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COMMISSION STAFF WORKING DOCUMENT

FITNESS CHECK

on endocrine disruptors

Accompanying the document

COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS

Chemicals Strategy for Sustainability
Towards a Toxic-Free Environment

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ABBREVIATIONS

Abbreviation	Explanation
3-BC	3-Benzylidene camphor
AOP	Adverse Outcome Pathway
AR	Androgen Receptor
BAT	Best Available Techniques
BBP	Benzyl Butyl Phthalate
BCF	Bioconcentration Factor
BREF	BAT reference documents
BPA	Bisphenol A
BPR	Biocidal Products Regulation
CA	Competent Authority
CF	Conceptual Framework (OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters)
CLP	Classification, Labelling and Packaging
CMR	Carcinogenic, Mutagenic or toxic for Reproduction
CPR	Cosmetic Products Regulation
DBP	Dibutyl phthalate
DEHP	Diethylhexyl phthalate
DIBP	Diisobutyl phthalate
DNT	Developmental neurotoxicity
DWD	Drinking Water Directive
EAS	Endocrine Active Substance
EATS	Estrogen, Androgen, Thyroid, Steroidogenic
EC	European Commission
ECHA	European Chemicals Agency
ED	Endocrine Disruptor
EFSA	European Food Safety Authority
ELoC	Equivalent Level of Concern
EOGRTS	Extended-One-Generation Reproductive Toxicity Study
EQS	Environmental Quality Standard
ER	Estrogen Receptor
ESAC	ECVAM Scientific Advisory Committee

Abbreviation	Explanation
EURL ECVAM	European Union Reference Laboratory for alternatives to animal testing
FAO	Food and Agriculture Organization
FC	Fitness Check
FCM	Food Contact Material
GD	Guidance document
GPSD	General Product Safety Directive
IATA	Integrated Approach(es) to Testing and Assessment
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPCS	International Programme on Chemical Safety
IVDR	In Vitro Diagnostics Regulation
JRC	Joint Research Centre
LMWP	Low Molecular Weight Phthalates
LOAEL	Lowest observed adverse effect level
LOEC	Lowest observed effect concentration
MDR	Medical Devices Regulation
MoA	Mode of Action
MRL	Maximum Residue Level
MSC	Member State Committee
MS	Member State
NAM	New Approach Methodology
NGO	Non Governmental Organisation
NGRA	Next Generation Risk Assessment
NOEC	No Observed Effect Concentration
NP	Nonylphenol
OECD	Organisation for Economic Cooperation and Development
OML	Overall Migration Limit
OSH	Occupational Safety and Health legislation
PBT	Persistent, Bioaccumulative and Toxic
PCB	Polychlorinated biphenyl
PEC	Predicted Environmental Concentration
PHS	Priority Hazardous Substance
PFAS	Per- and polyfluoroalkyl substances
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant

Abbreviation	Explanation
PPP	Plant Protection Product
PPPR	Plant Protection Products Regulation
PS	Priority Substance
RAC	(ECHA) Risk Assessment Committee
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RoHS	Restriction of Hazardous Substances
SEAC	(ECHA) Socio-Economic Analysis Committee
SCCP	Scientific Committee on Consumer Products (replaced by the SCCS)
SCCS	Scientific Committee on Consumer Safety
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SCoPAFF	Standing Committee on Plants, Animals, Food and Feed
SME	Small and Medium-sized Enterprise
SML	Specific Migration Limit
SPS	(Agreement on the Application of) Sanitary and Phytosanitary Measures
SVHC	Substance of Very High Concern
TG	Test Guideline
TBT	(Agreement on) Technical Barriers to Trade
TDI	Tolerable Daily Intake
UNEP	United Nations Environment Programme
UN GHS	United Nations Globally Harmonised System
UWWD	Urban Waste Water Directive
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
vPvB	very Persistent and very Bioaccumulative
WFD	Water Framework Directive
WHO	World Health Organization
WoE	Weight of Evidence
WTO	World Trade Organization

1 INTRODUCTION

- Endocrine Disruptors are chemicals that can negatively affect the health of humans or animals by altering the functioning of the hormonal system.
- The EU has taken a progressive series of actions on endocrine disruptors since 1999.
- Different regulatory approaches exist in different pieces of legislation.
- To address concerns about possible inconsistencies between different pieces of legislation, the Commission launched a Fitness Check in 2019.
- The Fitness Check focused mainly on the evaluation criteria of coherence and effectiveness, but also addressed efficiency, relevance and EU added value.

1.1 Background to the Fitness Check

Endocrine Disruptors (EDs) are chemical substances that can alter the functioning of the endocrine (hormonal) system and negatively affect the health of humans or animals. The EU response to EDs has developed over the past twenty years, in line with the actions outlined in the Community Strategy for Endocrine Disruptors[1]. Significant progress in understanding these substances has been made since then.

Overviews of the state of the science on EDs have been published by various bodies. Notably, in 2012, the United Nations Environment Programme (UNEP) and the World Health Organization (WHO) published an update (WHO/UNEP, 2012) of the 2002 International Programme on Chemical Safety (IPCS) report (IPCS, 2002). This report notes the increase in trends of many endocrine-related disorders in humans, and associations between exposure to EDs and some diseases. It also acknowledges the multi-causal nature of the diseases and the resulting difficulty in attributing a given disease to a single factor, such as chemical exposure. The report also emphasises the existence of critical windows of exposure (such as foetal development and puberty) during which exposure can lead to irreversible effects, some being detected only many years later. Furthermore, the report gives examples of wildlife populations recovering after decreased exposure to EDs. Finally, the need to develop appropriate testing methods is highlighted.

Endocrine disruption is a relatively new consideration in toxicological or eco-toxicological assessment, whereby the focus is on the way in which a chemical disrupts the development and functioning of humans or organisms (i.e. through disturbing hormonal balance) eventually leading to an adverse effect (or effects) on function that arises as a consequence of the disturbance, where the nature of the adverse effects may vary according to the timing of the exposure and the species exposed.

For some chemicals, adverse effects, such as cancers in hormone-sensitive organs, or reproductive and developmental disorders, may already be known, and the chemicals already flagged as substances

[1]COM(1999) 706.

of concern (e.g. through classification as hazardous under the EU Classification Labelling and Packaging (CLP) Regulation[2]), have been banned or restricted on the basis of these adverse effects.

The significance of non-monotonic dose–response relationships and low-dose effects of endocrine disruptors has been widely debated and there is still no consensus in the scientific community on whether and how certain toxicological principles such as the 'safe threshold', (i.e. the dose below which no adverse effect is expected to occur) are applicable in assessing the safety of EDs. This lack of agreement presents particular difficulties at the policy level in deciding how risk assessments should be conducted for these chemicals and whether to follow a generic risk approach or a specific risk approach[3] (Solecki et al., 2017).

A variety of EU regulatory measures address the risks from exposure to hazardous chemicals. Collectively, these measures aim to ensure a high level of protection of human health and the environment, while ensuring the smooth functioning of the internal market. Some pieces of legislation have specific provisions for EDs (i.e. chemicals in general (REACH), plant protection products, biocidal products, water and medical devices). For other pieces of legislation, with no ED-specific provisions, there are general provisions for the risk management of hazardous substances which may be used to control the risks posed by EDs (once they are identified).

EU action on EDs relies largely on work undertaken by the EU scientific assessment bodies, such as the independent scientific committees (on Consumer Safety – SCCS – and on Health, Environmental and Emerging Risks – SCHEER), the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA). Following the hazard or risk assessments conducted by these bodies, the Commission takes the final decision on risk management measures, together with the Member States and the other European Institutions (Council and Parliament) as appropriate. When scientific evaluation cannot conclude with sufficient certainty on a risk, the Commission is guided by the *precautionary principle* to take protective measures for its citizens and/or the environment.

For plant protection products and biocidal products, the co-legislators decided – as for other hazard properties of particular concern (such as substances classified as carcinogenic, mutagenic, or toxic to reproduction, categories 1A or 1B) that once it is proven that a substance is an endocrine disruptor, the substance in principle cannot be authorised for use; while there are very limited derogation possibilities. For biocides, the ban is only applicable in relation to ED properties for human health and not for the environment.

Criteria for identifying endocrine disruptors have been established under the legislation on plant protection products[4] and biocidal products[5]. These criteria were informed by various EU initiatives. These included the work of a Endocrine Disrupters Expert Advisory Group (Munn and Goumenou, 2013a, b) and of the EFSA Scientific Committee (EFSA Scientific Committee, 2013), as well as an

[2]Classification, Labelling and Packaging of substances and mixtures (EC) No 1272/2008

[3]In generic risk approaches (referred also as hazard-based approaches) risk management measures are taken directly based on the identified hazard classification (generic risk consideration). In specific risk approaches (referred also as risk-based approaches) risk management measured are taken based on the outcome of a risk assessment, considering both exposure and hazard.

[4]Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties (plant protection products)

[5]Commission Delegated Regulation (EU) 2017/2100 of 4 September 2017 setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council

impact assessment of different options for the criteria[6]. The criteria are based on the 2002 IPCS/WHO definition (IPCS, 2002), according to which 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". In practical terms, this means that the identification of a substance as an ED should be based on an adverse effect for which: a) there is convincing evidence of a biologically plausible causal link to an endocrine disrupting mode of action; and b) disruption of the endocrine system is not a secondary consequence of other non-endocrine-mediated systemic toxicity.

EU legislation in fields other than plant protection products and biocidal products does not contain such criteria. It has been argued by stakeholders that the same criteria should apply across the relevant pieces of EU chemicals legislation for reasons of legal certainty and in order to avoid the possibility that a substance is identified as an ED under one piece of legislation and not under another.
Different regulatory approaches exist in different pieces of legislation for substances that have endocrine disrupting properties. According to some pieces of legislation, these substances cannot in principle be authorised for use, unless limited derogation possibilities apply. Under other pieces of legislation, chemicals with endocrine disrupting properties may be authorised for a limited period or a limited range of uses, or under restricted conditions.

Other pieces of legislation do not mention EDs specifically, however, substances with such properties can be subject to case-by-case regulatory action based on the general requirements of the legislation.

Efforts to identify, assess and manage risk from EDs under REACH have been underway for some time and two EDs (ethoxylates of octylphenol and nonylphenol) have been placed on the list of substances (Annex XIV) requiring specific authorisations to be on the market. A further 15 substances have been identified as substances of very high concern (SVHCs) with endocrine disrupting properties and are included in the *Candidate list* of substances for possible inclusion in the authorisation list in the future; another 80 or more are currently being evaluated due to concern about their potential endocrine disrupting properties. Substances with ED properties can also be subject to restrictions, e.g. four phthalates at a sum level of 0.1% or higher in a variety of products[7]. Time has been relatively short since the criteria to assess active substances used in biocidal products and plant protection products came into force (2018). Nevertheless, three biocidal active substances and three active substances in plant protection products (PPP) have already been identified as EDs for both human health and the environment and a further four PPP active substances identified as EDs for human health[8]. **Table 1.1** provides a list of the substances identified as SVHCs with endocrine disrupting properties under REACH or identified as EDs under the Biocidal Products Regulation as of September 2020.

[6]SWD(2016) 211
[7]See Annex XVII of REACH.
[8]Relevant EFSA conclusions are adopted but not yet published and hence not included in Table 1.1.

Table 1.1 Substances identified as endocrine disruptors at EU level[9]

Name and abbreviation	CAS no.[10]	Effects	Legislation
2,2-dibromo-2-cyanoacetamide	10222-01-2	Human Health and Environment	BPR
Cyanamide	420-04-2	Human health and Environment	BPR
Cholecalciferol	67-97-0	Human Health and Environment	BPR
3-benzylidene camphor	15087-24-8	Environment	REACH
4-(1,1,3,3-tetramethylbutyl)phenol	140-66-9	Environment	REACH
4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated	N/A	Environment	REACH
4-heptylphenol, branched and linear	N/A	Environment	REACH
4-Nonylphenol, branched and linear	N/A	Environment	REACH
4-Nonylphenol, branched and linear, ethoxylated	N/A	Environment	REACH
4-tert-butylphenol	98-54-4	Environment	REACH
Benzyl butyl phthalate (BBP)	85-68-7	Human Health	REACH
Bis(2-ethylhexyl) phthalate (DEHP)	117-81-7	Human Health and Environment	REACH
Bisphenol A	80-05-7	Human Health and Environment	REACH
Butyl 4-hydroxybenzoate	94-26-8	Human Health	REACH
Dibutyl phthalate (DBP)	84-74-2	Human Health	REACH
Dicyclohexyl phthalate (DCHP)	84-61-7	Human Health	REACH
Diisobutyl phthalate	84-69-5	Human Health	REACH
p-(1,1-dimethylpropyl)phenol	80-46-6	Environment	REACH
Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear (RP-HP) with ≥0.1% w/w 4-heptylphenol, branched and linear	N/A	Environment	REACH
Tris(4-nonylphenyl, branched and linear) phosphite (TNPP) with ≥ 0.1% w/w of 4-nonylphenol, branched and linear (4-NP)	N/A	Environment	REACH

Under the legislation on water, the Commission has included several endocrine disruptors in the list of "priority substances" of particular concern in surface waters, for which environmental quality standards and emission controls apply. Furthermore, the Commission has included several demonstrated or suspected endocrine disruptors in the "watch list" of substances for which Union-wide monitoring data should be gathered.

[9]See also Table 5.1 for further details
[10]N/A: not applicable

Due to possible concerns of endocrine disruption, the chemical bisphenol A was banned from use in baby bottles and other containers for foods for infants and young children on the basis of the precautionary principle, and very low migration limits are set for other food contact materials. Bisphenol A is also subject to limit values in toys for young children under 36 months or intended to be placed in the mouth and paper used in receipts. An occupational exposure limit value for bisphenol A has also been set to protect workers from exposure through inhalable dust.

On 7 November 2018, the Commission adopted its Communication "Towards a comprehensive EU framework on endocrine disruptors"[11], updating the Strategy of 1999. The Communication confirms the Commission's commitment to protect EU citizens and the environment from EDs. It outlines actions to step up the EU approach in order to further progress and maintain the expected high level of protection. In particular, to address the concerns on the coherence of the EU legal framework, the Communication announced the launch of this cross-cutting Fitness Check on EDs. While evaluations or Fitness Checks of relevance for EDs had already been carried out or are under way, a systematic analysis of the coherence of relevant provisions on EDs across the EU regulatory measures had not yet been completed. This was therefore a particular focus of this Fitness Check.

1.2 Objectives of the Fitness Check

EU regulatory measures that address the risks from exposure to endocrine disruptors (EDs) have been developed at different points in time and have, in certain cases, different specific objectives. This has resulted in different approaches for managing endocrine disruptors, depending on the sector being regulated. Collectively, these measures aim to ensure a high level of protection of human health and the environment, while ensuring the smooth functioning of the internal market. While regulatory measures have allowed protective action to be taken against these substances (e.g. by introducing bans or restrictions on their use), questions have been raised by stakeholders on the overall coherence of the EU legal framework in relation to EDs.

To address the concerns on the coherence of the EU legal framework, the Commission launched a cross-cutting Fitness Check on EDs[12], with the objectives to assess:

1) the **coherence** of the relevant EU legislation, including an analysis of how different provisions in different legal instruments interact, identifying potential gaps or inconsistencies.
2) whether EU chemicals legislation is **effective** in delivering its objective to protect human health and the environment by minimising the overall exposure to endocrine disruptors.
3) to the extent possible, the **efficiency**, **relevance** and **EU added-value** of the relevant EU chemicals legislation.

