Institution: University of Roehampton		
Unit of Assessment: 3 - Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: From 'Legal' to 'Illegal': Neuroscience research on novel psychoactive drugs ('legal highs') has influenced drug policy and practice		
Period when the underpinning research was undertaken: 2012-2020		
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:**
Jolanta Opacka-Juffry	Professor	September 1999 – July 2020
Period when the claimed impact occurred: November 2013-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Research led by Prof Opacka-Juffry on health-relevant effects of novel psychoactive substances (NPS, formerly 'legal highs') - potentially dangerous recreational drugs - **has informed policy and practice internationally**. The research was instrumental in informing the Advisory Council on the Misuse of Drugs' recommendation that benzofurans be permanently classified as Class B substances in the UK. That recommendation was supported by Parliament which led, in June 2014 to a change of law in the form of the Amendments to the Misuse of Drugs Act 1971. Opacka-Juffry and colleagues have subsequently engaged with practitioners to enhance support for users of NPS in the UK, EU and USA. The research was used as evidence of the harmful effect of benzofurans in the Novel Psychoactive Treatment UK Network (NEPTUNE) clinical guidance around the management of harms of NPS, which altered the way frontline clinicians across the UK are advised to treat problems associated with these substances. Furthermore, Blenheim CPD, a major charity that supports some 11,000 people with addiction to drugs, have benefited from an understanding of the potential addictive properties of NPS through regular knowledge transfer workshops and jointly prepared online training materials, as the research findings improve staff training, practice and service delivery.

2. Underpinning research (indicative maximum 500 words)

Novel psychoactive substances (NPS) are increasingly prevalent worldwide; whilst their pharmacological characteristics are largely unknown, they can cause acute and long-term health effects, including mental ill-health and drug dependence or even death. NPS are associated with 10% of drug-related emergency hospitalisations in the EU and a mortality rate of 6% in the UK. To investigate the mechanisms underlying NPS addiction, Opacka-Juffry led neurobiological research with Sahai (University of Roehampton) and external collaborators: Davidson (St George's University of London, University of Central Lancashire), Schifano (University of Hertfordshire), De Luca (University of Cagliari) and Weinstein (Cornell University).

The first study (**R1**), co-led by Opacka-Juffry (neuroscience, research on receptors and dopamine transporter) with Davidson (pharmacology, voltammetry), assessed the addictive and hallucinogenic potential of 'benzofury' (main compound 5-APB). Anecdotally reported as addictive, benzofury was linked with at least 10 deaths of drug users between 2011 and 2013. The research assessed its effects on the dopamine transporter (DAT, molecular target of direct stimulants, associated with addiction) and 5-HT_{2A} receptor (associated with hallucinogenic effects), by means of neurobiological and neuropharmacological methods in rat brain tissue *in vitro*. The novel findings showed that 5-APB interacts with DAT and 5-HT_{2A} receptor in the rat brain, indicating that 5-APB has potential addictive and hallucinogenic properties, respectively. The work contributed original data on the mechanisms of benzofuran effects on the mammalian (rat) brain which are translatable to the human condition and thus were of critical relevance to policy makers and users of this drug. These research findings subsequently served as evidence in the change of law to make benzofurans illegal in the UK.

Adopting similar methodology, further research was undertaken to evaluate the addictive potential of cathinones, including mephedrone, a prevalent NPS linked to significant numbers of deaths in the UK (**R2**). This study found that mephedrone's actions at DAT were similar to those of amphetamine, a prevalent, potent and addictive stimulant drug, confirming the stimulant properties

of mephedrone and other cathinones in adolescent rat brain. This was also the first study to specifically examine the effects of such substances at this stage of brain development, corresponding to the stage at which many drug users first encounter 'legal highs'.

To further understand the core physical mechanisms that govern addictive properties of NPS, Opacka-Juffry led an investigation of the interactions between benzofuran NPS and DAT using as an exemplar benzofuran 5-MAPB. By means of neurobiological methods and molecular modelling with *in silico* approaches, a binding mode for 5-MAPB and, more broadly, structural context for NPS effects at DAT as the molecular target of stimulants, were explored (**R3**). This study demonstrated the amphetamine-like mechanism of action at the molecular level. The findings, which warn of the risk of addiction, are of relevance to the health risks linked with NPS use.

