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

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

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Background: Although 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) (‘legal highs’). These are new, mostly synthetic, substances that mimic the effects of existing drugs. Despite there being many causes for concern in relation to NPS, there has been little prior study of the burden associated with their 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 by reviewing existing data on their use, associated problems and potential responses to such problems.

Design: A scoping review and narrative synthesis of selected bodies of evidence was undertaken to summarise and evaluate what is known about NPS use and the related harms of, and responses to, such use. Relevant literature was identified from electronic databases (covering January 2006 to June 2016 inclusive), Google (Google Inc., Mountain View, CA, USA), relevant websites and online drug forums and by contacting experts. Articles were included if they were 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, the 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: A total of 995 articles were included in the scoping review, the majority of which related to individual-level health-related adverse effects attributable to NPS use. The prevalence of lifetime NPS use varied widely between (e.g. with higher prevalence in young males) and within population subgroups. The most commonly reported adverse effects were psychiatric/other neurological, cardiovascular, renal and gastrointestinal manifestations, 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 that develops existing responses, is multilevel and life course 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 on those that have previously been made and offer more evidence-based justification and detail, as previous recommendations have not yet been acted on. 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.

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

Funding: The National Institute for Health Research Public Health Research programme.
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<tr>
<td>A&amp;E</td>
<td>accident and emergency</td>
</tr>
<tr>
<td>ACMD</td>
<td>Advisory Council on the Misuse of Drugs</td>
</tr>
<tr>
<td>AIPS</td>
<td>All Ireland Prevalence Survey</td>
</tr>
<tr>
<td>BZP</td>
<td>benzylpiperazine</td>
</tr>
<tr>
<td>CSEW</td>
<td>Crime Survey for England and Wales</td>
</tr>
<tr>
<td>ED</td>
<td>emergency department</td>
</tr>
<tr>
<td>EMCDDA</td>
<td>European Monitoring Centre for Drugs and Drug Addiction</td>
</tr>
<tr>
<td>EWS</td>
<td>early warning system</td>
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<tr>
<td>GBL</td>
<td>gamma-butyrolactone</td>
</tr>
<tr>
<td>GHB</td>
<td>gamma-hydroxybutyrate</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HSCIC</td>
<td>Health and Social Care Information Centre</td>
</tr>
<tr>
<td>MDMA</td>
<td>3,4-methylenedioxymethamphetamine (ecstasy)</td>
</tr>
<tr>
<td>MDPV</td>
<td>methylenedioxypyrovalerone</td>
</tr>
<tr>
<td>MSM</td>
<td>men who have sex with men</td>
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<tr>
<td>NBOMe</td>
<td>N-methoxybenzyl</td>
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<tr>
<td>NEPTUNE</td>
<td>Novel Psychoactive Treatment: UK network</td>
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<tr>
<td>NPS</td>
<td>novel psychoactive substance</td>
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<tr>
<td>PI</td>
<td>public involvement</td>
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<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
</tr>
<tr>
<td>SALSUS</td>
<td>Scottish Schools Adolescent Lifestyle and Substance Use Survey</td>
</tr>
<tr>
<td>SCJS</td>
<td>Scottish Crime and Justice Survey</td>
</tr>
<tr>
<td>TCDO</td>
<td>Temporary Class Drug Order</td>
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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 undertaken to better understand NPS in ways that help to improve the health of the public.

What did we do?

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

What did we find?

We found that there are many gaps in knowledge and that available research is at an early stage in understanding NPS. Reported side effects of 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 research avenues we thought was most important.

What does this mean?

Much remains to be known about NPS. We suggest that there is no justified reason for investigating NPS in isolation from other illicit drugs. We have presented some options for what new research could be undertaken in the future. We hope that this will help experts on NPS to decide together what research would be most helpful to reduce harms for people who already use NPS, those who might be affected by NPS and those who might use NPS in the future, in the interests of better health across society as a whole.
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’ [Advisory Council on Misuse of Drugs. Consideration of the Novel Psychoactive Substances (‘legal highs’). London: ACMD; 2011]. There are a number of grounds for concern in relation to NPS use, 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 and a large degree of uncertainty about 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 its effects, the risks posed by its use and how these may be reduced. There are systems in place to monitor the emergence of new drugs nationally and internationally. The key UK policy development has been the implementation of the Psychoactive Substances Act (Great Britain. Psychoactive Substances Act 2016. London: The Stationery Office; 2016) 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, the extent to which existing evidence is able to inform public health responses is also unclear.

Objectives

Three specific objectives of the Novel Psychoactive Substances in the UK (NPS-UK) project were to:

1. summarise and evaluate what is known about NPS use and 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 an articulation of the key issues facing public health intervention research (objective 3).

Evidence synthesis

The following electronic databases were searched between 1 January 2006 and 29 June 2016 inclusive: MEDLINE, EMBASE, PsycINFO and Science Citation Index. Searches for grey literature included a Google (Google Inc., Mountain View, CA, USA) 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 that were published in English 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 to be the most promising for syntheses (e.g. 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 multisectoral public health challenges, such as public mental health, climate change and obesity, as well as 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 first stage research 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 and public involvement**
Research recommendations were developed from two distinct data sources. First, research recommendations made by authors of primary studies in the existing literature selected for narrative synthesis were thematically coded. Second, 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 NPS users and user carers as stakeholders to inform the study design and processes, interpret the findings and validate the study recommendations.

**Results**

**Scoping review**
A total of 995 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 prioritise those research areas that should be synthesised in more detail. We found few data on social and other risk factors, population-level risk factors, harms associated with long-term NPS use, the provision and effectiveness of prevention interventions, and treatment outcomes for NPS users. We undertook more detailed narrative syntheses on surveys on the prevalence and patterns of NPS use in the UK, on UK qualitative studies on the patterns and harms associated with NPS use, on systematic reviews (largely comprising data on harms associated with NPS use) and on evaluations of policy responses to NPS use.

**Narrative synthesis**

**UK survey data**
We identified 29 studies. The most robust nationally representative data were for mephedrone (the Crime Survey for England and Wales and the Scottish Crime and Justice Survey have been conducting national surveys since 2010–11). Lifetime mephedrone use is uncommon in adults (approximately 1–2%) but is about two to three times more prevalent in men than in women and in younger adults than in older adults. Prevalence rates of recent mephedrone use are declining substantially. Nationally representative data on NPS use as a whole and on use of particular NPS other than mephedrone are less developed, and comparisons across years are not yet possible. Nationally representative surveys of school children have found a similarly low prevalence for mephedrone and other NPS use as a whole. Data on particular sentinel populations that are likely to be at greater risk of NPS use are growing, although they 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 comprise 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 mostly to involve observation and supportive care and in severe cases may require hospitalisation. 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 use in the UK**

Qualitative studies on NPS use in the UK (n = 7) are at an early stage of development. Existing studies have the 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 to 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, health-care use and self-reported exposure and toxicity. Reductions in use, presentations or other outcomes were generally observed, although not always. Studies typically utilised 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. Further examination of the utility of routinely collected NPS data in different settings is needed to assess sources of information bias and to evaluate pharmacovigilance and other data.

**Conceptual framework**

**Stage 1**

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

We provide a conceptual map of key individual-level risks and harms attributable to NPS adapted from those developed for other forms of drug use (Figure a). 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 that dynamically interact with life-course stages. Intervention targets for prevention need to extend beyond those proximal to acts of drug use and include those within the social structural influences that shape individual risk. Other drug use, both licit and illicit, is expected to be implicated in the production of harm where other drugs are being used (it is rare that other drugs are not used).

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, or lost quality-adjusted life-years.

**Stage 2**

The empirical review findings indicated that the existing body of literature, although large, is at an early stage of development, and there are currently few data to inform directly what we hypothesised to be an
evidence-informed public health strategic response to NPS. The hypothesised need for research to inform public health responses has 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 nine 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

3. 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.
4. 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.
5. 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

6. Develop the science of prevention of NPS and other drug use. This should include the 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.
7. Evaluate the public health impacts of legislative prohibitions of NPS use or supply, and other major policy initiatives.

Recommendations for research commissioners

8. 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).
9. 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

Funding for this study was provided by the Public Health Research programme of the National Institute for Health Research.
This report presents the findings from a National Institute for Health Research (NIHR) Public Health Research (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 and the problems associated with, and the potential responses to, such use.

This 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, which represent the phases of the study:

- Chapter 2 – scoping review with a narrative synthesis of selected bodies of evidence on what is known about NPS use and the related harms of, and responses to, such use
- Chapter 3 – what might an evidence-informed public health approach to NPS use in the UK look like? A conceptual framework
- Chapter 4 – public involvement (PI)
- Chapter 5 – research recommendations.

Background

Although illegal drug use has largely been declining in the UK over the past decade, 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’, new psychoactive substances or NPS. The new/novel psychoactive substances 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 the 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’.

Novel psychoactive substance use causes a number of grounds for concern. First, technological advances mean that supply sources with the capacity for continuous product innovations can be offered, 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, 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). Third, by international standards, there are very high levels of cultural acceptability of NPS use in the UK. Fourth, NPS are perceived to be safe or to pose little risk. Fifth, there are many 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 its effects, the risks posed by its use and how these risks 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. In addition, although there has been valuable thinking about the implications for the regulation of drug use, dedicated attention to specifically public health responses has been limited. This project seeks to address these gaps.

UK general population surveys report the past year prevalence of mephedrone use, which has attracted most concern, ranging from 1.1% to 1.8% among those aged ≥16 years, with prevalence largely stable in more recent years (up to the end of 2014 when these data were assembled). However, among
those aged 16–24 years, past year use prevalence has been 3% or higher, which is similar to that of
3,4-methylenedioxyamphetamine [MDMA (ecstasy)].13,14 The most recent national drug survey identified
increases in the past year prevalence of nitrous oxide and salvia use, both in the 16–24 years age group and
in all adults.2 Among the former group, past year prevalence was 7.6%, which is approximately twice that of
both ecstasy and powder cocaine.2 Moreover, a number of deaths have been associated with mephedrone
use, both before and after it became controlled.15,16

The monitoring of the emergence of new drugs through early warning systems (EWSs) and of national
policy responses in Europe is undertaken by the European Monitoring Centre for Drugs and Drug
Addiction (EMCDDA).17,18 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, although 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.19
This is despite the strong focus on developing the evidence base to support responses to NPS in the UK
Drug Strategy.20 These needs have also been emphasised for some years by the ACMD.3

**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.13 Even if the present generation of NPS is not very problematic, and it is very unclear
whether or not this is the case, there is a need to develop the capacity for public health NPS responses to
new substances that 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, to identify new drugs that do
not seem likely to be problematic), in order to alter the course of possible future epidemics.21

There is, therefore, a pressing need to review what is known about NPS use in the UK, and the extent and
nature of problems associated with this use, and to consider potential public health responses. There have
been no systematic reviews that 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 the implications
for public health and for 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 coming years.

