In addition, there is a need to examine the utility of routinely collected NPS data in different settings, and pharmacovigilance data, including sources of information bias.

**Chapter 3: What might an evidence-informed public health approach to novel psychoactive substance use in the UK look like? A conceptual framework**

**Background**

There has been increasing international concern about the use of novel psychoactive substances (NPS), also known as “legal highs”.1063 NPS can be defined as narcotic or psychotropic drugs not currently controlled under the United Nations drug control conventions.987, 1064-1066 The principal drug types currently identified in the UK are presented in Table 7. The number of new substances reported annually to the EU Early Warning System increased seven-fold between 2008 and 2013.1067 Some NPS may be structurally similar to other known drugs, whereas others may be quite different. Nonetheless, many NPS have been previously synthesised and are therefore newly available, popular or ‘rediscovered’ rather than newly created as such.987, 1068 It is thus appropriate to question the precise meaning of the term, and the value of such a category.

**Table 7: Main NPS Types**

|  |  |  |
| --- | --- | --- |
| NPS type | Description | Example(s) |
| Synthetic cannabinoids | Chemicals often with similar molecular structure to Δ9- tetrahydrocannabinol (THC – the main psychoactive component in cannabis), and can also refer to the chemicals with different structures but similar effects. Effects: similar to cannabis. | ‘Spice Gold’ |
| Synthetic cathinones | Related to cathinone, a monamine alkaloid and a key stimulant in khat. The most common synthetic cathinone used as an NPS has been mephedrone. Effects: stimulant similar to amphetamine, cocaine and MDMA (‘ecstasy’). | ‘m-cat’ (mephdrone), ‘mexe’ (mexedrone) |
| Phenthylamines | Broader class of stimulants and hallucinogens, including mescaline, amphetamine, and MDMA. NPS used include benzodifurans and the 2C series. Effects: stimulant, hallucinogenic and/or empathogenic. | ‘Bromo-Dragonfly’, ‘FLY’ |
| Piperazines | Class of synthetic chemicals within a piperazine functional group. NPS include BZP (used extensively in New Zealand in the early 2000s as a legal and reliable alternative to MDMA) and *m*CPP. Effects: euphoric, similar to MDMA. | ‘party pills’, ‘smileys’ |

**Sources: EMCDDA, UNODC.**

Note: Definitions of NPS vary and Gamma-Hydroxybutyrate (GHB) and Ketamine are sometimes included. They are excluded here because they are extensively legally controlled and are not recently synthesised.

NPS have posed challenging problems for policy makers. They have become widely available through the internet at low cost, and their legal status can carry connotations of safety before they are made illegal to possess.1064, 1069 Technological developments and globalization of trade and communications have facilitated major innovations in drug production and supply.11 Refinements can be made to the design of synthetic mood altering drugs rapidly, in response to consumer demand, and produced and shipped on an industrial scale. The United Nations Office on Drugs and Crime has accordingly declared that “the international drug control system is floundering”.987 For the UK, the most obvious demand to date has been among existing drug users who have extended their repertoires, rather than the recruitment of new populations.1070 Nonetheless, the UK Government’s Advisory Council on the Misuse of Drugs has identified this phenomenon to have “changed the face of the drug scene remarkably and with rapidity”.1071

Concerns about the future is prominent in discussions of NPS, including possible epidemics of dangerous drugs, as well the health harms consequent on long-term use of less risky drugs.987, 1064, 1065 It is widely perceived that the most strongly evidenced public health approaches to psychoactive substances in general (controlling affordability through pricing and other demand reduction strategies, and regulating supply and other dimensions of availability such as cultural acceptability for tobacco, alcohol and illicit drugs) are inapplicable to NPS, leaving little capacity for evidence-based responses.1072-1076 For these reasons, we undertook a conceptual exercise that sought to elaborate what an evidence-informed public health approach to NPS use in the UK might look like.

**Methods**

This work was done iteratively in two main stages. We began with discussions about the nature of the phenomenon, as reflected in the preceding text. This process informed pragmatic decisions about literatures that might be helpful to consult, and we chose to consider the evidence bases on tobacco, alcohol and illicit drug use, and developments in drug policies. We discussed the nature of contemporary public health and possible similarities between NPS and other complex multi-sectoral and public health challenges, particularly in how they were conceptualised and strategically approached. We then developed a preliminary version of a hypothetical public health approach to NPS based on the literature examined and our interpretation of possible relevance. From this we identified possible research data needs to complete the first stage of this work. We then utilised this Stage 1 version to interpret the data from the review.

The review findings indicated that the existing literature, although large, is at an early stage of development, and there is currently meagre data to inform directly what we hypothesised to be an evidence-informed public health strategic response to NPS. The conceptual framework itself was thus not significantly altered in Stage 2. The main changes related to the Discussion section, where we substantially revised our interpretation of the possible implications of the framework given the review data.

**Results**

***The changing context of developments in drug policies***

Legal prohibition of drug possession has been the cornerstone of the societal response to illicit drugs for a century.1077 Although a public health approach to drugs is often counterposed to that of law enforcement, this can be regarded as a false dichotomy, as the illegality of drugs can in certain circumstances raise prices and restrict availability (both generally effective approaches for addictive behaviours), and reduce use and associated harms.1074 In addition, treatments such as opioid substitution treatment can reduce crime.1074 While initially introducing temporary class drug orders to rapidly bring individual NPS under legal control, the UK Government has decided to follow Ireland by making all psychoactive substances illegal to produce and supply, without prohibiting possession or considering potential harm.1078

Decriminalisation of drug use, and other recent global policy innovations including the quasi-legalization of cannabis production and supply in some US states and Uruguay1079, 1080 provide another context for thinking about NPS. Data are beginning to emerge on the effects of these policy changes,1081 though rigorous evaluation studies are needed. The use of drugs remains a controversial and difficult issue for society, though seemingly not as difficult as it once was.1082-1086 The goals of drug policy are now less contested, as there is greater recognition of the limitations of sole reliance on prohibition, and more willingness to address tobacco, alcohol and drugs together.1086 Use reduction is now more widely accepted as a vehicle for harm reduction, reducing problems among users, and those directly and indirectly affected by drug use, as well as reducing the overall societal burden.1076, 1084

***Contemporary evidence-informed public health***

The history of public health has been strongly influenced by the growth of scientific knowledge, the rise of the welfare state, and an increased focus on lifestyle risk factors in recent decades.1087-1089 The evidence required to inform any public health approach is to some extent determined by how public health itself is defined. Contemporary definitions highlight the improvement of population health and wellbeing.1090, 1091 The underpinning rationale for strategic public health approaches which move the entire population distribution of risk in a more healthy direction was based on data showing that a large number of people at lower risk can often result in greater health burden than a smaller group at higher risk (the prevention paradox).1092, 1093 In addition, individual or group behaviour is usually socially influenced and thus contextually dependent, so modifying population factors underlying the risk distribution may be more effective than seeking to encourage high risk individuals to act against social norms, both for those at high risk and for the rest of the population.1092, 1093

Many contemporary public health challenges have been conceptualised as requiring complex adaptive system changes.1087, 1089 Mehta and colleagues provide a useful example of how contemporary thinking on public mental health can draw upon well-established ideas such as the biopsychosocial model of health, and about levels of prevention, in addressing such complex challenges.1094 Complex challenges often require careful attention to future risks which are somewhat unpredictable in scale, and are likely to impact differently on different groups,1095 rather than current harms. For example, frameworks for responding to the health impacts of climate change highlight the importance of building the evidence-base through surveillance of morbidity, mortality and health system indicators, and modelling trend data for future risks including contextual factors impacting on risk of harm.1096, 1097

The social ecological framework offers one way of thinking about complex public health issues.1098 This also encourages multi-level conceptualisations of problems, and invites multi-level strategic responses.1099 For example, risk behaviours and intervention targets can be understood as shaped by interactions between the micro- (e.g. family, school, neighbourhood), meso- (interactions between the different micro-systems), exo- (systems that impact on the micro-system such as worksite policies) and macro- (cultural values, norms and laws) levels.1100

Obesity is another example of a socially structured public health challenge where risk differs substantially between groups in a given population, which may also be facing a malnutrition problem.1101 Relevant unhealthy behaviours cluster, particularly among more socio-economically deprived populations. The WHO Commission on childhood obesity uses a multi-level social-ecological approach to identify the need for interventions targeted at contextual factors such as political (e.g. fiscal policy), built (e.g. urban planning and design), social (e.g. norms in different groups), and family (e.g. parental knowledge, norms, behaviour) environments. In addition they recommended a life-course approach arguing that the key contextual risk factors that impact on obesity differ through the life-course.1102 Targets for prevention thus need to be conceptualised at environmental levels, and in long term individual developmental perspectives.

