Endocrine disruptors

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Abstract

Endocrine disrupting chemicals (EDCs) are at the centre stage of a scientific and regulatory controversy. Given the complexities, ambiguities and particularly the uncertainties surrounding the hazards of EDCs, the precautionary principle is of utmost relevance to the case. Even the definition of EDCs remains much contested, as do the scientific processes and methods through which to identify them. On the one hand, there is considerable societal pressure to regulate ECDs 'now'. On the other hand, this quick regulation is often impossible as the limited evidence available does not suffice in the context of traditional EU scientific risk assessment. This results in 'paralysis' and several controversies surrounding EDCs, such as regarding bisphenol A and a long delay by the European Commission to formulate scientific criteria for identifying endocrine disruptors. Bans on the use of particular EDCs have also led to so-called 'regrettable substitutions'. In turn, green chemistry can be regarded as one important innovation pathway in order to develop chemicals that are non-regrettable substitutions for EDCs.

Contents

List of abbreviations

BPA	Bisphenol A
BPS	Bisphenol S
BPR	Biocidal Products Regulation
Cefic	European Chemical Industry Council
CeHoS	Danish Centre on Endocrine Disruptors
CEO	Corporate Europe Observatory
CIA	Chemical Industries Association
DEHP	Di(2-ethylhexyl)phthalate (mainly used in plastics)
DES	Diethylstilbestrol (medical drug)
DG	Directorate General
DNEL	Derived no-effect level
ECHA	European Chemicals Agency
ECJ	European Court of Justice
ED	Endocrine disruptor
EDC	Endocrine disrupting chemical
EEA	European Environment Agency
EEB	European Environmental Bureau
EFSA	European Food Safety Authority
EP	European Parliament
ERF	European Risk Forum
EU	European Union
IPCP	International Panel on Chemical Pollution
IPCS	International Programme on Chemical Safety
NGO	Non-governmental organisation
OECD	Organisation for Economic Cooperation and Development
PNEC	Predicted no-effect concentration

PP	Precautionary principle
PPPR	Plant Protection Products Regulation
PVC	Polyvinylchloride
REACH	Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
SVHC	Substance of very high concern
UNEP	United Nations Environmental Programme
US	United States
WECF	Women Engage for a Common Future
WHO	World Health Organisation

1 Introduction

Endocrine disruptors, also called endocrine disrupting chemicals (EDCs), are at the centre stage of a scientific and regulatory controversy. Chemicals shown to have endocrine disrupting effects have mostly been man-made. They were originally engineered so as to produce benefits most importantly – but not exclusively – for industry and agriculture, households and consumers, as well as for medical and personal health care.

Yet there is a link between such widely used chemicals and disorders within the endocrine (hormonal) system. For example, EDCs are seen to be a cause for chronic diseases, including infertility, obesity, diabetes, hormone related cancers, and cardiovascular disease (WHO, 2012a, p. 22-26). And because EDCs can be found in many products that people use or consume on a daily basis – including paint, food packaging, toys, clothing, cosmetics, and medicines – they can be the cause of serious harm for human health. The most widespread and commonly known EDCs are "bisphenol A, phthalates, pesticides, persistent organic pollutants such as polychlorinated biphenyls, polybrominated diethyl ethers, and dioxins" (Gore et al., 2015).

Although EDCs can thus be seen as "a risk that concerns us all", they pose risks especially to unborn and young children (BEUC, 2016, p. 3). Moreover, the threats that EDCs pose are not limited to human health. Existing evidence indicates that exposure to EDCs also has a negative impact on wildlife health trends (WHO, 2012a, p. 11).

The health risks both for humans and wildlife associated with EDCs became increasingly clear over the course of the 1990s (see e.g. WHO, 2002). Various authorities, including the World Health Organisation (WHO) and the European Commission, subsequently issued studies investigating the potential harm caused by EDCs (e.g. EEA, 2012; WHO, 2012a). But problematically, even the very definition of EDCs remains very much contested, as do the scientific processes through which to identify them. To define which chemicals or substances are in fact to be considered as EDCs is key, however, because this has important implications for how they are regulated.

Indeed, the growing scientific evidence on the negative effects of EDCs for health and for the environment caused debate about the identification and regulation of EDCs within the European Union (EU). From 2014 to 2017, in particular, there has been controversy surrounding the Commission's delay to set out scientific criteria for the determination of endocrine disrupting properties. Despite the subsequent establishment of criteria for the identification of EDCs in several – but not all – EU legislative areas, there are ongoing concerns about the suitability of the EU's regulatory framework on EDCs. Such concerns include the absence of a horizontal definition of EDCs, which is a definition that cuts across various matters and subject areas, and more recent evidence that the "health risks associated with EDC *mixtures* are underestimated" (Bergman et al., 2019, p. 3).

This case study aims to better understand the complexities surrounding the application of the precautionary principle in the case of the governance of EDCs, as well as the controversies surrounding calls for innovation in this field.

Against this background, this case study aims to better understand the complexities surrounding the application of the precautionary principle in the case of the governance of EDCs, as well as the controversies surrounding innovation in this field. Because the governance of the risks posed by EDCs most importantly takes place at the level of the EU institutions in Europe, the study focuses on decisions and regulations within the EU,

starting with the first debates of the 1990s. While the case study focuses mostly on the – proven as well as potential – health risks of these chemicals, it also considers the governance of EDCs in the context of the risks to the wider environment and wildlife. This is because the latter risks have likewise received substantial attention in academic research, and in public, political and legal discussions.

More specifically, the case study examines 1) the origin of endocrine disruptors, 2) the risks and scientific controversy surrounding endocrine disruptors, 3) the political and legal dynamics concerning the application of the precautionary principle, and last but not least 4) to what extent there has been a tension between precaution and innovation.

The precautionary principle is of utmost relevance for the governance of EDCs. Relevant actors in this field, such as the WHO and the United Nations Environmental Programme (UNEP), but also non-governmental organisations (NGOs) and the European Parliament (EP), have previously invoked a need to act on the basis of the precautionary principle, with the aim to reduce or curb serious consequences of EDCs for human health and the environment. Most importantly, these stakeholders see a lack of data to lead to great uncertainties about the degree and extent of risks arising from EDCs. Many of these uncertainties arise from the complexities surrounding both the hazard of and exposure to EDCs, given that "endocrine-disrupting action breaks all the rules and assumptions that have guided toxicology through the era of modern chemical regulation" (Vogel, 2005).

Within the EU, the regulatory framework has been set up in such a way that regulation and the assessment of individual endocrine disruptors takes place within the context of various regulations. In the area of health and food safety, EDCs are regulated within the Cosmetics Regulation (1223/2009) and Food Contact Materials Regulation (10/2011). And within the area of the internal market, EDCs are regulated within the REACH regulation (1907/2006). In the area of environment, EDCs are regulated within the Plant Protection Products Regulation (PPPR) (1107/2009) and the Biocidal Products Regulation (BPR) (528/2012). Crucially, and also problematically, these pieces of legislation contain different regulatory approaches to EDCs (European Commission, 2018, p. 9).

There have been major controversies surrounding the development of these regulations. A main issue in this context is the process through which the European Commission has set scientific criteria for the identification of EDCs subsequent to these regulations. From a legal perspective, a milestone in this respect has been the 2015 judgment of the European Court of Justice (ECJ) in a case that Sweden brought against the Commission (T-521/14). The Court ruled that the Commission had failed to fulfil its obligations under the Biocidal Products Regulation. This was seen to be the case as the Commission had failed to adopt a delegated act[1] to set out the necessary scientific criteria for authorization. At the same time, stakeholders from industry have brought several cases against ECHA to the ECJ concerning the establishment of lists of substances subject to authorization.

Finally, when it comes to innovation pathways, there is some evidence that bans on the use of particular EDCs have led to so-called 'regrettable substitutions': the introduction or adoption of chemicals that may not be safer and potentially worse. The most prominent example of regrettable substitution is that of bisphenol A (BPA) with the substance bisphenol S (BPS). In turn, green chemistry may be regarded as an important innovation pathway in order to develop chemicals that are non-regrettable substitutions for EDCs. Nevertheless, scientists working within this field do still encounter the complexities and uncertainties in establishing the potential endocrine-disrupting activity of substitute chemicals. At the same time, some stakeholders in the discussion about EDCs, mostly from

[1] Delegated acts are legally binding acts that enable the Commission to supplement or amend non-essential parts of EU legislative acts, for example, in order to define detailed measures (https://ec.europa.eu/info/law/law-making-process/types-eu-law_en)

the chemicals industry, have invoked an 'innovation principle' so as to prevent further regulatory bans on EDCs.

Key timeline

The timeline below lists key events regarding the debate and regulation of endocrine disrupting chemicals. It focuses mainly on the EU institutions, and most importantly the European Commission, but also includes key international scientific reports and influential NGO activity.

In view of the timeline below, it is important to highlight that the case study focuses on the three main different regulatory approaches to EDCs that exist in the EU legal framework. These are

1. the Plant Protection Products Regulation (PPPR) and the Biocidal Products Regulation (BPR), which mostly concern pesticides;
2. the regulations on Food Contact materials and Cosmetics – which are not mentioned in the timeline below as their provisions do not explicitly contain regulations on endocrine disruptors;
3. the REACH regulation regarding production and use of chemical substances within the EU internal market.

