Institution: BRUNEL UNIVERSITY (H0113)

Unit of Assessment: 7 – Earth Systems and Environmental Sciences

Title of case study: Environmental regulation of pharmaceuticals in the aquatic environment

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

Over the past two decades, researchers at the Institute for the Environment (hereafter, the Institute) at Brunel University have generated substantive evidence supporting the case for regulation of discharges of pharmaceuticals into rivers and estuaries throughout Europe and for improved sewage treatment, with significant implications for water quality, aquatic life and public confidence. Their research has led to improved sewage treatment in some countries and to changes in the European Water Framework Directive (WFD; the primary legislation for protecting and conserving European water bodies), such that regulatory limits for environmental concentrations of the contraceptive pill hormones, ethinylestradiol and oestradiol, are now included in River Basin Management Plans for 2015. In 2011, a Queen's Anniversary Trust Prize was awarded to Brunel University in recognition of the Institute's considerable success in translating this research into European policy, also influencing countries outside Europe.

2. Underpinning research (indicative maximum 500 words)

Professor John Sumpter first made the startling and novel discovery of high levels of a *female-specific* yolk protein in the blood of *male* fish living downstream from sewage treatment works. This provided the impetus for a nationwide survey of sewage effluents (conducted between 1987 and 1990), which revealed that oestrogenic effluents were widespread throughout England and Wales (Purdom et al., 1994). Subsequent environmental forensic studies by **Dr Edwin Routledge** (then a postdoctoral researcher), using a newly-developed bench-top assay (the yeast oestrogen screen), showed that steroid oestrogens excreted by women, principally the contraceptive pill hormone, ethinylestradiol, were responsible for the oestrogenic activity of the effluent (Desbrow et al., 1998). In parallel, **Professor Susan Jobling** (then a postdoctoral researcher) revealed widespread feminisation of wild male fish in many UK rivers receiving these effluents (Jobling et al., 1998).

In a subsequent project funded by the UK Environment Agency, **Jobling and Sumpter** (together with NERC scientists Johnson and Williams) developed models predicting the effects of ethinylestradiol and other pharmaceuticals across the UK river network. Effect maps for oestrogens were compared with field data and were shown to correlate with real impacts observed in fish populations throughout the UK (Jobling et al., 2006). These findings provided the impetus for research showing similar effects in more than ten countries, which contributed to the weight of evidence for European regulation.

Laboratory studies carried out by **Sumpter** in collaboration with the pharmaceutical industry (Schering) showed effects of ethinylestradiol in fish at extremely low concentrations (Länge et al., 2001) and defined no observed effect concentrations for this chemical (Caldwell et al., 2008) that were later used in European regulation (see section on impact). Collectively, the Brunel group has now published 68 papers on steroid oestrogens. **Professors Sumpter and Tyler** (then a Brunel scientist) also designed standard laboratory tests using fathead minnows that could be used to test the effects of oestrogenic chemicals on pair-breeding fish (Harries et al., 2000). These tests were used to measure the efficacy of advanced wastewater treatment in removing the biological effects on fish during a Water Industry-funded UK Demonstration Programme, designed to demonstrate that existing wastewater treatment processes could remove ethinylestradiol and other steroid oestrogens from wastewaters.

Sumpter's team have conducted pioneering work on a range of other pharmaceuticals (35 papers during the period of assessment), including other steroids (progestogens and glucocorticoids) as well as cytotoxic drugs, leading to the development of a new area of ecotoxicology, pharmaceuticals in the environment (PIE). **Jobling** has worked on anti-androgenic drugs widely used to treat prostate cancer.

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

Peer reviewed research papers underpinning the impact of our research are listed below. Our

research papers are highly cited, demonstrating their considerable impact (citations from WoK).

1) Caldwell, DJ., Mastrocco, F., Hutchinson, TH., Lange, R., Heijerick, D., Janssen, C., Anderson, PD. and **Sumpter, JP**., 2008. Derivation of an aquatic predicted no-effect concentration for the synthetic hormone, 17α-ethinyl estradiol, Environmental Science and Technology 42 (19): 7046-7054. http://dx.doi.org/10.1021/es800633q (92 citations).

2) Desbrow, C., **Routledge, E.J**., Brighty, G.C., **Sumpter, J.P**. and Waldock, M. 1998. Identification of estrogenic chemicals in STW effluent. I : Chemical Fractionation and in vitro Biological Screening. Environmental Science and Technology 32, 1549-1558. http://dx.doi.org/10.1021/es9707973 (1150 citations).

3) Harries, JE., Runnalls, T., Hill, E., Harris, CA., Maddix, S., **Sumpter, JP**. and Tyler, CR., 2000. Development of a reproductive performance test for endocrine disrupting chemicals using pair-breeding fathead minnows (pimephales promelas), Environmental Science and Technology 34 (14): 3003-3011. http://dx.doi.org/10.1021/es991292a (132 citations).

4) **Jobling, S**., Nolan, M., Tyler, C.R., Brighty, G., and **Sumpter, J.P**. 1998. Widespread Sexual Disruption in Wild Fish. Environmental Science and Technology 32 (17): 2498–2506. http://dx.doi.org/10.1021/es9710870 (1052 citations).

