Overview Report III:
Existing national, regional, and global regulatory frameworks addressing Endocrine Disrupting Chemicals (EDCs)

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DISCLAIMER

This is the third report within a series of three reports on EDCs that UN Environment has commissioned the International Panel on Chemical Pollution (IPCP) to prepare, in response to its commitment to the third and fourth sessions of the International Conference on Chemicals Management (ICCM 3 and 4) Resolutions that had called for international cooperative actions to provide up-to-date information and scientific expert advice to relevant stakeholders, raise awareness and facilitate science-based information exchange.

The series of reports include the following: (1) compilation of worldwide initiatives by various stakeholders to identify EDCs or potential EDCs based on the WHO/IPCS 2002 definitions; (2) a compilation of the current understanding of: the life cycle, environmental fate and distribution, environmental exposure in different regions, and evidence of adverse endocrine-related effects of EDCs and selected potential EDCs; and (3) a compilation of existing regulatory frameworks and policy initiatives on EDCs.

Given the complexity, breadth, and rapid ongoing development of this scientific field and in the regulatory frameworks, it is neither feasible nor possible for these three reports to include in-depth detail and discussion related to all the potentially relevant aspects or to predict future developments within the field. It instead provides a snapshot of the overall situation when the reports were prepared as well as references to further detailed and relevant information.

Executive Summary

Endocrine disrupting chemicals (EDCs) are chemicals that alter function(s) of the endocrine system and consequently cause adverse health effects. International research efforts to better understand the presence of EDCs and associated effects on the environment have been intensified over the past three decades and led to an increasing level of concern about and action on EDCs. In particular, at the 4th session of the International Conference on Chemicals Management (ICCM 4), a Resolution was adopted by the stakeholders inviting UN Environment to generate and disseminate information on EDCs. This report is the third within a set of three Overview Reports commissioned by UN Environment to the International Panel on Chemical Pollution (IPCP) on EDCs in response to its commitment to the ICCM 4 Resolutions.

This report aims to serve as a compendium of information that provides an overview of existing national, regional and global regulatory frameworks and policy initiatives that address EDCs. In particular, the report has a focus on frameworks that explicitly address EDCs (i.e., frameworks that consider both adverse effects and their endocrine causes in the assessment of chemical(s)). Explicit frameworks from countries and regions across five continents are identified and information essential for understanding their basic functioning is summarized (including their scope and general processes, public participation and stakeholder involvement, processes relevant for EDCs, criteria utilized, and data requirements). It should be noted that this report provides a snapshot of the overall situation as of when the report was prepared.

Several general observations are made, including:

- Some explicit regulatory frameworks have been developed and are being implemented to address EDCs; most of them are in developed countries/regions. Publicly accessible information on existing frameworks (e.g., documents and websites) is often scattered, complex and/or inconsistently linked or referenced. The terminology and characteristics (e.g., scope, approach and processes) can differ considerably across existing explicit regulatory frameworks.
- A number of policy initiatives are working towards the creation of future explicit regulatory frameworks; some of them are in countries with economies in transition.
- In addition to the frameworks described here, many existing regulatory frameworks may address certain EDCs implicitly, i.e., they consider or regulate substances based on adverse effects and inherently do not require the understanding of the causes of such adverse effects. In comparison to explicit regulatory frameworks, implicit frameworks have both advantages and disadvantages.

Readers are encouraged to find further, relevant information in Report I on worldwide initiatives to identify EDCs and potential EDCs, and in Report II on the life cycles, environmental exposures, and effects of select EDCs and potential EDCs.

Contents

Abbreviations

AICS – Australian Inventory of Chemicals Substances

BPR – Biocidal Products Regulation

CAS – Chemicals Abstracts Service

CEPA – Canadian Environmental Protection Act

CMR – Carcinogenic, Mutagenic, and Reprotoxic

CoRAP – Community Rolling Action Plan

DSL – Domestic Substances List

EC – European Commission

ECHA – European Chemicals Agency

EDC – Endocrine Disrupting Chemical

EDSP – Endocrine Disruptor Screening Program

EEA – European Economic Area

EFSA – European Food Safety Authority

EFTA – European Free Trade Association

EPA – Environmental Protection Agency

EQS – Environmental Quality Standards

EU – European Union

EXTEND – Extended Tasks on Endocrine Disruption

FD&C – Food, Drug and Cosmetic

FIFRA – Federal Insecticide, Fungicide and Rodenticide Act

ICCM – International Conference on Chemicals Management

IMAP – Integrated Multi-tiered Assessment and Prioritisation

IOMC – Inter-Organization Programme for the Sound Management of Chemicals

IPCP – International Panel on Chemical Pollution

IPCS – International Programme on Chemical Safety

K-REACH – Korean Regulation on the Registration and Evaluation of Chemicals

MCLG – Maximum Contaminant Level Goal

MLC – Maximum Level of Contaminants

MoE – Ministry of Environment

NICNAS – National Industrial Chemicals Notification and Assessment Scheme

OECD – Organisation for Economic Co-operation and Development

PBT – Persistent, Bioaccumulative, and Toxic

PPPR – Plant Protection Products Regulation

QSAR – Quantitative Structure-Activity Relationship

RAC – Risk Assessment Committee

REACH - Registration, Evaluation, Authorisation and Restriction of Chemicals (EU Regulation)

SAICM – Strategic Approach to International Chemicals Management

SDWA – Safe Drinking Water Act

SEAC – Committee for Socio-Economic Analysis

SPEED – Strategic Programs on Environmental Endocrine Disruptors

SVHC – Substance of Very High Concern

UN – United Nations

UNEP – United Nations Environment Programme

US – United States

vPvB – very Persistent and very Bioacummulative

WFD – Water Framework Directive

WHO – World Health Organization

1. Background, Aims, and Scope

Endocrine disrupting chemicals (EDCs)[A] are chemicals that alter function(s) of the endocrine system and consequently cause adverse health effects. Potential EDCs[B] are chemicals that possess properties that might be expected to lead to endocrine disruption. The endocrine system consists of many interacting tissues that communicate with one another and the rest of the body by means of hormones. This system is responsible for controlling a large number of processes in the body from gamete formation, to conception and early developmental processes such as organ formation, and to most tissue and organ functions throughout adulthood. EDCs interfere in some way with hormone action and in doing so can alter endocrine function and lead to adverse effects on the health of humans and wildlife. Some of the observed health effects associated with EDCs include, but are not limited to, cancer as well as reproductive, developmental, immunological, and neurological disorders. For more background information on endocrine disruption including the makeup of the endocrine system and how EDCs act, see the report "State of the Science of Endocrine Disrupting Chemicals – 2012" [1].

Over the past three decades, international research efforts to better understand EDCs have been intensified [1]. This has resulted in growing global concern regarding EDCs. In 2012, the third session of the International Conference on Chemicals Management (ICCM 3) recognised EDCs as one of the Emerging Policy Issues[C] under the UN Strategic Approach to International Chemicals Management (SAICM) [2]. The fourth session (ICCM 4) in 2015 [3] affirmed to support further research and develop cooperative actions regarding EDCs. The ICCM 4 Resolution further requested all interested stakeholders to support cooperative actions led by the Inter-Organization Programme for the Sound Management of Chemicals (IOMC), including to address the needs identified by developing countries and countries with economies in transition[D] by generating and disseminating information on EDCs.

As part of its commitment to the IOMC's work plan, the United Nations Environment Programme (UN Environment) initiated the project "Provision of Information on EDCs" in August 2015 to increase and improve intergovernmental and intersectoral understanding, coordination and cooperation as well as awareness of EDCs. Among other activities under the project framework, UN Environment commissioned the International Panel on Chemical Pollution (IPCP) to develop a set of three overview reports that focus on existing scientific knowledge of environmental exposure and effects as well as regulatory frameworks and policy initiatives regarding identified and potential EDCs.

[A] According to the World Health Organization/International Programme on Chemical Safety (WHO/IPCS) 2002 definition, an endocrine disruptor is "*an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations*" [87].

[B] According to the WHO/IPCS 2002 definition, 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*" [87].

[C] All SAICM Emerging Policy Issues can be found at http://www.saicm.org [88].

[D] Regional resolutions on endocrine-disrupting chemicals from Africa (SAICM/RM/Afr.5/7), Asia-Pacific (SAICM/RM/AP.4/7), and Latin America and the Caribbean (SAICM/RM/LAC.4/11). See the SAICM website at www.old.saicm.org.

Chemicals that have been identified as EDCs and potential EDCs (for examples, see Report 1) consist of a large variety of chemicals across different regulatory domains, including industrial chemicals, pesticides and food contact materials. Within a regulatory framework or non-legally binding policy initiative (collectively referred to as "*frameworks*" hereafter), such chemicals can be addressed either explicitly or implicitly. In brief, when assessing the effects of a chemical as a basis for decision-making, explicit frameworks (e.g. the European Chemicals Regulation, REACH) may explicitly refer to the endocrine disrupting potential of a substance (i.e., both adversity and causality), whereas implicit frameworks (e.g. the UN Stockholm Convention or the US Toxic Substance Control Act) refer to the adversity of the substance only. This means that some substances addressed by implicit frameworks due to their toxicity or risk to cause adverse effects may be EDCs, but they are not necessarily clearly defined as such within an implicit framework. Both types of frameworks can be further divided into general frameworks that are suitable for many substances and into specific regulations that address certain individual substances or substance classes for a defined set of conditions. Considerations regarding explicit and implicit frameworks are presented in section 4.3.

Driven by the growing concern about EDCs and the substantial research outcomes over the last three decades, a number of countries have initiated actions to address EDCs on a regulatory level. In particular, some have made substantial efforts to explicitly address EDCs within new or existing frameworks, some of which have led to the establishment of initiatives that are discussed in Report I. One may argue that these explicit frameworks are an improvement compared to existing, implicit frameworks in terms of addressing EDCs. Although implicit frameworks are designed to encompass chemicals that may cause adverse effects, a number of characteristics of (many) EDCs (e.g., non-monotonic responses, low-dose effects, delayed effects, and sensitive exposure time windows [4]) may not necessarily be captured by the standardized regulatory toxicological endpoints and assessments under current implicit frameworks [5,6].

This report systematically analyses and summarizes the characteristics (including scope, criteria, data requirements and relevant processes) of existing explicit frameworks, including those in developing countries and countries with economies in transition. In particular, the report focuses primarily on frameworks that are applicable to many types of chemicals, and summary information for examples of some specific regulations is also presented. Overall, the report aims to provide clear, succinct information essential for understanding the basic functioning of existing frameworks in regards to EDCs, and appropriate references are provided where readers can find additional detailed information. It intends to provide a comprehensive, but not necessarily complete, overview of existing explicit frameworks addressing EDCs. The report is structured into four sections:

- Methodology: provides an overview of the methodology used including the mapping and selection of frameworks for analysis, the guiding principles of the analysis, and data sources.
- Summary and Highlights: provides a brief summary and general observations of the analysed frameworks.
- Detailed analysis of identified explicit frameworks: provides descriptions of existing regulatory frameworks and policy initiatives grouped by continent of origin. The description starts with a brief summary of the overarching scope and concept, followed by an analysis of EDC-related key aspects including relevant criteria, data requirements and processes.

— Overview of specific regulations: provides an example set of existing specific regulations for substances that have been previously discussed by various authorities and/or their related research institutions for endocrine disrupting potential.

2. General Terminology

The following are terms used throughout the report and the definitions that have been applied to describe them here in the context of EDCs:

Regulatory framework	A set of laws, regulations, rules and/or guidelines applied by regulatory bodies in order to regulate a specific issue.
Policy initiative	An initiative taken by a government or institution to address EDCs in a regulatory context.
Explicit framework	A regulatory framework that may assess both adverse effects and causality (i.e. primary endocrine mode-of-action) and consequently recognizes the endocrine disrupting potential of a substance.
Implicit framework	A regulatory framework that may assess the adversity of a substance only and does not consider the causality (i.e. primary endocrine mode-of-action).
Specific regulation	A specific law, regulation or rule addressing one or several substances (classes) for a defined set of conditions, for example a specific use.
General regulation	A regulation that is suitable or applicable to many (types of) substances.

3. Methodology

3.1 Mapping and selection of frameworks for analysis

As a first step, existing regulatory frameworks and policy initiatives at the national and international levels were reviewed to identify those that have the potential to address EDCs. This was done through a systematic search for frameworks within three main regulatory domains that were expected to involve EDCs: environmental protection, consumer safety, and occupational health and safety (see Figure 1). For example, in the context of environmental protection, EDCs can be addressed under frameworks concerning air pollution, water pollution, soil pollution, and waste. Frameworks on industrial chemicals, pesticides, and biocides usually span all three of these legislative domains, i.e., their scopes often include the protection of the environment, consumers, and professionals in occupational settings. The frameworks depicted in Figure 1 can also be interconnected, and their exact content can vary across different regions of the world. For example, the regulation of a substance under a framework for industrial chemicals can lead to the regulation of the same substance under another framework on consumer product safety. From all frameworks identified, only existing frameworks explicitly addressing EDCs were selected and then analysed in more detail. The search for frameworks was limited to those having publicly accessible information describing them in English, in combination with personal consultation with the following countries: Australia, Brazil, Canada, Japan, and Russia.