Political	***Legal***	***Science/risk assessment***	***Public debate***	***Other***

Year	***Event***	***Relevance to case study***
Around 1960	*Publications by Roy Hertz (1958) and Rachel Carson (1962)*	*First publications on the harm that chemicals can cause to ecosystems and human health. Set off a range of studies on reproductive health of wildlife in the 1960s*
Early 1970s	*Medical tragedies surrounding the drug diethylstilbestrol (DES)*	*First widespread evidence of adverse health effects of EDCs that only emerge after many years (in this case, vaginal cancer in young females after puberty)*
1990s	*Wingspread I conference in the US (1991) and Weybrdige conference in the EU (1996)*	*First international conferences on endocrine disruptors. Wingspread I was "a key turning point" and coined the term 'endocrine disruption' (Schug et al., 2016, p. 836)*
1998	*European Parliament resolution on endocrine-disrupting chemicals*	*Calls for "strict compliance with the precautionary principle" in establishing a regulatory framework on EDCs*
1999	*European Commission strategy for endocrine disrupters*	*First strategy of the Commission on endocrine disruptors, emphasizes the importance of the precautionary principle*

2002	*WHO report "Global Assessment of the State-of-the-Science of Endocrine Disruptors"*	*Finds "weak evidence" for adverse health effects of EDCs, but stresses need for more research*
2006	*"REACH" Regulation*	*Allows identification as industrial chemicals with endocrine disrupting potential*
2009	*Cosmetics Regulation*	*Requests Commission to review Regulation with regard to EDCs by January 2015*
2009	*Plant Protection Products Regulation (PPPR)*	*Requests Commission to present scientific criteria for determining EDCs by December 2013*
2012	*Biocidal Products Regulation (BPR)*	*Requests Commission to present scientific criteria for determining EDCs by December 2013*
2012	*WHO report "State of the Science of Endocrine Disrupting Chemicals—2012"*	*Finds that EDCs are a "global threat" to human health and that there is a severe lack of data on identifying EDCs*
2013	*Scientific opinion of the European Food Safety Authority (EFSA) on the hazard assessment of EDCs*	*Concludes that EDCs do not need to be regulated based on a hazard approach but can be regulated by means of risk assessment*
2013	*European Commission decision for an impact assessment of regulation on EDCs*	*Delayed the establishment of scientific criteria for the identification of EDCs*
2015	*ECJ judgment European Commission failed to act regarding scientific criteria to identify EDCs*	*Case brought by Sweden concerning the overdue deadline for setting scientific criteria in the Biocidal Products Regulation*
2015	*Corporate Europe Observatory report "A Toxic Affair"*	*A vital document in the debate. It reports on lobbying activity by the chemical industry, which led to the European Commission to* ***not*** *take any regulatory action on EDCs.*
2017	*Regulation amending the Biocidal Products Regulation*	*Sets out scientific criteria for the identification of EDCs*
2018	*Regulation amending the Plant Protection Products Regulation*	*Sets out scientific criteria for the identification of EDCs*
2018	*European Commission communication "Towards a comprehensive European Union framework on endocrine disruptors"*	*Concludes there are different approaches to endocrine disruptors within the EU legal framework. Launches "fitness check" of EU legislation on endocrine disruptors*

2019	*European Parliament resolution on Commission communication about EDCs*	*Considers the current EU framework for regulating EDCs to be inadequate*
2019	*European Commission consultation on EDCs*	*Launch of a consultation with both public and stakeholders*
2019	*EDC-MixRisk report and policy recommendations (Bergman et al., 2019; Bergman, Rüegg & Drakvik, 2019)*	*Finds that existing regulations for chemicals systematically underestimate the health risks of EDCs*

2 Use of chemicals with endocrine disrupting properties

Chemicals with (potentially) endocrine-disrupting properties are mostly man-made. They were originally engineered so as to produce benefits for various industries, consumers, and individuals. As such, EDCs can be found in many products. This most importantly, but not exclusively, includes products for industry and agriculture, for households and consumers, as well as for medical and personal health care.

In the field of agriculture, pesticides and herbicides have represented "a great benefit for human health", for example by helping to "control agricultural pests […] and plant disease vectors" and by insuring "increased food production [and] a safe and secure food supply" (Mnif et al., 2011). Yet industry has engineered various pesticides and herbicides that were later shown to have endocrine-disrupting effects, also on human beings. The pesticide DDT, for instance, was widely used until the 1960s to control insects. Amongst other issues, it has been related to an early onset of puberty and menopause in humans, as well as to "critical effects in pregnant and nursing" females (Schug et al., 2016, p. 841). DDT has been banned in the EU since the 1980s but remains present in the environment until today (European Commission, 2003). In turn, the herbicide Atrazine, about which there is evidence that it for example causes abnormal female cycles, has been banned in the EU but remains widely used in the US (see Sass & Colangelo, 2006).

In the area of household products, the most well-known chemicals with endocrine-disrupting properties were originally developed for the plastics industry. These, for instance, include bisphenol A (BPA) and phthalates. BPA is very widely used to make plastic products shatter resistant, colourless, and light weight. It is, for instance, used for various medical devices and for food packaging. Given its widespread use, BPA has been at the centre stage of scientific and public controversies, as the chemical has been related to cancers, changes in metabolism, and neurobehavioral issues such as attention deficit disorders – amongst other health effects (Schug et al., 2016, p. 840). In turn, phthalates such as DEHP (Di(2-ethylhexyl)phthalate) are used to increase the flexibility of plastics. This is useful for products such as toys, wires and cables, and building materials. Phthalates are also widely used in cosmetic products, like perfumes (see e.g. Al-Saleh & Elkhatib, 2016). Researchers have, however, linked phthalates to a wide variety of negative health effects, including also changes in metabolism and neurobehavioral issues, as well as male fertility issues (Schug et al., 2016, p. 840; Westervelt, 2015). The use of BPA and of various types of phthalates has been restricted within the EU.

Finally, some chemicals have been purposefully designed to have endocrine-disrupting properties so as to benefit human health. This particularly includes EDCs developed for female heath, such as for birth control and for the treatment of menopause symptoms. Most birth-control pills, for example, include the EDC 17β-ethinylestradiol (EE2). EE2,

however, has been shown to cause serious ecological issues as it ends up in water through urine and sewage. It causes harm to wildlife, as it is, for example, capable of "feminizing male fish" (Schug et al., 2016, p. 841).

> *"Even purposefully engineered chemicals aimed at benefiting humans can also harbor potential for harm" (Schug et al., 2016, p. 841).*

As Schug et al. write, then, these examples about the design and use of chemicals show that "even purposefully engineered chemicals aimed at benefiting humans can also harbor potential for harm" (2016, p. 841) – both for human health and for wildlife.

3 Risks and scientific uncertainties

3.1 Risk/threat

3.1.1 Potential risks

On the basis of a number of 'state of the art' reviews by The Endocrine Society, UNEP and the WHO, and the European Commission (see section 3), the current section describes the threats that EDCs pose to different societal groups, as well as to wildlife and the environment. Given that EDCs can have serious and irreversible health consequences "throughout life", the WHO has called them a "global threat that needs to be resolved" (WHO, 2012a, p. 27).

The scientific evidence on the risks posed by the endocrine disrupting properties of widely used chemical substances has significantly increased since the 1990s, and even more so since the early 2000s. In its influential report on EDCs of 2002, the WHO defines an endocrine disrupting chemical – also referred to as endocrine disruptor (ED) – as a substance that "alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations" (WHO, 2002, p. 1). Hence, in simple terms, EDCs are chemicals that interfere with the hormonal system and can thereby negatively affect the health of both humans and animals.

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Hormonal – or endocrine – systems control various important processes in the body, ranging from early embryonic development and organ formation, to "most tissue and organ functions" in adults (WHO, 2012a, p. 4). EDCs "act like hormones", and can mimic or block natural hormones (ibid., p. 6). As such, they interfere with the normal action of hormones. The most widespread and commonly known chemicals that have broad endocrine-disrupting properties are "bisphenol A, phthalates, pesticides, persistent organic pollutants such as polychlorinated biphenyls, polybrominated diethyl ethers, and dioxins" (Gore et al., 2015, p. 593). These and other EDCs can alter the function of hormones to the extent that they induce diseases, even at – and in some cases also particularly at – very low levels of exposure and concentration (Gore et al., 2013, p. 3958). The latter has also been called the 'low-dose effects' of EDCs.

There is indeed evidence that exposure to EDCs induces various types of diseases, which are related to any hormonal system in the body. Amongst other threats to human health, there is strong scientific evidence that endocrine disruptors induce negative health effects related to obesity, diabetes and cardiovascular diseases; female and male reproductive

health; hormone-related cancers in females – including breast cancer – and prostate cancer in males; thyroid health; and neurodevelopment and neuroendocrine systems (Gore et al., 2015; WHO, 2012a). With regard to the latter health effects, exposure to EDCs has been linked, *inter alia*, to the occurrence of dyslexia, IQ loss, ADHD, and autism (Bergman et al., 2019; Bergman, Rüegg & Drakvik, 2019; WHO, 2012a, p. 9).

Exposure to endocrine disruptors occurs on daily basis, as EDCs can, for example, be found in plastics, paint, toys, clothing, cosmetics and pesticides, and even in dust released from indoor sources. It is therefore clear that EDCs are a risk that concerns all consumers (BEUC, 2016, p. 3). Crucially, however, there is scientific consensus that the *timing* of exposure is critical. That is, the "most sensitive window of exposure" is during important moments of tissue development, and the effect of EDCs can be irreversible during these periods (WHO, 2012a, p. 6). This includes most importantly prenatal development, and the development of young children, but also of young adults (European Commission, 2018, p. 2; WHO, 2012a). (Unborn) children and pregnant females are thus most importantly threatened and potentially harmed, as are future generations (WHO, 2012b): changes caused by EDCs at an early stage "underlie disorders that may manifest later in adult life and contribute to 'diseased ageing' with a multitude of chronic diseases" (Bergman, Rüegg & Drakvik, 2019, p. 2). Fertile populations, workers exposed to EDCs in their environment, and people with low incomes are also among the societal groups that are most importantly at risk (Di Renzo et al., 2015; WHO, 2012a).

Additionally, there is increasing evidence that combined exposure to different (potential) EDCs provides leads to greater threats to human health, especially for children (Bergman et al., 2019). Endocrine disruptors working "together to produce additive effects" has also been called the 'mixture effect' or 'cocktail effect' (European Commission, 2018, p. 2; see further below).

