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| <p>Institution: University of Exeter</p> |
| <p>Unit of Assessment: Earth Systems and Environmental Sciences</p> |
| <p>Title of case study: Endocrine disrupting chemicals in aquatic ecosystems: Impacts on new policies and guidelines, and economic benefits for the UK.</p> |
| <p>1. Summary of the impact (indicative maximum 100 words)</p> <p>Research led by Professor Charles Tyler at the University of Exeter has provided critical data on the widespread adverse oestrogenic effects of endocrine disrupting chemicals in wild fish populations in the UK. This has triggered the UK government to take action through investment in research and development of policies and guidelines. The research has led to world-wide recognition that endocrine disrupting chemicals are an emerging policy issue, a £40 million demonstration project with the UK government and water industry, and multi-million pound benefits to the UK in terms of improved water quality and safeguarding freshwater wildlife.</p> |
| <p>2. Underpinning research (indicative maximum 500 words)</p> <p>Charles Tyler's research team at the University of Exeter has carried-out internationally-recognised research on the effects on fish of exposure to effluents from wastewater treatment works (WwTW). They have identified the Endocrine Disrupting Chemicals (EDCs) that produce feminising responses and thereby undermine fish reproduction, and the sustainability of wild fisheries.</p> <p>The team has proven that WwTW effluents feminise male fish (e.g., [1]) and the causative chemicals inducing these feminised responses include steroid, natural, and synthetic oestrogens discharged in waste waters (e.g., [2]). The team also established the widespread prevalence of a new group of EDCs that act as anti-androgens and have feminising effects in fish, and they played a significant role in helping to understand the effects of mixtures of EDCs on fish reproduction and health (e.g. [3]).</p> <p>Tyler's applied research in this area has developed methods that have been adopted for international test guidelines for testing EDCs in fish. A major research activity is the development and application of molecular approaches to unravel the mechanisms of endocrine disruption [4]. Applying these molecular approaches the team has recently shown feminised male fish in wild populations in UK rivers have a reduced reproductive capability with potential impacts for the sustainability of wild fisheries [5]. Further recently funded (NERC) work is now applying genome wide sequencing methods to understand the mechanisms of adaptation to EDCs in wild fish populations.</p> <p>Working with Kudoh in Biosciences at Exeter, Tyler's team recently developed a transgenic fish that is highly sensitive to environmental oestrogens and provides an unrivalled whole systems model of informing on the potential health impacts of exposure to environmental oestrogens [6]. The model developed is now being trialled for chemical and drug screening through a BBSRC funded Flexible Interchange Partnership with AstraZeneca. Further (NERC) funded work by Tyler (with Kudoh) is developing transgenic fish models for EDCs with other modes of action (e.g., anti-androgens).</p> <p>Tyler's work has further developed models for assessing effects of EDCs on behaviour to show lower threshold of effect compared with tissue disruptions, illustrating much wider ramifications of exposure to EDCs on population dynamics. This work is reported in leading environmental journals and government publications and is highly cited.</p> <p>In recognition of this research work on EDCs, in 2012 Charles Tyler was awarded The Fisheries Society of the British Isles Beverton Medal for ground breaking research in fish biology.</p> |

Impact case study (REF3b)

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

Key references to research that underpins the impact described in this case study:

1. Rodgers-Gray TP, Jobling S, Kelly C, Morris S, Brighty G, Waldock MJ, Sumpter JP, Tyler CR (2001). Exposure of juvenile roach (*Rutilus rutilus*) to treated sewage effluent induces dose-dependent and persistent disruption in gonadal duct development. *Environmental Science & Technology* 35, 462-470. #
2. Nash JP, Kime DE, Van der Ven LTM, Wester PW, Brion F, Maack G, Stahlschmidt-Allner P, Tyler CR (2004). Long-term exposure to environmental concentrations of the pharmaceutical ethynylestradiol causes reproductive failure in fish. *Environmental Health Perspectives* 112, 1725-1733. #
3. Thorpe KL, Cummings RI, Hutchinson TH, Scholze M, Brighty G, Sumpter JP, Tyler CR (2003). Relative potencies and combination effects of steroidal estrogens in fish. *Environmental Science & Technology* 37, 1142-114.
4. Filby AL, Thorpe KL, Maack G, Tyler CR (2007). Gene expression profiles revealing the mechanisms of anti-androgen-and estrogen-induced feminization in fish. *Aquatic Toxicology* 81, 219-231.
5. Harris CA, Hamilton PB, Runnalls TJ, Vinciotti V, Henshaw A, Hodgson D, Coe TS, Jobling S, Tyler CR, Sumpter JP (2011). The Consequences of Feminization in Breeding Groups of Wild Fish. *Environmental Health Perspectives* 119(3), 306–311. #
6. Lee O, Takesono A, Tada M, Tyler CR, Kudoh T (2012). Biosensor zebrafish provide new insights into potential health effects of environmental estrogens. *Environmental Health Perspectives* 120(7), 990-996.