In addressing these objectives, particular attention is paid to legislation that does not contain specific provisions for endocrine disruptors, such as the legislation on toys, cosmetics and food contact materials. Another focal point is on whether the different pieces of legislation take into account the protection of vulnerable population groups that are particularly sensitive to endocrine disruptors when assessing and regulating such substances. The international dimension is also assessed, taking into

[11]COM(2018) 734
[12]Fitness Check initiative and roadmap: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/2142-Fitness-Check-on-endocrine-disruptors

account the impact of EU provisions on trade flows within and outside the EU. The findings of this Fitness Check will feed into the forthcoming Chemicals Strategy on Sustainability.

2 METHODOLOGY

- The methodology identifies the legislation considered to be in the scope of the Fitness Check
- A series of questions were formulated to guide the interpretation of the five evaluation criteria (coherence, effectiveness, efficiency, relevance and EU-added value).
- Four main evidence streams were generated to inform the findings: a) mapping of regulatory provisions related to the identification or risk management of endocrine disruptors; b) review of key policy and scientific documents; c) chemical specific case studies to illustrate the interplay between different pieces of legislation; and d) the results of consultations with the public, stakeholders and SMEs.

2.1 Scope of the Fitness Check

The horizontal nature of the Fitness Check requires a broad scope, covering many legal acts addressing chemicals that are relevant to human health and the environment. For much of the chemicals *acquis*, Fitness Checks and other 'Better Regulation' activities addressing specific pieces of legislation had been completed or were ongoing.

On the basis of the mandate of the Fitness Check described in the Commission Communication "Towards a comprehensive EU framework on endocrine disruptors", in-scope legislation was defined as legislation including provisions for the identification, hazard assessment, risk assessment or risk management of chemicals with endocrine disrupting properties for human health and the environment. The legislation considered in scope is listed in **Table 2.1.**

Table 2.1 Legislation in scope for this Fitness Check

Legislation
Plant Protection Products Regulation (EC) No 1107/2009
Maximum Residue Levels of Pesticides Regulation (EC) No 396/2005
Biocidal Products Regulation (EU) No 528/2012
REACH Regulation (EC) No 1907/2006
CLP: Classification, Labelling and Packaging of substances and mixtures (EC) No 1272/2008
Persistent Organic Pollutants Regulation (EU) 2019/1021
Food contact materials Regulation (EC) No 1935/2004
Contaminants in food Regulation (EEC) No 315/93 and in feed Directive 2002/32/EC
Food Additives Regulation (EC) No 1333/2008
Cosmetic Products Regulation (EC) No 1223/2009
Medical Devices Regulation (EU) 2017/745
In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746

Legislation
Toy Safety Directive 2009/48/EC
Fertilising Products Regulation (EU) 2019/1009
Detergents Regulation (EC) No 648/2004
Medicinal Products for Human Directive 2001/83/EC * Coverage here limited to unintended exposure via the environment (see also **Annex 4**)
Veterinary Medicinal Products Regulation (EU) 2019/6 * Coverage here limited to unintended exposure via the environment (see also **Annex 4**)
General Product Safety Directive 2001/95/EC
Water Framework Directive 2000/60/EC
Priority substances Directive 2013/39/EU
Drinking Water Directive 98/83/EC
Groundwater Directive 2006/118/EC
Marine Strategy Framework Directive 2008/56/EC
Urban Waste Water Directive 91/271/EEC
Chemical Agents at Work Directive 98/24/EC
Carcinogens and Mutagens at Work Directive 2004/37/EC
Pregnant Workers Directive 92/85/EEC
Young People at Work Directive 94/33/EC
Waste Directive 2008/98/EC
Restriction of the use of certain hazardous substances in electrical and electronic equipment Directive 2011/65/EU
Industrial emissions (integrated pollution prevention and control) Directive 2010/75/EU
Seveso-III-Directive 2012/18/EU
Ambient Air Quality and Cleaner Air for Europe Directive 2008/50/EC
EU Ecolabel Regulation (EC) No 66/2010

*EU Pharmaceuticals Strategy is under development

2.2 Fitness Check questions and baseline

The evaluation questions placed emphasis on coherence issues across the different in-scope regulatory instruments in **Table 2.1**. To apply the Fitness Check questions, it was necessary to establish a baseline for comparison. When a temporal reference needs to be established, the baseline is the situation with no specific provisions in EU legislation, corresponding to the year of adoption of the first strategy on endocrine disruptors (1999). The evaluation questions relate to the specific policy interventions or non-interventions across the different regulatory sectors from 1999 to date (e.g. implementation of REACH or the establishment of ED criteria for plant protection products and biocidal products). Other points of reference, such as non-EU jurisdictions, were considered when appropriate.

2.3 Mapping of of regulatory provisions and review of key documents

Annex 3 describes the approach taken to map regulatory provisions related to the identification or risk management of endocrine disruptors, and to review key policy and scientific documents.

2.4 Case studies

Case studies were developed for specific chemicals that are regulated under different and interconnected legislative instruments, with the aim to provide representative examples illustrating how EDs are identified, assessed and managed across legislation for their effects on human health and the environment. Substances selected for the case studies:

- 3-Benzylidene camphor (3-BC; under assessment under REACH and the Cosmetic Products Regulation; endocrine disruptor with human health and environmental concern)
- Diethylhexyl phthalate (DEHP; regulated under several pieces of legislation: REACH, cosmetic products, medical devices, food contact materials, toys, Water Framework Directive (WFD); endocrine disruptor with human health and environmental concern)
- Nonylphenol (NP; regulated under REACH (covering many sectors: detergents, biocides, plant protection products, cosmetic products, medical devices), WFD; endocrine disruptor with environmental concern)

Two economic case studies were also carried out to explore possible associations between the implementation of risk management measures on selected chemicals and trade flows, both within and between the EU and non-EU countries (Canzian et al., 2020).

The main criterion for selecting case studies was that the substances should be relevant to more than one policy area, thereby enabling an analysis of the coherence of the assessment and risk management approaches applied. DEHP, 3-BC and nonylphenols and their ethoxylates are regulated by various pieces of in-scope legislation, including the ones specifically mentioned in the Fitness Check mandate. DEHP and nonylphenols are representative of two main groups of substances which have been identified as SVHCs with endocrine disrupting properties (phthalates, alkylphenols) and for which risk management measures have been applied. Thus, the case studies were chosen to be as representative and informative as possible, from the pool of SVHCs with endocrine disrupting properties that were identified at the time of selection. (see **Table 1.1**).

2.5 Consultation activities

2.5.1 External consultation activities

Consultation activities were carried out to gather inputs from a broad range of stakeholder groups as well as citizens to ensure that views from all interested parties were considered in the evaluation. The consultation activities relied primarily on the results of three surveys aimed at the general public, stakeholders and SMEs. The results were used as an additional source of evidence, recognising that they are associated with an inevitable bias towards those who have an interest in responding. Further information on the approach and findings is given in **Annex 2**.

3 STATE OF PLAY

Substances with endocrine disrupting properties can be present in a wide range of materials and products. Some are incorporated in formulations intended for direct applications to humans (e.g. cosmetic products) or in the environment (e.g. plant protection products). Some are directly released upon product application (cosmetic products, plant protection products). Others are incorporated in materials and may be released over longer time scales along the product life cycle, from manufacturing to waste and possibly from recycled material streams. The system of EU regulation dealing with chemicals aims at minimising exposure of humans and the environment to EDs from different sources and exposure pathways. **Figure 3.1** illustrates at which stage of a product's life cycle, from manufacturing to waste, specific legislation is intended to act. Overall, risk management provisions (intervention logic) aim to strike a balance between human health and environmental protection, the societal benefits of the use of chemicals and the smooth functioning of the EU single market.

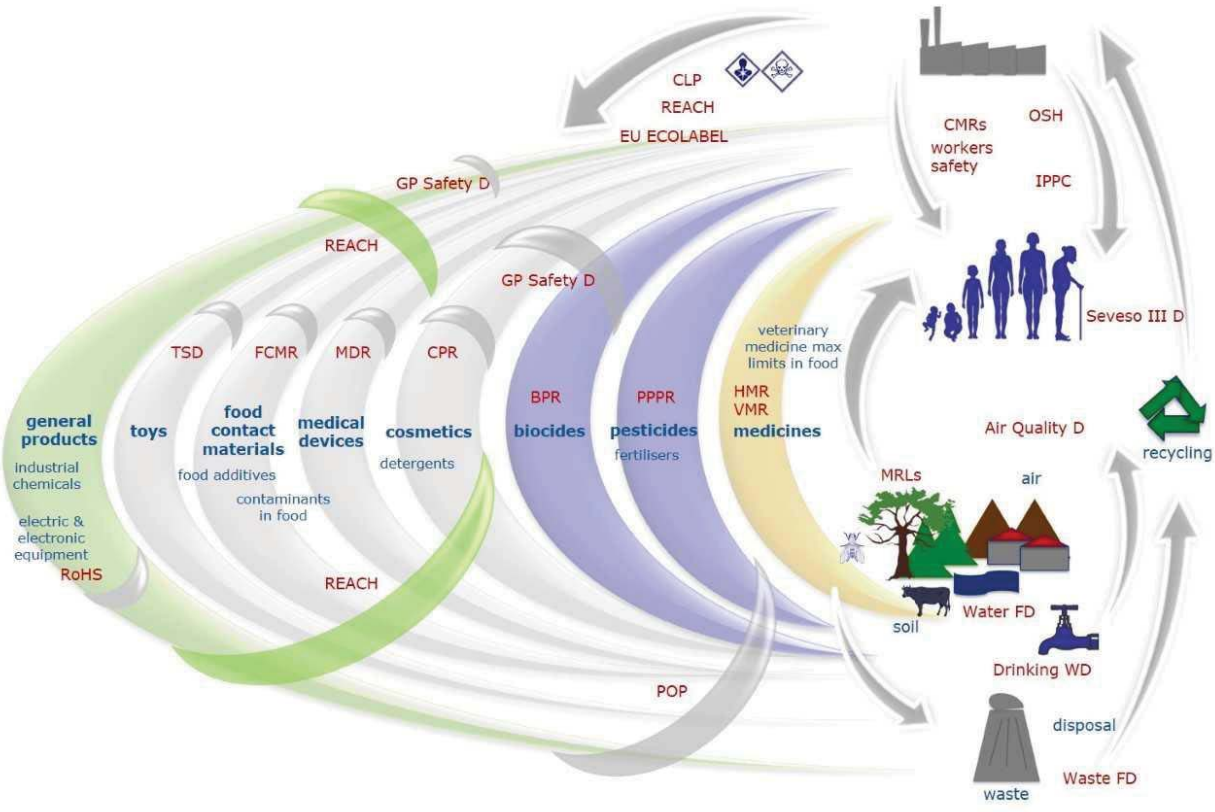


Figure 3.1. EU legislation (not exhaustive) mapped against pathways of endocrine disruptors' exposure to humans and the environment[13]

[13]See Annex 4 for a detailed description of legal provisions and processes for identification, assessment and management of EDs.

Annex 4 provides a detailed analysis of regulatory provisions and processes in place relevant to the control of endocrine disruptors for each piece of EU legislation in the scope of this Fitness Check. It also provides an overview of international legal obligations (WTO). Many pieces of legislation regulate the placing on the market of chemicals, and materials and products containing them (horizontal list in the centre of **Figure 3.1**). Their scope is complementary with respect to human and environmental protection, with the REACH regulation setting the baseline for general chemicals (**Figure 3.1**). These regulations and directives form the core of EU chemical legislation, together with the Classification, Labelling and Packaging (CLP) Regulation. **Table 3.1** summarises the intervention logic of each piece of 'in scope' legislation and highlights the different approaches implemented to manage EDs or which could be used to manage EDs (for those regulations that do not contain ED specific provisions). The Table also shows the main interlinkages between various pieces of legislation (more details are given in **Annex 4**).

Table 3.1 Overview of intervention logic and provisions for endocrine disruptors within in-scope legislation

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
Plant Protection Products Regulation (EC) No 1107/2009	Protection of human and animal health and the environment from exposure to hazardous chemicals in plant protection products by: • regulating the authorisation for placing on the market and use of plant protection products • regulating the approval of active substances, safeners and synergists	**Yes**	Criteria for ED identification introduced in 2018[14].	**ED-specific** and **generic risk approach** with limited options for derogation (negligible exposure and essential use).	Criteria for ED identification are in essence the same as for the Biocidal Products Regulation. Co-formulants in plant protection products have to be registered under REACH**.**
Maximum Residue Levels of Pesticides Regulation (EC) No 396/2005	Protection of consumers from unacceptable risk to pesticide residues in food and feed of plant and animal origin by: • determining maximum levels of pesticide residues	**No**		**Specific risk approach**	Hazard identification is covered under the Plant Protection Products Regulation.
Biocidal Products Regulation (EU) No 528/2012	Protection of human and animal health and the environment from exposure to hazardous chemicals in biocidal products by: • regulating the approval of active substances which may be used in	**Yes**.	Criteria for ED identification introduced in 2018[14].	**ED-specific** and **generic risk approach** with limited options for derogation (negligible risk, essential use, disproportionate negative impacts on society compared to the risk from use).	Criteria for ED identification are in essence the same as for the Plant Protection Products Regulation.

[14]Data requirements for plant protection products, biocidal products and REACH substances are currently under revision to increase their capacity for providing data on endocrine disrupting properties

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
	biocidal products regulating the authorisation for placing on the market and use of biocidal products				Co-formulants in biocidal products have to be registered under REACH.
REACH Regulation (EC) No 1907/2006	Protects the public (citizens, workers, consumers) and the environment from exposure to hazardous chemicals, while promoting alternative methods for assessment of hazards of substances by: • regulating the placing on the market of chemicals (on its own, in mixtures or from articles) through registrations, authorisation and restrictions • communication of hazards, risks and safe use conditions throughout supply chain	**Yes**, identification of ED as Substances of Very High Concern (SVHCs) possible through Art 57 (f).	Registration obligations require industry to assess hazards of substances. Data requirements depend on tonnage[14]. Assessment of endocrine disrupting properties through substance evaluation, SHVC-identification and as part of restrictions.	EDs are listed as SVHCs if meeting the "Equivalent Level of Concern" criteria. SVHC listing (**generic risk approach**) triggers notification provisions. SVHCs are regulated through authorisation and restrictions through **specific risk approaches** and **risk-benefit approaches**. Restrictions can be based on endocrine disrupting properties if they lead to an unacceptable risk. Registrants have to ensure that risks from manufacturing or use of chemicals are controlled or that emissions are minimised. Hazard properties including endocrine disrupting properties have to be reported via safety data sheets to ensure safe use throughout the supply chain.	Several provisions under REACH (e.g. on registration, authorisation, restriction) apply also to chemicals regulated under sector- or product-related legislation, unless explicitly excluded under REACH.
CLP: Classification, Labelling and	Protects human health and the environment by:	**No**	Endocrine disrupting properties are covered if they lead to a substance fulfilling	**Hazard-based.** Classification of substances as Carcinogenic, Mutagenic or toxic for the	CLP classification triggers provisions under many pieces of

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
Packaging of substances and mixtures (EC) No 1272/2008	• harmonised hazard classification as cross-cutting trigger for risk assessment and/or management in other legislation • harmonised labelling and packaging requirements ensuring hazard communication along supply chain		the criteria of other hazard classes (carcinogenic, toxic tor reproduction, specific target organ toxicity – repeated exposure, etc).	Reproduction (CMR) and other hazard classes triggers hazard communication (labelling, packaging).	legislation.
Persistent Organic Pollutants Regulation (EU) 2019/1021	Protects the environment from the risk posed by persistent organic pollutants by: • bans and restrictions applicable at international level • reporting data on uses and environmental monitoring to monitor progress and promote awareness	**No**	Criteria for Persistent Organic Pollutants (POPs) do not specifically address endocrine disrupting properties, although they can be taken into account for the T-criterion (toxicity).	The identification as POPs is mainly a **generic risk approach** and triggers ban and/or restrictions. Exemptions can be introduced based on risk-benefit considerations.	
Food contact materials legislation – Regulation (EC) No 1935/2004	Protects consumers and animals (feed Directive) from exposure to hazardous substances in food by: • setting rules on the composition of food contact materials, mainly for plastics, including an authorised list of substances and restrictions	**No**	Endocrine disrupting properties are taken into account as other hazards in risk assessment	Risk management of hazardous substances (authorisations, maximum levels), is mainly a **specific risk approach.**	Substances used in food contact materials have to comply with REACH registration provisions. Substances identified as SVHCs with endocrine disrupting properties with effects on the environment are subject to REACH authorisation provisions.

