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Letter to the Editor

The value of toxicological and forensic analyses in the global challenge to health risks caused by new psychoactive substances

Dear Editor,

In 2018, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported the appearance of new psychoactive substances (NPS) on European Union (EU) at a rate of about one per week for a total of 55 new drugs detected in 2018. On one hand, this figure is similar to that communicated in 2017 (N=51) and both of them are significantly lower if compared to those, above one hundred, appeared in 2014 and 2015. On the other hand, it has to be underlined that there has been a change in the type of substances coming into illegal market, since the most recent new psychoactive substances are increasingly more targeted in the long-term and to drug users with more addictive behavior. Specifically, new synthetic opioids and benzodiazepines are now the most reported substances by the EU Early Warning System, together with a distinct range of other recreational substances[1].

The epidemics of both classes of substances come from United States and Canada, where both caused severe intoxications and fatalities purposely related to the use of synthetic opioids, particularly fentanyl derivatives. Although these two phenomena have not been so diffused in Europe, concerns do exist also in this area. About 50 new synthetic opioids, mainly fentanyl illicit analogs, have been reported up to now to the EU Early Warning System and the seizures of carfentanil, one of the most hazardous and potent opioids, have been particularly alarming[2-5]. In this latter case and in that of many other fentanyl derivatives, due to the extreme potency of these compounds, they can be trafficked in very small quantities, which are difficult to detect[2]. In addition, the synthetic opioids and new illegal benzodiazepine share the occurrence that they have been sold as fake kinds of commonly prescribed pain-relievers and antianxiety drugs. Regarding synthetic opioids, the fake OxyContin tablets containing metoxyacetylfentanyl, or fentanyl itself, have been reported by EU early warning system in the last two years[6]. In case of new benzodiazepines, some of these are trafficked as fake types of Xanax, containing alprazolam or other compounds of the same class but illegally produced and sold, or even containing fentanyl and analogs[7].

In this concern, the values of accurate and immediately available toxicological and forensic data are crucial[8].

Indeed, the drug related severe intoxications and fatalities are seldom associated with the consumption of one substance alone. Drug consumption patterns are often characterized by polyconsumption of both classical drugs and NPS. For this reason, without good forensic and toxicological data, new health threats may be underestimated. The major risk, therefore, is that the role of the most toxic NPS, like fentanyl derivatives, in overdose deaths may be missed, especially when they are consumed together with classical psychotropic drugs, such as heroin, or when other newly marketed compounds such as the above reported new benzodiazepines are in place[7,9]. If on the one hand the EU Member States, particularly in northern Europe, where this new hazard is more diffused (e.g. Sweden or UK), have invested in improving the availability and sensitivity of the toxicological data implementing analytical protocols. On the other hand, in the majority of the remaining countries the pharmacotoxicological laboratories, both in clinical and in forensic, do not have the capacity to detect NPS and/or their metabolites in NPS related intoxications presenting at e.g. emergency departments and fatalities requiring medico-legal examinations[10,11]. The first striking problem is the unavailability of the reference standards for NPS in many laboratories. Several of these standards, especially in case of the newest NPS and metabolites, are out of the market, or

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when they are in, they are extremely expensive and/or complicated to obtain also for the different legal requirements between the foreign countries. In addition, since often just a minute amount of NPS is required for the psychoactive action, their concentration in the body fluids can be extremely low, requiring last generation hyphenated techniques (such as gas or liquid chromatography coupled to tandem mass spectrometry or high resolution mass spectrometry) for determination[12-17].

As an example of good practices to improve the monitoring and procedures in this area, the Italian Early warning system, funded by the Department of Antidrug Policy at the Presidency of the Council of Ministers, launched a project named "NPS-Lab-PT (standing for Laboratory Proficiency Testing). In the framework of this project, sixty network collaborative centers, located in clinical, forensic, and Police Forces analytical laboratories along the whole National Territory, received about sixty pure reference standards of principal NPS and metabolites, including fentanyl and analogs and new benzodiazepines and a pre-developed analytical method in ultra-performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) to identify and eventually quantify all of them. Furthermore, the National Early Warning System team offered to assist the laboratories participating in the project to set-up their own method, if instruments other than UHPLC-MS/MS were available. The majority of the laboratories implemented the methods to disclose the presence of NPS in seized material and more in general in non-biological materials (e.g. powders, tables, capsules). Nevertheless, twenty-five out of the sixty laboratories accepted to participate in a Proficiency Testing exercise for NPS in biological matrices where they are going to receive two hair and two oral fluid samples fortified with classical drugs and NPS at concentrations usually found in consumers. These two biological matrices have been chosen as test-matrices, since they are easy to be prepared, stored, and shipped, providing the objective assessment of repeated and current consumption of NPS, respectively. The web assistance has been implemented to support those latter laboratories for eventual difficulties, doubts, and to discuss the obtained results. At the end of the project, the National Early warning System will dispose of several Police forces laboratories able to recognize the presence of NPS in seizures and be able to provide National Health System with, at least, twenty five laboratories competent to determine NPS at least in one conventional and one non-conventional biological matrix[18].

In conclusion, since not only NPS but also synthetic drugs of all types are likely to continue to grow in importance, we believe that investments in toxicological and forensic analytical data sources are strongly needed.

Conflict of interest

The authors declare no conflicts of interest.

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