European Monitoring Centre
for Drugs and Drug Addiction

EMCDDA operating guidelines for the risk assessment of new psychoactive substances

About the guidelines

The purpose of these guidelines is to ensure compliance with the scope and requirements of Regulation (EC) No 1920/2006 (as amended) and Council Framework Decision 2004/757/JHA (as amended) in respect to the risk assessment procedure for and reporting on new psychoactive substances.

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1. Introduction and purpose

New psychoactive substances can cause serious cross-border threats to health. A three-step legal framework of early warning, risk assessment and control measures allows the European Union to rapidly detect, assess and respond to the public health and social threats caused by new psychoactive substances. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is responsible for the first two steps in this framework, namely operating the EU Early Warning System on new psychoactive substances (EMCDDA, 2019), in close cooperation with Europol, and conducting risk assessments. The European Commission is responsible for proposing control measures.

On 23 November 2018, legislation came into effect that strengthened the EU's ability to respond to the threats posed by new psychoactive substances ([1,2]). This is the third such legal framework to be introduced over the past 20 years and builds on the experiences gained during this period.

The legislation comprises:

- Regulation (EU) 2017/2101 of the European Parliament and of the Council of 15 November 2017 amending Regulation (EC) No 1920/2006 ([3]) as regards information exchange on, and an early warning system and risk assessment procedure for, new psychoactive substances ('the Regulation'); and
- Directive (EU) 2017/2103 of the European Parliament and of the Council of 15 November 2017 amending Council Framework Decision 2004/757/JHA ([4]) in order to include new psychoactive substances in the definition of 'drug' and repealing Council Decision 2005/387/JHA ('the Framework Decision').

The purpose of these guidelines is to ensure compliance with the scope and requirements of Regulation (EC) No 1920/2006 as amended by Regulation (EU) 2017/2101 in respect to the second step of the framework, i.e. the risk assessment procedure for and reporting on new psychoactive substances (Article 5c), and with Council Framework Decision 2004/757/JHA as amended by Directive (EU) 2017/2103. The text therefore includes appropriate references to the legal framework. To operationalise the technical aspects of the risk assessment, the guidelines are supported by a set of guidance notes developed by the EMCDDA. The guidance notes will be adapted as required in order to reflect developments in the field of new psychoactive substances and risk assessment.

([1]) Regulation (EU) 2017/2101 of the European Parliament and of the Council of 15 November 2017 amending Regulation (EC) No 1920/2006 as regards information exchange on, and an early warning system and risk assessment procedure for, new psychoactive substances, OJ L 305, 21.11.2017, pp. 1-7 (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R2101).

([2]) Directive (EU) 2017/2103 of the European Parliament and of the Council of 15 November 2017 amending Council Framework Decision 2004/757/JHA in order to include new psychoactive substances in the definition of 'drug' and repealing Council Decision 2005/387/JHA, OJ L 305, 21.11.2017, pp. 12-18 (https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32017L2103).

([3]) Regulation (EC) No 1920/2006 of the European Parliament and of the Council of 12 December 2006 on the European Monitoring Centre for Drugs and Drug Addiction (recast). OJ L 376, 27.12.2006, pp. 1-13 (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32006R19).

([4]) Council Framework Decision 2004/757/JHA of 25 October 2004 laying down minimum provisions on the constituent elements of criminal acts and penalties in the field of illicit drug trafficking. OJ L 335, 11.11.2004, pp. 8-11 (https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32004F0757).

The risk assessment has regard to the health and social risks of the use of, manufacture of and traffic in new psychoactive substances, including the involvement of criminal groups. The guidelines and guidance notes put in place a sound methodological and procedural basis for carrying out each risk assessment, ensuring that a systematic, reproducible and transparent approach is used throughout the risk assessment procedure. The guidelines draw from developments in the field of risk assessment ([5]), notably the use of a weight-of-evidence framework (SCHEER, 2018), as well as the practical experience gained by the EMCDDA and its Scientific Committee over the past 10 years.

The guidelines replace those previously published by the EMCDDA in 2010.

Guidance notes

- Guidance note 1: terminology and definitions.
- Guidance note 2: EMCDDA technical report.
- Guidance note 3: weight-of-evidence framework.
- Guidance note 4: analysing and assessing epidemiological data.
- Guidance note 5: analysing and assessing law enforcement seizure data.
- Guidance note 6: analysing and assessing serious adverse events.
- Guidance note 7: analysing and assessing social harms.

2. Legal basis and scope

The legal basis for the risk assessment of new psychoactive substances is provided in Regulation (EC) No 1920/2006 as amended by Regulation (EU) 2017/2101 and in Framework Decision 2004/757/JHA as amended by Directive (EU) 2017/2103.

Regulation (EC) No 1920/2006 (as amended) has regard to the Treaty establishing the European Community (TEC) ([6]), and in particular Article 152 thereof, and the Treaty on the Functioning of the European Union (TFEU) ([7]), and in particular Article 168(5) thereof. Article 168(1) of the TFEU provides that drugs-related health damage is considered a public health issue of concern for the EU.