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
					Substances with endocrine disrupting properties with effects on human health or the environment can be restricted under REACH.
Contaminants in food Regulation 315/93/EEC and in animal feed Directive 2002/32/EC	• establishing maximum levels or maximum tolerances for certain contaminants in food and animal feed				
Food Additives and food enzymes and food flavourings, Regulation (EC) No 1333/2008 and Regulation (EC) No 1331/2008	• establishing a common authorisation procedure for food additives, food enzymes and food flavourings by including also data required for safety assessment				
Cosmetic Products Regulation (EC) No 1223/2009	Protects consumers from exposure to hazardous chemicals in cosmetic products by regulating the placing on the market through two main channels:	**No**	Endocrine disrupting properties are taken into account as other hazards in the context of the product-level safety report or by the SCCS.	**Generic risk approach** to the extent that some hazardous substances (e.g. CMRs) are banned, with limited options for derogations. **Specific risk approach** for other substances.	Substances used in cosmetic products have to be registered under REACH. Substances identified as SVHCs with

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
	• all substances are assessed by industry through product-level safety assessment reports. These may be assessed by the Scientific Committee on Consumer Safety (SCCS) and managed by the Commission when safety concerns are identified. • certain groups of substances considered of higher hazard potential (colourants, preservatives, UV filters) must be assessed for safety by the SCCS and are managed through lists of approved ingredients.				endocrine disrupting properties with effects on the environment are subject to REACH authorisation provisions and can be restricted under REACH.
Regulation (EU) 2017/745 on medical devices Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices	Protects patient users and, where appropriate, other persons from exposure to hazardous chemicals in medical devices by: • setting general safety and performance requirements for medical devices and in vitro diagnostics • ensuring that the relevant scientific opinions of the relevant scientific committees are taken into account	**No**	Hazards from endocrine disrupting properties are taken into account in risk assessments.	Presence of EDs must be justified and approvals are based on **risk-benefit**.	ED identification refers to REACH and (for medical devices only) to Biocidal Products Regulation. Substances used in medical devices have to be registered under REACH. Substances identified as SVHCs with endocrine disrupting properties with effects on the environment are subject to REACH authorisation provisions.

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
					Substances with endocrine properties with effects on human health or the environment can be restricted under REACH.
Toy Safety Directive 2009/48/EC	Protects children from the exposure to hazardous chemicals in toys by: • prohibiting the use of substances which are Carcinogenic, Mutagenic or toxic for the Reproduction (CMR) with limited possibilities for derogation • establishing specific limit values for any chemical (including identified EDs) in toys for children under 36 months of age and for toys intended to be placed in the mouth	**No**	Hazards from endocrine disrupting properties are taken into account as other hazards.	Combination of **generic risk** (CMRs are banned in principle) and **specific risk approaches** (limit values).	All substances used in toys have to comply with provisions under REACH. Provisions for registration, authorisations and restrictions apply.
Fertilising Products Regulation (EU) 2019/1009	Protects human, animal and plant health, safety and the environment by: • regulating the placing on the market of chemicals in fertilising products	**No**	Hazards from endocrine disrupting properties are taken into account as other hazards.	**Specific risk approach**	All substances used in fertilising products have to comply with provisions under REACH. Provisions for registration, authorisations and restrictions apply.
Detergents	Achieves the free movement of	**No**	Not applicable	Not applicable	Substances used in

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
Regulation (648/2004/EC)	detergents while, at the same time, ensuring a high degree of protection of the environment and human health by: • regulating the placing on the market of surfactants in detergents based on biodegradability standards and phosphorus content • labelling detergents				detergents are also regulated via REACH, Biocidal Products Regulation and the Cosmetic Products Regulation. Provisions under those regulations apply.
Medicinal products for humans (Directive 2001/83/CE)[15]	Main emphasis on the therapeutic benefit for the target group evaluated in the context of possible adverse side effects and risks to patients. Provisions are in place to evaluate and minimise the unintended effects of medicinal products via the environment by: • requiring environmental risk assessment and risk mitigation measures for endocrine active substances	**No**[16]		**Risk-benefit** approach. The outcome of the environmental risk assessment does not influence the approval of human medicines but can trigger measures to minimise exposure (e.g. communication, monitoring).	
Regulation (EU) 2019/6 on veterinary	Main emphasis on the therapeutic benefit for the target group evaluated in the context of possible adverse side	**No**	Endocrine disrupting properties not specifically addressed.	**Risk-benefit** approach. Evidence of an environmental risk, which cannot be	

[15]In scope of this fitness check with respect to unintended exposure via the environment
[16]Identification and assessment of endocrine active substances considered in ongoing revision of guidance for environmental risk assessment

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
medicinal products[15]	effects and risks to target organisms (treated animals). Evaluates and minimises the unintended effects of veterinary medicinal products via the environment by: • requiring environmental risk assessment and establishing approval procedures considering environmental risks			controlled with risk management/mitigation measures, can prevent the granting of the authorisation, if the risk is considered to outweigh the benefits of the product.	
General Product Safety Directive (2001/95/EC)	Protects consumers health and safety by requiring that only safe products are placed on the market: • rapid exchange of information between member states on measures taken against unsafe products found on the market through the Rapid Alert System for dangerous non-food products (Safety Gate/RAPEX) • follow up risk management (e.g. market withdrawal)	**No**. Does not include provisions for hazard identification.		Identified EDs are included in market surveillance activities based on restrictions established in other legislation (e.g. REACH), or by evidence of risk (so far not the case for EDs).	Refers to the chemical legislation for hazard and generic risk assessment.
Water Framework Directive (2000/60/EC) Priority	Water legislation collectively aims at protecting and enhancing water resources to achieve good water quality. This includes the good chemical and ecological status of European surface waters, the good	**Yes**, given the obligation to identify priority (hazardous) substances under the Water Framework	The assessment of endocrine disrupting properties of candidate priority (hazardous) substances takes assessments under other legislation into account, if	Chemicals can be prioritised for monitoring and for risk mitigation measures based on a combination of **generic risk approaches** (including endocrine disrupting hazard	The identification of priority (hazardous) substances considers the selection of substances of concern undertaken in the

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
substances Directive (39/2013/EC)	chemical and quantitative status of groundwater and the good environmental status of marine waters. It does this by: • identifying substances of concern and setting quality standards • coordinating monitoring and reporting of priority substances and other pollutants at EU level • requiring Member States to identify pollutants of national concern • requiring the implementation of risk management measures to reduce risks, including through the implementation of adequate waste and drinking water treatment	Directive (WFD) (including substances that are toxic, persistent and liable to bio-accumulate and "substances of equivalent concern"), and the inclusion of endocrine disrupting substances in the indicative list of main pollutants.	available. When necessary (e.g. for substances in waste or transformation products) assessments are carried out considering evidence regarding the intrinsic hazard of the substance concerned.	properties) and **specific risk approaches**. This is the case for priority substances and priority hazardous substances under the WFD and for substances representative of endocrine disrupting effects under the Drinking Water Directive.	relevant legislation regarding hazardous substances (e.g. REACH or PPPR or BPR) or relevant international agreements
Drinking Water Directive (98/83/EC)					
Groundwater Directive (2006/118/EC)					
Marine Strategy Framework Directive (Directive 2008/56/EC)					
Urban Waste Water Directive (91/271/EEC)					
Chemical Agents Directive at Work (98/24/EC)	Protect safety and health of workers from risks arising, or likely to arise, from the effects of hazardous substances at work by: • taking preventing measures and proposing indicative and/or binding occupational exposure	**No**	Hazards from endocrine disrupting properties are taken into account as other hazards.	**Non ED-specific**. Combination of **generic and specific risk approaches**, following a hierarchy of measures going from preventing exposure to reducing it to the lowest level	Refers to Classification Labelling and Packaging (CLP) hazard classes for hazard identification.
Carcinogens and Mutagens					

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
at Work Directive (2004/37/EC) Pregnant Workers Directive (92/85/EEC) Young People at Work Directive (94/33/EC)	limit values • encouraging all necessary measures to adjust temporally the working conditions of pregnant, recently given birth or breastfeeding workers • prohibiting the employment of young workers (under 18) if it entails exposure to agents which are toxic, carcinogenic, cause heritable genetic damage, or harm to the unborn child or which in any other way chronically affect human health.			technically possible for hazardous chemicals such as carcinogens, mutagens or reprotoxicants.	
Directive 2008/98/EC on waste	Protection of human health and the environment against harmful effects caused by waste by: • establishing rules for waste management covering waste hierarchy, requirements for waste treatment, waste traceability and end-of-waste. Stricter rules apply for hazardous waste	**No**	Not applicable	**Generic risk approach**. Management of waste including hazardous substances is done through classification of hazardous waste. Notification of hazardous substances in material streams based on REACH listing of Substances of Very High Concern (including SVHCs with endocrine disrupting properties).	Notification of SVHCs in articles indirectly takes into account endocrine disrupting properties to the extent a substance has been identified as SVHC under REACH. Definition of hazardous waste refers to Classification Labelling and Packaging (CLP) hazard classes.

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
Restriction of the use of certain hazardous substances in electrical and electronic equipment (Directive 2011/65/EU)	Contributes to the protection of human health and the environment through environmentally sound recovery and disposal of waste electrical and electronic equipment by: • restricting the use of certain hazardous substances	**No**	Not applicable	**Specific risk approach**. **Risk-benefit** considerations apply. Substances to be regulated are identified based on their negative impact on waste treatment and recycling, potential for environmental and worker exposure and replacement options.	Substances identified as SVHCs with endocrine disrupting properties and which have been added to the REACH authorisation list, as well as substances that are restricted under REACH can be considered for restrictions under RoHS.
Industrial emissions (integrated pollution prevention and control) Directive (2010/75/EU)	Aims at environmental protection and improvement of environmental quality by: • setting rules to prevent or to reduce emissions into air, water and land and to prevent the generation of waste • requiring the application of Best Available Techniques (BAT) in installations.	**No**. Does not include provisions for hazard identification.	Not applicable	Emission limit values set in this directive are based on the BAT, not on (eco)toxicity criteria.	
Seveso-III-Directive (2012/18/EU)	Protection of human health and the environment by: • setting rules to prevent major-accidents involving dangerous substances	**No**. Defines "dangerous substances" based on certain Classification Labelling and	Not applicable	Mainly **generic risk approach** with consideration of potential exposure.	

Legislation	Intervention logic	ED identification provisions	Hazard assessment of endocrine disrupting properties	Provisions for management of substances with endocrine disrupting properties	Main links with other legislation
	• provisions to limit the consequences of such accidents	Packaging (CLP) hazard classes and volume.			
Directive 2008/50/EC on ambient air quality and cleaner air for Europe; Directive 2004/107/EC relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air.	Protection of human health and the environment by: • monitoring air quality against established air quality standards (i.e. maximum allowed concentrations) • taking measures to ensure compliance	**No**	Not applicable	The determination of quality standards follows a **specific risk approach**.	Ecolabel is not awarded to goods containing inter alia substances identified under REACH as SVHCs with endocrine disrupting properties.
Regulation (EC) No 66/2010 on the EU Ecolabel	Promotes products and services meeting high environmental standards throughout their life-cycle by: • implementing a voluntary labelling scheme (ecolabel)	**No**	Not applicable	The Ecolabel criteria are based on hazards (**generic risk approach**).	Ecolabel is not awarded to goods containing inter alia substances identified under REACH as SVHCs with ED properties.

4 COHERENCE

- The World Health Organization definition of endocrine disruptors is broadly accepted in EU legislation. The criteria for the identification of EDs under the Plant Protection Products Regulation and Biocidal Products Regulation, and as substances of very high concern under REACH, are based on this definition. EU Agencies (EFSA, ECHA) and the Commission's Scientific Committee on Consumer Safety (SCCS) have endorsed the definition and apply it in the assessment of EDs.

- Differences in data requirements reflect different exposure scenarios contributing to risk, socioeconomic proportionality and laboratory animal welfare considerations. Following the establishment of criteria for the identification of endocrine disruptors, data requirements are being updated for plant protection products and biocidal products. The data requirements under REACH are also being updated. Ready access to the data eventually generated would also be helpful in other policy areas that have provisions for ensuring the safety of products placed on the EU market, but no specific data requirements.

- Further work is required to fulfil the Commission's ambition of a horizontal approach to the identification of ED, which is a gap criticised by many stakeholders. It creates uncertainty and confusion about the consequences across legislation. Most stakeholders favour a horizontal approach to identification. Based on the limited number of cases to date, there is no evidence of inconsistent identification across the regulations currently requiring the identification of EDs (mainly BPR, PPPR and REACH).

- Currently there is no hazard class for endocrine disrupting properties under the Classification Labelling and Packaging (CLP) Regulation. Identification of a Carcinogenic, Mutagenic or toxic for Reproduction (CMR) substance as an ED for human health will probably not lead to any additional risk management measures, where they are already the strictest but may nevertheless contribute to the overall evaluation within a risk-benefit context. In addition, not all EDs for human health will be identified as CMRs and identification as an ED for the environment may also trigger additional risk management measures.

- There are different opinions among authorities and experts about the ability to demonstrate safe or unsafe uses of EDs using available methods in a risk assessment. The lack of consensus underlines the crucial role of the European Commission, its scientific committees and EU agencies to ensure alignment of assessment approaches and coordination of subsequent risk management. At EU level, agencies and scientific committees may in principle conclude on a level below which no risk is identified, if the evidence for a specific substance allows a threshold to be established. However, it is still debated which evidence and methods allow the establishment of a threshold below which no significant risk is expected for endocrine disruption.

- There are few examples of risk assessments based on endocrine disrupting properties. For DEHP (and other phthalates), both ECHA and EFSA concluded based on an exceeded safe threshold for anti-androgenic mediated toxicity to male reproduction. Octylphenol,

nonylphenol and their ethoxylates were identified as Substance of Very High Concern (SVHC) because of endocrine disrupting properties in the environment. In the case of the restriction of certain uses of these substances, ECHA's Risk Assessment Committee considered that effects from endocrine disruption could occur below the predicted no effect concentrations derived for other endpoints. However, risks were identified following standard risk assessment applied to non-ED specific endpoints, which was sufficient to justify the restriction. The uncertainties associated with the possible peculiarities of endocrine disrupting effects (i.e. non-threshold, non-monotonic behaviour) are recognised and in some cases have been taken into account through the use of uncertainty factors, defined on a case by case basis.