**Research objectives**

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

1. to summarise and evaluate what is known about NPS use, the related harms of, and responses to,
such use by means of a review of peer-reviewed and grey literature
2. to develop a dedicated conceptual framework for a public health approach to NPS use that 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: (1) a systematic mapping of available evidence and a narrative synthesis of selected bodies of evidence (in relation to objective 1), and (2) 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 scope 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 also used for the construction of a robust assessment of key evidence gaps and research priorities and an 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 a narrative synthesis of selected bodies of evidence on what is known about novel psychoactive substance use, related harms and responses

Background

Novel psychoactive substance use causes a number of grounds for concern, as 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 coping ability of the legal processes that control these substances,⁴ and easy accessibility via the internet.⁵ There has, however, been little consideration of the public health burden associated with NPS use,⁷–¹⁰ or of public health responses to NPS use.¹² It is unclear whether there is need for targeted responses to the existing generation of NPS, or the development of the capacity of public health NPS responses to new substances that 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 and 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 of 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 into three preliminary concepts of use, problems and responses. In addition, a small number of more methodological questions were 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 to 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/harms

4. Which acute intoxication problems are associated with NPS use?
5. What problems are associated with long-term regular NPS use?
6. 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

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

Methodological questions

13. What is the nature of the current EWS provision?
14. Are there sentinel populations capable of being monitored to provide early warnings of new trends?
15. What are the issues raised by uncertainties about the identities of substances being used?

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

Review methods

The review was registered with the international prospective register of systematic reviews (PROSPERO registration number CRD42016026415). Given that we decided not to conduct a systematic review, we did not use PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines, 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 electronic database searches, Google (Google Inc., Mountain View, CA, USA) searches, hand searches of websites relating to the UK, identifying 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 1 January 2006 and 16 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 of a number of NPS products. These names were selected by perusing the websites of three popular NPS headshops (i.e. globalweekends.co.uk, www.iceheadshop.co.uk and www.legalhighsworld.co.uk) and selecting those that appeared in all three for inclusion (see 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 portable document format (PDF), and the searches were conducted on 17 March 2016.

Hand search of websites relating to the UK and USA
Websites of the following institutions and organisations were hand searched on 13 May 2016 to identify national and international surveys, monitoring systems and EWSs: www.gov.uk (which includes the Department of Health, the Home Office and Public Health England), NHS Evidence, the Office for National Statistics, the National Drug Treatment Monitoring System, the EMCDDA, the Scottish Government, the National Assembly for Wales, Public Health Wales, Welsh Emerging Drugs and Identification of Novel Substances, Information Services Division Scotland, the Department of Health Northern Ireland, the Centres for Disease Control and Prevention, the National Institute on Drug Abuse, and the Substance Abuse and Mental Health Services Administration.

Search for relevant online drug forums
Relevant online drug forums were identified from published literature as well as by 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 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 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 included only 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 related to NPS use, problems and responses.

Participants/population
Articles were included if they reported on humans. No other limits were set on the population.

Response(s), exposure(s)
The exposure of interest was NPS use, and we were interested in any associated problems. Any intervention or response aimed at addressing NPS 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 the 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 were 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 reasons for their exclusion documented.

**Data extraction**
Data extraction was performed using EPPI-Reviewer 4 software (EPPI-Centre, Social Science Research Unit, Institute of Education, University of London, London, UK). 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 were 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, sex, ethnicity, sample size, NPS use status
- NPS 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.

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

- use – any use of a NPS
- problems – any acute or chronic health-specific, social or wider harm attributable to NPS use, experienced by the user or others
- responses – any intervention at policy, health or other service, or clinical levels, aimed at addressing NPS 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, a 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 the 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 undertaken in three stages: (1) evidence mapping, (2) identification of evidence gaps and (3) a narrative synthesis of selected research areas.

Evidence map
For reviews addressing complex topic areas, evidence mapping is a well-established tool by which to explore relevant literature before progressing to more advanced research design decision-making. The extracted data were utilised by one researcher to map the literature according to the 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 but concise descriptive map of the nature and breadth of research on NPS, and to 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 used 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 or not 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 a 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 that were manageable within the time and resources allocated to the project, and bearing in mind the large volume of 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 NPS use, related problems and responses from a public health perspective (PROSPERO registration number CRD42016026415).22 However, after the 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 sufficiently mature 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 up to the end of June 2016 (with a view to complete the project 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 13,772 records were identified through electronic databases searches. A further 3260 were obtained through other sources, including contacting key researchers and policy experts (Figure 1). 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

FIGURE 1 Flow of articles for the evidence mapping.
further records. A total of 995 articles were eligible for inclusion in the review after removing duplicates and screening titles, abstracts and, where necessary, full texts. Of the 542 records excluded after reviewing the full texts, the main reasons for exclusion were not being specific to NPS (e.g. recreational drug use, club drug use, substance use/abuse, psychoactive substance use without presenting data on NPS use separately) (n = 211); being on drugs that are not included as NPS in the review [e.g. specific to illicit drug use, alcohol, tobacco, ketamine, khat, gamma-hydroxybutyrate (GHB) or gamma-butyrolactone (GBL)] (n = 107); being on the detection, identification and quantification of NPS, including methods validation (n = 69); being comments, editorials or letters to an editor within new primary or secondary data (n = 65); or being in a language other than English (n = 56). Most of the remaining 34 records were either Acts, regulations or drug schedules, or descriptions of surveillance and pharmacovigilance systems.

**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 summarised in Table 1. The majority of articles reported on problems or harms attributable to the use of NPS. Many of the articles focused on multiple issues, as represented in Figure 2. Synthetic cannabinoids and synthetic cathinones were the NPS that were most reported on, with case report/series being the most popular study design, followed by non-systematic literature reviews. Most articles reported on general hospital settings, followed by specialist settings. Within hospital settings, most articles were for emergency departments (EDs) (n = 236 reports), while within specialist settings, most articles were for poison centres (n = 65 reports). A total of 252 of the included reports were not specific to a particular setting.

**TABLE 1 General characteristics of included articles**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Distribution (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principal focus</strong></td>
<td></td>
</tr>
<tr>
<td>Use</td>
<td>385</td>
</tr>
<tr>
<td>Problems/harms</td>
<td>773</td>
</tr>
<tr>
<td>Responses</td>
<td>148</td>
</tr>
<tr>
<td><strong>NPS type</strong></td>
<td></td>
</tr>
<tr>
<td>All NPS</td>
<td>259</td>
</tr>
<tr>
<td>Synthetic cannabinoids</td>
<td>310</td>
</tr>
<tr>
<td>Synthetic cathinones</td>
<td>271</td>
</tr>
<tr>
<td>Phenethylamines</td>
<td>69</td>
</tr>
<tr>
<td>Piperazines</td>
<td>29</td>
</tr>
<tr>
<td>Other</td>
<td>114</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
</tr>
<tr>
<td>Specialist settings (addiction treatment, psychiatric treatment, forensic and rehabilitation, poison centres, needle exchanges, other similar settings)</td>
<td>134</td>
</tr>
<tr>
<td>General hospital (inpatient, A&amp;ED, outpatient settings)</td>
<td>294</td>
</tr>
<tr>
<td>Primary care setting</td>
<td>3</td>
</tr>
<tr>
<td>Educational setting (school, higher educational institutions such as university/college)</td>
<td>32</td>
</tr>
<tr>
<td>Criminal justice</td>
<td>9</td>
</tr>
</tbody>
</table>

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### TABLE 1 General characteristics of included articles (continued)

<table>
<thead>
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<tr>
<td>Police</td>
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<tr>
<td>Defence forces (Air Force, Army, Navy)</td>
<td>9</td>
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<tr>
<td>Community setting</td>
<td>64</td>
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<tr>
<td>Home</td>
<td>27</td>
</tr>
<tr>
<td>Club/disco/dance scene</td>
<td>14</td>
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<tr>
<td>Internet</td>
<td>59</td>
</tr>
<tr>
<td>Data registry</td>
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<tr>
<td>EWSs</td>
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<tr>
<td>Research setting</td>
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<tr>
<td>Other</td>
<td>21</td>
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<tr>
<td>Not applicable</td>
<td>252</td>
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<tr>
<td>Not reported</td>
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#### Study design

<table>
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<th>Distribution (n)</th>
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<td>Systematic review</td>
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<tr>
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<td>RCT</td>
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<tr>
<td>Survey</td>
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<td>Laboratory sample analysis</td>
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<tr>
<td>Secondary quantitative data analysis</td>
<td>99</td>
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<td>Prospective cohort studies</td>
<td>6</td>
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<td>Case–control</td>
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<tr>
<td>Qualitative study</td>
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<tr>
<td>Case series/reports</td>
<td>367</td>
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<tr>
<td>Other</td>
<td>64</td>
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#### Publication type

<table>
<thead>
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<th>Publication type</th>
<th>Distribution (n)</th>
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<td>Peer-reviewed journal article</td>
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<tr>
<td>Peer-reviewed report</td>
<td>1</td>
</tr>
<tr>
<td>Non-peer-reviewed article/report</td>
<td>119</td>
</tr>
<tr>
<td>Conference abstracts</td>
<td>205</td>
</tr>
<tr>
<td>Book</td>
<td>4</td>
</tr>
<tr>
<td>Dissertation</td>
<td>1</td>
</tr>
<tr>
<td>Online discussion forum</td>
<td>4</td>
</tr>
</tbody>
</table>

A&E, accident and emergency; ED, emergency department; RCT, randomised controlled trial.
Most of the categories above are not mutually exclusive. For example, some articles use multiple study designs. Another example is presented in Figure 2 for principal focus.

**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 2.

**Use**

Of the 385 reports on NPS use, 117 presented survey data. The remaining 268 articles presenting NPS use data were case reports/series (n = 20); laboratory sample analyses (n = 39); qualitative studies (n = 39); randomised controlled trials (RCTs) (n = 1); reviews (n = 124); secondary qualitative data analyses (n = 49); systematic reviews (n = 1); prospective cohort studies (n = 2); or other designs (n = 21).

The 117 NPS use articles based on survey data comprise 13 national surveys and 104 surveys of subpopulations or convenience samples. Of the 13 national surveys, seven were conducted among adults, of which three were conducted in the UK, two in the USA, and one each in Canada and New Zealand. Two were conducted among young people (one covering Europe and the other covering Poland), and four were in schools (two in the UK, and one each in the USA and Romania). In terms of NPS type, of the 117 surveys presenting NPS use data, 54 provided data on all NPS, 28 provided data on synthetic cathinones, 25 provided data on synthetic cannabinoids, 4 provided data on piperazines, 1 provided data on phenethylamines and 19 provided data on other NPS.

UK survey data are presented in detail below (see UK survey data).

**Problems**

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

Of the 10 systematic reviews, one was on all NPS, five were on synthetic cannabinoids, two were on synthetic cathinones and two were on phenethylamines. More details of these 10 systematic reviews are provided within the narrative synthesis results section (see Systematic reviews).
Table 2: Study design of reports on problems/harms attributable to NPS

<table>
<thead>
<tr>
<th>Study design</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary studies and secondary quantitative data analyses (N = 566)</strong></td>
<td></td>
</tr>
<tr>
<td>RCTs</td>
<td>12</td>
</tr>
<tr>
<td>Surveys</td>
<td>44</td>
</tr>
<tr>
<td>Prospective cohort studies</td>
<td>4</td>
</tr>
<tr>
<td>Case-control</td>
<td>1</td>
</tr>
<tr>
<td>Secondary quantitative data analyses</td>
<td>78</td>
</tr>
<tr>
<td>Laboratory analysis</td>
<td>27</td>
</tr>
<tr>
<td>Qualitative studies</td>
<td>33</td>
</tr>
<tr>
<td>Case reports/series</td>
<td>367</td>
</tr>
<tr>
<td><strong>Evidence syntheses (N = 211)</strong></td>
<td></td>
</tr>
<tr>
<td>Systematic reviews</td>
<td>10</td>
</tr>
<tr>
<td>Reviews</td>
<td>201</td>
</tr>
</tbody>
</table>

Responses

Of the 148 reports on responses to NPS use, 17 were quantitative policy evaluation reports mainly evaluating legislative policy responses utilising before-and-after comparisons. Six reports were qualitative studies of legislative policy responses, 84 were policy discussion papers, 34 reports were on the clinical management of NPS users, 13 were on interventions to increase awareness and understanding of NPS among clinicians and members of the public and 5 were on harm reduction. 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 below (see Responses to novel psychoactive substance use and problems/harms).