The Framework Decision in its turn has regard to the Treaty on European Union (TEU) ([8]), in particular Article 31(e) and Article 34(2)(b) thereof, and the TFEU, in particular Article 83(1) thereof. These articles concern judicial cooperation in criminal matters between Member States of the European Union. Article 83(1) of the TFEU provides that illicit drug trafficking is considered a particularly serious crime with a cross-border dimension, motivating judicial cooperation in criminal matters within the EU.

([5]) This includes drawing from relevant advances in assessment methodologies of substances in a broader sense, especially within EU institutions and bodies. Consequently, the conceptual framework for the risk assessment has been adapted. Notably, a weight-of-evidence framework that includes an uncertainty analysis has been integrated into the risk assessment.

([6]) OJ C 325, 24.12.2002.

([7]) OJ C 326, 26.10.2012.

([8]) OJ C 326, 26.10.2012.

The Framework Decision provides for a common approach to tackle illicit drug trafficking, which poses a threat to the health, safety and quality of life of citizens of the Union, to the legal economy and to the stability and security of the Member States.

The Framework Decision was amended by Directive (EU) 2017/2103 in order to include new psychoactive substances in the definition of 'drug' and repealed Council Decision 2005/387/JHA. Simultaneously, the Regulation was amended by Regulation (EU) 2017/2101. Together, the Regulation and the Framework Decision replace the mechanism established by Council Decision 2005/387/JHA ([9]).

Article 1(4) of the Framework Decision defines a 'new psychoactive substance' as a substance in pure form or in a preparation that is not covered by the 1961 United Nations Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, or by the 1971 United Nations Convention on Psychotropic Substances ([10]), but may pose health or social risks similar to those posed by the substances covered by those conventions.

Article 1(1) of the Framework Decision defines a 'drug' as a substance covered by the 1961 United Nations Single Convention on Narcotic Drugs, as amended by the 1972 Protocol, or by the 1971 United Nations Convention on Psychotropic Substances; and any of the substances listed in the Annex to the Framework Decision. The substances listed in the Annex are those psychoactive substances that are already subject to control measures adopted in accordance with Joint Action 97/396/JHA ([11]) and Decision 2005/387/JHA, and those substances that will be subjected to control measures by delegated acts adopted in accordance with the Framework Decision, based on a risk assessment or combined risk assessments carried out pursuant to Article 5c of the Regulation.

Thus, while the Regulation focuses on public health, the Framework Decision concerns judicial cooperation in criminal matters. Both pieces of legislation work together. The Regulation has been designed to ensure a high level of human health protection and to complement the Member States' actions in reducing drugs-related health damage, including exchange of information and prevention, more specifically where this concerns new psychoactive substances, which can pose serious cross-border threats to health. The Framework Decision has been designed to support a common approach and provides for procedures to include new psychoactive substances within the definition of 'drug', thereby extending the application of the Union criminal law provisions that apply to illicit drug trafficking to new psychoactive substances posing severe public health risks and, where applicable, severe social risks. This approach also strengthens law enforcement and judicial cooperation across the Union after a new psychoactive substance is brought under the definition of a 'drug'.

The scope of the risk assessment is limited to new psychoactive substances, meaning that the substances may pose health or social risks similar to those posed by the substances covered by United Nations 1961 (as amended by the 1972 Protocol) and 1971 international drug control conventions. Whether or not a substance is considered a new psychoactive substance is based on an

([9]) OJ L 127, 20.5.2005.

([10]) UNODC (United Nations Office on Drugs and Crime) (2013), *The international drug control conventions*, UNODC, Vienna (https://www.unodc.org/documents/commissions/CND/Int_Drug_Control_Conventions/Ebook/The_International_Drug_Control_Conventions_E.pdf).

([11]) OJ L 167, 25.6.1997.

assessment by the EMCDDA of the available information reported through the Early Warning System in accordance with Article 2(f)(i) and Article 5a of the Regulation (EMCDDA, 2019).

The request for a risk assessment is made by the European Commission in accordance with Article 5c(1) and Article 5d, based on the initial report prepared by the EMCDDA in accordance with Article 2(f)(ii) and Article 5b of the Regulation (EMCDDA, 2019). The risk assessment procedure is organised by the EMCDDA in accordance with Article 2(f)(iii) and Article 5c(5) of the Regulation.

If the EMCDDA has collected information on several new psychoactive substances that it considers of similar chemical structure and if each of them gives rise to concerns that it may pose health or social risks at Union level, the EMCDDA shall in accordance with Article 5b(11) of the Regulation submit to the Commission and to the Member States individual initial reports or combined initial reports dealing with several new psychoactive substances. When a combined initial report is submitted, the Commission may request the EMCDDA to assess the potential risks posed by several new psychoactive substances with similar chemical structures and to draw up a combined risk assessment report.