5) **Jobling, S**., Williams, R., Johnson, A., Taylor, A., Gross-Sorokin, M., Nolan, M., Tyler, CR., van Aerle, R., Santos, E. and Brighty, G.,2006. Predicted exposures to steroid estrogens in U.K. rivers correlate with widespread sexual disruption in wild fish populations, Environmental Health Perspectives 114 (S-1): 32- 39. http://dx.doi.org/10.1289/ehp.8050 (158 citations).

6) Länge, R., Hutchinson, TH., Croudace, CP., Siegmund, F., Schweinfurth, H., Hampe, P., Panter, GH. and **Sumpter, JP**., 2001 Effects of the synthetic estrogen 17α-ethinylestradiol on the life-cycle of the fathead minnow (pimephales promelas), Environmental Toxicology and Chemistry 20 (6): 1216-1227. http://dx.doi.org/10.1002/etc.5620200610 (346 citations).

7) Purdom, C.E., Hardiman, P.A., Bye, V.V.J., Eno, N.C., Tyler, C.R., **Sumpter, J.P.** 1994. Estrogenic Effects of Effluents from Sewage Treatment Works. Chemistry and Ecology 8: 275 - 285. http://dx.doi.org/10.1080/02757549408038554 (1029 citations).

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

The Institute is widely recognised for its role in uncovering the threat of pharmaceuticals in the aquatic environment, and for its influence on shaping responses. Through engagement with policy makers, other regulators and industry, **Sumpter, Jobling and Routledge** ensured their findings were key components of evidence leading to regulation of pharmaceuticals. In 2004, the UK government accepted evidence that steroid oestrogens posed a significant risk to aquatic life. **End-of-pipe treatment of effluent was chosen as the risk management approach**, placing this responsibility on the water industry. In 2007, the Environment Agency developed a *draft* environmental quality standard (EQS) for ethinylestradiol - a target concentration which could be used for regulatory compliance - based on a predicted no effect concentration of 0.1ng/L, albeit this was further refined to 0.035ng/L by the European Commission, based on the results of **Professor Sumpter's** collaborative studies with the pharmaceutical industry (see Caldwell et al., 2008 in the research section).

To quantify the wider consequences and costs to society of the proposed management approach and balance them against the benefits, it was necessary to *evaluate* the efficiency of various existing sewage treatment approaches in removing steroid oestrogens and their biological effects. The water industry, therefore, conducted The Endocrine Disruptor Demonstration Programme (2006–2010), through which they gained an improved understanding of the effectiveness of different treatment technologies and the sources of chemicals entering the sewerage system. **Jobling** (then a senior research fellow) and **Dr Mark Scrimshaw** (senior lecturer) **were both advisors to the Environment Agency** during the development of the experimental protocols for the "Demonstration Programme" of work (budgeted £40 million). The standardised test protocols developed by **Tyler, Routledge and Sumpter** were used to test the efficacy of sewage treatment technologies in this programme and **Jobling** participated in the programme, performing testing for two water companies. The information gathered is currently supporting regulators and the Water

Industry in defining the best environmental solution to the problem, taking into account costs and carbon footprints. ***Sumpter and Tyler's' fish tests now form the basis of two OECD standard reproductive toxicity tests for (OECD tests 229 and 230[1]) adopted in 2009. The US EPA (2009) has also adopted modified versions of these tests for regulatory purposes.***

In large part due to the Institute's research, for the first time in history, the European Commission placed three pharmaceutical compounds (the contraceptive pill hormones, ethinylestradiol and estradiol, and the painkiller diclofenac) on a draft list[2] of priority chemicals (2012) thought to pose a risk to the safety of surface water. Priority chemicals require control under the Water Framework Directive (WFD; the primary legislation for protecting and conserving European water bodies). Lobbying by the pharmaceutical industry recently (2/07/2013) ensured movement of the three pharmaceuticals onto a new 'watch list'[3] of emerging aquatic pollutants and an extension of the deadline for achieving water quality targets for the pharmaceuticals from 2021 to 2027. **There is now a new article in the text of the Water Framework Directive stating the EC's intention to develop a strategic approach to pollution of water by pharmaceutical substances "aimed at reducing their discharges, emissions, and losses to the aquatic environment".** Once implemented, the standards for steroid oestrogens will be taken into account in the 2015 River Basin Management Plans and associated 'Programmes of Measures' for the Water Framework Directive across Europe. In the UK alone, this change in European law will eventually require the upgrade of almost 1400 sewage treatment works in order to produce effluent that allows compliance with the environmental standards set for pharmaceuticals and natural steroid oestrogens.

There is currently a vigorous debate over the economic costs of regulating pharmaceuticals (described in Owen and Jobling "The hidden costs of flexible fertility" ***Nature*, 485*, pp441, 24th May, 2012[4]*).** The pharmaceutical industry claims the combined pill is the most popular contraceptive in the UK and the most effective; a loss of **€4 billion in sales**, **217,000 additional unintended pregnancies** and a social cost of around **£26.2 million per year**, equivalent to around **£382 million** over 20 years would result if it was not used. The water industry claims the total costs of treating the ~1,360 wastewater treatment works in England and Wales with EE2 failures are between £27-31 billion over the same period[5].