Year of publication

The number of records by year of publication is shown in Figure 3.
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 the fact 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 or not this trend continued into 2015. This general trend is also observed for principal focus (Figure 4), for NPS type, except for synthetic cathinones and piperazines (Figure 5), and for peer-reviewed journal articles and non-peer-reviewed journal articles and reports (Figure 6). Our search also identified 198 records from 2016 and nine records that did not have a publication date.

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

Of the records identified for 2016 (up to 29 June 2016), 71 were for synthetic cannabinoids, 34 were for synthetic cathinones, 6 each were for phenethylamines and piperazines, 24 were for other NPS and 72 were on all NPS. Of the nine records with no publication year, one was on synthetic cathinones, one was on other NPS and seven were on all NPS types.

FIGURE 4 Number of records by year of publication and principal focus for 2006–15.

FIGURE 5 Number of records by year of publication and NPS type for 2006–15.
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 7 shows 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. However, there is a general increase in the number of qualitative studies, RCTs and other research designs. The nine 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 was also a prospective cohort study for both 2013 and 2015, and a case–control study in 2015. Of the identified 2016 records, 2 were systematic reviews, 40 were reviews, 34 were surveys, 53 were case reports/series, 20 were laboratory sample analyses, 12 were qualitative studies, 5 were RCTs, 26 were secondary qualitative data analyses and 4 were prospective cohort studies. A total of 15 fell into the ‘other’ category and there were no case–control studies identified for 2016.

Geographical location
Table 3 shows the number of articles included by geographic region where the study was conducted. A total of 19 of the 185 articles reporting on the UK 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 ‘Multiregional’ category). The ‘not applicable’ category comprises reviews and systematic reviews that are international in nature, summarising data from different regions.

Novel psychoactive substance type
The figures below show percentage of records by NPS type and study design (Figure 8), region (Figure 9), setting (Figure 10) and publication type (Figure 11).

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.

The majority of studies on synthetic cannabinoids, synthetic cathinones and phenethylamines were conducted in North America, whereas the majority of studies on piperazines were conducted in Australia/New Zealand. Articles that looked at NPS in general were mostly from the UK and the rest of Europe.

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

Most articles were peer-reviewed journal articles for each NPS category.

<table>
<thead>
<tr>
<th>Region</th>
<th>Distribution (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>185</td>
</tr>
<tr>
<td>Rest of Europe</td>
<td>200</td>
</tr>
<tr>
<td>North America</td>
<td>294</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>58</td>
</tr>
<tr>
<td>Africa</td>
<td>0</td>
</tr>
<tr>
<td>Asia</td>
<td>29</td>
</tr>
<tr>
<td>Middle East</td>
<td>7</td>
</tr>
<tr>
<td>Multiregional</td>
<td>22</td>
</tr>
<tr>
<td>Not applicable</td>
<td>216</td>
</tr>
</tbody>
</table>
FIGURE 8 Percentage of records by NPS type and study design.
Synthetic cannabinoids
Synthetic cathinones
Phenethylamines
Piperazines
NPS type
Other
All NPS
Study region
UK
Rest of Europe
North America
Australia/New Zealand
N/A
Multiregional
Asia
Middle East
Percentage of records by NPS type and study region.

FIGURE 9 Percentage of records by NPS type and study region.

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FIGURE 10 Percentage of records by NPS type and study setting. N/A, not applicable; NR, not reported.
Synthetic cannabinoids
Synthetic cathinones
Phenethylamines
Piperazines
Other
All NPS

Peer-reviewed journal articles
Non-peer-reviewed journal articles
Peer-reviewed reports
Non-peer-reviewed reports
Conference abstracts
Books
Online discussion forums
Dissertations

FIGURE 11 The percentage of records by publication type for each NPS category.
Study design

Figure 12 summarises 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, four 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 volume of literature in this area, large gaps in the evidence base still remain, presumably owing to its recent development. It is, therefore, challenging to both summarise this literature and 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 or not there were 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 (CSEW)\textsuperscript{963} and the Scottish Crime and Justice Survey (SCJS)\textsuperscript{1009}] and school children [such as the Smoking, Drinking, and Drug Use Among Young People in England in 2014 survey\textsuperscript{925}] which indicate that NPS use is relatively rare at the population level (between 1\% and 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 relate to attendees of gay-friendly nightclubs, where a similar pattern of a decline in mephedrone use has been identified. Therefore, the prevalence and patterns of NPS use in the UK is a promising area of research, which suggests that a more detailed synthesis of these data will be informative.

2. 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.

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

   There are nationally representative survey data suggesting that males rather than females and younger adults rather than adults as a whole are more likely to engage in NPS use. However, we identified very few data on other population-level risk factors that influence NPS use. Given the limited exploration of these risk factors, we concluded that there were insufficient data to conduct further evidence syntheses. However, we decided that data on age and sex should be considered in the context of the national survey data on prevalence (see Narrative synthesis).

**Novel psychoactive substance-related problems/harms**

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 [e.g. attending accident and emergency (A&E) services after NPS use]. However, there were little or no population-level data other than registries of drug-related deaths. These data have begun to be
FIGURE 12 The percentage of records by publication type for each study design category.
synthesised and we identified 10 published systematic reviews (see Table 5). 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 an assessment of the extent to which this large volume of literature on case reports and registry data has been covered by these reviews.

2. What problems are associated with long-term regular NPS use?
   We identified very limited epidemiological data on problems associated with regular NPS use (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 synthesise these studies in more detail in subsequent sections of the report.

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?
   Social and health harms associated with NPS use other than the types described above do not appear to have been investigated. Therefore, we concluded that 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.

2. Which generic interventions (early in life and early in drug-using careers) target NPS?
   We did identify some treatment audit data that show the proportions of people who use NPS receiving drug treatment services. However, no specific data exist on the content of these interventions and, therefore, there are very limited opportunities to conduct further syntheses.

3. 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 (see www.talktofrank.com) that incorporate NPS, there were no data available for inclusion.

4. 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.

5. 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 indicate the need for further exploration. For example, key policy responses at present in many countries around the world involve the prohibition of NPS possession or supply. We have identified studies that have begun to evaluate the effectiveness of such responses, which we shall therefore further examine in the narrative synthesis (see Table 6).

6. 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:

1. What is the nature of the current 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?
We did identify some data that were relevant to all three questions, although this related to the substantive areas such as descriptions of EWSs, 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 in which there has been very limited research. For example, there are 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 that 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 that we identified on long-term harms and other subjects to inform future research. Finally, there is a relatively large body of literature on harms and problems associated with NPS use, although this mainly consists of case reports and case series. In addition, we identified systematic reviews of harms and problems that seek to synthesise some of this literature. We judged that a detailed synthesis of the primary literature may be useful, although a review of existing systematic reviews should be considered before any synthesis of the primary literature. 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 focuses on UK survey data, which include 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 the 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).904,915,925,960,963,1009 Others focused on specific sentinel populations, such as attendees of nightclubs, people attending mental health services, homeless populations and prisoners.159,170,184,192,455,491,509,516,517,570,704,741,842,843,874,876,931,943 Finally, other surveys particularly targeted NPS users to investigate patterns of use.15,538,820,884,918,959,1001

Nationally representative prevalence studies

Adults

Data on adults’ NPS use are available from nationally representative surveys conducted by government agencies. The most extensive data are on mephedrone use; these have been collected annually since 2010/11 (questions on lifetime use of mephedrone were included from 2012/13) in the CSEW963 and the SCJS.1009 Other surveys focused on specific sentinel populations, such as attendees of nightclubs, people attending mental health services, homeless populations and prisoners.159,170,184,192,455,491,509,516,517,570,704,741,842,843,874,876,931,943 Finally, other surveys particularly targeted NPS users to investigate patterns of use.15,538,820,884,918,959,1001
### TABLE 4 Summary study characteristics of surveys of NPS use in the UK

<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Drug</th>
<th>Sampling</th>
<th>Participant characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N = 2535</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NPS</td>
<td>Reflective of the general population</td>
</tr>
<tr>
<td>Nationally representative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Department of Health, Northern Ireland (2015)</td>
<td>General population</td>
<td>NPS</td>
<td>Nationally representative sample of Ireland</td>
<td></td>
</tr>
<tr>
<td>European Commission (2014)</td>
<td>European youth (15- to 24-year-olds)</td>
<td>NPS</td>
<td>Nationally representative samples for Member States</td>
<td></td>
</tr>
<tr>
<td>Health and Social Care Information Centre (2015)</td>
<td>11- to 15-year-olds</td>
<td>NPS</td>
<td>Nationally representative sample of schools in England</td>
<td></td>
</tr>
<tr>
<td>Robertson (2016)</td>
<td>General population</td>
<td>NPS</td>
<td>Nationally representative sample of Scotland (SCJS)</td>
<td></td>
</tr>
<tr>
<td>Community sample: not nationally representative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corazza et al. (2014)</td>
<td>Pupils and students</td>
<td>NPS</td>
<td>Online (the Study Room forum)</td>
<td></td>
</tr>
<tr>
<td>Dargan et al. (2010)</td>
<td>Pupils and students</td>
<td>Mephedrone</td>
<td>Tayside area</td>
<td></td>
</tr>
<tr>
<td>Mounsey et al. (2016)</td>
<td>School children (15- to 18-year-olds)</td>
<td>NPS</td>
<td>Greater London (four private schools and four state schools)</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Population</td>
<td>Drug</td>
<td>Sampling</td>
<td>Participant characteristics</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>--------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Sentinel populations/subgroups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker (2015)(^{876})</td>
<td>Prisoners</td>
<td>Synthetic cannabinoids</td>
<td>Prison in Rochester</td>
<td>N = 101</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: 100% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 32 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(range 18–59 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity: 72% white,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12% black, 6% Asian,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6% mixed ethnicity,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4% other</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Offences for which convicted:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30% violent offences,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21% robbery, 26% drugs,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5% motoring related, 9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>acquisitive, 9% other</td>
</tr>
<tr>
<td>Homeless Link (2016)(^{931})</td>
<td>Homeless people</td>
<td>NPS</td>
<td>Clients of day centres for</td>
<td>N = 56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>homeless people</td>
<td>Sex: 59% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 29 years</td>
</tr>
<tr>
<td>Chung et al. (2014)(^{106})</td>
<td>HIV-positive MSM</td>
<td>NPS</td>
<td>HIV outpatient clinic</td>
<td>N = 223</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: 100% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sexuality: 100% MSM</td>
</tr>
<tr>
<td>Daskalopoulou et al. (2014)(^{20})</td>
<td>HIV-positive MSM</td>
<td>Mephedrone</td>
<td>HIV outpatient clinic</td>
<td>N = 2248</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: 100% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median age: 46 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity: 89% white</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sexuality: 100% MSM</td>
</tr>
<tr>
<td>Thurtle et al. (2016)(^{41})</td>
<td>Attendees of</td>
<td>NPS</td>
<td>Two clinics in London</td>
<td>N = 1472</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: 53% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 30 years</td>
</tr>
<tr>
<td>Lovett et al. (2014)(^{45})</td>
<td>Attendees of</td>
<td>Mephedrone,</td>
<td>Gay-friendly nightclubs</td>
<td>N = 397</td>
</tr>
<tr>
<td></td>
<td></td>
<td>methiopropamine</td>
<td></td>
<td>Sex: 89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 30 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex/gender: 82% male,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17% female, 1% transgender</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 30 years</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Ethnicity: 75% white,</td>
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<td>10% black, 10% mixed race,</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>4% Asian, 1% other</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sexuality: 70% homosexual,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9% bisexual, 17% heterosexual,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4% other</td>
</tr>
</tbody>
</table>