Further work, using computational and neurobiological methods, assessed interactions with DAT across a range of ketamine-like dissociative NPS (**R4**). Findings provided novel insights into the mechanisms that underpin the direct stimulant interactions between NPS and DAT, and revealed the unknown addictive potential of a prevalent dissociative NPS, diphenidine. This research demonstrated that despite their structural similarities, dissociative NPS exhibit different stimulant profiles, and explained at an atomistic level why subtle structural differences result in such varied stimulant features of relevance to the risk of addiction in users of these drugs. Given the high addiction potential of cocaine, the research also sought to identify the mechanism of action of NPS that act in a cocaine-like manner, choosing as an exemplar 2-DPMP, known by its users as 'Ivory Wave' (**R5**). The study, in collaboration with the University of Cagliari (*in vivo* work), explained the implications of the neurotransmitter dopamine in neurobiological responses to NPS that act like cocaine.

3. References to the research (indicative maximum of six references)

R1 Dawson* P., Opacka-Juffry* J., Moffatt J.D., Daniju Y., Dutta, N., Ramsey J., Davidson C. (2014) The effects of benzofury (5-APB) on the dopamine transporter and 5-HT_2-dependent vasoconstriction in the rat, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 48, pp.57-63. https://doi.org/10.1016/j.pnpbp.2013.08.013
**Joint first authors;* Output shortlisted by the European Monitoring Centre for Drugs and Drug Addiction for Scientific Paper Award 2014

R2 Opacka-Juffry J., Pinnell T., Patel N., Bevan M., Meintel M., Davidson C. (2014) Stimulant mechanisms of cathinones - Effects of mephedrone and other cathinones on basal and electrically evoked dopamine efflux in rat accumbens brain slices, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 54, pp.122-30. https://doi.org/10.1016/j.pnpbp.2014.04.009

R3 Sahai M.A., Davidson C., Khelashvili G., Barrese V., Dutta N., Weinstein H., Opacka-Juffry J. (2017) Combined *in vitro* and *in silico* approaches to the assessment of stimulant properties of novel psychoactive substances - the case of the benzofuran 5-MAPB, *Prog. Neuro-Psychopharmacology Biol. Psychiatry*, 75, pp.1-9. https://doi.org/10.1016/j.pnpbp.2016.11.004

R4 Sahai M.A., Davidson C., Dutta N., Opacka-Juffry J. (2018) Mechanistic Insights into the Stimulant Properties of Novel Psychoactive Substances (NPS) and their Discrimination by the Dopamine Transporter – *In Silico* and *In Vitro* Exploration of Dissociative Diarylethylamines, *Brain Sci.*, 8(4), 63. https://doi.org/10.3390/brainsci8040063
In the top 25% of all research outputs scored by Altmetric

R5 Loi B., Sahai M.A., De Luca M.A., Shiref H., Opacka-Juffry J. (2020) The Role of Dopamine in the Stimulant Characteristics of Novel Psychoactive Substances (NPS)—Neurobiological and Computational Assessment Using the Case of Desoxypipradrol (2-DPMP), *Front. Pharmacol.*, 11, 806. https://doi.org/10.3389/fphar.2020.00806 Listed in REF2.

4. Details of the impact (indicative maximum 750 words)

The use of NPS can have devastating and far-reaching consequences for the health of individual users, both through NPS's own effects and through their acting as a gateway to other drugs. The effects can also be felt by families and communities, as a result of the increased anti-social behaviour and crime associated with NPS use. It also has implications for social and health

services which have to deal with these detrimental effects. The research conducted by Opacka-Juffry (**R1**) has influenced changes in UK policy around NPS, namely amendments to the 1971 Misuse of Drugs Act, which were consequently associated with a decrease in the use of NPS in the UK. The body of work (**R1**-**R5**) has also informed professional practice of frontline clinicians and major drugs charities and organisations regarding NPS in the UK, EU and USA.