***Towards a hypothetical prevention systems approach to novel psychoactive substances***

We make a number of assumptions here, and will revisit them to interrogate their validity. We hypothesise that the challenges posed by NPS share many of the features of the complex problems previously discussed. Hypotheses on NPS can also take advantage of the conceptual frameworks already developed for other drugs.1072, 1076 Figure 15 provides a conceptual map of key individual-level risks and harms due to NPS adapted from those developed for other forms of drug use, and incorporating an overarching biopsychosocial perspective. Apart from the acute effects, most forms of harm develop over time. Beyond potency and toxicity, harms to individuals, whether they are health-specific or wider harms, will be strongly shaped by environmental and contextual influences, dynamically interacting with lifecourse stages. Prevention therefore has potential to interrupt the evolution of harm over time, and this is insufficiently recognised.1103 Intervention targets for prevention extend far away from those that are proximal to acts of drug use, as attention is warranted to social structural influences that shape individual risk. Other drug use, both licit and illicit, should be expected to be implicated in the production of harm where other drugs are being used, and it will be rare that none are.

**DRUG FACTORS**

Particular substance;

Other constituents;

Does/amount;

Patterns of use (with other substances);

Route of administration

**SUPPLY FACTORS**

New substances;

New technologies;

Online distribution;

Legal controls

**DEMAND FACTORS**

User characteristics (e.g. sociodemographic and psychosocial characteristics including reasons for use)

**Wider harms** **Health-specific harms**

Examples:

Arrests;

Interpersonal conflicts

**Time/ Risk**

Examples:

Injury;

Acute toxicity

Long term regular use

Episode of use

Short term regular use

Examples:

Occasional mental health problems

Examples:

Interruption to social roles;

Relationship problems

Examples:

Dependence;

Physical health problems;

Enduring mental health problems

Examples:

Poverty;

More enduring adverse effects on employment and relationships

**Figure 1: A model of risks and harms due to NPS use**

Problems also manifest themselves at levels beyond the individual user, for example involving family members and local communities.1104, 1105 Harms to society, for example, include the costs of health care, crime and law enforcement.1106 Health impacts incurred by NPS users can be aggregated with measures of physical and/or mental health, lost Quality Adjusted Life Years (QALYs), and by applying a monetary value to QALYs lost. Impacts upon education among young people can lead to adult employment and economic productivity harms, to which an economic cost can be attributed.

Box 1 provides a thought experiment. There are no obvious problems with NPS use, and one possibility is that there is no role for public health responses, and the Smith family just get on with their lives. Alternatively, we suggest that a prevention orientation, informed by appreciation of risk generation over time, offers the most appropriate long term public health response. This suggests the need to intervene environmentally, and early, in order to prevent harms, which may develop to become more widespread and more intractable in the absence of prevention.

**Box 1: A portrait of NPS use in “the Smith Family”**

|  |
| --- |
| The Smiths (father Peter, mother Jane, 18 year old son Tom, 16 year old daughter Karen, and 14 year old son Jack) are an unremarkable family. Both parents work locally and receive family credits to supplement their incomes. The children are doing OK at school, and the school itself is not bad. Tom doesn’t know what he will do after leaving school next summer and Karen is thinking about going to college. Outside school they do the same things as their friends; Tom plays football, Karen plays computer games and spends a lot of time online, and Tom and Jack are into music. They’re comfortable in their home, which they part-own, and live in an area that used to have a problem with burglaries.  There are no big health problems in the family. They are not into sports or exercise, apart from Tom. Peter drinks more alcohol than is good for his health though definitely wouldn’t consider himself an alcoholic, or feel comfortable talking to his GP about his drinking. He misses work occasionally on Mondays. Jane has times when she is depressed, for which she takes medication. She drinks occasionally and gave up smoking 5 years ago.  Tom does not smoke. He usually goes to nightclubs at the weekend, where he takes drugs that are sold to him and his friends as ecstasy and mephedrone. He also usually drinks alcohol in bars before going on to clubs. Karen smokes a few cigarettes each day and has a joint most days. She smokes herbal cannabis and sometimes spice, a synthetic cannabinoid with her 18 year-old boyfriend and his friends. She tends to smoke spice when they are out of cannabis or when they hear it is particularly good. Her mum worries about her. The group she smokes with have a reputation for getting into trouble. Jack has got really drunk twice, and drinks alcohol only at parties with his friends. Jack hasn’t used any drugs because, he says, he doesn’t like smoking, and has heard bad things about pills and powders. |

Table 8 offers a presentation of how a systems-based prevention approach may be applied in this situation. This presentation is illustrative, as it is also possible to conceptualise levels differently, for example separating family and peers, in such a system. Note there is no compelling logic to any NPS only response, as factors that impact on NPS use do not appear to differ from those that impact on the use of other drugs. Interventions may be designed to target a single level (e.g. family), and may be effective in so doing. Their effectiveness, however, will be limited by the influence of variables in other levels of this system, which is important to assess for intervention decision-making. This presentation calls attention to the adequacy of existing responses and their longer term consequences, as decisions not to intervene, or to intervene weakly will also have consequences that should be considered.

**Table 8: Examples of public health opportunities for responding to risk**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **National** | **Local** | **Family & peers** | **Individual** |
| **Health** | Health services and public health policies; tobacco control policies | Local health service provisions and public health actions | Parental general practice and other NHS contacts; peer network intervention projects; health promotion campaigns | NHS contacts (eg general practice, sexual health services, A & E); Online and telephone helplines; counselling services |
| **Multi-sectoral** | Housing, employment, education and welfare and economic policies; drug and alcohol policies | Policing, education, community development, licensing and other local authority policies and services | School drug education; youth services provisions; family support services; community groups | School mentoring & counselling; criminal justice system contacts |

How well does this approach address health inequalities issues? This is important to consider explicitly as whole population approaches have been shown to alter the shape of the distribution of risk within a population as it moves to the left (i.e. less risk for the population as a whole but greater absolute or relative risk in sub-groups) as has happened for example in relation to tobacco.1107 This happens because those with more psychosocial resources for health gain greater health benefits than those with fewer resources, for whom such inequalities exert pervasive health effects.1107 It is also well established that problematic drug use is more concentrated in deprived communities.1108-1110 This consideration suggests the need for an integrated strategy of multi-level whole population and vulnerable sub-population interventions that address the environmental causes of the distribution of risk within populations. Capacity to incorporate attention to health inequalities and their associated social determinants at the local level may already exist due to the devolved nature of UK public health system.1111

***A priori data needs***

Having considered hypothetical determinants of NPS use, risk and harm, and the breadth of possible responses, attention is warranted to the empirical data needed to inform public health decision-making. Acute health and wider problems will be experienced following particular episodes of use, most likely connected with intoxication or direct poisoning (*see Figure 15*).1074 Presentations to health services and community safety indicators may provide data on trends in potency and toxicity of NPS, taking account of possible sources of information bias in existing routine monitoring systems. Chronic mental health, physical health and social problems may develop over the longer term as a consequence of regular use, with risk accumulating over time as involvement in drug use continues. Where drug use escalates, and consumption become heavier, risks will accumulate faster.1072 Existing routine data sources are quite likely to be relatively insensitive to changes in patterning of risks, and prevalence and incidence of harms, unless they become severe. Dedicated research studies or highly sophisticated monitoring approaches may be more likely to be needed to provide more fine grained investigations of these sorts of issues.

This discussion has largely avoided disaggregating the category of NPS, as the points made may be seen to apply with greater or lesser force to all NPS drugs. Dedicated attention is also needed for individual NPS drug types, as the public health burden associated with each will vary according to the harms that are consequent on their use, and use prevalence. Capacity to early identify new NPS, particularly those that are more potent or more toxic, and to track their spread, is foundational to appropriately calibrating the required responses. Indeed distinctions between NPS and existing drugs may be expected to reduce over time, with particular NPS drug types considered alongside more established drugs if and when they become more prevalent.