**TABLE 4** Summary study characteristics of surveys of NPS use in the UK \((continued)\)
<table>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Drug</th>
<th>Sampling</th>
<th>Participant characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measham et al. (2012)</td>
<td>Attenders of nightclubs</td>
<td>NPS</td>
<td>Nightclubs in Lancashire</td>
<td>N = 343</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: 48% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 23 years (range 17–55 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity: 96% white</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex(gender: 82% male, 15% female, 1% transgender, 2% other)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 30 years</td>
</tr>
<tr>
<td>Roche and Huke (2016)</td>
<td>Psychiatric populations</td>
<td>NPS</td>
<td>Eating disorders outpatients</td>
<td>N = 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No further data on study characteristics reported</td>
</tr>
<tr>
<td>Moore and Lesser (2015)</td>
<td>Psychiatric populations</td>
<td>NPS</td>
<td>Acute mental health services in Devon</td>
<td>N = 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No further data on study characteristics reported</td>
</tr>
<tr>
<td>Stanley et al. (2016)</td>
<td>Psychiatric populations</td>
<td>NPS</td>
<td>General adult psychiatric wards in a Scottish city</td>
<td>N = 388</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: 49% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 36 years (NPS users), 43 years (non-NPS users)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity: not reported</td>
</tr>
<tr>
<td>Winstock et al. (2011)</td>
<td>NPS users</td>
<td>Mephedrone</td>
<td>Recruited through dance music and clubbing website</td>
<td>N = 947</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: 60% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 24 years</td>
</tr>
<tr>
<td>Winstock et al. (2011)</td>
<td>NPS users</td>
<td>Mephedrone</td>
<td>Recruited through involvement in the dance music scene (subsample of Winstock et al. (2011))</td>
<td>N = 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: 77% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 25 years</td>
</tr>
<tr>
<td>Winstock et al. (2016)</td>
<td>Polydrug users</td>
<td>Methoxetamine</td>
<td>Online survey of UK-based polydrug users</td>
<td>N = 5367</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: 82% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: 25 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity: 91% white, 9% other</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sexuality: 78% heterosexual, 9% homosexual, 7% bisexual, 6% other</td>
</tr>
<tr>
<td>Fletcher et al. (2014)</td>
<td>NPS users</td>
<td>NPS</td>
<td>Tayside area</td>
<td>N = 687</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex: ratio of female to male participants was approximately 5 : 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age: most respondents were 20–64 years</td>
</tr>
</tbody>
</table>
Data on generic NPS use from nationally representative surveys are more limited. The CSEW\textsuperscript{963} and the AIPS\textsuperscript{904} began collecting data on generic NPS use only in 2014/15. The SCJS has been collecting data on generic NPS use since 2010/11.\textsuperscript{1009} However, comparisons of prevalence over time are difficult because specific substances included in this category have changed. Of particular note, the 2014/15 SCJS no longer categorised mephedrone as a ‘new drug’, which has a substantial impact on prevalence estimates of NPS use.\textsuperscript{1009} However, the advantage is that this is comparable to the CSEW\textsuperscript{963} and AIPS, thereby making comparisons across surveys possible in 2014/15 and potentially in the future. The European Commission\textsuperscript{915} also conducted a nationally representative survey of NPS use in Member States, including the UK.

Mephedrone use The lifetime prevalence of mephedrone use for all adults (aged $\geq$ 16 years) has remained relatively constant in the past 3–5 years of surveys. Estimates were similar in the CSEW\textsuperscript{963} and the AIPS\textsuperscript{904} with 2% of the population using mephedrone, compared with 1% in the SCJS.\textsuperscript{1009} Past year prevalence declined in both the CSEW\textsuperscript{963} (2010/11: 1.3% to 2014/15: 0.5%) and the SCJS (2010/11: 0.7% to 2014/15: 0.3%);\textsuperscript{1009} we could not find data to assess this on the AIPS.

Estimates for younger adults (aged 16–24 years) were two to three times higher than for all adults. Mephedrone lifetime use was 5–6% across years (2012/13, 2013/14, 2014/15) in the CSEW,\textsuperscript{963} and 4% in the SCJS (2012/13)\textsuperscript{1009} and AIPS (2010/11).\textsuperscript{904} Past year use declined from 4.4% in 2010/11 to 1.9% in 2014/15 in the CSEW,\textsuperscript{963} we could not assess whether there was a similar decline in SCJS\textsuperscript{1009} or AIPS.\textsuperscript{904} 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 focus only on the 2014/15 data.

For all adults, the prevalence of lifetime NPS use (excluding mephedrone) was 2% in the AIPS and SCJS\textsuperscript{1009} and slightly higher (3%) in the CSEW.\textsuperscript{963} NPS use was approximately two to three times higher in younger...
adults, at 4% (SCJS: 16–24 years), 6% (CSEW: 16–24 years) and 7% (AIPS: 15–34 years). The UK prevalence estimate of lifetime NPS use from the European Commission (2014) survey was higher (10%) than the other UK national surveys and higher than the average prevalence across European countries (8%).

All three UK national surveys found that men were approximately two to three times more likely than women to engage in NPS use. However, the European Commission did not find that NPS use differed by sex.

**Young people (aged 11–15 years)**

**NPS use** A Health and Social Care Information Centre (HSCIC; now NHS Digital) survey in England of 11- to 15-year-olds found that lifetime prevalence of NPS use was 2.5%. This was similar to the Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS), which found a prevalence of 2%. Both surveys found that 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. In Scotland, 1% of 13-year-olds and 4% of 15-year-olds reported NPS use. NPS use was slightly higher for boys than for girls in the SALSUS (2% boys and 1% girls) but there was no evidence of sex differences in the HSCIC survey.

**Mephedrone and other individual NPS** Mephedrone use was low in both the HSCIC survey (0.5%) and SALSUS (1%). In England, the prevalence remained relatively constant across the years 2012–14. In Scotland, there was a reduction from 2% in 2010 to 1% in 2013.

The SALSUS provided more data on individual NPS. 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 a 1% reported prevalence.

**Subpopulation studies**

**School children and university students**

Four additional studies 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. conducted an online survey using the Study Room website (see www.thestudentroom.co.uk). Participants’ ages ranged from 13 to 30 years, with a mean of 19 years. They reported the highest lifetime prevalence estimate (31%) of NPS use for any subpopulation in this group of website users. This was much higher than national surveys looking at a similar age group, for which lifetime prevalence of NPS use ranged from 4% to 10%. Corazza et al. found that the most commonly reported NPS used were mephedrone (41%), salvia (20%) and synthetic cannabinoids (11%). Mounsey et al. in a questionnaire survey of the schools population of eight schools (four private and four state schools) of 15- to 18-year-olds in Greater London, found a lifetime prevalence rate of 8% for NPS use. In contrast, Penney et al. 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- to 15-year-olds).

**Mephedrone and other individual NPS use** Estimates of mephedrone use differed widely in subpopulation surveys. The highest estimate (20%) was found by Dargan et al. in a survey of schools, colleges and universities in Tayside. Corazza et al. also found a relatively high rate of 13% for mephedrone use. This contrasted with the Penney et al. survey of school children, which reported a much lower prevalence (0.5%). All data reported here refer to lifetime prevalence.
Data on other individual NPS were limited. Corazza et al reported prevalence rates of 6% for salvia and 3% for synthetic cannabinoid use. Penney et al. provided prevalence data on synthetic cannabinoids (0.7%) and methoxetamine (0.2%).

**Attendees of nightclubs**

Surveys were conducted by the same research team in gay-friendly nightclubs in south-east London in 2010, 2011, 2012 and 2013. Lifetime use of mephedrone was high: 54% in 2011 and up to 72% in 2013. 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 was 21% in 2010. In 2011, this increased to 53% for past month use and 41% for use that night. However, in 2013, past month use had declined to only 6%. Other NPS use was much less frequent across all years of the surveys including 5,6-methylenedioxy-2-aminodioanide (MDA), benzylpiperazine (BZP), methiopropamine and methoxetamine.

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

**Cybernauts**

O’Brien et al. conducted an online survey of ‘cybernauts’ (n = 183). Frequency of NPS use was high, with 32% of participants reporting using in the past week. Participants identified themselves as knowledgeable consumers, who used the internet to accumulate information about NPS and who also shared their own experiences and informed fellow users of potential harms.

**Psychiatric populations**

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

Stanley et al. 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, to be male and to have a forensic history than non-NPS users.

Moore and Lesser also conducted a retrospective review of 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 that their use was associated with their clinical presentation.

**Attendees of sexually transmitted infection clinics**

Chung et al. conducted a retrospective case review of 431 sexually transmitted infection screens in 223 human immunodeficiency virus (HIV)-positive men who have sex with men (MSM). Prevalence was high, with 24% reporting lifetime mephedrone use. However, a larger study (n = 2248) of HIV-positive MSM attending 10 HIV clinics found a much lower prevalence estimate for mephedrone use (7%).

Thurtle et al. surveyed attendees of two sexual health clinics in central London (n = 1626), 44% of whom were MSM. Regular monthly use was relatively low (1.6%) in the total sample and lower in 16- to 24-year-olds (0.3%). Prevalence for other NPS, such as ivory wave, spice, naphyrone and methylone, was even lower.
**Prisoners**
Baker conducted a non-randomly sampled survey in a prison in Rochester. Questionnaires were provided in classrooms and activity areas within prison, as well as to prisoners employed as cleaners. A total of 66% reported that it was fairly easy or very easy to buy spice, but the figure was higher for those who reported using spice (88%). A total of 43% reported any use of synthetic cannabinoids (‘spice’), 39% reported use in prison, 22% reported being a current user of spice. Of those using spice in prison, 21% said that they would still use spice outside, 39% said that they would use an alternative drug and 23% reported that they would not have used anything. The most frequently given reasons for using spice were making time pass quicker (37%), relaxation (22%) and it 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 that spice was more dangerous than cannabis (56%), and 13% thought that spice was as safe as cannabis. A total of 57% of those who used spice viewed it as fairly or very addictive.

**Homeless populations**
Homeless Link 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 who reported using NPS did so on a daily basis (66%). A further 14% engaged in NPS use 5 or 6 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 and spice). Most used at least three types of NPS (84%).

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

**Targeted studies of novel psychoactive substance users**

**General novel psychoactive substance use**
All studies described here do not employ random or other formal sampling methods. Fletcher et al. 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 1 year previously and were thus no longer users. In addition, 10% had used in the past week, 20% had used in the past month, and 20% had used between 6 months and 1 year ago. Mephedrone was the most common drug reported. NPS were most commonly used as tablets or powder, and were snorted or smoked. A NPS was most commonly first tried between the ages of 16 and 19 years. A total of 19% reported that a NPS was the first drug that they had ever taken. Cannabis was much more commonly reported as the first drug taken (51%), and cocaine rather than a NPS being the first drug taken was slightly less common (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. 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 methylenedioxypyrovalerone (MDPV) (2%) use. Among participants who had reported lifetime mephedrone use, 94% reported use in the past year and 80% reported use in the past month. The most common route of administration was snorting (66%). Those who snorted mephedrone rated it as more addictive than cocaine and as carrying more risk.
Winstock et al.\textsuperscript{15} conducted a more detailed telephone survey of 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% used ecstasy. Possible stimulant dependence (three or more dependence symptoms) was reported in 30% of participants.