The risks posed by the new psychoactive substance are assessed by the Scientific Committee of the EMCDDA, which may be extended as deemed necessary, in accordance with Article 5c(4) and Article 13(2) of the Regulation. The Scientific Committee shall assess the risks on the basis of the available information and any other relevant scientific evidence, in accordance with Article 5c(5) of the Regulation. It shall take into account all opinions held by its members.

3. Conceptual framework for risk assessment

Based on the experience gained with risk assessments of new psychoactive substances and consistent with advances in methodologies used for the risk assessment of substances in areas such as food safety, chemicals, consumer products and medicines, a weight-of-evidence approach is considered appropriate for assessing the risks posed by new psychoactive substances. In line with the definition provided by the European Commission's Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) ([12],[13]), a weight-of-evidence approach is 'a process of weighted integration of lines of evidence to determine the relative support for hypotheses or answers to a question'. To reach valid conclusions or answers to questions, a structured methodology needs to be followed, containing the elements of:

- a problem statement;
- the identification, collection and selection of possible sources of evidence;
- an assessment and weighing of individual lines of evidence and integration of lines of evidence; and
- an uncertainty analysis (description of uncertainties)

([12]) https://ec.europa.eu/health/scientific_committees/scheer_en

([13]) SCHEER (Scientific Committee on Health, Environmental and Emerging Risks) (2018), *Memorandum on weight of evidence and uncertainties — revision 2018*, European Commission (https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_014.pdf).

Detailed information on the weight-of-evidence framework for use in the risk assessment of new psychoactive substances is provided in Guidance Note 3.

3.1. Problem statement

The problem statement for the risk assessment of a new psychoactive substance is the request from the European Commission to the EMCDDA to perform a risk assessment of a new psychoactive substance or several new psychoactive substances with similar chemical structures. The request is based on indications in the initial report to suggest that the substance may pose severe public health risks and, where applicable, severe social risks at Union level. Based on the risk assessment by the Scientific Committee of the EMCDDA, the Commission needs to consider whether to adopt a delegated act, in accordance with the Framework Decision, which would add the new psychoactive substance to the Annex of the Framework Decision. For this, the Commission has to take into account whether the new psychoactive substance can be included in the definition of a 'drug'. Article 1a(2) of the Framework Decision provides the elements that need to be considered by the Commission. Consequently, the risk assessment performed by the Scientific Committee of the EMCDDA should provide the relevant information on these elements. Thus, by default, the problem statement can be derived from the legislation and summarised by three questions:

1. Are the extent or patterns of use of the new psychoactive substance and its availability and potential for diffusion within the Union significant?

2. Is the harm to health caused by the consumption of the new psychoactive substance, associated with its acute or chronic toxicity and abuse liability or dependence-producing potential, life threatening?

3. Is the social harm caused by the new psychoactive substance to individuals and to society severe?

The Framework Decision provides additional details on these questions. These will be further discussed in Section 5.

3.2. Identification, collection and selection of possible sources of evidence

The identification, collection and selection of possible sources of evidence begins before the request for a risk assessment is made. Important sources are the EMCDDA's Reitox national focal points and Europol national units, who collect and report information as part of the Early Warning System in accordance with Article 5a of the Regulation. Together with other sources of information, including available information in the literature, this information is added to the initial report on the basis of which a risk assessment is requested (Article 5b). Subsequently, the available information is compiled and analysed in a technical report prepared by the EMCDDA in order to support the risk assessment. To support the uncertainty analysis (Section 3.4), the technical report should also qualify the available information. Details on the structure and information included in the EMCDDA technical report are provided in Guidance Note 2.

3.3. Assessment and weighing of individual lines of evidence and integration of lines of evidence

The next step in the risk assessment is that in which the lines of evidence are assessed, weighed and integrated. The use of a weight-of-evidence approach means that each piece of evidence is taken as part of a line of evidence. It should be considered to what extent each line of evidence is supported by evidence and what the strength of that evidence is. Where different lines of evidence exist, it should be considered to what extent these lines of evidence are congruent or whether there are conflicts between the lines of evidence. Together, this weight-of-evidence approach should determine the relative support for hypotheses or answers to the questions posed in the problem statement. It is important to note that, because of the typically short period of time between a new psychoactive substance emerging on the market and the need for a risk assessment arising, the extent of data available will often be limited and the available data will vary in quality (Section 4.3).

3.4. Uncertainty analysis

In the uncertainty analysis, uncertainty is used as a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question. Uncertainty is due to lack of knowledge regarding the true value of a quantity, and is also termed epistemic uncertainty, lack-of-knowledge uncertainty or subjective uncertainty. Uncertainty analysis is an integral part of the risk assessment, rather than a separate phase. Yet by specifically addressing uncertainty analysis, the existing uncertainties can be made explicit.

Uncertainty analysis begins by weighing the strength of the evidence. The strength of the evidence is affected by various factors.

- First, the reliability of the pieces of evidence need to be considered. The qualification of the evidence is provided in the technical report, as this qualification is an elementary part of the risk assessment. It is a task of the EMCDDA Scientific Committee to agree or disagree with qualifications provided in the technical report. In this respect, Article 5c(5) of the Regulation establishes that the risk assessment shall take into account all opinions held by the members of the Scientific Committee.