Gradual deterioration of organ function due to toxicity may be a key biological mechanism involved in stable longer term patterns of use and this will be difficult to detect early in all but the most severe instances. The development of dependence may occur at different rates for different drugs and patterns of use,1112 though it is largely driven by extent of involvement in drug use.1113 Dependence may occur in isolation from other psychosocial difficulties, though this is rare in addiction treatment populations.1114 Dependence itself is also an important mediator of other harms.1074 Scrutiny of routine health services data will be useful for examination of trends in dependence and other presenting problems,1115 and will quite likely need to be supplemented by dedicated studies that capture population data on the prevalence of dependence and other problems.

There are two key issues revealed by this preliminary consideration of data needs. Firstly, existing data sources are likely to be profoundly biased, towards both severe and episodic problems, and less likely to be directly informative about patterns of use, risk and harm in the general population over the longer term. Secondly, it is assumed that NPS use is identifiable, either as a result of self-presentation or toxicology, provision for which will vary importantly across settings. There may be many circumstances in which this is problematic, for example when episodic or regular use occurs alongside other drugs and/or when it is not clear what the cause of the problem may be or the contribution of NPS to it. NPS markets may be thought of as more complex drug markets, where products may be branded without there being any necessary correspondence to contents, and consumers may be more willing to accept unbranded and unknown content. As part of an effective pharmacovigilance system, simple case finding approaches may need to rely in the first instance on generic screening tools for drug use, which appear effective for other forms of drug use, prior to more in-depth drug use assessment.1116 Again data from healthcare services and other sectors will identify NPS use where it is most obvious, and be vulnerable to missing the contribution that NPS use makes to other presenting problems (e.g. mental health). Communicating the risks associated with particular NPS drug types poses challenges even when such data are in place.

Basic epidemiological data on the prevalence and incidence of NPS use and problems may be difficult to obtain in a timely manner due to rapidly changing trends, hence the prominence of toxicological surveillance and the development of “early warning” systems in the existing first wave of responses to NPS.987, 1067, 1117 Qualitative and quantitative studies investigating patterns of use in potentially important sub-populations (such as homeless people, those with serious long term mental health problems, and prisoners), or derived from emergency healthcare presentations, can be informative on issues such as constituents, doses and other drugs being used simultaneously.995, 1118 The more such studies give rigorous attention to sampling the more straightforward will be consideration of generalisability.

NPS data collection can be added to existing large population cohort studies.1119 “Prevention systems” approaches,1120 as hypothesised here to be relevant to NPS, require strong health services research investment in attention to both NPS and indeed in drug use more broadly. Observational studies of the actual operation of prevention systems, with robust designs capable of identifying key characteristics associated with effectiveness are needed, as are evaluation studies of any innovations.1115

Consideration of NPS data needs also calls attention to scrutiny of the adequacy of existing drug research infrastructure. The past year prevalence of ecstasy use declined among 16 to 24 year olds from approximately 6.8% in 2001/2 to average approximately 3.8% over the past five years.1070 It is not known to what extent, if any, this may be due to NPS use and/or whether other factors may be responsible for this fall. There have also been reductions in the prevalence of alcohol consumption among young people across the world,1121 and a similar question could be posed. We suggest that consideration of the need to build the NPS evidence base should examine such inter-relationships, and give attention to research capacity for drug and alcohol research more generally.

***Validity issues***

We now offer a brief assessment of the validity of the underlying assumptions, and discuss some study implications. We suggest there are five key logical steps taken in building this framework for which counterfactual reasoning can be applied as follows:

1. NPS are not in fact like other drugs; there is something different about them.
2. The complex systems conceptualisation is not appropriate for NPS.
3. The lifecourse approach is inapplicable to NPS.
4. The prevention system can’t or won’t operate in the way proposed; the multi-level contribution of system elements is unattainable even if desirable.
5. A high risk population approach only may be preferable as it is easier to implement.

Steps 1-3 are dealt with together because individually and collectively they are foundational to much thinking in contemporary public health. It is either implausible that they are true, or it is the case that existing public health evidence and ideas are much weaker than they seem. We prefer the former explanation. Although production, distribution and retail of NPS may have features which distinguish them from other drugs, in other respects the user populations and drivers of demand and supply are similar, and in the future they may be even more so.

There are, of course, likely limits to the extent to which approaches for NPS can be informed by comparisons with addressing challenges such as public mental health, climate change or obesity. Perhaps this is less true of drawing on thinking about other forms of drug use, though a key weakness in the latter is that arguably too much of existing thinking about risk and harm occurs at the individual rather than the population-level (reflecting the historical development of addiction sciences for alcohol and drugs in particular). Drawing together population-level data on risk and harm may be a sensible response to this conceptual weakness. Similarly, whilst the prospect of early (in lifecourse) interventions for prevention may be alluring, what are the clinical, public health and wider public policy responses to harms that are occurring now, and how extensively do they provide a firm foundation on which to build?

Step 4 is difficult to rebut. Although multi-sectoral contributions self-evidently have some role to play, it is highly aspirational that they can work in synergy to meaningfully form a system, as is proposed. This will require resources and high level political commitments that may seem far-fetched in times of austerity in public sector finances. Whilst a counter argument in terms of the long term costs and consequences may seem reasonable, this does not diminish the extent to which major efforts to initiate and maintain such systems are probably required. This is a serious objection.

Step 5 is valid in its own terms, and is also particularly limited in respect of the neglect of action on upstream determinants. This ignores much that has been learned in public health about the importance of prevention. High risk sub-populations may be difficult to reliably identify, particularly where evidence is limited. Note that we do not suggest avoiding the targeting of high risk sub-populations rather that this should be undertaken alongside whole population interventions in line with the strategic approach developed by Rose.1093

If the counterfactual reasoning to both steps 4 and 5 appears attractive, one might look more bleakly on the prospect of influencing, never mind exercising control over, future trends in drug use. One may also be sceptically inclined towards researchers calling for more research, though we suggest there is a strong case that existing evidence is not adequate to inform public health strategic responses. This does not necessarily mean that new research is needed in all cases, as existing data collection efforts may be usefully extended, even though the need to build a more secure research platform is an overarching conclusion we do draw. We may be wrong in our thinking and invite readers to judge the adequacy of our approach and the conceptual findings themselves. A favourable assessment may lead the reader to be interested in the research recommendations presented in the next chapter. A more critical reader may like to test the assumptions we have made here (and transparently reported), and/or the evidence gap analysis in the review, to produce a different research agenda.

***Implications***

Assessing the population impacts of the use of, and possible responses to, NPS thus requires the capture of routine data and the generation of scientific data, and modelling of these data. Modelling may be particularly important early on to help inform coherent policy strategies, for example on potential future impacts on health care resources, as well as helping to identify epidemiological and other research priorities. The value of such early models is bounded by the assumptions used in the models themselves, which may need to be crude in the absence of high quality empirical data. The nature of contemporary drug trends poses big challenges to conventional practices in research and in informing policy making with research summed up as “how to speed up science, increase knowledge and get responsible regulatory policies enacted.1122”. The regulation of drugs arguably shares this problem with other cultural forces in which the internet is central, from organised crime to consumer protection, offering opportunities for knowledge transfer.1123

As the NPS phenomenon is global in character, comparative studies of the diffusion of new drugs in other countries and continents should be valuable. The UK, and Europe as a whole, has so far avoided the epidemics of methamphetamines and prescription opioid use seen elsewhere. It is reasonable to suppose that future generations of NPS will have effects on users that are similar to existing drugs, and that a more extensive and complex range of drugs might be used. In the future the most optimistic scenario possible is that the most harmful drugs are largely avoided because they are harmful, regardless of their attractiveness. In such a scenario harmful drugs are still likely to be used by vulnerable or high risk populations, complicating and making more intractable existing problems and probably deepening health inequalities. Cross-national studies using quasi-experimental designs may have capacity to be informative about the effectiveness of different policy measures and approaches.

There is a dose-response relationship between the prevalence of many forms of drug use and the consequent public health and societal harms and the shape of the risk functions vary for different drugs.1072, 1074 Public health approaches thus seek to find ways to manage demand and supply. The need to embrace the complexity and daunting scale of the challenge is widely recognised, so it is timely to develop public health approaches to drugs new and old, and to promote the use of scientific evidence in shaping society’s evolving responses.

