Institution: Liverpool John Moores University (LJMU)		
Unit of Assessment: UOA 3		
Title of case study: Implementing multidisciplinary research to facilitate international drug control and protection of global public health		
Period when the underpinning research was undertaken: 2005–2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Simon D. Brandt	Reader in Bioactive Drug Chemistry	2005 – present
Period when the claimed impact occurred: 2014 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

New psychoactive substances (NPS) are newly emerging drugs that pose significant challenges to people who use drugs, health care professionals, law enforcement and policymakers. Lack of drug control and an absence of knowledge about drug identity and properties, exacerbate the harms experienced by people who use drugs. Using the example of the lethal NPS 4,4'-DMAR, we provide a powerful example of how multidisciplinary approaches to research and research-led services resulted in efforts to protect global public health. For example, the occurrence of 18 deaths in the UK initiated intensive efforts that led to: a) the identification of the drug causing the fatalities; b) elucidating the mechanisms of toxicity involved; and c) providing expert advice to facilitate European and international drug control to remove this drug from the streets.

2. Underpinning research

The unprecedented emergence of so-called new psychoactive substances (NPS) or "designer drugs" has created significant challenges for, people who use drugs; clinicians; law enforcement; health care professionals; and policy makers, which requires a multidisciplinary approach to research. NPS are designed by large-scale drug manufacturers to mimic the properties of traditional (and controlled) drugs of abuse such as MDMA, methamphetamine, LSD, cannabis, and heroin in an effort to circumvent drug control legislation. The appearance of these drugs of abuse on the streets occurs at an unparalleled rate and information about their identity, purity, and toxicological properties is typically unavailable.

A multidisciplinary research programme carried out at LJMU with collaborators in Europe and the USA has been designed specifically to detect and evaluate these drugs. The exploration of the chemical, analytical and biological properties of NPS underpinning the ability to understand the harms associated with their use, has resulted in the publication of over 80 papers (2014–2020). This research has provided data and research-led expertise to scientific audiences and policy-oriented stakeholders working in the drugs of abuse arena in an effort to reduce risks to society associated with drugs use.

For example, in 2014, research at LJMU was instrumental in identifying the NPS 4,4'-DMAR, a designer drug responsible for and contributing to a cluster of 18 deaths in the UK where it was surreptitiously sold as ecstasy (MDMA) and other illicit drugs (R1, R2). Further investigations confirmed the exact form (isomer) of the drug using organic syntheses and established methods for drug identification, followed by pharmacological studies. Most importantly, these studies revealed the mechanisms involved in the acute toxicity of 4,4'-DMAR that displays a significantly higher potency than other controlled dugs with similar toxicological behaviour such as amphetamine, aminorex and MDMA (R2-R4). It was shown, for the first time, that 4,4'-DMAR functioned as a substrate-type releaser, capable of inducing transporter-mediated reverse transport of key neurotransmitters in the brain, which provided important insights into the

mechanisms of action involved in the fatal intoxications due to monoaminergic toxicity (R2–R4). Test purchases and subsequent analyses also confirmed that this drug was available on the Internet at the time of its emergence, which highlighted the dangers of uncontrolled drugs of abuse being available for legal purchase in the UK (R2). This particular work programme set the stage for risk evaluations at a European, national, and global scale leading directly to drug control.

Another example is the pharmacological evaluation (*in vitro* and *in vivo*) of MDPV, a designer drug associated with significant adverse effects, including death that occurred worldwide. Our research was the first to show that this drug was 10-times more potent than cocaine in affecting monoaminergic transition in the living brain (R5) within brain areas related to drug addiction. Follow-up studies confirmed the high potential for abuse liability and dependence (R5, R6) and this work impacted on international drug policy level, leading to its control.

3. References to the research

All outputs were subject to rigorous peer review processes (mean impact factor: 3.94).

R1. Cosbey S, Kirk S, McNaul M, Peters L, Prentice B, Quinn A, Elliott SP, **Brandt SD**, Archer RP (2014). Multiple fatalities involving a new designer drug: *para*-methyl-4-methylaminorex. *J Anal Toxicol*; 38: 383-384. https://doi.org/10.1093/jat/bku03 (IF: 3.513)

R2. **Brandt SD**, Baumann MH, Partilla JS, Kavanagh PV, Power JD, Talbot B, Twamley B, O'Brien J, Mahony O, Elliott SP, Archer RP, Patrick J, Singh K, Dempster NM, Cosbey SH (2014). Characterization of a novel and potentially lethal designer drug, (±)-*cis*-*para*-methyl-4-methylaminorex (4,4'-DMAR, or 'Serotoni'). *Drug Test Anal*; 6: 684-695. https://doi.org/10.1002/dta.1668 (IF: 2.903)

R3. McLaughlin G, Morris N, Kavanagh PV, Power JD, Twamley B, O'Brien J, Talbot B, Dowling G, Mahony O, **Brandt SD**, Patrick J, Archer RP, Partilla JS, Baumann MH (2015). Synthesis, characterization, and monoamine transporter activity of the new psychoactive substance 3',4'-methylenedioxy-4-methylaminorex (MDMAR). *Drug Test Anal*; 7: 555-564. https://doi.org/10.1002/dta.1732 (IF: 2.903)