- Another factor determining the level of uncertainty is the existence of knowledge gaps, limiting the ability to assess appropriately the risks. Where data are available but the extent is limited, the precision of an answer given would be affected. The more data available, the more precise the answer can be.

- Finally, the accuracy of the available data will be affected by the methods that were used to gather or generate these data. The cruder the methods are, the greater is the chance that the data are less accurate. When the data are less accurate, the answer to the questions will also be less accurate.

In addition to uncertainties stemming from limitations in the data, uncertainty also depends on the risk assessment methodologies used. In view of the paucity of data and the limited time available for the risk assessment of new psychoactive substances, the principal method used is expert judgement. This method relies on the knowledge and experience of the experts involved. It is the responsibility of the EMCDDA to organise the risk assessment so as to minimise bias where risk assessment depends on

expert judgement. In this respect, Article 5c(4) of the Regulation allows for the Scientific Committee to be extended as deemed necessary by the Director, acting on the advice of the chairperson of the Scientific Committee, by including experts representing the scientific fields relevant for ensuring a balanced assessment of the risks posed by the new psychoactive substance under assessment.

4. General considerations for risk assessment

When assessing the risks posed by a new psychoactive substance as required by Article 5c, the following general principles need to be taken into consideration.

4.1. Risk, hazard and harm

The risks that need to be assessed in the EU risk assessments for new psychoactive substances relate to public health risks and, where applicable, social risks, including those related to criminal activities. Risk assessment methodologies have advanced in health sciences, where the dual functionality of risk is firmly established: both the likelihood of a harmful health effect occurring and the severity of that effect are taken into account. To extend this methodology to the risk assessment of new psychoactive substances, a broadened definition of risk is used to include both harmful health effects and social harms: risk is taken as a combination of the likelihood of occurrence of a hazard generating harm in a given scenario and the severity of that harm.

Within the context of an EU risk assessment for new psychoactive substances, harm is taken as injury or damage to the health of people or disruption of social functioning or public order resulting in injury or damage to the health of the user or other persons, damage to property or criminal activities as described in the procedure for including new psychoactive substances in the definition of ‘drug’. Risk should not be confused with hazard, which is something that has a potential to cause harm.

Both the likelihood of harm and the severity of harm should be assessed and, to the extent possible, quantified. Verbal expressions expressing the likelihood or the severity of a risk can be used. However, it should be made explicit what is meant by words such as ‘rare’, ‘low’, ‘moderate’, ‘high’ and ‘serious’. The comparison of the substance under assessment with the similar substances scheduled under the UN conventions is included in the technical report.

To express the overall magnitude of a risk, i.e. the risk level, both likelihood and severity may be expressed in a risk matrix, where both an increased likelihood of harm occurring and the increased severity of the harm would increase the risk level. The use of risk matrices (Guidance Note 3) should be considered supportive in the risk assessment and serves to provide consistent and objective and transparent assessments.

4.2. Risk-modifying factors

The risks posed by new psychoactive substances are not a simple function of the pharmacological or toxicological properties of the substance. The physical, social, cultural, economic and political environment as well as user-related elements affect the likelihood that harm will actually occur and the severity and outcome of the harm. Therefore, these factors can be seen as risk-modifying factors. Modalities of substance use may include patterns of use (including routes of administration, dosage forms, dosage regimens) and the context of use. Concerning the social environment, regulatory

policies, informal norms, criminal involvement, living standards (poverty), the availability of information and peer support can affect the likelihood of harm. Individual vulnerabilities and personal circumstances such as age, gender, genetics, pre-existing medical conditions, personality, education and employment are examples of individual user characteristics affecting the likelihood of harm.

4.3. Availability and quality of data

Because of the typically short period of time between a new psychoactive substance emerging on the market and the need for a risk assessment arising, the extent of the data available will often be limited and the available data will vary in quality. Whereas forensic reports of law enforcement seizures or toxicology reports related to serious adverse events, such as acute poisonings and deaths, may contain high-quality data, surveys investigating the use of new psychoactive substances are often lacking or limited to non-representative targeted surveys. To deal with these limitations, the data that are considered in a risk assessment need to be assessed for reliability and relevance (Guidance Note 3). This information on the quality of data should be included in the technical report.

Gaps in information can lead to the conclusion that some questions cannot be answered. Yet sometimes answers can be inferred from existing knowledge on other substances. For instance, μ-opioid receptor agonists display a well-described general pharmacological and toxicological profile. This makes it possible to assign class-related behavioural or toxicological effects to a novel μ-opioid receptor agonist, based on this pharmacological property, provided that other information is available demonstrating that the substance is effectively reaching the central μ-opioid receptors. On the other hand, substances with pharmacological profiles that are less well defined may be less amenable to this type of extrapolation. Extrapolation based on chemical similarity can be done only with great caution and would normally require a group of comparators with similar chemical and pharmacological characteristics. Extrapolation of risks based on a single analogue would rarely suffice.