- There is an opportunity to introduce or improve the consistency of definitions of vulnerable groups across legislation and to clarify the scientific rationale (degree of exposure or biological susceptibility) for triggering specific provisions for vulnerable groups. In the meantime, some flexibility in the consideration of vulnerable groups (definitions, relevant hazard endpoints, data requirements) will be needed to adapt the methodology currently in use.

- Different approaches to risk management (e.g. generic risk approaches vs specific risk approaches vs risk-benefit approaches) are pragmatic approaches reflecting policy-specific considerations. This situation has been criticised by many stakeholders, who expressed concern that differences in risk management measures may not be justified. Indeed, the rationale for some of the differences should be made more transparent. Based on a limited number of examples this Fitness Check found no cases of inconsistent risk management of specific substances caused by ED-specific issues.

- The difficulty in choosing a risk management approach is partly related to the fundamental scientific question of whether EDs are (all) threshold or non-threshold substances. In the absence of scientific consensus, legislation can either opt for an approach that does not require an answer to the question (e.g. generic risk approach with derogations as done for plant protection products and biocidal products) or it can determine case by case whether or not a safe (or acceptable) threshold can be quantified and consequently apply an appropriate risk management approach, as done in REACH. Certain pieces of sectorial legislation (e.g. Cosmetic Products Regulation, Food Contact Materials Regulation) not only lack specific provisions for assessing EDs but also lack specific guidance on how to deal with EDs for which it is not possible to quantify a safe (or acceptable) threshold. In practice, in cases where a threshold cannot be established the regulatory approach followed under EU legislation is to minimise exposure as far as possible, including the option to prohibit the use of a substance. Options for consolidation compatible with the Commission's ambition of "one substance one assessment" should therefore be explored.

- The current regulatory frameworks for different products do not provide a comprehensive framework for integrated exposure assessment across sectors and material life cycles as a basis for an overarching risk assessment and subsequent coordinated intervention. This has led to differences in the extent of risk management when the same (group of) substances, such as phthalates including DEHP, have been assessed under different regulatory frameworks.

- When judged from a broader health and environmental protection perspective, the inherent complexity of the legislative framework for chemical risk assessment and management is a

challenge to systematic and harmonised consideration of aggregate and combined exposure scenarios.

- Lack of coordination between chemical, product, water and waste legislation (e.g. safety vs recyclability targets, or cessation of emissions to water) has a negative impact on effectiveness and efficiency. Sector-specific approaches to identification and management of EDs cannot be effective for the identification and management of EDs in waste streams (e.g. consumer products ending in municipal waste), except in cases where material streams are collected and managed separately.

- The EU regulatory system is the only one worldwide that has implemented scientific criteria to define EDs in legislation. The implementation of a generic risk approach to regulate EDs in plant protection products and biocidal products has been frequently criticised by WTO members.

Q1 – To what extent are the different provisions on and approaches to endocrine disruptors coherent across regulatory areas (e.g. horizontal legislation on chemicals, sector-specific and media-related legislation)?

4.1 Data requirements

Data requirements (sometimes known as information requirements) are legal obligations placed on manufacturers or importers to generate data, such as results from toxicity tests, and to provide them to authorities. Establishing data requirements in legislation requires balancing the need for information on the (eco-)toxicological properties of substances with the burden on economic operators and with animal welfare considerations. Provisions should also avoid multiple generation of data for the same substance subject to different pieces of legislation.

Some regulations such as the Biocidal Products Regulation and the Plant Protection Products Regulation, require comprehensive data sets, justified by substances used in those sectors purposely being designed to be biologically active and/or with potential high exposure to humans or the environment. The general legislation on chemicals (REACH) obliges the registrant to register substances and to provide data as set out in the REACH annexes on standard information requirements with increasing requirements according to the production volume for all substances on their own or in mixtures (and in some cases also for articles) manufactured or placed on the market unless there is an exemption. *Inter alia*, substances manufactured or imported in low quantities (< 1 tonne per year) or polymers do not require a registration. The obligation to register does not apply to active substances, safeners and synergists used in plant protection products, as active substances in biocidal products, in medicinal products for human or veterinary use, or substances intentionally added to food and animal feed. Chemical substances used in other sectors such as toys, food contact materials or cosmetic products are not exempted from the obligation to register and provide data under REACH. Other legislation such as the Cosmetic Products Regulation (CPR) and the Food Contact Material (FCM) Regulation require further information that are specific for the products or the sector they regulate.

In general, further provisions are in place (such as the substance evaluation procedure under REACH) to request further data if a concern arises that is not covered with the standard obligations.

Legislation with no or limited obligations to generate (eco-)toxicological data (such as toys, medical devices or environmental legislation) uses all available scientifically sound data for assessing risks, such as data generated under other regulations, data from academic literature or data supplied voluntarily at the initiative of the industry parties concerned.

The recent fitness check on the EU chemicals legislation concluded that differences in data requirements "*can for the most part, be explained and justified on the grounds of differing likelihood of exposures (risks), of costs and proportionality and of laboratory animal welfare considerations. Differences are mostly justified and do not seem to lead to major incoherence issues"*[17]. This overall conclusion can also be regarded as applicable to the data requirements for the evaluation of endocrine disrupting properties. However, it should be recognised that these differences are policy decisions driven by proportionality balancing costs and animal welfare against generic exposure considerations.

Provisions for the generation of toxicological data related to chemicals or products that can inform on endocrine-mediated effects on human health are included in the legislation on plant protection products, biocidal products, REACH, food contact materials, food additives, cosmetics and pharmaceuticals. Provisions for the generation of ecotoxicological data that can inform on endocrine-mediated effects on wildlife are included in the legislation on plant protection products, biocidal products, REACH and pharmaceuticals. At present, data requirements under these regulations focus primarily on *in vivo* repeated dose, reproductive or developmental toxicity testing in mammals, and tests with aquatic (or terrestrial) organisms, providing data on adverse effects. Further investigations to confirm an endocrine mode of action are triggered based on observations of potentially endocrine-mediated adverse effects from these tests. Specific *in vitro* or *in vivo* tests investigating endocrine modes of action (mechanistic tests) are not currently part of the standard data requirements. The ongoing revisions of standard data requirements for biocidal products and plant protection products consider the inclusion of additional tests for endocrine properties as part of the core data set. Under REACH, work on incorporating further tests for endocrine properties has started.

Legislation and/or regulatory guidance on data requirements and hazard assessment for plant protection products, biocidal products, REACH, food contact materials, food additives and cosmetics refer to accepted international guidance such as OECD Test Guidelines (TGs). The TGs relevant for testing of EDs are grouped in the OECD Conceptual Framework for Testing and Assessment of Endocrine Disrupters. The OECD Guidance Document 150 (which includes the Conceptual Framework) provides guidance on the interpretation of the tests and suggestion on possible next steps in testing (OECD, 2018). The Conceptual Framework comprises five evidence levels listing the OECD TGs and standardised tests methods available, under development or proposed, that can be used to evaluate chemicals for endocrine disruption. Many of the *in vivo* TGs (at levels 4 & 5 of the Conceptual Framework) are the standard toxicity TGs used for the evaluation of toxicity and ecotoxicity in general and are not specific to endocrine disruption. They are listed because they investigate toxic effects that may be endocrine-mediated. Levels 2 & 3 list the methods developed specifically to investigate endocrine modes of action and need to be used in combination with the methods at levels 4 &5. Level 1 refers to existing data and non-test information (e.g. computational predictions).

Data generated using OECD TGs are subject to Mutual Acceptance of Data (MAD), allowing data generated in one OECD Member Country to be accepted by all OECD Member Countries as well as other adherents to MAD, thus removing the need for repetition of tests when seeking regulatory

[17]COM (2019) 264, p79

approvals across different global regions. EU regulations generally require consideration of all available information, i.e. not only data from accepted international guidelines, but also data coming e.g. from peer-reviewed literature.

For active substances regulated under the Plant Protection Products Regulation (PPPR), EDs can be identified based on level 4 and 5 tests from the Conceptual Framework (i.e. *in vivo* assays providing data on adverse effects on endocrine relevant endpoints, and *in vivo* assays providing more comprehensive data on adverse effects on endocrine relevant endpoints over more extensive parts of the life cycle of the organism) which are required for human health assessments. Some mechanistic tests, informing on specific endocrine modes of action can be triggered, namely the uterotrophic assay (OECD TG 440), the Hershberger assay (OECD TG 441), or the *in vitro* assays for the detection of estrogenic activity and measurement of steroidogenesis (OECD TG 455 and 456). For non-target organisms, data required are mainly based on level 3 and level 4 fish and amphibian tests. The data requirements for active substances and plant protection products are described in Regulations (EU) No 283/2013 and (EU) No 284/2013, respectively, and the accompanying Commission Communications (2013/C 95/01 and 2013/C 95/02).

For biocidal products, tests required for human health safety assessment in Annexes II and III to the Biocidal Products Regulation (BPR) are similar to the ones required for plant protection products, with mechanistic studies being also only triggered on the basis of observations in *in vivo* tests. For the ecotoxicological assessment however, data requirements listed in the Annexes are less specific than for plant protection products. However, the BPR requires applicants to provide the relevant information necessary to carry out the evaluation.

For these two Regulations (PPPR and BPR), a joint guidance document 'Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009' (ECHA et al., 2018) describes which information should be provided in order to conclude on the potential endocrine disrupting properties of a substance.

Under REACH, standard information requirements depend on the tonnage manufactured or imported (Annex VII to Annex X). Further tests can also be triggered by conditions listed in column 2[18]. However, the REACH substance evaluation process offers the possibility to require registrants to submit data derived with an accepted test method that is not listed in the standard information requirements, if there is a specific concern such as endocrine disruption. To date, "endocrine disruption" was a concern mentioned for launching this procedure in more than 80 cases. The need to align the framework with the newly established criteria under the PPP and BP Regulations and the latest methods available has been recognised. The process has been initiated within a REACH CARACAL subgroup, which met for the first time in February 2020.

Substances in food contact materials (FCM) for which an authorised list has been established in the framework of the Regulation (EC) no 1935/2004, such as plastics, are assessed by the European Food Safety Authority (EFSA) in accordance with its own Note for Guidance (EFSA Panel on Food Contact Materials et al., 2008). This EFSA Note sets out the data requirements for the safety assessment based on the migration of the substances from the plastic food contact material into the food. As a general principle, the greater the exposure through migration, the more toxicological information is required. Although there are no specific provisions for EDs in the FCM legislation, in

[18]For example, effects observed in the screening study (OECD TG 421 or TG 422) may serve as triggers, leading to more comprehensive reproductive toxicity studies which in the case of suspected ED properties may trigger the request for an Extended One-Generation Reproductive Toxicity Study (EOGRTS) as well as consideration of inclusion of the developmental neurotoxicity and immunotoxicity cohorts

the case of plastic FCM, where migration is relatively high (i.e. migration 5–60 mg/kg food) studies investigating reproductive and developmental toxicity are required (EFSA Panel on Food Contact Materials et al., 2008). Business operators using substances in the FCM or the applicant are also required to inform the Commission immediately should any new scientific information become available that may affect the authorisation. This could include changes in the migration or additional toxicological information e.g. from the scientific literature or new data available under REACH. If necessary, further assessment by EFSA should be carried out. Moreover the EFSA scientific opinion on recent developments in the safety assessment of chemicals in food (EFSA Panel on Food Contact Materials et al., 2016) supports consideration of additional studies on specific endpoints including those resulting from possible endocrine disruption (as from OECD GD150, 2012), as well as immunotoxicity and neurotoxicity, regardless of the level of exposure. Regarding food additives, there are no specific provisions for EDs, however the repeat dose and reproductive/developmental testing methods listed in the EFSA Guidance for submission of food additive evaluations (EFSA Panel on Food Additives and Nutrient Sources added to Food, 2012) do include endocrine-relevant endpoints. Moreover, the guidance refers to other studies (in addition to the core areas for evaluation) that may be relevant and useful for assessing the risk and establishing the safety of an additive include immunotoxicity, hypersensitivity and food intolerance, neurotoxicity, endocrine activity and mechanisms and modes of action.

Substances used in cosmetic products are also subject to the registration obligation under REACH, (based on the tonnage band), and thus the relevant REACH data requirements have to be fulfilled. There are no explicit data requirements specified in the Cosmetic Products Regulation (CPR), which instead refers to the Scientific Committee for Consumer Safety's Notes of Guidance (SCCS, 2018). These describe the types of data that may be used or generated by the manufacturers to make an assessment for each toxicological endpoint relevant to human health, which the manufacturer takes into account when there is a need to submit a safety dossier under the CPR authorisation procedures. Data relevant to endocrine modes of action may be provided through the assessment of reproductive toxicity or through special investigations on suspected endocrine disruptors for human health.

The guidance refers to the OECD Conceptual Framework, however, due the ban on animal tests, only *in silico* and *in vitro* methods can be used to evaluate safety for human health, while data from *in vivo* studies may be used if they are already available or generated through other regulatory processes such as under the PPPR, the BPR and REACH. The relevant toxicological studies described in the guidance cover standard apical endpoints, including reproductive toxicity. For reproductive toxicity, three *in vitro* embryotoxicity screening tests have been validated by ECVAM to support assessment of reproductive toxicity. Overall, the complex endpoint of reproductive toxicity is not covered by the above systems and no alternative methods are currently available covering all aspects of reproductive and developmental toxicity. Many recent SCCS opinions have relied on *in vivo* reproductive/developmental toxicity studies (e.g. OECD TGs 416, 414, 421, 422 and 443) performed before the animal testing ban (e.g. **Annex 5A** - 3-BC case study). The guidance does not require tests addressing the four E-A-T-S modalities. Results from available *in silico* and *in vitro* tests for endocrine activity do not fit in the risk assessment framework followed by the SCCS for safety evaluations. In addition, according to the SCCS, such tests would only inform on endocrine activity but not adversity. According to the SCCS, the animal testing ban would not enable the identification of EDs according to the WHO definition or according to the criteria for biocides and pesticides, which require information on three elements, namely endocrine activity, adverse effect and plausible causal link. However, the SCCS recognises the need to transition toward an animal-free risk assessment methodology, sometimes called Next Generation Risk Assessment (NGRA). However, this will

require methodological developments and experience in the application and interpretation of New Approach Methodologies (NAMs) (Rogiers et al., 2020).

The combination of provisions for data requirements under REACH (tonnage-based) and the CPR together with the incremental restrictions on animal testing over time explain the current differences in data packages available for individual substances. For some cosmetic ingredients evaluated and approved in the past, including substances listed in the annexes to the CPR (positive list of approved colourants, preservatives and UV-filters), data for the evaluation of endocrine-mediated effects can be very limited if the substance is not registered under REACH or registered at the lowest tonnage level (1 to 10 tonnes per year) (see also **Annex 5A**, 3-BC case study). In case the substance is not registered in REACH (i.e. not on the market in a tonnage of at least 1 t/y or above), there are no mechanisms to know if those substances on the positive lists continue to be used at all.

