Institution: Brunel University London		
Unit of Assessment: 7 Earth Systems and Environmental Sciences		
Title of case study: Enabling European Commission decision making for protecting consumer health from endocrine disruptors		
Period when the underpinning research was undertaken: 2013 to 2016		
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:**
Andreas Kortenkamp	Professor	07/2011 to present
Susan Jobling	Professor	10/1995 to present
Olwenn Martin	Lecturer	08/2011 to present
Period when the claimed impact occurred: 2015 to Dec 2020		
Is this case study continued from a case study submitted in 2014? No		

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

Brunel research enabled the European Union to define criteria for identifying and regulating endocrine disrupting chemicals (EDCs) impacting on the health of its 445,000,000 citizens. EDCs can cause serious irreversible harm, such as birth defects and certain cancers. Brunel scientists established the foundations for protecting EU citizens against these harmful effects that then allowed the EU to define regulatory criteria for EDCs in the Delegated Regulations for biocides in 2017 and pesticides in 2018. This paves the way for the safe use of pesticides, biocides and other chemicals across the EU. It also gives manufacturers the regulatory certainty needed to develop and invest in the manufacture of safer products in compliance with EU law.

2. Underpinning research (indicative maximum 500 words)

Protection from exposures to EDC is of great importance to people's health. EDCs (certain pesticides and biocides, plastic plasticisers, dioxins) interfere with hormone systems during specific windows of susceptibility (e.g. during fetal life or in childhood) when they produce irreversible harm (e.g. congenital malformations, decline in semen quality). Exposures outside these windows are considerably less harmful (Ref 1).

When the European Commission proposed draft criteria for the identification of EDCs in 2013, a controversy about the toxicological principles that should guide their identification flared up among scientists. The dispute had confused EU decision makers and had blocked progress with developing regulatory criteria for EDCs. Defining such criteria by December 2013 was a legal obligation for the European Commission, set out in the EU Plant Protection Product Regulation (Reg EU No 1107/2009) and the Biocidal Product Regulation (Reg EU No 528/2012). Without developing these criteria, the provisions for protection against harmful effects from EDCs could not be realized. The research of Kortenkamp, Jobling and Martin untangled some complications and helped find common ground in the scientific underpinnings for regulating EDCs. In particular they developed a rigorous method for drawing conclusions about the strength of evidence linking EDC exposure to adverse health effects. With funding from the Swedish Foundation for Strategic Environmental Research (MISTRA) they were instrumental in setting up a novel, 7-step-framework for the systematic review and assessment of EDC toxicological studies (Ref 2).

Regulatory practice relies on establishing doses below which no health concerns arise. However, this is difficult when, paradoxically, toxicity increases at low exposures and then diminishes as exposures escalate, as occurs with some EDCs. Such phenomena were contested by many traditional toxicologists and this controversy complicated the regulation of EDCs. On the invitation of the US National Academy of Sciences, Kortenkamp contributed to a

review of the scientific evidence on this topic. The review concluded that non-monotonic dose-response relationships with some EDCs are a reality (Ref 3).

Even so, differences persisted among scientists about the principles that should underpin the identification of EDCs. Kortenkamp and Jobling reviewed the approaches that govern the identification of other classes of harmful substances, such as carcinogens and mutagens, and conducted an exegesis of EU law for EDCs. In framing the first step of EDC regulation as an issue of hazard identification, they established the basis for a consensus (Ref 2,4,5). This meant that disputes about contentious issues such as non-monotonic dose-response relationships need not complicate the development of criteria for EDC identification, as these relate to hazard characterisation and risk assessment, not hazard identification. Accordingly, differences in opinion regarding the existence of non-monotonic dose-response curves were revealed as irrelevant for identifying EDCs and could thus be neutralised. This new principle was offered as the basis for a consensus among scientists with diverging views on endocrine disruption.

To reach a consensus, Kortenkamp and Jobling initiated a workshop with international scientists engaged in the dispute. It was held under the auspices of the German Federal Institute of Risk Assessment, the government body dealing with chemical risk assessment, in Berlin, Germany, 11-12 April 2016. Kortenkamp drafted the blueprint for this consensus, which was presented at the workshop, chaired by the former Chief Scientific Adviser to the President of the European Commission, Prof Anne Glover. A consensus about the scientific principles of defining EDC criteria was reached and published as a paper (Ref 6).