Finally, the threats that EDCs pose are not limited to human health but have implications for the environment as a whole and the well-being of wildlife. Existing evidence indicates that "exposure to endocrine disrupting contaminants plays a significant role in wildlife health trends", and that there is a relation between exposure to EDCs of wildlife and population decline (WHO, 2012a, p. 11; see also EEA, 2012). This has been shown to be the case for "molluscs, crustacea, fish, reptiles, birds and mammals" (DG Environment, 2019a).

3.2 Scientific analysis

Scientific analysis of the risks posed by endocrine-disrupting chemicals to wildlife, laboratory animals, and humans most importantly includes many "thousands of published studies" (Gore et al., 2013). There are also several major scientific research projects on EDCs that are ongoing or have just been completed. Although there were earlier signs for a link between chemicals and health problems (see the 'Key timeline' in part 1 of this report), most of scientific evidence originates from the decades after the 1990s (European Parliament, 2019, p. 2-3). In Europe, a first international meeting on endocrine disruptors took place in Weybridge, in 1996. It was sponsored by the European Commission and resulted in the publication of a future research agenda in the so-called 'Weybridge Report' (DG Environment, 2019b).

Publications on the risk of EDCs have subsequently been reviewed in a number of influential reports (see also European Parliament, 2019, p. 4-7). The first of these was the 2002 report "*Global Assessment of the State-of-Science of Endocrine Disruptors*" from the International Programme on Chemical Safety (IPCS) – a programme jointly set up by the WHO, UNEP and the International Labour Organisation (WHO, 2002). It was a response to the recommendation of the 1997 Intergovernmental Forum on Chemical Safety. Most importantly, the document systematically assessed existing literature on the effects of EDCs for human health and wildlife. It most importantly concluded that there was still insufficient data to draw conclusions about the threats posed by EDCs (WHO, 2002).

The follow-up to the 2002 WHO report, entitled "*State of Science of Endocrine Disrupting Chemicals*" was published in 2012. It provided an "assessment of the strength of the evidence supporting the hypothesis that chemicals with endocrine activity are a causal factor in the manifestation of specific conditions" (WHO, 2012a, p. 1). It identified such evidence for several threats to human and wildlife health, but also identified a major lack of data and testing of chemicals suspected to have endocrine disrupting properties.

The publication of the 2012 report of the WHO was preceded by a few other scientific reviews, including the "*Scientific Statement*" of the Endocrine Society (Diamanti-Kandarakis et al., 2009), the "*State of the Art Assessment of Endocrine Disrupters*" from the EU Directorate-General (DG) for the Environment (Kortenkamp et al., 2011), and "*The Weybridge+15 (1996–2011) report*" of the European Environment Agency (EEA) (EEA, 2012).

The EU has also funded several research projects on endocrine disruptors. Most recent projects include the Innovative Training Network "*PROTECTED*" on detecting EDCs that are not synthetic, and the Horizon 2020 projects "*EDCMixRisk*", on the health effects of combined or additive exposure to EDCS, "*EndocRine Guideline Optimalisation*", on the tools for hazard assessment of EDCs and "*FREIA"* on female reproductive toxicity of EDCs (see below under section 2.3.1.5 regarding the latter project). Another relevant Horizon 2020 project is *ERGO*, "which aims to improve hazard assessment of EDCs (…) by breaking down the wall that currently exists between the different research fields that investigate adverse effects of EDCs" (ERGO, project overview). ERGO and FREIA are part of the larger EURION project, "*European Cluster to improve Identification of Endocrine Disruptors*".

Additionally, important reviews on identifying, regulating and testing EDCs have been published by UNEP and the Organisation for Economic Cooperation and Development (OECD). The UN's International Panel on Chemical Pollution (IPCP) has published a series of three reports to provide an overview of 1) initiatives of various stakeholders to identify (potential) EDCs; 2) the environmental exposure and effects of EDCs; and 3) regulatory frameworks and policy initiatives on EDCs (UNEP 2017a; 2017b; 2017c). The OECD published a first "*Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption*" in 2012, and a second, updated, version in 2018 (OECD, 2012; 2018).

Finally, various national consumer agencies have engaged in researching the presence of chemicals with endocrine-disrupting properties in products that people use on a daily basis (see e.g. BEUC, 2016; 2019).

3.3 Scientific uncertainty

3.1.2 Complexity

The risk properties of endocrine disruptors are highly complex. Complexity in this context refers to "the difficulty of identifying and quantifying causal links between a multitude of potential candidates and specific adverse effects" (RECIPES conceptual framework). To understand such complexity for EDCs, it is helpful to distinguish between four forms of complexity, two of which are related to the biological and environmental system in question, and two of which are related to the wider regulatory and political system under which EDCs are governed. It is important to note that the intrinsic complexity of human physiology and of the hormonal system also adds to the complexities of researching EDCs.

First, regulating the risk of endocrine disruptors is complicated by hazard complexity and exposure complexity (Vogel, 2005). *Hazard complexity* means that it has been highly complicated to disentangle the causal relationship between exposure to EDCs and biological changes and diseases in humans and wildlife. Most importantly, this is because "endocrine-disrupting action breaks all the rules and assumptions that have guided toxicology through

the era of modern chemical regulation" (Vogel, 2005). This is primarily the result of two characteristics of the health hazard of EDCs, namely low-dose and mixture effects.

> *"Endocrine-disrupting action breaks all the rules and assumptions that have guided toxicology through the era of modern chemical regulation" (Vogel, 2005).*

To start with, standard toxicology assumes that increasing exposure to a substance leads to increased effect – a simplifying assumption that has been coined the "monotonic-dose relationship" (Vogel, 2005). EDCs, however, behave differently. That is, they do not behave as 'usual' toxic substances, but rather behave like hormones. And therefore, "like hormones, EDCs exhibit complex dose-response curves, and they can act at extremely low concentrations" (Gore et al., 2015, p. 594). This is known as 'non-monotonic dose-response curves'. For example, the relation between exposure to and the health hazard of some EDCs takes the form of an inverted U-curve, in which higher levels of exposure are associated with a lower health hazard (Vogel, 2005). As a result, one cannot extrapolate the effects (or lack of effects) at the high doses to the low doses, which is the common assumption in toxicology testing. Such non-linearity is a key aspect of complexity.

In addition, the toxicity and hazard of chemicals is commonly established on a case-by-case basis. Yet EDCs are clearly "being added on top of the endogenous hormonal milieu, such that complex mixtures, dose additivity, and synergism between and among hormones and chemicals are the norm" (Gore et al., 2015, p. 594). Thus, the effect of a particular EDC has to be considered in terms of its addition to a 'mixture' of chemicals and hormones, rather than in isolation. The EDC-MixRisk project, for example, concludes that prenatal exposure to various EDCs simultaneously is related to health and developmental effects to an extent that is much greater than was previously estimated on the basis of case-by-case assessment (Bergman et al., 2019). This is likewise an example of non-linearity. Here, the effect of multiple hazards is larger than the sum of its parts, because of interaction.

Whereas hazard complexity thus concerns the measurement of the causal mechanisms of EDCs, *exposure complexity* concerns the measurement of how humans and wildlife are exposed to EDCs. In brief, exposure complexity refers to the situation that it has been difficult to determine the levels at which both humans and the wider environment are actually exposed to EDCs. Determining such exposure levels becomes all the more significant given that exposure to EDCs at a low dose and during a specific moment in time "can be just as or more dangerous" than exposure at a high dose for a longer period of time (Vogel, 2005). Because the endocrine system very much changes over time, the effect of an EDC can be different at different moments in the development of an individual – either being evident at birth or leading to diseases at a later stage in life (Gore et al., 2015).

In this context, it is crucial to understand that "endocrine disruptors are everywhere" (van Kessel, 2019). Yet the level of exposure to EDCs depends on human and wildlife behaviour, for example on the ways in which people encounter, interact with or use products that contain EDCs (Vogel, 2005; see also Di Renzo et al., 2015).

Second, besides the complexities related to the biological and environmental system, regulating the risk of endocrine disruptors is complicated by the broader system in which EDCs are governed. Clearly, to detect which chemicals have endocrine-disrupting properties, scientists have had to abandon the conventional, simplifying assumptions for establishing the toxicity of chemicals. This has led to *regulatory complexity*. That is, the regulatory system in which EDCs are governed is 'path-dependent' (RECIPES conceptual framework; see also below under 2.4.2). At its very basis, the system is developed around conventional testing schemes, which were designed for the identification of hazards in

chemicals other than endocrine-disrupting properties. Given the hazard and exposure complexities just described, these schemes "have serious deficiencies in estimating EDCs' likely impact on human health and wildlife" (EEA, 2012, p. 19). The development of alternative procedures for testing EDCs has been very costly both in terms of time and resources (EEA, 2012, p.19-20; Vogel, 2005).

Moreover, different regulations and the different regulatory agencies involved have had different understandings of how best to regulate these chemicals – depending on matters such as their expertise and regulatory framework (European Commission, 2018; see further below).

Finally, the complexity of endocrine disruptors as a risk also gives rise to important, wider *political complexity*. This is so as different stakeholders adhere to different positions; a trend which we do not only see within the EU (see section 4 of this report), but also beyond. One major political complexity concerns international trade agreements. To facilitate free trade, international actors seek to "flatten out" regulatory differences, as such differences may constitute trade barriers (Horel, 2015, p. 4). Given that EDCs are used in many products that are globally exchanged, there is external pressure – most importantly from the US – to change or influence the basis on which the EU acts with regard to EDCs (see Horel, 2015).