R4. Maier J, Mayer FP, Luethi D, Holy M, Jantsch K, Reither H, Hirtler L, Hoener MC, Liechti ME, Pifl C, **Brandt SD**, Sitte HH (2018). The psychostimulant (±)-*cis*-4,4'-dimethylaminorex (4,4'-DMAR) interacts with human plasmalemmal and vesicular monoamine transporters. *Neuropharmacology*; 138: 282-291. https://doi.org/10.1016/j.neuropharm.2018.06.018 (IF: 4.431)

R5. Baumann MH, Partilla JS, Lehner KR, Thorndike EB, Hoffman AF, Holy M, Rothman RB, Goldberg SR, Lupica CR, Sitte HH, **Brandt SD**, Srihari RT, Cozzi NV, Schindler CW (2013). Powerful cocaine-like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive "bath salts" products. *Neuropsychopharmacology*; 38: 552-562. https://doi.org/10.1038/npp.2012.204 (IF: 6.751)

R6. Schindler CW, Thorndike EB, Goldberg SR, Lehner KR, Cozzi NV, **Brandt SD**, Baumann MH (2016). Reinforcing and neurochemical effects of the "bath salts" constituents 3,4-methylenedioxypyrovalerone (MDPV) and 3,4-methylenedioxy-*N*-methylcathinone (methylone) in male rats. *Psychopharmacology*; 233: 1981-1990. https://doi.org/10.1007/s00213-015-4057-0 (IF: 3.13)

4. Details of the impact

A response to the threat to public and social health caused by new psychoactive substances (NPS), and the need for developing strategies for strengthening preparedness, created the

framework for this multidisciplinary research on NPS. Significant impact ranges from, identification of unknown drugs on the streets; evaluation of NPS toxicity; risk assessments on the harms of these substances; and changes in national and global drug policy. Brandt's expertise led to appointment as a regular senior expert advisor for questions related to legislative control and harm assessments of NPS in the European Union (EU) and worldwide (United Nations).

Impact on European level (examples):

Due to his research activity and expertise, Brandt has been appointed as an extended member of the European Monitoring Centre for Drugs and Drug Addiction Scientific Committee (EMCDDA), 2011-present). The EMCDDA, in cooperation with the European Union Agency for Law Enforcement Cooperation (Europol), collect EU-wide information to detect (via early-warning systems, EU-EWS); assess (via risk assessments); and respond to health and social threats caused by NPS. The results of risk assessments are provided to the European Commission, the Council of the European Union and the European Parliament as a basis for introducing control measures to reduce drug-related harms. EMCDDA are monitoring the EU drug market and collect drug data in a specific information system including the European Database on New Drugs (EDND), which provides EU-wide dissemination of critical data to stakeholders related to drug harms and policy. Examples of Brandt's involvement in risk assessments that included provision of evidence and data are provided.

The EMCDDA carries out risk assessments on NPS once they are deemed a threat to public health and, between 20014-2017, Brandt has authored/co-authored 9 technical reports on the NPS, 5-IT; 25I-NBOMe; 4,4'-DMAR; α-PVP; furanylfentanyl; ADB-CHMINACA; CUMYL-4CN-BINACA; THF-F; and 4F-iBF (CS1), which included provision of research data and expertise on these substances, thereby demonstrating direct impact on EU policy-making since these assessments are used to implement EU-wide drug control measures. For example, the identification of the street drug 4,4'-DMAR and its involvement in multiple deaths in the UK triggered a notification to the EMCDDA and set the stage for the EMCDDA risk assessment. The research data (R1–R3) formed a key part of the 2014 assessment (CS2, pages 14–37). Moreover, the technical report underpinning the evidence within the risk assessment was authored by Brandt (CS2, pages 14–37) and, on the basis of this report, in 2015 the EU Council decided to subject 4,4'-DMAR to an EU-wide ban (CS2, pages 38–41) in 2015. The identification of 4,4'-DMAR led to immediate removal of this drug from product catalogues of Internet retailers and no further deaths or appearances related to 4,4'-DMAR have been reported to EMCDDA since that time.

Since 2014, Brandt has been frequently invited to contribute to EMCDDA risk assessments of 20 NPS providing expertise and research data to help with evaluations of health and social risks caused by NPS (CS1). Brandt's also contributed substantial chemical, analytical and pharmacological data to EMCDDA's EDND, (CS1, see also examples related to 4,4'-DMAR). The data available on this EU database is considered essential for detecting, assessing, and responding to threats posed by NPS at an EU-level (CS1).

Impact on national level:

The UK's Advisory Council on the Misuse of Drugs make recommendations to government on control measures of drugs and drug policy. The ACMD's assessment of 4,4'-DMAR in late 2014 led to recommendations to control this drug as a Class A, Schedule 1 compound was based on both the work cited by Brandt and the EMCDDA's risk assessment documentation (co-authored by Brandt, CS2) (CS3, pages 3–20). The control of 4,4'-DMAR in the UK came into force following this recommendation in 2015 (CS4).