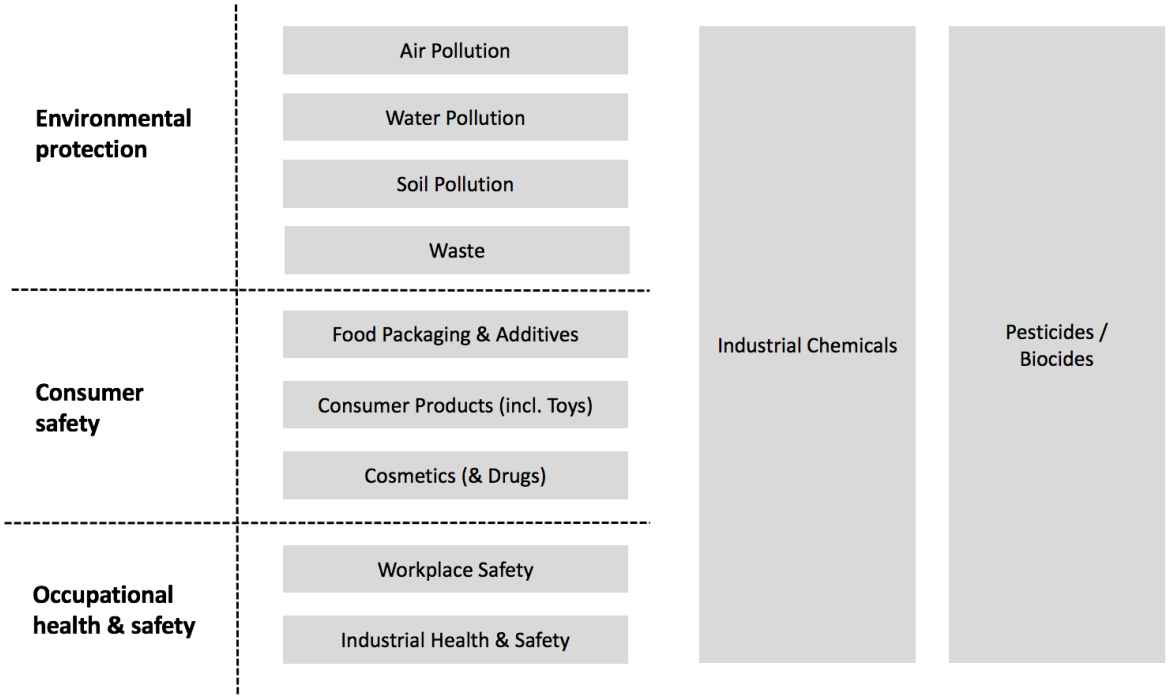

Figure 1. Overview of the different frameworks across three main regulatory domains that were expected to involve EDCs (adopted from [7]**).**

3.2 Detailed analysis of individual frameworks

The in-depth analysis of identified, explicit frameworks was conducted by reviewing each framework against a set of pre-defined descriptors that cover key aspects of EDC-related concepts and processes (see Table 1). In addition, considerations on implicit frameworks are provided in section 4.3.

Table 1. The set of descriptors used in the analysis of individual frameworks in the context of EDCs.

Category	Descriptor
Regulatory concepts	Regulatory approach (e.g. risk vs. hazard based)
	Criteria for identification of EDCs
	Characterization of EDCs and/or assessment of risks
Regulatory processes	Data requirements
	Decision making process
	Instruments for risk management
	Administrating authorities
	Stakeholder involvement

3.3 Data sources

Data were gathered and synthesized by reviewing publicly accessible documentation such as legal texts, guidelines and webpages published by the respective competent authorities, together with personal consultations with relevant key stakeholders such as the corresponding governmental agencies.

4. Summary and Highlights

4.1 General observations across existing frameworks

- A number of explicit frameworks have been developed and are being implemented to address EDCs, and most are in developed countries/regions. A few have also been established in some countries with economies in transition; almost no information was found regarding developing countries. This lack of information may be caused by either a true scarcity of such frameworks in developing countries, by language barriers (i.e., frameworks exist, but are described in languages not covered during the search), or by limitations in placing such information online (e.g. websites that are not yet extensively developed).
- The terminology and characteristics (e.g., scope, approach and processes) can differ considerably across existing explicit frameworks. As no harmonized criteria for the identification of EDCs are available across jurisdictions (even though the WHO/IPCS definition has been commonly accepted by many stakeholders), there are no EDC-specific data requirements in these frameworks. According to the available information, it even remains unclear in some frameworks how they have defined EDCs.
- Many existing regulatory frameworks may address certain EDCs only implicitly, i.e., they consider or regulate substances based on adverse effects and do not require the understanding

of the causes of such adverse effects. In comparison to explicit regulatory frameworks, implicit regulatory frameworks have both advantages and disadvantages (see section 4.3 below).

- Publicly accessible information on existing frameworks (e.g., documents and websites) is often scattered, complex and/or inconsistently linked or referenced. This can make it challenging for stakeholders who are not familiar with them to obtain necessary background information on the creation of these frameworks, as well as on the assessment or review processes involved.
- Responsible regulatory authorities have often published outcomes of completed evaluations of individual substances within frameworks considered in this report. These publications (many publicly available on the authorities' websites) could serve as valuable sources of information for other regulatory authorities conducting substance evaluations.
- A number of policy initiatives are working towards the creation of future explicit regulatory frameworks; some of them are in countries with economies in transition.

4.2 Overview of Identified Explicit Frameworks and Policy Initiatives

Table 2 provides an overview of the analysed frameworks and policy initiatives. Detailed descriptions of each are included in section 5: *Detailed analysis of identified explicit frameworks*.

Table 2. Overview of the analysed frameworks and policy initiatives discussed in this report.

	Characteristics in the context of EDCs				Section in this report
	Scope	**Regulatory approach / policy initiative content**	**Applicable processes**	**Available management options**	
European Union					
European Chemicals Regulation (REACH)	industrial chemicals	Substances are generally evaluated for risks. EDCs can be recognized as Substances of Very High Concern (SVHC) and can be subject to authorization or restriction.	Identification as an SVHC based on hazard assessment using the WHO/IPCS 2002 definition of EDCs. Authorization and restriction based on additional risk and socio-economic assessments	(1) Recognition as an SVHC. (2) Authorization, which can include conditions for use, manufacture or import. (3) Restriction.	5.1.1
Plant Protection Products Regulation (PPPR)	active substances, safeners, synergists used in plant protection products	Substance can only be approved if it is not considered to have endocrine disrupting properties. Exemptions can be made when a substance is required in order to control a serious danger or if exposure is negligible.	Identification of EDCs based on hazard assessment. In the case of exemptions: following a risk assessment, a substance can be approved regardless of its hazards when it is necessary to control a serious danger.	Approval as an active substance, safener or synergist granted or denied.	5.1.2
	basic substances	Substance can only be recognized as a basic substance if it is not considered to have endocrine disrupting properties.	Identification of EDCs based on hazard assessment.	Approval as a basic substance granted or denied.	5.1.2
Biocidal Products Regulation (BPR)	active substances used as biocides	Substance can only be approved if: 1) it is not considered to have endocrine disrupting properties or 2) the risk for humans, animals, or the environment is negligible, or 3) not approving the substance would have disproportionate negative impacts on society compared to the risk.	Identification of an EDC based on a hazard assessment. Decision made on approval or denial of a substance based on a risk assessment.	Approval as an active substance in biocides granted or denied.	5.1.3
Water Framework Directive (WDF)	pollutants of water bodies	Member States are required to prevent further deterioration of all water bodies and to implement	EDCs are recognized as "main pollutants" and can be included in the list of priority chemicals based	Establishment of environmental quality standards (EQS) on an EU-wide or member state level.	5.1.4

		measures for the protection, enhancement and restoration of water bodies. The status of water bodies is quantified by a combination of chemical and ecological parameters.	on an assessment of their risks to or via the aquatic environment.	Any measure for the control and progressive reduction of emissions to water bodies on the member state level.	
United States					
Federal Food, Drug and Cosmetic Act (FD&C Act)	pesticide chemicals	A pesticide can be registered if using it according to the specification will not generally cause a human dietary risk from residues. As part of the endocrine evaluation, pesticides must not pose an unreasonable risk to either human health or the environment.	Screening of pesticide chemicals for endocrine disrupting potential under the Endocrine Disruptor Screening Program (EDSP). Assessment of dietary risks considers endocrine disruption potentials and maximum residue levels in individual crops, and dietary intake across crops. It also considers potential environmental effects of endocrine-active substances.	(1) Approval or denial of pesticide registration for a specific use; (2) Imposing conditions on the use of the pesticide; (3) Setting of maximum residue levels for crops	5.2.1.1
Safe Drinking Water Act	drinking water contaminants	Drinking water contaminants can be regulated if the Environmental Protection Agency (EPA) concludes that the contaminant may have an adverse effect on human health, the contaminant is likely to occur in public water systems in concerning levels, and regulation poses a meaningful opportunity for reduction of health risk.	Screening of contaminants for endocrine disrupting potential under the Endocrine Disruptor Screening Program (EDSP) if a substantial population may be exposed. Risk assessment completed in order to determine a safe maximum level of the contaminant.	(1) Decision to regulate a drinking water contaminant. (2) Setting of a maximum level contaminant goal and maximum contaminant levels in drinking water. (3) Setting of treatment technique standards.	5.2.1.2
Regulatory framework on new drug approval	new pharmaceutical drugs	Evaluation for the potential of unintended endocrine-related toxicity in order to be approved for use.	Evaluation performed based on the standard non-clinical battery of toxicity tests. Additional studies can be warranted following the initial assessment.	Approval of the drug granted or denied.	5.2.1.3

Canada					
Canadian Environmental Protection Act (CEPA)	industrial / commercial chemicals	Evaluate whether a new or existing substance is "toxic" according to CEPA.	Completion of a risk assessment for the evaluation of new and existing substances considering endocrine disrupting effects.	(1) Establishment of pollution prevention plans or environmental performance agreements. (2) Establishment of conditions for manufacture or import. (3) Issuance of a "significant new activity" notice. (4) Prohibition of manufacture or import.	5.2.2.1
Pest Control Products Act (PCPA)	pest control products, including chemicals, devices, and organisms	A pesticide can be registered if there is reasonable certainty that no harm to human health or the environment will result from exposure to or use of the pesticide, based on its conditions or proposed conditions of registration.	Assessment of health and environmental risks considers endocrine disruption potential, in accordance with the OECD conceptual framework for testing and assessment of endocrine disrupters.	(1) Registration of pesticides for approved conditions of use according to label only; (2) Setting of maximum residue levels for crops	5.2.2.2
Proposed regulatory framework under the Food and Drug Regulations	active pharmaceutical ingredients in new human and veterinary drugs	A new active pharmaceutical ingredient would be subject to the proposed regulations when an application for a drug submission requiring a new Drug Identification Number is made to Health Canada. This would require industry to provide data that allows for an environmental risk assessment of these substances.	Under the proposed regulatory framework, EDCs are considered special category substances, meaning Health Canada has the authority to ask for additional data that is not normally required for an environmental assessment.	To be determined at a later time.	5.2.2.3
Brazil					
Federal Law 7802/1989	pesticides and their components	Pesticides and their components can only be approved if they are not considered to have endocrine disrupting properties.	Identification of EDCs based on hazard assessment.	Registration for the use in Brazilian agriculture granted or denied.	5.3.1.1

Initiative to establish a national legislation on industrial chemicals	industrial chemicals	Substances on the national registry of industrial chemicals considered to have endocrine disrupting properties can be selected for risk assessment.	Risk assessment for selected chemicals.	(1) Voluntary agreements between the government and industry. (2) Providing information for substances produced or imported in quantities < 1 tonnes per year; (3) Prohibition or restrictions of the production, import, export, trade and uses. (4) Setting of concentration limits of a substance in intentional mixtures or finished products. (5) Prior authorization for the production and import of a substance.	5.3.1.2
China					
13th Five-Year Plan of National Environmental Protection	unclear	Control pollution by EDCs.	Assessment of the endocrine disrupting properties of chemicals.	(1) Phase-out of a substance (2) Restriction of a substance (3) Replacing of a substance	5.4.1
Industry standard on evaluation methods of endocrine disrupting effects of pesticides	pesticides	Testing guidelines outlining in vitro and in vivo testing kits for the evaluation of endocrine disrupting effects of pesticides.	Not applicable	Not applicable	5.4.1
Japan					
Japanese environmental regulation	chemicals detected in the ambient aquatic environment	Adverse effects caused by endocrine disrupting effects of chemicals are expected to be considered in existing regulatory risk assessment practices.	Studies have been conducted to identify adverse effects caused by endocrine disrupting effects of chemicals under the government's programmes for testing and assessment: EXTEND 2010 and 2016.	Under development.	5.4.2

South Korea					
Korean Regulation on the Registration and Evaluation of Chemicals (K-REACH)	industrial / commercial chemicals	Substances are evaluated for potential risks. EDCs can be recognized as substances subject to authorization, restriction or prohibition.	Completion of a hazard evaluation and risk assessment can lead to a substance being subject to authorization.	(1) Authorization of a substance (2) Restriction of a substance (3) Prohibition of a substance	5.4.3
Australia					
National Industrial Chemicals Notification and Assessment Scheme (NICNAS)	industrial / commercial chemicals	Substances on official inventory evaluated for risks they pose.	Consideration of potential endocrine disrupting activity (as determined by the European Commission) as a hazard indicator, automatically causing a substance to be further evaluated in a risk assessment.	Make recommendations of measures for regulators in individual states and territories.	5.5.1
	Ultraviolet filters for cosmetics	Substances used in cosmetics evaluated for risks they pose.	Evaluation and assessment of the risk of potential endocrine activity.	Creation of recommended measures for regulators in individual states and territories.	5.5.1

4.3 Considerations on Implicit Frameworks

4.3.1 Terminology and Limitations of the Report

As introduced in section 1, explicit frameworks in the context of this report are those that assess both adverse effects and their cause (i.e. mode-of-action) and consequently recognize the endocrine disrupting potential of a substance. In contrast, implicit frameworks are those that refer to the adverse effect of the substance only. In this way, the definitions of 'explicit' and 'implicit' frameworks do not refer to how chemicals are managed, but only refer to if the cause of the adverse effects is additionally considered during chemical assessment.