In addition to the data prescribed to ensure therapeutic efficacy and safety (not in the scope of this Fitness Check), regulations on human and veterinary medicines include data requirements to evaluate potential unintended ecotoxicological effects. A draft guidance by the European Medicines Agency (EMA) on the environmental risk assessment (ERA) of human medicines was released for public consultation in 2019[19] and is currently under revision. According to this draft guidance, testing for endocrine active substances may be triggered as part of a tailored risk assessment for endocrine active substances (**Annex 4**). The draft Guidance published for public consultation lists recommended tests to address (anti)estrogenic, anti(androgenic) and thyroid effects (OECD TGs 234, 240, 241) Testing on thyroid agonist or antagonist effects is recommended, even though the definition of endocrine active substance given in the guidance does not cover the thyroid modality. Discussions on the finalisation of the Guidance are ongoing.

Guidelines on environmental safety assessments for non-target organisms of veterinary medicines refer to the VICH guidance (EMA, 2000, 2005). The tiered approach consists of a two-phase approach. Only when environmental exposure from the use of the veterinary medicine is considered to be significant (by exceeding established threshold values), a higher-tier assessment based on a risk ratio will be triggered. This second phase will be conducted starting from basic risk assessments using short term (acute) toxicity to chronic aquatic toxicity studies with standard aquatic species from three trophic levels. Required studies do not include endpoints that are relevant and can identify endocrine-mediated effects. The ability to identify potential EDs is limited to evidence from changes indicative of endocrine dysfunction reported in the mammalian repeated dose toxicity studies (performed to establish a maximum residue limit to ensure the safety of veterinary drug residues in human food) or to scientific literature. Such evidence may prompt the member state competent authority or EMA to request additional studies targeted to investigate ED properties.

To conclude, ongoing revisions of standard data requirements for biocidal products, plant protection products and for REACH consider the inclusion of additional tests for endocrine properties as part of the mandatory data set .Currently test guidelines are only available to cover the estrogen, androgen, thyroid and steroidogenesis modalities (EATS) but this is likely to increase over time, as more OECD Test Guidelines covering other endocrine modes of action are validated and adopted. Since many substances used in products subject to product-specific legislation in the scope of this fitness check are required to be registered under REACH, the information requirements in REACH can be used as a centralised way to gather the relevant data, thus avoiding repetition of studies on the same substance in other regulatory domains. In relation to arguments of proportionality of costs and considerations of

[19]https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use#current-version-section

animal welfare, when adopting REACH the co-legislators have chosen to use production volume of substances as a surrogate of exposure (and consequent risk) potential and thus substances produced at volumes below 10 tonnes/producer/year have a data set which does not give any indications of endocrine disrupting properties. However, all available information, including from *in vitro* tests, QSARs and read-across to other substances has to be taken into account by manufacturer or importers. The OECD GD 150 lists several *in vitro* tests that provide information on endocrine activity. Currently, these *in vitro* tests are not a mandatory part of data requirements of the relevant regulations. Substances produced at less than 1 tonne/producer/year are currently not registered under REACH and thus it is important to be aware that REACH will not provide any data in these cases to support ED identification for such substances used in other product-specific legislation. Legislation covering the food additives and food contact materials which has data requirements independent of, or additional to REACH, respectively, follows a similar approach whereby concerns for endocrine disrupting activity may be identified from the required toxicity tests. Coordination is required between REACH and these regulations to avoid the duplication of testing and ensure the best use of resources.

4.2 Hazard identification

4.2.1 Identification of endocrine disruptors

Three EU Regulations contain provisions to identify EDs, i.e. the Biocidal Products Regulation (BPR), the Plant Protection Products Regulation (PPPR) and REACH.

Identification of active substances as endocrine disruptors is mandatory for plant protection products and biocidal products (for the latter also non-active substances need to be assessed), following scientific criteria established in 2017 and 2018. It is pursued, to the extent possible, under REACH. It is not required in other sectors. The identification of EDs requires: i) a definition, ii) clear criteria to determine whether the definition is met, iii) data requirements to establish if criteria are met, and iv) guidance for implementation of the assessment process.

Across chemical legislation, there is wide acceptance of the WHO definition: "*an endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations*". The definition is supported by most stakeholders ((European Commission, 2015). However, differences exist in the wording used across regulations. Although all relevant provisions refer to ED properties, regulations vary in the emphasis on the adversity and causality attributes, as analysed in the Fitness Check of EU chemicals legislation (excluding REACH)[20]. Differences in wording might create uncertainty as regards which chemicals are considered EDs by the legislative provisions and what level of evidence is required to identify such chemicals.

Criteria, data requirements and guidance to enable the identification of EDs exist for the Plant Protection Products and Biocidal Products Regulations. The European Chemical Agency (ECHA) and the European Food Safety Authority (EFSA) jointly published a guidance document (ECHA / EFSA 2018) based on these criteria. The guidance has been recognised as a major milestone providing clear and scientifically sound interpretation of the WHO definition (PETI Committee for the European Parliament 2019). It provides a starting point for any future cross-sectorial definition of EDs. ECHA, EFSA and Member State authorities are sharing first experiences to ensure consistent application of

[20]SWD (2019) 199, Annex 7 p.302

the guidance and to identify possible improvements[21]. The Agencies are also collaborating on ED assessments for specific substances of common interest.

Currently, REACH does not contain criteria for EDs, but bases the identification of Substances of Very High Concern (SVHCs) with ED properties on the IPCS/WHO definition. The identification of an ED as SVHC needs also to consider whether the effects give rise to an "equivalent level of concern" to those of other SVHC categories. This assessment is done on a case-by-case basis. In case of lack of consensus in the REACH Member State Committee, the Commission takes the final decision through the REACH comitology process.

The Cosmetic Products Regulation (CPR) does not require the identification of EDs. However, substances used in cosmetics, may be identified as EDs under REACH in relation to environmental concerns or, for substances that are registered for other uses, with respect to human health. According to the Scientific Committee on Consumer Safety (SCCS), it would not be feasible in the context of the animal testing ban to implement all the criteria established for plant protection products and biocidal products in the CPR, i.e. the requirement to demonstrate an adverse effect, which currently is mainly demonstrated through *in vivo* animal studies. The Commission can request the SCCS to evaluate the safety of substances identified as potential endocrine disruptors but the specific risk approach that underpins the SCCS safety evaluations does not depend on formal identification of EDs (SCCS 2018).**Error! Bookmark not defined.**. Chemicals used in medical devices, food contact materials, cosmetic products, detergents and toys as well as in other sectors can in principle be identified as SVHCs with endocrine disrupting properties via REACH and therefore the absence of specific provisions for ED identification in the sector-specific legislation does not necessarily represent a regulatory gap across legislation.

Although the absence of horizontal criteria creates a potential for inconsistent identification across regulation, which is further compounded through different data requirements and different interpretations of the same data, no inconsistent identification has occurred so far. The targeted stakeholder survey provided insights into the different views about the lack of a horizontal approach to identification and classification of EDs (**Box 4.1**). There is wide agreement among stakeholder groups that the lack of a harmonised approach is a problem. However, there are diverging stakeholder views on the way forward for how to accomplish a harmonised approach, for instance via the SVHC-identification procedure under REACH, a dedicated hazard class under Classification, Labelling and Packaging (CLP) Regulation and/or the UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS) with or without categories, or via a separate legislation. In a similar way, the implementation of a category of suspected endocrine disruptors would have the advantage of stimulating assessments and substitutions but could lead to the exclusion of substances that could be used safely. Another consideration is in the context of the PPPR and BPR, where the criteria for EDs do not include a suspected category. The implementation of an additional hazard class in the CLP regulation and possibly categories could help to define clear regulatory triggers as part of assessment workflows from screening assessments to risk management measures.

[21]Targeted consultation with ECHA and EFSA – May 2020. See also: https://echa.europa.eu/documents/10162/28327874/vanderlinden_bshd19_en.pdf/d2813dbe-a8db-f630-1dfe-24d02c308fc5

4.2.2 Identification through Classification, Labelling and Packaging Regulation hazard classes

Currently there is no hazard class for endocrine disrupting properties under the Classification Labelling and Packaging (CLP) Regulation. Many known EDs are classified as carcinogenic or toxic to reproduction, or both. Along with mutagenic substances, these hazardous properties are considered to produce effects of a serious and irreversible nature and are collectively referred to as CMRs (Carcinogenic, Mutagenic or toxic for Reproduction). The CMR categories include important ED-mediated effects, such as cancers in hormone sensitive organs, and reproductive and developmental disorders, which might be ED-mediated. Six of the seven chemicals identified so far as Substances of very High Concern (SVHCs) for endocrine disrupting properties with respect to human health under REACH are also classified as reproductive toxicants (category 1A or 1B) under the CLP regulation.

However, the substance butyl 4-hydroxybenzoate (butyl paraben) was identified as ED for human health in REACH in June 2020, but is not classified as CMR, since effects related to fertility and development has not led to a harmonised classification as toxic for reproduction. In addition, available toxicological data triggering CMR classification may not capture certain effects potentially mediated by endocrine disruption, such as certain neurodevelopmental and metabolic disorders. As methods and data on thyroid disruption, steroidogenesis and other less studied modalities of endocrine disruption become available, it is expected that more substances will be identified as EDs based on effects beyond those defining CMRs. Other hazard classes, under the CLP Regulation, relevant to human health, focus on specific target organ toxicity (STOT) and include potency considerations such that a substance toxic to e.g. the thyroid may not be classified if the effects are only seen above a certain exposure concentration. Such substances would remain unclassified in relation to the adverse effect, but may still fulfil the definition of an ED.

In relation to wildlife, CLP classification for ecotoxicity is generic and does not refer to specific modes of toxic action. Many known EDs happen to be also classified using the aquatic hazard classification scheme (chronic categories 1 to 4). However, data triggering this classification are the chronic no observed effect concentration (NOEC) if available, fish bioconcentration factor (BCF) and/or degradable properties of the chemical. This means that if the chronic NOEC is based on a test which does not have specific endocrine-mediated endpoints (e.g. OECD TG 210), an ED may or may not be classified as a chronic aquatic toxicant.

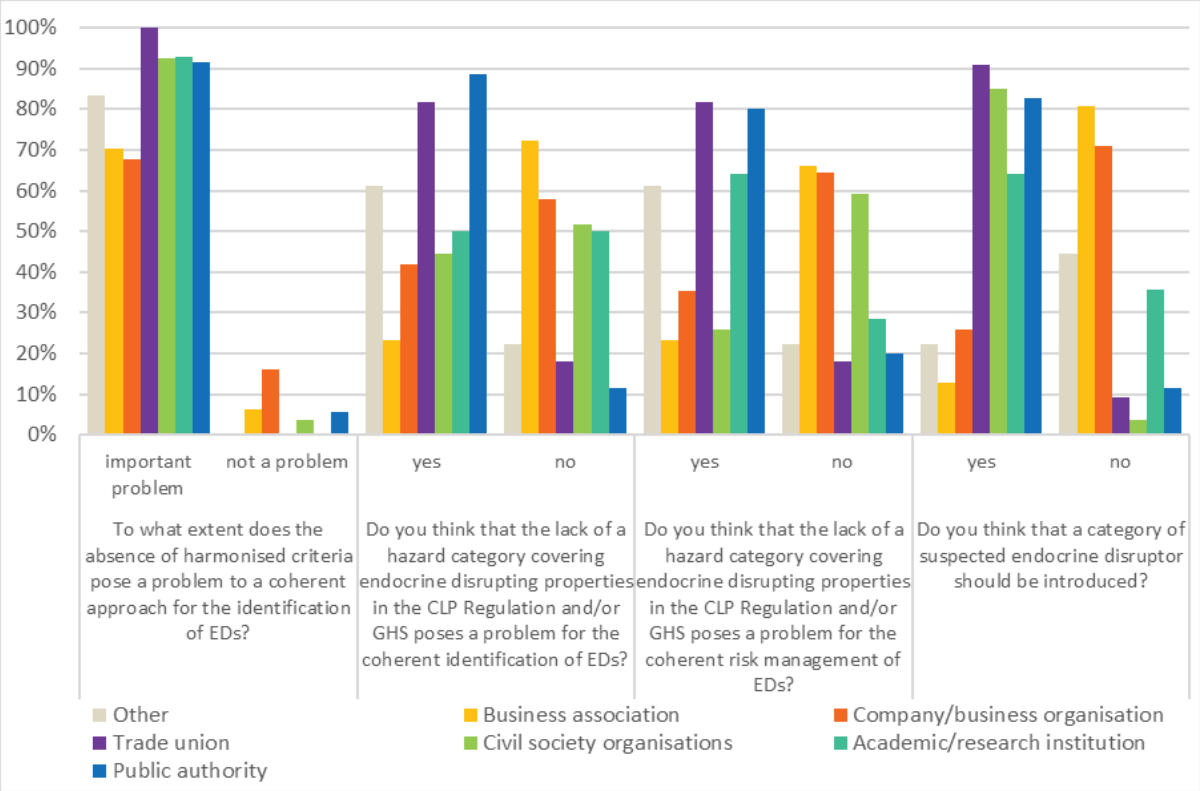
The importance of horizontal classification of EDs under the CLP Regulation is widely recognised[22] since a hazard classification may be used to trigger risk management measures in many so-called 'downstream' product and sector-specific regulations and directives. For example, the CLP hazard classification of substances is also the basis for the identification and classification of hazardous waste containing them.

CMRs of categories 1A or 1B can be identified as substances of very high concern (SVHC) under REACH and also fulfil the cut-off criteria for non-approval under the plant protection products and biocidal products regulations (unless the limited derogation possibilities in the Regulations apply). Identification of a CMR as an ED for human health will probably not lead to any additional risk management measures, where they are already the strictest (see 4.4 Risk Management) but may nevertheless contribute to the overall evaluation within a risk-benefit context and facilitate assessments of combined exposure/mixtures. In addition, as described above, not all EDs for human

[22]SWD(2019) 199

health are identified as CMRs and identification as an ED for the environment may also trigger additional risk management measures.

Box 4.1: Stakeholders' answers to questions related to the lack of a horizontal approach to identification and classification of EDs.*,**



From the targeted stakeholders survey, the majority of respondents from all stakeholder groups think that the absence of harmonised criteria poses a problem to a coherent approach for the identification of EDs. The main motivations reported are:

a. Potential for inconsistent identification between pieces of legislation/contradictory conclusions on the same chemical. For example, the adopted ED criteria under Biocidal Product Regulation (BPR) are applicable both to biocidal active substances and non-active substances, i.e. co-formulants. Co-formulants are regulated under REACH, yet they may also be evaluated under the BPR against the ED criteria. Therefore, there is potential for inconsistencies between REACH and BPR regarding data evaluation, requirements and conclusions on co-formulants.
b. Creates regulatory uncertainty and ambiguity among all groups of stakeholders.
c. Potential for duplication of efforts by authorities/higher costs for companies/unnecessary duplication of *in vivo* tests.
d. Gaps and incoherent level of protection from exposure of people and wildlife to EDs. For example, inconsistent identification and lack of control measures in occupational settings.
e. Difficulty in defining a hazard class and to develop OECD standardised methods accordingly.

Respondents answered in a similar way to the two questions on whether the absence of an ED hazard class in Classification Labelling and Packaging (CLP) Regulation and/or the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) poses a problem for the coherent identification and for the coherent risk management of EDs. Most public authorities and trade unions answered "yes"; most companies/business organisations and business associations answered "no", with more mixed responses from the other stakeholder groups

Among those who answered "yes", the main arguments were:
a. Only a hazard class ensures a consistent approach for all manufacturers/formulators/downstream users communicating and managing the risks associated with using EDs.
b. A hazard class would lead to coherent identification of EDs, as with Carcinogenic, Mutagenic and toxic to Reproduction (CMR) substances, creating a common basis for identification and risk management.
c. A hazard class would allow better labelling and better protection.
d. Lack of a hazard class hinders identification of EDs and appropriate management of materials and waste streams.
e. A GHS hazard class could lead to coherent identification of EDs worldwide.