Brookman\textsuperscript{884} 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). A total of 46% used mephedrone on a daily basis, 15% used it every other day, 19% used mephedrone once a week, 6% used it every other week and 13% used it once a month. Almost two-thirds (63%) snorted the drug, 56% injected it and 45% injected it orally. 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 the 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 becoming violent as a result of mephedrone use.

\textbf{Methoxetamine}

Winstock et al.\textsuperscript{1001} reported on a subsample ($n=326$) of past year users of methoxetamine from a larger online survey (Global Drug Survey) of 7700 UK-based polydrug users (other material from this survey is reported only as news items in mass media and thus is not eligible for inclusion, as there were no reports of study findings available). This comprised 4% of the overall survey population. A total of 25% of past month methoxetamine users reported use on 4 or 5 days of that month. Motivations for use of methoxetamine rather than ketamine were that it was easier to get hold of, that it was less damaging to their kidneys or bladder or that users preferred the effects. A total of 89% reported first use via the intranasal route.

\textbf{Injecting drug users}

A harm-reduction service in Lothian conducted a survey of their NPS-using clients ($n=100$).\textsuperscript{959} 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. methiopropamine) and mephedrone. Heroin (73%), methadone (49%) and benzodiazepines (51%) were also commonly used in this sample. Twenty per cent reported sharing needles, and approximately half shared injecting equipment. A total of 22% of participants had stopped using NPS. The most common reason was the physical or mental health impact, with 54% receiving medical treatment as a result of NPS use.

\textbf{Summary}

The most robust nationally representative data on NPS use are for mephedrone, for which CSEW and SCJS have been conducting national surveys since 2010/11. However, we acknowledge that there are a number of limitations to the data on mephedrone use and NPS use in general. For example, although participants may report using a substance (such as mephedrone), the names of NPS are used interchangeably, with a number of other types of drug going by the same name. Therefore, there is inherent uncertainty in the reported use 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 in women and in young adults than in older adults. It appears that prevalence rates of recent mephedrone use are declining substantially; for example, the CSEW found a halving of prevalence from 2010/11 to 2014/15 in both adult and young adult samples. Nationally representative data on NPS use as a whole and on the use of particular NPS other than mephedrone are much less developed, and comparisons across years are not yet possible. Considerable uncertainties about basic data therefore persist in terms of monitoring this issue.
Surveys of school children have also found low prevalence for mephedrone use and NPS use as a whole. Prevalence rates are higher in older children than in younger children and higher in boys than in 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, differences in prevalence among particular subgroups of school children or methodological issues.

Data on particular sentinel populations likely to be at greater risk of NPS are growing, although they remain limited. At present, there are some data on attendees of gay-friendly nightclubs for whom trends in mephedrone use can be assessed. However, the main limitations of such studies regard their generalisability across the UK and the 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 nightclub attendees, prisoners, homeless people and 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 to enable such work to contribute substantially to decision-making.

**Systematic reviews**

The 10 included systematic reviews118,127,137,286,293,409,502,561,710,714 (see Chapter 2, Methods, Definitions) are summarised in Table 5 by NPS type. The majority address clinical problems/harms attributable to NPS, with one also including data on clinical management. One was on all NPS, five were on synthetic cannabinoids, two were on synthetic cathinones and two were on phenethylamines.

**All novel psychoactive substances**

Gray et al.286 focused on mental and physical health effects and fatalities attributable to NPS use among adults with a diagnosis of severe mental illness. Fourteen 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 psychotic symptoms (in some cases they were different in form and content from the patients’ usual symptoms) and 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.286 reported one death from the case reports.

**Synthetic cannabinoids**

**User groups**

Castaneto et al.137 included nine surveys on synthetic cannabinoid use. One study was a world-wide online survey and another was an online survey of online drug forum users. The rest were single-country surveys of self-selected individuals (five in the USA, including two among military personnel and one among high school students; one in Australia; and one in the UK). They reported that the majority of synthetic cannabinoid users are young adults who perceive synthetic cannabinoid to be safer than non-cannabinoid illicit drugs and a favourable cannabis alternative that elicits a cannabis-like ‘high’ while avoiding detection by standard drug screens. Most synthetic cannabinoid smokers are men aged between 13 and 59 years, many of whom have a history of polydrug use (e.g. cannabis, alcohol and nicotine).

**Side effects**

Brewer and Collins118 summarised 24 case reports (settings and study regions were not specified in the report) with > 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. reported on nine studies (five case reports of toxicity, three human toxicology studies evaluating synthetic cannabinoid detection in serum and urine samples, and one semistructured interview qualitative study among inpatients on a forensic and rehabilitative psychiatric unit) with a total of 28 cases. They reported side effects including an alteration in mood or perception, conjunctival injection, xerostomia, increased pulse, hypertension, hyperventilation, diaphoresis, numbness and tingling, nausea, vomiting, tremors, muscle twitching and seizures, as well as more severe adverse effects including acute anxiety and psychotic reactions, particularly in those with an underlying biologic vulnerability.

**TABLE 5** Systematic reviews

<table>
<thead>
<tr>
<th>Study</th>
<th>Principal focus</th>
<th>Population</th>
<th>NPS type</th>
<th>Types of included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewer and Collins (2014)</td>
<td>Problems/harms: clinical manifestations</td>
<td>Adolescents and adults: age range 12–67 years</td>
<td>Synthetic cannabinoids</td>
<td>Case reports</td>
</tr>
<tr>
<td>Busardo et al. (2015)</td>
<td>Problems/harms: fatalities</td>
<td>Cases with analytically confirmed presence of mephedrone</td>
<td>Synthetic cathinone: mephedrone</td>
<td>Case reports</td>
</tr>
<tr>
<td>Castaneto et al. (2014)</td>
<td>Use</td>
<td>Not specified</td>
<td>Synthetic cannabinoids</td>
<td>Wide ranging including surveys, case reports, series and retrospective case reviews</td>
</tr>
<tr>
<td>Gray et al. (2016)</td>
<td>Problems/harms: mental and physical health effects and fatalities</td>
<td>Adults (aged 18 years or over) with a diagnosis of SMI and a history of NPS use</td>
<td>All NPS</td>
<td>Case reports/series, qualitative interviews, explorative questionnaire study</td>
</tr>
<tr>
<td>Gunderson et al. (2012)</td>
<td>Problems/harms: clinical manifestations</td>
<td>Not specified</td>
<td>Synthetic cannabinoids</td>
<td>Case reports; semistructured interviews; toxicology laboratory studies</td>
</tr>
<tr>
<td>Miotto et al. (2013)</td>
<td>Problems/harms: physical and neuropsychiatric adverse effects; withdrawal</td>
<td>Not specified</td>
<td>Synthetic cathinones: bath salts</td>
<td>Retrospective studies, toxicology data, chemical analyses studies and case reports</td>
</tr>
<tr>
<td>Papanti et al. (2013)</td>
<td>Problems/harms: clinical manifestations (psychosis)</td>
<td>Psychiatric treatment patients; A&amp;E patients; general public calls to toxicology/poison centres</td>
<td>Synthetic cannabinoids</td>
<td>Retrospective toxicology surveys; case reports/series; human laboratory studies; interviews/surveys with synthetic cannabinoids users</td>
</tr>
<tr>
<td>Suzuki et al. (2015)</td>
<td>Problems/harms: clinical manifestations and fatalities</td>
<td>Not specified</td>
<td>Phenethylamines: NBOMe</td>
<td>Case reports</td>
</tr>
<tr>
<td>Tait et al. (2016)</td>
<td>Problems/harms: adverse events</td>
<td>Hospital presentations and poison centre data</td>
<td>Synthetic cannabinoids</td>
<td>Case series (≥ 10 cases)</td>
</tr>
<tr>
<td></td>
<td>Responses: clinical management (associated treatment of adverse events)</td>
<td></td>
<td></td>
<td>Case reports (≤ 10 cases)</td>
</tr>
</tbody>
</table>

NBOMe, N-methoxybenzyl; SMI, serious mental illness.
Papanti et al.\textsuperscript{56} reported on 41 studies with > 2200 individuals with an average age of 23 years and a male-to-female ratio of more than 3 : 1. The studies included retrospective toxicology surveys (\(n = 9\)), case reports/case series (\(n = 25\)), human laboratory studies assessing potential acute toxicological effects (\(n = 4\)) and interviews/surveys focusing on self-reported harms/unwanted effects identified in users (\(n = 3\)). Eleven studies were carried out in psychiatric treatment settings, five in consultation/liaison psychiatry settings following presentation to A&E departments, two in substance abuse services and one in a forensic setting. Furthermore, 15 studies were carried out in A&E settings, whereas nine included retrospective toxicology/poison centres’ studies analysing 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 synthetic cannabinoid recorded psychotic disturbances in 19–41\% of cases. Other psychopathological issues reported in association with synthetic cannabinoid intake included paranoid thoughts/combative ness/irritability (nine studies), altered perceptions/mental status (six studies), thought disorganisation (four studies), confusion (three studies), agitation/anxiety/panic attacks/restlessness (nine studies), and depression/suicidal thoughts (three studies).

Tait et al.\textsuperscript{710} reported on 106 papers, letters and conference abstracts representing > 4000 cases. They also included \(\approx 1900\) cases from the USA National Poison Data System for 9 months in 2010 in their report. They reported a prototypical ED presentation 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 perimesencephalic subarachnoid haemorrhage, middle cerebral artery occlusion, myocardial infarction in adolescent males and cardiac arrest. Acute kidney injury was reported in 29 cases in total, all of which required hospitalisation. Generalised tonic–clonic seizures were reported in 4\% of poison centre synthetic cannabinoid reports, 14\% of ED synthetic cannabinoid presentations and 15\% of paediatric (0–19 years) poison centre synthetic cannabinoid reports. Gastrointestinal side effects included nausea and vomiting (13–94\% of presentations) and abdominal pain, which was relieved by hot showers; these effects are 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 the onset of psychosis (10 cases reported) in many cases with concurrent use of other substances. These cases required hospitalisation and symptoms persisted for up to 5 months and potentially included affective, suicidal or psychotic symptoms, significant self-injury, catatonic features and Capgras delusion. Synthetic cannabinoids were reported to potentially worsen existing psychosis attributable to other causes. Withdrawal symptoms were also reported in two cases. The treatment of adverse effects was reported to be mostly observation and supportive care (intravenous fluids, benzodiazepines, oxygen) with discharge within 8 hours.

Castaneto et al.\textsuperscript{137} reported acute synthetic cannabinoid intoxication that could lead to ED presentation and hospitalisation and that required supportive care, benzodiazepines and fluids. Although most such patients were released within 24 hours of admission, severe adverse effects such as cardiotoxicity, acute kidney injury and psychosis resulted in hospitalisation for as long as 2 weeks. Some chronic synthetic cannabinoid users experienced withdrawal symptoms when they stopped drug intake.