3.1.3 Uncertainty

Uncertainty refers to a "lack of knowledge about the outcomes or likelihoods, or both, of an event or process" (RECIPES conceptual framework). There are several scientific uncertainties about substances with endocrine-disrupting properties, and some of this uncertainty is likely to remain also over time. These uncertainties can be linked to three main factors:

1. Lack of data;
2. Lack of testing methods;
3. Indeterminacy about effects.

Firstly, uncertainty about endocrine disruptors is the result of practical limitations in combination with the hazard complexity of EDCs. This combination leads to a large *lack of data* about the identification, the degree and the extent of risks arising from EDCs. Notably, in its 2012 report, the WHO writes that about 800 chemicals are known or suspected to be endocrine disruptors, but that "only a small fraction of these chemicals have been investigated in tests capable of identifying overt endocrine effects in intact organisms" (2012a, p. 2). More urgently, "the vast majority of chemicals in current commercial use have not been tested at all" for endocrine-disrupting properties (ibidem). Around the turn of the century, for example, the US Environmental Protection Agency (EPA) estimated that there are 87,000 chemicals that can potentially be endocrine disrupting (Vogel, 2005; see EPA, 2000, p. 8).

> *"The vast majority of chemicals in current commercial use have not been tested at all" for endocrine-disrupting properties (WHO, 2012a, p. 2).*

Secondly, tests for the endocrine-disrupting properties of chemicals are highly time-consuming and as such there is still a great lack of *testing methods*. For example, testing schemes are still in the process of being developed and revised (compare e.g. OECD, 2012; 2018); the hazard complexities of EDCs can only really be understood through multi-generational studies (EEA, 2012, p. 19); and scientists question if current test methods are sufficiently sensitive to screen for EDCs (Hass et al., 2019, p. 8). Thus, given large

practical limitations and hazard complexity, uncertainty about EDCs in the form of a lack of data is likely to persist into the future.

Thirdly, scientific uncertainty about EDCs also arises from *indeterminacy,* that is, scientific uncertainty of the effects of EDCs. It is incredibly difficult to determine the precise causal chains through which EDCs act on the hormonal system of both humans and wildlife. A report of the Danish Centre on Endocrine Disrupters (CeHos) identifies three such major uncertainties when it comes to the effects of EDCs (Hass et al., 2019, p. 5). Firstly, it is "uncertain whether or not there is a threshold for effects of EDs", regardless of the mode of action of the particular EDC (p. 6). Such thresholds cannot be experimentally proven, as the notion of a threshold is an assumption based on current biological and toxicological knowledge.

Secondly, the delayed effects of endocrine disrupters are uncertain. This is mostly the result of time lags of many years – or even several decades – between exposure during the 'sensitive window' of post-natal development and the development of disease at a later stage in life (p. 6).

And thirdly, the complex mechanisms through which natural hormones and endocrine disruptors may work together to cause a non-monotonic response to doses of EDCs remain uncertain. This uncertainty is particularly significant for understanding endocrine active drugs against hormone-related cancers, including breast cancer (p. 10).

Given the complexity of EDCs, both in terms of hazard and exposure, some of this uncertainty "probably cannot be resolved" (Vogel, 2005).

3.1.4 Ambiguity

From an analysis of the governance of EDCs in the US context, Vogel (2005) finds that the risk property of ambiguity is "the single greatest limitation to the use of endocrine disruption science in policy". Ambiguity refers to the fact that there are "different legitimate viewpoints from which to evaluate whether there are or could be adverse effects and whether these risks are tolerable or even acceptable" (Renn, Klinke & van Asselt, 2011, p. 240). Scientific experts have indeed been deeply divided about the (potential) adverse health effects of EDCs (see e.g. Zoeller et al., 2014; see also below).

That is, the definition of endocrine disruptors put forward in the 2002 WHO report has become widely accepted (see section 3.1.1). Yet adhering to this definition implies two things. First, that it is possible to make a clear distinction between adverse effects of endocrine disruption and normal physiological modulations of the endocrine system. And second, that adverse health effects are caused by a chemical's hormonal activity. However, and as discussed above, currently there seems to be insufficient knowledge to universally define what constitutes an adverse endocrine effect. There are also no adequate standardised test methods to identify such possible effects. This means that adversity, and thus the identification of EDCs, would have to rely on weight-of-evidence approaches; relying on expert judgment and done on a case-by-case basis.

> *On the one hand, the definition of endocrine disruptors put forward in the 2002 WHO report has become widely accepted. On the other hand, "the practical application of this definition is surrounded by controversy" (Clahsen et al., 2019, p. 65).*

As Clahsen et al. (2019) note, this "practical application" of the WHO definition "is surrounded by controversy" (Clahsen et al., 2019, p. 65). Ambiguities surrounding endocrine disruptors most importantly relate to the complexities of the risk. They include, among others, disagreements about the specific evidence that is required, particularly in

view of identifying causal links between endocrine-disrupting properties and adverse health effects. They also include differences of opinion about the evaluation of results from studies performed outside of living organisms; and the question of threshold effects (Clahsen et al., 2019, p. 65).

Such debates about EDCs are too technical to describe in detail here. For the purpose of the present case study, however, it is valuable to consider the work of Clahsen et al. (2019) on the structure of the argumentation put forward by different experts on EDCs. Their analysis concerned the discussion between Lamb et al. (2014) and Bergman et al. (2015) about various aspects of the science on EDC, with a view to the merits of the 2012 WHO report. They concluded that, out of five differences in starting points between the two sides, only one pertains to an ambiguity concerning the interpretation of data (*interpretive ambiguity*).

The authors explained remaining differences of opinion about establishing causality and about the function of a state of the science report most importantly by divergent ethical and normative assumptions (*normative ambiguity*). Finally, the authors argued that differences pertaining to evaluating the weight of different pieces of evidence reflect a mix of interpretive and normative ambiguity. In turn, differences in the perception of the functioning of the endocrine system – for instance as a "resilient" or as a "vulnerable" system – were primarily cultural (Clahsen et al., 2019, p. 71-77).

In the context of these disagreements, it is important to note that Bergman et al. are the authors of the WHO State of the Science review and that the critique of Lamb et al. received funding from various North American and European chemistry and crop protection councils. A similar debate took place about the merits of the *State of the Art Assessment of Endocrine Disruptors* commission by DG Environment (Kortenkamp et al., 2011), namely between Rhomberg et al. (2012) and Kortenkamp et al. (2012). Also here, it is important to note that Kortenkamp et al. are the authors of the original report and that the critique of Rhomberg et al. received funding from the American Chemistry Council.

4 Risk governance and the precautionary principle

4.1 General framework for risk governance

4.1.1 Interdisciplinary risk estimation

Given the nature of endocrine disruption, the risk assessment of EDCs has been a mostly interdisciplinary endeavour. This is not least because the way in which EDCs act seems to run counter to many of the old assumptions of toxicology, for instance concerning the existence of a threshold of damage. Amongst other disciplines, the risk estimation has involved "reproductive biology, endocrinology, medicine, genetics, behaviour, development biology, and toxicology" (Gore et al., 2013, p. 3958). Leading institutes and science communities in the field of research on EDCs, such as the Danish Centre on Endocrine Disruptors (CeHos), The Endocrine Society, and Horizon2020 EDC MixRisk project, also work on an interdisciplinary basis.

Some experts have nevertheless challenged the interdisciplinary approach to risk assessment of EDCs. In a 2013 editorial on the decision of the European Commission to develop a regulatory framework on EDCs, various international toxicologists and pharmacologists advocate a 'classical' toxicological approach to the assessment of EDCs. They, for example, contend that "an assessment of a substance should be based on data obtained from toxicity testing on this specific substance and derived information on

potency" (Dietrich et al., 2013, p. 2112). Other experts, including those from The Endocrine Society, have responded with reference to the complex nature of EDCs and argued that "we need the fields of toxicology, endocrinology and other stakeholders to work together to address these issues" (Gore et al., 2013, p. 3958).

When it comes to actual scientific practices to assess the risks of EDCs within the regulatory framework of the EU, two major bottlenecks stand out.

Given mixture-effects of EDCs, the single substance risk assessment paradigm potentially severely underestimates risks of endocrine disruption.

First, and as the EDC-MixRisk project has concluded, "although it is clear that real life exposure entails mixtures of chemicals, risk assessment is performed by a compound-by-compound approach" (Bergman, Rüegg & Drakvik, 2019, p. 2; see also EEA, 2012, p. 19-20; Gore et al., 2015). Testing EDCs on a substance-by-substance basis results from the "single substance risk assessment paradigm", which adopts the assumption that substances are released in an original, unspoiled environment (ibidem). Yet EDCs "enter into the environment or a human body" in which other EDCs are already present (ibidem). Given mixture-effects of EDCs, which is however not a challenge specific to EDCs, the single substance risk assessment paradigm potentially severely underestimates risks of endocrine disruption.

Second, and relatedly, "international testing schemes were not designed for EDCs" and have serious shortcomings in estimating adverse effects for both humans, wildlife, and the environment (EEA, 2012, p. 19). The OECD, as well as other organisations, have developed various guideline documents for testing and evaluating EDCs (see also section 2.2.1). Yet tests remain highly costly, time-consuming, and detrimental to animal welfare, so that the EEA has concluded that it is "unsustainable to subject every suspect chemical to such exhaustive testing" (ibid., p. 20).

4.1.2 Risk characterization and risk evaluation

At the level of the EU, the key actors involved in the decision process regarding whether the risk of endocrine disruptors are acceptable, tolerable, or intolerable are most essentially the legislative institutions of the European Parliament and the Council. Indeed, the European Court of Justice writes in its judgment on Du Pont de Nemours that "the responsibility for determining the level of risk which is deemed unacceptable for society lies […] with the institutions responsible for the *political choice* of determining an appropriate level of protection for society" (case T-31/07, paragraph 145, emphasis ours).