Explicit frameworks included in this report are referenced to official, publicly accessible documentation identifying that the cause of the adverse effects is considered within the framework. Given the complexity, breadth, and ongoing development of chemicals regulations, it is neither feasible nor possible for this single report to exhaustively include all explicit frameworks across the globe or to predict future developments within the field. For example, some regulations may not explicitly mention endocrine disruption or endocrine mode-of-action in their legal text and related testing guidance documents, but endocrine disruption or endocrine mode-of-action may be de facto considered by the relevant regulators now or in the future. Such frameworks should be regarded as 'explicit' frameworks, but they cannot be included here due to the limited access by the authors of this report to (publicly available) information identifying that the cause is considered in addition to the adverse effects. The report instead provides a snapshot of the overall situation representing the time when the report was prepared, and it provides references to further detailed and relevant information.

4.3.2 Roles of Implicit Frameworks

Although the scope of this report is on analysing explicit frameworks, implicit frameworks can also play a significant role in managing certain EDCs. It is important to note that some substances addressed by existing implicit frameworks due to their toxicity or potential to cause adverse effects may also be EDCs. Examples of such implicit frameworks in the context of endocrine disruption include the Stockholm Convention on Persistent Organic Pollutants (POPs) as well as many national frameworks that have led to specific regulations banning or restricting individual chemicals for specific uses. However, regulatory decisions under such implicit frameworks are made without identifying the cause of the adverse effects, and chemicals addressed under such implicit frameworks therefore may or may not be EDCs. Identifying any endocrine disrupting potential of chemicals addressed under such implicit frameworks requires additional consideration of the cause of the adverse effects.

In comparison to explicit frameworks, implicit frameworks are simpler since they only need to assess adverse effects, without addressing the cause. Addressing the cause would require an additional burden of proof. Hence, given the scientific complexity of the topic and the ongoing development and discussions surrounding the identification of EDCs, implicit frameworks may be both effective and more efficient in addressing those EDCs for which their toxicity and potential to cause adverse effects is already a cause of concern for action, without having to also understand their causes.

5. Detailed analysis of identified explicit frameworks

5.1 Europe

5.1.1 European Union

Within the politico-economic European Union (EU),[E] an internal single market has been established over the course of the past decades, and a standardized system of regulatory frameworks has been established and implemented in all EU Member States. In addition, Iceland, Lichtenstein, and Norway, which are part of the European Free Trade Association (EFTA), also have access to the EU internal single-market via the agreements on the European Economic Area (EEA). These three countries generally adopt the EU's standardized system of regulatory frameworks with only a few exceptions. In general, the EU's standardized system of regulatory frameworks covers all the domains in Figure 1, and the following sub-sections analyse the three EU frameworks that explicitly address EDCs.

Within the EU's standardized system of regulatory frameworks, EDCs are explicitly addressed within the frameworks on industrial chemicals, plant protection products, biocidal products, and water pollutants. These frameworks are governed by the following regulations:

- Industrial chemicals: Regulation (EC) 1907/2006, concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) [8]
- Plant protection products: Regulation (EC) 1107/2009, concerning the placing of plant protection products on the market (Plant Production Regulation or PPPR) [9]
- Biocidal products: Regulation (EU) 528/2012, concerning the making available on the market and use of biocidal products (Biocidal Products Regulation or BPR) [10]
- Water pollutants: Directive 2000/60/EC, establishing a framework for Community action in the field of water policy [11]

In addition to these four regulations, relevant EU sector specific regulations such as the EU cosmetics regulation (Regulation (EC) No 1223/2009 on cosmetic products) are expected to address EDCs once the European or international community agrees on identification criteria.[F] These sector-specific regulations therefore are not analysed further in this report.

5.1.1.1 REACH

Scope and general processes

The REACH regulation lays down provisions on substances used as industrial/commercial chemicals within the EU internal market. A "substance" under REACH is defined as a chemical element and its compounds in the natural state or obtained by any manufacturing process including any additive or impurity. It encompasses regulations for their manufacture, placement on the market, and use of them

[E] Member states of the EU as of May 2017 are: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom

[F] Regulation (EC) No. 1223/2009, Art. 15(c). For further information see reference [89]

either on their own, in preparations, or in articles. The legal definitions of the terms “substance” and “articles” are given in Table A1 in the annex.

The general regulatory processes are illustrated in Figure 2. Under REACH, every substance to be manufactured or imported into the EU in a quantity above 1 tonne per year (t/yr) must be registered with the European Chemicals Agency (ECHA) before it can be placed on the market. For this registration, information on physicochemical properties and uses of the substance must be provided by the registrant. The exact information requirements for an assessment of hazards and risks are dependent on the substance quantity (i.e., >1 t/yr, >100 t/yr, or >1000 t/yr). Registered substances can be selected by ECHA or the EU member states and be placed on the List of the Community Rolling Action Plan (CoRAP) for substance evaluation. This selection process is carried out according to defined hazard- and risk-based criteria by ECHA and the Member States. Selected substances are then evaluated individually by Member State(s) to clarify whether the use of such substances poses a risk to human health or the environment. There are three possible outcomes of a substance evaluation:

1. If the existing information is sufficient to come to the conclusion that the initial concern was non-justified, then the substance evaluation is terminated without further action.

2. If the existing information is sufficient to conclude that the initial concern was justified, appropriate risk management measures are considered, including:
    a) harmonized classification and labelling (not relevant for EDCs as there is no harmonized classification for endocrine disrupting effects),
    b) to identify the substance as a Substance of Very High Concern (SVHC),
    c) to restrict the substance, or
    d) actions outside the scope of REACH, such as a proposal for EU-wide occupational exposure limits, national measures, or voluntary industry actions.

3. If the initial concern cannot be resolved based on existing information, the Registrant is requested to provide additional information (e.g. test data). This request for further data is decided by the Member State Committee.

A proposal for identification as an SVHC (measure b, above) is the first step in the authorization process. The Member State Committee decides on the final identification of a substance as an SVHC, which leads to the inclusion of the substance in the so-called REACH Candidate List. The inclusion in the Candidate List obligates suppliers of the substance to provide their customers with a safety data sheet. If the substance is included in an article, suppliers of this article are furthermore obligated to provide sufficient information to allow safe use of this article to their customers upon request. Substances on the REACH Candidate List can later be included on the so-called Authorisation List. The European Commission makes the final decision on inclusion in the Authorisation List. Once set for authorization, all manufacturing, uses, and imports of (but not articles containing) the substances have to be authorized [12]. ECHA’s Risk Assessment Committee (RAC) and Committee for Socio-economic Analysis (SEAC) evaluate applications for authorizations and provide opinions to support the decision on authorization by the European Commission.

A proposal for restriction (measure c, above) is the first step in the restriction process of REACH. When a proposal for restriction is made by a Member State, ECHA’s Risk Assessment Committee (RAC) first gives its opinion as to whether the proposed restriction is appropriate for reducing the risk to human health or the environment. Subsequently, ECHA’s Committee for Socio-economic Analysis

(SEAC) gives its opinion about the socio-economic impacts of the proposed restriction. Based on the two committees' opinions, the European Commission prepares a draft restriction. The final decision is taken in a process involving the Member States and the European Parliament. Once restricted, a substance may be imported, manufactured, and/or used only according to the conditions of its restriction. A restriction applies to any substance on its own, in a mixture or in an article, including those that do not require registration. In contrast to the authorization, a restriction applies to imports of articles containing a restricted substance [12].

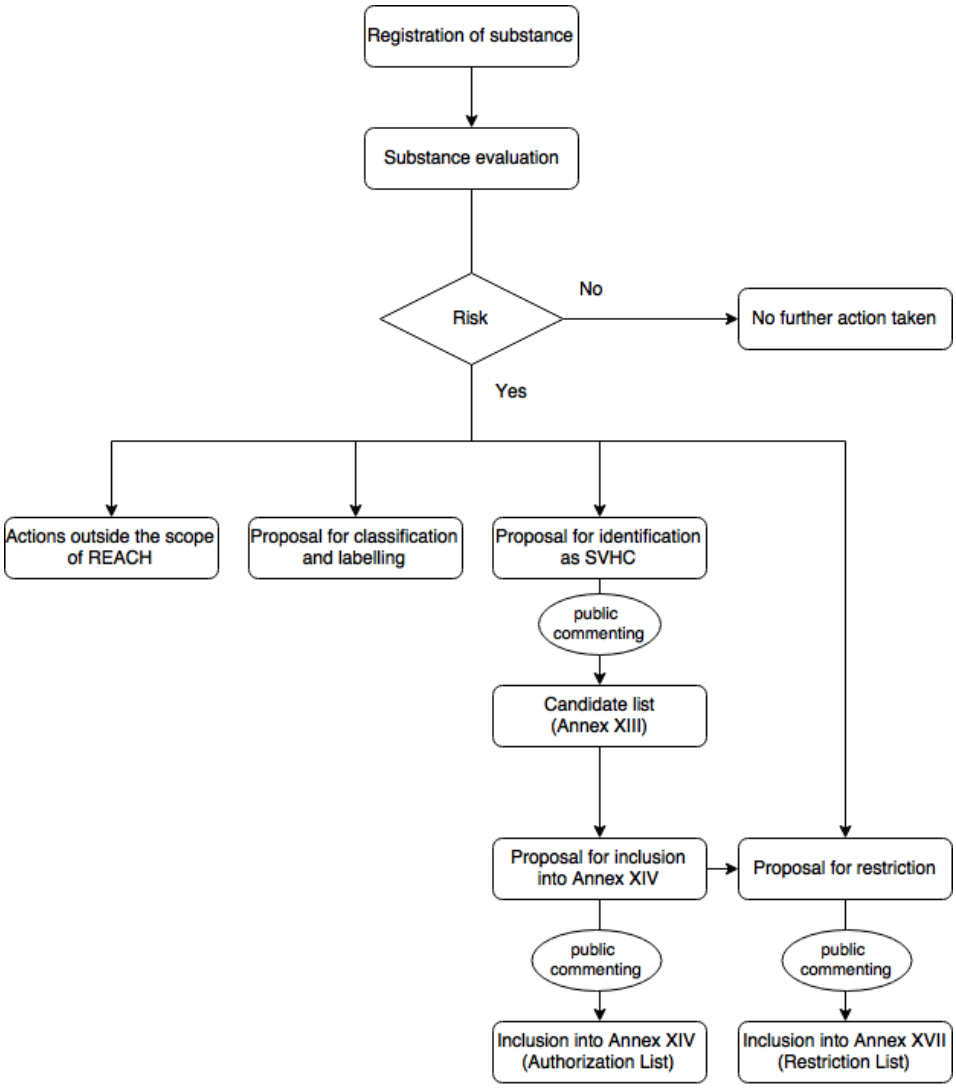

Figure 2. Illustration of the general regulatory process under REACH.

Public participation and stakeholder involvement

At several stages of the processes under REACH, stakeholders (e.g., substance registrants or the public) have opportunities to provide comments and/or information. The substance registrant can, for example, formally comment on the requests for additional information during substance evaluation. In addition, interested stakeholders (e.g., substance producers, industry associations, other stakeholder organizations, or the general public) have the opportunity to comment on the proposal when a

substance is proposed for inclusion into the candidate list, Annex XIV (Authorisation list) or Annex XVII (Restriction list). These comments will be considered in the final proposal and, therefore, also in the final decision.