References that best indicate the quality of the underpinning research.

Grant support related to this research:

Tyler was PI (or co PI; NERC, Env Agency, DEFRA, EU, BBSRC, Wellcome Trust, approx £3M over reporting period) for the funding for all of this work and since 2000 he has received 19 CASE awards with industry partners and 7 CASE awards with government and regulatory authorities. Examples of these grants as PI are:

- NERC: Population-level Consequences of Exposure of Fish to Oestrogenic Wastewater Treatment Works Effluents (2009-2011, £560 000 with £340 000 to Exeter).
- NERC: Knowledge transfer - Impacts of inbreeding on the responses to pharmaceuticals and fitness consequences in fish - a molecular approach (2008-2009, £82 224).
- Severn Trent Water: Impacts of EDCs in WwTW effluents (2008-2009, £71 500).
- The Environment Agency: Impacts of EDCs in the River Itchen (2008-2009, £31 500).
- DEFRA: Application of Reporter Gene Assay for Screening Endocrine Disrupting for OECD test guidelines (2009-2010, £20 300).
- AstraZeneca – DTI KTP: Implementation of Molecular Tools into chemical testing (2009-2010, £60 000).

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

The research outlined in Section 2 has influenced strategic policy decisions by UK government agencies, the EU, and organisations globally. Examples of this include: the £40M UK National Endocrine Disruption Programme [a]; the development of OECD Test Guidelines for the detection of endocrine disrupters; and within REACH (Registration, Evaluation, Authorization, and restriction of Chemicals) where internationally the registration of new chemicals will now need to provide evidence for a lack of endocrine disrupting activity [b-d]. Additional examples of the international influence of the work include the development of chemical test guidelines by the US EPA [e] and the significant investments (tens of £M) in programmes of research into endocrine disruption in Japan.

The research influenced the development of guidelines for the testing of chemicals by the Organization for Economic Cooperation and Development (OECD). Research on fathead minnow has informed the development of several tests adopted by the OECD. A short-term screening test for estrogenic and androgenic activity, and aromatase inhibition in fish was adopted in September 2009 [b], an assay to assess early-life stage effects of EDCs on fish sexual development was adopted in July 2011 [c], and an *in vivo* reproductive screening assay, the Fish Short Term Reproduction Assay, was adopted in October 2012 [d]. The US Environmental Protection Agency's Endocrine Disruptor Screening Program has based its general validation principles on the harmonized scientifically peer-reviewed principles by the OECD [e]. The Norwegian company Biosense commercialised the vitellogenin assay developed by Tyler and his colleagues, developing them in accordance with the recommendations from the OECD.

Gina Solomon, Senior Scientist for the Natural Resources Defence Council referenced Tyler's research as part of her witness testimony before the US Congress Committee on Energy and Commerce, Subcommittee on Energy and Environment in February 2010, in the session addressing the risks of EDCs in drinking water [f].

The research is listed as supporting evidence in the listing of the chemical 4-(1,1,3,3-tetramethylbutyl)phenol, 4-tert-octylphenol as a substance of very high concern. The European Chemicals Agency adopted this listing on 9 December 2011, stating that the conclusion was based on "strong evidence from high quality studies of adverse effects in two fish species, which are oestrogen mediated" [g].

In September 2012, The International Conference on Chemicals Management (ICCM) adopted a resolution to include EDCs as an emerging issue under the Strategic Approach to International Chemicals Management (SAICM). Tyler's work was presented by Professor Susan Jobling from Brunel University, as part of the technical briefing on EDCs [h]. His work is further explicitly mentioned in the United Nations Environment Programme and the World Health Organization. Report (2012) on the *State of the science of endocrine disrupting chemicals* [i].

The Department of Environment, Fisheries and Rural Affairs (Defra) has supported Tyler's research as it has direct relevance to policy needs. A spokesperson for the Chemicals & Emerging Technologies Division at Defra said the research "...informed our approach to implementing the Water Framework Directive as it set the evidence baseline against which we could objectively assess Commission proposals."