**Conclusions**

The set of questions that we identified before we began the development of this conceptual framework (*see Chapter 2 under ‘research questions’*), and the review findings indicate that the literature is at an early stage of development in all cases. The substantive content of the conceptual framework presented here is thus largely unchanged by the review.

In the planning of this study we had anticipated a more mature empirical literature that would lead to the refinement of the conceptual material (for example drawing attention to the ways in which the NPS phenomenon poses challenges to public health that are at least somewhat distinct from those faced elsewhere).However, we found no reason to change the conceptual content on the basis of what has been published to date on NPS. Therefore it is important to emphasise that this conceptual work is fundamentally hypothetical in nature, not having been developed with the aid of empirical research on NPS. As the research literature develops, this necessarily preliminary conceptual work will therefore need to be revisited, with a view to elaborating the strengths and limitations of this model. The disjunction between the empirical review and the conceptual framework findings is worthy of careful attention in developing research recommendations and drawing conclusions based on the overall NPS-UK study (*see Chapter 5)*.

**Chapter 4: Public Involvement**

**Background**

Public Involvement (PI) for this project involved engagement with policy makers, researchers and Novel psychoactive substance (NPS) users and user carers in the United Kingdom as stakeholders in informing the study design and processes, interpreting the findings, and validating the study recommendations. During the preparation of the proposal only we discussed the project with the Scientific Director of the EMCDDA at the European level, the Chief Executive of Drugscope, and a member of the ACMD.

Also relevant to PI is the work done with the steering group. The NPS-UK steering group consisted of five researchers who were independent of the research team: an expert on addictions treatment & prevention, policy & interventions, one on addictions clinical issues and NPS, another on NPS and early warning systems, and two on systematic reviews and complex interventions in public health. All five researchers also act in different capacities to inform policy with evidence and occupy policy roles. Three do so specifically in relation to NPS as well as other drugs, and two are involved in public health. We had also recruited a researcher who is also an NPS user to incorporate the user perspective, however they pulled out and we were unsuccessful in recruiting another NPS user to the steering group. Two steering committee meetings took place in June and October 2016, supplemented by meetings and calls with individual members of the committee. PI relevance of steering committee inputs is judged highest in relation to the Stage 1 conceptual framework that we developed. We also involved the different stakeholders in interpreting and reflecting on our findings, and research recommendations, as well as on the research process itself. The methods used and findings from this process are detailed below.

**Recruitment and engagement**

***Policy makers***

PI work on this project also involved engagement with purposively selected policy actors with responsibilities directly relevant to NPS, and in one case we selected an addictions policy actor without any NPS role. This involved face-to-face meetings, and telephone and e-mail discussions.

We first discussed the Stage 1 conceptual framework with both the external policy actors and with the steering committee (with whom we also discussed the scoping review findings at that point). In a second round of contacts, the draft final report was discussed, by phone with individuals or during the steering committee meeting, with additional comments also received by e-mail.

***Novel psychoactive substance users and user carers***

We recruited NPS users for PI through fliers sent to the following key organizations that work with NPS users or networks: Crew2000 and Newcastle City Council. We also recruited through posting recruitment messages on Bluelight.org which is an online drug user forum, as well as on The Loop Facebook page (We are the loop (Manchester)). The Loop is involved in conducting forensic testing of drugs at UK festivals and nightclubs and provides associated welfare support. Its Facebook page provides information to drug users including NPS users. We supplemented this recruitment strategy by making one-to-one contact with key individuals within these organizations, as well as other individuals who are connected to other NPS user networks, either via e-mail or telephone. To be able to contribute as a PI member one had to be a current NPS/ Legal high user or user carer and be resident in the United Kingdom.

Individuals who were interested to participate contacted the researcher (Noreen Mdege) by email, and were sent an email and information sheet with a summary of the project and what participation as a PI member would entail. This included being sent two sets of documents to comment on: one containing a summary of the findings from the systematic review and the conceptual framework, and the other containing the research recommendations made in light of the findings. Each set of document would take 30-60 minutes to read and consider. They were also informed that they could choose to decline anything that wasn't suitable for them and withdraw at any time. Potential PI contributors were also informed that their preferences for how contact was made and maintained would be respected, as well as preserving anonymity and confidentiality as they required. We offered £10 for commenting on each of the document sets as compensation for time.

**What we learnt**

***Feedback from policy makers and the steering group***

Feedback was gathered through face-to-face meetings with three staff of Public Health England (two of whom had specific responsibilities for NPS and one who did not) in January 2016, e-mail comments from the Home Office Drugs and Alcohol Research Team and Drug and Alcohol Policy Unit, and a follow-up discussion by phone with one member of staff from the former in the spring.

The Stage 1 conceptual framework document was seen to be highly congruent with both scientific and policy perspectives, and to combine both in ways which were useful. The public health orientation was also seen to be complementary to more clinically focused endeavours such as NEPTUNE. There was strong support for not “reinventing the wheel” for NPS and articulating perspectives on NPS separate from those for other drugs. Indeed NPS as a category or label was viewed to have limited utility, as this was obviously not a unitary phenomenon, and attention to the specific issues and harms involved in each new drug type was recommended. It was also suggested that there was much to be learned from earlier epidemics of new drugs in places other than the UK. One example given concerned MPTP compounds produced during the manufacture of MPPP (a synthetic opioid) which led to irreversible Parkinson’s Disease in six drug users in California.

We also learned that coverage of existing responses, which tend to be more treatment rather than prevention orientated, was seen to be limited, and the document not very practical. It was nonetheless seen to be valuable in offering a broader context for existing responses.

We were also able to be informed about developments including forthcoming Public Health England and Home Office plans, and established connections with the Clinical Network Working Group and other fora via which we distributed calls for information.

Comments on the draft final report conveyed appreciation of the review findings, scale and challenges involved in summarizing such a large body of literature in a relatively short space of time. They strongly endorsed the importance of the evidence gap analysis and the broad thrust of the research recommendations made. Comments were received on individual research recommendations and these led to textual refinements in some cases though not substantive content changes.

These efforts at policy engagement were quite modest and principally limited by time available. Two particular limitations should be borne in mind. Firstly, we had intended to engage with the Department of Health, and to have done so would have been valuable. Secondly, the movement of the key contact and resource constraints within the Home Office precluded any contribution in the second round of contacts. This work nonetheless provides a useful basis for dissemination and broader knowledge exchange work that will take place after the completion of the project itself.

***Feedback from novel psychoactive substance users and user carers***

Four individual NPS users expressed interest in being PI contributors to the project. Of these, three provided correct e-mail addresses and were contacted and recruited in July and August 2016. Their preference was to be contacted by e-mail throughout their involvement, with no telephone or any other means of contact. These three individuals were kept up-to-date about the project through e-mail. They were then sent one set of documents in October 2016, with a two weeks deadline, for comments on the findings from the systematic review, conceptual framework, and the research recommendations made in light of the findings. Only one NPS user responded with comments via e-mail.

The Newcastle User Carer Forum agreed to host a discussion of the NPS-UK project and its findings and recommendations for an hour as part of their regular fortnightly forum meetings. This discussion occurred in October 2016 with two discussion facilitators (a researcher and the Newcastle City Council Service User Involvement Officer), and was attended by five male forum members all of whom were in drug recovery and volunteering as peer supporters for drug users in treatment or seeking treatment. Their ages ranged from late 20s to mid-50s.

The views on the NPS user and the five Newcastle User Carer Forum members are reported below.

*Novel psychoactive substance use and problems*

The findings of the scoping review and narrative synthesis concurred with the user carer forum members’ observation from the field that NPS/ legal highs are mainly used by young people aged 11-18. The reasons for use include the fact that they are cheaper and easier to get; and the police do not know how to deal with them. For many of these users ‘legal’ translated to ‘good stuff’ or being safe. However, many users of other drugs who switch to NPS usually switched back to their old drug due to NPS being much stronger and exhibiting worse side effects. They reported that a number of people in drug treatment who use NPS show signs of dependency to NPS, particularly craving.

However, the NPS user’s view was quite different; from his experience on online drug forums NPS users tended to be mid-late 20s to mid-40s but not exclusively male. They agreed with the side effects profile of NPS with the exception of gastrointestinal manifestations which he viewed as rare. They also agreed that NPS tend to have ‘stronger’ side effects and many users tend to switch to older illicit drugs.