Processes relevant for EDCs

REACH explicitly addresses EDCs as substances that may be included in the Authorisation List (Annex XIV). It states that "substances – such as those having endocrine disrupting properties" may be considered for inclusion in Annex XIV if there is scientific evidence of probable serious effects to human health or the environment, which gives rise to an equivalent level of concern to that of substances meeting the criteria for classification as: carcinogenic, mutagenic, or toxic for reproduction (CMR) (category 1 or 2, according to the GHS criteria), as persistent, bioaccumulative and toxic (PBT), or as very persistent and very bioaccumulative (vPvB) (according to the criteria set in Annex XIII of REACH).[G] According to the regulatory procedure set out by REACH (see section 5.1.1.1), EDCs can therefore be identified as SVHCs and eventually be included in Annex XIV (Authorisation List). Once a substance is identified as an SVHC, it triggers certain reporting requirements as set in Article 33. Once included in Annex XIV, all manufacturing, uses and imports of the substances have to be authorized.

Criteria utilized

To date, REACH does not provide explicit criteria for the identification of EDCs. The identification of EDCs is currently conducted on a case-by-case basis using the WHO/IPCS 2002 definition, together with the recommendations from the European Commissions' Endocrine Disrupters Expert Advisory Group [13].

Data requirements

No specific data requirements for the evaluation of endocrine disrupting potential have been set.

5.1.1.2 Plant Protection Product Regulation

Scope and general processes

The Plant Protection Product Regulation[H] (PPPR) sets rules for the authorization of commercial plant protection products, their placement on the market, as well as use and control within the European Union. It also lays down provisions for the approval of individual components of plant protection products, namely active substances, safeners, synergists, basic substances, co-formulants and adjuvants. The exact definitions of these terms under the PPPR are provided in Table A2 of the annex.

To place a plant protection product on the market, it has to be evaluated and subsequently granted an authorization. This evaluation and authorization takes place on the basis of geographical zones. In an individual zone, a Member State can evaluate and authorize a plant protection product, and other Member States can then recognize that authorization. A plant protection product can be granted authorization only if all of its components (i.e., active ingredients, safeners and synergists, and basic

[G] Regulation (EC) No. 1907/2006, Art. 57(f). For further information, see ref. [8]
[H] Regulation (EC) No. 1107/2009. For further information, see ref. [9].

substances) have been evaluated and granted a separate approval. This evaluation and approval of takes place on the EU-wide level, and the evaluation is conducted by one Member State on behalf of all other member states with the final decision on approval made by the European Commission.

The approval process for a new active substance, safener or synergist is illustrated in Figure 3 and briefly explained here [14]:

1. The producer submits an application to a Member State (the Rapporteur Member State, RMS).
2. The RMS carries out an independent, objective, and transparent assessment and compiles a draft assessment report.
3. The draft assessment report, which subsequently undergoes a peer-review process by the other member states and EFSA, is published for public comments. After the commenting period, the European Food Safety Authority (EFSA) adopts a conclusion on whether or not the substance can be expected to meet the approval criteria in Art. 4 of the PPPR.
4. Based on the conclusion by EFSA, the Standing Committee for Food Chain and Animal Health votes on approval or non-approval.
5. The decision is then adopted and published by the European Commission.

The approval process of a basic substance is different from an active substance: An application for approval of a basic substance contains any evaluations of possible effects on human or animal health or the environment. It can be submitted by a member state or any interested party to the European Commission, which then decides on approval or non-approval. The first approval of a basic substance is granted for an unlimited amount of time, different from the 10-year limitation imposed on the first approval of active substances.[I]

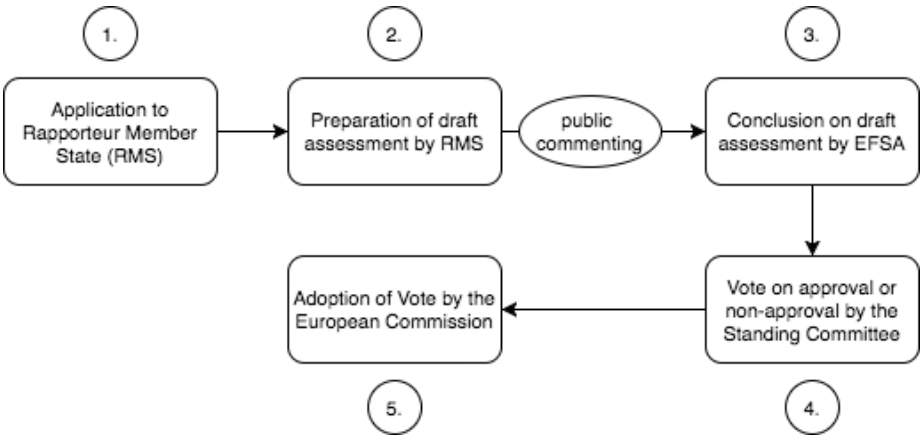

Figure 3. Illustration of the approval process of active substances, safeners and synergists under the Plant Protection Product Regulation.

Public participation and stakeholder involvement

During the approval process of an active substance, safener or synergist, the draft assessment report prepared by the RMS is made available to all Member States, the applicant, and the general public or

[I] Regulation (EC) No. 1107/2009, Art 23. For further information, see ref. [9].

stakeholder organizations for a commenting period of 60 days. All comments received are considered by EFSA for its final conclusion [15].

In contrast, during the process of authorization of a plant protection product, no public stakeholders are involved, and there is no process for public consultation on the EU level [16].

Processes relevant for EDCs

Under the PPPR, an active substance, safener or synergist shall only be approved if it is not considered to have endocrine disrupting potential to cause adverse effects in humans. Exemptions can be made when a substance is required in order to control a serious danger to plant health or the exposure of humans to the active substance, safener or synergist is negligible under realistic proposed conditions of use. A negligible exposure is reached if the product is used in a closed system or under conditions excluding contact with humans, and where residues of the active substance, safener or synergist of concern do not exceed 0.01 mg/kg on food and feed.[J]

In addition to this criterion for active substances, safeners and synergists, the PPPR contains a further clause explicitly addressing EDCs: Article 23(1)(b) states that for the purpose of this regulation, a basic substance is defined as an active substance which: “does not have an inherent capacity to cause endocrine disrupting, neurotoxic or immunotoxic effects […]” Therefore, a substance exhibiting endocrine disrupting properties cannot be recognized as a basic substance and has to undergo the regulatory process of an active substance.

Criteria utilized

Annex II of the PPPR mandated the European Commission to draft specific scientific criteria for the determination of endocrine disrupting properties of substances. A draft was presented by the European Commission in June 2016. As of March 2017, no official criteria have yet been adopted. The current legal provision is: “Pending the adoption of these criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties. In addition, substances such as those that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties.” [K]

Data requirements

Data requirements for the evaluation of active substances are laid out in the regulation (EC) 283/2013[L]. Many of the toxicological and ecotoxicolgical tests require the evaluation of endpoints related to the endocrine system. If there is evidence that the active substance may have endocrine disrupting properties, additional information or specific studies shall be required to (1) elucidate the mode(s)/mechanism(s)-of-action and (2) provide sufficient evidence for relevant adverse effects. The

[J] Regulation (EC) No. 1107/2009, Art 4(7) and Annex II, point 3.6.5. For further information, see ref. [9]
[K] Regulation (EC) No. 1107/2009, Annex II, point 3.6.5. For further information, see ref. [9]
[L] Regulation (EU). No. 283/2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council considering the placing of plant protection products on the market. For further information, see ref. [9,90]

design of such studies shall be on an individual basis and taking into account Union or internationally agreed guidelines such as OECD test guidelines.[M]

5.1.1.3 The Biocidal Products Regulation

Scope and general processes

The Biocidal Products Regulation (BPR)[N] sets the rules and provisions regarding the placement on the market and use of biocidal products. These products are intended to protect humans, animals, materials or articles against harmful organisms such as pests or bacteria [17]. It also sets provisions for the approval of active substances contained in biocidal products. The exact definitions of these terms under the BPR are provided in Table A3 of the annex.

All biocidal products must be authorized before they can be placed on the market. This authorization is granted by individual EU Member States and can also be recognized by other Member States [17]. If an applicant for authorization intends to place the product on the market of several Member States, they can also apply directly for union-wide authorization. In this case, the evaluation process is carried out by the competent authority of a Member State on behalf of all other Member States. The European Commission takes the final decision on grating a union-wide authorization.

A biocidal product can be granted authorization only if the active ingredients contained have been evaluated and granted a separate approval. The evaluation and approval of active ingredients takes place on a EU-wide level. The evaluation is conducted by one Member State on behalf of all other member states, and the final decision on approval is made by the European Commission. Figure 4 illustrates the approval process outlined in the BPR for active substances. Below is a brief explanation of the individual steps [18]:

1. The applicant submits the application to the European Chemicals Agency (ECHA), which is then evaluated by the competent authority of a Member State.
2. The competent authority evaluates if the applied active substance fulfils the provisions laid down in the BPR and compiles a draft assessment report with its conclusions. The applicant is given the possibility to provide written comments on the draft assessment report.
3. The draft assessment report undergoes a peer review by the Biocidal Products Committee. If the evaluated substance has been designated as candidate for substitution, the peer reviewed assessment report is made open for public commenting.
4. The Biocidal Products Committee finalizes an opinion based on the peer-reviewed assessment report.
5. The European Commission takes a final decision on the EU-wide approval of the substance.

[M] Regulation (EU) No. 283/2013, Annex point 5.8.3, see ref. [90]
[N] Regulation (EU) No. 528/2012. For further information, see ref. [10]

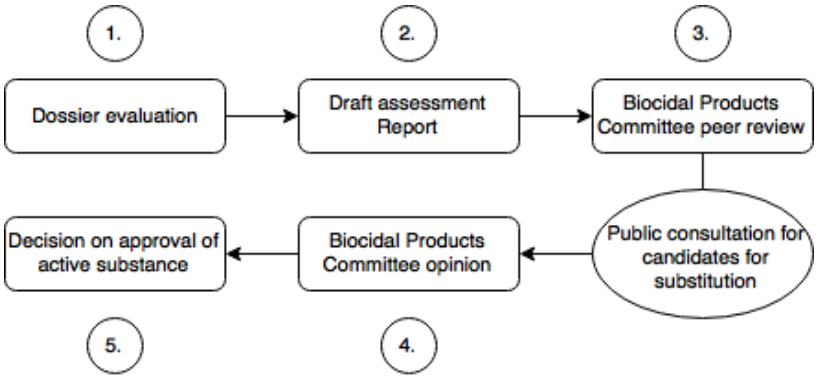

Figure 4. Illustration of the approval process of active substances as outlined in the Biocidal Product Regulation.

Public participation and stakeholder involvement

In the approval process of active substances, stakeholders are only involved when a substance has been designated as a candidate for substitution. In this case, a public consultation of the peer-reviewed assessment report is launched, and this gives third parties possibilities to submit relevant information, including information on alternative substances. The comments and information are then considered in the final opinion of the Biocidal Products Committee. For substances that are not considered candidates for approval, stakeholders are not involved for commenting [18].

In the approval process of a biocidal product for EU-wide authorization, no stakeholders are involved.

Processes relevant for EDCs

In the BPR, EDCs are explicitly addressed in the context of the approval process of an active substance. According to Article 5, active substances that are considered as having endocrine-disrupting properties that may cause adverse effects in humans shall not be approved. This exclusion from approval also applies to substances that are identified as EDCs under REACH. An exception from this provision can be made if the risk to humans, animals or the environment from the exposure to the active substance under realistic worst case conditions of use is negligible, in particular where the product is used in closed systems or under other conditions that aim at excluding contact with humans and release into the environment. Other conditions for an exception from the exclusion of EDCs from approval as an active substance can be made if: 1) it is essential to prevent or control serious danger to human health, animal health or the environment or 2) not approving the active substance would have a disproportionate negative impact compared to the risk caused by the exposure. If an active substance is still approved despite being an identified endocrine disruptor, it is considered to be a "candidate for substitution" and will only be approved for shorter time periods compared to other active substances.

In addition to the exclusion criteria for the approval of active substances, a Member State may not authorize a biocidal product for use by the general public if the product itself has endocrine disrupting properties (due to, for example, other components it contains).[O] Furthermore, the evaluation of the biocidal product must include a comparative assessment, and biocidal products containing active

[O] Regulation (EU) No. 528/2012, BPR, Art. 19. For further information, see ref. [10].

substances that fall under the exclusion criteria stated in Art. 5 of the BPR are not eligible for union-wide authorization.[P]

Criteria utilized

Annex II of the BPR mandated the European Commission to develop specific scientific criteria for the identification of EDCs. Draft criteria were presented by the European Commission in June 2016. As of March 2017, no official criteria have yet been adopted. The current legal provision is: "Pending the adoption of those criteria, active substances that are classified in accordance with Regulation (EC) No 1272/2008 as, or meet the criteria to be classified as, carcinogen category 2 and toxic for reproduction category 2, shall be considered as having endocrine-disrupting properties. Substances such as those that are classified in accordance with Regulation (EC) No 1272/2008 as, or that meet the criteria to be classified as, toxic for reproduction category 2 and that have toxic effects on the endocrine organs, may be considered as having endocrine-disrupting properties." [Q]

Data requirements

Data requirements for the evaluation of biocidal products are laid out in the annex for regulation (EC) 528/2012.[R] It states that if there is evidence that the active substance may have endocrine disrupting properties, additional information or specific studies should be required to (1) elucidate the mode(s)/mechanism(s)-of-action and (2) provide sufficient evidence for relevant adverse effects.

