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Endocrine disruptors

An overview of latest developments at European level in the context of plant protection products

STUDY

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Endocrine disruptors: An overview of latest developments at European level in the context of plant protection products

Endocrine disruptors are chemical substances present in many products used in daily life, which interact with the hormonal system and can disrupt its proper functioning. There is a growing interest in understanding endocrine disruptors and progress has been made on both the scientific and regulatory side. However, the topic remains of high concern at decision-making and societal levels because of the challenges it continues to pose.

This paper provides a desk research-based overview of the key moments of the (scientific and regulatory) debate on endocrine disruptors, with a focus on the latest developments at European level, namely Commission Regulation (EU) 2018/605, which establishes scientific criteria for endocrine disruptor properties, and the Commission communication published in November 2018, 'Towards a comprehensive European Union framework on endocrine disruptors', in the particular context of plant protection products.

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Executive summary

Endocrine disruptors (EDs) are a topic of much current debate and concern; there is a growing interest in understanding EDs and progress has been made in both the scientific and policy fields. Nevertheless, the challenges ahead remain important, especially because of the difficulty in evaluating the precise impact of endocrine disrupting chemicals within disease in humans or other organisms.

These chemical substances, present in many products used in daily life, have a similar chemical structure to hormones naturally produced by the body; once in contact with the hormonal system, they can disrupt its proper functioning.

This paper provides an overview of the key moments of the (scientific and regulatory) debate on EDs, with a focus on the latest developments at European level, Commission Regulation (EU) 2018/605, which establishes scientific criteria for endocrine disruptor properties, and the Commission communication published in November 2018, 'Towards a comprehensive European Union framework on endocrine disruptors', in the particular context of plant protection products (PPPs).

Concerns about the harmful effects of certain chemicals on human health began to emerge in the late 1950s, but it is especially since the 1990s that their possible harmful consequences for the hormonal system has begun to be perceived more concretely, following a scientific conference held in 1991 ('Wingspread'), where the term 'endocrine disruptors' was coined.

The progress made in the understanding of endocrine disruptors mainly occurred as a result of a multidisciplinary approach in the field, combining different perspectives, such as endocrinology, toxicology, ecotoxicology, environmental studies or chemistry. Despite an important quantity of evidence on the impact of the chemicals with hormonal disrupting properties on the human body and the agreement reached by the scientific community on a number of related issues, science could not address all the challenges posed by EDs, and knowledge gaps and uncertainties persist. This also has consequences on the way regulators tackle the issue, given that the decision-making process relies on scientific evidence.

At EU level, the first important step towards addressing ED-related questions was the adoption of a Community strategy in 1999 that included short, medium and long-term actions. Since then, several related pieces of legislation have been adopted, including: Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH); Regulation (EC) No 1107/2009 on the Placing on the Market of Plant Protection Products (PPPR); and Regulation (EU) No 528/2012 on Biocidal Products (BPR).

The PPP Regulation, which provides the context for this paper, calls on the European Commission (in Annex II) to draft 'specific scientific criteria for the determination of endocrine disrupting properties'. While the deadline set in the regulation was 2013, the criteria were adopted only in 2018.

In practice, the elaboration of the scientific criteria proved to be a long and difficult endeavour, which was finalised in May 2018 with the adoption of Commission Regulation (EU) 2018/605. The decision-making process was also complicated by both knowledge gaps and scientific uncertainties and the very different opinions of the main stakeholders (NGOs, chemical manufacturers, Member States) as to what the criteria and focus should be. In the definition of the scientific criteria, the Commission claimed to have taken into consideration the main concepts on which the scientific and the regulatory debates are based, such as the definition of endocrine disruptors given by the World Health Organization; the definition of 'adverse effect'; the causality link between mode of action and adverse effect; the issue of 'categorisation of EDs'; the 'safety threshold' problem; the dose-effect relation; or the hazard vs risk debate. The new scientific criteria were criticised on all sides. Chemical

manufacturers claimed that important elements (such as 'potency') were omitted, while safety, public health and environmental NGOs expressed the view that the new criteria are insufficiently protective and ambitious.

In June 2018, the two European agencies dealing with food security and chemicals, the European Food Security Agency (EFSA) and European Chemicals Agency (ECHA), published guidance on identifying substances with endocrine disrupting properties in pesticides and biocides. The document aims at ensuring consistent implementation of the scientific criteria when assessing biocides and pesticides in the EU, by providing guidance on how to gather, evaluate and consider all relevant information for the assessment, conduct a mode of action (MoA) analysis, and apply a weight of evidence (WoE) approach, while checking the ED criteria, and groups the parameters to be used in the identification of potential EDs.

Some months later (in November 2018, when the criteria began to apply), the European Commission also published a new strategy on endocrine disruptors, which outlined the EU approach in the field for the years to come. The new strategy aims at minimising exposure, developing a solid scientific basis for public policies and encouraging dialogue among scientists, public authorities and private actors. The text of the strategy is rather succinct and limited to general observations, no specific actions are defined and no timetable is included. While the actors welcomed the adoption of the strategy, their reactions to its content were rather moderate and their interests turned more towards the future than focusing on what the strategy itself adds to the debate.

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List of abbreviations

ANSES	National Agency for Food Safety, Environment and Labour
BEUC	European Consumer Organisation
BMDL	Bench Mark Dose Low
CAGs	Cumulative assessment groups
CEFIC	European Chemical Industry Council
CEO	Corporate Europe Observatory
CoR	European Committee of the Regions
DDT	Dichlorodiphenyltrichloroethane
DES	Diethylstilbestrol
EATS	Estrogenic, androgenic, thyroidal and steroidogenic
ECHA	European Chemicals Agency
ECPA	European Crop Protection Association
EDs/ EDCs	Endocrine disruptors/Endocrine disrupting chemicals
EEA	European Environment Agency
EESC	European Economic and Social Committee
EFSA	European Food Security Agency
EIA	European Implementation Assessment
ENVI	European Parliament Committee on Environment, Public Health and Food Safety
EPPA	European Public Policy Advisors
GHS	UN Globally Harmonized System of Classification and Labelling of Chemicals
HEAL	Health and Environmental Alliance
IA	Impact Assessment
IPCP	International Panel on Chemical Pollution
MoA	Mode of action
NGOs	Non-governmental organisations
NMDR	Non-monotonic dose responses
OECD	Organisation for Economic Co-operation and Development
PAFF	Standing Committee on Plants Animals Food and Feed
PAN Europe	Pesticides Action Network Europe
PETI	European Parliament Committee on Petitions
POPs	Persistent pollutants
PPPs	Plant protection products
US EPA	United States Environmental Protection Agency
WHO	World Health Organization
WoE	Weight of evidence

1. Scope, methodology and data sources

In April 2018, in the context of an implementation report[1] prepared by the European Parliament regarding Regulation (EC) 1107/2009,[2] the European Parliamentary Research Service (EPRS) published a dedicated European implementation assessment (EIA) on the matter.[3] Through this EIA, a general evaluation of the implementation of the regulation was carried out, focusing on different issues of concern at public and decision-making level (such as the scientific evaluation of substances, the performance of competent authorities, or the transparency aspects related to procedures). As mentioned in the EIA, other elements covered by the regulation also raise concern and/or call for attention at the European level. This is the case, for instance, of **endocrine disruptors** (EDs), considered to be substances with a harmful effect on the hormonal system.

The current analysis is a complementary piece of research which focuses on EDs. Its scope is rather limited and it will mainly look at the latest developments at European level on endocrine disruptors in the context of plant protection products, as many chemicals identified as endocrine disruptors are pesticides.[4] Thus, the main purpose of this research is to provide additional and up-to-date information on this particular subject.

Given the complexity of the topic, as well as the differences of view within the scientific community, leading to different regulatory approaches, this analysis does not claim to be exhaustive. Furthermore, the scientific debate itself is not a central element of this research, but serves as a basis for better situating and understanding the different approaches at the decision-making and regulatory level.

This desk-research based analysis provides an overview of publicly available material on the topic, including input from EU institutions and bodies, as well as external organisations. The research endeavours to present divergent points of view expressed by key stakeholders on the issues, however, it does not claim to have exhausted all the opinions, statements or positions taken by all the actors involved in the debate.

Since the publication of the EIA on the implementation of Regulation (EC) 1107/2009, the European Commission has published two new related documents: Commission Regulation (EU) 2018/605,[5] which establishes scientific criteria for endocrine disruptor properties, and a communication, 'Towards a comprehensive European Union framework on endocrine disruptors', which outlines the Commission's strategic approach on the topic for the future. Looking at these documents in more detail, as well as at the stakeholders'[6] opinions and feedback, is the main point of interest of this analysis.

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1 See European Parliament resolution of 13 September 2018 on the implementation of the Plant Protection Products Regulation (EC) No 1107/2009.

2 Regulation (EC) 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.

3 The document is available on the EPRS website.

4 Following the two relevant EU regulations (… and …) the term pesticides includes plant protection products ('substances used for destroying insects, weed plants, and other unwanted organisms harmful to cultivated plants') and biocidal products ('active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to destroy, deter, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism by chemical or biological means'). See also EPRS, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market. European Implementation Assessment, 2018.

5 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, OJ L 101/33, 20 April 2018.

6 We will consider the relevant interested and concerned parties in the debate as 'stakeholders'.

2. Background

2.1. Key developments

Humans have always interacted with the environment and humans and the environment have always influenced each other, both positively and negatively. The more societies developed, the more these interactions and connections became various and complex.

Every year, a many man-made chemical substances are marketed and released; however, some of them can damage both human health and the environment. This is why, over time, it has become necessary to address the challenges posed by chemicals with adverse health and environmental effects. Nevertheless, the intricacy of the different interdependencies and relations that may occur makes this a difficult task.

Chemicals, environment and human health

In 1938, Diethylstilbestrol (DES), the first synthetic oestrogen, was created and tested for biological activity[7] and used for years to prevent miscarriage and ensure healthy babies (although the results were rather to the contrary). Two decades later, Roy Hertz, a researcher at the US National Cancer Institute, referred in its work[8] to the potential for human exposure to hormones used in cattle feed. Between these two complementary sides of the scientific work – development of chemical substances for different uses and study of their potential risks – a great deal of literature on the interaction between different chemicals and human (as well as environmental) health has developed over the years.

The publication of *Silent Spring*, in 1962,[9] had a great impact on public awareness of the link between (potentially dangerous) chemicals realised in the environment and human health. Biologist Rachel Carson drew attention to the many harmful effects of pesticides[10] on the environment and human health and called for moderation and care in their use. Carson's book also left its mark on the decision-making process; by arguing that the commonly used (at that time) insecticide Dichlorodiphenyltrichloroethane (DDT), as well as other pesticides, lead to health problems (cancers) and affect wildlife (especially bird populations). Carson's book served as evidence in campaigns against the use of DDT, which was banned in the United States in 1972 (and at international level in 2004).[11]

At the same period, another book drew public attention to the link between chemical substances and endocrine disruption. Based on the endocrine disruptor hypothesis developed by Theo Colborn, *Our stolen future,*[12] published in 1966, highlighted the fact that common contaminants can disrupt human reproductive patterns and interfere with the natural signals

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7 See Dodds EC., Goldberg L., Lawson W., Robinson R. (1938), Oestrogenic activity of certain synthetic compounds, *Nature 141*, 247–249.

8 See, for instance, Hertz, R, The role of steroid hormones in the etiology and pathogenesis of cancer, *American Journal of Obstrectics and Ginecology*, 98 (7), 1967, 1013–1019.

9 Carson R., *Silent Spring. Anniversary Edition*, New York, Houghton Miffin Co., 1962.

10 For more details on pesticides, see also Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market, EPRS, European Parliament, 2018; Bourguignon D., EU policy and legislation on pesticides. Plant protection products and biocides, EPRS, 2017.

11 Through the Stockholm Convention on Persistent Organic Pollutants, signed in 2001 and entered into force in 2004; the use of DDT is still permitted for the control of malaria-causing mosquitoes.

12 Colborn Th., Dumanoski D., and Myers JP, *Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival? A Scientific Detective Story*, New York: Dutton, 1996.

controlling development of the foetus, causing problems such as birth defects, sexual abnormalities, and reproductive failures. The book influenced American policy-making, contributing to the enforcement of environmental protection and research activities, as reflected in the work of the United States Environmental Protection Agency (EPA) in the field.

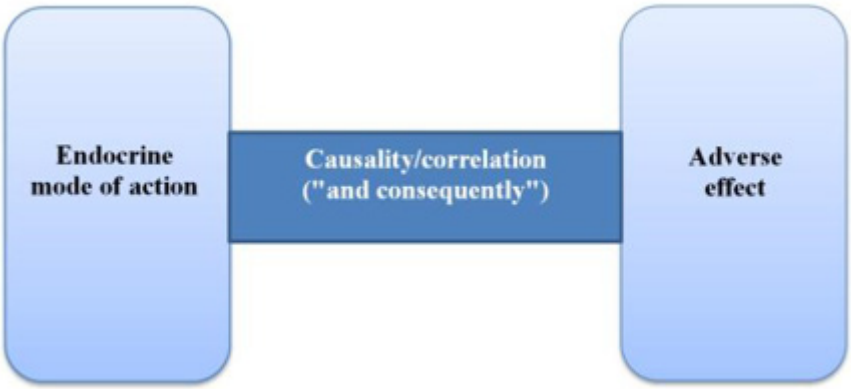
From the 1970s, researchers increasingly found links between certain chemicals and health problems. For instance, the commonly-used DES was associated with serious consequences, such as cancers and reproductive malformations as a result of *in utero* exposure.

