Forensic Science International 274 (2017) 2–6

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Toxicology in international drug control—Prioritizing the most harmful, persistent and prevalent substances

Susan C. Ifeagwu[a], Martin Raithelhuber[a], Conor Crean[a], Dimitri Gerostamoulos[b], Heesun Chung[c], Justice N. Tettey[a,*]

[a] Laboratory and Scientific Section, United Nations Office on Drugs and Crime, Vienna, Austria
[b] Department of Forensic Medicine, Monash University & Victorian Institute of Forensic Medicine, Southbank, Australia
[c] Chungnam National University, Daejeon, South Korea

ARTICLE INFO

Article history:
Available online 20 November 2016

Keywords:
New psychoactive substances
Toxicology
Early warning
NPS

ABSTRACT

The nature of the global drugs market has evolved rapidly and has become more complex with the emergence of new psychoactive substances (NPS), some of which have been associated with increased abuse, hospital emergency admissions and sometimes fatalities. NPS are characterized by geographic heterogeneity, with some only transient in nature and others not satisfying the criteria for harm required for international control. Consequently, a pragmatic response of the international community is to prioritize the most harmful, persistent and prevalent substances for action — an objective, which is hampered by the paucity of data on harms. The report describes a United Nations Office on Drugs and Crime (UNODC) initiative, in collaboration with the International Association of Forensic Toxicologists (TIAFT), to collect, analyze and share toxicology data at a global level to reinforce the ability of the international community in making informed decisions using a scientific evidence-based approach, in identifying the most harmful NPS.

1. Introduction

In recent years, the unprecedented emergence of potentially dangerous new psychoactive substances (NPS) that are not under international control has led to their increased abuse, hospital emergency admissions and sometimes fatalities. These substances, while often marketed as "legal" alternatives to substances under international control, may inadvertently pose a public health risk. To date, the continuously rapid emergence of NPS on the market makes it necessary to identify and understand their associated adverse health effects and social harms [1]. Notwithstanding the unprecedented emergence of NPS, the national and international responses, for example in the form of the risk assessments of substances for scheduling, has been hampered by the paucity of data on the harms due to their use.

By September 2016, the UNODC Early Warning Advisory (EWA) on NPS [2] had received reports of the emergence of over 730 NPS in over 100 member states and territories, more than three times the number of substances controlled by the International Drug Conventions [3]. Despite these high numbers, it is documented that the NPS are diverse in nature and pharmacological action [4]; there is heterogeneity in their emergence around the world; some NPS only show transience on the drug market; and that not all NPS that have emerged on the global market satisfy the criteria for the risk of harm required for international control [5].

At a special session of the United Nations General Assembly (UNGASS) on the World Drug Problem in April 2016, member states recognized the need for a comprehensive strategy to tackle the *harmful* NPS, i.e. substances causing deaths or clinical admissions, and reinforced the need to prioritize "the most harmful, persistent and prevalent NPS for action" [6,7]. Member states agreed on a set of practical operational recommendations, which, inter alia, reinforced the importance of enhancing national forensic capacities to identify and detect these substances, and actively participating in early warning networks to identify and monitor trends of NPS and assess their risks to health and safety.

Since its launch in 2013, the UNODC EWA system has helped in establishing emerging global trends of NPS and in identifying new and emerging threats. With over 12,000 data points on more than 730 NPS collected since 2008, including information on substances, country and year of emergence, and national legislative responses, the UNODC EWA provides a means of determining, through trend analysis, the global prevalence of a substance and

* Corresponding author.
E-mail address: justice.tettey@unodc.org (J.N. Tettey).

http://dx.doi.org/10.1016/j.forsciint.2016.11.022
0379-0738/

also its market persistence, including disappearance, market stability and post-legislative effects. The direct connection of the UNODC EWA to a network of over 220 national drug-testing laboratories in over 66 countries participating in the UNODC International Collaborative Exercises (ICE) Programme ensures that forensic evidence is used in enriching trend analyses of the NPS phenomenon [8]. However, the paucity of data on the harms associated with NPS remains an obstacle to the UNODC EWA fully contributing to the international community's objective of identifying the most harmful, prevalent and persistent NPS for international action [9].