**Fatalities**

Castaneto et al.\textsuperscript{137} reported that deaths directly linked to synthetic cannabinoid use were quite rare (only four fatalities identified). Tait et al.\textsuperscript{710} reported at least 26 synthetic cannabinoid deaths: 22 (maximum 27) in the USA, three in Europe and one in Japan.
Synthetic cathinones

Side effects
The systematic review by Miotto et al.502 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 oedema, diaphoresis, hyper-reflexia, hypertension, hyperthermia, jaw tension, muscle spasms, mydriasis, myocardial infarction, respiratory distress, seizures, tachycardia, palpitations, chest pain, tremors, nausea, headaches, infections, sweating with a 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 is described as similar to, or more intense than, withdrawal from other stimulants.502 Surveyed mephedrone users identify withdrawal symptoms similar to the Diagnostic and Statistical Manual of Mental Disorders criteria for stimulant withdrawal.502

Fatalities
The review by Busardo et al.127 of fatalities attributable to mephedrone use included 10 case reports representing 18 fatal cases with analytically confirmed mephedrone in biological samples taken from the deceased. Of these fatalities, 14 were male, 2 were female and the sex was unknown in 2 cases; the average age was 28 years (range 17–55 years). Death was attributed to mephedrone intoxication in nine cases (range of post-mortem blood mephedrone concentration 1.33–22 mg/l). Six deaths were 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.409 included 14 case reports in total, of which nine reported 17 cases of intoxication (including one case of attempted suicide) attributable to N-methoxybenzyl (NBOMe). Only one of these studies had a clearly identified study region/country, namely the UK. Clinical manifestations of intoxication included serotonergic and sympathomimetic symptoms.

The review by Suzuki et al.714 included 10 case reports, representing 20 individual patients [85% male, average age of 20.3 years (range 15–31 years)]. The most common adverse effects included agitation (85%), tachycardia (85%), hypertension (65%), dilated pupils (55%), delirium (40%), hallucinations (40%), seizures (40%), tachypnea (25%) and fever (25%). The most common laboratory abnormalities were elevated creatine kinase levels (45%), leucocytosis (25%), hyperglycaemia (20%), transaminitis (15%) and elevated creatinine levels (10%), which were identified in only three (15%) cases. Seven cases were discharged after a short period (<15 hours) of observation, whereas eight (40%) required admission to an intensive care unit. One (5%) required surgery for a self-inflicted stab wound.

Fatalities
From the 14 case reports in the review by Kyriakou et al.409 four reported on five deaths. Suzuki et al.714 reported three fatalities.

Summary
The literature categorised here 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 neurological manifestations, and cardiovascular, renal and gastrointestinal manifestations being the most commonly reported. Treatment of these effects appears mostly to involve observation and supportive care, although in severe cases may involve hospitalisation.
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 International Classification of Diseases, Tenth Edition codes by which to identify these.10 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 a population context, including dedicated attention to use prevalence and policy issues, or to 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).183,483,544,876,881,884,940,1011

Effects of particular novel psychoactive substances

Mephedrone
Two studies (reported in four papers) focused on the effects and side effects of mephedrone. Participants were recruited through personal contacts of the researchers and through internet forums. The findings from O’Neill544 combine data from McElrath and Van Hout940 and McElrath and O’Neill;483 therefore, the focus will be on the O’Neill544 paper for this study. The author interviewed two samples of mephedrone users in Northern Ireland (study 1 n = 23 and study 2 n = 45) with a similar age range (19–51 years and 19–49 years, respectively). Study 2 had a higher proportion of males (62%) than study 1 (48%). Brookman884 interviewed a sample of 12 mephedrone users in Wales with a mean age of 28 years, 75% of whom were male.

Both studies544,884 reported similar findings in terms of subjective effects, such as positive feelings (e.g. euphoria and well-being), and physical side effects (e.g. damage to the 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.884 Just over half of 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 to be a result of the ‘come down’ phase or to be associated with acquisitive crime needed to fund the drug habit.

Salvia
Dalgarno183 conducted e-mail interviews with 10 salvia users recruited from internet forums, 70% of whom were male and who ranged in age from 23 to 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: sometimes users experienced pleasant hallucinogenic effects, although not every time they used salvia. Two participants reported some similarities to ketamine, although the effects were less predictable.

Subgroups

Chemsex
One study881 conducted interviews of 30 gay men in London, of whom most (27/30) used mephedrone, typically in combination with GHB/GBL. Their mean age was 36 years and just under half (13/30) were HIV positive. Frequency of use during sex differed among participants; some used chemsex drugs only infrequently with a regular partner, and some used them 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 of participants engaged in more adventurous sexual activity (e.g. ano-brachial intercourse and being analy receptive to multiple men in quick succession) than when they were not using drugs. However, it is unclear whether or not this led to a greater risk of health harm. Although one-third reported injecting drugs, 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 employment (missing work owing to withdrawal effects and a lack of career development associated with apathy and depression).

**Prisoners**

There was one small study of prisoners (four males in a young offenders’ prison) that focused on ‘spice’ (a synthetic cannabinoid) use. All four had tried spice first in prison, after having used illegal drugs outside prison. The main reasons reported for use were it not being detected in mandatory drug testing and that it made time go quicker. The most common side effects were paranoia, a racing heart 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. 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 Orders (TCDOs) that were being employed at that time.

O’Neill 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.

Wallis conducted interviews with retailers and early innovators in NPS use, and also with enforcement professionals, policy-makers and EWS representatives (sample size not reported). Participants expected that the supply of NPS was unlikely to be affected by the most recent UK legislation (Psychoactive Substances Act 2016) designed to prohibit all NPS. They thought that such legislation would be unlikely to affect 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 through which to communicate 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 the use of particular NPS receiving attention in the mass media, even when reported negatively as dangerous drugs.

**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 summarises data from quantitative policy evaluation studies by country. Seven of these studies were conducted in the UK, five were conducted in the USA, two were conducted in New Zealand and one each was conducted in Australia, Finland and the Republic of Ireland. The study characteristics including country, intervention/response, study setting, publication type, NPS type and study design are summarised in Table 6. There was also one study for which the country was not specified. Sixteen of these studies were on legislative control and one was on a multpronged approach that included surveillance and reporting, in addition to law enforcement and legislative changes.
<table>
<thead>
<tr>
<th>Study country</th>
<th>Setting and publication type</th>
<th>Intervention</th>
<th>NPS type</th>
<th>Study design</th>
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<tbody>
<tr>
<td>Brown et al. (2014),</td>
<td>Poisons Centre; conference abstract</td>
<td>9 June 2013: legislation and enforcement by state and federal governments to restrict the sale of synthetic cannabinoids</td>
<td>Cannabinoids</td>
<td>Before-and-after comparison through retrospective review of Poisons Information Centre Data (5 months prior to and 5 months after ban)</td>
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<tr>
<td>Christie and MacFarlane (2016),</td>
<td>Addiction treatment setting; letter to editor</td>
<td>May 2014: ban of NPS under the Psychoactive Substances Act</td>
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<td>Dargan et al. (2011),</td>
<td>Community setting; peer-reviewed journal article</td>
<td>December 2009: the classification of synthetic cannabinoid receptor agonist constituents of spice was Class B in the UK</td>
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<td>Kriikku et al. (2015),</td>
<td>Police custody: driving under the influence of drugs; toxicology unit: autopsy cases; peer-reviewed journal article</td>
<td>Ban of MDPV in June 2010</td>
<td>Cathinone: MDPV</td>
<td>Before-and-after comparison</td>
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<td>Finland</td>
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<td>Loeffler and Craig (2013),</td>
<td>Poison centre; letter to editor</td>
<td>The 21 October 2011 temporary federal ban on a number of bath salt compounds in the USA</td>
<td>Cathinones: bath salts; mephedrone; methoxetamine</td>
<td>Before-and-after comparison using data from national poison control centres</td>
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<td>USA and UK</td>
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<td>April 2010: mephedrone ban in the UK</td>
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<td>April 2012: ban on methoxetamine in the UK</td>
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<tr>
<td>Pettie et al. (2016),</td>
<td>General hospital inpatient setting; conference abstract</td>
<td>10 April 2015: control of methylphenidate-based NPS by the UK government under the Misuse of Drugs Act 1971 (Temporary Class Drug Order)</td>
<td>Methylphenidate-based NPS</td>
<td>Before-and-after comparison using hospital admissions data</td>
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<tr>
<td>UK</td>
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<tr>
<td>Plumb et al. (2012),</td>
<td>Poison centre; conference abstract</td>
<td>A state law making spice illegal</td>
<td>Cannabinoids</td>
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<td>Reuter (2016),</td>
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<td>Ryan and Arnold (2012),</td>
<td>Poison centre; conference abstract</td>
<td>Control of six cathinones under Schedule I in Louisiana on 6 January 2011</td>
<td>Cathinones</td>
<td>Before-and-after comparison through secondary analysis of the National Poison Data System (December 2010 – month prior; and February 2011– month after ban)</td>
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TABLE 6 Characteristics of and results from quantitative policy evaluation studies (continued)

<table>
<thead>
<tr>
<th>Study country</th>
<th>Setting and publication type</th>
<th>Intervention</th>
<th>NPS type</th>
<th>Study design</th>
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<td>Sheridan et al.</td>
<td>Internet; peer-reviewed journal article</td>
<td>Prohibition of BZP-containing party pills and related substances from 1 April 2008 (provided for a 6-month amnesty period in which possession of small quantities for personal use was permitted)</td>
<td>Piperazines: BZP and related substances</td>
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<td>Smyth et al.</td>
<td>Specialist alcohol treatment service: Youth Drug and Alcohol service; peer-reviewed journal article</td>
<td>2010: legislative changes in Ireland – adding &gt; 100 NPS to the Misuse of Drugs Act and restrictions on the sale of psychoactive substances</td>
<td>All NPS</td>
<td>Before-and-after comparisons (before: 6 months prior to 10 May 2010; after: 6 months after 10 May 2011) using data from the National Drug Treatment Report System</td>
</tr>
<tr>
<td>Wahl and Theobold</td>
<td>Poison centre; conference abstract</td>
<td>A multipronged approach of surveillance, reporting, law enforcement partnership and legislative changes</td>
<td>All NPS</td>
<td>Before-and-after comparison with national averages</td>
</tr>
<tr>
<td>Winstock et al.</td>
<td>Internet survey; letter to editor</td>
<td>April 2010: classification of mephedrone and similar compounds as Class B substances in the UK under the Misuse of Drugs Act</td>
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</tr>
<tr>
<td>Wood et al.</td>
<td>ED; conference abstract</td>
<td>Control of cathinones under the UK Misuse of Drugs Act 1971 on 16 April 2010</td>
<td>Cathinones: mephedrone</td>
<td>Before-and-after comparison through secondary analysis of ED data (8 months each side)</td>
</tr>
<tr>
<td>Wood et al.</td>
<td>ED; peer-reviewed journal article</td>
<td>Control of cathinones under the UK Misuse of Drugs Act 1971 on 16 April 2010</td>
<td>Cathinones: mephedrone</td>
<td>Before-and-after comparison through secondary analysis of ED data (12 months each side)</td>
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<tr>
<td>Wood et al.</td>
<td>Nightclubs (gay-friendly); conference abstract</td>
<td>Control of methoxetamine under the Temporary Class Drug Order (TCDO) legislation in March 2012</td>
<td>Methoxetamine</td>
<td>Before-and-after survey comparison (July 2011 and July 2012)</td>
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UK
Dargan et al. 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. found a decrease in the number who 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 et al. reported a decrease in the number of poison control centre contacts regarding mephedrone. Wood et al. reported a reduction in the levels of presentations to the ED with toxicity associated with self-reported mephedrone use, from 57 in the 8 months before the reclassification to 47 in the 8 months after. In another study, the level of presentations fell significantly in the first 6 months following reclassification to a steady level of three to five presentations every 2 months in months 7–12 following reclassification.