In this context, increased attention has been paid to the effects of different chemical substances on the human body and more specifically on the functioning of the endocrine system, which is one of the human body's main interfaces with the environment. In this regard, a growing body of literature within the past few decades has been consecrated to endocrine-disrupting substances/chemicals (EDs or EDCs).[13] The scientific interest in this issue has been completed by policy and regulatory concerns. It can be safely said that EDs are today of great interest to scientists, decision-makers and citizens, and are a focus for dynamic and controversial debates.

EDs are 'an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental processes.[14] This means that 'EDs can interfere with the steps in hormone signalling. They can trick a receptor by mimicking a hormone, which can turn on a hormone response and inappropriately trigger hormonal processes. Or they can bind to a hormone's receptor and block activation, prevents appropriate hormonal processes from taking place'.[15] EDs may be either synthetic or of natural origin.

For the European Commission, EDs are characterised by three cumulative characteristics: hormonal activity, adverse effect, and causality between the two.

Figure 1 – Three cumulative characteristics of EDs



Source: European Commission website.

[13] The term 'endocrine disruptor' was used for the first time in 1991, at a conference in Wisconsin; for more details, see Colborn T, vom Saal FS, Soto AM, Developmental effects of endocrine-disrupting chemicals in wildlife and humans, *Environmental Health Perspectives*, 1993 (101), 378–384.

[14] According to the US Environmental Protection Agency (EPA), quoted by Diamanti-Kandarakis E, Bourguignon JP, Giudice L, et all. *Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement*, Endocrine Reviews, 30(4), 2009, 293–342.

[15] Endocrine Society website.

The human body is in permanent contact with chemicals, which are essential components of our daily lives.[16] They enter our bodies through eating, drinking, or breathing. While this 'contact' with chemicals cannot be totally avoided, the question is how they affect/interact with our health. From this perspective, the main challenge in terms of public health as regards EDs is the very high number of chemicals released into the environment and on the market without being (completely) tested for safety. At scientific and regulatory level, this is reflected in the search for solutions to limit EDs' effects on human health.

Broadening the approach in EDs study: from the 1990s to today

The discovery in the 1970s of the adverse short- and long-term effects of DES on human health was a warning that a change of approach in the study of hormone-interferences is necessary. In this respect, researchers, mainly in the 1990s, across different fields (such as endocrinology, toxicology, ecotoxicology, environmental studies), have tried to piece their findings together and work towards a consensus on the larger picture of EDs and their health and environmental effects. At the same time, at the decision-making level, different structures were created to develop legal instruments and programmes meant to ensure a better protection of human health and the environment.

Worldwide, research on EDs began to contribute to important advances in the field. An essential moment in the developing of the 'endocrine disruptor' concept was the 1991 Wingspread Conference, that produced a stark consensus statement from participating scientists: 'We are certain of the following: A large number of man-made chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans'.[17] In the United States in 1995 and 1996, the American Environment Protection Agency (US EPA) organised two international meetings to evaluate the existing level of knowledge on EDs and also to identify future needs, with a focus on both ecological and human health effects.[18] EPA also started implementing testing and screening activities on endocrine disruptors and evaluated the hormonal activity of a large number of compounds. In the mid-1990s, Japan also began to actively investigate endocrine disruptors. In 1998, the first endocrine disruptor strategy was published (SPEED '98), followed by a second (ExTEND), in 2005, which looked in more detail at the possible endocrine disrupting effects of all chemicals.

The same interest in understanding EDs has been shown in the European Union, which held the first Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife in 1996 (in Weybridge, United Kingdom), followed by a second in 2006 (Weybridge+10). In 1999, the EU adopted the 'Community strategy for endocrine disruptors', aiming at: 1) identifying 'the problem of endocrine disruption, its causes and consequences'; and 2) identifying 'appropriate policy action on the basis of the precautionary principle in order to respond quickly and effectively to the problem, thereby alleviating public concern'.

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[16] Chemicals can be found in products we use every day: plastic containers, toys, furniture, fabric, automobiles, TVs, water bottles, medical supplies, cosmetics, etc. They include substances such as dioxins, polychlorinated biphenyls (PBs), phthalates, parabens, bisphenol A.

[17] Colborn T, Clement C, *Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection*, Princeton, 1992.

[18] Kavlock RJ, Daston GP, De Rosa C, at al., Research Needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the US EPA-sponsored workshop, *Environmental Health Perspectives*, 1996, 104 (4), 715-740.

In 2002[19] and 2012,[20] the World Health Organization (WHO) published comprehensive assessments on the state of scientific knowledge on endocrine disruptors. In 2002, WHO concluded that 'there is little information on linkages between exposures to putative EDs and health outcomes in both humans and wildlife. Progress has been made in the identification and quantification of a wide array of chemicals with endocrine-active properties. Predominantly, research efforts have focused on compounds that persist and bioaccumulate in organisms and their environment. Only recently have efforts been directed at exposure studies of less persistent compounds and in the development of biologically based assays, which would enable more direct assessments of endocrine-active compounds. Given the dynamic nature of the endocrine system, future efforts in the study of EDs need more focus on the timing, frequency, and duration of exposure to these chemicals'. Some years later (2006), in a more general chemicals-related context,[21] an overall objective was set up, aiming to 'achieve the sound management of chemicals throughout their life cycle so that, by 2020, chemicals are used and produced in ways that minimise significant adverse effects on human health and the environment'. In this context, the 2012 report described the effects of EDs on humans and wildlife in detail. As shown in the document, several main evidence-based concerns are related to EDs, such as:

- the high incidence and the increasing trends of many endocrine-related disorders in humans;
- observations of endocrine-related effects in wildlife populations;
- the identification, in laboratory studies, of chemicals with endocrine disrupting properties linked to disease.[22]

It is also noteworthy that about 800 chemicals are known or suspected to interact with the hormone system, but only a small number of these has been tested for their endocrine effects.

The report underlined the progress made in the study and understanding of EDs, but also future challenges. On the one hand, it concluded that 'it is clear' that: 'a large number of non-communicable diseases have their origin during development'; 'environmental factors interact with our genetic background to increase susceptibility to a variety of diseases and disorders'; 'one of the important environmental risk factors for endocrine disease is exposure to EDs during development'; 'we are exposed to perhaps hundreds of environmental chemicals at any one time'. At the same time, 'trends indicate an increasing burden of certain endocrine diseases across the globe in which EDs are likely playing an important role, and future generations may also be affected'.[23] For the authors of the report, all this indicates future needs and actions to be taken, such as: improving knowledge about EDs (understanding the effects of the mixtures of chemicals, strengthening interdisciplinary approaches, identifying other possible EDCs); better tests for EDs (including new

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[19] World Health Organization, Global assessment of the state-of-the-science of endocrine disruptors, WHO/PCS/EDC/02.2, 2002.

[20] WHO/UNEP, State of the science of endocrine disrupting chemicals - 2012: An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme (UNEP) and WHO, 2012.

[21] In 2006, the First International Conference on Chemicals Management (ICCM) established a Strategic Approach to International Chemicals Management (SAICM) aiming at putting in place a policy framework to promote chemical safety around the world.

[22] WHO/UNEP, State of the science of endocrine disrupting chemicals - 2012: An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme (UNEP) and WHO, 2012, p.2.

[23] WHO/UNEP, State of the science of endocrine disrupting chemicals - 2012: An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme (UNEP) and WHO, 2012, p.27.

approaches); identifying chemicals with endocrine disrupting properties; reducing exposures; and developing a favourable environment for science, innovation and disease prevention.

In 2011, the European Commission published the 'State of the art assessment of endocrine disrupters' report.[24] Its aim was 'to analyse and summarise results of regulatory relevance of the scientific debate in the field of endocrine disrupting properties of substances, and to describe and characterise any relationships among the different levels of the expanded OECD conceptual framework'.

One year later (in 2012), the European Environment Agency (EEA) also published a report[25] on the impact of endocrine disruptors on wildlife, people and their environments, which presented the progress made in the field from 1996 to 2011. The report began from the observation that the 'rates of endocrine diseases and disorders, such as some reproductive and developmental harm in human populations, have changed in line with the growth of the chemical industry, leading to concerns that these factors may be linked'.

While focusing on the potential harmful effects of EDs, the report highlighted the progress made (from the previous workshop, in 1996), in the understanding of these compounds and their interactions with the human body and the wildlife and, at the same time, drawn up a list of findings, challenges and recommendations as regards EDs in the context of new scientific data, such as the cocktail-effects of chemicals[26] or human life stages with high sensitivity to EDs.

The main overall findings and conclusions were:

- chemicals with disrupting properties are affecting both human and wildlife health, but 'a much better understanding of the role of chemicals as causal factors of a wide range of endocrine diseases and disorders is needed'.
- current screening tests to identify endocrine disruptors are not enough to address all existing inadequacies;
- not all hormones and hormones disruptors are fully understood;
- given the variety of interactions with the endocrine system, it would be necessary to know what types of EDs most affect the human body and wildlife;
- the potential benefits of using 'omics' technologies[27] in the study of EDs.
- the risks related to mixtures of endocrine disruptors seem to be cumulative;
- it is important to obtain more data on the dose-response curves, given that low-dose effects of EDs often cannot be predicted from high-dose testing;
- EDs can have effects over time (the exposure may have occurred during early life or in past generations);

[24] European Commission, *State of The Art Assessment of endocrine disrupters*, Final report, 2011.

[25] European Environment Agency, *The impact of endocrine disruptors on wildlife, people and their environments: The Weibridge+15 (1996-2011)*, Luxembourg, Publications Office of the European Union, 2012.

[26] The scientific studies provide information on the effects of one chemical at a time. Nevertheless, a mixture of chemicals might have different effects on the human body, given that different chemicals can threaten or weaken each other's effects. This is a topic of increasing interest among researchers.

[27] Omics technologies refer to emerging technologies that are used together to explore the roles, relationships, and actions of the various types of molecules in the cells of an organism. They include: genomics (he study of genes), transcriptomic (the study of the Messenger ribonucleic acids – mRNA), proteomics (the study of proteins), metabolomics (the study of molecules involved in cellular metabolism), glycomics (the study of cellular carbohydrates), and lipomics (the study of cellular lipids).

- studies on EDs should take 'the distribution of susceptibility, response and dose among the population members' into consideration, given that 'what is within 'normal' for one person may not be so for another';
- possible effects (based on the existing evidence obtained as regards wildlife, domestic and laboratory animals), of chemically induced EDs in humans represent a failure in environmental protection that should be addressed; the precautionary principle and a limited exposure seem a rational answer to this.

In 2017, United Nations (UN) Environment published an overview report (from a series of three) prepared by the International Panel on Chemical Pollution (IPCP), focusing on worldwide initiatives to identify endocrine disrupting chemicals (EDCs) and potential EDCs.[28] With regard to the aim, scope and sources of information of the report, it is said that it can 'serve as a compendium of information that provides an overview of global initiatives identifying EDCs and potential EDCs, including a comparison of the existing efforts as well as highlighting current gaps', by reviewing 'existing, publicly accessible initiatives by various stakeholders (governments, industry, civil society and academia)'. The report looked at and took into consideration 28 initiatives.

The main observations of the report were:

- important resources are used in identifying EDs, leading to a variety of initiatives;
- there is a diversity of purposes and criteria used to identify EDs;
- the degree of development and publicity of the different initiatives varies considerably (from early stages to very well known);
- lack of input and representation from developing countries and economies in transition;
- absence of commonly agreed criteria to identify EDs (however, the recent Commission Regulation (EU) 2018/605 was mentioned in this context).

The third report,[29] published in July 2018, ('Existing national, regional and global regulatory frameworks addressing Endocrine Disrupting Chemicals (EDCs) as for July 2017'), also contains a list of identified EDCs that consists of 45 substances from 18 chemical groups, including phthalates, bisphenols and parabens.

One of the main actors in the field of endocrine disruptors is the Organisation for Economic Co-operation and Development (OECD), which has been working on developing harmonised methods for screening and testing chemicals for endocrine disruption. In 2012, the organisation published the first guidance document for evaluating chemical using standardised test guidelines. The intention of the document 'is primarily to provide guidance on how test results might be interpreted based on the outcome of standardised assays', as well as 'advice on the next step in testing (if any) which might be appropriate for a regulatory authority to take, given the various data scenarios'.[30] The document was updated in 2018, 'to reflect new and updated OECD test guidelines'.[31]

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[28] United Nations Environmental Programme, Overview Report I: Worldwide initiatives to identify endocrine disrupting chemicals (EDCs) and potential EDCs, 2017.

[29] UN Environment Programme, Scientific knowledge of endocrine disrupting chemicals, 2018. The second report is an overview of current scientific knowledge on the life cycles, environmental exposures, and environmental effects of select endocrine disrupting chemicals (EDCs) and potential EDCs as for July 2017.

[30] OECD, Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption, 2012.

[31] OECD, Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption, 2018.