Among those who answered "no", the main arguments were:
a. Endocrine activity is a mode of action, while GHS/CLP focus on adverse effects. Adverse effects triggered by endocrine activity are already covered by existing GHS/CLP hazard classes. ED classification would be redundant.
b. Classification is not necessary for risk management. For example, REACH already allows ED identification and management of associated risks.
c. International agreement on a new hazard class under GHS will take years and may delay identification of EDs.
d. There are other alternatives to CLP classification, such as a dedicated identification system.

The possibility of introducing a category of suspected ED is favoured by most respondents from public authorities, civil society organisations and trade unions, but not favoured by most respondents from companies/business organisations and business associations.

Respondents with a favourable opinion were asked what the consequences of a suspected ED category should be. They responded that the main regulatory consequences should be:
a. Application of a similar level of management as for CMRs (which have suspected categories), resulting in ban/restriction of uses with possible derogations.
b. Enabling authorities to prioritise chemicals for regulatory action.

c. Communication of information to the supply chain, workers and consumers by e.g. appropriate labelling.

According to the same group of respondents, the introduction of a suspected ED category could:
a. Decrease the exposure to EDs, leading to better protection for human health, particularly vulnerable groups, and the environment.
b. Stimulate searches for substitutes with potential for innovation and economic development
c. Stimulate further investigations of the suspected compounds.
d. Decrease health costs, increase protective measures for workers, increase costs for further testing and evaluations.

The respondents against the introduction of a "suspected" endocrine disruptors category suggested
a. A suspected category may cause unnecessary public concern.
b. Such a category would have a high economic impact, by stigmatising compounds, and by the additional complexity and bureaucracy that would be involved by such a category.

*Answers are given in percentage of respondents from each stakeholder group. For more details see Annex 2.
**Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Some of the stakeholders who disagree with the introduction of a hazard class covering endocrine disrupting properties in the CLP Regulation and/or GHS state that it would be redundant as adverse effects triggered by endocrine activity are already covered by existing GHS/CLP hazard classes. However, this would be true only for some endocrine–related effects, excluding for example effects of obesogens, as tests generally used for classification in the existing hazard classes cannot identify such EDs. Regarding the statement that classification is not necessary for risk management, this may be the case. However, the CLP Regulation may have advantages with respect to simplification since it is often the instrument currently used for hazard classification. It is also referred to by many of the current product and sector-specific regulations in relation to invoking specific risk management measures and thus an ED hazard class could be considered for use in a similar way. Communication is also an important aspect of classification through the CLP Regulation with respect to protection of workers and consumers (especially vulnerable groups) although this issue has been partially resolved for workers through the requirements to indicate endocrine disrupting properties on safety data sheets.

There is a commitment of the EU to explore the possibility to harmonise classification at the international level through the UN GHS. However, it could take many years to reach agreement at international level, if at all, and thus delay action at EU level with the consequent implications on effectiveness. Alternatively, as also stated by some stakeholders, REACH could also be a potentially suitable instrument that could be further reinforced to ensure consistent ED identification and appropriate risk management measures across sectors and products.

The views on the introduction of a suspected category of EDs are more polarised across the different stakeholder groups. Ideally, testing for endocrine disruption should proceed until a decision can be made that the substance is or is not an ED. In practice it may be difficult to generate sufficiently conclusive evidence one way or the other for all substances to inform on regulatory decision making in a reasonable timeframe. Hence the suggestion for a 'suspected' category. Proponents of a suspected category argue that it would be prudent to flag the possible hazardous properties of the substance, while the detractors consider that it would "stigmatise" a substance that may not have such properties and discourage users from its use. Important considerations in the discussion are deciding where on the spectrum of evidence the criteria for a 'suspected ED' should be set, and what risk management

measures, if any, should be applied to such a category. In the context of setting the criteria for biocidal and plant protection products the Commission Communication[23] stated that establishing different categories of what *may* be an endocrine disruptor does not help to define what *is* an endocrine disruptor and would decrease legal certainty for regulators and stakeholders without established benefits in terms of protection of health and the environment. However, this approach with categories is, for example, already followed for CMRs.

4.3 Risk assessment

4.3.1 Feasibility of risk assessment

Risk assessment is the cornerstone of safety evaluation procedures across many pieces of chemicals legislation. Risk is quantified as the ratio of the chemical exposure in an organism or in an environmental media to an exposure level considered safe**.** The approach builds on the concept that, for a given substance, a biological threshold often exists for a given toxicological effect, below which exposure does not exert any adverse effect in organisms. Within a given regulatory framework, risk assessment is feasible, when such a threshold can be derived using the (eco)toxicological data available.

There is an ongoing debate in the scientific community about the viability of performing risk assessment for EDs. The debate is reflected in the views of members from the Endocrine Disrupters Expert Advisory Group (ED EAG), which was composed of toxicologists and ecotoxicologists with regulatory and/or endocrinology backgrounds, nominated by Member State Competent Authorities for REACH, the Biocidal Product Regulation (BPR), and the Plant Protection Products Regulation (PPPR), relevant industry associations and non-governmental consumer/environmental protection organisations (Munn and Goumenou, 2013b). According to this report, most experts considered that biological thresholds of adversity are likely to exist; several maintained that it is difficult to estimate them based on currently available test methods, while others considered it is possible to estimate them with appropriate testing. There was lack of consensus on the sensitivity of existing methods to detect responses at low doses.

The debate also exists in the context of EU regulatory assessments. For example, in 2013, in its restriction dossier on nonylphenol ethoxylates, the Swedish competent authority for REACH stated that "*identifying safe concentration limits for all possible endpoints within the endocrine system that can be affected by EDs is not possible within the current test methods and would be inconsistent with the objective in REACH to reduce animal testing"* (see **Annex 5C**, nonylphenol case study). The Risk Assessment Committee (RAC) abstained from any opinion about whether a threshold proposed during its discussions was sufficiently protective for all hazards of nonylphenol (NP), including those posed by endocrine disrupting properties, pointing to the then on-going discussion in the EU Commission on the possibility to derive a safe level of exposure[24]. Instead, it based its opinion on the identified risks for endpoints not related to endocrine disrupting properties.

In the context of REACH authorisation, the Commission indicated in 2016 that EDs might or might not have a threshold and that *"it remains the responsibility of applicants to demonstrate that a threshold exists and to determine that threshold. Even though this might be particularly difficult for EDs, it cannot be excluded on the basis of current knowledge that it will be possible. It is up to RAC to assess the validity of the assessment and ultimately decide on the possible existence or not of this*

[23]COM(2016) 350
[24]RAC and SEAC (2014): Opinion on an Annex XV dossier proposing restrictions on NP and NPnEO

threshold"[25]. In the authorisation procedure, the application of risk assessment to demonstrate safety has been termed the 'adequate control route'. However, adequate control based on risk assessment is not an option if a threshold cannot be demonstrated. For example, NP ethoxylates (NPnEO) were added to the Authorisation list (Annex XIV) for their endocrine disrupting properties for the environment (**Annex 5C**, nonylphenol case study). In a note intended to provide general advice to companies intending to apply for authorisation of uses of octylphenol and nonylphenol ethoxylates, the RAC *"did not consider that exposure values below* [a conventionally derived] *predicted no effect concentration were consistent with a 'safe level', specifically noting the uncertainties associated with the endocrine disrupting properties of NPnEO*" (ECHA RAC 2017). To date no applicant tried to demonstrate a safe threshold and applied for the adequate control route. In this case authorisations are granted based on risk-benefit considerations, provided that exposure is minimised and alternative substances are not available. REACH restrictions require evidence of an unacceptable risk to human health or the environment, arising from the manufacture, use or placing on the market of the substance. In cases where it is difficult to derive safe thresholds, a qualitative assessment of the likelihood that effects are avoided can be used when implementing measures. In recent restrictions on chemicals with endocrine disrupting properties (e.g. DEHP, nonylphenol ethoxylates), the unacceptable risk was proven since risk ratios exceeded the value of 1. In both cases, the endpoint assessed was not explicitly related to endocrine properties.

In its 2013 opinion, EFSA's Scientific Committee considered that biological thresholds of adversity do exist and considered human and environmental risk assessment (taking into account hazard and exposure data/predictions) the best approach to inform risk management decisions in regulations that base decisions on the risk and level of concern (EFSA Scientific Committee, 2013). According to EFSA's Scientific Committee "*EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment*". Risk assessment had been applied to assess the risk of bisphenol A (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids, 2015) and phthalates (based on reprotoxic effects) in food contact materials (**Annex 5B**, DEHP cases study) before their identification as EDs under REACH. In these cases, the assessment factors applied to derive tolerable daily intakes can account for uncertainties related to endocrine-mediated effects. In the 2015 EFSA risk assessment of BPA, for example, uncertainty in mammary gland, reproductive, neurobehavioural, immune and metabolic system effects justified an additional assessment factor of 6.

The Scientific Committee on Consumer Safety (SCCS) endorsed the 2013 EFSA opinion on EDs (SCCS 2014, and COM (2018) 739) and evaluates cosmetic ingredients based on risk assessment, including the derivation of safe exposure thresholds. To date the SCCS has not completed an evaluation for substances after these have been identified as EDs under other legislation. However, the SCCS is currently evaluating five substances with potential endocrine disrupting properties (homosalate, octocrylene, benzophenone-3, resorcinol and propylparaben).

Rather than being a means of demonstrating safety, risk assessment is also applied in some sectors to assess the probability of harm and conclude on tolerable risk levels for risk-benefit evaluations or risk mitigation. This is also the case for biocidal products, medical devices (human health risks as part of the benefit-risk analysis), pharmaceuticals (for environmental risks), veterinary medicines (for environmental risks as part of the benefit-risk analysis).

[25]COM (2016) 814

4.3.2 Differences in risk assessment

The subdivision of assessment activities across policy areas means that the same chemical (or group of chemicals) might need to be assessed for human health or environmental endpoints under multiple frameworks (**Figure 3.1**). Although agencies and Scientific Committees have increasingly sought alignment in recent years, stakeholders expressed the need for better coordination of agencies and committees[26].

The three case studies performed for this Fitness Check (**Annex 5**) were chosen to evaluate the horizontal coherence of regulatory assessments for EDs across policy areas. Differences in risk assessments may emerge at different levels – chemical grouping, exposure pathways assessed, methodology or data used. Where EDs have been assessed, our analysis did not identify significant deviations from the standard methodology, described in the guidance documents, owing to ED-specific considerations. In one case, when conducting the risk assessment for nonylphenol in the REACH restriction report, the Swedish competent authority introduced an extra assessment factor of 10 in the calculation of safe environmental concentrations to account for the incomplete knowledge and the uncertainties related to its ED properties. The ECHA Risk Assessment Committee (RAC) opinion did not endorse the approach but referred to the risk ratios obtained with the standard approach, which already indicated a risk (**Annex 5C**, nonylphenol case study). The uncertainties associated with the possible peculiarities of endocrine disrupting effects (i.e. non-threshold, non-monotonic behaviour) are recognised and in some cases have been taken into account through the use of uncertainty factors, defined on a case by case basis.

Differences in risk assessments performed for the same substance(s) under different pieces of legislation reflect differences in the legislative scope (especially, in the cases identified, the scope of the exposure assessment and the chemical grouping). The case of low molecular weight phthalates recently assessed by ECHA and EFSA illustrates the challenge (**Annex 5B**, DEHP case study). Both agencies performed a risk assessment based on the same hazard (reproductive toxicity) and toxicity data. The two assessments differed in terms of the definition of chemical grouping (DIBP was not assessed by EFSA since it is not authorised as an additive in FCM) as well as the approach and data used to estimate exposure (e.g. exposure sources considered, population age grouping, food intake estimates). ECHA concluded that there is risk to human health from combined exposure and especially of significant exposure to DEHP from the diet based on modelling estimates. EFSA's assessment concluded that dietary exposure did not result in group-based or individual tolerable daily intakes being exceeded. A risk is obviously more likely to be found if aggregate exposure from all possible sources is considered rather than only a single source. The two assessments are consistent within their respective mandates, but the different scopes and approaches to estimate exposure resulted in different regulatory interventions, reflecting the absence of a coherent cross-sector approach.

The case study on nonylphenol revealed an example where hazard datasets are not harmonised across chemical and water legislation, leading to differences in derived threshold values (**Annex 5C**, nonylphenol case study).

Evidence from the case studies suggests that where the same substance(s) have been assessed under different frameworks it is difficult to ensure coherence of assessments. The problem is generic and does not relate specifically to EDs. Regarding the exposure assessments, when differences in the exposure scenario(s) and exposure routes assessed are linked with the specific scope of sectorial

[26]SWD(2019) 199

legislation, the issue cannot be easily solved in the current framework. While most stakeholders largely agree on working towards a framework when one substance is associated with one assessment, based on a shared data set across all regulatory sectors, the current framework does not provide a systematic approach to integrate total aggregate exposure with sector-specific exposure scenarios. The Commission's ambition to develop a one substance-one assessment approach may provide a means to address this issue.

4.3.3 Consideration of vulnerable groups

(Sub)population groups may be at higher risk due to numerous factors, including those affecting external exposure, internal exposure and biological susceptibility (**Table 4.1**). Factors affecting external and internal exposure are relevant in general but are not specific to EDs.

Table 4.1. Factors contributing to higher risk of (sub)population groups and possible options to address them in risk assessment

Factors contributing to higher risk		(Sub)populations groups at higher risk	Possible options in risk assessment
Factors affecting (external) exposure dose	Behaviours: crawling, mouthing, chewing	Babies, toddlers	Tailored exposure scenarios
	Diet habits: higher intake of specific food categories such as baby food, food contact materials	Babies, toddlers, children	Tailored exposure scenarios
	Exposure to specific environments: working place, outdoor lifestyle, indoor environments	Workers, children	Tailored exposure scenarios
	Ability to avoid exposure: intellectual and physical conditions	Babies, toddlers, disabled, elderly	Tailored exposure scenarios
Factors affecting internal exposure	Surface area to body weight	Babies and young people	Correction factors, use of biomonitoring
	Underdeveloped/ slow metabolism and elimination rates	Foetus, elderly	Correction factors, use of biomonitoring
	Underdeveloped blood-brain barrier/ placental transfer	Foetus	Sensitive test methods/long term epidemiological studies
Factors affecting biological susceptibility	Sensitive development stage/ immature organs	Foetus, new-borns, adolescents, pregnant woman	Sensitive test methods/long term epidemiological studies
	Poor nutrition/health conditions	Ill people, elderly, low income population	Assessment factors for population variability

Several pieces of legislation within the scope of this Fitness Check consider risks to vulnerable groups. Where such risks are taken into consideration, the definition of vulnerable population varies as there is no horizontally applicable definition of 'vulnerable group'. The Plant Protection Products Regulation and the Biocidal Products Regulation specifically define vulnerable groups in relation to chemical risks: both refer to '*pregnant and nursing women, the unborn, infants and children, the elderly and workers and residents subject to high exposure to active ingredients over long term'*. The rationale for explicitly mentioning specific vulnerable groups in legal provisions is not always clear[27]. For example, legislation on detergents and food contact materials does not include specific provisions,

[27]SWD(2019) 199

but cosmetic products and other food legislation (e.g. food additives) does. However, lack of reference or definition of vulnerable groups in legislation does not necessarily lead to lack of assessment or action, as exemplified by the risk assessment of and restrictions on substances in food contact materials.