Impact on international level:

At international level, the World Health Organisation's (WHO) Expert Committee on Drug Dependence (ECDD) has to assess the health risks and benefits of using psychoactive substances (drugs of abuse, NPS and medicines). Whenever it is brought to the WHO's attention that a substance is of especially serious risk to public health and society, the ECDD carries out a Critical Review to evaluate the substances with regards to international control under the United Nations drug control conventions. ECDD's recommendations for international control to the Commission on Narcotic Drugs (CND) are based on these Critical Reviews, prepared by specifically invited experts that function as Temporary Advisors and are appointed annually by WHO, depending on their expertise.

In the period between 2014–2019, Brandt has been continuously appointed as a Temporary Advisor to participate and contribute his expertise (including research data) to 6 meetings of the ECDD (including for 4,4'-DMAR) where a total number of over 80 drugs were assessed for their social and public harms for evaluations of control measures. Brandt has authored a total number of 16 Critical Reviews that serve as the basis for these evaluations.

The threats related to the poisonings caused by 4,4'-DMAR triggered a Critical Review at the WHO which drew extensively from the research data provided by Brandt and collaborators (CS5). The review carried out by the ECDD was based on the technical report written by Brandt for the EMCDDA risk assessment (CS2, pages 14–37) (CS5, page 5) which resulted in recommendations for 4,4'-DMAR to be listed as a Schedule II drug in the Convention on Psychotropic Substances of 1971 followed by confirmation by CND in 2016 (CS6, page 13). Internationally, the occurrence of drug deaths associated with 4,4'-DMAR have not been reported in the literature since this time.

One example was the preparation of a Critical Review on the NPS MDPV (CS7) that cited research by Brandt et al. on the effects of MDPV (R5) (CS7, pages 11–15). The Critical Review set the stage for WHO's recommendation to control MDPV as a Schedule II drug under the Convention on Psychotropic Substances of 1971, followed by confirmation by CND (CS8, page 14).

Another contribution reflecting the impact of Brandt's expertise on international drug policy was his involvement in the formulation of scheduling recommendations as part of the ECDD assessment procedures. For example, Brandt recommended that the NPS, U-47700, become a controlled drug (Schedule I of the 1961 Single Convention, as amended by the 1972 Protocol) (CS9). The recommendation was accepted by the ECCD and CND to become a controlled substance worldwide in the suggested schedule in 2017 (CS10, page 12).

5. Sources to corroborate the impact

CS1. Corroborating reference letter EMCDDA. Dr Roumen Sedefov, Head of Unit, Risks to Public Safety and Security Unit. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal.

CS2. 4,4'-DMAR. Report on the risk assessment of 4,4'-DMAR in the framework of the Council Decision on new psychoactive substances. European Monitoring Centre for Drugs and Drug Addiction, Lisbon. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_233321_EN_4,4%27-DMAR%20Risk%20Assessment%20Report.pdf

CS3. Advisory Council on the Misuse of Drugs' recommendation on the synthetic stimulant 4,4'-DMAR. Available at:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/374844/ACMD_44_-DMAR_final.pdf

CS4. The Misuse of Drugs Act 1971 (Amendment) Order 2015. Statutory Instrument 2015 No. 215. Available at: https://www.legislation.gov.uk/uksi/2015/215/pdfs/uksi_20150215_en.pdf

CS5. *para*-Methyl-4-methylaminorex (4,4'-DMAR). Critical Review Report. Expert Committee on Drug Dependence. World Health Organization. Thirty-seventh Meeting. Geneva, 16-20 November 2015. Available at: https://www.who.int/medicines/access/controlled-substances/5.5_44_DMAR_CRev.pdf

CS6. WHO's Expert Committee on Drug Dependence (2015). Thirty-eighth Report. Available at: https://apps.who.int/iris/bitstream/handle/10665/255046/9789241210140-eng.pdf?sequence=1

CS7. 3,4-Methylenedioxypyrovalerone (MDPV). Critical Review Report. Expert Committee on Drug Dependence. World Health Organization. Thirty-sixth Meeting. Geneva, 16-20 June 2014. Available at: https://www.who.int/medicines/areas/quality_safety/4_13_Review.pdf

CS8. WHO's Expert Committee on Drug Dependence (2015). Thirty-Seventh Report. Available at: https://apps.who.int/iris/bitstream/handle/10665/206452/WHO_TRS_998_eng.pdf?sequence=1

CS9. Expert Peer Review No. 2 and expert reviewer's view on scheduling with rationale. U-47700. World Health Organization. Expert Committee on Drug Dependence. Thirty-eighth Meeting, Geneva, 14-18 November 2016. Available at: https://www.who.int/medicines/access/controlled-substances/4.1_U-47700_PeerReview_2.pdf?ua=1

CS10. WHO's Expert Committee on Drug Dependence (2015). Thirty-ninth Report. Available at: https://apps.who.int/iris/bitstream/handle/10665/260546/9789241210188-eng.pdf?ua=1