In November 2013, the Advisory Council on the Misuse of Drugs (ACMD), an independent expert body that advises government on drug-related issues in the UK, provided a report to the Home Secretary reviewing the evidence of misuse and harm in relation to benzofuran-type substances, entitled ***Benzofurans: A review of the evidence of use and harm***. This ACMD review used the research finding that 5-APB has potential addictive and hallucinogenic properties (**R1**), which was first published online in September 2013, following Opacka-Juffry's presentation of **R1** data at the Festival of Neuroscience in April 2013 and related global press coverage. The research findings (**R1**) were used by ACMD to demonstrate that benzofury has affinity to DAT (in brain tissue *in vitro*) and $5HT_2$ receptors (*in vitro* and *in vivo*), establishing its potentially addictive and hallucinogenic nature (**IMP1**). Among the 17 research publications, original reports and reviews constituting evidence used by the ACMD, **R1** was one of only two benzofuran papers in the Pharmacology section. The research was therefore instrumental scientific evidence in the recommendation to permanently ban benzofury and related compounds as class B substances under the Misuse of Drugs Act 1971.

The Misuse of Drugs Act 1971 can be amended by a parliamentary order. The ACMD request to the Home Secretary in 2013 that benzofuran compounds become permanently controlled as Class B substances (**IMP1**), based upon evidence including the research co-led by Opacka-Juffry, resulted in Amendments to the Misuse of Drugs Act. Statutory Instruments No 1274/2014 were made on 16th May 2014, laid before Parliament on 20th May and came into force on 10th June (**IMP2**), bringing benzofuran compounds (including benzofury) under permanent control as Class B drugs under the Misuse of Drugs Act in England, Scotland and Wales. The same applies to the Statutory Rules of Northern Ireland 2014 No. 158 on The Misuse of Drugs (Amendment No.2) (**IMP3**). These legislative changes paved the way, in May 2016, for a further Act of Parliament, the Psychoactive Substances Act 2016, which was introduced to ban all new NPS in the UK, restricting their production, sale and supply. This new act was the governmental response to the growing body of evidence of harmful effects of NPS and their prevalence, derived from both practice and research.

Following the legislative changes, reductions in NPS use have been reported by the Drug Misuse Statistics branch of the Home Office since 2014, evidencing the reach of the impact: from 8.4% in 2014/15, down to 7.7% in 2015/16 and 4.2% in 2016/17 (as a percentage of adults using NPS). Furthermore, a Home Office ***Review of the Psychoactive Substances Act 2016*** published in 2018 indicated the significance of the impact, demonstrating that as a result of the introduction of the Act there was a fall in the number of individuals in treatment for NPS, particularly for NPS with a predominantly stimulant effect. There was a 29% reduction in England in the number of adults (aged 18 or over) presenting to treatment citing NPS, from 2,042 in 2015/16 to 1,450 in 2016/17 (**IMP4**).

Opacka-Juffry's research on benzofury (**R1**) has also influenced professional practice in the UK and the EU. It was used in March 2015 as evidence of the harmful effect of benzofurans in the Novel Psychoactive Treatment UK Network (NEPTUNE) report ***Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances*** (**IMP5**). The NEPTUNE report provides guidance to practitioners in the UK on the clinical management of NPS use. This guidance has also reached other countries in the EU as it is promoted by The European Monitoring Centre for Drugs and Drug Addiction. In addition, the ***UK Government 2017 Drug Strategy*** (July 2017) was informed by, refers to and endorses the NEPTUNE Guidance which cites **R1**, along with other national clinical guidance and policy documents, including ***Drug misuse and dependence: UK guidelines on clinical management*** (Department of Health, July 2017). By informing targeted, setting-specific, evidence-based resources produced by NEPTUNE, the research has contributed to changes in