Both the quality of the information and the gaps in information will affect the level of uncertainty in the answers to the questions posed. To deal with the limitations of information in a scientifically sound manner, uncertainty needs to be made explicit in the conclusions of the risk assessment (Section 3.4; Guidance Note 3).

5. Risk assessment report

According to Article 5c of the Regulation, following the assessment of the potential risks of a new psychoactive substance by the Scientific Committee, it should draw up a risk assessment report ([14]) that contains:

- available information on the chemical and physical properties of the new psychoactive substance and the methods and the precursors used for its manufacture or extraction;
- available information on the pharmacological and toxicological properties of the new psychoactive substance;

([14]) Or draw up a combined risk assessment report in the case of the assessment of several new psychoactive substances with similar chemical structures in accordance with Article 5c(2) of the Regulation.

- an analysis of the health risks associated with the new psychoactive substance, in particular with respect to its acute and chronic toxicity, abuse liability, dependence-producing potential and physical, mental and behavioural effects;
- an analysis of the social risks associated with the new psychoactive substance, in particular its impact on social functioning, public order and criminal activities, and the involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking of the new psychoactive substance;
- available information on the extent and patterns of use of the new psychoactive substance, its availability and potential for diffusion within the Union;
- available information on the commercial and industrial use of the new psychoactive substance, the extent of such use, as well as its use for scientific research and development purposes; and
- other relevant information, where available.

The headings given below reflect those required for the risk assessment report by Article 5c(3) of the Regulation.

5.1. Problem statement

By default, the problem statement is aligned with three questions as required by Article 1a(2) of the Framework Decision (Section 3.1):

- Are the extent or patterns of use of the new psychoactive substance and its availability and potential for diffusion within the Union significant?
- Is the harm to health caused by the consumption of the new psychoactive substance, associated with its acute or chronic toxicity and abuse liability or dependence-producing potential, life threatening?
- Is the social harm caused by the new psychoactive substance to individuals and to society severe?

5.2. Description of the substance

The description of the substance(s) should be a summary extracted from the technical report. The description should be precise to avoid any ambiguity about the actual substances assessed.

5.2.1. Chemical and physical properties

In accordance with Article 5c(3)(a) of the Regulation, the report should contain the available information on the chemical and physical properties of the new psychoactive substance.

Information on the following should be included: the names of the substance, and the chemical structure, molecular formula and molecular weight of the substance and its physico-chemical

properties; the chemical similarity of the substance to substances scheduled under the UN conventions; and relevant considerations related to the analytical identification of the substance.

5.2.2. Methods and the precursors used for the manufacture or extraction

In accordance with Article 5c(3)(a) of the Regulation, the report should contain the available information on the methods and the precursors used for the manufacture or extraction of the new psychoactive substance. Such information may come from analyses of chemicals found at production sites or from the literature. The description should include the most likely routes of synthesis as well as impurities/side products of synthesis, if known.

5.3. Pharmacological and toxicological properties

In accordance with Article 5c(3)(b) of the Regulation, the report should contain the available information on the pharmacological and toxicological properties of the new psychoactive substance. This would include both *in vitro* and *in vivo* data. Of great interest are data characterising the new psychoactive substance with respect to its receptor pharmacology. Therefore, receptor binding data and functional activity data are important. Data concerning receptors implicated in substance dependence especially need to be considered. In addition, for a better understanding of potential side effects, secondary pharmacological data are relevant as well. Data from *in vivo* models may further demonstrate the pharmacological activity of the new psychoactive substance. Regarding the function of vital organs (principally the heart, lungs and central nervous system), pharmacological safety data need to be considered.

Usually, pharmacokinetic data on the new psychoactive substance are very limited. When available and where pharmacokinetic data are considered relevant for the risk assessment, these should be included in Section 5.3 of the report, for example distribution data showing the uptake in brain tissue or metabolism data showing the formation of a metabolite with relevant activity at receptors implicated in substance dependence.

In vitro and animal data demonstrating the toxicological properties are considered relevant for characterising the new psychoactive substance. Usually, human toxicological data are limited to case reports on serious adverse events such as acute poisonings and medico-legal death investigations. These data should be included in Section 5.6.

5.4. Legitimate use and other relevant information

In accordance with Article 5c(3)(g) of the Regulation, the report should contain the available information on the commercial and industrial use of the new psychoactive substance, the extent of such use, as well as its use for scientific research and development purposes. This information will be collected during the preparation of the initial report and should be included in this section.

In accordance with Article 5c(3)(h) of the Regulation, the report may contain other relevant information, which can also be included in this section.

5.5. Extent and patterns of use, availability and potential for diffusion within the Union

In accordance with Article 5c(3)(e) of the Regulation, the report should contain the available information on the extent and patterns of use of the new psychoactive substance, and its availability and potential for diffusion within the Union. This information is derived from the EMCDDA technical report (Guidance Note 2). The risk assessment should provide the information relevant for answering the question of whether the extent or patterns of use of the new psychoactive substance and its availability and potential for diffusion within the Union are significant.

