Policy Position

September 2020

Risk-based Regulation for Endocrine Disrupting Chemicals (EDCs)

Regulation continues to evolve for EDCs around the world and this policy position in intended to inform the continuing debates by bringing a perspective following an expert round table involving the scientific community. Similarities and differences of approach have emerged for the characterisation and authorisation of EDCs as used in products and processes. As the UK leaves the EU, it is necessary to decide how EDCs are best regulated in the context of promoting globally harmonised regulation, informed by collaborative science and research evidence. Differences in the approaches taken to protecting citizens and the environment may impact on future trade deals.

Summary points

- **The WHO IPCS 2002 definition of an endocrine disrupting chemical remains valid globally.**
- **Endocrine disruption is not an adverse effect in itself, but is a mechanism of action that for some chemicals and in some circumstances contributes to adverse biological outcomes that can be assessed experimentally but at present only in vivo.**
- **Endocrine 'active' and endocrine 'disruptor' have separate scientific meanings and should be carefully used in regulatory frameworks .**
- **In vitro assays can only show whether a chemical is endocrine active not a disruptor according to the WHO definition.**
- **In regulatory terms, if practical thresholds of concern for EDCs can be determined, chemicals that distrurb the endocrine system are no different in principle to chemicals that affect other types of biological pathways that result in an adverse effect.**
- **On the basis of the scientific evidence to date for EDCs, it is pragmatic and responsible to assure the safety of citizens and wildlife using risk assessment.**
- **Exposure should be managed at defined levels of 'acceptable risk' as determined by society and policymakers taking into account the best scientific and socio-economic evidence with transparent decision-making.**
- **Ethical biomonitoring in humans and environmental monitoring, together with identifying impactful and persistent sources of chemical exposures in society, hold the key to prioritising, monitoring and managing risks from chemicals in the environment that are regarded as potent endocrine disrupting substances.**
- **Regulatory decision making frameworks are needed for EDCs based upon identifying and prioritising the greatest risks, incorporating in vitro data on endocrine activity and relative potency, biomonitoring data and environmental monitoring to measure exposure trends over periods of years.**

What is the concern about endocrine disrupting chemicals?

Humans and wildlife are exposed everyday to hundreds of natural and man-made chemicals from products and their environment, usually with no attributable adverse effects thanks to the effective regulation and risk management of hazardous chemicals. Scientific studies have shown that some environmental chemicals at low concentrations or during critical windows of an organism's development, disrupt the finely tuned molecular and cellular mechanisms of hormone regulation within the endocrine (hormonal) system[1]. It is then possible that adverse outcomes can occur in living organisms. Examples in humans include: tumours, altered reproductive function including male infertility, developmental abnormalities, cognitive diseases, obesity, even diabetes. In wildlife, especially for persistent chemicals, reduced populations of species can arise over time and in a transgenerational way to affect the ecological balance. Given the potential severity of adverse outcomes, concerns about protecting citizens and wildlife by adequately assessing the potential for harm from EDCs are valid[2]; the question is how we regulate to protect at the same time as supporting sustainable and responsible innovation in the chemicals sector.

Not all chemicals have the potential to act as an 'endocrine *disruptor*'. Some chemicals are known, from studies in animals, to cause adverse effects that are caused by changes in hormone levels or action; some chemicals may cause similar types of adverse effect but without the endocrine system being involved; and some chemicals may be active in the endocrine system but lead to no adverse effects. In this last case, a chemical can be shown to be 'endocrine *active*' (e.g. interacting with receptors in an in vitro cell-based system) but this does not mean it would necessarily exert a function and lead to adverse outcomes in an intact organism.

WHO IPCS Definition of an EDC

A carefully worded definition for an EDC was developed by the World Health Organisation (WHO) International Programme for Chemical Safety (IPCS) in 2002 to aid in developing harmonised regulation and this definition has been adopted by many of the world's regulatory authorities. This definition continues to be supported by the WHO in the State of the Science of Endocrine Disrupting Chemicals Report in 2012[3] and in European, Canadian, Japanese and USA regulations amongst others. So there is potentially a common starting point to achieving globally harmonised regulation.

The World Health Organisation IPCS 2002 definition
"An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations."

The complexity, gaps and uncertainty in EDC science and the controversy over thresholds

Even with this definition, developing harmonised, pragmatic and science-based regulation that manages the risks and benefits for citizens and the environment from EDCs has proved challenging as the science is evolving. Understanding how EDCs impact biological function and cause adverse effects in intact organisms is a complex and uncertain area of science involving chemical, toxicological and epidemiological evidence. A group of international scientists suggest there are 10 key characteristics (KC) (early molecular initiating events (MIEs)) of EDC action in mammalian systems (see Table 1)[4] and that data on these KC could be used to organise evidence as a basis for hazard identification, prioritisation and provide a foundation for human health risk assessment. However, these authors also point out these KCs

may evolve as new science emerges and there are no guideline assays to date for seven of these key characteristics and hence, for the vast majority of chemicals, currently no data on endocrine disruption (ED) potential. These characteristics are a starting point for further research and data generation to understand the mode of action of endocrine active substances better.