the way health professionals across the UK are being advised to treat problems associated with NPS (**IMP5**). This research has also had impact outside the UK and Europe. Rehabilitation centres in the USA have used the research findings to warn vulnerable people against benzofury use as it can lead to dependence and addiction. For example, patient advice 'What Is Benzo Fury?*'* issued by Lasting Recovery rehabilitation treatment centre in San Diego, USA, 2016 cites the research (**R1**): '"*The risk of addiction is very real," Professor Jolanta Opacka-Juffry of Britain's University of Roehampton says, "Pure hallucinogens are not addictive as such because they do not cause an increase in dopamine release, unlike amphetamine or cocaine. But benzofury with its mixed properties is a trap, as its repetitive use for the hallucinogenic effects could lead to dependence"*" (**IMP6**).

In 2016, Opacka-Juffry was awarded a place in The Royal Society Pairing Scheme and spent a week in Westminster carrying out knowledge transfer of the underpinning research on NPS (**R1**-**R3**), which she shared with civil servants by invitation from the Home Office Drugs and Alcohol Unit**.** In March 2017, the Head of the Home Office Drug Legislation visited the University of Roehampton to meet with Opacka-Juffry, collaborators and the Chief Executive and staff of Blenheim CPD, a major charity that supports approximately 11,000 people each year who suffer from drug and alcohol misuse. This facilitated further discussion of NPS research outcomes (**R1**-**R3**) and enhanced the stakeholders' understanding of health risks associated with NPS. The research was shared with the Home Office and Blenheim (**IMP7**). The ***UK Government 2017 Drug Strategy*** was informed by the research and the NEPTUNE report**.**

Opacka-Juffry has also used the body of research on NPS (**R1**-**R5**) to raise awareness amongst practitioners in professional support services, who use this knowledge to prevent vulnerable communities from using NPS and to inform existing NPS users of their addictive properties. The significance of Opacka-Juffry's research is demonstrated through her sustained engagement with Blenheim, with whom she delivered five annual workshops to training staff between 2015 and 2019. These events were attended by more than 90 Blenheim 'trainers' who together instructed approximately 400 staff and volunteers, who worked directly with some 11,000 people affected by drug misuse. In Spring 2019, Blenheim became part of a UK-wide charity, following a merger with Humankind, focused on addressing health and social inequalities across the country. Blenheim regards the Knowledge Transfer (KT) sessions with Opacka-Juffry as a key development and innovation activity (**IMP8**). As Blenheim's Lead Trainer attests: *'Prof. Opacka-Juffry's body of research and evidence of the addictive properties of NPS has helped us work more effectively with our service users; the KT sessions have been of enormous value in helping our workers and volunteers understand the functions of the brain and the short and long term effects of various drugs on brain function.*'(**IMP9**).

Blenheim has utilised the research to challenge preconceptions about the 'safety' of NPS amongst users. For example, the research findings demonstrating that mephedrone's stimulant effects are similar to those of amphetamine (**R2**) have been used in staff training and practice, as mephedrone is commonly misused. In their words: *'As some clients still think of mephedrone as a "safe" or "clean" drug, this research helps us to demonstrate to clients that the harm of their drug use may be comparable to amphetamine, which many see as a more harmful or "dirty" drug. This information is extremely useful in helping us to motivate clients towards change.'* (**IMP9**). Blenheim described the sessions on the research on DAT (**R3**) as being very valuable for training and updating practitioners: *'NPS are often regarded as "safe" and non-addictive so it is very useful to be able to refer to research that shows that these substances do have very addictive qualities'* (**IMP9**). Blenheim further confirmed the impact of the research findings on their practice related to dissociative NPS (ketamine substitutes) and their interactions with DAT (**R4**, **IMP9**). The recent study (**R5**) has also been translated into Blenheim practice: '*In 2019 Prof. Opacka-Juffry presented her findings on the dopamine involvement in the addictive potential of 2-DPMP (aka Ivory Wave)… imparting this information to our service users can help them understand the potential unpredictable impact of their own substance use and, for some, can act as a motivating factor in eliciting positive behaviour change.'* (**IMP9**).