Following the weight-of-evidence approach, the key data should be presented as evidence and the strength of the evidence should be evaluated, thus weighing the evidence and showing how the evidence contributes to the conclusions reached (Guidance Note 3). Concerning the extent of use, formal epidemiological data would be considered to have a greater weight than for example survey data from an internet forum, as, in the latter case, biases are likely to be greater. Detailed information on analysing and assessing epidemiological data is provided in Guidance Note 4.

As information on the extent and patterns of use of the new psychoactive substance and its availability and potential for diffusion within the Union is likely to be very limited at the time of risk assessment, information will be based largely on information from case reports of seizures reported by law enforcement agencies, including information on frequencies and circumstances of seizures, and the quantities of the new psychoactive substance seized. Guidance Note 5 provides detailed information on the analysis and assessment of such data relevant for the risk assessment of new psychoactive substances. Data from online vendors of new psychoactive substances may also provide relevant information.

In addition to an estimate on the current use and availability (if possible, considering the limited data), the anticipated trends in use and availability would also be considered relevant for inclusion in a risk assessment report.

5.6. Health risks

In accordance with Article 5c(c) of the Regulation, the health risks associated with the new psychoactive substance should be analysed with respect to its acute and chronic toxicity, physical, mental and behavioural effects, and abuse liability and dependence potential (Section 5.7).

The Commission needs to take into account whether the harm to health caused by the consumption of the new psychoactive substance is life threatening. Following from Article 1a(2) of the Framework Decision, the risk assessment report needs to provide information enabling the Commission to take into account whether the new psychoactive substance:

- is likely to cause death or lethal injury;
- is likely to cause severe disease;
- is likely to cause severe physical or mental impairment;
- is likely to cause a significant spread of diseases, including the transmission of blood-borne viruses.

In addition to animal toxicity data, which have been discussed in Section 5.3, acute toxicity data are mainly based on forensic reports describing cases of serious adverse events, such as acute poisonings and medico-legal death investigations. Guidance Note 6 provides detailed information on the analysis and assessment of serious diverse events relevant for the risk assessment of new psychoactive substances. This may concern both reports through the Early Warning System from the Member States, as well as reports published in the medical and scientific literature.

For a full appreciation of the severity and seriousness of the effects, a detailed description from reliable sources would be required.

To evaluate the association of the use of the new psychoactive substance with harmful health effects, toxicological data from body fluids or tissues demonstrating the actual intake of the new psychoactive substance would provide the strongest evidence (Guidance Note 6). An analysis of dosage forms present at the scene could further support the association. Self-reported information from users on the other hand is evidence with a high level of uncertainty, as the actual contents of the substances taken may differ from what the user may believe or claim to have taken. As in many cases several substances may have been consumed, the contribution of the new psychoactive substance under evaluation or its metabolites to causing the harmful health effect needs to be assessed. A review of case reports by forensic experts would support this assessment.

Data on the physical, mental and behavioural effects may rarely come from studies in a controlled setting. Other data may come from surveys among users or from users self-reporting on internet forums. The level of uncertainty associated with self-reporting would be high.

The likelihood of harmful health effects occurring is not merely a function of the pharmacological and toxicological properties of the new psychoactive substance. In a risk assessment, all known risk-modifying factors increasing or decreasing the likelihood of harmful health effects need to be considered (Section 4.2; Guidance Note 6).

The uncontrolled preparation of dosage forms can also lead to high variability in the concentration of the new psychoactive substance in the final preparation. This poses a potential risk of overdosing, especially with new psychoactive substances with high pharmacological potency. For instance, a mixture of synthetic cannabinoids with herbal preparations may result in a large variability in cannabinoid content, which increases the risk of overdosing.

The purity and presence of side products depend on the route of synthesis and the capabilities of the manufacturer (Section 5.2.2). The conditions under which new psychoactive substances are produced may vary from reasonably controlled for new psychoactive substances that are still not subject to control measures to very poor when they are synthesised in locations run by criminal organisations or other locations where they are manufactured non-professionally. Larger variability in purity and higher levels of side products would increase the likelihood of harmful health effects.

Oral dosage forms may be associated with increases in time of onset of effects due to slow pharmacokinetics and/or dissolution profiles. Such a delay may cause the user, assuming the dose taken was too low, to take additional doses, again leading to an increased risk of overdosing.

A specific risk associated with injectable dosage forms (e.g. intravenous, intramuscular or subcutaneous routes) or insufflation is the transmission of blood-borne viruses.

New psychoactive substances, having a propensity to allow the development of tolerance, may lead to an increase in the dose needed for the sought effect if the new psychoactive substance is consumed regularly. This same dose could in a person not or no longer tolerant to the new psychoactive substance lead to an overdose.

Other user-related characteristics such as age and experience with the use of drugs in general may also affect the likelihood of harmful health effects.