*Responses*

Again, the user carer forum members agreed with the review findings on legislative controls for NPS. They indicated that in Newcastle the UK blanket ban of NPS in 2016 had resulted in closure of all headshops and a decrease in availability and increase in price (underground market). They had witnessed a massive decrease in use in Newcastle, even among those seeking treatment for drug use, with a switch to old illicit drugs for many NPS users. Hence, they viewed the blanket ban of NPS in the UK as a good strategy.

The NPS user however felt that all banning strategies had not been as successful as intended, and had resulted in some negative impact as well. The piecemeal approach had led to more dangerous drugs appearing on the market. On the other hand the blanket ban had led to people, particularly those who are already addicted to NPS, feeling ‘stranded’. They highlighted that there had been a huge slump in NPS related post counts on online drug forums since the blanket ban, not only due to decrease in supply but also because more people are now not willing to disclose their NPS use. This was viewed as potentially having a negative impact on harm reduction and treatment seeking, and on routinely collected data where NPS use and consequences could be underestimated.

In terms of the views on our proposed conceptual framework in Chapter 3, all five user carer forum attendees as well as the NPS user recruited from the online drug forum agreed that it was an appropriate framework, as NPS are not different from older or illicit drugs, hence the responses should be for all drugs and not only for NPS. They however highlighted the potential need to distinguish between individual drug types when considering the health related consequences, as different drugs will have different toxicity profiles.

*Research recommendations*

For research recommendations, user carer forum members recommended more investment in interventions, for example examining which treatments are effective and how services can be made more effective. They highlighted the need to explore more the use of peer counsellors or peer supporters, and investing in educating them so that they also understand the science of drug use and drug treatment for them to be more effective in delivering care. They reiterated the need to consider NPS in the context of drug use in general and exploring interventions that are already known to work for other drugs. They also recommended exploring why people use drugs, and engaging more with frontline staff in treatment services and A&E; as well as the police and paramedics to understand some of the problems they face in dealing with users of NPS.

*Reflections on the approach used in carrying out the project*

The forum members as well as the NPS user highly commended the approach taken by the NPS-UK project as being rigorous and thorough, particularly going back to look at how the approach to other drugs has developed and its applicability to NPS.

**Conclusions**

Our PI strategy was successful in engaging a small selection of stakeholders providing a useful sounding board to test emerging findings and generating some lines of enquiry which would need to be tested by more qualitative research to provide definitive assessment of impact on users.

PI activities had demonstrable value in validating our study design, findings and recommendations. The project was successful in engaging with policy makers and researchers at different stages of the research process. However, we were less successful with NPS user involvement despite the efforts described above. The feedback we received from other researchers that have conducted similar work in the area was that there was need for investment in trust and building mutually beneficial relationships with NPS users over time. This could be done for example through advice provision on some of the problems that they might be encountered due to their NPS use, to enhance willingness to engage with research projects like this. However, for short-term projects such as this, implementing this approach is challenging and would need significant early investment. Sustainability of NPS user involvement throughout the project also proved difficult due to lack of willingness on the part of the NPS users to be contacted in ways other than e-mail. Although there is a clear need to move beyond an expert driven discourse on NPS and drug use by involving NPS users and others affected by NPS, our project experience with NPS user involvement indicates a need to develop methods for patient and public involvement that take into account the nature of the subject.

**Chapter 5: Research recommendations**

This chapter provides a brief integrative overview of earlier chapters, by way of introducing the research recommendations. Chapter 2 found that there were many evidence gaps in relation to the original set of research questions that we identified *a priori*. We selected a number of areas that were judged to warrant fuller presentation and synthesis of data, without there being a substantial basis for a full systematic review. Following this, we concluded that this literature was at an early stage of development in capacity to inform strategic public health responses. This conclusion was reached through the contextualisation of review findings within a conceptual framework developed for the purposes of this research. This sought to address what might an evidence-informed public health approach to novel psychoactive substance use in the UK look like. The framework was initially developed prior to the review, and the developmental process is described in detail in Chapter 3. We used this framework to interpret the data from the review, and we subsequently revised the conceptual material in minor ways in light of the review data, as there was no rationale for substantive change. Stakeholder contributions are described in Chapter 4. Together the conceptual framework and review indicate a need for a major research effort to be directed at NPS, and which should also address NPS together with other forms of licit and illicit drug use.

Research recommendations were developed from two distinct data sources. Firstly, research recommendations were made in studies included in the review. This data source offers the perspectives of the authors who have been involved in accumulating the existing research literature on how it needs to develop further. Secondly, we use the conceptual framework for NPS developed by the present authors to identify what may be missing from this literature.

Research recommendations made by authors of primary studies in the four bodies of existing literature selected for narrative synthesis (UK prevalence surveys and qualitative studies, policy evaluation studies and systematic reviews) were extracted and coded independently by two reviewers. The resulting codes were similar and were integrated through attention to detailed content and frequency, and discussion among the reviewers. This led to higher level coding to produce recommendations in three broad thematic areas; research relating to pharmacology, epidemiology and intervention research respectively. Many recommendations previously made were quite generic in nature, and the detailed content of the recommendations proposed adds substance to earlier recommendations based on the review work, and thus involving the interpretation of the authors.

Work on the conceptual framework paid particular attention to possible research data needs, as part of the elaboration of a hypothesised evidence informed public health approach to NPS. This involved identification of both material that is present in, and absent from, the other data source. As the conceptual material has quite a different evidential status to the previously identified research recommendations, we have sought to use a transparent approach to our handling of it.

The research recommendations are targeted at both researchers and commissioners of research, with a view to informing discussions between both parties about, and decision-making on, future research needs and how they may be met. Research recommendations targeting researchers were primarily based on the synthesis of prior research recommendations. Recommendations for research commissioners were based on the conceptual framework and from conclusions drawn by the researchers across the project as a whole. It was intended that these different approaches would be complementary and that overlaps between material from both sources would be particularly informative. The key recommendations are thus those which are drawn from both data sources. It is noteworthy how far the conceptual framework based on evidence from other parts of the public health literature reflects and builds upon the recommendations previously made by authors of the NPS literature.

**Study limitations**

This chapter has thus far concentrated on the process of generating the research recommendations. Attention is also warranted to wider limitations of the NPS-UK study in respect of implications for drawing conclusions and interpreting the resulting research recommendations.

By its nature, a study such as this is not capable of in-depth interrogation of the issues identified as warranting further research. For example, whilst issues concerning existing evidence on prevalence rates based on self-reported drug use in surveys may be described, consideration of how these issues may be most appropriately addressed is necessarily limited. This example relates to a body of evidence chosen for narrative synthesis, and these cautionary remarks apply with greater force to bodies of evidence not selected. Although a scoping review can map existing research, the breadth of the literature examined necessarily constrains the ability to investigate study limitations or risk of bias in any depth. Therefore it is appropriate to be careful about how evidence from primary studies is presented and used in this study. With these caveats borne in mind, we suggest that the findings of the scoping review study should be regarded as providing a reliable broad overview of existing research in this area, permitting identification of the evidence gaps, and thus serving as a platform for the consideration of future research needs.

The disjunction between the scoping review and the conceptual framework findings is worthy of careful attention, and we invite readers to consider two alternative explanations that would challenge our conclusions. It is possible that we have not captured relevant empirical research that should have been included. We suggest this is highly unlikely to be the case for peer-reviewed literature, particularly studies that are published in scientific journals. We acknowledge the risk that relevant grey literature that is not peer reviewed may not have been fully captured. Our inclusion of a category of “responses” which permits letters, commentaries and other material that do not constitute research per se is particularly noteworthy. This means that there may be other material espousing views about appropriate responses that may have been missed. We have no specific grounds for concern in this regard.

The other possibility is that our conceptual work based on wider bodies of evidence has not synthesized relevant material in a sufficiently rigorous way. As we did not develop a dedicated methodology for this strand of the work, whose limitations may be carefully assessed, we do regard this as presenting a risk to our conclusions, and hence state them below in a way which draws attention to this possibility. Our approach throughout has been to be as transparent as possible about both the handling of evidence and the processes of inference generation, so that readers may assess the limitations of our study.