Table 1 10 Key characteristics of EDCs and related standard guideline tests[4]

Key Characteristic	Guideline Assay
KC1 Interacts with or activates hormone receptors	Androgen receptor binding (rat): USEPA 890.1150 Oestrogen receptor binding (rat): US EPA 890.1250; OECD TG493 Oestrogen receptor transcriptional activation (human stable transfection): USEPA 890.1300; OECD TG455 Androgen receptor transcriptional activation (human stable transfection): OECD TG458 Uterotrophic assay (rat): USEPA 890.1600; OECD TG 440 Herschberger assay (rat): US EPA 890.1400; OECD TG441
KC2 Antagonises hormone receptors	Oestrogen receptor transcriptional activation (human stable transfection): USEPA 890.1300; OECD TG455 Androgen receptor transcriptional activation (human stable transfection): OECD TG458 Herschberger assay (rat): US EPA 890.1400; OECD TG441
KC3 Alters hormone receptor expression	None
KC4 Alters signal transduction in hormone-responsive cells	None
KC5 Induces epigenetic modifications in hormone-producing or hormone-responsive cells	None
KC6 Alters hormone synthesis	Aromatase (human): USEPA 890.1200 Steroidogenesis (human): USEPA 890.1550; OECD TG456
KC7 Alters hormone transport across cell membranes	None
KC8 Alters hormone distribution or circulating hormone levels	None
KC9 Alters hormone metabolism and clearance	None
KC10 Alters fate of hormone-producing or hormone-responsive cells	None

The OECD have worked for many years to generate testing guidelines for the identification of endocrine active chemicals and EDCs in both mammalian and ecological species[5]. There are a range of OECD guideline tests in non-mammalian species such as fish and amphibians. The interpretation of data for humans usually focuses on the potential effects in a human individual, whereas ecotoxicological test data is usually interpreted in terms of the potential effects on populations of species, and given the huge diversity of species, extrapolation across species is often needed.

Gaps in knowledge and lack of available tests for all hormone-mediated effects lead to a high degree of scientific uncertainty for EDCs and indeed scientific controversy has arisen as this complex science evolves, mainly around whether a biological threshold of adversity of an EDC can be defined experimentally. Brescia (2020)[6] discusses the many types of thresholds that can exist in four main categories: the true threshold (theoretical, absolute, mathematical); the biological/toxicological threshold; the experimental (statistical and apparent) threshold and the regulatory/practical threshold. The focus of regulatory risk assessment for all chemicals has always been centred around practical and experimental thresholds, and this should be no different for EDCs than for other chemicals e.g. those that work through other types of receptor.

The choice of leading with either a hazard-based or a risk-based approach to regulation of EDCs defines the nature of the scientific research needed to make due progress. Developing tests to address the scientific gaps and seeking to define practical thresholds could lead to a large increase in animal testing

for EDCs. There are currently no in vitro alternative approaches that are considered acceptable by regulators to assess ED potential in an intact organism according to the WHO definition. In vitro assays can only show endocrine activity, according to the WHO definition.

One way forward may be to further develop exposure-driven approaches to risk assessment, that can also take into account potential cumulative exposure to mixtures. One could prioritise attention on substances by assessing their potential for endocrine *activity* and relative potency using in vitro screens (e.g. with standardised OECD guideline protocols for KCs). It is important that in vitro assays are regarded as screens for prioritising concerns and not proof of adversity for regulatory action. Establishing the use of human and wildlife biomonitoring data, monitored over years (e.g. from programmes like the National Health and Nutritional Examination Survey (NHANES) since the 1980s in USA and the Human Biomonitoring for EU (HBM4EU) research programme in Europe)[7] could help to assess the scale of real life exposure of 'suspected EDCs' in citizens, to then help focus scientific efforts in areas where there are the greatest potential risks and impacts. It is not currently possible to assess all tens of thousands of chemicals in use today with current techniques, therefore there needs to be criteria for prioritisation and implementation as outlined in our 'principles for the management of chemicals in the environment'[8] document such that problems relating to the greatest risks and adverse impacts are tackled effectively and urgently.

The need for globally harmonised risk-based regulation for EDCs

To take regulatory action in the context of scientific uncertainty, the precautionary principle[8] could be invoked, but different parts of the world can view the precautionary principle in different ways and accept different levels of precaution according to different levels of acceptable risk. In a zero harm regulatory model, a precautionary approach can mean avoiding exposure altogether through substance bans; in regulation that seeks to avoid and minimise harm whilst keeping the benefits of substances in society, authorisations for use of EDCs are based on minimal risk by restricting, minimising and effectively managing exposure to as low as reasonably practicable (ALARP). Defining what is an acceptably minimal risk is a choice taken by citizens and governments, and should be well informed by the scientific and socio-economic evidence. This is best done in a transparent and open way to ensure citizens know the rationale of why a decision has been taken.