Toxicology data on NPS are vital to understanding the associated harms and the knowledge gained by toxicologists is pivotal to informing early warning systems. With a membership of over 2000 scientists in 109 countries, the International Association of Forensic Toxicologists (TIAFT) represents an important stakeholder in establishing the first point of contact to identifying NPS of potential harm at a global level. A UNODC-TIAFT collaboration in sharing toxicology data in a timely way would reinforce the ability of the international community to make informed decisions using a scientific evidence-based approach in identifying the most harmful NPS. This collaboration will also facilitate the tailoring of UNODC's support to forensic science institutions, including toxicology laboratories, with the provision of reference standards, proficiency testing schemes and the development of recommended methods of analyses for drugs and their metabolites in biological fluids.

This report describes an exercise conducted by the UNODC, in partnership with TIAFT, to pilot a new and innovative tool for the collection of toxicology data for use in the prioritization of NPS for international action, i.e. in the identification of NPS that provide the greatest potential harm and informs a decision to be taken at the international level regarding scheduling. It reviews the feasibility of progressing this to an online system, linked to the UNODC EWA, to enable information sharing and aid the forensic toxicology community in anticipating the threats due to NPS and to identify the measures needed to increase their analytical preparedness to deal with the threat.

2. Methodology

2.1. Study design

A geographically representative group of forensic toxicologists, drawn from the membership of TIAFT and laboratories participating in the UNODC ICE, represented practices in twenty (20) countries from six (6) continents, namely Australia, Chile, Colombia, Cyprus, Finland, France, Ghana, Greece, Italy, Japan, Kenya, Korea, Mexico, Serbia, Singapore, Sweden, Switzerland, the Russian Federation, the United Kingdom and the United States of America. The meeting aimed at the development of a data collection tool for toxicology data on NPS with the primary objective of addressing the obstacle, which the paucity of such data poses to international efforts to prioritize the most harmful substances for action and accurately inform scheduling decisions.

The following indicators/parameters were identified as suitable for the collection of toxicology information on adverse events due to NPS, from a global perspective: country of notification; date and type of event (death, clinical admission, etc.); case commentary/circumstances; subject (age and gender); analyte (substance/metabolite identified); biomatrix (blood, urine, tissue [if post mortem]); sampling location (if post-mortem); sample concentration in biomatrix; analytical methodologies used; means of verification; route of administration; relative/probable contribution of the substance to the reported event; and any other relevant additional information.

The initial data collection form was completed by toxicologists participating in a pilot exercise with the instruction to submit relevant data and information on the ten (10) most recent cases encountered related to NPS use and provide feedback in order to evaluate, among others, the ease of completing the data form, completeness of information or indicators provided and clarity of terminology used.

This exercise was principally conducted to pilot the tool for collecting toxicology data related to NPS on a limited number of recent cases. Consequently, data obtained from the current exercise are neither representative nor fully indicative of current NPS trends, and should not be interpreted in that context.

3. Results

Information was obtained on a total of 128 separate cases, submitted by fifteen (15) respondents (Table 1). Of these cases, 97 (76%) were associated with the presence of more than one substance (poly-drug use, an example of which is shown in Table 2) with over 190 substances and metabolites, including substances under international control. Respondents reported an average time of approximately 5–15 min for completing the form per case record (range 5–30 min).

The feedback from participants also enabled refinement of all terminology used in the data collection tool to ensure clarity.

Fatalities and clinical admissions (e.g. due to acute drug poisonings) were the major events linked to the substances reported (Table 3). In addition, drug use in driving, urine testing for substances of abuse, monitoring of drug use in opioid substitution therapy, non-fatal intoxications and use in a sexual context were included in the range of events reported.

The data from the pilot study illustrates the potential of a full exercise to allow for the association of substances to post-mortem cases and clinical admissions and thus should provide an indication of the most harmful substances, based on frequency of reporting and allowing for isolated cluster events (Fig. 1). A similar set of information can be obtained for monitoring drug use in driving and at the workplace, among others.

Data obtained on the means of verification used in the identification of substances/metabolites show that a majority of identification is carried out using reference standards (66%) and comparison to instrument libraries and/or online databases.

4. Discussion

Results obtained and the feedback received from participants indicate that the objective of having a simple, comprehensible and user-friendly tool with a minimum data set (or defined minimum inputs) was to a large extent achieved with the completion of a case record requiring on average 5–15 min. The terminology used (see Supplementary material) provided sufficient clarity for completing the forms.