5.1.1.4 The Water Framework Directive

Scope and general processes

The Water Framework Directive (WFD) lays down the goals and processes for the EU-wide protection and management of water bodies. It institutionalizes ecosystem-based objectives and planning processes for the protection of inland surface waters, transitional waters, coastal waters, and groundwater. Specifically, the main goals[S] are:

- the prevention of further deterioration of water bodies,
- the protection, enhancement and restoration of water bodies and the achievement of "good status" for all waters by 2015, and
- the reduction, limitation or prevention of pollution of all water bodies.

The status of a surface water body is determined by its ecological and chemical status, whereas the status of a groundwater body is determined by its quantitative and chemical status.[T] To achieve the stated objectives, Member States are required to establish monitoring programmes, as well as programmes of measures and management plans on the basis of river basins or catchment areas. In order to prevent the deterioration of water bodies by chemical pollution, Member States are required to

[P] Regulation (EU) No. 528/2012, BPR, Art. 42(1). For further information, see ref. [10].
[Q] Regulation (EU). No. 528/2012, BPR, Art 5.3. For further formation, see ref. [10].
[R] Regulation (EU). No. 528/2012, BPR, Annex II, Title I, section 8.13.3 For further formation, see ref. [10].
[S] Directive 2000/60/EC, Art. 4. For further information, see ref. [11].
[T] Directive 2000/60/EC, Art. 2. For further information, see ref. [11].

regulate the discharge of pollutants into water bodies.[U] Furthermore, the WFD mandates the European Parliament and Council to establish specific measures against pollution by individual pollutants or groups of pollutants that present a significant risk to or via the aquatic environment.[V] For this, the European Commission establishes a list of priority substances that present such a significant risk. The Commission is also mandated to identify a sub-set of priority hazardous substances from the list of priority substances. Based on these lists, the Commission establishes controls for (1) the progressive reduction of discharges of priority substances and (2) the cessation and phasing-out of discharges of priority hazardous substances.[W] Furthermore, the Commission also sets EU-wide environmental quality standards (EQS) for all priority substances in surface waters, sediments or biota. In order to achieve the goal of "good status", all surface water bodies must not exceed these EQS. Individual Member States must therefore integrate measures concerning the control, reduction, or cessation of discharges of priority substances or priority hazardous substances into their programmes of measures. Such measures can also include the establishment of environmental quality standards at the level of individual Member States.

Due to its integrated ecosystem-based approach, the WFD is closely linked to a number of other EU directives, including directives relating to the protection of habitats, specific water uses, and directives concerned with the release of chemical substances into the environment.

Public participation and stakeholder involvement

Under the WFD, Member States are required to encourage the active involvement of all interested parties in the implementation of the directive. Specifically, for the establishment of river basin management plans, Member States are required to publish time tables and work programmes for the production of such a plan, as well as an interim overview of the significant water management issues identified in the river basins. The public commenting period must last at least six months to allow for active involvement and consultation.[X]

Processes relevant for EDCs

The WFD focuses on chemicals with significant risk to or via the aquatic environment. It recognizes "substances and preparations, or the breakdown products of such, which have been proved to possess carcinogenic or mutagenic properties or properties which may affect steroidogenic, thyroid, reproduction or other endocrine-related functions in or via the aquatic environment" as so-called "main pollutants".[Y] Member States may therefore be required to take measures to control or prevent the release of such EDCs into water bodies. Furthermore, EDCs may be listed as priority chemicals by the EU Commission [19].

The WFD itself does not contain any provisions on the identification or risk assessment of substances, but refers to other relevant EU legislation, such as REACH, for this process. However, the derivation of environmental quality standards for individual environmental compartments requires a risk assessment of substances. If there is an indication that a substance may cause adverse effects via the

[U] Directive 2000/60/EC, Art. 11. For further information, see ref. [11].
[V] Directive 2000/60/EC, Art. 16. For further information, see ref. [11].
[W] Directive 2000/60/EC, Art. 16(5). For further information, see ref. [11].
[X] Directive 2000/60/EC, Art. 14. For further information, see ref. [11].
[Y] Directive 2000/60/EC, Annex VIII. For further information, see ref. [11].

disruption of the endocrine system, the current technical guidance for the derivation of environmental quality standards explicitly states that the standard assessment factor for the derivation of the EQS needs to be carefully evaluated. Furthermore, it states that a larger assessment factor might be needed in order to protect against the effects caused by such an endocrine mode-of-action [20].

Criteria utilized

The WFD itself does not contain provisions on the identification of EDCs or risk assessment of any individual (or group of) substances, but refers to other relevant EU legislation, such as REACH, for this process. Therefore, no criteria for the identification of EDCs are specified in the directive.

Data requirements

Similarly, no data requirements for the identification or risk assessment of EDCs are specified in the WFD itself. It instead refers to other relevant EU legislation, such as REACH, for this process.

5.2 North America

5.2.1 United States of America

In the United States of America (US), EDCs are explicitly addressed in the regulatory frameworks on pesticides, drinking water safety, and for approval of new drugs.

5.2.1.1 Regulatory framework on pesticides

Scope and general processes

The US regulatory framework on pesticides consists of two statutes: the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) [Z] and the Federal Food, Drug and Cosmetic Act (FD&C Act)[AA].

FIFRA requires conventional chemical pesticides, biopesticides, and antimicrobial pesticides (for the legal definition of these terms, see Table A4 in the annex) to be registered by the US Environmental Protection Agency (US EPA) for a specific application before they can be placed on the market. In brief, the US EPA develops a risk assessment with data provided by the pesticide producer (i.e. the applicant for the registration) to check that the use of the pesticide according to the specifications [21]: [i] will not pose any unreasonable risks to humans or the environment, taking into account the economic, social and environmental costs and benefits of using the pesticide, and [ii] will not pose a human dietary risk from residues that result from using the pesticide that would be inconsistent with the respective provisions of the FD&C Act. Based on the risk assessment outcomes, the US EPA makes a decision whether to approve or deny the registration of the pesticide for a specific use and sets tolerances (also called maximum residue limits in many other countries) on the amount of pesticides that may remain in or on foods that are sold within the US. A registration can also be classified for

[Z] 7 U.S.C. Ch. 6, §136 et seq.
[AA] 21 U.S.C. Ch. 9 §301 et seq.

"restricted use"[BB], whereby the pesticide is only to be used by certified applicators [22,23]. There are three types of applications for registration [24]:

- New chemical or new active ingredient: a pesticide registration application for a product that contains a pesticide active ingredient that is not contained in any other product currently registered.
- New use: a pesticide product containing one or more previously registered active ingredient(s), where the requested use is a "New Use" (i.e. any use pattern that the active ingredient is currently not registered for or would change the level or route of exposure for humans or any other organisms[CC]).
- Identical or substantially similar product: a pesticide product that is identical or substantially similar in its uses and formulation to one or more products currently registered.

Public participation and stakeholder involvement

Several stages of the pesticide registration process provide opportunities for public participation. First, after receipt of a pesticide registration application, the US EPA notifies the public on the application. This notification contains basic information on the product type, active ingredient, proposed use and target pests, and it is opened for public commenting. Second, after completing the risk assessment, the US EPA publishes a proposed decision on granting or refusing the registration. This proposed decision is open for comments from the public. In response to the comments, the US EPA prepares a response-to-comment document and revises assessments and related decision documents as needed [25].

Similarly, the process for establishing pesticide tolerance values also provides opportunities for public participation. First, when the US EPA intends to set a new tolerance value, the intention is made public for commenting. Second, after completing the risk assessment, the US EPA publishes the final tolerance value and the underlying risks assessment. After this publication, any person may file objections to the tolerance value(s) within a certain time period. Upon receiving such an objection, the US EPA can revise the tolerance value [26].

Processes relevant for EDCs

In August 1996, the US Congress passed the Food Quality Protection Act, which amended the FD&C Act requiring the US EPA to find that a pesticide poses a "reasonable certainty of no harm" before it can be registered for use on food or feed. In addition, it set out several factors that must be addressed before a tolerance can be established. These factors include, among others, that the US EPA needs to review "whether the pesticide produces an effect in humans similar to an effect produced by a naturally-occurring estrogen or produces other endocrine-disrupting effects" [27]. This mandated the US EPA to develop a screening programme to identify pesticides for possible endocrine disrupting effects, and today this is done through the Endocrine Disruptor Screening Program (EDSP). When a substance is found as a result of EDSP to have an endocrine effect on humans, the US EPA will take available, appropriate action as necessary to ensure the protection of public health and the

[BB] 40 CFR 152.160 – 152.175. For further information, see ref. [91].
[CC] 40 CFR 152.3. For further information, see ref. [91].

environment.[DD] If EDSP data exist at the time of a pesticide's registration review, the US EPA will consider it.

Criteria utilized

Neither FIFRA nor FD&C Act state any statutory criteria for EDCs. Pesticides with endocrine disrupting potential are to be identified under the ongoing EDSP, which is elaborated below.

Data requirements

To determine whether pesticide products may have endocrine effects, the Endocrine Disruptor Screening Program (EDSP) consists of a two-tiered test battery. Tier 1 is used to identify substances that have the potential to interact with the estrogen, androgen, and thyroid hormone systems. If a chemical is found to have the potential to interact with any of the three hormonal systems considered, it will proceed for Tier 2 testing. The Tier 2 test battery is designed to identify any adverse endocrine-related effects caused by the substance and establishes a quantitative relationship between the dose and the adverse effect [28]. The test guidelines for the assays of Tiers 1 and 2 are further detailed in Table 3 and Table 4. The information obtained from both test batteries is used to characterize potential endocrine activity and for the chemical's risk assessment.

Table 3. Assays included in Tier 1 of the EDSP [29].

Number of the test guideline (OPPT[EE])	Title
890.1100	Amphibian Metamorphosis (frog)
890.1150	Androgen Receptor Binding (Rat Prostate)
890.1200	Aromatase (Human Recombinant)
890.1250	Estrogen Receptor Binding
890.1300	Estrogen Receptor Transcriptional Activation
890.1350	Fish Short-Term Reproduction
890.1400	Hershberger (Rat)
890.1450	Female Pubertal (Rat)
890.1500	Male Pubertal (Rat)
890.1550	Steroidogenesis (Human Cell Line – H295R)
890.1600	Uterotrophic (Rat)

Table 4. Assays included in Tier 2 of the EDSP [29].

Number of the test guideline (OPPT[S])	Title
890.2100	Avian Two-Generation Toxicity Test in the Japanese Quail
890.2200	Medaka Extended One-Generation Reproduction Test
890.2300	Larval Amphibian Growth and Development Assay

[DD] 21 U.S.C. Ch. 9 §346a(p)(6)
[EE] US EPA Office of Prevention, Pesticides and Toxic Substances

5.2.1.2 Regulatory framework on drinking water contaminants

Scope and general processes

The US regulatory framework on drinking water contaminants is governed by the Safe Drinking Water Act (SDWA) to ensure safe drinking water for the public [30]. It gives the US EPA the authority to establish a regulation of either non-enforceable health goals or enforceable standards for the levels of a contaminant[FF] in public drinking water systems[GG] if it finds that:[HH]

- the contaminant may have an adverse effect on the health of persons;
- the contaminant is known to occur or is likely to occur in public water systems with a frequency at levels of concern to public health; and
- the regulation of a contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

When the US EPA decides to regulate a drinking water contaminant, it first determines a maximum contaminant level goal (MCLG). This is the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of a person would occur. For carcinogens, the MCLG is set at zero, and for non-carcinogen contaminants, the MCLG is based on a reference dose (i.e. the estimated amount that a person can be exposed to on a daily basis that is not anticipated to cause an adverse effect). The MCLG is a non-enforceable health goal [30].

Based on the established MCLG, the US EPA may then set an enforceable standard. This standard is a maximum level of contaminants (MLC) allowed in any public drinking water system. If there is no reliable economically or technically feasible method for the measurement of the contaminant at the required concentrations, the US EPA sets a "treatment technique". This technique is an enforceable procedure or level of technological performance that public drinking water systems must follow in order to ensure control of a contaminant [30].

Public participation and stakeholder involvement

The process of regulating drinking water contaminants provides opportunities for public participation. When the US EPA intends to regulate a substance as a drinking water contaminant, it first publishes this intention for public commenting [30]. Furthermore, when the US EPA proposes a drinking water regulation containing a MLC or a treatment technique, the public has the opportunity to comment on this proposal, including on the US EPA's underlying analysis on health risk reduction and costs.[II]

Processes relevant for EDCs

Similarly to the FD&C Act, the Food Quality Protection Act passed in 1996 amended the SDWA explicitly mandating the US EPA to test a drinking water contaminant for possible endocrine disrupting effects when it determines that a substantial population is exposed to such a contaminant.[JJ]

[FF] 42 U.S.C. §300g-1(f)(6): The term "contaminant" means any physical, chemical, biological or radiological substance or matter in water.
[GG] 42 U.S.C §300g-1(f)(4)(A): A drinking water system is a public drinking water system, if it has at least 15 service connections or serves at least 25 individuals.
[HH] 42 U.S.C §300g-1(b)(1)(A)
[II] 42 U.S.C. §300g-1(b)(3)(C)
[JJ] 42 U.S.C. §300j-17

Criteria utilized

The SDWA does not state any statutory criteria for EDCs. The testing and identification of possible endocrine disrupting effects of a water drinking contaminant is conducted within the ongoing EDSP.

