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7th July 2017

REGULATION 28: REPORT TO PREVENT FUTURE DEATHS arising from the investigation into the death of Nature Barr (also known as Howard Jeffers): response by the Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, University of Hertfordshire.

Dear Dr Brittain,

Thank you for your Regulation 28 Report to prevent future deaths, dated 15th May 2017, bringing to my attention the Coroner's concerns arising from the inquest into the death of Nature Barr. The members of the Psychopharmacology, Drug Misuse and Novel Psychoactive Substance Research Unit at the University of Hertfordshire have given careful consideration to the concerns outlined. I set out the actions we have taken and plan to take in response to the concerns below.

(1) "… [the] risk that future deaths may occur unless NPS can be more accurately analysed and detected by toxicological testing."

Novel Psychoactive Substances (NPS) is the scientific name of mind-altering substances also misleadingly known as "legal highs". The phenomenon of NPS began, among a small group of individuals, about a decade ago but in the last few years it has grown exponentially and represent now a major treat in terms of public health.

There is a growing evidence of negative effects secondary to the use of NPS. This evidence was at first anecdotal (e.g. media coverage), but recently the scientific community has focused its interest on NPS and therefore there is now a growing number of scientific studies and related publications. The Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit at the University of Hertfordshire is actively engaged in research to facilitate the accurate identification of NPS from "seized" samples, and to provide clinicians with updated guidelines to help them better manage patients presenting with toxicities associated with abuse of NPS. The head of the unit, Professor Fabrizio Schifano, is a full member of the Advisory Council on the Misuse of Drugs (ACMD). Both he and another member of the unit, Mr John Corkery, are members of the ACMD's Technical and NPS Committees. In addition, Prof. Schifano has recently been appointed chair of the ACMD's new committee on Performance and Image-Enhancing Drugs.

Overall, unprecedented knowledge has been provided by our research group on the epidemiological, psychopathological and overdose issues related to the misuse of NPS. To this respect, Professor Schifano has been the Principal Investigator of 6 consecutive EU Commission-funded, multi-centre (i.e. 12 EU countries), Novel Psychoactive Substance-based, research

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programmes (since 2002). These have included the following: 'Psychonaut 2002' (2002-2004); 'Psychonaut Web Mapping system' (2008-2009); 'EU-ReDNet/Recreational Drug Network' (2010-2012); EU-MADNESS (2014-2016); and EPS/NPS (2015-2016) projects. In particular, the University of Hertfordshire and St George's University of London co-led the EU-funded EU-MADNESS project "EUropean-wide, Monitoring, Analysis and knowledge Dissemination on Novel/Emerging pSychoactiveS". The objective was to develop integrated monitoring and profiling of Novel Psychoactive Substances (NPS) in Europe in order to prevent health harms and update relevant professionals. The project aimed: to monitor, test, profile, and feed back into education and prevention knowledge relating to the types of NPS emerging, their associated characteristics and potential harms.

Specific actions taken to address the concern: Very little is known of the effect of NPS in individuals with mental health conditions. Our University of Hertfordshire (UH)-based NPS Unit has started to collect data on the effect of the NPS in individuals admitted in the Highgate Mental Health Centre.

This particular project is being carried out in collaboration with two Highgate Mental Health Centre psychiatrists who have also enrolled for a PhD with our University (supervisor: Dr Ornella Corazza). The aim of their study is to gather new information on the effect of the NPS among vulnerable individuals, but also to develop evidence-based policies that will help to control and reduce the damage caused by these compounds.

In 1997 whilst working at the Home Office, John Corkery helped to set up the National Programme on Substance Abuse Deaths (NPSAD), which is based at St George's University of London. He also served on the Council's reconvened Drug-Related Deaths Working Group, having worked as a Home Office Official on the original Working Group in 1999-2000. Professor Fabrizio Schifano joined the NPSAD in 2000. Although their formal association with NPSAD has ended, they both continue to work together on research projects and publish together.

Our efforts are also focused to improve in-field methods of NPS identification in products using analytical approaches (led by Dr Jacqueline Stair). The main approach we are currently researching in handheld Raman spectroscopy which allows the identification of key molecular scaffolds *via* the scattering of light. This tool is to enable the quick identification of NPS at borders, from seizures, or from individuals. Due to the > 650 NPS that exists, Raman spectroscopy can differentiate between closely related NPS analogues which can vastly reduce the number of substances sent to forensic labs for full analytical testing, which can be costly and time-consuming. A particular challenge is that NPS products are often available as complicated mixtures of NPS, adulterants, and cutting agents. To this end, we are focused on examining sophisticated mixture algorithms for their effectiveness of NPS identification in product mixtures often found with 'street' samples. As only a sample of suspected products can usually be send for full analytical testing/ NPS subsequently identified, this technology can improve presumptive analysis throughput for identification of more NPS products arriving in the EU and UK. The idea is to greatly reduce the NPS making it to the UK market for human consumption *via* improved identification.