Loeffler et al. reported a decrease in the number of poison control centre contacts regarding methoxetamine after its ban in the UK in April 2012. However, Wood et al. reported a significant increase in lifetime, past year and past month use of methoxetamine from 2011 to 2012 among ED attendees (lifetime 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 TCDO legislation in March 2012. Data were collected via two non-randomly sampled surveys, with 315 respondents in July 2011 and 330 respondents in July 2012, respectively.

A study by Pettie et al. 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 6 months before and 263 in the 6 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 to eight post-control. However, synthetic cannabinoid admissions increased from 22 patients before to 60 patients after the legislation, as stimulant NPS admissions (methiopropamine and cathinones) increased 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 2 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. found that the ban resulted in a decrease in the number of poison centre contacts regarding mephedrone and bath salt compounds. Reuter 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 criminalisation. Control of six cathinones under Schedule I in Louisiana on 6 January 2011 was reported to have resulted in a 94.5% decrease in the number of synthetic cathinone calls to the Louisiana Poison Centre from 110 to 6.

A conference abstract by Wahl and Theobold reported that a state-based multipronged 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. reported on a state law making spice illegal which resulted in significant decrease in the rates of synthetic cannabinoid exposures reported to the poison centre from 16 months before to 13 months after the legislation.

New Zealand

On 1 April 2008, BZP-containing party pills and related substances were prohibited in New Zealand. The prohibition provided for a 6-month amnesty period in which possession of small quantities for personal use was permitted. A study by Sheridan et al. 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 MacFarlane\textsuperscript{162} 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.\textsuperscript{119} reported a reduction in the number of synthetic cannabinoid cases reported to the poison information centre from 70 in the 5 months prior to June 2013 legislation and enforcement by state and federal governments to restrict their sale to 20 cases in the 5 months following.

Finland
Kriikku et al.\textsuperscript{950} reported that the number of MDPV-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 > 100 NPS being added onto the Misuse of Drugs Act, and restrictions on the sale of psychoactive substances. Smyth et al.\textsuperscript{978} 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, health-care utilisation and self-reported exposure and toxicity. Positive outcomes are generally observed, although studies typically utilised 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 the 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 terms of being capable of informing public health decision-making. Nationally representative surveys on prevalence are available for the UK. However, the most comprehensive data are 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 are not yet possible. Data on reasons for, and patterns of, use are largely limited to a small number of qualitative studies.

For problems or harms attributable 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 neurological manifestations and cardiovascular, renal and gastrointestinal adverse effects, the treatment of which 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 attributable 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. Seventeen of these studies were quantitative evaluation studies, 16 of which evaluated the effects of legislative prohibitions of NPS use or supply, and one of which evaluated a multicomponent 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, health-care utilisation 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 utilised a multistaged, multipronged analytical approach, as summarised in Figure 13. This involved the development of a conceptual framework hypothesising an evidence-informed public health approach to NPS use in the UK (see Chapter 3) and systematic review work that 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 minimise 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 of 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 13, the findings of the review work, conceptual framework and the draft research recommendations derived from these were shared and

![Diagram](https://via.placeholder.com/150)

**FIGURE 13** Overarching analytical approach. 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.
discussed with one NPS user, 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 was utilised to refine and finalise 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.

Limitations
A risk-of-bias assessment was not conducted because of the large number of articles identified. In addition to the size of this body of 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. In most cases the study designs 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 while mindful of time pressures and in light of the need to undertake this work quickly in order for it 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 in which literature is scarce (a priori research questions 2, 3, 5–10 and 12). Second, even in those areas in which 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 attributable 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, as well as 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 NPS, also known as ‘legal highs’.¹⁰¹⁶ NPS can be defined as narcotic or psychotropic drugs that are not currently controlled under the United Nations drug control conventions.⁹⁸²,¹⁰¹⁷ The principal drug types currently identified in the UK are presented in Table 7. The number of new substances reported annually to the European Union EWS increased seven-fold between 2008 and 2013.⁹⁰⁹ 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.⁹⁷⁹,⁹⁸² It is thus appropriate to question the precise meaning of the term, and the value of such a category.

Novel psychoactive substances have posed challenging problems for policy-makers. They have become widely available through the internet at a low cost, and their legal status may promote connotations of safety before their possession is made illegal.⁹¹⁰,¹⁰¹⁷ Technological developments and the globalisation of trade and communications have facilitated major innovations in drug production and supply.¹² Refinements can be made to the design of synthetic mood-altering drugs rapidly, in response to consumer demand, and such drugs can be 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’.⁹⁸² For the UK, the most obvious demand to date has been among existing drug users who have extended their repertoires.

<table>
<thead>
<tr>
<th>NPS type</th>
<th>Description</th>
<th>Example(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic cannabino</td>
<td>Chemicals that are often similar in molecular structure to THC, the main psychoactive component in cannabis. The term may also describe chemicals with different structures but similar effects. Effects: similar to cannabis</td>
<td>‘spice gold’</td>
</tr>
<tr>
<td>Synthetic cathinones</td>
<td>Related to cathinone, a monamine alkaloid and a key stimulant in khat. The most common synthetic cathinone used as an NPS is mephedrone. Effects: stimulant similar to amphetamine, cocaine and MDMA</td>
<td>‘m-cat’ (mephedrone), ‘mexe’ (mexedrone)</td>
</tr>
<tr>
<td>Phenthylamines</td>
<td>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</td>
<td>‘Bromo-Dragonfly’, ‘FLY’</td>
</tr>
<tr>
<td>Piperazines</td>
<td>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 mCPP. Effects: euphoric, similar to MDMA</td>
<td>‘party pills’, ‘smileys’</td>
</tr>
</tbody>
</table>

mCPP, meta-chlorophenylpiperazine; THC, Δ⁹-tetrahydrocannabinol.
Sources: EMCDDA and UNODC.

Note
Definitions of NPS vary and GHB and ketamine are sometimes included. They are excluded here because they are extensively legally controlled and are not recently synthesised.

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rather than the recruitment of new populations. Nonetheless, the UK Government’s ACMD has identified this phenomenon as having ‘changed the face of the drug scene remarkably and with rapidity’. 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. 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 literature 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 multisectoral 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 on 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 are 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. Although a public health approach to drugs is often counterpoised 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. In addition, treatments such as opioid substitution treatment can reduce crime. While initially introducing TCDOs 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.

Decriminalisation of drug use and other recent global policy innovations, including the quasi-legalisation of cannabis production and supply in some US states and in Uruguay, provide another context for thinking about NPS. Data are beginning to emerge on the effects of these policy changes, although rigorous evaluation studies are needed. The use of drugs remains a controversial and difficult issue for society, although seemingly not as difficult as it once was. 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. 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.
**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.\(^{1036-1038}\) 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 well-being.\(^{1039,1040}\)

The underpinning rationale for strategic public health approaches that 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).\(^{1041,1042}\) 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.\(^{1041,1042}\)

Many contemporary public health challenges have been conceptualised as requiring complex adaptive system changes.\(^{1036,1038}\) Mehta et al.\(^{1042}\) provide a useful example of how contemporary thinking on public mental health can draw on well-established ideas, such as the biopsychosocial model of health, and about levels of prevention in addressing such complex challenges. Complex challenges often require that careful attention is given to future risks, which are somewhat unpredictable in scale and are likely to impact differently on different groups,\(^{1044}\) rather than to 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.\(^{1045,1046}\)

The social ecological framework offers one way of thinking about complex public health issues.\(^{1047}\) This also encourages multilevel conceptualisations of problems and invites multilevel strategic responses.\(^{1048}\)

For example, risk behaviours and intervention targets can be understood as being 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.\(^{1049}\)

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.\(^{1050}\) Relevant unhealthy behaviours cluster, particularly among more socioeconomically deprived populations. The World Health Organization Commission on childhood obesity uses a multilevel 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.\(^{1051}\)

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, which we shall revisit to interrogate their validity. We hypothesise that the challenges posed by NPS have 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.\(^{1052,1056}\) *Figure 14* provides a conceptual map of key individual-level risks and harms attributable 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 life-course stages. Prevention therefore has the potential to interrupt the evolution of harm over time, and this is insufficiently recognised.\(^{1052}\)

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 health.
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.

Problems also manifest themselves at levels beyond the individual user, for example involving family members and local communities. Harms to society, for example, 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, quality-adjusted life-years (QALYs) lost, and by applying a monetary value to QALYs lost. Impacts on 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 that 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.
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 that 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 doing so. 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.

**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 does not 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 are 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, although he definitely would not consider himself an alcoholic or feel comfortable talking to his general practitioner 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 such 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 has not used any drugs because, he says, he does not like smoking and has heard bad things about pills and powders.

**TABLE 8** Examples of public health opportunities for responding to risk

<table>
<thead>
<tr>
<th>Approach</th>
<th>National</th>
<th>Local</th>
<th>Family and peers</th>
<th>Individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health</td>
<td>Health services and public health policies; tobacco control policies</td>
<td>Local health service provisions and public health actions</td>
<td>Parental general practice and other NHS contacts; peer network intervention projects; health promotion campaigns</td>
<td>NHS contacts (e.g. general practice, sexual health services, A&amp;E); online and telephone helplines; counselling services</td>
</tr>
<tr>
<td>Multisectoral</td>
<td>Housing, employment, education and welfare and economic policies; drug and alcohol policies</td>
<td>Policing, education, community development, licensing and other local authority policies and services</td>
<td>School drug education; youth services provisions; family support services; community groups</td>
<td>School mentoring and counselling; criminal justice system contacts</td>
</tr>
</tbody>
</table>
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 subgroups), as has happened, for example, in relation to tobacco.\textsuperscript{1056} 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.\textsuperscript{1056} It is also well established that problematic drug use is more concentrated in deprived communities.\textsuperscript{1057-1059} This consideration suggests the need for an integrated strategy of multilevel whole-population and vulnerable subpopulation 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 owing to the devolved nature of the UK public health system.\textsuperscript{1060}

\section*{A priori data needs}

Having considered hypothetical determinants of NPS use, risk and harm, and the breadth of possible responses, attention to the empirical data needed to inform public health decision-making is warranted. Acute health and wider problems will be experienced following particular episodes of use, most likely in relation to intoxication or direct poisoning (see Figure 14).\textsuperscript{1024} Presentations to health services and community safety indicators may provide data on trends in the 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 becomes heavier, risks will accumulate faster.\textsuperscript{1022} 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 detailed 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. Dedicated attention to individual NPS drug types is also needed, as the public health burden associated with each will vary according to the harms that are consequent on their use and to their use prevalence. Capacity to identify new NPS early, 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 as a result of 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,\textsuperscript{1061} although it is largely driven by the extent of involvement in drug use.\textsuperscript{1062} Dependence may occur in isolation from other psychosocial difficulties, although this is rare in addiction treatment populations.\textsuperscript{1063} Dependence itself is also an important mediator of other harms.\textsuperscript{1024} Scrutiny of routine health services data will be useful for the examination of trends in dependence and other presenting problems,\textsuperscript{1064} and will be quite likely to 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. First, 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. Second, it is assumed that NPS use is identifiable, either as a result of self-presentation or toxicology, the provision for which will vary across settings. There may be many circumstances in which this is problematic, for example when episodic or regular use occurs alongside other drug use 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 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 to be effective for other forms of drug use, prior to more in-depth drug use assessment.1065 Again, data from health-care services and other sectors will identify NPS use where it is most obvious, and will 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 owing to rapidly changing trends, hence the prominence of toxicological surveillance and the development of EWSs in the existing first wave of responses to NPS.909,982,1066 Qualitative and quantitative studies investigating patterns of use in potentially important subpopulations (such as homeless people, those with serious long-term mental health problems and prisoners), or derived from emergency health-care presentations, can be informative on issues such as constituents, doses and other drugs being used simultaneously.757,761 The more such studies give rigorous attention to sampling, the more straightforward the consideration of generalisability will be.