Data requirements

Making use of the EDSP, data requirements are the same as described for pesticides in section 5.2.1.1.

5.2.1.3 Regulatory framework on new drug approval

Scope and general processes

EDCs are explicitly addressed in the US' regulatory framework on new drug approval based on the Federal Food, Drugs and Cosmetics Act (FD&C Act).[KK] According to this statute, every new drug has to be approved by the Food and Drug Administration (FDA) before it can be placed on the market. This approval is based on the evaluation of extensive non-clinical and clinical test data demonstrating the drug's safety and effectiveness for its proposed use and that its benefits outweigh the risks [31].

Public participation and stakeholder involvement

The pre-market approval process for new drugs in the United States was not identified to provide a possibility for public participation.

Processes relevant for EDCs

During the non-clinical testing of a drug, its potential unintended endocrine-related toxicity can be evaluated and considered during the application process by the FDA. The evaluation of unintended endocrine-related toxicity can be based on the standard battery of toxicity tests generally recommended by the FDA's Center for Drug Evaluation and Research (CDER). If endocrine effects are identified, other tests might be warranted based on additional factors such as the indication, target population or level of exposure relative to the expected clinical exposure [32].

Criteria utilized

The industry guidance document for the non-clinical evaluation of endocrine-related drug toxicity defines "endocrine-active compounds" as "compounds that can interfere with the endocrine system of an organism or its progeny resulting in adverse effects in one or more sensitive tissues". The document states that for pharmaceuticals, only effects seen at clinically relevant exposures are of concern [32].

Data requirements

Under the FDA's drug approval process, the evaluation of unintended endocrine-related toxicity of drugs is generally based on the standard non-clinical battery of toxicity tests. These tests generally encompass receptor-binding assays, pharmacology studies, repeat-dose toxicity studies, developmental and reproductive toxicity studies, and carcinogenicity studies. If endocrine effects are identified during this assessment and it is not known whether the endocrine-related finding will be relevant to humans

[KK] 21 U.S.C. Ch. 9 §301 et seq.

under conditions of use, additional studies might be warranted. Such studies can include mechanistic studies, non-clinical juvenile studies, and even clinical studies [32].

5.2.2 Canada

EDCs are explicitly addressed in several regulatory frameworks in Canada including the Canadian Environmental Protection Act of 1999 (CEPA), the Pest Control Products Act (PCPA), and the proposed framework within the Food and Drugs Act (F&DA).

5.2.2.1 CEPA

Scope and general process

CEPA aims at preventing pollution and protecting the environment and human health, and includes specific requirements for the assessment and management of substances [33]. Under CEPA, Environment and Climate Change Canada (ECCC) and Health Canada conduct risk assessments of substances proposed for introduction to the Canadian market (new substances) or present in Canada (existing substances), to determine whether these substances present or may present a risk to the environment or to human health [34]. CEPA (and associated regulations) defines the process for notification and evaluation of substances and activities that are new to Canada. These notifications are received on a continuing basis and require risk assessment under CEPA [35]. CEPA also requires that a screening assessment be conducted on existing substances identified as priorities through the Categorization process, which was a goal set under CEPA to sort through or "categorize" all 23,000 chemical substances on the Domestic Substances List (DSL)[LL] [36]. In addition to Categorization, other mechanisms exist for the identification of priorities for risk assessment such as decisions of other jurisdictions and emerging science and monitoring [37].

CEPA provides the Minister of ECCC and the Minister of Health Canada with the authority to determine if a new or existing substance is toxic, and it defines regulatory instruments for risk management as needed [34,38]. If a substance is found to be toxic under CEPA, it can be added to the "List of Toxic Substances" and regulatory actions can be taken for any aspect of the substance's life cycle [39]. A substance is considered 'toxic' if it is entering or may enter the environment in a quantity or concentration or under conditions that: [MM]

a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or

b) constitute or may constitute a danger to the environment on which life depends; or

c) constitute or may constitute a danger in Canada to human life or health

If determined to be toxic or capable of becoming toxic, then risk management measures are considered to reduce, eliminate or prevent risks identified. Follow up activities may be undertaken for those

[LL] More than 23,000 chemical substances were in use in Canada prior to the development of the New Substances Notification Program. This group of older, or "existing substances", form what is known as the Domestic Substances List (DSL).
[MM] CEPA, 1999, section 64. For further information, see ref. [92].

substances recognized for their potential effects of concern [34,40]. Examples of policy instruments for risk management are outlined in Table 5. For new substances specifically, when no actions for risk management are needed, the substance can be added to the DSL.

Table 5. Examples of policy instruments provided by CEPA for the risk management of substances.

Policy instrument	Comment
Regulations	Enforceable laws that can restrict the use or release of a chemical substance, set limits on the concentrations allowed under various conditions, or prevent the use of chemical substances in certain products.
Pollution prevention planning notices	Require companies to prepare and implement a pollution prevention plan in order to minimize or avoid the creation of pollution or waste.
Release guidelines or codes of practice	Recommend limits and best practices to manage the use, release or disposal of a chemical substance.
Significant new activity notices	Require any major changes in the way a chemical substance is used to be reported so that the government can decide whether to control the new use.
Environmental performance agreement	Agreement negotiated among parties to achieve specific environmental results. Can address a variety of environmental issues, such as reducing use or emissions, advancing product stewardship or conserving sensitive habitats.
Permission for manufacturing / importing under certain conditions	Applicable conditions can include restrictions on certain uses or emissions regulations.
Request for additional information	Mandatory surveys issued under section 71 of the CEPA gather information needed to inform priority setting, risk assessment and, if necessary, subsequent risk management activities for substances that are toxic or proposed to be toxic as defined under section 64 of CEPA 1999.
Prohibition of manufacture / import	As per Section 84 of CEPA, the Ministers may prohibit the import or manufacture of a substance suspected of being toxic or capable of becoming toxic, or request additional information or submission of results of any testing that the Ministers consider necessary for the purpose of assessing whether the substance is toxic or capable of becoming toxic.
Ministerial Condition	As per Section 84 of CEPA, manufacture or import of the toxic substance is subject to any conditions that the Ministers may specify.

Public participation and stakeholder involvement

Canada's Chemicals Management Plan (CMP) provides a roadmap for assessing and managing chemical substances under CEPA and is delivered jointly by ECCC and Health Canada. Stakeholders remain informed and contribute to the CMP through regular public information sessions and consultations. The CMP Stakeholder Advisory Council also offers advice and input from industry, non-governmental organizations and Aboriginal groups on the implementation of the plan [41].

With respect to existing substances, risk assessment documents must be published in the Canada Gazette for a 60-day public comment period [42]. If the final screening assessment maintains the toxic conclusion, the risk management approach document is published and outlines in more detail the plan

for risk management; consultations continue throughout the development and implementation phases of the risk management tool [40].

Processes relevant for EDCs

CEPA, in subsection 44(4), places mandatory obligations on the Minister of ECCC and the Minister of Health Canada with respect to research on EDCs [26]. The scope of the research mandate includes "research or studies relating to hormone disrupting substances, methods related to their detection, methods to determine their actual or likely short-term or long-term effect on the environment and human health, and preventive, control and abatement measures to deal with those substances to protect the environment and human health" [26]. Research conducted by the Government of Canada is used in risk assessments conducted under the CEPA when available for both existing and new substances [29].

Research on EDCs is mentioned in CEPA as one line of evidence amongst many types of hazards and adverse effects in human health and environmental risk assessments when determining whether a substance may pose a risk [29].

Criteria utilized

Section 43 of CEPA defines an EDC (originally noted as a "hormone disrupting substance") as: *"*a substance having the ability to disrupt the synthesis, secretion, transport, binding, action or elimination of natural hormones in an organism, or its progeny, that are responsible for the maintenance of homeostasis, reproduction, development or behaviour of the organism*"*. However, CEPA does not state any quantitative criteria (e.g. test conditions and thresholds) for the identification of an EDC.

Data requirements

For the assessment of endocrine-related effects, information from a variety of sources is used including research results, peer-reviewed scientific literature, public or in-house databases, read-across information from structural analogues or quantitative structure-activity relationships (QSAR), as well as data that may be submitted by manufacturers and importers [43].

The notification of a new substance under CEPA does not require assays or data specifically for the purpose of determining the endocrine disrupting potential; however, certain mammalian-based assays that are required may be used to evaluate potential endocrine-related effects. Specifically, a higher tiered final schedule notification requires the submission of a 28-day repeated-dose toxicity study, e.g., OCED repeated dose 28-day oral, dermal, and oral inhalation toxicity studies in rodents (OECD Test Guideline numbers 407, 410 and 412). Results from these tests are used to assess potential adverse effects and to conduct a cursory screen for potential endocrine-related effects of estrogenic, androgenic and thyrogenic systems and the adrenals. Assessment of the pituitary is optional.

5.2.2.2 Regulatory framework for pesticides under the PCPA

Scope and general processes

The Pest Control Products Act (PCPA) [NN] prohibits the manufacture, import, and use of, amongst other things, any unregistered pest control product. Before a pesticide is considered for registration in Canada, it must undergo testing to determine the risks posed to human health and the environment and the pesticide's value (including efficacy of product claims). Decision to register or deny registration is based on an objective scientific assessment of the risks and the value.

Health Canada applies quantitative risk assessment principles when determining whether a product can be registered for use in Canada, or to determine if it can remain registered (in the case of post-market evaluation). This involves determining the amount of human exposure to a given pesticide through both dietary and non-dietary (i.e., occupational & residential / bystander) exposures, as well as assessing environmental exposures.

Additionally, as part of the assessment process, prior to the registration of a pesticide, Health Canada must determine whether or not the consumption of the maximum amount of residues expected to remain on food products (when a pesticide is used according to label directions) will be a concern to human health. This maximum amount of residues expected is then legally established as an MRL and is regulated under the PCPA.

For chemicals exhibiting endocrine-mediated effects, the environmental risk assessment considers any observed endocrine effect(s) that directly relates or results in a measurable holistic effect endpoint (e.g., reproduction, growth development, behavioural) that would potentially cause harm at the community/population level and at environmentally relevant concentrations.

Public participation and stakeholder involvement

The PCPA offers several opportunities for the public to participate in the regulatory process. Under the Act, the public is able to:

- Provide comments on proposed major registration decisions
- Inspect Confidential Test Data
- Request a Reconsideration of Decision
- Request a Special Review

The consultation documents outline major findings of the evaluations and the proposed decisions, and they are made available to the public. Public comments are also considered for regulatory policies, regulatory directives, and guidance documents.

The current process for establishing MRLs in Canada involves the publication of a Proposed MRL (PMRL) document, which is subject to a 75-day consultation period (both domestic and international). Following the consultation, an Established MRL (EMRL) is then entered into the MRL database at which point it is legally in effect.

[NN] Pest Control Products Act, 2002. For further information, see ref. [78].

Processes relevant for EDCs

The potential for endocrine disruption is considered in the current risk assessment of pesticides under the PCPA [44]. This is highlighted in the response to Environmental Petition #320: "Endocrine disruptor potential (such as interference with the production of sex hormones) is evaluated in the course of examining the information from reproduction, developmental toxicity, and short- and long-term toxicity studies. If the results of these studies indicate the need for further information regarding interference with normal endocrine function, additional testing may be required" [45].

Criteria utilized

The PCPA does not state any statutory criteria for EDCs.

Data requirements

Endocrine disrupting potential is evaluated within the PCPA in accordance with the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters and associated OECD Test Guidelines. There are several standard toxicology data requirements existing within this framework that assess for potential effects on endocrine function. The key standard toxicity data requirements and corresponding OECD Test Guidelines for a food-use pesticide registration application typically include endpoints such as growth and development/maturation, reproduction, carcinogenicity, mutagenicity, neurotoxicity, thyroid effects, and changes in clinical chemistry and hematology. If study results indicate the need for further information regarding interference with normal endocrine function, additional testing may be required. In addition, data can also come from studies at the gene and cellular level (in vitro), from computer models, and as well as from epidemiological studies.

5.2.2.3 F&DA

Canada's *Food and Drugs Act* (F&DA) and regulations govern the sale and advertisement of foods, drugs, cosmetics, natural health products, and medical devices. Currently, the potential environmental risk of new substances in F&DA products is assessed and managed under the *New Substances Notification Regulations* (NSNR) of CEPA.

Health Canada is in the process of developing a proposed regulatory framework that would allow for environmental assessment of active pharmaceutical ingredients in human and veterinary drugs to be conducted at the time when an application for a drug submission requiring a new Drug Identification Number (DIN) is made to Health Canada [46]. Under the proposed regulatory framework, EDCs are considered special category substances because their risk to the environment may not be fully characterized by the proposed data requirements normally required for an environmental assessment. Therefore, drug submissions for EDCs may be subject to provide additional data to Health Canada. The challenge within this framework remains to define EDCs and the scope of substances that would be subject to this special category. Test data requirements for EDCs are still under development.