This implies that there are two levels of governance in the EU when it comes to risk characterization and risk evaluation:

1. Legislative level, which includes the Council of the EU and the EP;

2. Level of competent authorities, which encompasses EU agencies.

It is thus subsequently up to ECHA and EFSA, as the competent authorities on EDCs, to make an assessment about "the level of risk deemed unacceptable for society [for] each individual case" (paragraph 147; see further below under 2.3.1.4).

As discussed in the sections above, however, it has been very difficult and time-consuming to characterise the risks that EDCs pose, given the very complex nature of these chemicals and the resulting uncertainty about their adverse health effects. The EU criteria for assessing the level of the risks of chemicals in general have, however, been science based.

This means that they draw on a 'weight of evidence' approach. Given the complexity of endocrine disruptors, a report of the Dutch National Institute for Public Health and the Environment, for example, mentions that the "data requirements in the current legislation [do] not supply enough information" for identifying EDCs (Dang et al., 2016, p. 3).

Crucially, therefore, the discussion about endocrine disruptors has not just concerned the question of whether the risk that EDCs pose is acceptable, but more importantly also the question of whether it is acceptable to postpone the (further) development of a "risk assessment and regulatory framework for dealing with incomplete knowledge about EDCs" (EEA, 2012, p. 20). Several parties and stakeholders in the debate have deemed this unacceptable. Apart from scientists (e.g. EEA, 2012), these include NGOs and consumer organisations (see e.g. BEUC 2016), as well as the European Parliament.

4.1.3 Risk management

At the stage of making legislation on endocrine disruptors, it is thus up to the co-legislators of the European Parliament and the Council to take decisions. Notably, the European Parliament has explicitly emphasized the precautionary principle in several of its resolutions on endocrine disruptors. Its 2013 "*resolution on the protection of public health from endocrine disrupters*" is most notable in this regard. In this resolution, the EP "call[ed] on the Commission to revise its EU strategy on endocrine disrupters so that it delivers effective protection of human health by placing greater emphasis on the precautionary principle, while observing the proportionality principle, to work towards reducing human exposure to endocrine disrupters where necessary" (European Parliament, 2013, paragraph 17, emphasis ours).

At the stage of risk assessment and management of (potential) EDCs, it is usually the European Commission that is most importantly tasked with the formulation of the scientific criteria for the identification of EDCs, and that has to take the final decisions on risk assessment and management. EU agencies ECHA and EFSA have a very important 'advisory' role by producing so-called 'opinions' about the risk. The roles of the European Commission and the EU agencies, however, depend on the specific piece of legislation (see further below).

The stage of risk assessment involves the various committees of the two agencies. These are the Committee for Risk Assessment and the Committee for Socio-Economic Analysis of ECHA, and the Scientific Panels and Scientific Committee of EFSA. At EFSA, the scientific committees mostly only deal with the risk assessment and leave all considerations in relation to the precautionary principle up to risk managers. At ECHA, the strict division of roles between risk assessors and risk managers is less clear. These differences reflect the different traditions in these two agencies, namely, to regulate based on a risk approach or on a hazard approach (see further below).

Finally, at the stage of disputes, the ECJ is involved in making judgments about the (correct) application of the precautionary principle (see further below).

4.2 Legal and regulatory framework

4.2.1 Legal and regulatory history

As chemical substances that are by far and large synthetic, endocrine disruptors are regulated under EU law. The precautionary principle is detailed in Article 191 of the Treaty on the Functioning on the European Union and may thus be invoked for the risk management of EDCs. In practice, EDCs are regulated under various pieces of EU regulation (see the 'List of EU legal acts under which EDCs are regulated' below). This is the result of their use in diverse products that are regulated under different pieces of legislation, including pesticides, food contact materials and cosmetics. Strikingly, "different regulatory approaches exist in different pieces of legislation for substances identified as

endocrine disruptors" (European Commission, 2018, p. 9). There is thus no harmonised EU legal framework on EDCs (see e.g. Dang et al., 2016).

There is no harmonised EU legal framework on EDCs.

First, the regulation of EDCs relating to the environment, which is established in the Biocidal Products Regulation (BPR) and Plant Protection Products Regulation (PPPR), is explicitly "underpinned by the precautionary principle" (Article 1(4) of Regulation 1107/2009 and Article 1(1) of Regulation 528/2012). Thus, for the BPR and PPPR, a substance that has been identified as an EDCs is "as a general rule […] banned on the basis of hazard". There are only limited possibilities for derogation – that is, deviating from the rules for a limited period – in view of risks or socio-economic issues (Dang et al., 2016, p. 11). In developing these pieces of legislation, the EP and the Council considered that there is ongoing scientific uncertainty regarding the assessment of EDCs (European Commission, 2018, p. 9).

The European Court of Justice has also established the applicability of the precautionary principle in this area. In its judgment on Du Pont Nemours, the Court established that the precautionary principle must be applied in the authorisation of chemicals and assessment of approval criteria under the Plant Protection Products regulation (T-31/07, paragraphs 133, 152-153). Previously, in its judgment on Gowan, the ECJ considered that the existence of differing scientific opinions provides sufficient ground for uncertainty to apply the precautionary principle (C-77/09, paragraphs 76-79).

It is crucial to note, however, that the development of scientific criteria for the identification of EDCs under the BPR and the PPPR was severely delayed by the European Commission. These criteria had been due by December 2013. In the case of Sweden against the Commission, the ECJ ruled that the impact assessment proposed by the European Commission proposed was unnecessary (see further below, under section 2.5). In an unprecedented judgment, the Court ultimately concluded that the Commission had failed to act in accordance with EU law by failing to adopt, in time, the necessary delegated acts to establish scientific criteria on EDCs (T-521/14).

Second, and in contrast to legislation on the environment, regulation of EDCs relating to the area of health and food safety is not based on the precautionary principle. Rather, endocrine disruptors are considered "like other substances that can negatively affect human health" (European Commission, 2018, p. 9). Different authorities can, however, still prohibit the use of chemicals that have – or are suspected to have – endocrine disrupting properties on a case by case basis. At the level of the EU, this has, for example, been the case for the substance of bisphenol A (see the table below). Some national authorities, such as in Denmark, had already previously banned bisphenol A from specific products.

Third, also under REACH, which is part of EU regulation on the internal market, EDCs can be subject to authorisation. Here, chemicals suspected of having endocrine-disrupting properties are subject to a risk assessment or socio-economic analysis to establish "whether a threshold (safe level) or non-threshold approach is to be applied" (Dang et al., 2016, p. 11). Yet the essential element in comparison with the BPR and the PPPR is that there is no general legislative ban for EDC. Under REACH (1907/2006), EDCs are mentioned in Article 57(f) and thereby subject to the authorization procedure for a so-called 'substance of very high concern' (SVHC) under article 59. If the criteria of Article 57 (f) are fulfilled, the (potential) EDC can be put first on the candidate list and then in Annex XIV containing substances of very high concern. Only then, the EDC is subject to the authorisation requirement.

Two judgments of the European Court of Justice are important with regard to the standard of proof required to identify a substance as a SVHC based on endocrine-disrupting properties. First, in its ruling on Deza versus ECHA (T-115/15 and C-419/17), the Court considered that the "*probability* that an endocrine disruptor may have adverse effects on the environment is sufficient" to label a chemical as a SVHC (paragraph 173, emphasis ours).

Second, in its ruling on Plastics Europe versus ECHA, the Court confirmed this judgment with regard to identifying a chemical as an endocrine disruptor to human health. It considered that findings about the hazard of chemical "should be based on the 'possible' undesirable effects of that substance, not the 'probable' effects". The Court also considered the risk properties of ambiguity and uncertainty. That is, it found that "negative or merely inconclusive epidemiological studies cannot invalidate positive studies in animals", given that there are uncertainties in such studies (T-636/17).

Importantly, these judgments demonstrate that the ECJ in fact interprets Article 57 (f) in line with the precautionary principle, despite the wording of the article being rather strict in terms of establishing the threshold of damage (see further below).

List of EU legal acts under which EDCs are regulated

Regulations relating to the environment
Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC
Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products
Commission Delegated Regulation (EU) 2017/2100 of 4 September 2017 setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council
Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties

Regulations relating to health and food safety
Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC
Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food
Commission Implementing Regulation (EU) No 321/2011 of 1 April 2011 amending Regulation (EU) No 10/2011 as regards the restriction of use of Bisphenol A in plastic infant feeding bottles Text with EEA relevance
Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products
Commission Regulation (EU) 2018/213 of 12 February 2018 on the use of bisphenol A in varnishes and coatings intended to come into contact with food and amending Regulation (EU) No 10/2011 as regards the use of that substance in plastic food contact materials

Regulations relating to the internal market
Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

List of key European Court judgments on EDCs

Case	Parties	Subject	Details
T-31/07	Du Pont de Nemours (France) and Others v Commission	Agriculture and Fisheries - Plant health legislation Environment	Action against restrictions on the use of flusilazole under Directive 91/414. ECJ dismissed action.
C-77/09	Gowan Comércio Internacional e Serviços	Agriculture and Fisheries - Plant health legislation	Action against restrictions on the use of fenarimol under Directive 2006/134/EC. ECJ dismissed action.
T-521/14	Sweden v Commission	Failure to act	Action against failure to adopt delegated acts specifying scientific criteria for identifying EDCs under Article 5(3) of Regulation (EU) No 528/2012. ECJ adjudged action.
T-115/15	Deza v ECHA	Environment Public Health	Application seeking annulment of ECHA decision to identify DEHP as a substance with endocrine-disrupting properties under Article 57(f) of REACH. ECJ dismissed action.
T-108/17	ClientEarth v Commission	Research and technological development	Application seeking annulment of a Commission letter rejecting a request for internal review of the authorization of DEHP under REACH. ECJ dismissed action (that is, the Commission was correct in rejecting the internal review request).
T-125/17	BASF Grenzach v ECHA	Research and technological development	Action for the partial annulment of an ECHA decision dismissing an appeal against a decision requesting further information about Triclosan and fixing a deadline for presenting that information. ECJ dismissed action.
C-419/17	Deza v ECHA	Environment Public health Research and technological development	Appeal to the ECJ's judgment in T-115/15. The ECJ dismissed appeal.
T-636/17	PlasticsEurope v ECHA	Research and technological development	Application seeking annulment of ECHA decision to identify bisphenol A as a substance with endocrine-disrupting properties under Article 57(f) of REACH. The ECJ dismissed action.
T-207/18	PlasticsEurope v ECHA	Environment Public health	Application seeking annulment of ECHA decision to identify bisphenol A as a

			substance of very high concern based on Article 57(f) of REACH. Judgment pending.
T-640/19	Sasol Germany and Others v ECHA	Research and technological development	Application seeking annulment of ECHA decision to include 4-tert-butylphenol (PTBP) as a substance of very high concern in Annex XIV of REACH. Judgment pending.