Novel psychoactive substance data collection can be added to existing large population cohort studies.1067 ‘Prevention systems’ approaches,1068 as hypothesised here to be relevant to NPS use, require strong health services research investment on both NPS use and 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.1064

A consideration of NPS data needs also calls attention to the scrutiny of the adequacy of the 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 5 years.1020 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,1068 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 pay attention to the 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 that 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 life-course approach is inapplicable to NPS.
4. The prevention system cannot or will not operate in the way proposed; the multilevel contribution of system elements is unattainable, even if desirable.
5. A high-risk population approach may be preferable only 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 the production, distribution and retail of NPS may have features that 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 to be limits to the extent to which approaches to NPS can be informed by comparisons to 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, although a key weakness in this area is that arguably too much 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, although the prospect of early (in the life course) 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 multisectoral contributions self-evidently have some part 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. Although 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 learnt in public health about the importance of prevention. High-risk subpopulations may be difficult to reliably identify, particularly where evidence is limited. It should be noted that we do not suggest avoiding the targeting of high-risk subpopulations but rather that this should be undertaken alongside whole-population interventions in line with the strategic approach developed by Rose.\textsuperscript{1042}

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, although we suggest that 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 that we do draw. We may be wrong in our thinking and we 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 that 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, the generation of scientific data and the 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.”\textsuperscript{1070} 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.\textsuperscript{1071}

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, have 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 those of 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. 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 both 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, 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 (e.g. 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 for this project involved engagement with policy-makers, researchers and NPS users and their carers in the UK 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, with the Chief Executive of Drugscope and with 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, namely an expert on addictions treatment and prevention, policy and interventions, one on addictions clinical issues and NPS, another on NPS and EWSs, 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 a 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 the interpretation of and reflection 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

Public involvement work on this project 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, as well as 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 either by telephone 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 flyers sent to the following key organisations that work with NPS users or networks: Crew2000 and Newcastle City Council. We also recruited by posting recruitment messages on Bluelight.org, which is an online drug user forum, as well as on The Loop Facebook (Facebook, Inc., Menlo Park, CA, USA) 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 organisations, 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 UK.
Individuals who were interested in participating contacted the researcher (NDM) by e-mail and were then sent an e-mail and an 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 was not 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 from Public Health England (two of whom had specific responsibilities for NPS and one of whom 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 telephone 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 that 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 learnt from earlier epidemics of new drugs in places other than the UK. One example given concerned MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) compounds produced during the manufacture of MPPP (1-methyl-4-phenyl-4-propionoxypiperidine, a synthetic opioid), which led to irreversible Parkinson’s disease in six drug users in California.

We also learnt that coverage of existing responses, which tend to be more treatment than prevention orientated, was seen to be limited, and the document was 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 forums via which we distributed calls for information.

Comments on the draft final report conveyed appreciation of the review findings, scale and challenges involved in summarising 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, although not to substantive content changes.

These efforts at policy engagement were quite modest and limited principally by time available. Two particular limitations should be borne in mind. First, we had intended to engage with the Department of Health, and to have done so would have been valuable. Second, 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 2-week deadline for return of any 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 1 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 years. The reasons for use include the fact that they are cheaper and easier to get and that 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 owing 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 on 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- to 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 that many users tend to switch to other 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 the closure of all headshops, a decrease in availability and an 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 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 not all banning strategies had 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. However, the blanket ban had led to people, particularly those who were 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 owing to a 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 applicable 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
In terms of 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 in greater detail the use of peer counsellors or peer supporters and to invest 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 to explore 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 and the NPS user highly commended the approach taken by the NPS-UK project as being rigorous and thorough, particularly in terms of looking at how the approach to other drugs has developed and how it may be applicable to NPS.

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

Public involvement 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 that we received from other researchers who have conducted similar work in the area was that there was a 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 might be encountered as a result of NPS use to enhance willingness to engage with research projects such as this. However, for short-term projects such as this, implementing this approach is challenging and would need significant early investment. The sustainability of NPS user involvement throughout the project also proved difficult owing to a lack of willingness on the part of 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 PI 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 its 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 an evidence-informed public health approach to NPS use in the UK might 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, which should address NPS together with other forms of licit and illicit drug use.

Research recommendations were developed from two distinct data sources. First, 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 and assessing how it needs to be developed further. Second, we use the conceptual framework for NPS developed by the authors of this report to identify what may be missing from this literature.

Research recommendations made by the 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 by means of paying attention to detailed content and frequency, as well as by discussion among the reviewers. This led to higher-level coding to produce recommendations in three broad thematic areas, namely research relating to pharmacology, epidemiology and intervention research. 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, 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 the identification of material that is both present in and absent from the other data source. As the conceptual material has quite a different evidential status to previously identified research recommendations, we have sought to use a transparent approach in our handling of it.

The research recommendations are targeted at both researchers and commissioners of research, with a view to inform discussions between both parties about, and to enable 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 on 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 that 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 on 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 should also be given 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, although 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 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 from which future research needs may be considered.

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 that 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’ that permits letters, commentaries and other material that does 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 synthesised relevant material in a sufficiently rigorous way. As we did not develop a dedicated methodology for this strand of the work, the limitations of which may be carefully assessed, we do regard this as presenting a risk to our conclusions, and hence state them below in a way that 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 the Novel Psychoactive Substances in the UK Project research recommendations**

The research recommendations have been generated using the methodological approach previously described. Key recommendations are identified as such (in bold 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 nine 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 pay attention to detailed contents, potency, toxicity, doses and other psychopharmacological and other individual factors.

**Epidemiology and related research**

4. **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.

5. **Develop the behavioural epidemiology and related science of patterns and correlates of NPS use and problems in the context of involvement in alcohol, tobacco and other drug use.**

6. **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.**

7. Develop the study of NPS use in subpopulations (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 MSM and adolescents.

8. **Undertake methodological research on NPS behavioural measurement, including the validity of self-report, psychometrics and online survey design.**

**Interventions**

9. **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.

10. **Evaluate the public health impacts of legislative prohibitions of NPS use or supply, and other major policy initiatives.**

11. Evaluate the effectiveness of existing psychosocial interventions for drug users in relation to NPS outcomes. In addition, develop and evaluate other novel treatment interventions for NPS and other drug use in light of the limitations of the effectiveness of existing interventions.

**Recommendations for research commissioners**

12. **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).**

13. **Evaluate existing strategic provision for, and develop as necessary, a long-term planning system for research on NPS and other drug use.**

14. **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.

15. **Evaluate the existing burden of, and responses to, NPS and other drug use in generic and specialist services, and the contributions made therein to prevent and treat problems.**

16. **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 gaining a better understanding of the influences of price, availability and marketing on demand and supply.
17. Develop research capacity for the design, implementation and rigorous evaluation in comparative studies of any emerging local or regional multilevel strategic responses. Such approaches could include provision for the identification of the national policy influences on observed NPS and other drug outcomes.
18. Strengthen the contribution of social sciences to the study of NPS and other drug use. These approaches should build on methodological advances on similar forms of online-mediated behaviour.
19. Develop empirical research on the public understanding of drug use more broadly, including NPS use, and how this may be enhanced.
20. 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 globalisation.

Conclusions

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

The UK Government Home Office Expert Panel Report 2014 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 owing 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, with the exception of 7 and 11).

The NPS export report prepared by Fraser for the Scottish Government, also in 2014, identified evidence gaps in relation to epidemiology, the changing nature of drug markets, including NPS markets, acute and longer-term consequences, policy-level interventions and the applicability of existing interventions, and considered 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, with the exception of 11 and 15).

Other expert reports could also be used for comparison purposes. For example, the 2016 EMCDDA report on health responses to new psychoactive substances was not designed to make research recommendations and notes, for example, the lack of data on use, harms and effectiveness. The report does, however, endorse the targeting of subgroups 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. First, 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. Second, it is noteworthy that all the key recommendations for researchers are supported by earlier UK expert reports and have not yet been acted on. We suggest that 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, King’s College London), 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, London School of Hygiene and Tropical Medicine), Amanda Sowden (Deputy Director, Centre for Reviews & Dissemination, York) and John Strang (Director, National Addiction Centre, King’s College London).

Contributions 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 the 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 made revisions to all chapters.

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

Steve Parrott (Reader, Health Economics) contributed to the health economics aspects of the 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.
Data sharing statement

As this is a review study, there are no primary data available for sharing.
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Appendix 1  Novel psychoactive substances
electronic database literature search (original search: 16 November 2015; updated search: 29 June 2016)

We searched the EMBASE, MEDLINE, PsycINFO and Science Citation Index databases and a total of 13,772 records were identified. These were imported into bibliographic software and deduplicated, leaving a total of 9165 records.

EMBASE (via Ovid)

Date range searched: 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 arylalkylamine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrididine$ or piperazine$ or arycyclohexylamine$ or aminoindane$ or tryptamine$)).ti,ab.
12. (synthetic adj (cannabinoid$ or phenethylamine$ or arylalkylamine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrididine$ or piperazine$ or arycyclohexylamine$ 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
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 bumphin).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 pycclone).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)
Date range searched: 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 arylalkylamine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyroline$ or piperezine$ or arylcyclohexylamine$ or aminoindane$ or tryptamine$)).ti,ab.
12. (synthetic adj (cannabinoid$ or phenethylamine$ or arylalkylamine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrolidine$ or piperazine$ or arylcyclohexylamine$ or aminooindane$ 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$.ti,ab.
21. dicalzepam.ti,ab.
22. gamma butyrolact$.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
exp animals/ not humans/ 
59 not 60
limit 61 to yr="2006 -Current"

PsycINFO (via Ovid)
Date range searched: 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 arylalkylamine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrididine$ or piperazine$ or arylycyclohexylamine$ or aminoindane$ or tryptamine$)).ti,ab.
12. (synthetic adj (cannabinoid$ or phenethylamine$ or arylalkylamine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrididine$ or piperazine$ or arylycyclohexylamine$ 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. MDAL.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 benzo fury or benzo fury or berry bomb or black mamba or bromo-dragonfly or bullet or bumpy).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 butyroolact* 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*) NEAR (cannabinoid* or phenethylamine* or arylalkylamine* or cathinone* or opioid*)
or benzodiazepine* or pyridine* or pyrrolidine* or piperazine* or arylcyclohexylamine* or aminoisobutane* or trypamine*)) OR
TS=synthetic NEAR (cannabinoid* or phenethylamine* or arylalkylamine* or cathinone* or opioid* or benzodiazepine* or pyridine* or pyrrolidine* or piperazine* or arylcyclohexylamine* or aminoisobutane* or trypamine))

#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

<table>
<thead>
<tr>
<th>Name</th>
<th>Global weekends (see <a href="http://www.globalweekends.co.uk">www.globalweekends.co.uk</a>)</th>
<th>Ice headshop (see <a href="http://www.iceheadshop.co.uk/">www.iceheadshop.co.uk/</a>)</th>
<th>Legal Highs World (see <a href="https://legalhighsworld.wordpress.com/">https://legalhighsworld.wordpress.com/</a>)</th>
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<td>Legal Highs World (see <a href="https://legalhighsworld.wordpress.com/">https://legalhighsworld.wordpress.com/</a>)</td>
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This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.