In addition, Opacka-Juffry worked with Blenheim to develop online training materials 'The Brain Toolkit', which includes elements based on the NPS research (**R1**-**R3**). The first stage was launched in July 2017 (**IMP10**). These materials have directly informed Blenheim practitioners and their training, and their service delivery to people with addiction. More than 120 Blenheim trainers have used the Brain Toolkit so far; they cascade their knowledge to people who misuse drugs. As the Lead Trainer at Blenheim attests: '*This knowledge and training can only improve the quality of information and services that our service users receive.*' (**IMP9**).

5. Sources to corroborate the impact (indicative maximum of 10 references)

IMP1 Advisory Council on the Misuse of Drugs recommendation to the Home Secretary to reclassify benzofuran compounds: ***Benzofurans: A review of the evidence of use and harm*** (2013). Cites **R1** as evidence on page 6.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/261783/Benzofuran_compounds_report.pdf

IMP2 The Misuse of Drugs Act 1971 (Ketamine etc.) Amendment Order 2014 – Amendments to the Act brought benzofuran compounds under permanent control as Class B drugs in England, Scotland and Wales: https://www.legislation.gov.uk/ukdsi/2014/9780111110904
Statutory Instruments No 1274/2014 came into force on 10th June 2014:
https://www.legislation.gov.uk/uksi/2014/1274/pdfs/uksi_20141274_en.pdf

IMP3 Statutory Rules of Northern Ireland 2014 No. 158 on The Misuse of Drugs (Amendment No.2). –Amendments to the Act brought benzofuran compounds under permanent control as Class B drugs in Northern Ireland:
https://www.legislation.gov.uk/nisr/2014/158/pdfs/nisr_20140158_en.pdf

IMP4 Home Office ***Review of the Psychoactive Substances Act 2016*** (2018). Details changes in outcomes as a result of implementation of the Act.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/756896/Review_of_the_Psychoactive_Substances_Act__2016___web_.pdf

IMP5 Novel Psychoactive Treatment UK Network report ***Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances*** (2015). Provides clinical guidance to practitioners; cites **R1** on page 258.
http://www.emcdda.europa.eu/attachements.cfm/att_236560_EN_UK10_NEPTUNE%20NPS%20guidance%20(2015).pdf
Also, translated into German (2016) https://docplayer.org/38346365-Neptune-handlungsempfehlungen-zum-klinischen-umgang-mit-akuten-und-chronischen-schaeden-durch-partydrogen-und-neue-psychoaktiven-substanzen.html
UK Government Drug Strategy (2017) refers to and promotes Project NEPTUNE, cites **R1**
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/628148/Drug_strategy_2017.PDF

IMP6 'What You Need to Know about Benzo Fury' outpatient advice from drug and alcohol rehabilitation treatment centre 'Lasting Recovery', San Diego, USA, 2016. Warns against the risk of addiction in people who use benzofury on the basis of Opacka-Juffry's research (**R1**):
https://lastingrecovery.com/need-know-benzo-fury/

IMP7 Research-derived meeting materials that were passed on to Home Office, as part of the Royal Society Pairing Scheme, March 2017.

IMP8 ***Blenheim Impact Report*** (2016/17). Highlights Opacka-Juffry on Knowledge Transfer sessions and collaboration on Brain Toolkit as key development and innovation activity.
https://blenheimcdp.org.uk/wp-content/uploads/2014/07/Blenheim-Impact-report-Online.pdf

IMP9 Testimonial from Lead Trainer, Blenheim CPD dated 31 July 2019. Outlines the role of Opacka-Juffry and colleagues' research in informing the support service's understanding of effective practice in substance misuse and directing services offered to clients.

IMP10 The Brain Toolkit - A chemsex & NPS multimedia programme, July 2017. Online training materials developed jointly by Opacka-Juffry and Blenheim CPD based on **R1**-**R3** and used by Blenheim for their staff training.
https://web.archive.org/web/20200226153015/https://blenheimcdp.org.uk/training/the-brain-toolkit-a-chemsex-nps-multimedia-programme/