**Statement of NPS -UK project research recommendations**

The research recommendations have been generated using the methodological approach previously described. Key recommendations are identified as such (emboldened below) because they emerged both from the research recommendations identified in the primary studies included in the review and from the conceptual framework developing a hypothesised public health approach to NPS. The 9 key recommendations are derived from the full set of 20 research recommendations as follows:

***Research recommendations for researchers (with key recommendations in bold)***

*Pharmacology related research*

1. **Evaluate the effectiveness and sustainability of the existing pharmacovigilance system for NPS and the effects of planned innovations.**
2. **Evaluate the pharmacological, toxicological and related scientific base needed to inform the pharmacovigilance and public health surveillance systems.**
3. Undertake studies of the simultaneous use of multiple substances. Such studies should include attention to detailed contents, potency, toxicity, doses, and other psychopharmacological and other individual factors.

*Epidemiology and related research*

1. **Evaluate the effectiveness and sustainability of the existing public health surveillance system for monitoring NPS markets and other new online drug trends. This evaluation should cover monitoring actions, both quantitative and qualitative research, and associated commissioning arrangements, and be cognisant of opportunities for innovations such as test-purchasing new brands online as they become available.**
2. **Develop the behavioural epidemiology and related science of patterns and correlates of NPS use and problems in the context of alcohol, tobacco and other drug involvements.**
3. **Use cohort study designs to better understand the determinants of NPS use and related physical health, mental health and psychosocial problems, and how patterns of involvement and consequences change over time.**
4. Develop the study of NPS use in sub-populations (In addition to rather than instead of general population studies). Priority groups could include psychiatric patients with severe mental illness, prisoners, homeless people, existing defined populations of drug users including men who have sex with men, and adolescents.
5. Undertake methodological research on NPS behavioural measurement including the validity of self-report, psychometrics and online survey design.

*Interventions*

1. **Develop the science of prevention of NPS and other drug use. This should include evaluation of existing interventions and the development and evaluation of novel interventions addressing both proximal and distal determinants of NPS and related drug use, and how risks should be communicated to different groups.**
2. **Evaluate the public health impacts of legislative prohibitions of NPS use or supply, and other major policy initiatives.**
3. Evaluate the effectiveness of existing psychosocial interventions for drug users in relation to NPS outcomes. In addition, develop and evaluate further novel treatment interventions for NPS and other drug use in light of the limitations of the effectiveness of existing interventions.

***Recommendations for research commissioners***

1. **Consider using the research recommendations presented here as a possible basis for conducting a formal research priority setting exercise using consensus development methods (such as those developed by the James Lind Alliance).**
2. **Evaluate existing strategic provision for, and develop as necessary, a long term planning system for research on NPS and other drug use.**
3. Consider designing systems for investigating the drug dependence potential of different types of NPS at optimally early points in epidemics if indicated by the outcomes of research relating to Recommendation 2 above. These data should aim to inform assessments of future prevalence and potential problems, and implications for treatment interventions.
4. Evaluate the existing burden of, and responses to, NPS and other drug use in generic and specialist services, and the contributions made therein to prevention and treatment of problems.
5. Develop the contribution of economics to this subject area. Possible study foci include evaluation of the societal costs of NPS and other drug use, modelling the possible benefits and costs of a range of policy and intervention options, and better understanding of the influences of price, availability, and marketing on demand and supply.
6. Develop research capacity for the design, implementation and rigorous evaluation in comparative studies of any emerging local or regional multi-level strategic responses. Such approaches could, include provision for identification of the national policy influences on observed NPS and other drug outcomes.
7. Strengthen the contribution of social sciences to the study of NPS and other drug use. These approaches should build upon methodological advances on similar forms of online mediated behaviour.
8. Develop empirical research on the public understanding of drug use more broadly, including NPS, and how this may be enhanced.
9. Move beyond an expert driven discourse on NPS and drug use by developing methods for patient and public involvement. These methods should be capable of dealing with the controversial nature of this subject, engage local, national and international policy actors, and take a long term view of how societies may adapt to technology driven problems in the context of globalization.

**Conclusions**

The research recommendations presented here cover broadly similar areas to earlier UK expert research recommendations. They are also more detailed in content, partly as they arise from a systematic search and review of the already large and quickly growing research literature, and used a transparent methodology for producing recommendations.

The UK Government Home Office Expert Panel Report in 2014933 recommended various kinds of data collection to inform surveillance systems in health and non-health settings, alongside research recommendations on prevention and treatment, as it was not possible at that time to provide recommendations on evidence-based intervention delivery due to the absence of available evidence. The Home Office Expert Panel Report thus provides some validation support for Recommendations 1, 2, 4, 5, 7, 9 and 11 above (all key recommendations here apart from 7 and 11).

The NPS export report prepared by Fraser924 for the Scottish Government also in 2014 identified evidence gaps in relation to epidemiology, the changing nature of drug markets including NPS, acute and longer term consequences, policy-level interventions, the applicability of existing interventions and consideration of possible new approaches including psychosocial treatments for NPS users. The Scottish Government document thus provides some validation support for Recommendations 4-6 and 9-11 inclusive and 15 (all key recommendations here apart from the latter two).

Other expert reports could also be used for comparison purposes. For example, the 2016 EMCDDA917 report on health responses to new psychoactive substances was not designed to make research recommendations, and for example notes the lack of data on use, harms and effectiveness. The report however does endorse the targeting of sub-groups and the adaptation of existing interventions to incorporate NPS, in line with recommendations 7 and 11 here.

We conclude with two sets of observations on the research recommendations presented here. Firstly, caution should be exercised in relation to the interpretation of the set of recommendations for research commissioners, hence the articulation of key recommendations 12 and 13, which also draw on support from sources other than the conceptual framework. All other recommendations for research commissioners should be regarded as primarily originating in bodies of research evidence other than that existing for NPS, as interpreted by the authors. Further consideration is needed to determine whether the validity of this set of recommendations should be enhanced via further work with research commissioners, policy makers, researchers, and the public. Secondly, it is noteworthy that *all* the key recommendations for researchers are supported by earlier UK expert reports and have not yet been acted upon. We suggest the case for decision-making on commissioning new research based on the present recommendations is both strong and urgent.

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***Steering group membership***

The research team are extremely grateful to the steering group members listed in

alphabetical order: Paolo DeLuca (Senior Research Fellow, National Addiction Centre, KCL), Luke Mitcheson (Consultant Clinical Psychologist, Head of Addictions Psychology, South London and Maudsley NHS Foundation Trust & Drug & Alcohol Team, Public Health England), Mark Petticrew (Professor of Public Health Evaluation, LSHTM), Amanda Sowden (Deputy Director, Centre for Reviews & Dissemination, York), and John Strang (Director, National Addiction Centre, KCL).

***Contribution of authors***

All authors were involved in the conduct of this research, including data interpretation, and drafting the report and have approved the final version of the report.

*Noreen Dadirai Mdege*(Research Fellow, Addiction) was responsible for the day-to-day running of the research project. She conducted the scoping review and narrative synthesis, contributed to conceptual framework development, and led on the drafting of Chapters 1 (with JM), 2 and 4.

*Nick Meader* (Research Fellow, Centre for Reviews and Dissemination) conducted the scoping review and narrative synthesis, contributed to conceptual framework development, and revisions to all chapters.

*Charlie Lloyd* (Reader, Addiction) contributed to the conceptual framework development.

*Steve Parrott* (Reader, Health Economics) contributed the health economics aspects of conceptual framework development

*Jim McCambridge*(Professor, Addictive Behaviours and Public Health) led on the design and conduct of, and had overall responsibility for all research components. He led on the drafting of Chapters 1 (with NDM), 3 and 5.

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**Appendix 1:** **Novel Psychoactive Substances electronic database literature search (original search: 16th November 2015; update search: 29 June 2016)**

We searched the Embase, MEDLINE, PsycINFO and Science Citation Index databases and a total of 13772 records were identified. These were imported into bibliographic software and deduplicated leaving a total of 9165 records.

**Embase via OVID**

**<1980 to 2015 Week 46>**

1 exp designer drug/

2 psychotropic agent/

3 substance abuse/

4 2 and 3

5 (designer adj (drug$ or stimulat$ or amphetamine$)).ti,ab.

6 legal high$.ti,ab.

7 ((club or street) adj drug$).ti,ab.

8 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive drug$).ti,ab.

9 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive agent$).ti,ab.