The data submitted was evaluated in terms of establishing a connection between a substance and an event, such as death, non-fatal intoxications, etc. In this regard, a three-tier classification system, where the contribution of a substance to an event is described as 'causal', 'contributory' or 'present but non-contributory', was used, with the initial aim of identifying causality of the adverse event, for example a death. With poly-substance use represented in almost 76% of cases reported, direct assignment of causality to a specific substance is difficult. As an illustration, Table 2 provides an example of one case of poly-drug use, wherein 4-MEC and MDPV were reported as the main substances implicated in the death. Difficulties arise in deciding which substance was the major cause of death or which was contributory or synergistic. With potential substance — substance interactions

Table 1
Summary of key data obtained from the pilot study.

Summary of data from pilot study	
Total number of respondents that provided case data	15
Total number of cases	128
Number of poly-drug use cases	97 (76% of all cases)
Number of cases in which only a single compound/metabolite was detected	31
Number of substances reported (including non-NPS and scheduled substances)	More than 190
Total number of substances mentioned (including duplicates or a substance mentioned multiple times)	402
Matrices reported	
Blood	89 (in combination with others)
Urine	73 (in combination with others)
Hair	2
Other (bile, vitreous humour, lung, brain, etc.)	18
Sampling location options provided	Aorta Bladder Cardiac blood Cavity Different parts of the corpse Eye Femoral blood Gastric content Heart Stomach Peripheral blood Urine patient sample
Means of verification (n = 402)	
Reference standard	266
Instrument database	57
Online database	40
Scientific literature	19
N/A	16
Internal (own) database	2
Other	2
Route of administration (n = 402)	
Inhalation	35
Injection	26
Nasal insufflation	8
Oral consumption	26
Other (e.g. ocular, placenta)	4
N/A	303[a]
Patient information	
Gender (of all case reports, n = 128)	
Male	110 (85.9%)
Female	17 (13.3%)
N/A	1 (0.8%)
Age (of all case reports, n = 128)	
Mean	30
Median	28
Range	14–58 (including a new-born)
Standard deviation	8.7

[a] A majority of cases (n = 303 of all total substances reported) were noted as 'N/A' within the case reports. Thus, it is clear that the information on the route of administration is not always readily available.

Table 2
An example of a case of poly-drug (or multiple substance) use from the pilot group.

Type of event	Age	Substance	NPS substance group	Effect group	Matrix	Sampling location	Concentration	Contribution
Post-mortem	36	4-MEC	Synthetic cathinone	Stimulant	Blood	Cardiac blood	5594 μg/L	Causal (high)
		Methoxetamine	Phencyclidine-type substance	Dissociative	Blood	Cardiac blood	3415 μg/L	Contributory (medium)
		MDPV	Synthetic cathinone	Stimulant	Blood	Cardiac blood	628 μg/L	Causal (high)
		Mephedrone	Synthetic cathinone	Stimulant	Blood	Cardiac blood	5 μg/L	Present but non-contributory (low)
		Methylone	Synthetic cathinone	Stimulant	Blood	Cardiac blood	67 μg/L	Contributory (medium)
		Nordiazepam	N/A	Sedative/ hypnotic	Blood	Cardiac blood	205 μg/L	Present but non-contributory (low)
		Ethanol	N/A	Sedative/ hypnotic	Blood	Cardiac blood	0.95 μg/L	Present but non-contributory (low)

Table 3
Types and frequency of events from the pilot study.

Type of event	Count
Clinical admission (acute drug poisoning, coma, etc.)	42
Post-mortem (death)	66
Drug driving	2
Drugs of abuse testing in urine	2
Methadone treatment by the specialized institution	5
Non-fatal intoxication	8
Sexual context	1
Other (please specify)	2

not being clear and concentration ranges of NPS associated with adverse events either being unknown or not well defined, a causal relationship may be difficult to establish. A more prudent approach would be to initially establish 'association' of substances with adverse events in cases of poly-substance use, with a view to assigning causality only after detailed analyses of a large sample set of such 'associations' [10].

A potential difficulty occurs with the reporting of metabolites in circumstances where the metabolites cannot be linked back to the parent substance, e.g. for many of the synthetic cannabinoid receptor agonists (SCRAs) that share common metabolites [11]. In such situations, the completion of the case commentary, for example with information on the product used or found at the scene, has shown to be useful in confirming the NPS implicated in the event.

Since in most cases it is often difficult to distinguish the primary substance, the data collection tool has been modified to provide a simple listing of all substance(s) or metabolite(s) identified within the analyses, without a specific order or reference to the 'primary' substance.