There has been extensive debate on EDCs over many years in the European Union that culminated in the regulation of EDCs in both the Biocidal Products Regulation (BPR) and Plant Protection Products Regulation (PPPR). By virtue of the function of biocide and pesticide chemicals, these products claimed regulatory attention first as they are designed to harm targeted undesired 'pest' species often by attacking their endocrine and metabolic systems, and therefore are more likely to cause undesired effects in non-target biological systems. Inconsistencies have emerged in these EU regulations, where risk assessment and risk-benefit analysis can be invoked under Article 5(2) of the biocidal products regulation (BPR) whereas this approach is not possible for Plant Protection Products (PPP). The underlying science is the same, but different political decisions have been taken on the balance of risk-benefit. It is not the case that science leads to different conclusions around the existence of thresholds in these two policy areas and the ability to assess risk for different product types, therefore the different regulations here must be driven by socio-political factors. If one supports the concept that practical/regulatory thresholds can be set for EDCs in any scenario and exposures can be estimated, then risk assessment of suspected EDs can be applied for all use and product scenarios to minimise risk.

We should take care in banning EDCs without understanding what new substances could replace their function in products and processes, such that unintended and potentially worse consequences do not occur from the use of other more harmful substances. It is also not responsible to have a status of inaction, due to the lack of scientific certainty, as the concerns by stakeholders are valid and should be addressed.

For the latter, it is then important as to how the precautionary principle is implemented in the face of uncertain or lack of evidence[8].

Concluding Remarks

Many regulatory authorities in the world support risk assessment and risk management of EDCs as a pragmatic, protective and effective basis of regulation (e.g. US EPA[9], Japan[10], Canada[11], EU biocidal products regulation 528/2012[12]). We advocate the use of exposure-driven risk-based approaches and state-of-the-art evidence integration to support decision-making for EDCs. A risk-based approach based on pragmatism and due precaution is compatible with the current state of the science and research recommendations, as presented by The Endocrine Society in their second scientific statement on endocrine disrupting chemicals[13]

References

1. Lagarde F, Beausoleil C, Belcher SM, et al. Non-monotonic dose-response relationships and endocrine disruptors: a qualitative method of assessment. *Environ Health*. 2015;14:13. Published 2015 Feb 11. doi:10.1186/1476-069X-14-13.
2. Andersson et al (2016) Endocrine disrupters: we need research, biomonitoring and action. Andrology 4, 556-560.
3. World Health Organisation (2012) State of the Science of Endocrine Disrupting Chemicals Report
4. La Merrill et al (2020) Consensus statement on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nature Reviews Endocrinology 16, 45-55.
5. OECD (2018) Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption. https://doi.org/10.1787/9789264304741-en
6. Brescia (2020) Thresholds of adversity and their applicability to endocrine disrupting chemicals. Critical Reviews in Toxicology. https://doi.org/10.1080/10408444.2020.1740973
7. Human Biomonitoring 4 EU Programme (HBM4EU) https://www.hbm4eu.eu/
8. RSC Principles for the management of chemicals in the environment https://www.rsc.org/globalassets/04-campaigning-outreach/tackling-the-worlds-challenges/environment/rsc_principles_for_chemicals_in_the_environment.pdf
9. US Environmental Protection Agency – How does EPA use information from the endocrine disruptor screening program. Website at https://www.epa.gov/endocrine-disruption/how-does-epa-use-information-endocrine-disruptor-screening-program
10. Ministry of Environment Japan (2010) Further actions to Endocrine Disrupting Effects of Chemical Substances – EXTEND 2010 http://www.env.go.jp/en/chemi/ed.html
11. Government of Canada (2017) Consideration of endocrine related effects in risk assessment. https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/consideration-endocrine-related-effects-risk-assessment.html
12. ECHA Consultation on the derogation to the exclusion criteria (to the BPR) https://echa.europa.eu/derogation-to-the-exclusion-criteria-current-consultations
13. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev. 2015 Dec;36(6):E1-E150. doi:10.1210/er.2015-1010. Epub 2015 Nov 6. PMID: 26544531; PMCID: PMC4702494.

Contact

The Royal Society of Chemistry would be happy to discuss any of the issues raised in our statement in more detail. Any questions should be directed to the RSC Policy & Evidence Team at policy@rsc.org.

About us

With about 50,000 members in over 100 countries and a knowledge business that spans the globe, the Royal Society of Chemistry is the UK's professional body for chemical scientists, supporting and representing our members and bringing together chemical scientists from all over the world. Our members include those working in large multinational companies and small to medium enterprises, researchers and students in universities, teachers and regulators.

The Royal Society of Chemistry developed this position following a round table of UK scientific and regulatory experts working in the field of endocrine disruption, at RSC Burlington House in November 2019.