4.2.2 Threshold of damage

The EU regulations that govern endocrine disruptors require an evaluation of whether there is an acceptable level of exposure to EDCs – that is, a 'threshold' – or not (see below under section 2.4.1). The REACH regulation, for example, stipulates that a chemical safety report "requires a quantification of the risk to human health, unless it is not possible to determine a derived no-effect level (DNEL) and a predicted no-effect concentration (PNEC) (ECJ, case T-108/17). For chemicals suspected of having endocrine-disrupting properties, the relevant regulatory agencies, EFSA and ECHA, have thus evaluated whether there is an acceptable level of exposure – that is, a 'threshold' – for both humans, animals, and the wider environment, or not.

At the same time, from the scientific analysis of and scientific uncertainty about endocrine disruptors, it follows that the way in which EDCs act "undermines the traditional risk assessment paradigm of a threshold dose below which a chemical fails to produce effects" (EEA, 2012, p. 18-19). This is most importantly the result of the issues of the mixture and low-dose effects discussed above (see also Gore et al., 2015). A large degree of uncertainty also remains about the hazard of EDCs.

Against this background of regulatory practices and requirements, on the one hand, and scientific complexities and uncertainties about EDCs, on the other, there has been debate about the 'threshold of damage'. Industry has, for example, challenged the level of exposure of various EDCs that would require or justify regulatory measures, also in legal cases at the ECJ (see the table above). Strikingly, given that there is no harmonized EU regulatory framework on EDCs, the threshold of damage can be – and has been – defined differently by different authorities, even in cases in which it concerns the same (potential) endocrine disruptor.

Perhaps the most illustrative court case in this regard is that of Plastics Europe versus ECHA (T-636/17) concerning the chemical bisphenol A (BPA). Plastics Europe sought the annulment of an ECHA decision to include BPA on the candidate list for substances of very high concern. It referred to opinions of EFSA. Indeed, for bisphenol A, there are safe levels for use in EU legislation on food contact materials and on chemicals in toys (T-636/17). In this respect, EFSA has issued an opinion on a "Tolerable Daily Intake" of bisphenol of 4 µg/kg body weight (EFSA, 2015).

The threshold of damage can be – and has been – defined differently by different authorities, even in cases in which it concerns the same (potential) endocrine disruptor.

ECHA, however, has nevertheless listed bisphenol A as a substance of very high concern in the candidate list for authorisation under the REACH regulation. This means that it can be considered as a non-threshold substance, which means that it is dangerous at any level. The agency most importantly considered that it was too difficult to establish a safe threshold. Amongst other reasons, this was due to uncertainties about the dose-response relationship; studies that showed effects at doses lower than previous starting points used for deriving a no-effect level; and changing levels of sensitivity depending on the window

of exposure. The European Court found that specific limits being established in the context of some legislation does not preclude different conclusions in the context of other legislation, given the existence of overall uncertainties about safe thresholds (case T-636/17).

4.2.3 Reversal of burden of proof

As one of the co-legislators in the EU, the European Parliament has in the past explicitly requested a reversal of the burden of proof on EDCs in the context of the 1999 Community strategy for endocrine disrupters (resolution A5-0197/2000). That is, the responsibility for providing the information necessary to approve a chemical should be with the producer rather than with the national or European authorities.

In principle, some regulations that concern chemicals with (potentially) endocrine-disrupting properties indeed specify a reversal of the burden of proof. The Plant Protection Products Regulation states that "an application for the approval of an active substance or for an amendment to the conditions of an approval shall be submitted by the producer of the active substance […] together with a summary and a complete dossier". Such a dossier should include summaries and tests of all data requirements that the Commission has set out for the chemical (1107/2009, article 7). The BPR likewise requires an authorisation, so that one could argue that the regulation has reversed the burden of proof: to get an authorisation, certain information and proof needs to be provided.

Yet also here, the standards for the information that producers have to submit are, however, different in the context of different regulations (e.g. compare 528/2012, articles 6, 7 and 8; 1907/2006; 10/2011, article 16). It has also been argued that in practice, even when standards for information that producers need to supply are comparatively high, "poor information provided […] in the registration dossiers shifts the burden" to complete risk assessment information 'back' to national authorities and EU agency committees (EEB, 2017).

In the context of regulation 1107/2009 on plant protection products, the ECJ has made some relevant judgments regarding the precautionary principle and the burden of proof. Most notably, while the ECJ confirmed the reversal of the burden of proof, it also pointed out that the burden of proof is on the Commission when the Commission reviews a chemical before the end of a temporary approval period. The Court explained that this is also the case if the Commission invokes the precautionary principle for such a review. Nonetheless, the Court establishes that "the Commission discharges the burden of proof" if the Commission establishes that the initial approval criteria are "invalidated by subsequent regulatory or technical developments". Since the PP can be one basis for the withdrawal or amendment of approval, the Commission "need do no more than provide […] solid and convincing evidence which, while not resolving scientific uncertainty, may reasonably raise doubts as to" whether the substance satisfies the criteria (see cases T-429/13 and T-451/13).

The REACH regulation is different from the PPPR and the BPR. Here, the regulation itself does not establish the authorisation requirement. Only in case the Commission has added a substance to Annex XIV, the authorisation requirement applies. Therefore, first, the Commission has to proof that criteria of Article 57(f) are met. One could therefore argue that the burden of proof is not reversed by the regulation itself, but may be reversed in case the Commission adds an endocrine disruptor to first the candidate list and then Annex XIV.

4.3 Gender considerations and the risk governance framework

For both females and males, endocrine disruptors have been linked to the presence of hormone-related cancers and infertility (see section 3 on the on the threat posed by EDCs). There was "a major international review of environmental influences on male health"

already in the 1990s, after Scandinavian research showed a relation between environmental exposures and falling sperm counts (Schug et al., 2016, p. 836). Yet it is also clear that female and male bodies are affected by endocrine disruptors in different ways, given their different hormonal systems. Two further considerations are important to mention concerning gender differences in knowledge about and exposure to EDCs.

First, and "in contrast to male infertility, there is surprisingly limited knowledge on the mechanisms by which EDCs can impair female reproduction and test methods to address this" (FREIA, female reproductive health). One of the underlying problems is that it is more difficult to assess how EDCs affect the quality of egg cells other than in terms of their sheer number, particularly in comparison to sperm cells – not least because the retrieval procedure is more invasive. Moreover, disturbance of the embryonic development of the female reproductive system can lead to infertility only at a much later stage, for instance at the age of thirty (van Kessel, 2019). Current test protocols are especially ill-suited to pick up the effects of such early exposure (FREIA, improving test methods). Apart from infertility, EDCs can or may also be linked to endometriosis, polycystic ovary syndrome, premature ovarian insufficiency or failure, irregular menstrual cycles and ovarian cysts (FREIA, female reproductive health).

> *"In contrast to male infertility, there is surprisingly limited knowledge on the mechanisms by which EDCs can impair female reproduction* (FREIA, female reproductive health)*"*

Second, precautionary or preventive measures against the adverse health effects of EDCs by far and large concern females, as exposure during pregnancy can harm both the embryonic and later development of a child. This is why pregnant females are often mentioned as being "vulnerable" to EDCs (e.g. Wemos, 2018). The extent to which government organisations provide information about the potential hazards of endocrine disruptors during pregnancy varies, however, between member states. Some member states, such as Denmark, provide extensive information about how to prevent exposure to (potentially) harmful chemicals during pregnancy (Danish Ministry of the Environment, n.d.). Other member states, such as the Netherlands, do not (van Kessel, 2019; Wemos, 2018).

Indeed, there seems to be inadequate access to information about what are the effects of EDCs for pregnant women across EU member states. On a more positive note, one can point to several initiatives - such as 'Gender and chemicals' Initiative, the EDC-Free Europe Initiative or the FREIA project. All these try to raise attention for the effects of the exposure of EDCs for women, children and the unborn.

It is not entirely clear in how far EU risk governance of endocrine disruptors is sensitive to such gender differences. The lack of proper tests for establishing the health hazards of EDCs is seen as a key problem when it comes to female reproductive health (FREIA, improving test methods). The latest Communication on the development of a new EU framework on endocrine disruptors mentions that "the Commission will encourage Member States *which deem it necessary* to develop specific information and educational campaigns" on EDCs (European Commission, 2018, p. 11, emphasis ours). All in all, it seems that the EU's current, evidence-based, risk management approach to endocrine disruptors can be deficient particularly for protecting the health of females and for ensuring adequate access to information about exposure to EDCs during pregnancy across EU member states.

On a more positive note, the NGO 'Women Engage for a Common Future' (WECF) has started the 'Gender and Chemicals' Initiative. It is one attempt to raise more awareness for the adverse effects of chemicals in general – and EDCs in particular – for women's health. Here women's priorities for stronger waste and chemical policies are disseminated through TV and social media, for example (see WECF, n.d.). The EDC-Free Europe Initiative

also tries to raise attention for the effects of the exposure of EDCs for women, children, and the unborn (see EDC-Free Europe, n.d.).