2.2. Scientific and regulatory approaches: general remarks

It is known today that EDs interact with the normal activity of the body in different ways: by activating or blocking the hormone receptors, disrupting the synthesis of hormones, altering the degradation of hormones, as well as that some EDs have negative effects even at low doses. However, there are limits to scientific evidence and it is difficult to achieve absolute certainty, especially because it is very difficult to make a causal link between exposure and a disease outcome.

EDs: a topic of great interest and debate

Scientists have been attempting to synthesise knowledge on EDs in order to answer a large variety of questions and complex issues ranging, inter alia, from the long-held concerns regarding the global consequences of EDs on our health to the more recent disquiet regarding the long-term and intergenerational effects of these chemicals; from basic questions on the properties that allow EDs to interfere with hormones in human bodies, to a more manifold questioning on exposure-related issues; or on identifying a possible 'safe threshold' under which no negative impact on health occurs, as well as on the methodological limits of the different scientific disciplines that study EDs.

Endocrine disrupting chemicals are a controversial societal topic, but also a lively and challenging subject within the research community, given the gaps that still exist as regards both knowledge and testing methods. It can however be maintained that a generally cooperative approach has driven scientific research, leading to progress in the field. Firstly, this cooperation today allows a multidisciplinary approach to the challenges posed by EDs. Taking elements from different fields (such as environmental health, toxicology, ecotoxicology, chemistry, 'omics') into consideration in the study of EDs, seems to be the key to a deeper and broader understanding of the effects of these chemicals on human health. At the same time, scientists agree on a number of elements, such as: the fact that interactions between EDs and the human body can take different forms; there is high sensitivity to EDs during certain periods of development (for instance, during foetal development and puberty); or the more general issue of the 'cocktail effect' of exposure to a mixture of substances including EDs. Scientists also agree on several challenges, such as the need to: increase knowledge of EDs; improve testing methods; and define (agreed) methods for evaluating evidence or creating and encouraging new programmes and approaches and stimulating multi-disciplinary science. As to the very definition of EDs, even though a universally-accepted version is still missing, efforts have been made to clarify this issue and the WHO[32] definition is widely accepted today.

Nevertheless, for the time being, science does not have definitive answers for all the challenges posed by EDs, both because of the complexity of the topic (research shows that ED action mechanisms are wider than initially thought), and the limitations of the existing methods to evaluate and test the effects and risks of the chemicals with endocrine-disrupting properties (in real life, the human body is exposed to different mixtures of different EDs, which are not tested as such in the laboratory;[33] the lack of a widely agreed system[34] for evaluating the strength of evidence of associations between exposures to EDs (and chemicals in general); and adverse health outcomes).

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[32] The definition provided by the UN International Programme on Chemical Safety (IPCS) on 2012 states that an endocrine disruptor is 'an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations', while a potential endocrine disruptor is 'an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations' (WHO/IPCS, Global assessment of the state-of-the-science of endocrine disruptors, 2002).

[33] There is still uncertainty as regards the relevance of *in vitro* tests, knowing that in vitro systems often represent simplified or artificial systems; at the same time, laboratory tests cannot completely reproduce the real (external) environment.

[34] OECD's work on the harmonisation of tests is a very important step in this direction.

Despite cooperative efforts and discussions, divisions still persist on definitions, methodologies and practices and this disagreement even led to a 'paradigm war' between toxicologists and endocrinologists, not only regarding the lack of data or differences concerning interpretations, but the very definition of the phenomenon and the type of evidence needed to assess it.[35] Studies also question the effects of EDs on humans[36] by relativising certain data or some knowledge; one example in this sense is the impact of particular substances (for instance bisphenol A, phthalates) with respect to development during puberty,[37] or obesity.[38] This scientific uncertainty[39] has consequences for the regulatory process, providing it is an evidence-based decision-making process.[40]

Regulatory issues: some examples

At national, European and international level, there is a growing interest in developing strategies, programmes and tests that allow for a better evaluation of the impact of chemicals (including EDs) on human and wildlife.

The US EPA was the pioneer in the regulatory field as regards EDs, following the US Congress decision to include a related provision in the Food Quality Protection Act of 1996[41] amending the Federal Food, Drug and Cosmetics Act, which requires EPA to 'develop a screening program, using appropriate validated systems and other scientifically relevant information, to determine whether certain substances may have an effect on humans that is similar to an effect produced by a naturally occurring oestrogen, or other such endocrine effect'.

At the European Union level, following publication of the first strategy on endocrine disruptors in 1999 (Community stategy on endocrine disruptors),[42] several pieces of legislation dealing with EDs were adopted. The strategy includes short-, medium- and long-term actions, such as:

- short-term: establishement of a priority list of substances for further evaluation of their role in endocrine disruption, establishement of monitoring programmes to estimate exposure to and effects of the substances on the ED priority list, cooperation and exchange of information;

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35 Bozzini, E, Pesticide Policy and Politics in the European Union. Regulatory Assessment, Implementation and Enforcement, Palgrave Macmillan, 2017.

36 See, for instance, in this direction, Rhomberg LR, Goodman JE, Foster WG, Borgert CJ, Van Der Kraak G, A critique of the European Commission document, 'State of the Art Assessment of Endocrine Disrupters', *Critical Reviews in Toxicology*, 42(6), 2012, 465-73.

37 See, in this sense, *inter alia*, Leonardi A, Cofini M, Rigante D, Lucchetti L, Cipolla C, Penta L, Esposito S, The Effect of Bisphenol A on Puberty: A Critical Review of the Medical Literature, International Journal of Environmental Research and Public Health , 14(9):1044, 2017.

38 Goodman M, Lakind JS, Mattison DR, Do phthalates act as obesogens in humans? A systematic review of the epidemiological literature, *Critical Reviews in Toxicology*, 44, 151–175, 2014, Lakind JS1, Goodman M, Mattison DR, Bisphenol A and indicators of obesity, glucose metabolism/type 2 diabetes and cardiovascular disease: a systematic review of epidemiologic research, *Critical Reviews in Toxicology*, 44(2),121-150, 2014.

39 Here, the scientific uncertainty means the situation where incomplete scientific understanding may result in a lack of clarity from a regulatory point of view.

40 On the 'link' between differences in scientific interpretation, expert positions and policy-making see, *inter alia*, Pielke, R. A. J., *The Honest Broker: Making Sense of Science in Policy and Politics*, Cambridge, UK: Cambridge University Press, 2007; Spruijt, P., Knol, A.B., Vasileiadou, E., Devilee, J., Lebret, E., and Petersen A.C., Roles of Scientists as Policy Advisers on Complex Issues: A Literature Review, *Environmental Science & Policy*, 40/2014, 16-25.

41 The full text is available here.

42 European Commission, Communication from the Commission to the Council and the European Parliament - Community strategy for endocrine disrupters - A range of substances suspected of interfering with the hormone systems of humans and wildlife, COM (1999)706 final, 1999.

- medium-term: identification and assessment of endocrine disruptors, development of internationally agreed test methods, research and development;
- long-term: legislative action.

In 2011, the fourth implementation report on the strategy[43] noted that a priority list of substances was established.[44]

The table below presents the European legislation related to endocrine disruptors:

Table 1 – EU legislation related to EDs

Title	Description
Main EU legislation	
Regulation (EC) No 1907/2006 – REACH	Under this regulation, endocrine disruptors, identified on a case-by-case basis, are considered as substances 'of very high concern' (Article 57(f)), meaning that suitable alternatives should be identified in order to progressively substitute these substances.
Regulation (EC) No 1107/2009 – Plant Protection Products and Regulation (EU) No 528/2012 – Biocides	Both regulations ban products containing substances with endocrine-disrupting properties. They also require that the European Commission establish the scientific criteria for the identification of endocrine disruptors by December 2013.
Other EU legislation related to EDs	
Directive 2000/60/EC – Water Framework Directive; Regulation (EC) 1272/2008 on classification, labelling and packaging of substances and mixtures – CLP; Directive 2009/48/EC – Toy Safety; Regulation (EC) 1223/2009 on cosmetic products; Directive 2011/8/EU restricting the use of Bisphenol A in plastic infant feeding bottles.	

In the EU, national bodies also pay special attention to EDs and constantly provide new scientific insights on the topic. To give just a few examples among the most recent, the Swedish Chemicals Agency published a report[45] in 2017 that identified 37 bisphenols (from the 39 existing on the EU market) with potential endocrine-disrupting properties. The study developed a new method of screening (Kemi method), which groups substances based on their chemical structure, their possible use in different applications, and their potential endocrine-disrupting properties according to data simulations.[46] The same year, the Danish Environmental Protection Agency also published a study[47] that screened thousands of chemicals for endocrine-disrupting properties. On the one hand, the study found nine substances[48] with endocrine-disrupting activities that fulfil the WHO definition of an endocrine-disrupting chemical (as well as the EU scientific criteria for EDs established in 2018, see

[43] See the Commission staff working paper 4th report on the implementation of the 'Community strategy for endocrine disrupters' a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (1999) 706), SEC(2011) 1001 final.

[44] The priority list, together with information on the basis of concern and the way the concerns were addressed are available on a European Commission dedicated webpage.

[45] Available in Swedish only.

[46] ChemicalWatch, Sweden identifies 37 bisphenols as potential EDCs, September 2017.

[47] Danish Centre of Endocrine Disruptors, List of Endocrine Disrupting Chemicals. Final report, December 2017.

[48] The nine substances are: bisphenol AF – humans and environment; di-n-pentylphthalate – humans; fenitrothion – humans; isobutyl paraben – humans; octamethylcyclotetrasiloxane (D4) – humans; prochloraz – humans and environment; triclocarban – humans; tris(methylphenyl) phosphate – humans; and salicylic acid – humans.

below), and four others are suspected EDCs. On the other hand, 'a literature screening of 52 of the prioritised substances showed that there was a lack of relevant MoA (mode of action) data and/or adverse effect data for around 40-50 % of the substances'. The study was based on a 'list of lists' that compiled several existing lists (from authorities and NGOs) of hazardous chemicals, including a 'master list' of some 7 200 substances from ECHA. The study recommended a further literature review of 119 non-screened prioritised chemicals, as well as new studies 'to address data gaps with regards to both ED MoA and ED relevant adverse effects for many substances suspected to be EDCs. Also, more data on risk for exposure are recommended as many of the suspected EDs were not prioritised due to lack of such data'. In early 2019, the Danish EPA published a new report on the risks regarding the interpretation of knowledge on EDs.[49] As presented in the report, its overall scope was 'to provide a science-based input to the ongoing work in the EU with regards to specifically risk assessment of endocrine disruptors'. Four uncertainities were considered in the study as the most important in relation to EDs, namely: the lack of studies with exposure during sensitive windows; the limited sensitivity of many regulatory testing methods with regard to relevant endpoints addressed and power/robustness of study; the occurrence of ED-induced non-monotonic dose responses (NMDR) and the existence of thresholds. The authors of the study concluded that: the two first uncertainties are more important; the current risk assessment of EDs is limited in its scope; there is an urgent need to address uncertainties related to ED assessment, because of its possible irreversible effects, so a non-threshold approach is recommended when deriving reference doses for EDs, as well as a Bench Mark Dose Low[50] approach (BMDL) as point of departure for the derivation of references levels (even though the researchers were divided on the approach to follow).[51]

As already mentioned, all the scientific findings, as well as the knowlege gaps and uncertainities, influence the EU regulatory and decision-making process, given that policy-makers and regulators rely on scientific evidence. At the same time, the regulatory process lies at a crossroads, seeking: political efforts to provide answers to existing challenges; legal measures to translate general strategies and objectives into concrete politics; and input from stakeholders, whose lives are affected by the established rules.

In the European Union, precautionary principle[52] is the driving principle when it comes to chemicals, which allows for precautionary measures when scientific evidence regarding an environmental or human health hazard is uncertain and the stakes are high.[53] For the European Commission, the precautionary principle is applicable 'where scientific information is insufficient, inconclusive, or uncertain and where there are indications that the possible effects on the environment, or human, animal or plant health may be potentially dangerous and inconsistent with the chosen level of protection'.[54] In practice, this means the evaluation of the level of danger (risk assessment) of certain substances for human health or the environment is uncertain. Put simply, there are three main components to the risk assessment: hazard assessment (including hazard identification and hazard characterisation); exposure assessment; and risk characterisation. For regulators, this translates into

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[49] Danish Centre of Endocrine Disruptors, Report on Interpretation of knowledge on endocrine disrupting substances (EDs) – what is the risk?, February 2019.

[50] A benchmark dose (BMD) is a dose or concentration that produces a predetermined change in the response rate of an adverse effect. For more details, see the ChemSafetyPro website.

[51] The second scenario supported by certain researchers was the derivation of a reference dose (DMEL). For more details, see the ChemSafetyPro website.

[52] On the precautionary principle in the plant protection products context see also Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market, European Implementation Assessment, EPRS, 2018.

[53] Bourguignon, D, The precautionary principle: Definitions, applications and governance, European Parliamentary Service, 2015.

[54] European Commission, Communication from the Commission on the precautionary principle, COM(2000) 1, 2000.

two types of possible approaches to taking decisions on chemicals: hazard-based or risk-based. A hazard is therefore anything that has the potential to cause harm, while a risk is the likelihood, or possibility, that harm occurs from exposure to a hazard. Both approaches are applied in related EU legislation.