Ultimately, information on the relative contribution of substances can reveal patterns of common substances linked to adverse events, help generate a profile of substances most often associated with severe adverse events e.g. deaths, emergency room admissions, etc., and improve our understanding of the mechanism of action and resulting effects of substances.

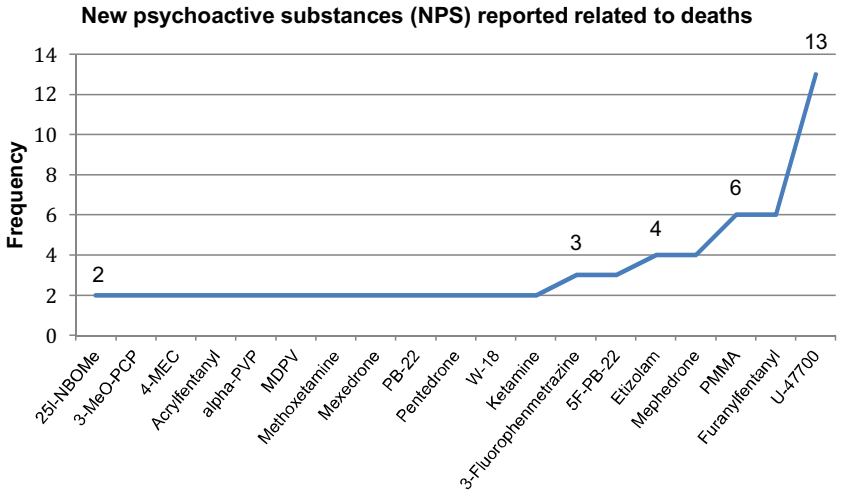

Fig. 1. Frequency of NPS associated with post-mortem cases in the pilot study.

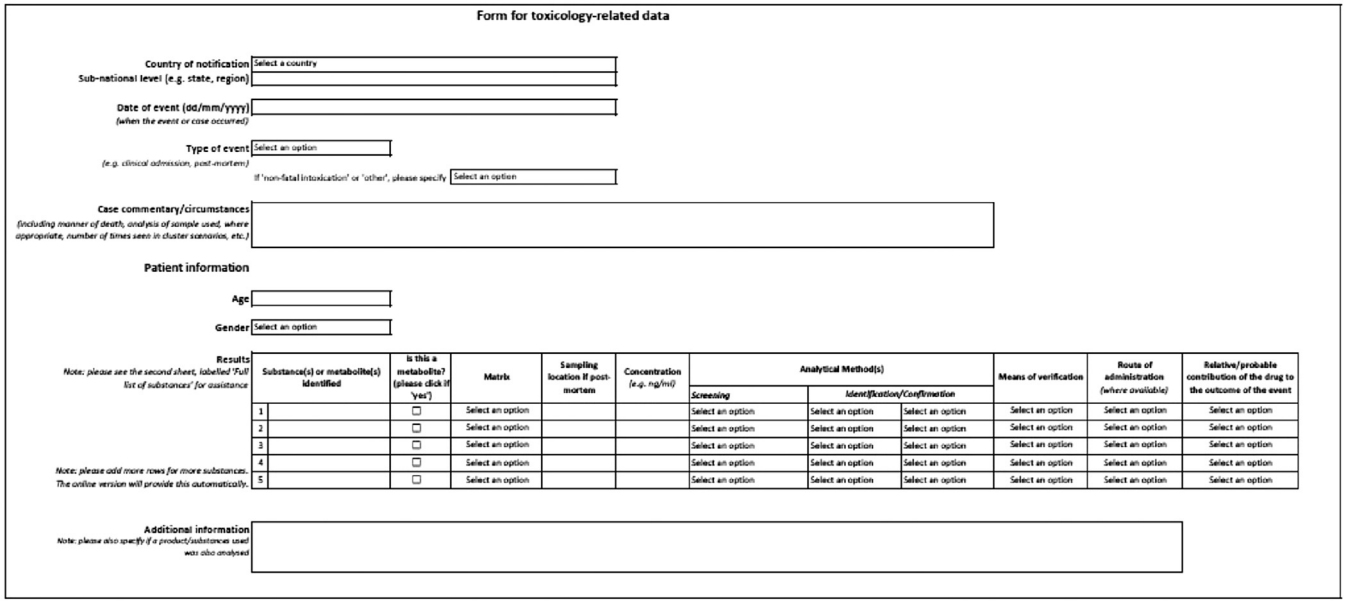

Fig. 2. Final NPS toxicology data collection tool.
Note: Drop-down menus are provided for fields with 'select an option' (see Supplementary material), and substances will be linked to the UNODC EWA.