5 The precautionary principle and its future

5.1 Reflection on the PP in the literature

There has been considerable public pressure to adopt a more comprehensive precautionary approach to the regulation of endocrine disruptors. This pressure comes both from academia, stakeholders such as consumer organisations, think tanks and NGOs, as well as from (some political parties in) the European Parliament. To them, the issue of endocrine disruptors is a pressing and major societal risk, of which regulation through the traditional science-based EU regulatory framework would take too long. However, there are differences between those who advocate a scientific and a "non-scientific use of the precautionary principle" (Lofstedt, 2014, p. 155).

In advocating more precaution, academics from various disciplines often make reference to the uncertainties surrounding both the hazard and exposure to endocrine disruptors (see above under section 3.1.3) (e.g. EEA, 2012; Gochfeld, 2003; Klinke & Renn, 2001; Tijani et al., 2016). Influentially, also the Endocrine Society has invoked the precautionary principle. In its first Statement, for example, the Society considered that "in the absence of direct information regarding cause and effect, the precautionary principle is critical to en- hancing reproductive and endocrine health" (Diamanti-Kandarakis et al., 2009, p. 326).

In its second Statement, it further elaborated on the application of this principle. Importantly, it considers that inferences about adverse human health effects drawn from studies that show that a chemical interferes with hormones that "are essential for normal development" are often considered to be precautionary (Gore et al., 2015, p. 601). Yet even though such inferences about adverse effects may not fully characterise the adverse effect, they are still *science-based*. The Society advocates more precaution not just given the uncertainties surrounding EDCs and their potential long-term and chronic effects, but also noting that "it simply is not reasonable to assume a chemical is safe until proven otherwise" – as exemplified by the introduction of regrettable solutions (p. 602; see further below).

Given the tension or "dilemma" between a perceived need for precaution and time-consuming frameworks for risk regulation (Munck af Rosenschöld, Honkela & Hukkinen, 2014), there have been several public controversies over particular chemicals with (suspected) endocrine disrupting properties. The most well-known controversy is that of bisphenol A (BPA). That is, whereas there are many hundreds of studies of BPA, there are still two sides to the debate of whether the evidence is sufficiently strong and conclusive to ban BPA – most importantly from food packaging and other consumer products. The combination of public pressure and the scientific "division in opinion has resulted in different countries' regulatory agencies deciding on different risk-management strategies for BPA" (Siva, 2012).

This is also the case within the EU, in which Denmark was the first BPA from food containers for young children in April 2010. Other EU member states followed suit, including Belgium, Sweden, and France – the latter banning BPA from all food contact materials (European Parliament, 2018). Commission Directive 2011/8 on plastic feeding bottles did invoke the precautionary principle to prohibit use of BPA. Yet in 2015, EFSA nevertheless established that there is "no health concern for […] dietary exposure" and "low health concern from aggregated exposure". It hence identified a tolerable daily intake for BPA (EFSA, 2015).

The EFSA opinion was heavily criticized by various stakeholders in the public debate, who want to ban BPA also from other products than baby bottles by invoking the (non-scientific use of the) precautionary principle. Other organizations want to embed the precautionary principle more comprehensively in the system of risk governance. The European Consumer Organization BEUC, for example, finds that the "precautionary principle should therefore be enshrined in the legal text of the FCM Regulation as the basis for risk identification, assessment, and management" (2019, p. 8; see also WEMOS, 2018).

Indeed, in this context, Lofstedt (2014) has criticised the way in which the precautionary principle is currently applied by and in the European Union – drawing on the regulation of EDCs as an example of poor use of the precautionary principle. He, for example, notes that the 2013 EFSA opinion on the hazard assessment of EDCs did not mention the 2002 Commission Communication on the precautionary principle. Yet neither did the European Parliament's resolution on the EFSA opinion that did invoke the precautionary principle contain an explanation of what the implementation of the PP would actually entail. In view of the "dilemma" concerning the regulation of EDCs, in the long term he – amongst other recommendations – calls for open support to the EU regulatory agencies from "neutral, evidence-based and trusted third parties such as senior academics". To him, such alliances may help to rebuild public trust in "science-based policy making" (2014, p. 155).

5.2 Effect of the PP on innovation pathways

We did not find evidence that potential benefits of innovation were taken into account in applications of the precautionary principle in regulatory decisions on EDCs. Rather, bans on the use of particular EDCs have in the past led to 'regrettable substitutions' – that is, the introduction or adoption of chemicals that may not be safer and potentially worse.

It can be argued that such substitution is facilitated by the case-by-case approach of current EU regulations that govern endocrine disruptors. That is, a chemical that is highly similar to a previously banned chemical is not automatically also banned. Rather, it has to go through the time-consuming process of risk assessment and risk management separately (van Kessel, 2019). Financially, there is thus an incentive for industry to develop substitutes that are similar to those chemicals that have been regulated – even when the hazard of these substitutes to humans, animals and the environment are uncertain (see e.g. Camboni, 2017, p. 76-78).

The most prominent example of regrettable substitution is that of bisphenol A (BPA) with the substance bisphenol S (BPS). BPA can be found in a great many products that people use on a daily basis, such as baby and water bottles, food storage boxes, and sales receipts. After scientists discovered the adverse health effects of BPA – and particularly after regulatory restrictions on BPA and societal pressure in the 2010s – the plastics industry sought an alternative to BPA. Manufacturers even started to sell products with a 'BPA-free' guarantee. Yet to produce such BPA-free products, the industry "turned primarily" to BPS, which is "a structural analogue of BPA (Žalmanová et al., 2016, p. 440). BPS has been shown to have endocrine-disrupting properties highly similar to BPA (Žalmanová et al., 2016), as have other varieties of bisphenol that became more commonly used as substitute chemical (for an overview, see CHEMTrust, 2018, p. 12).

The regulation of certain EDCs can thus lead to a domino effect, in which there are new complexities, uncertainties and ambiguities about the hazards and risks of regrettable substitutes. At the same time, it has also been argued that the presence of certain exceptions regarding the use of EDCs, which, for example, exist for medical devices, has been a disincentive for the development of alternatives. This, for example, was said to concern the presence of phthalates in blood bags. From this perspective, hence, "innovation must be driven by focusing on the demand side" rather than by legislation, which "takes too long" (Jones, 2013). Possible pathways to create such 'demand' for innovation are the development of letters of intent to buy new products that are free of EDCs, as well as public scrutiny of the behaviour of global brands (ibidem).

Green chemistry seems to be one important innovation pathway towards developing chemicals that are non-regrettable substitutions for identified or suspected EDCs. Whereas reducing the risk of chemicals has conventionally been focused on reducing or avoiding *exposure*, green chemistry is based on avoiding *hazard* in the first place (e.g. Khetan, 2014; Schug et al., 2013). Moreover, the current approach to regulating (potential) endocrine disrupting substances has been on a case-by-case basis, while green chemistry advocates a re-thinking of the sector approach. In journals such as *Green Chemistry*, scientists have reported on the absence of endocrine activity of bio-based alternatives for EDCs. This, for example, included chemicals like 2,5-FDA which can substitute the commonly used industrial polyesters phthalates, such as in re-useable water bottles and textile fibres (e.g. van Vugt-Lussenburg et al., 2020).

Scientists working within the area of green chemistry, however, also encounter the complexities and uncertainties in establishing potential endocrine-disrupting activity of substitute chemicals, as these are inherent to the current state of science on EDCs. To forestall this, it has been proposed that chemists and toxicologists in Green chemistry work more closely together on endocrine disruption (Schug et al., 2013).

Green chemistry seems to be one important innovation pathway towards developing chemicals that are non-regrettable substitutions for identified or suspected EDCs.

Political initiatives and policy steps towards the development of a circular or bio-based economy can be seen as another important 'push' for innovation on the front of substituting EDCs (e.g. BEUC, 2018, p. 5-6; RIVM, biobased materials). This includes the European Green Deal, which recalls the need to establish a "ensure a toxic-free environment" (European Commission, 2019, p. 14). The European Green Deal does not, however, mention the precautionary principle as a tool towards stimulating green or sustainable innovation. Rather, the Commission highlights the importance of "simplifying and strengthening the legal framework", including a "move towards a process of 'one substance – one assessment'" (ibid., p. 14). In this context it is noteworthy that stakeholders and NGOs have called for a chemicals strategy as part of the European Green Deal in 2019. Here, the Commission is reminded of her commitment to manage the risks arising from EDCs and as such to deliver on the EU strategy to address ECDs, which is 20 years old (see e.g. EEB, 2019).

Indeed, NGOs and think tanks, as well as political parties on the left/green spectrum of the political debate have brought up so-called 'sustainable innovation' as an alternative to the current approach (e.g. IEEP, 2019). These organisations, for example, contend that applying the precautionary principle to all EDCs can "boost eco-innovation in finding sustainable and safer substitutes" (IEEP, 2019).

Also here, however, there are numerous complexities linked to innovation pathways when it comes to the circular economy. Clearly, one of the "greatest obstacles" to a circular economy is that of "'legacy substances'". These are substances that remain in the environment, as older products contain(ed) chemicals that were restricted or banned at a later stage only (BEUC, 2017, p. 4). For example, the phasing out of the phthalate DEHP would take about 15 years, while the phasing out of BPA would take about 30 years (EEA, 2017, p. 10). Some have therefore also invoked the precautionary principle on the basis of the argument that the EU needs to avoid such legacy, toxic substances in the move towards a circular economy (BEUC, 2017; 2018).