There is, however, no common view on endocrine disruptors. Some EU Member States support a hazard-based approach and others a risk-based approach,[55] NGOs support a more hazard-oriented approach, while industry is in favour of a risk-based approach (see below).

In the policy-making process, (public) agencies are an important actor. Their role is to provide independent support for the policy-making process through their expertise in their specific fields. Their positions are all the more important as they can influence the interpretation and/or the implementation of the legislation. In the European Union, two agencies are involved in the regulatory process with regards to chemicals: the European Food Safety Agency (EFSA), which 'provides independent scientific advice to the decision makers who regulate food safety in Europe',[56] and the European Chemicals Agency (ECHA), which works for the safe and sustainable use of chemicals 'in implementing the EU's groundbreaking chemicals legislation for the benefit of human health and the environment as well as for innovation and competitiveness'.[57]

Within this policy-making frame, responding to a European Commission request, EFSA, in its capacity as risk assessor, released a scientific opinion[58] on endocrine disruptors in 2013.[59] The agency backed the WHO definition of endocrine disruptors and concluded that 'to inform on risk and level of concern for the purpose of risk management decisions it is the opinion of the Scientific Committee (SC) that risk assessment (taking into account hazard and exposure data/predictions) makes best use of available information. EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment'.

This opinion raised various reactions[60] from the two main categories of stakeholders. Environmental NGOs like CHEM Trust, Health and Environmental Alliance (HEAL) and Pesticides Action Network (PAN) Europe criticised the position of the European risk assessor as going against the EU legislation on pesticides, under which endocrine disruptors are banned on a hazard-basis. Moreover, according to PAN Europe, 'EFSA had ignored the so-called 'cocktail effects', while in real life people are not exposed to only one pesticide'.[61]

On the other hand, industry representatives, such as the European Crop Protection Association (ECPA), considered that the legislation should take real and not potential risks into consideration.[62]

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55 Scholz, N, Setting criteria on endocrine disruptors. Follow-up to the General Court judgment, EPRS, 2016.

56 EFSA website.

57 ECHA website.

58 The final decision is made by the Commission (and the Member States), in its capacity of risk managers.

59 European Food Safety Agency, Scientific Opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment, 2013.

60 The examples selected in this paper (position documents from stakeholders) present opposing opinions whenever possible.

61 EurActiv, EFSA paves way for regulating endocrine disruptors in food, March 2013. The article presents several points of view as regards the EFSA opinion on EDs, from both NGOs representatives and industry.

62 EndsEurope, EFSA's EDC opinion reopens hazard versus risk debate, March 2013.

As for ECHA, the agency drew up a list[63] (regularly updated) of substances assessed against ED properties. Nevertheless, this assessment list only 'includes the substances undergoing an ED assessment under the REACH or Biocidal Products regulations that have been brought for discussion to ECHA's ED Expert Group'.

In conclusion, the long-running debate on EDs seems far from over, and addressing a scientific question in a regulatory context only adds further complexity to the topic.

[63] ECHA's endocrine disruptor (ED) assessment list.

3. EU approach to endocrine disruptors: latest developments

3.1. Legal framework: endocrine disruptors in the context of Regulation (EC) 1107/2009

The presence on the EU market of an important number of chemicals without sufficient information on the hazards and risks they pose to human health and the environment being available led to the adoption of several pieces of legislation meant to reduce their possible negative impact.

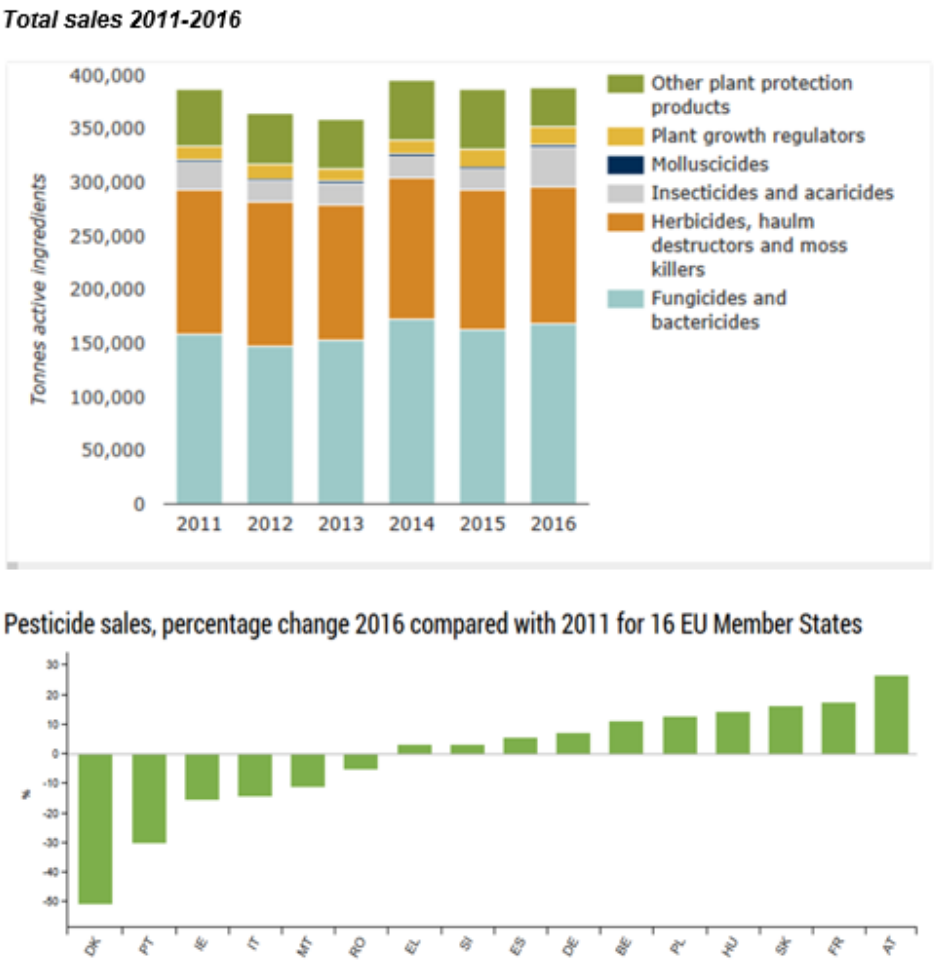
The focus of this analysis is Regulation (EC) 1107/2009 on the Placing on Plant Protection Products on the Market (PPPR hereafter), the main objectives of which are (according to Article 1(3): to ensure a high level of protection for humans, animals and environment; and to 'improve the functioning of the internal market through harmonisation', while providing clearer rules to make the approval process for plant protection products more effective.

The particular interest in this piece of legislation, explained at the beginning of this paper, is also strengthened by the fact that many chemicals that act as endocrine disruptors are pesticides.[64] The use of pesticides in the EU remains at high levels, despite the objectives set up by the seventh EU environment action programme (7th EAP) as regards the harmless and sustainable use of pesticides by 2020. The figures below give an indication of the total sales of pesticides[65] in the EU between 2011 and 2016, as well as of the percentage change in 2016 compared with 2011 (in 16 EU Member States).

[64] See, for instance, Andersen, H.R.; Cook, S.J.; Waldbillig, D., Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase *activity in vitro, Toxicology and Applied Pharmacology*, 2002(179), 1-12; Lemaire, G.; Mnif, W.; Mauvais, P.; Balaguer, P.; Rahmani, R. Activation of alpha- and beta- estrogen receptors by persistent pesticides in reporter cell lines, *Life Science*, 2006 (79), 1160-1169.

[65] This could be a realistic indication of the quantities actually used because of the assumption that pesticides are bought with the intention of use (this argument was suggested by Dr. Emanuela Bozzini in the context of the discussions related to her research paper on 'Assessing criteria and capacity for reliable and harmonised 'hazard identification' of active substances', which is part of the European Implementation Assessment on Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market, EPRS, 2018).

Figure 2 – Pesticide sales in the EU (2011-2016)



Source: Eurostat.

Regulation (EC) 1107/2009 introduced 'cut-off criteria' for the first time, which means that a chemical substance is banned from use in any plant protection product if it presents a hazard for human health (carcinogens, mutagens, toxic to reproduction, endocrine disruptors), or the environment (persistent organic pollutant – POP; persistent, bioaccumulative and toxic – PBT; very persistent and very bioaccumulative – vPvB). In other words, the intrinsic danger posed by a substance is enough to prohibit its placing and its use on the market. From a regulatory perspective, this means that the regulator opted for a hazard-based approach, which is also a departure from similar legislation on chemicals outside Europe or in other EU sectors.[66] As stated by some authors, Regulation (EC) 1107/2009 can be seen as a strong example of the use of the precautionary principle in EU legislation.[67]

Endocrine disruptors, defined as substances of high concern in REACH, are therefore banned by the legislation on plant protection products[68] based on the hazard they pose. This means that PPPR only

[66] Bozzini E, Pesticide Policy and Politics in the European Union. Regulatory Assessment, Implementation and Enforcement, Palgrave Macmillan, 2017.

[67] Bozzini E, Pesticide Policy and Politics in the European Union. Regulatory Assessment, Implementation and Enforcement, Palgrave Macmillan, 2017.

[68] As well as by the regulation on biocidal products, adopted few years later (Regulation (EU) 528/2012).

allows the marketing and use of chemical products if they do not induce endocrine disruption in humans or wildlife.

Nevertheless, the PPPR creates a kind of 'breach' by introducing, in its Annex II, a derogation based on 'negligible exposure'. This means that, following the working definition provided by a draft Commission guidance document, the level is 'so small that it does not appreciably add to the risk and can safely be ignored'. Thus, according to points 3.6.3 / 3.6.4 / 3.6.5 (human exposure) of Annex II, the substances with endocrine-disrupting properties[69] cannot be approved 'unless the exposure of humans to that active substance, [herbicide] safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of 63 Regulation (EC) No 396/2005'.[70] Moreover, according to point 3.8.2 (environment) of the same Annex, an 'active substance, safener or synergist shall be approved only if … it is not considered to have endocrine disrupting properties that may cause adverse effects on non-target organisms[71] unless the exposure of non-target organisms to that active substance in a plant protection product under realistic proposed conditions of use is negligible'.

The rationale of this derogation is explained in the draft guidance document[72] on the interpretation of negligible exposure: 'The fact that Regulation (EC) No 1107/2009 is providing for the approval of active substances if exposure is negligible, implies that a zero release policy is not intended by the legislator and that a certain – negligible – exposure to humans or non-target organisms could be tolerated. For instance, if a zero release policy would be the intention of the legislation, points 3.6.3 to 3.6.5 would not be so clearly different from point 3.6.2 of the same Annex, where no reference to negligible exposure is made indicating a zero release policy. This is in particular evident by the fact that residues, although at the default level set in accordance with Article 18 of Regulation (EC) No 396/2005, are allowed under points 3.6.3 to 3.6.5, but not under point 3.6.2'.

With this interpretation, the emphasis placed by PPPR on hazard (through the definition of the cut-off criteria) seems to move slightly to a more risk-based approach. For instance, in its comments on the guidance document, CHEM Trust also highlighted this change of approach, which contradicts, in the NGO's opinion, the purpose of the PPPR: 'In our view it is clearly not in line with the legal text to interpret the "negligible exposure" provision mainly by prohibiting the non-professional use, applying a "stricter" risk assessment with additional safety factor applied and recommending risk mitigation measures. The proposed approach in this guidance document seems to make the exception to the rule by introducing more risk-based considerations instead of strictly limiting use scenarios'. At the same time, considered CHEM Trust, the 'transition from "negligible exposure" to "negligible risk" is not covered by the legal text of the PPPR'.[73] Similar criticism was made by Pesticide Action Network (PAN) Europe, which considered that the evaluation of ED pesticides is a priority and the guidance document does not provide (any or appropriate) answers in the absence of defined

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69 Annex II introduced the same derogations for carcinogenicity and toxicity for reproduction.

70 Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin.

71 Organisms affected by a pesticide although not the intended object of its use (according to IUPAC Glossary of Terms Used in Toxicology, 2nd Edition).

72 European Commission, Technical guidance on the interpretation of points 3.6.3. to 3.6.5, and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, in particular regarding the assessment of negligible exposure to an active substance in a plant protection product under realistic conditions of use, 2015.

73 CHEM Trust's comments on Draft technical guidance on the interpretation of points 3.6.3 to 3.6.5 and 3.8.2 of Annex II to regulation (EC) No 1107/2009, in particular regarding the assessment of negligible exposure to an active substance in a plant protection product under realistic conditions of use (Version May 2015), 2015.

criteria for identifying the endocrine disruptors.[74] This change of approach was hailed by the European Public Policy Advisors (EPPA) consultancy, which considered that the European Commission (DG SANTE) '**rightly goes in this direction**,[75] bringing this aspect of the PPP Regulation closer to that on biocides (which is more risk-management oriented, with three possible derogations), through an interpretation of "negligible exposure" in line with the "negligible risk" of the biocides legislation. In their opinion, this approach would also streamline both pieces of legislation in this area and avoid the paradoxical situation in which the same substance could be authorised for use as a biocidal product but not as plant protection.[76] The European Crop Protection Association (ECPA) considered that 'the current measures are extremely challenging and it will be extremely difficult to meet the additional requirements'. For ECPA, the negligible exposure should 'take into account several factors, for instance the populations to be considered, the potential routes of exposure including the mixtures (formulations) used, and the risk thresholds set for the decision-making'.[77]

In practice, the prohibitive effect of the cut-off criteria is also sometimes bypassed by an inappropriate use of another derogation established by the regulation, which operates by the way a loophole – under Article 53 – as shown in a study carried out for the EPRS European implementation assessment of Regulation (EC) 1107/2009.[78] Article 53 allows Member States, in exceptional situations, to authorise products that do not comply with the conditions provided for in the regulation. The EPRS study revealed that 'a relatively small number of Article 53 authorisations are granted for emergency situations, with the majority of such authorisations not relating to special circumstances', a context in which 'the number of derogations granted by Member States has increased significantly' (from 59 in 2007 to almost 400 in 2017). The figures below indicate the number of derogations for plant protection products in 2016 and 2017 (containing approved,[79] banned, or active substances for which approval was pending).