The research helped provide sufficient data to "act as a policy trigger for taking action" (area manager at the Environment Agency). The National Endocrine Disruption Demonstration Programme was funded by the Environment Agency and the water industry and was managed by UK Water Industry Research (UKWIR); all ten water and sewerage companies in England and Wales participated in the programme, which produced extensive data regarding the occurrence, treatment and release of various EDCs from conventional wastewater treatment works. The collaborative programme was considered to yield "valuable efficiencies" by "avoiding the need to fund separate work programmes" [j].

The impact of the research has largely been facilitated by Charles Tyler's active participation in expert panels, authorship of government reports and as an advisor to government. Tyler was the UK Coordinator for the UK-Japan Joint Research on Endocrine Disruptors between 2005 and 2010 and is currently its Chief Science Advisor (2010-2015). Tyler has been an expert witness to the European Commission and has advised the US EPA, EA and Defra.

Significant economic benefits have been realised in the UK as a result of the work of Tyler's team at Exeter. An independent evaluation of these benefits, using HM Treasury "Green Book" methods, attributed the following economic impact to the research produced at the University of Exeter: Long term collaborative links between the Tyler lab and industry partners, such as AstraZeneca, Syngenta and UK water companies, has resulted in an estimated total of £4.9M efficiency savings each year.

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

- [a] UK Water Industry Research (2013) *Completion of the monitoring programme at WwTW* [website] <<http://www.ukwir.org/site/web/news/endocrine-disrupting-compounds-edcs?xpm64409=65123>> accessed 03May2013.
- [b] OECD (2009) *OECD Guideline for the Testing of Chemicals: 21-day Fish Assay: A Short-Term Screening for Oestrogenic and Androgenic Activity, and Aromatase Inhibition*. Adopted 7 September 2009. Test No. 230 <<http://www.oecd-ilibrary.org/docserver/download/9723001e.pdf?expires=1367588135&id=id&accname=guest&checksum=0A29327F8994CDDCA12BF8624B3128DB>>
- [c] OECD (2011) *OECD Guideline for the Testing of Chemicals: Fish Sexual Development Test*. Adopted 28 July 2011. Test No. 234 <<http://www.oecd-ilibrary.org/docserver/download/9723401e.pdf?expires=1367587536&id=id&accname=quest&checksum=E7304C4B026C4C406060AE3E364FC5FB>>
- [d] OECD (2012) *OECD Guideline for the Testing of Chemicals: Fish Short Term Reproduction Assay*. Adopted 2 October 2012. Test No. 229 <http://www.keepeek.com/Digital-Asset-Management/oecd/environment/test-no-229-fish-short-term-reproduction-assay_9789264185265-en>
- [e] US Environmental Protection Agency Endocrine Disruptor Screening Program (2012) *Universe of Chemicals and General Validation Principles*. Jointly developed by the Office of Chemical Safety & Pollution Prevention, the Office of Water and the Office of Research and Development <http://www.epa.gov/endo/pubs/edsp_chemical_universe_and_general_validations_white_paper_11_12.pdf>
- [f] Solomon GM (2010) Testimony of Gina M. Solomon at hearing entitled: *Endocrine disrupting chemicals in drinking water: risks to human health and the environment*. US House of Representatives, Committee on Energy and Commerce, Subcommittee on Energy and Environment. One Hundred Eleventh Congress, Second Session. February 25, 2010. <<https://www.hsdl.org/?view&did=28738>>
- [g] European Chemicals Agency (2011) *Member State Committee Support Document for Identification of 4-(1,1,3,3-tetramethylbutyl)phenol, 4-tert-octylphenol as a Substance of Very High Concern*. <http://echa.europa.eu/documents/10162/13638/svhc_suppdoc_4-tert-octylphenol_20111211_en.pdf>
- [h] Jobling, S. (2012) *Endocrine Disruption in Wildlife Populations*. PowerPoint presentation given at the Third Session of the ICCM. 17-21 September 2012, Nairobi, Kenya. <<http://www.unep.org/hazardoussubstances/Portals/9/EDC/Jobling%20-%20ICCM3%20EDCs%20Side%20Event%20-%20Endocrine%20Disruption%20in%20Wildlife%20Species%20Nai.pdf>>
- [i] Bergman Å, Heindel JJ, Jobling S, Kidd KA, Zoeller RT (eds.) (2012) *State of the science of endocrine disrupting chemicals*. United Nations Environment Programme and the World Health Organization. ISBN: 978-92-807-3274-0.
- [j] Burke, M. (2004) U.K. to tackle endocrine disrupters in wastewater. *Environmental Science and Technology*, 38 (9):362A-363A. DOI: 10.1021/es040631j