5.3 Innovation principle

Some stakeholders in the discussion about EDCs, mostly from the chemicals industry, have invoked an 'innovation principle'. Their idea is that an innovation principle would

"require[e] to take into account the potential impacts of precautionary action on innovation" and "protect Europe's ability to innovate and to compete with other countries" (see RECIPES conceptual framework). Stakeholders who have advocated this include the UK-based Chemical Industries Association (CIA), the Brussels-based European Chemical Industry Council (Cefic), and the European Risk Forum (ERF), but not the pan-European association of plastics manufacturers, PlasticsEurope.

There are a few explicit communications that link the innovation principle to the topic of chemicals suspected or proven to have endocrine-disrupting properties. Interestingly, these communications draw on examples of the regulation of chemicals with (potential) endocrine disrupting properties to argue in favour of an innovation principle.

Notably, the UK-based Chemical Industries Association has argued that "there is a danger […] that innovation be hindered where benefits of new technologies and solutions cannot be considered alongside potential risks, an example being a cancer treatment drug that uses the mechanism of *endocrine disruption* to kill cancer cells" (CIA, 2019, emphasis ours). CIA goes on to signal a dilemma between precaution and innovation, and to argue that "this dilemma can not be solved by the precautionary principle alone, but should be addressed by application of both principles, alongside each other, in a complimentary sense" (CIA, 2019).

As one example of a "hampering" regulation showing the necessity for an innovation principle, CIA brings up the labelling of the phthalate DEHP as a substance of very high concern under the REACH regulation. It argues that this labelling resulted in the closing down of a recycling plant for the plastic polyvinylchloride (PVC) that had obtained authorisation to recycle PVC containing DEHP. This was because "customers no longer wanted to buy PVC containing an SVHC" in part due to the "loss of the 'green' credentials of the recyclate". For CIA, this "unfortunate and unintended consequence" would have been prevented by including the innovation principle in EU legislation.

It is also notable that in its influential 2015 document setting out the 'innovation principle', the ERF explicitly mentions examples of chemicals that were regulated given (uncertain) evidence about endocrine-disrupting activity. Discussing public attitudes towards risks, ERF brings up EU regulation of endocrine-disrupting neonicotinoid insecticides. It argues that this is an example of a regulation that is not based on scientific risk assessment and established toxicological models. For ERF, such "systemic short-term risk aversion" and "inappropriate and disproportionate" use of the precautionary principle unnecessarily amplifies public concerns (ERF, 2015, p. 15).

6 Synthesis

Endocrine Disrupting Chemicals (EDCs) are a 'textbook case' for the complexities surrounding the application of the precautionary principle as they:

- Are **widely prevalent** and can be found in products we use every day – reaching from shampoo to medication. The potential hazards stemming from EDCs are thus not limited in scope. Health risks both for humans and wildlife associated with EDCs became increasingly apparent during the 1990s. A number of authorities, reaching from the World Health Organisation to the European Commission, commissioned studies to investigate the potential harm caused by EDCs.
- Yet problematically, even the very **definition** of EDCs remains very much contested, as do the scientific processes and methods through which to identify them. While this an issue not limited to EDCs (see e.g. the RECIPES case studies of Urlings on microplastics, or Gaszo and Pavlicek on nanotechnologies), to define which chemicals or substances are in fact to be considered as EDCs is key. This in turn has important implications for how they are regulated.

- This then gives rise to a **dilemma** with the regulation of ECDs as Munck af Rosenschöld, Honkela and Hukkinen (2014) point out. On the one hand, there is considerable societal pressure to regulate ECDs 'now'. This quick regulation is, on the other hand, impossible as there is not enough quantitative evidence for the risk that prevails. To come up with such evidence is time intensive, which leads to postponing regulation and only "increases the societal pressure to regulate now" (p. 29-30).

- This dilemma is very much apparent in what has been coined a "**regulatory stalemate**" that the EU is currently facing when it comes to "the risk assessment required under the **precautionary principle"** (Garnett, van Calster & Reins, 2018, p. 12). It is the nature of the system – or the 'path dependency' of the EU criteria for the regulation of risks – that makes quick action on the basis of invoking a precautionary principle impossible. Several of the controversies surrounding EDCs, such as on bisphenol A and on the Commission's delay to formulate scientific criteria for identifying endocrine disruptors, are illustrative of this "paralysis" (Munck af Rosenschöld et al. 2014). This is also linked to the fact that there is always a 'need for more research'. Science, by its nature, searches for the remaining uncertainties, which then overemphasizes the amount of uncertainty.

- Closely linked to this observation is the fact that reversing the **burden of proof** is often practically unfeasible and very costly, when the precautionary principle is playing 'catch-up'; is lagging behind. If one needs to test for a very large number of potential EDCs this could bring the entire chemical industry to a halt. Moreover, reversing the burden of proof is also often ineffective. In practice, even when standards for information that producers need to supply are comparatively high, poor information is provided in the registration dossiers, which in turn can shift the burden to complete risk assessment information 'back' to national authorities and EU agencies (EEB, 2017).

- As shown in our case study, even if ECDs are regulated, this can lead to **regrettable substitutions**, which can be seen as a 'lose-lose scenario': it is costly for the regulator and costly for the company in question. This could be avoided by way of more coordination. Closely linked is the fact that case-by-case regulation creates incremental innovation, while far-reaching regulatory approaches – by way of joining forces with industry – can lead to radical innovation. It comes as no surprise that companies are hesitant to embrace radical innovation such as Green chemistry. At the global level we thus see a **coordination problem**: locally, incremental innovation is safer and more profitable, given that other industries are not co-investing. However, globally, radical innovation can be seen as more profitable. Here public-private cooperation is required to create the critical mass necessary for radical innovation. In this context we also need more of a debate on the role of regulatory agencies in the context of radical innovation. Could they play an active role in creating incentives for radical innovation and reward respective initiatives?

- Overall, **time** available is of the essence for a thorough regulation of ECDs. As pointed out above, the precautionary principle calls for quick action, which is difficult to address due to the lack of clarity on *how* to regulate. Taking decisions too quickly can on the one hand lead to sub-optimal solutions. Yet taking a slow regulatory approach can cause delays. As shown, in the EU the delay by the Commission to take regulatory decisions concerning EDCs has been the result of lobbying activities, especially by the chemical industry. Here we come back to the dilemma raised at the outset: *How to take time, but address the issue in a diligent and thorough manner?* This in turn is linked to larger societal issues of transparency and the role of lobbyists: *How can the public distinguish between 'regulators taking a slow but diligent approach' and 'regulators being delayed by lobbying activities'?* We thus see the need for **regulatory transparency**. Processes and the inclusion of different interests and views have to be apparent to stakeholders and the interested public.

7 Conclusion

Endocrine disruptors are at the centre of a scientific and regulatory debate since several decades. Following debates and the 1991 Wingspread conference on EDCs in the United States, the EU did try to be 'ahead of the game' by compiling scientific evidence on EDCs already in the 1990s. The 1996 meeting in Weybridge, which was sponsored by the European Commission, brought together experts from the WHO, the OECD, and Ministries and Institutes and Ministries of the Member States. Here, a considerable degree of consensus was noted between the "various assessments and reports on the **need to take urgent action** to address the uncertainties and gaps in our knowledge and the potential dangers to human and wildlife populations from endocrine disrupting chemicals" (Bergman et al., 1997, p. 103). Moreover, a definition of what can be seen as an EDC was provided.

The fact that this issue of regulating EDCs was on the EU's radar rather early, could lead one to expect a high level of regulation and a coherent approach. The opposite is the case, however. EDCs can be seen to have sparked **institutional controversy**. As mentioned above, the development of scientific criteria for the identification of EDCs under specific regulations in the environmental domain was severely delayed by the European Commission. A Member State (Sweden) then took the Commission to Court in 2014. Here, the ECJ ruled in a landmark case that the Commission had failed to act in accordance with EU law.

The European Court of Justice has also established the applicability of the precautionary principle in this area. Accordingly, the Court established that the precautionary principle must be applied when authorising chemicals and assessing approval criteria. The European Parliament has also explicitly emphasized the **precautionary principle** in several of its resolutions on endocrine disruptors. For instance, in a 2013 resolution the EP called on the Commission to put greater emphasis on the precautionary principle in order to reducing human exposure to endocrine disrupters where necessary.

This, however, did not change the **regulatory approach** of the EU regulatory authorities towards EDCs substantially, nor did this impact on its use and application of the precautionary principle. The Commission can be seen as not to act systematically on the basis of the precautionary principle in the context of EDCs. Most notably, a 'horizontal definition' of EDCs is missing and the Commission's formulation of standards of proof are seen to be unattainable in practice. Moreover, "different regulatory approaches exist in different pieces of legislation for substances identified as endocrine disruptors" (European Commission, 2018, p. 9). There is thus no harmonised EU legal framework on EDCs.

One key problem for establishing the health hazards of (potential) EDCs is the **absence of proper tests**. This is seen as a major issue especially when it comes to **female reproductive health.** Overall, it seems that the EU's current, evidence-based, risk management approach to endocrine disruptors can be deficient particularly for protecting the health of women.

The question is to be raised of how to **move forward** given that the risk properties of endocrine disruptors are not only highly complex, but that endocrine-disrupting action is seen to go against all the rules and assumptions that toxicology builds on. Bans on the use of particular EDCs have actually led to so-called 'regrettable substitutions': that is, the introduction or adoption of chemicals that may not be safer and potentially worse. The most prominent example of regrettable substitution is that of bisphenol A (BPA) with the substance bisphenol S (BPS).

In this context, **green chemistry** can be regarded as one important innovation pathway in order to develop chemicals that are non-regrettable substitutions for EDCs. Green

chemistry is based on avoiding *hazard* in the first place. Note that scientists working within this field, however, also encounter the complexities and uncertainties in establishing the potential endocrine-disrupting activity of substitute chemicals. To overcome this dilemma, it has been proposed that chemists and toxicologists in Green chemistry join forces. It remains to be seen whether this will lead to the much sought for breakthrough in a highly complex domain characterised by high uncertainty and unpredictability.

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