[74] PAN Europe's comments on the guidance document on negligible exposure, 2015.

[75] Highlighted in bold as in the original text.

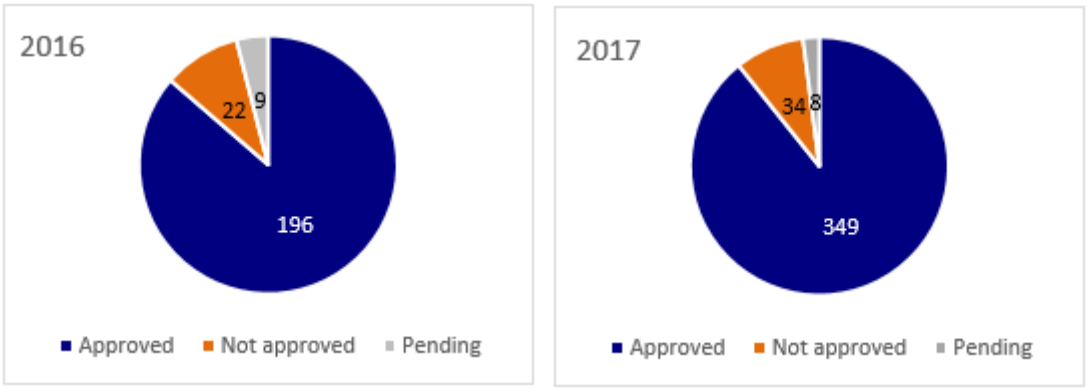
[76] EPPA's comments on the guidance document on negligible exposure, 2015.

[77] ECPA comments on the guidance document for negligible exposure, 2015.

[78] Milieu Ltd and IEEP, Evaluation of the implementation of Regulation (EC) No 1107/2009 and its impacts. Mapping the usage made by Member States of the derogations laid down by Article 53 of the Regulation in *Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market,* European Implementation Assessment, EPRS, 2018.

[79] The derogations relating to PPPs containing approved active substances cover other uses than the authorised ones or a use not authorised in a Member State.

Figure 3 – Total derogations for plant protection products in 2016 and 2017



Source: EPRS, Regulation (EC) 1107/2009 on the Placing of Plant Protection Products on the Market, European Implementation Assessment, 2018.

For instance, within these derogations, three related derogations were granted in 2016 and two in 2017 for one substance considered to have endocrine-disrupting properties (Thiacloprid – approved as candidate for substitution).

Given that no agreed scientific criteria and guidance on how to identify and evaluate endocrine activity and disruption existed at the moment of the adoption of Regulation (EC) 1107/2009, the legislation envisages that 'by 14 December 2013, the Commission shall present to the Standing Committee on the Food Chain and Animal Health a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties (point 3.6.5 Annex II, Regulation (EC) 1107/2009)'. Even though harmonised guidance on EDs is highly important for regulatory purposes, the definition of scientific criteria proved to be a very difficult process in practice, mainly as a consequence of an apparent lack of consensus among scientists, but also at stakeholder level.

3.2. Defining the scientific criteria on endocrine disruptors

Both Regulation (EC) 1107/2009 and Regulation (EU) No 528/2012 on biocidal products (BPR) requested that the European Commission establish scientific criteria for endocrine disruptors by December 2013, with the difference that under the PPPR, the role of the Commission is limited to the submission of a draft 'of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties', while under the second regulation the Commission is mandated to adopt the criteria. The Commission opted for and encouraged the Member States to achieve harmonised criteria, so as to have the same criteria under both regulations. At the end of a long process of consultation, analysis and decision-making, the scientific criteria were finally published and entered into force in May 2018.

Defining the scientific criteria: a difficult exercise

Three major axes featured in the process leading to the definition and adoption of the scientific criteria:[80]

- discussions at political level between the EU and Member States;

[80] The process leading to the definition of scientific criteria involved an important number of activities, events, and meetings. This paper will only refer to some of them. For more details, see the European Commission's dedicated webpage.

- impact assessment carried out by the European Commission;
- dialogue with stakeholders.[81]

In 2011, the European Commission report 'State of the art assessment of endocrine disrupters',[82] also known as the 'Kortenkamp report' prompted opposing reactions, raising both approval and criticism.[83]

The authors of the report considered that the regulatory approach to endocrine disruptors 'will have to rely on criteria for adversity and endocrine-related modes of action'. They developed 'a decision tree approach (...) that proceeds in a step-wise manner by excluding substances that neither produce adverse effects, nor show endocrine-related modes of action. Substances producing effects shown to be of no relevance for humans or wildlife can also leave the decision tree, but in the absence of appropriate evidence, relevance should be assumed by default. The final regulatory decision rests on a consideration of the toxicological profile of the substances in a weight-of-evidence approach. This weight-of-evidence approach will have to consider potency[84] together with other factors such as severity and specificity of effect and irreversibility. Rigid potency-based cut-off values as decisive decision criteria are not recommended. Procedures that incentivise the provision of data in the case of data gaps are suggested. Regulatory decisions about endocrine disrupters will have to rely on weight-of-evidence procedures which are yet to be developed'.[85]

The report was just one contention in the complex story leading to the definition of scientific criteria. One of the elements that generated strong reactions, for instance, was the potency approach. Potency is the amount of a substance required to produce a specific effect of given intensity as compared to a standard reference. The way potency should be reflected in the classification of chemicals is one of the divergent issues that animates the debate on EDs. For instance, it was supported by some Member States, but categorically rejected by others, as well as by several NGOs. To give just a few examples, Member States' contributions to the debate showed different views on how the question of endocrine disruptors should be regulated: if for Germany and the UK, the approach should rely on potency-based cut-off criteria, Denmark proposed three categories of EDs: confirmed EDs (category 1); suspected EDs (category 2a); and indicated EDs (category 2b), and completely ignored the potency-based scenario. While the French National Agency for Food Safety, Environment and Labour (ANSES) suggested two cumulative parameters to identify an ED as a substance of very high concern: classification for category 1 (carcinogenicity) or 2 (reprotoxicity); and identification of an endocrine disruption mode of action for the adverse effect leading to the classification, based on weight-of-evidence.

The scientific opinion issued by EFSA in 2013 (mentioned above) did not really clarify the situation, given that the opinion itself raised controversy because of the change of approach (EFSA suggested

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81 For details on the activities and steps involved in the process of elaboration of the scientific criteria, see the European Commission dedicated webpage.

82 European Commission, State of the art assessment of endocrine disrupters, Final Report, 2011.

83 See, inter alia: CEO and Horel, A toxic affaire. How the chemical lobby blocked action on hormone disrupting chemicals, May 2015; BEUC, Hormone-disrupting chemicals: when will the EU act against these everyday toxicants?, 2016; Lorenz Rhomberg L, Goodman J, Foster W, Borgert Ch, & Van Der Kraak, G, A critique of the European Commission Document, 'State of the art assessment of endocrine disrupters', Critical Reviews in Toxicology, 42 (6), 2012; Hazardous Substances Advisory Committee (Defra), Comments on Kortenkamp et al (2012) 'State Of The Art Assessment Of Endocrine Disrupters', 2012.

84 Potency is the amount of a substance required to produce a specific effect of given intensity as compared to a standard reference. The way the potency should be reflected in the classification of chemicals is one of the divergent issues that animates the debate on EDs. For instance, it was supported by some Member States (Germany and the UK), but categorically rejected by others (Denmark, France), as well as by several NGOs, such as CHEM Trust and PAN Europe).

85 European Commission, State of the art assessment of endocrine disrupters, Final Report, 2011, p. 8.

that EDs should be subject to risk assessment and not only to hazard assessment, as envisaged in the PPP Regulation).

The EU Court of Justice also entered this rather complicated context for progress in 2014, when referred by Sweden,[86] which filed against the European Commission for delays in establishing scientific criteria for the identification of chemicals with endocrine-disrupting properties (as planned under by the Biocidal Products Regulation). In its judgment[87] of December 2015, the Court concluded that the Commission failed to comply with its 'clear, precise and unconditional' obligations established in Regulation (EU) No 528/2012. Furthermore, there is no legal obligation for the Commission to carry out an impact assessment, which would have prevented it from fulfilling its obligations on time, as the Commission suggested.[88]

From draft proposals to adopted criteria

In June 2016, the Commission published a communication on endocrine disruptors and the draft Commission acts setting out scientific criteria for their determination in the context of the EU legislation on plant protection products and biocidal products,[89] together with an impact assessment presenting the results of a screening of the available evidence of approximately 600 chemicals covered by different EU legislations, beyond PPPR and BPR: REACH, cosmetics, medical devices and the water framework directive. In its document, the Commission claimed to have taken the main concepts on which the scientific and regulatory debates are based into consideration, such as:

- definition of endocrine disruptors: 'an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations';[90]
- definition of 'adverse effect': 'a change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences';[91]
- causality link between mode of action and adverse effect: 'the Commission intends to follow a concept of a reasonable evidence ("biological plausibility") to determine causality';
- 'categorisation' of EDs: 'The Commission considers that establishing different categories of what may be an endocrine disruptor does not help to define what is an endocrine disruptor in the context of biocides and pesticides. Furthermore, such categorisation for pesticides and biocides would decrease legal certainty for regulators and stakeholders, without established benefits in terms of protection of health and the environment';

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86 EU Court of Justice, *Sweden* v *European Commission*, Case T-521/14, 2014.

87 EU Court of Justice, *Sweden* v *European Commission*, Case T-521/14, Judgement of the Court, 2015.

88 See also Scholz, N, Setting criteria on endocrine disruptors. Follow-up to the General Court judgment, EPRS, 2016.

89 Communication from the Commission to the European Parliament and the Council on endocrine disruptors and the draft Commission acts setting out scientific criteria for their determination in the context of the EU legislation on plant protection products and biocidal products, COM/2016/0350 final.

90 World Health Organization International Program on Chemical Safety, *Global assessment of the state-of-the-science of endocrine disruptors*, 2002, WHO/PCS/EDC/02.2.

91 World Health Organization. International Program on Chemical Safety, Principles and methods for the risk assessment of chemicals in food. Environmental Health Criteria, 2009.

- existence of a 'safety threshold': 'The Commission considers that answering the question of whether a threshold exists is neither necessary nor appropriate when defining scientific criteria for determining what is an endocrine disruptor';
- dose-effect relation – the potency: 'for the specific purpose of setting scientific criteria, it is not necessary to include considerations of how "potent" an endocrine disruptor is';
- hazard versus risk: it is recalled that, as a general rule, under PPPR – as well as under the regulation on biocides – 'endocrine disruptors are banned on the basis of hazard, without undergoing a specific risk assessment on the basis of considerations of exposure (although in some cases derogations – either hazard, risk or considering socio-economic issues – may apply on a case by case basis), as stipulated by the legislation'; nevertheless, the communication added that 'in the context of endocrine disruptors, the European Food Safety Authority scientific opinion from 2013 has supported the principle of a risk-based approach for plant protection products', so the Commission, 'in line with the mandate given by the co-legislators, has concluded that the grounds for possible derogations for plant protection products should be updated so as to refer – in line with the biocides legislation – to 'negligible risk', while fully maintaining the concept of a hazard-based ban of endocrine disruptors, thereby ensuring an equally high level of protection of health and the environment'.