Current risk assessment methodologies across chemical safety legislation aim to cover risks to the general population including the most sensitive sub-populations (i.e. vulnerable groups). In practice, the default safety/assessment factors applied when extrapolating from the animal data to humans may not be considered large enough and additional assessment factors are sometimes used to cover these vulnerable groups. Thus, risks to vulnerable groups are addressed on a case-by-case basis through triggers and guidance established under sector-specific legislation. Assessments for specific vulnerable groups are mostly triggered by factors affecting internal and external exposure and focussed mainly on neonates and young children. Some examples of how vulnerable groups are considered in regulatory assessments are reported in **Box 4.2**.

Under REACH, guidance exists to account for specific exposure situations and to derive specific no-effect levels (DNELs) for vulnerable groups (non-ED specific) with an emphasis on reproductive toxicity[28]. The REACH guidance on exposure refers to the OECD considerations when assessing children's exposure to chemicals and a decision tree for deciding when to trigger tailored assessments for children (OECD, 2019). In this context, children are broadly defined as any human from birth to 21 years old, according to the WHO definition.

The Cosmetic Products Regulation requires a specific assessment for products intended for children under 3 years. The Scientific Committee on Consumer Safety (SCCS) Notes of Guidance mention certain circumstances, which might require specific margins of safety for certain subpopulations, such as children**Error! Bookmark not defined.**. Correction factors are reported for different age groups to account for higher surface area per body weight. Other factors listed that can affect vulnerability of new-borns are toxicokinetic parameters (slower metabolism and elimination rates), and sensitivity to inflammation for specific uses (i.e. for products intended for use in the nappy area).

Considerations about the level of protection of vulnerable groups to EDs are presented in **Section 5**, including responses from stakeholders and citizens surveys (**Box 5.9**).

Box 4.2 Examples of how vulnerable groups are considered in regulatory assessments

- DEHP and other low molecular weight phthalates under REACH and Food Contact materials Regulation (**Annex 5B**, DEHP case study). The 2017 RAC assessment acknowledged that Derived No Effect Levels (DNELs) derived for reproductive toxicity from developmental studies are relevant to pregnant women and the foetus but less so to children. Nonetheless, DNELs were deemed conservative and therefore acceptable to evaluate risks for children. The EFSA approach to DNEL derivation for phthalates was consistent with ECHA's. However, the subpopulations (age ranges) considered in the exposure assessment of low molecular weight phthalates by ECHA and EFSA reflected differences in available datasets.
- 3-BC under the Cosmetic Products Regulation. The SCCS found that 3-BC was not safe for human health and did not consider it necessary to tailor the assessment to specific vulnerable groups (**Annex 5A, 3-BC** case study). In the general case, an assessment factor of 10, accounting for intra

[28]REACH guidance on information requirements and chemical safety report: chapters R.15.2.5, Appendix R.15.6 and chapter R.8

species (between human) variability of toxicokinetic and toxicodynamic parameters, is factored into the overall default margin of safety required of 100.

- Propyl- and butylparabens under the Cosmetic Products Regulation. In its assessment the SCCS took into consideration additional risk factors for children below the age of 6 months. Although the dermal absorption in new-borns is similar to that in adult skin, in the light of both the immature metabolism and the possibly damaged skin in the nappy area, the SCCS could not rule out a risk, based on worst case scenarios of aggregate exposure and higher but unquantified dermal absorption. A realistic quantitative risk assessment for children was not possible as information on internal exposure was not available.

4.3.4 Prioritisation and Environmental Quality Standards under the water legislation

The regulation of EDs under water-related legislation is largely dependent on data generation and evaluation carried out under other regulatory frameworks, such as REACH, or in scientific studies. In recent years, substance prioritisation and setting of Environmental Quality Standards (EQS) have taken advantage of the increased amount of ecotoxicological information, including information on ED-mediated effects, which has become available through chemical registration dossiers under REACH, the Plant Protection Products Regulation and the Biocidal Products Regulation[29].

The Water Framework Directive (WFD) applies a combination of generic and specific risk considerations from both experimental and modelling data for the classification of chemicals as priority substances (PS) and priority hazardous substances (PHS). The first list of PS followed a scoring-based ranking approach, including elements of exposure and effects as well as biodegradability and bioaccumulation potential[30]. Nonylphenol and DEHP, for example, were recommended for inclusion in the list for their relatively high modelling-based ranking combined with additional evidence of environmental occurrence and endocrine disrupting effects (Fraunhofer-Institut, 1999).

The designation of PS or PHS considers both generic (e.g. for Persistent, Bioaccumulative and Toxic, PBT substances) and specific risk criteria[31]. For the final designation, "additional considerations", including suspected endocrine disrupting potential, can influence the designation. For nonylphenol, evidence of "*widespread risk to or via the aquatic environment*" [32] assessed under pre-REACH regulation 793/93 determined the classification[33]. DEHP was not originally designated as a priority hazardous substance, but it was designated as such in 2013.

Prioritisation approaches have evolved over the years, but have maintained a combination of generic (PBT, Substances of Very High Concern (SVHC), and Persistent Organic Pollutant (POP) criteria) and specific risk approaches from experimental and modelling data. An early step of the prioritisation carried out in 2011 comprised scoring against four criteria: persistence, bioaccumulation, toxicity and endocrine disrupting properties[29].

[29]SEC(2011) 1544
[30]Working Document ENV/191000/01
[31]Checks 1 to 6 of Working Document: https://ec.europa.eu/environment/water/water-dangersub/pdf/wd_env_191000_01_final.pdf
[32]ECB 4/15/00
[33]COM/2001/17

Environmental Quality Standards are established for both PS and PHS, even though the WFD aims to ensure the phase-out of PHS emissions to water, not only a reduction in those emissions as in the case of the other PS. The logic of setting EQS for PHS has been questioned by some stakeholders, but it is generally accepted that there is a need for a benchmark in the context of chemical water quality assessments. The persistent nature of many PHS makes it difficult to comply with the EQS, let alone a more ambitious target. EDs are treated like other chemicals when deriving EQS (e.g. **Annex 5C**, nonylphenol case study). However, if there are indications of adverse effects via endocrine activity (e.g. *in vivo* bioassays) an additional assessment factor may be considered to cover the anticipated effects[34].

Recently, the Drinking Water Directive (DWD) has stepped up efforts to monitor risks from exposure to EDs. Under the Drinking Water Directive, three substances have been proposed as indicators of estrogenic contamination from sewage effluents, based on WHO recommendations: β-oestradiol, bisphenol A and nonylphenol[35]. Bisphenol A was added to Annex I with a health-based parametric value based on a 2015 EFSA opinion (EFSA Panel on Food Contact Materials et al., 2015), and nonylphenol and β-oestradiol will be added to a watchlist, for assessing their occurrence and treatment efficacy where necessary.

4.4 Risk management

4.4.1 Management approaches across legislation on chemicals

Generally, regulatory intervention on chemicals can be based directly on their hazardous properties (generic risk approach), on the result of risk assessments (specific risk approach), or on risk-benefit considerations[36]. Legislation often combines elements of the different approaches. For example, under REACH the listing as Substance of Very High Concern (SVHC) is hazard-based (generic risk approach); application for authorisations may be based on (adequately controlled) risk or on risk-benefit arguments; restrictions require that there is evidence of an unacceptable risk to human health or the environment. Restriction specifications are also substantiated by (socioeconomic) risk-benefit considerations. Product-level legislative instruments, such as the Cosmetic Products Regulation (CPR), Toy Safety Directive and the Food Contact Materials (FCM) Regulation apply generic risk approaches for Carcinogenic, Mutagenic and toxic to Reproduction (CMR) hazard classes, with specific risk approaches for the risk management of other types of hazardous substances. Exceptions exist where the specific risk approach can also be applied to CMRs. While based on assessments by EU Agencies and scientific committees, decisions can also be subjected to the application of the precautionary principle.

The Fitness Check on chemical legislation (excluding REACH) concluded: "*In many instances, these differences reflect variations in legal scopes and objectives and thus different needs in terms of depth of analysis and evidence required to draw conclusions and decide upon any risk management*

[34] https://rvs.rivm.nl/sites/default/files/2019-04/Guidance%20No%2027%20-%20Deriving%20Environmental%20Quality%20Standards%20-%20version%202018.pdf

[35] Drinking Water Parameter Cooperation Project of the WHO Regional Office for Europe "Support to the revision of Annex I Council Directive 98/83/EC on the quality of water intended for human consumption (Drinking Water Directive) Recommendation", 11 September 2017

[36] In the context of this fitness check "specific risk" approaches imply the use of safe (or acceptable) thresholds to determine whether or not there is a risk. "Risk-benefit" approaches do not always require that a risk is quantified.

measures that may be needed. Therefore, these differences do not necessarily imply incoherence. They illustrate the legislator's intention to provide a framework that is tailored to the specific circumstances of the substances used and/or the likely hazards and exposure"; and further on risk management of known adverse effects: "*The majority of currently known adverse effects on human health and the environment are covered* [in legislation]". However, "*some inconsistencies occur regarding risk management decisions for EDs* […]"[37]. This analysis did not go in depth, referring to the decision by the Commission to launch the present Fitness Check on EDs.

Substances with endocrine disrupting properties pose specific challenges for their assessment. The identification of EDs demands a significant amount of information to clarify potential modes of action and different effects, which often necessitates additional testing (possibly including further animal testing). Risk assessment approaches have limitations for ED-mediated effects in those cases for which it is difficult to derive a safe (or acceptable) threshold based on the available scientific evidence. The same limitations add to the uncertainty of risk-benefit analysis. However, socioeconomic considerations based on other approaches can be applied for non-threshold substances. The legislator has opted for different approaches to risk management, considering policy-specific objectives and constraints (See **Table 3.1** and **Annex 4** for a complete description). Under the Plant Protection Products Regulation (PPPR) and the Biocidal Products Regulation (BPR) the legislator chose to ban EDs but put in place specific derogation possibilities. The approach implemented under REACH is also a generic risk approach insofar as EDs can be identified and listed as SVHCs. The intended consequence of listing SVHC in Annex XIV of REACH is substitution as soon as technically and economically feasible. Authorisation may be granted if risks are adequately controlled or if benefits outweigh risks (e.g. authorisations of DEHP and nonylphenol ethoxylates). Restrictions under REACH follow a specific risk approach and take socioeconomic considerations into account. Regulations on medical devices and *in vitro* diagnostic medical devices require a risk-benefit justification for EDs (identified via REACH and, only for medical devices, via the BPR). Thus, in PPPR, BPR, and the medical devices regulation, the management approach for EDs is comparable to that applied to CMRs. In the case of REACH, however, the automatic ban applied to CMRs in mixtures for consumer use is not applicable to EDs.

Where legislation does not make specific reference to EDs (e.g. Cosmetic Products Regulation, Food Contact Materials Regulation) the specific risk approach is applied. Also the Toy Safety Directive does not refer to EDs but this is a particular case because risk management overlaps with REACH with regard to human health concerns. Classification as hazardous chemicals (including carcinogens and mutagens) is the main trigger to risk management provisions under Occupational Safety and Health (OSH) legislation through a hierarchy of measures from preventing exposure to reducing it to the lowest level technically possible, and in waste legislation through the classification of hazardous waste.

The legislator opted for different risk management approaches based on specific policy objectives and considerations, including:

- **Application of the precautionary principle.** When there are reasonable grounds for concern that potential hazards may affect the environment or human, animal or plant health, or when the available data do not allow to conclude on the absence of risk following a detailed risk evaluation, the precautionary principle has been politically accepted as a risk management strategy. The approach under both the PPPR and the BPR is "*underpinned by the precautionary principle*" taking into

[37]SWD(2019) 199, part 1

account the specific nature of the products in question and the scientific uncertainties regarding their assessment (for example as regards the existence of a safe limit of exposure)[38]. In other cases, the precautionary principle is invoked for substance-specific decisions. For instance, it served as a basis for the currently applicable ban of Bisphenol A (BPA) in baby bottles since 2011 (Commission Implementing Regulation (EU) 321/2011) and more recently for FCM aimed at infants and young children (Regulation (EU) 2018/213).

- **Risk-benefit analysis**. In combination with an evaluation of available alternatives, risk-benefit analysis is the principle of approval procedures for medical devices (e.g. DEHP). It is also applied under REACH for authorisations (e.g. socioeconomic route in REACH authorisations of nonylphenol ethoxylates) and restrictions, and under the Biocidal Products Regulation for derogations to the general non approval of active substances identified as EDs. For human medicines, therapeutic benefits have the priority. Unintended effects on the environment need to be assessed and to some extent managed (e.g. through waste management) but do not impact approval procedures.

- **Trade-offs between policy objectives.** Differences in the objectives between chemical, product and waste regulation (e.g. safety vs recyclability targets) unavoidably result in trade-offs. For example, decisions on authorisation for certain SVHCs in secondary materials is influenced by consideration of the benefits of recycling (**Annex 5B**, DEHP case study).

While policy-specific objectives and considerations, such as the ones highlighted above, generally explain the rationale behind the current differences in risk management approaches, the rationale is not always clear and explicit. For example, the co-legislator's choice for plant protection products and biocidal products was justified by "*the specific nature of the products*"[38]*,* which can be interpreted as the likelihood of exposure and toxicity. This argument is not clear or always supported by scientific evidence of higher ED-related risks compared to other sectors. Another more specific example is the different derogation principles under the Plant Protection Products Regulation (negligible exposure or essential use) and the Biocidal Products Regulation (negligible risk, essential use, or risk-benefit considerations). Stakeholders often criticise situations where substances are restricted under some regulations but not under others and consider them not justified (**Box 4.3**).

Even where regulations apply the same risk management approach, differences in the scope of a risk assessment can also result in different risk management measures for the same substance(s). While not ED-specific, this issue poses a challenge to the coherence of interventions across sectors, as described in Chapter 4.3.2 and **Annex 5B** (DEHP case study).

Overall, it can be concluded that different approaches to risk management have arisen as solutions to specific policy considerations. Although based on a limited number of examples (**Table 1.1**), this Fitness Check found no cases of inconsistent risk management caused by ED specific issues, such as the lack of a horizontal approach to identification.

However, the difficulty in choosing a risk management approach is partly related to the fundamental scientific question of whether EDs are (all) threshold or non-threshold substances. There is no scientific consensus on the threshold question. In fact, since EDs cover a multitude of modes of action, in some cases it may be justified to assume that a threshold exists and to follow a specific risk approach. In the absence of scientific consensus, legislation can either opt for an approach that does not require an answer to the question (e.g. generic risk approach with (limited) derogations as used for plant protection products and biocidal products) or it can determine case by case whether or not a safe (or acceptable) threshold can be quantified and consequently apply an appropriate risk management

[38]COM(2018) 734

approach, as done in REACH, where a risk/impact-benefit approach applies if it is not possible to determine a threshold[39]. Certain pieces of sectorial legislation (e.g. Cosmetic Products Regulation, Food Contact Materials Regulation) not only lack specific provisions for assessing EDs but also lack specific guidance on how to deal with EDs for which it is not possible to quantify a safe (or acceptable) threshold. In practice, in cases where a threshold cannot be established the regulatory approach followed under EU legislation is to minimise exposure as far as possible, including the option to prohibit the use of a substance. Options for consolidation compatible with the Commission's ambition of "one substance one assessment" should be explored, with the specific aim to minimise exposure to EDs. If the current situation persists, many stakeholders will continue criticising the *status quo* for its lack of coherence, effectiveness and efficiency (**Box 4.3**).