10 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive substance$).ti,ab.

11 ((new or novel or emerg) adj (cannabinoid$ or phenethylamine$ or arylalkylamaine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrolidine$ or piperazine$ or arylcyclohexylamine$ or aminoindane$ or tryptamine$)).ti,ab.

12 (synthetic adj (cannabinoid$ or phenethylamine$ or arylalkylamaine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrolidine$ or piperazine$ or arylcyclohexylamine$ or aminoindane$ or tryptamin)).ti,ab.

13 (psychotropic adj (drug$ or substance$ or agent$)).ti,ab.

14 13 and 3

15 ((psychotropic adj2 (drug$ or substance$ or agent$)) and (abuse or misuse)).ti,ab.

16 (herbal adj (blend$ or high$ or incense$)).ti,ab.

17 (party pill$ or research chemical$ or smoking mixture$).ti,ab.

18 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 14 or 15 or 16 or 17

19 benzylpiperazine$.ti,ab.

20 cannabimimetic$.ti,ab.

21 diclazepam.ti,ab.

22 gamma butyrolact$.ti,ab.

23 mephedrone.ti,ab.

24 methiopropamine.ti,ab.

25 methoxetamine.ti,ab.

26 naphyrone.ti,ab.

27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28 substance abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

29 27 and 28

30 BZP.ti,ab.

31 MPVD.ti,ab.

32 NRG-1.ti,ab.

33 MDAI.ti,ab.

34 25i-NBOMe.ti,ab.

35 30 or 31 or 32 or 33 or 34

36 Substance abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

37 35 and 36

38 (Annihilation or Armageddon).ti,ab.

39 (bamboo or bathsalt$ or bath salt$ or benzofury or benzo fury or berry bomb or black mamba or bromo-dragonfly or bullet or bumpin).ti,ab.

40 (charly sheen or cherry bomb or chillout or china white or ching or c-liquid or clockwork orange).ti,ab.

41 (disco biscuits or doves ultra).ti,ab.

42 (exodus damnation or exodus nightshade).ti,ab.

43 focus.ti,ab.

44 (gogaine or green beans).ti,ab.

45 (happy joker blueberry or happy joker juice fruit or happy rasta or head trip or hipster or hooter).ti,ab.

46 insane joker.ti,ab.

47 jammin joker.ti,ab.

48 (K2 or king joker or kronic).ti,ab.

49 lotus.ti,ab.

50 (Mexecat or mcat or m-cat or mind melt).ti,ab.

51 (pandora$ box or pink panthers or plant feeder$ or plant food$ or pond cleaner$ or psyclone).ti,ab.

52 (salvia or sensate or sexy v or spice or super lemon haze or synthacaine).ti,ab.

53 timeless.ti,ab.

54 voodoo.ti,ab.

55 (White MM or white widow or wicked).ti,ab.

56 38 or 39 or 40 or 41 or 42 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55

57 Substance abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

58 56 and 57

59 18 or 29 or 37 or 58

60 exp animals/ not humans/

61 59 not 60

62 limit 61 to yr="2006 -Current"

**MEDLINE via OVID**

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>**

1 exp designer drug/

2 psychotropic drugs/

3 drug abuse/

4 2 and 3

5 (designer adj (drug$ or stimulat$ or amphetamine$)).ti,ab.

6 legal high$.ti,ab.

7 ((club or street) adj drug$).ti,ab.

8 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive drug$).ti,ab.

9 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive agent$).ti,ab.

10 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive substance$).ti,ab.

11 ((new or novel or emerg) adj (cannabinoid$ or phenethylamine$ or arylalkylamaine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrolidine$ or piperazine$ or arylcyclohexylamine$ or aminoindane$ or tryptamine$)).ti,ab.

12 (synthetic adj (cannabinoid$ or phenethylamine$ or arylalkylamaine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrolidine$ or piperazine$ or arylcyclohexylamine$ or aminoindane$ or tryptamin)).ti,ab.

13 (psychotropic adj (drug$ or substance$ or agent$)).ti,ab.

14 13 and 3

15 ((psychotropic adj2 (drug$ or substance$ or agent$)) and (abuse or misuse)).ti,ab.

16 (herbal adj (blend$ or high$ or incense$)).ti,ab.

17 (party pill$ or research chemical$ or smoking mixture$).ti,ab.

18 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 14 or 15 or 16 or 17

19 benzylpiperazine$.ti,ab.

20 cannabimimetic$.ti,ab.

21 diclazepam.ti,ab.

22 gamma butyrolact$.ti,ab.

23 mephedrone.ti,ab.

24 methiopropamine.ti,ab.

25 methoxetamine.ti,ab.

26 naphyrone.ti,ab.

27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28 Drug abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

29 27 and 28

30 BZP.ti,ab.

31 MPVD.ti,ab.

32 NRG-1.ti,ab.

33 MDAI.ti,ab.

34 25i-NBOMe.ti,ab.

35 30 or 31 or 32 or 33 or 34

36 Drug abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

37 35 and 36

38 (Annihilation or Armageddon).ti,ab.

39 (bamboo or bathsalt$ or bath salt$ or benzofury or benzo fury or berry bomb or black mamba or bromo-dragonfly or bullet or bumpin).ti,ab.

40 (charly sheen or cherry bomb or chillout or china white or ching or c-liquid or clockwork orange).ti,ab.

41 (disco biscuits or doves ultra).ti,ab.

42 (exodus damnation or exodus nightshade).ti,ab.

43 focus.ti,ab.

44 (gogaine or green beans).ti,ab.

45 (happy joker blueberry or happy joker juice fruit or happy rasta or head trip or hipster or hooter).ti,ab.

46 insane joker.ti,ab.

47 jammin joker.ti,ab.

48 (K2 or king joker or kronic).ti,ab.

49 lotus.ti,ab.

50 (Mexecat or mcat or m-cat or mind melt).ti,ab.

51 (pandora$ box or pink panthers or plant feeder$ or plant food$ or pond cleaner$ or psyclone).ti,ab.

52 (salvia or sensate or sexy v or spice or super lemon haze or synthacaine).ti,ab.

53 timeless.ti,ab.

54 voodoo.ti,ab.

55 (White MM or white widow or wicked).ti,ab.

56 38 or 39 or 40 or 41 or 42 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55

57 Drug abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

58 56 and 57

59 18 or 29 or 37 or 58

60 exp animals/ not humans/

61 59 not 60

62 limit 61 to yr="2006 -Current"

**PsycINO via OVID**

**<1987 to November Week 2 2015>**

1 prescription drugs/

2 neuroleptic drugs/

3 drug abuse/

4 (1 or 2) and 3

5 (designer adj (drug$ or stimulat$ or amphetamine$)).ti,ab.

6 legal high$.ti,ab.

7 ((club or street) adj drug$).ti,ab.

8 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive drug$).ti,ab.

9 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive agent$).ti,ab.

10 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive substance$).ti,ab.

11 ((new or novel or emerg) adj (cannabinoid$ or phenethylamine$ or arylalkylamaine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrolidine$ or piperazine$ or arylcyclohexylamine$ or aminoindane$ or tryptamine$)).ti,ab.

12 (synthetic adj (cannabinoid$ or phenethylamine$ or arylalkylamaine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrolidine$ or piperazine$ or arylcyclohexylamine$ or aminoindane$ or tryptamin)).ti,ab.

13 (psychotropic adj (drug$ or substance$ or agent$)).ti,ab.

14 13 and 3

15 ((psychotropic adj2 (drug$ or substance$ or agent$)) and (abuse or misuse)).ti,ab.

16 (herbal adj (blend$ or high$ or incense$)).ti,ab.

17 (party pill$ or research chemical$ or smoking mixture$).ti,ab.

18 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 14 or 15 or 16 or 17

19 benzylpiperazine$.ti,ab.

20 cannabimimetic$.ti,ab.

21 diclazepam.ti,ab.

22 gamma butyrolact$.ti,ab.

23 mephedrone.ti,ab.

24 methiopropamine.ti,ab.

25 methoxetamine.ti,ab.

26 naphyrone.ti,ab.

27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28 Drug abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

29 27 and 28

30 BZP.ti,ab.

31 MPVD.ti,ab.

32 NRG-1.ti,ab.

33 MDAI.ti,ab.

34 25i-NBOMe.ti,ab.