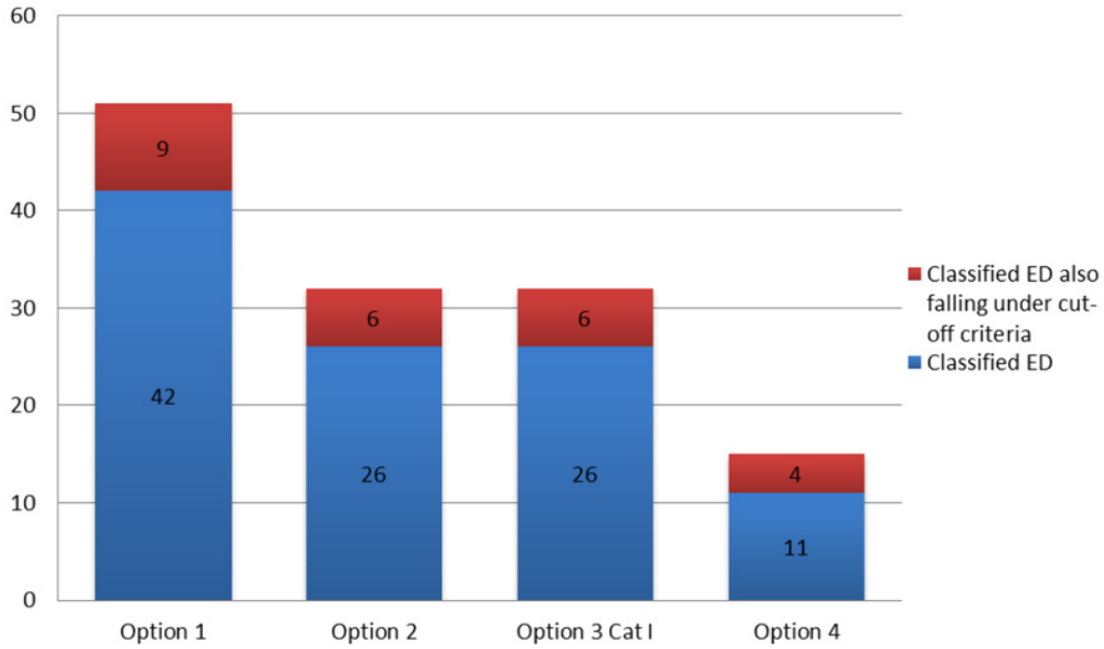
The Commission communication is accompanied by an impact assessment (IA),[92] which provides 'an estimation of which substances are expected to fall under each of the four options for the criteria to identify EDs'. The policy options, presented in the roadmap published by the European Commission in July 2014, range from no change in the EU regulatory framework (option one), to scenarios that include the identification based on the definition given by WHO (option two), plus additional categories (option three), or the inclusion of potency (option four).

Briefly, the Commission maintained the hazard-based approach for PPPs in its draft, with exceptions for professional use granted in very specific situations (if negligible risk can be demonstrated, or the necessity of the substance to combat serious pests, which cannot be contained by other available means).

For the plant protection products, the screened active substances identified by the Commission as potential EDs under each of the options are summarised in the following figures:

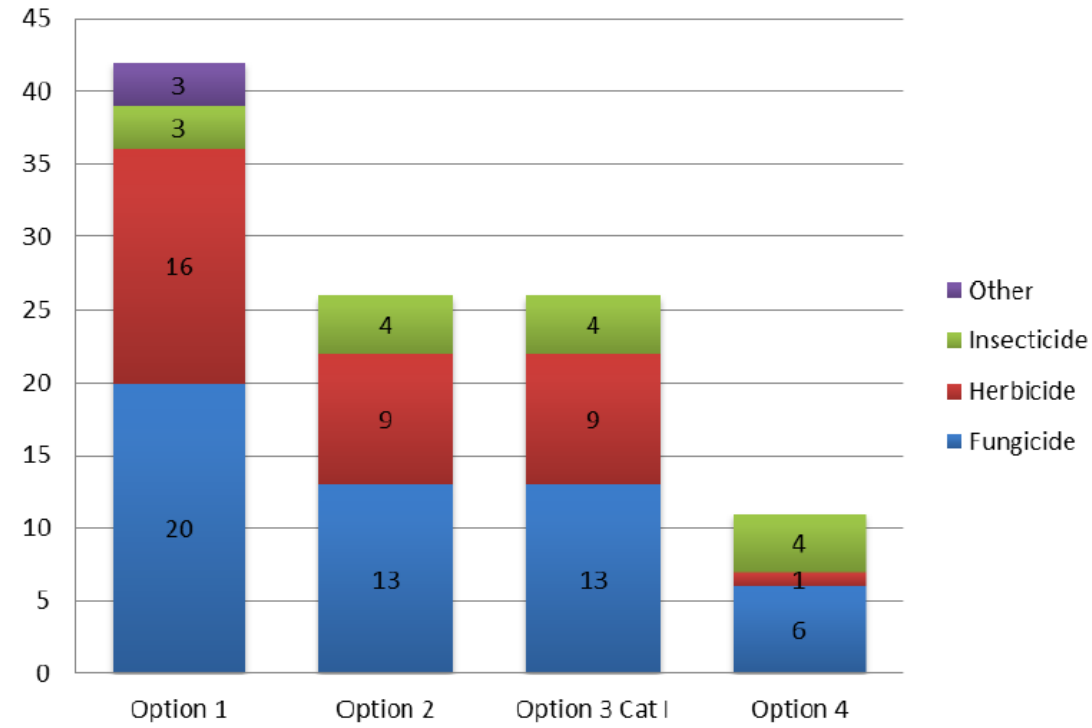
[92] European Commission, staff working document. Impact assessment. Defining criteria for identifying endocrine disruptors in the context of the implementation of the plant protection products regulation and biocidal products regulation, SWD(2016) 211 final, 2016.

Figure 4 – Number of active substances used in PPP identified as potential EDs under each of the four options



Source: European Commission.

Figure 5 – Number of substances classified as potential ED by PPP major group, excluding substances that are classified as C1 or R1[93]



Source: European Commission.

[93] C1/R1: substances that are classified as carcinogenic or toxic.

Reactions to the draft were immediate, representing the main (opposing) views involved in the debate on endocrine disruptors. Some of these are presented below.

Generally, industry voices advocated an approach that considers the WHO/IPCS definition of EDs as not insufficient to allow for a clear distinction between substances that pose a risk and substances that do not, and also pleaded for consideration of potency when evaluating the endocrine-disrupting properties of a substance. In this context, the President of ECPA said that the 'criteria fail to distinguish between those substances which may cause actual harm and others which pose no threat to safety' and 'this could lead to bans on crop protection products with the same endocrine-disrupting properties found in everyday products like coffee'. The ECPA President added 'We certainly recognise the significant public interest in this topic but believe we need a proposal that targets only those substances which cause actual harm otherwise we risk taking away tools from farmers which they need to sustainably produce our safe, healthy, affordable food'. For its part, the European Chemical Industry Council (CEFIC) considered that 'unless potency is taken into account, we will fail to address only those substances that cause harm. Many years down the road, we now have a restatement of the WHO definition. This provides further clarity, but it is not sufficient. We need to ensure the highest standards of protection and also allow for innovation'. Along the same lines, a representative of Plastics Europe underlined that 'the criteria to identify endocrine disruptors are out. We still lack a commonly accepted working criteria that would allow differentiation between a substance of regulatory concern and a substance of no or low concern'.

Environmental NGOs and consumers' associations expressed their concerns about the ability of the criteria proposed by the Commission to ensure a high protection of human health and the environment. The Health and Environment Alliance (HEAL) stressed that the vision put forward by the Commission 'will not prevent diseases related to endocrine-disrupting chemicals. The requirements are so strict, the burden of proof so high that we'll have years of harm to health before we can remove them. This is not what the legislation requires, which is, that EDCs that may cause adverse effects are banned', while a representative of the biggest European consumer organisation (BEUC) added: 'This proposal will not properly protect consumers from harmful endocrine disruptors as only a few substances would be defined and regulated as EDCs. This goes against the precautionary principle where protective action should prevail even in the face of scientific uncertainty. Sadly today's package seems to confirm our concerns that the Commission has lowered its ambition concerning strong EDC criteria'.[94] PAN Europe also published an assessment on the impact of the criteria for endocrine disrupting pesticides, highlighting that, based on the regulatory option to be chosen, 'very few pesticides will be banned because of their endocrine disrupting properties, or even zero', while one regulatory option 'makes no sense in the assessment of pesticides to protect public health'; moreover, the assessment estimated that the impact on agriculture will be quite limited, concluding that 'the ban of a number of harmful pesticides with endocrine disrupting properties from the market is not only favourable for society and the environment but also feasible for agriculture', where alternative solutions are already available.[95] In September 2017, the Commission presented two draft proposals[96] establishing the criteria to identify substances with endocrine-disrupting properties, in accordance with PPPR and BPR. While the draft on biocidal products was adopted in the form of Delegated Regulation (EU) 2017/2100[97] to implement Regulation (EU) 528/2012, the draft concerning the PPPs was rejected by the

[94] All the positions quoted here (both industry and NGOs) are available on EurActiv website.

[95] PAN Europe, Impact assessment of the criteria for endocrine disrupting pesticides, 2016.

[96] More details on the previous versions of the draft implementing regulation presented in September 2017 can be found here.

[97] 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.

European Parliament because of a derogation for substances with harmful effect on non-target organisms. The Commission presented a new draft regulation in late 2017, leaving out the controversial exemption (Member States voted in its favour[98] within the Standing Committee on Plants Animals Food and Feed – PAFF) and the scientific criteria for the identification of endocrine disruptors were finally adopted in May 2018 through Commission Regulation (EU) 2018/605.[99]

The new regulation sets out scientific criteria for the determination of endocrine-disrupting properties in PPPs,[100] which apply from 10 November 2018 to all new and ongoing applications [101]for plant protection products. It states that a substance is considered as an endocrine disruptor if the following three criteria are met:

- 1) it shows an adverse effect in an intact organism or its progeny, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences; and
- 2) it alters the function(s) of the endocrine system; and
- 3) the adverse effect is a consequence of the endocrine mode of action, as regards humans or non-target organisms.

If there is evidence demonstrating that the adverse effects identified are not relevant to humans or at the (sub)population level for non-target organisms, the substances are not considered EDs.

With regard to the scientific evidence and knowledge that supports the identification of EDs, the regulation envisages that the following should be taken into consideration:

- all available relevant scientific data *(in vivo* studies or adequately validated alternative test systems predictive of adverse effects in humans or animals; as well as *in vivo*, *in vitro*, or, if applicable, *in silico* studies[102] providing information about endocrine modes of action); scientific data generated in accordance with internationally agreed study protocols; other scientific data selected applying a systematic review methodology, in particular following guidance on literature data;
- an assessment of the available relevant scientific data based on a weight of evidence approach;
- using a weight of evidence approach, the link between the adverse effect(s) and the endocrine mode of action shall be established based on biological plausibility;
- adverse effects that are non-specific secondary consequences of other toxic effects shall not be considered for the identification of the substance as an endocrine disruptor.

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98 18 Member States in favour, representing 65.79 % of the EU population, three Member States against (5 %) and seven Member States abstaining (29.21 %).

99 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.

100 The same criteria apply for biocidal products.

101 As for the assessment of endocrine disruptors properties in the case of old substances, this will proceed as long as they are re-evaluated in the context of re-approval, meaning at the expiry of the first approval (after 10 years).

102 *In vitro* refers to the technique of performing a given procedure in a controlled environment outside of a living organism; *In vivo* refers to experimentation using a whole, living organism as opposed to a partial or dead organism; *In silico* means 'performed on computer or via computer simulation', according to the Marshall Protocol Knowledge Base.

To support the ED identification and assessment process, the European Commission tasked EFSA and ECHA with the preparation of a guidance document on how to identify substances with endocrine-disrupting properties in pesticides and biocidal products, in order to ensure a coherent approach at EU level. As explained by the document, its aim is 'to provide guidance to applicants and assessors of competent regulatory authorities on how to identify endocrine disruptors in accordance with the ED criteria laid down in Commission Delegated Regulation (EU) No 2017/2100 and Commission Regulation (EU) No 2018/605 for biocidal products (BP) and plant protection products (PPP), respectively. The guidance document describes how to gather, evaluate and consider all relevant information for the assessment, conduct a mode of action (MoA) analysis, and apply a weight of evidence (WoE) approach, in order to establish whether the ED criteria are fulfilled'.[103] Based on OECD tests and methodologies, the guidance document gathered in four groups all the parameters to be used in the identification of potential EDs, based on their capacity to indicate endocrine activity and related adversity. In this respect, 'some effects are considered to be strong indicators of effects being mediated by an EATS (estrogenic, androgenic, thyroidal and steroidogenic) modality, while some others are considered to be potentially sensitive to, but not diagnostic of, EATS modalities'.

Both the adopted criteria and the guidance document raised criticism among some key stakeholders.

The Endocrine Society[104] expressed its concerns[105] as regards the EU's new criteria, considering that they 'do not go far enough to protect public health' and 'the final criteria require an excessively high level of proof that a chemical is an endocrine disruptor'. In its view, 'the finding of an adverse effect that involves hormones or endocrine systems should be sufficient to identify an EDC. A detailed study of action and mechanisms should not be required'. In a position statement[106] from May 2018, the Endocrine Society had already communicated its concerns, referring at that time to the fact that 'the European public may be placed at risk because critical information about potential health effects of endocrine-disrupting chemicals is being overlooked in the development of guidelines and regulations, hindering the efficient identification of EDCs'. As for the EFSA/ECHA guidance document, the Endocrine Society considered that it creates 'unnecessary barriers to regulating harmful EDCs' and has 'a limited scope', because it looks at only four pathways regulated by well-studied nuclear receptors, and fails to address 'other pathways that affect important functions such as metabolism, body weight and insulin action'.

The new scientific criteria adopted in the EU were also denounced by both parties whose views are traditionally opposed in the debate on endocrine disruptors, for different reasons, namely NGOs such as Corporate Europe Observatory (CEO) and the Pesticides Action Network (PAN Europe), on the one hand, and the manufacturers, on the other. CEO noted that the new approach creates 'significant obstacles in the way of effective public health and environment regulation', given the 'impossibly high burden of proof prior to any potential ban of chemicals acting as endocrine disruptors'.[107] Furthermore, demonstrating the causality link between adverse effect in humans and endocrine mode of action is, one the one hand, very difficult, given that scientific research cannot yet offer strong evidence on this and, on the other hand, 'goes against standard classification

[103] EFSA/ECHA, Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009, 2018.