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

[1] WHO, UNEP (2013) State of the science of endocrine disrupting chemicals – 2012, An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme (UNEP) and WHO. ISBN: 978 92 4 150503 1. Available https://www.who.int/ceh/publications/endocrine/en/

[2] Vandenberg, LN., Ågerstrand, M., Beronius, A., Beausoleil, C., Kortenkamp, A., Jobling, S., Martin O.V. et al. (2016) 'A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals'. *Environmental Health*. doi: 10.1186/s12940-016-0156-6

[3] NRC (2014) National Research Council of the National Academies. Review of the Environmental Protection Agency's State-of-the-Science evaluation of nonmonotonic dose-response relationships as they apply to endocrine disruptors. ISBN-13: 978-0-309-29754-7. https://www.nap.edu/read/18608/chapter/1

[4] Slama, R., Bourguignon, J-P., Demeneix, B., Ivell, R., Kortenkamp, A. et al. (2016) 'Scientific Issues Relevant to Setting Regulatory Criteria to Identify Endocrine Disrupting Substances in the European Union'. *Environmental Health Perspectives*. doi: 10.1289/EHP217

[5] Zoeller, RT, Bergman, A, Becher, G., Bjerregaard, P., Kortenkamp, A. et al. (2016) 'The Path Forward on Endocrine Disruptors Requires Focus on the Basics'. *Toxicological Sciences*, 149 (2). pp. 272 - 272. doi: 10.1093/toxsci/kfv255

[6] Solecki, R., Kortenkamp, A., Bergman, Å., Chahoud, I., et al. (2016) 'Scientific principles for the identification of endocrine-disrupting chemicals: a consensus statement.'. *Arch Toxicol*. doi: 10.1007/s00204-016-1866-9

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

The consensus reached at the Berlin workshop put European Commission decision makers in a position to deliver on legal obligations to protect the 445,000,000 EU citizens against the harmful effects of EDCs in pesticides and biocides. This provided the foundations for improving the safe use of such products where endocrine disruption was not previously considered as a form of

harm. It gives manufacturers the certainty needed for developing safer products in compliance with EU law on biocides and pesticides.

As the European Commission takes steps not only to deal with pesticides and biocides, but also to regulate endocrine disrupting properties of industrial chemicals and substances used as food additives or personal care product ingredients, the new regulatory principles for EDCs begin to radiate out into other regulatory domains.

In 2013, the European Commission started the regulatory process with an impact assessment on defining the scientific criteria, in which several regulatory options were set out (Comm 2016). The impact assessment was not completed in time to meet a legally binding deadline (December 2013) and even continued until 2016, leading to a case brought by Sweden to the European Court of Justice.

The April 2016 “Berlin consensus” initiated by Kortenkamp and Jobling created an environment in which it became possible to realise the protection of people from harmful effects of EDCs. The President of the German Federal Institute of Risk Assessment, Professor Andreas Hensel, declared the consensus a “**breakthrough in the scientific discussion on endocrine disruptors and of great importance for the consumer health protection in Europe**” (S1).

As an immediate and direct consequence of the consensus, the European Commission abandoned one option (option 4) of their impact assessment. If not withdrawn, this option would have weakened protection from EDCs in the EU. A Commission executive summary of the impact assessment, published as a staff document (S2) noted (page 2): “**Recent scientific consensus made evident that Option 4 could no longer be pursued from a scientific point of view, although it is supported by some stakeholders and member states**”.

The way was free to implement science-based regulatory criteria for EDCs and to provide the foundations for protection of human health and the environment from harmful effects of EDCs in pesticides and biocides.

In replacing intermediate regulatory criteria for EDCs which targeted substances classed as carcinogens or reproductive toxicants, the consensus improved the quality of the regulation by providing the principles for directly addressing endocrine disruption. The intermediate criteria would have led to restrictions for many chemicals which in fact do not pose endocrine disrupting harm. This situation would have compromised acceptance of EU law and would have disoriented manufacturers.

The new criteria were enshrined in the form of Delegated Regulations, first for biocides in 2017 (S3), then for pesticides in 2018 (S4).

The Delegated Regulations implemented the provisions for health protection against EDCs that are laid down in the EU Biocidal Product Regulation and the Plant Protection Product Regulation. These provisions stipulate that manufacturers can only place active biocidal or pesticidal substances with endocrine disrupting properties on the EU market if risks (biocides) or exposures (pesticides) are minimal. Without the development of regulatory criteria for EDCs these legal obligations could not have been realized and the protection of human health and the environment from harm through EDC exposures would have been delayed.

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

S1 BfR (2016) Press release, https://www.bfr.bund.de/en/press_information/2016/13/breakthrough_in_the_scientific_discussion_of_endocrine_disruptors-197254.html

S2 Comm (2016) Commission staff document, Executive summary of the impact assessment, SWD 2016/212 final, https://ec.europa.eu/health/sites/health/files/endocrine_disruptors/docs/2016_impact_assessment_annex_en.pdf

S3 Commission Delegated Regulation (EU) 2017/2100 setting out criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council, Official Journal of the European Union L301/1, 17.11.17

S4 Commission Regulation (EU) 2018/605 of 19.4.18 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties, Official Journal of the European Union L101/33, 20.4.18