Despite this debate, in some countries, full-scale treatments aimed at removing pharmaceuticals have already been implemented, ahead of the inevitable EU regulation. For example, such treatment technologies are now operating on more than 100 Swiss WWTP, treating about 80 % of the Swiss municipal wastewater. Comparable programmes have been carried out in other European countries and in the USA, Japan and Australia, through the Institute's efforts to promote the transfer of their knowledge and practice in this area to many other countries. Practical examples of knowledge transfer include the "effect mapping techniques", pioneered by the Institute and now applied in projects in Japan and Australia (the UK-Japan initiative http://www.uk-j.org and the Australia-UK initiative www.ecotox.org.au/edcsig/history.html), together with the dissemination of the yeast oestrogen screen (used to identify pharmaceuticals as the oestrogenic culprits of the feminisation of fish) to more than 200 laboratories across 32 countries of the world, along with training in its use. The raised awareness of pharmaceuticals in water has led to much media attention and to a study commissioned by the Drinking Water inspectorate (DWI) to determine the worst case scenario of potential human exposure to pharmaceuticals in drinking water in England and Wales and a WHO report also on this topic[6]. In the USA, steroid oestrogens are included on a list of 104 contaminants EPA will evaluate to determine if national drinking water regulations are needed to protect public health[7]. As a leading example of excellence in impact, contributing to positive change on an international scale, the Institute's work in this area was awarded a **Queen's Anniversary Trust Prize[8]** in November 2011. **Professor Sumpter** was awarded the **2009 Toxicology Award from the Royal Society of Chemistry[9]** for transforming our view of ecotoxicity, particularly our understanding of the role of pharmaceutical pollutants in the aquatic environment.

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

1) OECD Guidelines for the Testing of Chemicals, Section 2, Test No. 229: Fish Short Term Reproduction Assay (02 Oct 2012) http://dx.doi.org/10.1787/9789264185265-en and OECD

Guidelines for the Testing of Chemicals, Section 2, Test No 230: 21-day Fish Assay (08 Sept 2009) http://dx.doi.org/10.1787/9789264076228-en

2) 31st January 2012. The contraceptive pill hormone EE2 & the natural oestrogen E2 are put on a draft dangerous substances list to be regulated under the Water framework Directive http://ec.europa.eu/environment/water/water-dangersub/pdf/com_2011_876.pdf This is a link to the proposal. For news release, see http://www.euractiv.com/health/new-chemicals-pharmaceuticals-ad-news-529073

3) 'Surface waters: 12 new controlled chemicals, three pharmaceuticals on watch list', European Parliament News (02/07/2013)

http://www.europarl.europa.eu/news/en/news-room/content/20130701IPR14760/html/Surface-waters-12-new-controlled-chemicals-three-pharmaceuticals-on-watch-list

4) Richard Owen & Susan Jobling Environmental science: The hidden costs of flexible fertility *Nature, 485* pp 441 (24 May 2012) http://dx.doi.org/10.1038/485441a

5) UK Water Industry Research (2009) Endocrine disrupting chemicals national demonstration programme. Assessment of the performance of WwTW in removing oestrogenic substances. Report ref 09/TX/04/16 http://www.ukwir.org/ukwirlibrary/92721

6) World Health Organization, 'Pharmaceuticals in Drinking-water' (2011) http://www.who.int/water_sanitation_health/publications/2011/pharmaceuticals_20110601.pdf

7) Strategy for Addressing Pharmaceuticals and Personal Care Products in Water, US Environmental Protection Agency http://water.epa.gov/scitech/swguidance/ppcp/basic.cfm

8) Queen's Anniversary Prizes for Higher and Further Education (25 Nov 2011) http://www.royalanniversarytrust.org.uk/news/winners-announced

9) Professor John Sumpter's Toxicology Award (2009): http://www.rsc.org/ScienceAndTechnology/Awards/ToxicologyAward/2009winner.asp

Contacts

1)Senior Scientific Officer, Chemicals & Emerging Technologies Division UK National Co-ordinator (Environment) OECD Test method Development Programme, DEFRA chemicals and emerging technologies division (corroborates our involvement in OECD tests and role in demonstration programme)

2) Scientific Officer, European Commission, Research Directorate-General, Environment Directorate, Climate Change and Environmental Risks Unit (corroborates the Institute's role in regulation of pharmaceuticals)

3) Director of CHEMTrust and one of Britain's most effective environmentalists (corroborates the Institute's role in regulation of pharmaceuticals)

4) Area Head, Environment Agency UK (corroborates the Institute's role in demonstration programme and case study generally)

5) Chair Environmental Policy (formerly of the Environment Agency) Exeter University. (corroborate the Institute's contribution to the regulation of discharges of pharmaceuticals into rivers, thereby improving sewage treatment internationally)