[104] The Endocrine Society is the global oldest and largest association of professionals in the field of endocrinology, which provides the field with evidence-based recommendations for clinical care and practice.

[105] Endocrine Society, EU criteria fall short of protecting public from endocrine disrupting chemicals, June 2017

[106] Endocrine Society, Endocrine-Disrupting Chemicals in the European Union, Position statement, May 2018.

[107] Corporate Europe Observatory, Worse than expected: Commission criteria for endocrine disruptors won't protect human health, June 2016.

practice for similar substances, such as those with adverse effects on reproduction'. For CEO this means that 'should the current criteria be upheld, many, if not all, suspected EDCs will escape a ban'. In the same vein, PAN Europe also underlined that with the new legislation, 'meeting the criteria will have no impact and ED pesticides will be kept on the market'.[108] On the industry side, ECPA (European Crop Protection Association) expressed its disappointment and 'still fundamentally believes that the criteria are missing crucial elements', which 'will lead to the loss of a number of substances, without consideration being given to the significant agronomic impact this could have on Europe's farmers'.[109]

In the context of the publication of the new criteria and the new scientific information emerged in the recent years, the European Commission also announced the preparation of a new strategy on endocrine disruptors in July 2017, aiming at reducing the exposure of EU citizens to endocrine disruptors, beyond pesticides and biocides.[110] In its position statement of May 2018, the Endocrine Society already stressed the necessity for the EU to revise its strategy on EDS, by 'taking into account new scientific information developed in recent years, and with the aim of minimising exposure to hazardous EDCs throughout the environment and in consumer products'.[111]

3.3. European Commission communication on endocrine disruptors (2018)

In November 2018, when the two regulations stipulating the ED criteria entered into force, the European Commission published the new EU strategy: 'Towards a comprehensive European Union framework on endocrine disruptors'.[112] The document recalls the main achievements in the field since the adoption of the first strategy (1999) and puts forward the future EU approach.

The strategy recalls the importance of endocrine disruptor-related issues for the environment, health and consumer safety, as well as the steps taken at European level to limit their impact. It also underlines some of the main knowledge gaps (and, at the same time, controversial topics), such as the impact of ED exposure on human health and the environment, the threshold-dose level, and the cocktail effects of EDs.

Four main elements underpin the new European strategy, aiming at 1) minimising exposure; 2) developing a solid scientific basis for public policies; and 3) encouraging 'dialogue' between scientists, public authorities and private actors in the field:

- Precaution: 'When scientific evaluation cannot conclude with sufficient certainty, the Commission is guided by the so-called precautionary principle to take protective measures for its citizens and the environment'.
- Coherence: 'the Commission considers that there should be a coherent approach to the identification of endocrine disruptors across all relevant Union legislation, based on the broadly accepted definition of the World Health Organization'. In the future, the Commission will also consider the possibility of establishing horizontal criteria to

[108] PAN Europe, The collapse of the Endocrine Disruptors' policy: Commission's ultimate gift to the pesticide industry, July 2018.

[109] Chemical Watch, EU adopts EDC criteria for plant protection products, April 2018.

[110] European Commission, Press Release, Brussels, July 4 2017.

[111] Endocrine Society, Endocrine-Disrupting Chemicals in the European Union, Position statement, May 2018.

[112] Communication from the Commission to the European Parliament, the Council, The European Economic and Social Committee and the Committee of the Regions, *Towards a comprehensive European Union framework on endocrine disruptors*, COM/2018/734 final.

identify EDs in the legislation, 'for reasons of legal certainty and to avoid the potential risk that a substance is identified as endocrine disruptor under one piece of legislation and not under another one'.

- Up-to-date scientific evidence: the European Union will continue to support research (mainly through Horizon Europe), as being an essential element to deepen understanding of endocrine disruptors and a strong basis for effective policy-making.
- Inclusiveness, both at EU and international level: 'In order to be able to progress in effectively addressing endocrine disruptors, the Commission will follow an inclusive approach that is open, transparent and brings together all interested parties'.

To protect both human health and the environment from endocrine disruptors, the Commission 'is launching a comprehensive screening of the existing legislative framework (...). This reflection exercise will allow an assessment of whether EU legislation on endocrine disruptors delivers on its overall objectives to protect human health and the environment'.[113] As the Commission explained, this will be the first cross-cutting perspective on chemicals, and the focus will be areas that are less specifically regulated today, such as toys, cosmetics, and food contact materials.

Otherwise, the text is limited to general observations, such as the organisation of an annual forum on endocrine disruptors and the creation of an online one-stop shop on the issue, a commitment to examine the possibility of including endocrine disruptors in the existing UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS), as well as support for the development of test guidelines within OECD. As we can see, the strategy is rather succinct and vague, and does not define very specific or ambitious actions. No timetable is proposed.

The main actors' reactions[114] to the new strategy were mixed. Even before its publication, the draft strategy was critically received by some. For instance, in July 2018, while collecting input[115] from interested parties on the roadmap of the future strategy, Générations Futures, a French NGO and member of EDC-FREE Europe, noted in its feedback: 'Regrettably, the EU Commission's roadmap is disappointing. It formulates general observations but still does not detail any specific actions and structured political action plan. This lack of firmness is incompatible with the need to reduce immediately human exposure to endocrine disrupters. The Commission mainly welcomes actions already implemented with the 'Strategy for endocrine disruptors' adopted in 1999. Acknowledging that the "concerns of European citizens on endocrine disruptors remain high", the Commission seems to have lost its determination to develop an ambitious and coercive strategy. It is no longer about implementing a "strategy" but merely a "framework"'.

In its comments on the proposed revised EU strategy, the Endocrine Society also highlighted several aspects that should be considered (low-dose effects, non-monotonic dose-response,[116] developmental origins of disease,[117] and other features of EDCs recognised and characterised for

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[113] In an email to Politico, a representative of the European Commission said that 'Commission services are now ready to begin the technical work' and 'hope to finalise the exercise as soon as possible next year so that the new College will have all the relevant information in its hands to decide on the next steps' (Politico, *Commission: Fitness check for endocrine disruptors to be finished in 2020*, 5 March 2019).

[114] A general debate on the EU framework on EDs is also planned to be on EU Council's agenda in May 2019. Ministers 'will be asked to indicate what they think would be the best approach to develop a coherent framework and what actions could be taken in the short term to accelerate the implementation of the commitments made under the 7th Environmental Action Programme', according to Agence Europe.

[115] The 44 comments received by the Commission are available here.

[116] Unconventional dose-response relationships that go against predictable or typical dose-response patterns.

[117] Exposure to certain environmental influences during critical periods of development and growth may have significant consequences on humans' short- and long-term health (see: Barker, DJ, The origins of the developmental origins theory, *Journal of Internal Medicine*, 261(5), 2007, 412-417.

some individual chemicals should be included in the areas of study), or reconsidered (the reference to 'scientific uncertainty' is confusing for citizens and stakeholders); 'public interest is amplified not by scientific uncertainty over effects, but rather the steady increase in scientific knowledge and education from public health groups and medical/scientific organisations'; the 'clear and comprehensive information' for the public should include consideration for vulnerable/susceptible populations such as pregnant women, adolescents, and workers with elevated exposures), as well as more concrete issues that should be addressed (such as specific measures for how legal gaps will be closed, ambitious targets for identifying EDCs, better test methods, biomonitoring, and screening).

Once the strategy was published, CEFIC, on the industry side, welcomed 'the proposal for a fitness check to make sure that our approach to dealing with endocrine disruptors is coherent, consistent and science-based. As science on endocrine disruption is still developing, investing more into research on endocrine disruption and improving testing methods for EDs is rightfully identified as one of the focus areas for the Commission. The chemical industry looks forward to contributing to the upcoming fitness check proposed by the European Commission',[118] while some NGOs criticised precisely the idea of carrying out a fitness check, according to CHEM Trust: 'the proposal to launch a fitness check to assess whether EU relevant legislation on endocrine disrupters delivers on the protection goals will lead to further delays instead of solving known inadequacies in the risk management of EDCs in the EU'. HEAL underlined the positive elements of the strategy, such as 'commitments for more international collaboration, research, and information on EDCs for citizens, including encouraging EU Member States to run awareness-raising campaigns', criticised the idea of a fitness check and noted some shortfalls (the lack of concrete steps to minimise exposure), and missed opportunities (the absence of a specific plan to adapt EU laws to address the EDC cocktail effect). EDC-free Europe welcomed the goal of minimising exposure, but deplored the lack of 'specific measures and timelines on how people and the environment can be better protected from these harmful chemicals'.[119] A few months later, PAN Europe also criticised the new strategy and qualified it as 'an empty document'. The Commission proposal for a fitness check is seen as 'time delay and spending of public resources'. Moreover, PAN Europe underlined that the strengthening of the PPP Regulation did not produce concrete results, given that 'in 2018 zero pesticides have been banned due to their EDC properties' ... 'not even those identified from the Commission's own impact assessment' and 'a few that have been banned is due to their multiple toxicity'.[120]

As to the Member State reactions, representatives of the French government[121] pleaded for 'tougher' EU action on endocrine disruptors and stressed the need, for the new strategy, 'to be "reinforced" and given an implementation timeline'.[122] In March 2019, Member States' representatives meeting within the EU Council also debated the Commission communication. They were asked to answer two questions, one on the best approach to develop a coherent framework and the second on the action to take in the short-term to accelerate the implementation of the commitments made under the seventh environmental action programme. In this context, Ministers[123] insisted on three concrete actions: review data sets to better identify endocrine

[118] https://cefic.org/media-corner/newsroom//cefic-welcomes-commission-communication-on-endocrine-disruptors/

[119] EDC-free Europe, New Communication on endocrine disruptors lacks concrete measures to reduce harmful exposures, 7 November 2018.

[120] PAN Europe, Why are our EU regulators so reluctant to protect us from hormone disruptors?, 12 March 2019.

[121] France has been running a process of evaluation and strengthening of its own national strategy on endocrine disruptors.

[122] Paris demands tougher EU endocrine disruptor action, Ends Europe, 12 November 2018.

[123] The representative of Denmark qualified the Commission action plan as 'disappointing', according to Agence Europe, Member States call for a coherent framework on endocrine disruptors, 5 March 2019.

disrupters; establish a dynamic European list which also covers substances that are potentially endocrine disrupters; ban the presence of these disrupters in cosmetics, toys and consumer products.[124]

The European Economic and Social Committee (EESC) presented its opinion[125] on the strategy in March 2019. The EESC expressed support, but estimated that the 'strategy should be reinforced with a realistic action plan which sets targets and deadlines'. Moreover, the EESC underlined several elements that should be taken into consideration by the Commission when addressing ED-related issues, such as: a framework that respects the principle 'one substance, one toxicology' and includes a harmonised use of the precautionary principle, an adequate budget, with different specific budget lines, supporting independent research, financial support for more sustainable production, a permanent and structured system of information exchange and communication between stakeholders, creation of an open data bank for POPs (persistent pollutants) and EDs.

Members of the Committee of Regions (CoR) also adopted a draft opinion on the strategy, the rapporteur (Uno Silberg) saying in this context that 'we need public awareness actions and coordinated measures at all levels to prioritise citizens' health while also considering the interests of consumers and industry'.[126] The draft opinion is to be adopted at the CoR's plenary session on 26-27 June 2019.

While the publication of the strategy could have been generally hailed by the actors involved in the debate, their reactions, regardless of their position, give the impression that the important subjects of the debate actually go beyond the scope of the strategy, and are more oriented towards the future than based on what the contents of the present strategy.

3.4. European Parliament position on endocrine disruptors

Endocrine disruptors appear to be a topic of great interest for the European Parliament (EP), as shown by positions directly related to the subject, and in the broader context of chemicals related-issues, or regarding the protection of public health and the environment. Some of Parliament's positions and reactions focused on the debate on EDs are presented below.

In 2000, the European Parliament reacted to the Community strategy for endocrine disruptors[127] (1999) through a resolution[128] which showed, *inter alia*, the importance, for the EP, of immediate action as regards endocrine disruptors: whether the European Commission proposed to draw up a list of substances suspected of being endocrine disruptors and proceed to further tests. The Parliament called for identification of the substances and action against them under the precautionary principle. The European Parliament also played an active role during the policy formulation of Regulation (EC) 1107/2009, insisting that the Commission include EDs among cut-off criteria.

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[124] Agence Europe, Member States call for a coherent framework on endocrine disruptors, 5 March 2019. See also the provisional version of the Outcome of the Council Meeting, p. 8.

[125] EESC, Towards a more comprehensive EU framework on endocrine disruptors, Opinion, 20 March 2019.

[126] CoR, Blue economy in European regions: a gateway to sustainable growth and jobs, press release, 29 March 2019.

[127] Which was elaborated following the adoption by the European Parliament of a resolution calling on the European Commission to improve the European legislation in the field of endocrine disruptors and to strengthen the research and communication to the public in this area.