Increasing the availability of information among users, through internet forums, educational material or otherwise, could help to reduce the likelihood of harmful health effects, as it may encourage users to use more appropriate procedures for consuming the new psychoactive substance.

The context and circumstances of use also affect the likelihood of harmful health effects. For instance, taking new psychoactive substances alone at home poses the risk that no one is around to intervene should an overdose occur. The presence and availability of antidotes to users, friends or relatives, or first-response personnel may decrease the likelihood of fatalities due to overdoses, an issue that has been shown to be relevant for opioids. Co-administration of other substances (polydrug use), including alcohol and medicines, may lead to interactions, which could increase the likelihood of harmful health effects. Other circumstances such as continuous dancing in a hot environment may increase the likelihood of pharmacologically triggered hyperthermia.

Information on the effects of the new psychoactive substance on the ability to drive and operate machinery, although rarely available at the time of risk assessment, should be included if possible.

The legal status of a new psychoactive substance may also affect the likelihood of harmful health effects. In places where the new psychoactive substance is an illicit drug, the user will obtain the product through illicit routes, affecting the risks in various ways, as described. Use of an illicit product may also diminish the likelihood that a user will admit to using it, which can delay proper treatment in healthcare facilities when needed.

5.6.1 Elements to consider for assessing health risks

- Acute toxicity, including safety profile and information on poisonings.
- Chronic toxicity, including functional brain damage, reproductive toxicity, genotoxicity and carcinogenic potential.
- Abuse liability and dependence-producing potential (physical and psychological).
- Psychosocial dysfunction.
- Similarities to and differences from other reference substances.
- Extent, frequency and patterns of use.
- Availability and quality of the new psychoactive substance on the market (purity, adulterants, etc.).
- Availability of information, degree of knowledge and perceptions among users concerning the psychoactive substance and its effects.

- Characteristics and behaviour of users (including risk factors, vulnerability, etc.).
- Nature and extent of health consequences (e.g. acute poisonings, chronic poisonings, road traffic accidents).
- Long-term consequences of use (e.g. irreversible toxicity leading to deterioration of health at later stages of life).
- Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks (e.g. continuous dancing in hot environments, other substances used).

5.7. Abuse liability and dependence potential

In accordance with Article 5c(c) of the Regulation, the health risks associated with the new psychoactive substance should be analysed with respect to abuse liability and dependence-producing potential.

In the context of a risk assessment of a new psychoactive substance and in line with the definition provided by the World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) and similar to the ICD-10 definition ([15]) of substance dependence syndrome, dependence-producing potential is the propensity of a new psychoactive substance to lead to a cluster of physiological, behavioural and cognitive phenomena of variable intensity, in which the use of a new psychoactive substance takes on a high priority. The necessary descriptive characteristics are preoccupation with a desire to obtain and take the drug and persistent drug-seeking behaviour. Determinants and the problematic consequences of drug dependence may be biological, psychological or social, and usually interact.

The term 'abuse liability' is sometimes used interchangeably with 'dependence-producing potential', but sometimes these terms are given separate definitions. The WHO *Lexicon of Alcohol and Drug Terms* ([16]) defines abuse liability as the propensity of a particular psychoactive substance to be susceptible to abuse, defined in terms of the relative probability that use of the substance will result in social, psychological or physical problems for an individual or for society. The term 'abuse liability' puts more emphasis on the harmful consequences of use. Even if the use of a new psychoactive substance lacks specific characteristics of dependence, such as preoccupation with a desire to obtain and take the drug and persistent drug-seeking behaviour, the use may still have harmful effects. If a new psychoactive substance is used despite its harmful consequences, we could still speak of abuse liability. For the purpose of the risk assessment of new psychoactive substances, both terms could be taken together such that the relevant elements of dependence-producing potential and abuse liability are all assessed.

One line of evidence comes from *in vitro* data showing the ability of a substance to interact with receptors known to be involved in substance dependence, such as μ-opioid agonists or substances causing increased dopaminergic transmission in the nucleus accumbens. Receptor binding or activity

([15]) ICD-10 is the WHO's 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD) (https://icd.who.int/browse10/2016/en).

([16]) WHO (World Health Organisation) (1994), *WHO Lexicon of alcohol and drug terms* (https://www.who.int/substance_abuse/terminology/who_ladt/en).

alone would not constitute sufficient evidence of dependence potential. This should rather be seen as a hazard. Other factors such as pharmacokinetics and dosage form would affect the likelihood that the new psychoactive substance indeed can induce the physiological processes leading to substance dependence.

Further evidence may come from behavioural studies in animals or humans aimed at evaluating dependence potential. In general, the paradigms used in these studies have been shown to have a high level of predictivity. However, unconfirmed studies should be interpreted with caution, especially where unexpected results are reported.

Social field work studies or reports from healthcare professionals may provide observations indicating the existence of the elementary characteristics of dependence potential such as preoccupation with a desire to obtain and take the drug and persistent drug-seeking behaviour.