Stakeholder consultations on the proposed regulatory framework are scheduled to be held during the fall of 2017. Publication of the F&DR amendments in *Canada Gazette*, Part I, is planned for 2018/2019.

5.3 South America

5.3.1 Brazil

In Brazil, EDCs are explicitly addressed in the context of the regulatory framework on pesticides and in the policy initiative to establish a national legislation on industrial chemicals.

5.3.1.1 Regulatory framework on pesticides

Scope and general process

The Brazilian regulatory framework on pesticides consists of the Federal Law 7802/1989 [47] and the Decree 4074/2002 [48]. It sets provisions for pesticides and their components in Brazil, including rules on their production, import, packaging and labelling, use, and disposal.

The Federal Law 7802/1989 requires a pesticide and their components to be registered before they can be produced, imported, marketed or used, which consists of an efficacy assessment by the Ministry of Agriculture, a toxicological assessment by the Ministry of Health, and an assessment of potential environmental hazards by the Ministry of Environment. The data required for this registration process must be provided by the registrant. The final registration is granted by the Ministry of Agriculture after consultation with the two other Ministries involved in the assessment process [49]. Once granted, a registration does not have an expiration date. However, a pesticide may be re-evaluated when the responsible authorities might have indications that the pesticide poses harm to human health or the environment, or that its agronomical efficiency is no longer sufficient [48,49].

Public participation and stakeholder involvement

Before a new active ingredient is authorized, the monograph containing data about the authorized active ingredient is opened for public consultation for 30 days via the Ministry of Health's (ANVISA) website.

Regulatory processes relevant for EDCs

According to the Federal Law 7802/1989 and the Decree 4074/2002, it is prohibited to grant a registration to pesticides or their components if they are considered to disrupt endocrine systems.[OO] The Ministry of Health therefore assesses potential endocrine disrupting activity of a pesticide or any of its components during the registration process [50].

Criteria utilized

The Brazilian regulatory framework on pesticides does not state any statutory criteria for the identification of EDCs. The toxicological assessment of potential endocrine disrupting properties of a pesticide is performed on a case-by-case basis using a weight of evidence approach [50].

[OO] Federal Law 7802/1989, Art. 3 §6D. For further information, see ref. [47].

Data requirements

For the evaluation of potential endocrine disrupting properties of a pesticide, the Ministry of Health requests data from sub-chronic and chronic toxicity tests in rats, mice and dogs. Furthermore, in-vitro tests or tests in other animal species may also be required. For the re-evaluation of a pesticide product, the Ministry also considers academic publications and reports from other regulatory agencies or scientific organizations [50].

5.3.1.2 Initiative to establish a national legislation on industrial chemicals

Despite several regulatory schemes and instruments for regulating specific chemical substances and uses, no systematic framework for regulating industrial chemicals currently exists in Brazil. In 2014, the Ministry of Environment along with the National Commission on Chemical Safety established a working group with the mandate to draft a new legislation in view of managing industrial chemicals in Brazil. Among other things, the legislation intends to establish: (a) a national register for industrial chemicals produced and imported into Brazil, (b) a risk assessment process, and (c) a risk management programme to regulate chemicals and impose use restrictions. The risk management options proposed in the draft encompass (Communication by the Brazilian Ministry of Foreign Affairs, 2017): (a) voluntary agreements between the government and industry, (b) providing information in the national registry for substances produced or imported in quantities below 1 tonne per year, (c) prohibition of production, import, export, trade and uses of a substance, (d) restrictions on the production, import, export, trade and uses of a substance, (e) limit of concentration of a substance in intentional mixtures or finished products, and (f) prior authorization for the production and import of a substance.

The draft states that chemicals in the national register for industrial chemicals can be selected for risk assessment by the Risk Assessment Technical Committee. A second committee (the Deliberative Committee for Industrial Chemicals) will make the final decision on the risk management measures. Endocrine disrupting characteristics are set out as one of the selection criteria for the risk assessment of substances on the national register [50].

5.4 Asia

5.4.1 China

In China, EDCs are addressed in the context of a policy initiative on environmental protection and in an industry standard.

5.4.1.1 13th Five-Year Plan of National Environmental Protection

EDCs are explicitly addressed in the 13th Five-Year Plan of National Environmental Protection released by the State Council of the People's Republic of China in November 2016. The plan states that the pollution by endocrine disrupting chemicals will be strictly controlled. Furthermore, it lays out intended actions including completing a survey of the production and use of EDCs, monitoring and evaluating risks at water source and aquaculture regions and agricultural planting zones, and the implementation of measures including phase-out, restriction and replacement of EDCs by 2017 [51].

This policy initiative has been publicly released in a rather high-level formulation with no technical details reported.

5.4.1.2 Industry standard on evaluation methods of endocrine disruption effects of pesticides

In December 2015, the publication of industry standard NY/T2873-2015 "Evaluation Methods of the Endocrine Disruption Effects of Pesticides" was announced by the Chinese Ministry of Agriculture. This standard entered into force on 1 April 2016. It comprises a two-tiered approach with seven in-vitro or in-vivo testing guidelines for the evaluation of endocrine disruption effects of pesticides (see Table 8).

Table 6. Testing guidelines included in the Chinese industry standard NY/T2873-15 "Evaluation Methods of the Endocrine Disruption Effects of Pesticides".

Stage	Title
Tier 1 in-vitro testing	Oestrogen receptor transactivation
	Steroidogenesis in-vitro
Tier 2 in-vivo testing	Hershberger assay
	Uterotrophic assay
	Female pubertal assay & thyroid functionality testing
	Male pubertal assay & thyroid functionality testing
	Two-generation in-vivo testing

5.4.2 Japan

Adverse effects caused by endocrine disrupting properties of chemicals are expected to be considered in the regulatory risk assessment within Japanese regulations. The government has launched several consecutive national programmes investigating EDCs since the first strategic programme (SPEED '98) announced in May 1998. The recent national programmes (EXTEND 2010 and 2016) have, among others, focused on testing and assessment under the newly-developed programme to identify EDCs based on the WHO/IPCS definition [35]. Similarly to the US EDSP, the Japanese programme is based on a two-tiered testing strategy including in vitro and in vivo tests. The focus of the first tier of testing is the confirmation of an effect of a substance on the endocrine system. The second tier aims to identify adverse effects caused by the endocrine disrupting properties of chemicals. The programme generally focuses on effects on reproduction, the thyroid system, and growth. Some of the test methods and guidelines are still under development [36]. Knowledge obtained in the programme, especially results of the Tier 2 testing and assessment, will be referred to existing risk assessment practices for relevant regulation [35].

5.4.3 Korea

In the Korean regulatory frameworks, EDCs are explicitly addressed in the Act on the Registration and Evaluation of Chemicals (K-REACH). The regulation entered into force on January 1st, 2015 and sets provisions on the registration and assessment of chemicals on the Korean market. It also includes regulatory instruments for the management of potential risk posed by these chemicals. It is administered by the Korean Ministry of Environment (MoE).

5.4.3.1 K-REACH

Scope and general processes

K-REACH regulates chemical substances, which are defined as: i) elements, ii) compounds and substances from artificial chemical reactions, or iii) substances obtained by chemical modification, extraction, or purification of substances in their natural state. In addition, it includes provisions for chemical substances in products [52]. It does not apply to pharmaceuticals, cosmetics, pesticides, fertilizers, or food and animal feeds.

Similarly to many other regulatory frameworks, K-REACH distinguishes between "existing chemical substances" and "new chemical substances". The category of "existing chemical substances" includes all substances that were on the Korean market before February 2, 1991 or that have been subject to hazard reviews under the former Toxic Chemicals Control Act.[PP] "New chemical substances" include all substances which are not "existing chemical substances" [52].

K-REACH requires every person who intends to manufacture or import a new chemical substance, or at least 1 tonne per year of certain existing chemical substances, to apply for registration with the MoE before the start of manufacture or import. Such a registration is also required for the manufacture or import of products that contain a hazardous substance in the quantity of >1 tonne per year, if the hazardous substance can be released from the product. Within the registration, data on hazard properties and risks (such as exposure scenarios, controls, and management actions over the course of the life cycle of the chemical substance) have to be provided to the MoE. Following the registration, an assessment of hazards and, if necessary, risks is performed by the MoE. When the MoE determines that the substance fulfils certain hazard categories or poses a risk, the substance will be regulated. Regulatory instruments include placement on the authorization list, restriction of use, or prohibition of the substance [52]. Figure 5 provides a summary of the regulatory processes under K-REACH.

Public participation and stakeholder involvement

In order to designate a substance as subject to authorization, an evaluation is first completed on the risks to human health and the effects on social economy. The result of this evaluation is notified to the public and opened for commenting. The draft of this designation is also discussed with stakeholders.

Processes relevant for EDCs

EDC are explicitly addressed by K-REACH: Article 25(1) states that substances that cause or are likely to cause endocrine disrupting effects may be designated as substances subject to authorization. A substance subject to authorization requires permission by the MoE before its manufacture, import or use. Furthermore, any substance that is found to pose a risk but is not designated as a substance subject to authorization can also be regulated by restriction or be subject to prohibition.

Criteria utilized

No specific criteria for the identification of EDCs are stated.

[PP] Korean Act on the Registration and Evaluation of Chemicals, K-REACH, Art. 2(3)

Data requirements

No specific data requirements for the evaluation of the endocrine disrupting potential are stated.

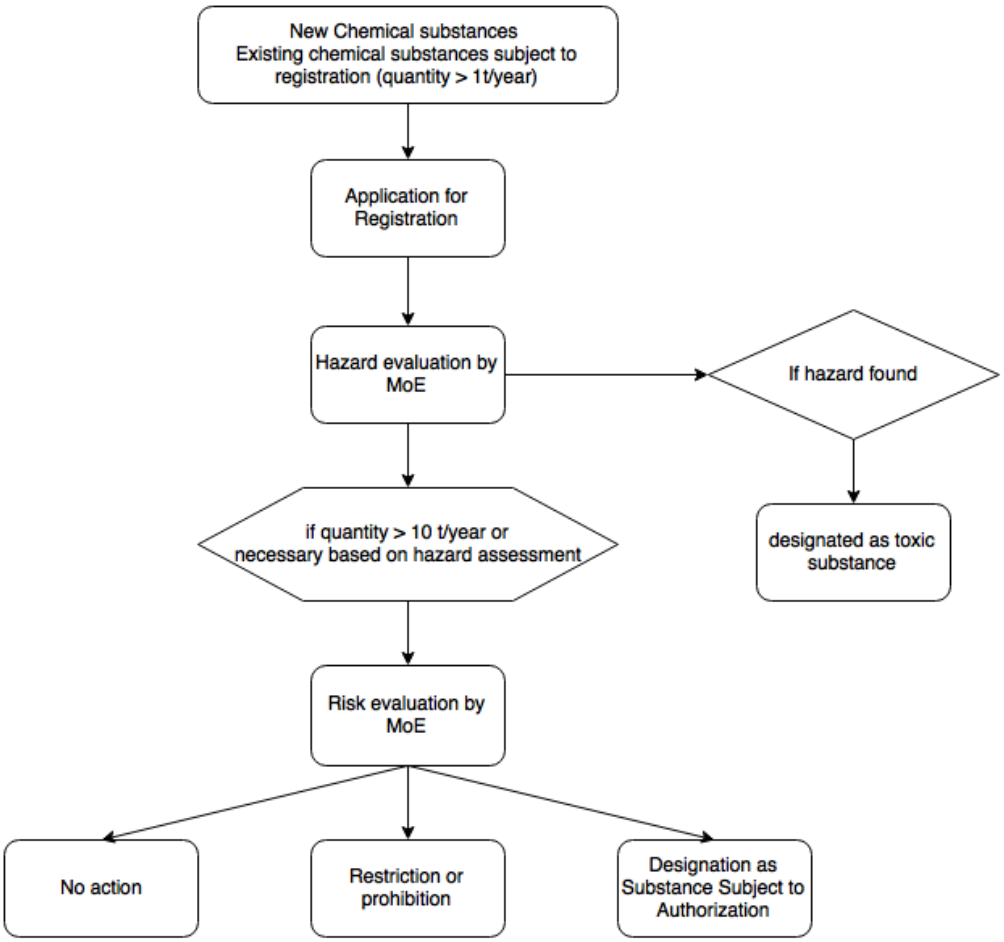

Figure 5. Summary of the regulatory framework for the registration and assessment of chemical substances under K-REACH.

5.5 Oceania

5.5.1 Australia

In Australia, EDCs are explicitly addressed under the assessment framework of industrial chemicals, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS).

5.5.1.1 NICNAS

Scope and general processes

The aim of NICNAS is to protect the Australian people and the environment from risks posed by industrial chemicals and to provide information to promote safe use of these chemicals. The scope of NICNAS includes industrial chemicals and any substances used in cosmetics, soaps or consumer products, and it excludes articles, pesticides or veterinary chemicals, medicines and medicinal

products, food, and food additives. The main aspects of NICNAS are the registration and assessment of health and environmental risks posed by chemical substances newly introduced to Australia, the maintenance of the Australian Inventory of Chemicals Substances (AICS), and the assessment of existing substances [53].