[128] European Parliament resolution on the Commission communication to the Council and the European Parliament on a Community strategy for endocrine disrupters – a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM(1999) 706 – C5-0107/2000 – 2000/2071(COS)).

More recently (2013), the European Parliament expressed its views on EDs in a resolution on the protection of public health from endocrine disruptors.[129] Referring to both the context of the legislative process at European level and the increase of hormone-related disorders and illnesses in humans over the last 20 years, the Parliament, considering that 'where adverse effects of endocrine disrupting substances can reasonably be presumed, measures to protect human health have to be implemented', insisted on the fact 'that the absence of precise knowledge, including final proof of causal links, should not prevent health protection measures to be taken in line with the precautionary principle, keeping in mind the principle of proportionality', provided 'the potential of endocrine disrupting substances to cause harmful or irreversible effects'. The Parliament called on the Commission to take steps against EDs by defining scientific criteria in accordance with the definitions provided by the World Health Organization's international programme on chemical safety (WHO/IPCS) (including the 'adverse effect' and 'endocrine mode of action') and based 'on a comprehensive hazard assessment carried out on the basis of state-of-the-art science, taking potential combination effects into account as well as long-term effects and effects during critical windows of development', with different categories based on the strength of evidence.

During the current legislative term (2014-2019), the European Parliament reiterated its interest in the topic. In June 2016, following the ruling of the Court of Justice in Case T-521/14 *Sweden* v *European Commission* (see section 3.2), the Parliament adopted a resolution[130] calling on the Commission 'to comply immediately with its obligations (...) and to adopt immediately hazard-based scientific criteria for the determination of endocrine-disrupting properties'.

In October 2016, within its resolution on the implementation of the Food Contact Materials (FCM) Regulation (EC) No 1935/2004, the European Parliament also called for 'horizontal criteria for all products', which is reflected in the strategy of November 2018 (under the coherence approach).

One year later (October 2017), the Parliament adopted a resolution reacting to the proposal establishing new scientific criteria for endocrine disruptors, raising opposition to the text submitted by the Commission.[131] The co-legislator estimated that the European Commission surpassed 'the implementing powers provided for in Regulation (EC) No 1107/2009' and did not agree with the idea of exempting some chemicals from the scope of criteria for identifying endocrine disruptors in pesticides, calling on the Commission to prepare a new proposal (the Commission duly complied). Prior to this resolution, during an exchange of views with the European Commission[132] in June 2016, Members expressed concern and (sometimes different) opinions about issues such as: the restrictive definition of what constitutes an EDC; the introduction of wider exemptions; the fact that the system of derogations does not take the cocktail effect into account; the absence of categories for different degrees of scientific evidence; the fact that the proposed criteria apply to biocidal products and plant protections products only; the fact that the criteria have to rely on 'biological plausibility' rather than conclusive evidence; that risk assessment should be an integral part of the legislation, and derogations should be exceptions; the question as to whether the changes of wording

[129] European Parliament resolution of 14 March 2013 on the protection of public health from endocrine disrupters (2012/2066(INI)), 2013.

[130] European Parliament resolution of 8 June 2016 on endocrine disruptors: state of play following the judgment of the General Court of the European Union of 16 December 2015 (2016/2747(RSP)).

[131] European Parliament resolution of 4 October 2017 on the draft Commission regulation amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine-disrupting properties (D048947/06 – 2017/2801(RPS).

[132] Represented by Commissioner Vytenis Andriukaitis, responsible for health and food safety; the debate can be watched on the European Parliament website.

interpreted as a shift from a hazard-based to a risk-based approach were in line with the Commission's legal mandate.[133]

As regards the more recent (2018) strategy on EDs, the file is in a 'preparatory phase' in Parliament, the institution has therefore not yet adopted an official position. Some Members of Parliament's Committee on Environment, Public Health & Food Safety (ENVI) presented their criticisms of the new strategy in the context of a presentation of the document by the Commission's representative to the ENVI committee meeting in January 2019. Certain MEPs referred to the absence of 'measurable results and indicators and clear allocated funds', the lack of ambition of the strategy, its interest 'more in the world of the internal market than in the field of public health'.[134]

In March 2019, the European Parliament published a study commissioned by its Committee on Petitions (PETI), dedicated to endocrine disruptors: 'Endocrine disruptors: from scientific evidence to human health protection policy'.[135] The study reviewed 'the scientific evidence regarding the concept of endocrine disruption, the extent of exposure, associated health effects and costs' and called on the EU to develop coordinated regulations governing all types of endocrine-disrupting chemicals in order to minimise human exposure. The authors of the study came to the following main conclusions: 1) EDs are present in all media (water, diet, food contact materials, cosmetics…), and that a large majority of EU citizens' bodies contain dozens of suspected EDs; this figure is expected to increase, with exceptionally high societal costs; 2) the existing evidence justifies considering EDs as a specific class of hazard and therefore deserving of treatment with an equivalent level of concern to CMRs (carcinogens, mutagens, substances toxic for reproduction); 3) the existing uncertainties cannot be a reason to postpone regulatory action, at least not for the substances that are most likely to be EDs; 4) the existing regulatory procedures are inefficient in filtering EDs to allow their identification and the limitation of their use before being marketed, which 'is clearly detrimental for the environment, human health, society, sustainability and most probably for our economy'. Based on these conclusions, the authors made several recommendations to policy-makers as regards policy goals, ED definition, guidance documents, test development and requirements, ED management in specific sectors and across sectors, surveillance of production, use and exposure to EDs, and research priorities.

The report was welcomed by the Endocrine Society, which 'applauded the European Parliament's release of a report demonstrating that endocrine-disrupting chemicals (EDCs) pose a serious threat to the health of current and future generations and illustrating the need for additional action by policy-makers in the EU to address this issue'.[136]

Even though the study does not represent the official position of the European Parliament, it is another example of the constant interest the institution shows in the topic.

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[133] As presented in Scholz, N, Commission proposals on identifying endocrine disruptors, EPRS, 2016.

[134] Chemical Watch, MEPs blast Commission over lack of practical measures on EDCs, January 2019.

[135] Endocrine Disruptors: from Scientific Evidence to Human Health Protection Policy, Policy Department for Citizens' Rights and Constitutional Affairs, European Parliament, 2019.

[136] Endocrine Society, Endocrine Society praises European Parliament report's call to regulate endocrine-disrupting chemicals, 21 March 2019.

4. Conclusions

This paper outlines three main axes of the debate on EDs, which have also impacted the latest regulatory and strategic approaches in the EU:

- gaps and divergences at scientific level;
- regulatory issues at stake;
- strongly opposing views between the two main categories of stakeholders: those representing safety, public health and environmental protection interests (referred to as 'NGOs'), and industry actors.

A large body of evidence has been accumulated indicating that some substances (both natural and man-made) interfere with the function of hormones in the body and have disruptive effects. These substances (such as pharmaceuticals, pesticides, plasticisers) are present in everyday products (plastic bottles, detergents, food, toys, cosmetics, plant protection products, etc.), and are practically impossible to completely avoid. For this reason, efforts have been made at **scientific** (identification of EDs and their mode of action), **political** (definition of policies that address the main challenges in terms of public health and environmental protection), and **regulatory** (establishing rules that help minimise the negative impact of EDs on human health and wildlife) levels, to ensure better protection of humans and the environment. Nevertheless, general knowledge gaps related to EDs, as well as limitations regarding the ability of the current testing methods to adequately screen for endocrine-disrupting properties still exist, implying uncertainties when it comes to assessment of the risk of exposure to EDs.

On the scientific side, the multidisciplinary approach to EDs allowed the researchers to make significant progress in some areas and to agree on an important number of issues (such as the widely accepted definition of EDs, high sensitivity to EDs during certain periods of development, the variety of interactions between EDs and the human body), as well as on challenges to be addressed in the coming years (for instance, more effective ways to identify EDs, determining levels of exposure, the 'cocktail effects, improving testing methods). One of the main questions related to the impact of EDs is likely to remain the direct causal link between endocrine disruptors and certain disease outcomes (cancers, for instance), given all the issues that scientific research has to face. These include the limited number of patients available for study, the different types of exposure, combined (confounding) factors that may impact the human body (strengthening or diminishing each other's effect),[137] and the heterogeneity of the population. In this context, it seems that an important role will be played, in the years to come, by multidisciplinary cooperation and communication between different scientific fields, allowing for the creation of a strong knowledge base while also informing the decision-making process. Risk assessment is also an essential scientific process for decision-makers. The more comprehensive the risk assessment, the more risk managers can develop appropriate toolboxes to safely deal with chemicals. It is important, for instance, that the combined actions of chemical substances are also addressed in the future risk assessment process. In this sense, EFSA 'set up a working group of experts to develop guidance on combined exposure to multiple chemicals' (called MixTox). Its conclusions were expected by the end of 2018, but have been delayed to June 2019, because of 1) the comments received during a public consultation on how the cumulative assessment groups (CAGs) of pesticides to be used in the assessments were established; and 2) a request to consider a set of assumptions concerning risk management aspects

[137] It was demonstrated that farmers, even though exposed to many ED pesticides, are also physically active and exposed to the sun, which protects them against hormonally-related cancers (see Aydin Z. D., Sun exposure may confound physical activity – prostate cancer association, Archives of Internal Medicine, 165(21), 2005, 2538-2539.

of cumulative exposure agreed on by the Commission and EU Member States.[138] This issue is all the more important as the overarching conclusions of the EU Horizon 2020 EDC-MixRisk project (which investigated how effects caused by real-life relevant mixtures could be studied) recently indicated that 'current regulation of man-made chemicals systematically underestimates health risks associated with combined exposures to EDCs or potential EDCs'.[139]

As regards the regulatory approach, numerous bodies exist today at national, European and international levels, which try to provide concrete answers to the public concerns related to EDs. The European Union has one of the most rigorous regulatory systems for dealing with chemicals, underpinned by the precautionary principle and combining hazard-based and risk-based approaches. In the case of plant protection products, which were the focus of this paper, substances with endocrine-disrupting properties are completely banned, based on their hazard, (unless negligible risk can be demonstrated, or the substance is essential to combat serious pests that cannot be contained by other available means). This shows that the European regulator decided to adopt a very strict approach on the matter. Moreover, the identification of EDs relies on scientific criteria recently defined and already applied at European level, which takes scientific evidence and knowledge into consideration, as well as internationally agreed methodologies and protocols. Nevertheless, current knowledge gaps, uncertainties, complexities and a lack of coordinated approach (for instance, coordinated guidelines), make risk assessment difficult, with consequences for risk management too. In this regard, developing new risk assessment tools, to 'investigate' EDs in a more accurate way, might benefit policy-makers and regulators, by proving a more solid and clear scientific basis for developing public policy.

It is today indisputable that, despite both scientific and regulatory progress in addressing ED-related issues, the topic remains of great interest at all levels and attracts increasing public attention.[140] This is not only due to the challenges that it still poses, but also because of the very dynamic opposition of the two main categories of stakeholders, NGOs and chemical manufacturers. While the former advocate precaution, hazard-based assessment, restrictions and bans, the latter insist on innovation, risk-based assessment, and potency. For regulators, this translates into one of the most important challenges they have to face, developing rigorous but efficient regulatory processes, ensuring product safety and consistency, as well as encouraging innovation and marketing (commercialisation) of products.

Within this very complex frame, scientists, decision-makers and industry are called upon to provide appropriate answers and to address the societal concerns related to endocrine disruptors. This means that pressure as regards ED-related issues is great, and that regulators are today expected to be able efficiently and reliably to identify, characterise and risk-assess EDs. In this perspective, it can only be beneficial to also strengthen risk communication in relation to EDs, exchanging information with other relevant actors and providing information to the public about the harm and benefits of chemicals. Risk communication should also include information on scientific and methodological limitations and data uncertainty. This would, on the one hand, lead to more informed decision-making, and, on the other, improve public understanding and perception of risks.

All in all, to achieve the objectives of ensuring a high level of protection for humans and the environment and to reduce human exposure to harmful substances, it seems appropriate that the

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[138] EFSA, Pesticides: new deadline for cumulative risk assessments, 5 December 2018.

[139] Stockholm University, Health risks associated with mixtures of man-made chemicals are underestimated, Public Release, 26 March 2019.

[140] A good example in this sense is the large number of contributions (over 27 000) from EU citizens in the context of the public consultation organised by the European Commission on defining criteria for identifying endocrine disruptors in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation, which took place took place from 26 September 2014 to 16 January 2015.

attention of policy-makers and regulators' should be focused on the need to address the issue more comprehensively and coherently under the existing regulations. Furthermore, given that chemicals are currently regulated as separate classes based on their use, and that only BPR and PPPR have criteria to identify chemicals as endocrine disruptors, going beyond this approach is an option that is worth considering.

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Endocrine disruptors (EDs) are chemical substances present in many products of daily life, which interact with the hormonal system and can disrupt its proper functioning. There is a growing interest in understanding EDs and progress has been made on both the scientific and regulatory side, but the topic remains of high concern at decision-making and societal levels because of the challenges it still poses.

This paper provides a desk-research based overview of the key moments of the (scientific and regulatory) debate on EDs, with a focus on the latest developments at European level, namely Commission Regulation (EU) 2018/605 and the 2018 Commission communication 'Towards a comprehensive European Union framework on endocrine disruptors', in the particular context of plant protection products (PPPs).

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