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As an extension of this work, Dr Amira Guirguis recently completed a PhD (supervised by Dr Jacqueline Stair, Dr Stewart Kirton and Dr Suzanne Fergus) on the 'identification of NPS using spectroscopic and chemometric approaches'. Her work examined the issues surrounding the appropriate selection of analytical conditions and instrumentation for the detection of NPS; a scientifically-robust approach to construct compound libraries that have relevance to 'in-field' analysis and data analytical science that examined approaches that can be employed to develop accurate NPS identification algorithms from spectroscopic information for use by non-experts. This work aimed at providing advice and support in the following areas: General education on NPS for pharmacists, common cutting agents and adulterants in NPS samples, what they are, how to identify and classify them, health harms posed by NPS and harm reduction techniques. Additionally, research was carried out with respect to education on the strengths and limitations of in-field techniques used for the identification of NPS, education on using handheld Raman techniques in the field and advice on improving the signals obtained and hence increasing the chances of detecting NPS. The technical aspects of these studies to aid accurate identification of NPS in "street" samples included:

- Strategies to reduce fluorescence and enhance signal to noise in field Raman measurements.
- Approaches to validate and use spectral libraries that can identify and categorise chemical species present in complex mixtures of poorly-defined provenance.
- Signal processing approaches that can be employed to introduce greater discrimination for adulterants that often contribute to the noise in Raman spectra, which pose a barrier to identification of unknown constituents in typical mixtures.
- Development of chemometric approaches to build a spectral library that provides appropriate cover of the entire chemical space underlying known NPS.
- Incorporation of common adulterants and cutting agents into high resolution spectral databases in order to develop categorisation approaches using an expanded 'importable' library and subsequent attempts to deploy that strategy for hand-held device, remote analysis.

Dr Guirguis is also leading on potential collaborations with the Royal Pharmaceutical Society (RPS), consultant psychiatrists, addiction specialists, general community pharmacists, mental health pharmacists and mental health nurses in the UK to assess the baseline knowledge on NPS and the design of education and training courses on NPS targeting healthcare professionals. Future work over the next year will include collaborations with French psychiatrists and addiction specialists to design a tool that clinicians can use for the efficient identification of NPS. She is also leading on a two-fold study: 1) to train and educate police officers on the use of handheld Raman instruments which could be employed on road-sides as well as in prisons for the identification of solid samples confiscated from prisoners and 2) to train and educate police officers and healthcare professionals who work in prisons on NPS and their categorization, which may potentially enhance the management of NPS use and assist in treatment decision-making. Her work is currently exploring developing undergraduate pharmacy curricula on NPS, which can be piloted nationally.

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In order to compliment and extend the work carried out to systematically classify existing NPS, Dr Stewart Kirton, Dr Jacqueline Stair and Dr Suzanne Fergus are leading research into predicting the next generation of chemical scaffolds that could be exploited by those who synthesize and distribute NPS. One PhD student (Michelle Botha) has used computers to identify a series of commercially available compounds that have the potential to bind to the CB1 receptor, but crucially are significantly different with respect to their chemical structures from any of the identified synthetic cannabinoids. Currently, biological testing is underway to establish if the activity predicted *in silico* is apparent *in vitro/in vivo*. Where biological activity exists, the spectral properties of the active compounds will be fed into the computational models that have previously been described. For the first time, this will provide a technology capable of identifying and classifying molecular scaffolds prior to them appearing on the market. Funding will be sought to extend the scope of this research into other classes of NPS beyond that of the synthetic cannabinoids.

We hope that our response demonstrates the actions that are being taken here in the Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit at the University of Hertfordshire to address the concerns around the real and significant dangers posed by the abuse of NPS. As you can see our approaches to tackling the problem are multi-faceted and extend from physical science and informatics, through medicinal chemistry and biological evaluation to clinical guidance and epidemiology. However, it is important to be clear that at this time we have no plans to develop techniques for the identification of NPS and their metabolites from biological matrices (e.g. blood and urine). The expertise of the members of the group does not extend to this type of biological analysis, and we feel others are better placed to address this issue.

Yours Sincerely,

Stewart Kirton PhD, CChem, FRSC, SFHEA
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Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit
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