The relevance of providing data on the concentration of substances present was highlighted in the feedback received from the pilot group. It was noted that for NPS, the absence of information equivalent to 'therapeutic' concentrations for medicines or more established substances of abuse makes interpretation of quantitative data very difficult and perhaps unnecessary to collect. Nonetheless, these data are available from laboratories (76% of respondents), and their collection and analyses could ultimately form the basis for establishing what concentrations of particular substances in biomatrices can be considered lethal and inform future decisions on assigning causality [12].

The initial data collection tool has been suitably adapted to reflect geographical difference in practice and capacities of toxicology institutions. For example, an option of 'undetermined' has been included under the 'relative contribution' indicator in cases where a causal relationship could not be established. In addition, flexibility has been introduced in the reporting of 'identification' and 'confirmation' methods to reflect the practices in different laboratories and options for more toxicology-specific analytical techniques have been incorporated. The final revised data collection tool, which will form the basis for online submission of data to the UNODC EWA, is shown in Fig. 2.

5. Conclusions

Looking forward, this new initiative, a product of the innovative collaboration between TIAFT and UNODC, aims to ultimately close the current knowledge gap of toxicology and health-related data on NPS. The initiative will facilitate information sharing between the toxicology community and related stakeholders, while supporting the prioritization of the *most harmful, prevalent and persistent* NPS for international control. Furthermore, it will enable the development of a more complete global overview of data within the UNODC EWA database, provide visibility and help raise awareness of harmful substances and assist in the development of laboratory capacity, through the sharing of information regarding analytical techniques, among other criteria, and finally, support efforts to reducing drug supply and protecting the health and welfare of mankind.

The revised data collection tool will be incorporated into the UNODC EWA enabling the global forensic toxicology community, including TIAFT and laboratories participating in UNODC ICE to share, in a timely manner, toxicology data on NPS and access trend analysis of the most harmful, prevalent and persistent.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.forsciint.2016.11.022.

References

[1] United Nations Office on Drugs and Crime (UNODC), World Drug Report, (2016) Sales No. E.16. XI.7.
[2] UNODC, Early Warning Advisory (EWA). Available from: www.unodc.org/nps
[3] United Nations, The International Drug Control Conventions. Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol; Convention on Psychotropic Substances of 1971 of United Nations; United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, 2013. https://www.unodc.org/unodc/en/commissions/CND/conventions.html (Accessed 28 September 2016).
[4] P.I. Dargan, D.M. Wood, Novel Psychoactive Substances: Classification, Pharmacology and Toxicology, Elsevier Inc., San Diego, 2013.
[5] UNODC, New Psychoactive Substances: Overview of Trends, Challenges and Legal Approaches, (2016) E/CN.7/2016/CRP.2.
[6] United Nations, Our Joint Commitment to Effectively Addressing and Countering The World Drug Problem, (2016) A/RES/S-30/1.
[7] UNODC, Global SMART Update Volume 16. Post-UNGASS 2016: NPS Trends, Challenges, and Recommendations, (2016) .
[8] UNODC, International Collaborative Exercises (ICE) Programme. www.unodc.org/ice .
[9] World Health Organisation, Expert Committee on Drug Dependence: Thirty-seventh Report (Geneva, Switzerland, 2015), (2016) .
[10] S. Elliott, J. Evans, A 3-year review of new psychoactive substances in casework, Forensic Sci. Int. 243 (2014) 55–60.
[11] J.L. Knittel, J.M. Holler, J.D. Chmiel, S.P. Vorce, J. Magluilo, B. Levine, G. Ramos, T. Z. Bosy, Analysis of parent synthetic cannabinoids in blood and urinary metabolites by liquid chromatography tandem mass spectrometry, J. Anal. Toxicol. 40 (3) (2016) 173–186.
[12] D. Gerostamoulos, S. Elliott, H.C. Walls, F.T. Peters, M. Lynch, O.H. Drummer, To measure or not to measure? That is the NPS question, J. Anal. Toxicol. 40 (4) (2016) 318–320.