35 30 or 31 or 32 or 33 or 34

36 Drug abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

37 35 and 36

38 (Annihilation or Armageddon).ti,ab.

39 (bamboo or bathsalt$ or bath salt$ or benzofury or benzo fury or berry bomb or black mamba or bromo-dragonfly or bullet or bumpin).ti,ab.

40 (charly sheen or cherry bomb or chillout or china white or ching or c-liquid or clockwork orange).ti,ab.

41 (disco biscuits or doves ultra).ti,ab.

42 (exodus damnation or exodus nightshade).ti,ab.

43 focus.ti,ab.

44 (gogaine or green beans).ti,ab.

45 (happy joker blueberry or happy joker juice fruit or happy rasta or head trip or hipster or hooter).ti,ab.

46 insane joker.ti,ab.

47 jammin joker.ti,ab.

48 (K2 or king joker or kronic).ti,ab.

49 lotus.ti,ab.

50 (Mexecat or mcat or m-cat or mind melt).ti,ab.

51 (pandora$ box or pink panthers or plant feeder$ or plant food$ or pond cleaner$ or psyclone).ti,ab.

52 (salvia or sensate or sexy v or spice or super lemon haze or synthacaine).ti,ab.

53 timeless.ti,ab.

54 voodoo.ti,ab.

55 (White MM or white widow or wicked).ti,ab.

56 38 or 39 or 40 or 41 or 42 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55

57 Drug abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

58 56 and 57

59 18 or 29 or 37 or 58

60 exp human males/

61 exp human females/

62 60 or 61

63 exp animals/

64 63 not 62

65 59 not 64 (2345)

**Science Citation Index via Web of Science**

|  |  |
| --- | --- |
| #12 | #11 OR #9 OR #7  *DocType=All document types; Language=All languages;* |
| #11 | #10 AND #6  *DocType=All document types; Language=All languages;* |
| #10 | TS=(Annihilation or Armageddon or bamboo or bathsalt\* or "bath salt\*" or benzofury or "benzo fury" or "berry bomb" or "black mamba" or bromo-dragonfly or bullet or bumpin or "charly sheen" or "cherry bomb" or chillout or "china white" or ching or c-liquid or "clockwork orange" or "disco biscuits" or "doves ultra" or "exodus damnation" or "exodus nightshade" or focus) OR TS=(gogaine or "green beans" or  "happy joker blueberry" or "happy joker juice fruit" or "happy rasta" or "head trip" or hipster or hooter or "insane joker" or "jammin joker" or K2 or "king joker" or kronic or lotus or mexecat or mcat or m-cat or "mind melt") OR TS=("pandora\* box" or "pink panthers" or "plant feeder\*" or "plant food\*" or "pond cleaner\*" or psyclone or salvia or sensate or "sexy v"or spice or "super lemon haze" or synthacaine or timeless or voodoo or "white MM" or "white widow" or wicked)  *DocType=All document types; Language=All languages;* |
| #9 | #8 AND #6  *DocType=All document types; Language=All languages;* |
| #8 | TS=(benzylpiperazine\* or cannabimimetic\* or diclazepam or "gamma butyrolact\*" or mephedrone or methiopropamine or  methoxetamine or naphyrone) OR TS=(BZP or MPVD or NRG-1 or MDAI or 25i-NBOMe)  *DocType=All document types; Language=All languages;* |
| #7 | #6 AND #5  *DocType=All document types; Language=All languages;* |
| #6 | TS=("drug abuse" or "drug use" or "drug misuse")  *DocType=All document types; Language=All languages;* |
| #5 | #4 OR #3 OR #2 OR #1  *DocType=All document types; Language=All languages;* |
| #4 | TS=(herbal NEAR (blend\* or high\* or incense\*)) OR TS=(("party pill\*" or "research chemical\*" or "smoking mixture\*"))  *DocType=All document types; Language=All languages;* |
| #3 | TS=((psychotropic NEAR (drug\* or substance\* or agent\*)))  *DocType=All document types; Language=All languages;* |
| #2 | TS=("legal high\*") OR TS=(((club or street) NEAR drug\*)) OR TS=((new or novel or emerg\* or illicit\* or illegal) NEAR "psychoactive drug\*")  OR TS=((new or novel or emerg\* or illicit\* or illegal) NEAR "psychoactive agent\*") OR  TS=((new or novel or emerg\* or illicit\* or illegal) NEAR "psychoactive substance\*") OR  TS=((new or novel or emerg\*) NEAR (cannabinoid\* or phenethylamine\* or arylalkylamaine\* or cathinone\* or opioid\*  or benzodiazepine\* or piperidine\* or pyrolidine\* or piperazine\* or arylcyclohexylamine\* or aminoindane\* or tryptamine\*)) OR  TS=(synthetic NEAR (cannabinoid\* or phenethylamine\* or arylalkylamaine\* or cathinone\* or opioid\* or benzodiazepine\* or  piperidine\* or pyrolidine\* or piperazine\* or arylcyclohexylamine\* or aminoindane\* or tryptamin))  *DocType=All document types; Language=All languages;* |
| #1 | TS=((designer NEAR (drug\* or stimulat\* or amphetamine\*)))  *DocType=All document types; Language=All languages;* |

**Appendix 2: Legal high brand/ trade names included in the electronic searches**

| **Name** | **Global weekends** | **Ice headshop** | **Legal Highs World** |
| --- | --- | --- | --- |
| Annihilation | ✓ | ✓ | ✓ |
| Armageddon | ✓ | ✓ | ✓ |
| Bamboo | ✓ | ✓ | ✓ |
| Berry bomb | ✓ | ✓ | ✓ |
| Black mamba | ✓ | ✓ | ✓ |
| Bullet | ✓ | ✓ | ✓ |
| Bumpin | ✓ | ✓ | ✓ |
| Charly sheen | ✓ | ✓ | ✓ |
| Cherry bomb | ✓ | ✓ | ✓ |
| Chillout | ✓ | ✓ | ✓ |
| China white | ✓ | ✓ | ✓ |
| Ching | ✓ | ✓ | ✓ |
| C-liquid | ✓ | ✓ | ✓ |
| Clockwork orange | ✓ | ✓ | ✓ |
| Diclazepam | ✓ | ✓ | ✓ |
| Disco biscuits | ✓ | ✓ | ✓ |
| Doves ultra | ✓ | ✓ | ✓ |
| Exodus damnation | ✓ | ✓ | ✓ |
| Exodus Nightshade | ✓ | ✓ | ✓ |
| Focus | ✓ | ✓ | ✓ |
| Gogaine | ✓ | ✓ | ✓ |
| Green beans | ✓ | ✓ | ✓ |
| Happy joker blueberry/ juicy fruit | ✓ | ✓ | ✓ |
| Happy rasta | ✓ | ✓ | ✓ |
| Head trip | ✓ | ✓ | ✓ |
| Hipster | ✓ | ✓ | ✓ |
| Hooter | ✓ | ✓ | ✓ |
| Insane Joker | ✓ | ✓ | ✓ |
| Jammin’ joker | ✓ | ✓ | ✓ |
| K2 | ✓ | ✓ | ✓ |
| King joker | ✓ | ✓ | ✓ |
| Kronic | ✓ | ✓ | ✓ |
| Lotus | ✓ | ✓ | ✓ |
| Methiopropamine | ✓ | ✓ | ✓ |
| Mexecat/Mcat/ M-cat | ✓ | ✓ | ✓ |
| Mind melt | ✓ | ✓ | ✓ |
| Pandora’s Box | ✓ | ✓ | ✓ |
| Pink panthers | ✓ | ✓ | ✓ |
| Psyclone | ✓ | ✓ | ✓ |
| Salvia | ✓ | ✓ |  |
| Sensate | ✓ | ✓ | ✓ |
| Sexy V | ✓ | ✓ | ✓ |
| Spice | ✓ | ✓ | ✓ |
| Super lemon haze | ✓ | ✓ | ✓ |
| Synthacaine | ✓ | ✓ | ✓ |
| Timeless | ✓ | ✓ | ✓ |
| Voodoo | ✓ | ✓ | ✓ |
| Voodoo gold | ✓ | ✓ | ✓ |
| White MM | ✓ | ✓ | ✓ |
| White widow | ✓ | ✓ | ✓ |
| Wicked | ✓ | ✓ | ✓ |