Under the current system, all new chemicals (i.e. chemicals that are not already included in the AICS) must be notified to NICNAS prior to their import or manufacture in Australia. The NICNAS provides the NICNAS Director with the authority to assess the new substance for its human health-related and environmental risks. Under the Industrial Chemicals (Notification and Assessment) Act of 1989, chemicals that are already listed in AICS may be used for any industrial purpose (subject to conditions of use, if any) without further assessment by NICNAS. However, such chemicals may be subject to review (e.g. under Inventory Multi-tiered Assessment and Prioritisation). However, NICNAS does not have authority to regulate industrial chemicals. Instead, the Director can make recommendations on policy instruments for risk management to other competent authorities [53,54]. Once a substance has passed the assessment under NICNAS, it can be imported to or manufactured in Australia. During the first five years as a new substance, all imports and production must be notified to the Ministry. After 5 years, the substance can then be listed on the AICS and is available for anyone to introduce into Australia without further notification and assessment under NICNAS. The Director of NICNAS may, however, include a "condition of use" in the AICS listing of the substance. Any use of the substance differing from the "condition of use" is regarded as a new chemical and requires a notification and assessment under NICNAS [53,55].

NICNAS also provides the authority to its Director to identify and assess substances on the AICS (i.e. existing chemical substances) for their human health-related or environmental risks under the Integrated Multi-tiered Assessment and Prioritisation (IMAP) framework [56]. Similarly to the assessment of new chemicals, NICNAS does not have any authority to regulate existing chemical substances, but only to make recommendations on policy instruments for risk management to other competent authorities [57].

Public participation and stakeholder involvement

At several stages of the assessment processes under NICNAS, stakeholders (e.g., the substance notifier or the general public) have opportunities to provide comments and/or information. The Director can also seek consultation from stakeholders such as industry and the general public during the assessment of new and existing chemicals. Furthermore, the public has the opportunity to comment on the proposed "conditions of use", listing or removal of chemicals on the AICS, and intention of re-assessing an existing chemical under the IMAP framework [53,58].

Processes relevant for EDCs

New chemicals

For new chemicals, explicit provisions for endocrine disrupting properties exist for UV-filters that are used in cosmetics applied to the skin. For the notification of these chemicals, the potential for endocrine disruption should be evaluated [53,59].

Existing chemicals

Endocrine disruption is considered in the current assessment framework for selected existing chemicals (IMAP). This framework consists of a three-tiered risk assessment scheme. The first tier comprises a matrix based screening for potential risks of chemicals by categorizing identified hazards and human exposure levels. If a certain matrix score is reached by a substance, it will be evaluated in the second tier, which further characterizes the potential risk using exposure and toxicity data. The third tier of the framework consists of a detailed, individual chemical assessment. Within this framework, endocrine disrupting properties are addressed as a hazard category in Tier 1. If a substance is identified as having endocrine disrupting properties, it automatically receives a matrix score that requires it to be further assessed in Tier 2 [56,60].

Criteria utilized

New chemicals

For assessing the potential for endocrine disruption by UV-filters used in cosmetics, no specific criteria are stated under NICNAS [53,59].

Existing chemicals

Tier-1 assessment of IMAP defines a substance as an EDC based on the list of priority substances developed under the EU-Strategy for endocrine disruptors [56].

Data requirements

No specific data requirements for the evaluation of the endocrine disrupting potential of a UV-filter is given by NICNAS. It is, however, suggested that such an evaluation is performed as a part of repeated dose and/or reproductive toxicity studies [53,59].

6. Overview of specific regulations

Regulatory frameworks can lead to the creation of regulations for specific, individual substances or for substance classes within a defined set of conditions. Table 9 provides a comprehensive, but not exhaustive example set of such specific regulations for substances on the national and regional level. These chemicals have been previously discussed by some authorities and/or their related research institutions for potential endocrine disrupting properties. However, this discussion of endocrine disrupting potential may not necessarily have formed the basis for the specific regulation. A reference is provided in the table to both the existing regulation and to previous regulatory discussion(s) regarding the chemical's endocrine disrupting properties. It is important to note that the examples in this table highlight specific regulations that have been created and implemented by some national or regional authorities. Other authorities may have also assessed these chemicals and decided not to specifically regulate them.

Table 7. Non-exhaustive set of examples of specific regulations of substances that have been discussed by authorities and/or their related research institutions for potential endocrine disrupting properties.

	Substance	Specific regulation	Reference to specific regulation	Reference to discussion on endocrine disruption
European Union	Bis(2-ethylhexyl) phthalate (DEHP); CAS No. 117-81-7	Restricted for the use of plasticised materials in toys and childcare articles in an amount >0.1% by weight.	[8]	[61]
	Dibutyl phthalate (DBP) CAS No. 84-74-2		[8]	[62]
	Benzyl butyl phthalate (BBP), CAS: 85-68-7		[8]	[63]
	4,4'-isopropylidenediphenol (Bisphenol A); CAS No. 80-05-7	Restricted for the manufacture of polycarbonate infant feeding bottles; Specific migration limit of 0.6 mg substance / kg food in plastic materials intended to come into contact with food.	[64]	[65,66]
	Nonylphenol and nonylphenol ethoxylates; CAS No. 25154-52-3 and others not identified	Restricted (not >0.1% by weight) for use in industrial and domestic cleaning, textiles/leather processing, metal working, and cosmetic products, among others.	[67]	[68]
France	Bisphenol A	Ban for use in food contact materials.	[69]	[65,66]
Sweden	Bisphenol A	Ban for the use in varnishes and coatings of food packaging for 0 to 3-year-old children. Ban for the use in two-component epoxy used for household water pipes.	[70,71]	[65,66]
Belgium	Bisphenol A	Ban for the use in food contact materials intended to come in contact with food for 0 to 3-year-old children.	[70]	[65,66]
Denmark	Bisphenol A	Ban for the use in food contact materials intended to come into contact with food for 0 to 3-year-old children.	[70]	[65,66]

	Substance	Specific regulation	Reference to specific regulation	Reference to discussion on endocrine disruption
United States	DEHP	Restricted for the use in children's' toys and child care articles in an amount of >0.1% by weight.	[72]	[61]
	BBP	Restricted for the use in children's toys and child care articles in an amount of >0.1% by weight.	[72]	[63]
Canada	Nonylphenol and nonylphenol ethoxylates	Pollution prevention plan to reduce the annual use by paper mills by at least 97% compared to 1998; Pollution prevention plan to reduce the annual use in manufacture and import in any product by 95% compared to 1998.	[73,74]	[75]
	Bisphenol A	- Prohibition for importation, sale, and advertising of polycarbonate baby bottles made with. - Notice requiring the preparation and implementation of pollution prevention plans in respect of Bisphenol A in industrial effluents. - Addition to cosmetics Ingredient Hotlist.	[76]	[65,66]
	DEHP	Vinyl in a toy or child care article must not contain more than 1000 mg/kg of compound.	[77]	[61]
	DBP			[62]
	BBP			[63]
	Lindane	Registration discontinued: neurotoxic endocrine active compound that indicated unacceptable health and environmental risk.	[78]	[79]
Brazil	DEHP	Restricted for the use in plasticized material in toys made out of vinyl in an amount of > 0.1% by mass.	[80]	[61]
	DBP			[62]
	BBP			[63]
	Bisphenol A	Ban for manufacture or importation of baby bottles for the feeding of infants.	[81]	[65,66]
Hong Kong	DEHP	The sum of the amounts of DEHP, DBP and BBP in toys or children's products must be ≤0.1% by weight.	[82]	[61]
	DBP			[62]
	BBP			[63]
South Korea	Nonylphenols and nonylphenol ethoxylates	Restriction of manufacture, import, sale, storage, transport or use of household cleaners, inks, paints, industrial or business cleaners, detergents, textile or leather finishing containing these substances.		[75]

	Substance	Specific regulation	Reference to specific regulation	Reference to discussion on endocrine disruption
South Africa	Bisphenol A	Ban for the manufacture of baby bottles.	[83]	[65,66]
India	Bisphenol A	Ban for the manufacture of baby bottles.	[84]	[65,66]
Israel	DEHP	Ban for use in the formula for preparation of toys and products for the care of children.	[85]	[61]
	DBP			[62]
	BBP			[63]
	Bisphenol A	Ban for the manufacture of baby bottles and drinking cups for babies.	[86]	[65,66]

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Annex

A.1 European Union

A.1.1 REACH

Table A1. Definitions of the terms "Substance" and "Article" under REACH.

	Definition	
Substance	"A chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition"	Art. 3(1)
Article	"an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition."	Art. 3(3)

A.1.2 PPPR

Table A2. Terms and their definitions under the Plant Protection Product Regulation.

	Definition	
Plant protection product	"[…] products, in the form in which they are supplied to the user, consisting of or containing active substances, safeners or synergists, and intended for one of the following uses: protecting plants or plant products against all harmful organisms or preventing the action of such organisms, unless the main purpose of these products is considered to be for reasons of hygiene rather than for the protection of plants or plant products; influencing the life processes of plants, such as substances influencing their growth, other than as a nutrient; preserving plant products, in so far as such substances or products are not subject to special Community provisions on preservatives; destroying undesired plants or parts of plants, except algae unless the products are applied on soil or water to protect plants; checking or preventing undesired growth of plants, except algae unless the products are applied on soil or water to protect plants"	Art. 2(1)
Active substance	"[…] substances, including micro-organisms having general or specific action against harmful organisms or on plants, parts of plants or plant products. […]"	Art. 2(2)
Safener	"substances or preparations which are added to a plant protection product to eliminate or reduce phytotoxic effects of the plant protection product on certain plants, […]"	Art. 2(3a)
Synergist	"substances or preparations which, while showing no or only weak activity as referred to in paragraph 1, can give enhanced activity to the active substance(s) in a plant protection product, […]"	Art. 2(3b)
Basic substance	"[…] an active substance which: is not a substance of concern; and does not have inherent capacity to cause endocrine disrupting, neurotoxic or immunotoxic effects is not predominantly used for plant protection purposes but nevertheless is useful in plant protection either directly or in a product consisting of the substance and a simple diluent; and is not placed on the market as a plant protection product. For the purpose of this Regulation, an active substance which fulfils the criteria of a 'foodstuff' as defined in Article 2 of	Art. 23(1)

	Regulation (EC) No 178/2002 shall be considered as a basic substance."	

A.1.3 BPR

Table A3. Terms and their definitions under the Biocidal Products Regulation.

	Definition	Article
Biocidal Product	"any substance or mixture, in the form in which it is supplied to the user, consisting of, containing or generating one or more active substances, with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action any substance or mixture, generated from substances or mixtures which do not themselves fall under the first indent, to be used with the intention of destroying, deterring, rendering harmless, preventing the action of, or otherwise exerting a controlling effect on, any harmful organism by any means other than mere physical or mechanical action A treated article that has a primary biocidal function shall be considered a biocidal product."	Art. 3(1)(a)
Active substance	"[…] a substance or micro-organism that has an action on or against a harmful organism;"	Art. 1(c)
Harmful organism	"[…] an organism, including pathogenic, agents, which has an unwanted presence or detrimental effect on humans, their activities or the products they use or produce, on animals or the environment;"	Art. 1(g)

A.2 North America

A.2.1 FIFRA

Table A4. Terms and their definition under the US Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

	Definition	
Pesticide	"The term "pesticide" means (1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and (3) any nitrogen stabilizer, except that the term "pesticide" shall not include any article that is a "new animal drug" within the meaning of section 321(w) [1] of title 21, that has been determined by the Secretary of Health and Human Services not to be a new animal drug by a regulation establishing conditions of use for the article, or that is an animal feed within the meaning of section 321(x) of [U.S.C.] title 21 bearing or containing a new animal drug. The term "pesticide" does not include liquid chemical sterilant products (including any sterilant or subordinate disinfectant claims on such products) for use on a critical or semi-critical device, as defined in [U.S.C.] section 321 of title 21. For purposes of the preceding sentence, the term "critical device" includes any device which is introduced directly into the human body, either into or in contact with the bloodstream or normally sterile areas of the body and the term "semi-critical device" includes any device which contacts intact mucous membranes but which does not ordinarily penetrate the blood barrier or otherwise enter normally sterile areas of the body."	7 U.S.C §136(u)
Biopesticide	A category of pesticides encompassing three different classes: i. Microbial pesticides ii. Plant-incorporated protectants iii. Biochemical pesticides	[24]
Antimicrobial pesticide	"a pesticide that – a) Is intended to i. disinfect, sanitize, reduce, or mitigate growth or development of microbiological organisms; or ii. protect inanimate objects, industrial processes or systems, surfaces, water, or other chemical substances from contamination, fouling, or deterioration caused by bacteria, viruses, fungi, protozoa, algae, or slime; and b) in the intended use is exempt from, or otherwise not subject to, a tolerance under section 346a of [U.S.C] title 21 or a food additive regulation under 348 of [U.S.C] title 2."	7 U.S.C §136(mm)