Poor psychosocial conditions of living could increase the likelihood that a new psychoactive substance will be used despite harmful consequences, whereas the occurrence of untoward side effects may deter others. These interdependencies should be considered when assessing the likelihood that a new psychoactive substance will lead to harmful use or a state of dependence.

In addition, the attractiveness of the subjective effects of a new psychoactive substance to specific groups may be considered with regard to the likelihood that the new psychoactive substance may have abuse liability for these groups.

5.8. Social risks

In accordance with Article 5c(d) of the Regulation, the social risks associated with a new psychoactive substance should be analysed — in particular its impact on social functioning and public order, including disruption to public order as well as violent or anti-social behaviour, resulting in harm to the user or to other persons or damage to property. In addition, criminal activities and the involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking of the new psychoactive substance should also be analysed, including those related to organised crime. The analysis should assess whether they are systematic and provide information on the illicit profits involved and the economic costs related to the involvement of criminal groups. Guidance Note 7 provides detailed information on the analysis and assessment of social harms for the risk assessment of new psychoactive substances.

5.8.1 Elements to consider for assessing social risks

- Individual social risks (e.g. impact on education or career, problems with personal relationships).
- Possible effects on direct social environment (e.g. neglect of family, violence).
- Possible effects on society as a whole (public order and safety, acquisitive crime).
- Economic costs (demands on healthcare).
- Possible effects related to cultural context, for example marginalisation.

- Possible appeal of the new psychoactive substance to specific population groups within the general population.
- Evidence that criminal groups are involved in production, trafficking or distribution for financial gain.
- Impact on the production, trafficking and distribution of other substances, including existing as well as new psychoactive substances.
- Evidence that the same groups or people are involved in different kinds of crime.
- Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety).
- Evidence of money-laundering practices or the impact of organised crime on other socioeconomic factors in society.
- Economic costs and consequences (evasion of taxes or duties, costs to the judicial system).
- Use of violence between or within criminal groups.
- Evidence of strategies to prevent prosecution, for example through corruption or intimidation.

5.9. Risk assessment and uncertainty analysis

In accordance with Article 5c(3)(c) of the Regulation, the report should contain an analysis of the health risks associated with the new psychoactive substance, in particular with respect to its acute and chronic toxicity, abuse liability, dependence-producing potential, and physical, mental and behavioural effects. Together, these sections should provide the relevant information for answering the question of whether the harm to health caused by the consumption of the new psychoactive substance, associated with its acute or chronic toxicity and abuse liability or dependence-producing potential, is *life threatening*.

In accordance with Article 5c(3)(d) of the Regulation, the report should contain an analysis of the social risks associated with the new psychoactive substance — in particular its impact on social functioning, public order and criminal activities, and the involvement of criminal groups in the manufacture, distribution and distribution methods, and trafficking of the new psychoactive substance. This section should provide the relevant information for answering the question of whether the social harm caused by the new psychoactive substance to individuals and to society is *severe*.

In accordance with Article 5c(3)(e) of the Regulation, the report should contain the available information on the extent and patterns of use of the new psychoactive substance, and its availability and potential for diffusion within the Union. This section should provide the relevant information for answering the question of whether the extent or patterns of use of the new psychoactive substance and its availability and potential for diffusion within the Union are *significant.*

When addressing the topics in each subsection below, the weight-of-evidence approach as described in the chapter on the conceptual framework in these guidelines should be followed, as well as Guidance Note 3. Both the likelihood and the severity of the consequences should be weighed. The

relevant evidence should be summarised and it should be shown how this evidence contributes to the lines of evidence supporting possible answers to the questions posed. In addition, the existing uncertainties should be identified and their impact on the range of possible answers should be discussed.

5.10. Conclusion

In this section, the questions formulated in the problem statement (Section 5.1) should be answered. This requires:

- a summary description of the extent and pattens of use of the new psychoactive substance and its availability and potential for diffusion within the Union, along with an indication of whether these are considered *significant*;
- a summary description of the main harms to health caused by the consumption of the new psychoactive substance, associated with its acute or chronic and abuse liability and dependence-producing potential, that takes into account the likelihood and severity of the harms, along with an indication of whether these harms are considered *life threatening*; and
- a summary description of the main social harms caused by the new psychoactive substance to individuals and society, along with an indication of whether these harms are considered *severe*.

For all three elements — extent and patterns of use, health risks and social harm — the level of uncertainty in the assessment should be expressed.

6. References

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) (2010), *Risk assessment of new psychoactive substances – Operating guidelines*, Publications Office of the European Union, Luxembourg (https://www.emcdda.europa.eu/guidelines/2010-risk-assessments-nps_en).

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The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is the central source and confirmed authority on drug-related issues in Europe. For 25 years, it has been collecting, analysing and disseminating scientifically sound information on drugs and drug addiction and their consequences, providing its audiences with an evidence-based picture of the drug phenomenon at European level.

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More information

More information about the work and main outputs of the EU Early Warning System on new psychoactive substances:

| Early Warning System on NPS:
www.emcdda.europa.eu/publications/topic-overviews/eu-early-warning-system

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