4.4.2 Management of EDs through water legislation

Chemicals listed as Priority Substances (PS) under the Water Framework Directive (WFD) require EU-wide monitoring as well as measures to achieve the progressive reduction in the emissions of Priority Substances, the cessation of emissions of Priority Hazardous Substances (PHS) in a reasonable time frame, and compliance with the Environmental Quality Standards (EQS). Provisions in the water sector, however, are mostly limited to end-of-pipe interventions, such as increasing wastewater treatment standards. The identification per se of a substance as a priority substance under the WFD does not necessarily trigger any risk management process beyond the WFD, although several pieces of legislation require consideration of the need to meet the EQS set for them. Similarly, the identification of EDs through chemical legislation does not automatically have regulatory consequences under the WFD (see 4.3.4). For PS and PHS substances that are authorised under upstream legislation on chemicals for uses leading to environmental emissions, it is problematic to minimise or eliminate emissions to the aquatic environment. This is a challenge for PS in general, including EDs such as nonylphenol (**Annex 5C**, nonylphenol case study) and was mentioned by several stakeholders (see **Annex 2**). The issue reflects a generic lack of coordination between the WFD and risk management measures taken under other upstream legislation on chemicals, as pointed out by the recent fitness check of EU water legislation[40], despite recent efforts to require better coordination[41]. For example, there is no link to the objectives of the WFD in legislation on human and veterinary pharmaceuticals.

Regulatory efforts to manage chemicals of concern including EDs have been stepped up recently also in other pieces of water legislation. The coherence of the Drinking Water Directive (DWD) with the WFD is especially important as the protection of drinking water resources is established as an indispensable part of the plans and measures under the WFD. The proposal for a new DWD to be adopted by the end of 2020 implements a specific risk approach, requiring further prevention and mitigation measures to protect drinking water sources. It requires a risk assessment of the catchment area(s) to be carried out aimed at reducing the level of treatment required for the production of water intended for human consumption, for instance by reducing the pressures causing the pollution of the water bodies. MS are asked to pay particular attention in their risk assessment to endocrine disrupting substances, and should, where necessary, require water suppliers to also monitor those substances and other parameters included in the DWD watch list if considered a potential risk to human health, and to treat the water accordingly.

[39]COM(2016) 814 final
[40]SWD (2019) 439
[41]Article 7a of the EQSD

Box 4.3: Inconsistencies, gaps or overlaps in the way endocrine disruptors are regulated in the EU: summary of the views of stakeholders taken from the surveys conducted as part of this fitness check (Annex 2)*

- Inconsistencies exist in how EDs are identified (e.g. lack of horizontal criteria for EDs and/or suspected EDs under Classification, Labelling and Packaging (CLP) Regulation) and regulated across different EU legislative frameworks; e.g. whereas EDs are regulated based on hazard-based cut-offs (with very limited derogation possibilities) in the context of pesticides and biocides, other frameworks such as cosmetic products, toys and medical devices (may) regulate endocrine disruptors based on case-by-case risk assessment. These inconsistencies may lead to different conclusions on restrictions across regulations (if indeed the same substances are present in all these products), which may be difficult to communicate to the citizens.
- There are inconsistencies with regard to restrictions across sectors for several substances that are still present in consumer goods: DEHP has been identified as a human endocrine disruptor under REACH and it is still allowed at high concentrations in plastic medical devices; low molecular weight phthalates such as DEHP are authorized for use in food contact materials (FCMs) with restrictions of use and on migration into food; while REACH restricted their use in most of the consumer products; bisphenol A has been banned from FCM specifically for infants and young children including feeding bottles but it is still used in other products or packaging containing foods that are also fed to infants and young children; triclosan cannot be used in food contact materials and is not approved as a biocide but it is allowed in personal care products; butylated hydroxytoluene (BHT) is allowed in certain foods and in food packaging, while it is currently under evaluation in cosmetic products.
- Detailed exposure data are not always available and, therefore, as for any group of chemicals, it may be problematic for a risk-based approach.
- There is a theoretical possibility for inconsistencies in evaluation e.g. of co-formulants for biocides and plant protection products, which are also regulated under REACH. ED assessment of co-formulants is not foreseen for plant protection products, whereas it is for biocides. Moreover, biocides authorities could reach a different conclusion than the REACH authorities for the same substance unless coordination is ensured. Gaining access to information could be an issue for applicants under the Biocidal Products Regulation (BPR), since suppliers may not be willing to grant access to data generated as part of consortia under REACH.
- Removal of an exemption from authorisation for the use of some substances may be a problem if suitable substitutes are not available within the envisaged timeframe for sunsetting the use (e.g. more flexibility needed in authorisation of the use of DEHP in medical devices, including blood bags, while current alternatives do not match the performance of DEHP).
- There are inconsistencies regarding regulation at national and EU level. For example, France has regulated certain EDs more severely than at EU level. Several categories of food contact materials are not yet harmonised by specific EU measures and although in that case national provisions apply, not all national provisions take EDs into consideration. The new Mutual Recognition of goods Regulation allows free circulation in such cases.
- Many EU regulatory frameworks lack ED-specific provisions: food/feed additives, food contact materials, veterinary drugs, cosmetic products, toys, workers regulations, consumer products, hazardous substances in electric and electronic equipment, waste.
- Lack of understanding/assessment of aggregate exposure and mixed (combined) exposure, which may lead to insufficient protection.
- Lack of a chemical grouping approach for identification and regulation of similar substances to speed up evaluation and to avoid regrettable substitutions (e.g. case of bisphenols).
- There is a lack of adequate test methods and therefore there is a need to invest more in New Approach Methodologies. Authorities should consider accepting more alternative methods to increase the depth of their data sets.
- Where regulations technically allow for ED management, test requirements for EDs are inadequate (REACH, pesticides, biocides, and medical devices).

- The process between ED identification and regulation under REACH takes many years and this leads to protection gaps (e.g. vulnerable groups).
- Protection gaps: protection of children is particularly incoherent (e.g. bisphenol A is not banned in all baby food containers). Similarly, the foetus is not protected as pregnant women are exposed to substances via their food.
- Sector-specific identification of EDs leads to duplication of work with potentially inconsistent outcome, thus creating regulatory uncertainty and ambiguity for the industry. There is a perceived overlap between substances that are used as biocides under the Biocidal Products Regulation and preservatives in the Cosmetic Products Regulation.
- EU legislation and national authorities have insufficient controls on the safe use of recycled materials (e.g. recycling plastic in food contact materials versus recycled paper and board food packaging; products containing chemicals that now are restricted or banned; REACH sets different standards for cadmium content in virgin and recovered rigid PVC; different standards for lead and DEHP in virgin and recycled PVC).
- It is key to achieve a degree of harmonisation between risk assessment processes at EU and international level.
- REACH struggles to capture the environmental impact of substances in food contact materials and cosmetic products.
- There is the need to dedicate more resources to enforcement to block the flow of non-compliant products in the market.
- Some substances are active on the endocrine system but have no negative effects. We are lacking studies to differentiate these substances from those that do have negative effects. At international level, only 66 substances are recognised as EDs.

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

4.5 Coherence with non-EU jurisdictions

Q2. To what extent is the regulation of EDs in the EU coherent with international legal obligations (e.g. WTO) and regulatory approaches in other jurisdictions? What are the impacts of incoherencies and overlaps?

4.5.1 Differences across jurisdictions

The EU framework for assessing and managing chemicals is recognised globally as the most ambitious in its objectives to achieve a high level of protection for human health and environment[42]. Compared to other jurisdictions, the EU legal framework for testing and assessment of chemicals places a bigger burden on the chemicals industry than on governmental institutions.

Common to many jurisdictions is the fact that the risk posed by EDs is the subject of general chemicals legislation, as well as specific regulatory domains such as plant protection products, food legislation, pharmaceuticals etc. (Milieu Ltd et al., 2017; UNEP IPCP, 2017). Plant protection products are subject to regulations and restrictions in all major global jurisdictions. Assessment values (acceptable daily intakes) applied for pesticide residues are rather uniform across different jurisdictions, which is probably the result of the internationally harmonised procedures for the hazard characterisation of pesticides (Milieu Ltd et al., 2017). The Codex Committee on Pesticide Residues, for example, operating under the umbrella of FAO and WHO, is responsible for establishing Codex Maximum Residue Limits (CXLs) for pesticide residues in specific food items or in groups of food, as well as providing international standards for food safety and fostering international trade[43]. The US Endocrine Disruptors Screening Program uses information on endocrine activity or exposures to prioritise screening and testing programs (EC 2016b). A similar approach is used in the EU for general chemicals. ECHA screens chemical substances in their databases for available information on ED properties, combined with methods such as Quantitative Structure-Activity Relationships (QSARs) and read-across[44]. The screening serves for setting priorities for further regulatory action (for which tonnage information can be taken into account as well), such as setting up the REACH Community Rolling Action Plan for Substance Evaluation[45] or to develop the regulatory management options[46] for a (group) of substance(s).

4.5.2 International legal obligations

International laws, such as the Stockholm Convention on Persistent Organic Pollutants (POPs), as well as internationally developed guidelines and standards on chemical safety (e.g. the Globally Harmonised System on Classification and Labelling, and Codex Maximum Residue Limits (MRLs)) do not contain specific provisions on EDs. By establishing specific approaches to assess and regulate EDs, the EU applies higher standards of human health and environmental protection, compared to those established by international standards. WTO rules allow higher standards, provided they are duly notified and scientifically justified. The EU has regularly notified new measures, including changes in legal provisions, restrictions and safety standards on EDs. Starting from 2014, a specific

[42] SWD(2019) 199
[43] http://www.fao.org/fao-who-codexalimentarius/thematic-areas/pesticides/en
[44] https://echa.europa.eu/screening
[45] https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table
[46] https://echa.europa.eu/substances-of-potential-concern

trade concern was raised by Argentina, China, Ecuador, Guatemala, India, Panama, Paraguay, and the United States of America with the support of another 38 members in relation to the EU's intention to publish a road map outlining different options to assess, classify and regulate EDs in the context of the Plant Protection Products Regulation (PPPR)[47]. WTO members have since then repeatedly and frequently challenged the consistency of the generic risk approach in the PPPR with the obligation of the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS agreement) to base more restrictive measures on "an assessment of the risks to human, animal or plant life or health". The EU maintained in the meeting of the WTO Committee on Sanitary and Phytosanitary Measures in November 2019[47] that the criteria for EDs are legitimate and motivated by scientific and societal concerns (low level of tolerance to risk from residues of pesticides in the EU). Moreover, criteria for ED identification are in line with the IPCS/WHO definition. The debate has continued ever since and remains unresolved, although it has not escalated to a formal dispute.

Several WTO members also requested the European Union to harmonise its import tolerances for active substances which were not re-approved with existing levels (MRLs with Codex standards) to allow for trade to continue in line with the SPS agreement. In response, the EU has clarified that whereas the use of substances falling under the exclusion criteria was not allowed in the European Union, import tolerance requests would be nevertheless processed under the MRL Regulation (EC) 396/2005, and a risk assessment would be carried out by an evaluating EU Member State and EFSA[47]. So far, no MRL has been reduced solely due to a substance meeting the exclusion criteria.

[47]Specific Trade Concern (STC) ID 382. http://spsims.wto.org/en/SpecificTradeConcerns/View/382

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- Some endocrine disruptors can be identified using regulatory test guidelines, while for others methods are still under development and require validation. The Commission is funding research into developing new methods and promoting their adoption (once validated) as OECD Test Guidelines.
- Data requirements under the Plant Protection Products Regulation (PPPR), Biocidal Products Regulation (BPR) and REACH are being updated to include already existing OECD test guidelines relevant to ED assessment, in particular to include the so-called 'mechanistic' tests, which can pinpoint a specific endocrine activity.
- It is too early to assess the effectiveness of the PPPR and BPR in protecting health and the environment, since only a limited number of substances have been identified as EDs or not being EDs according to the criteria for identifying EDs adopted in 2018.
- Under REACH all substances registered by June 2018 have been screened for possible endocrine activity as far as possible based on structural alerts, grouping approaches and existing data. Seventeen substances have been identified as Substances of Very High Concern (SVHC) so far, due to their endocrine disrupting properties with respect to human health and/or the environment. However, only octylphenol, nonylphenol and their ethoxylates have been restricted under REACH with explicit reference to their endocrine disrupting properties. Other restricted substances, which are possibly endocrine disruptors, have been restricted without explicit reference to ED properties or due to other toxicities (e.g. organo-tin compounds).
- Under REACH, inclusion of endocrine-disrupting effects as a concern regarding substances in the Candidate List triggers additional provisions for risk assessment (Chemical Safety Report) and risk communication (Safety Data Sheets) and requires specific consideration of endocrine effects in authorisations.
- Some pieces of sector specific legislation can take into account the identification of EDs under the BPR or PPPR, or the identification of substances under REACH as SVHC with ED properties. However, other sectorial legislation such as food contact materials, food additives and cosmetic products have further requirements for products or sectors they regulate but these do not, as yet, specifically address endocrine disruption, hindering the systematic consideration of endocrine disrupting properties for substances regulated only in these specific areas.
- Due to the animal testing ban in the cosmetics sector, as for many other toxicological endpoints an issue arises in relation to the need to demonstrate an adverse effect for an ED, which currently requires *in vivo* testing.
- Identification of EDs is currently mainly based on animal testing. New approach methodologies need to be developed and integrated into the regulatory assessment process. This will not only reduce the need for animal testing, but also increase the efficiency, relevance and reliability of the assessments.
- A "one substance-one assessment" approach was seen by many stakeholders as a way of increasing the effectiveness of regulatory procedures while avoiding potential discrepancies in ED identification.
- Communication on the presence of EDs in products is required under REACH and the Biocidal Products Regulation. However, stakeholders report that information is difficult to

find and to understand. They call for more and better information on EU activities regarding EDs.

- For some EDs, environmental monitoring data and/or human biomonitoring data has provided evidence that restriction measures have been successful in reducing exposure levels. Monitoring data can also provide information on relevant mixtures of EDs in the environment, wildlife and humans.
- In relation to health and environmental impacts an increase in the main non-communicable diseases/disorders that are suspected to be associated with exposures to endocrine disrupting substance has been observed. However, it is difficult to conclude to what extent exposure to EDs from manufactured products contributes to the observed adverse effects. Consequently, it is not possible to draw firm conclusions regarding the effectiveness of legislation on EDs in reducing the increased incidence of those diseases.
- Regarding vulnerable groups, the involvement of the endocrine system in the control of processes such as embryonic development, puberty, pregnancy or menopause puts foetuses, infants, adolescents, pregnant woman and elderly at higher risk regarding endocrine disruption. It is important that data requirements for ED assessment include methods that address these sensitive life stages.
- Knowledge of the way in which substances exert their effects is important when carrying out the assessment of mixtures, specifically when considering potential additive or synergistic effects. This is particularly relevant in the context of ED assessment, i.e. knowledge of the (endocrine) modes of action of the respective components of a mixture facilitates an accurate assessment.

Q3 To what extent has EU legislation been effective in identifying endocrine disruptors and managing risks related to their exposure across different legal frameworks, ensuring the protection of human health and the environment?

It is important to bear in mind that many substances may have more than one hazardous property and indeed this is often the case with EDs since the adverse effect associated with the endocrine mode of action might also be reproductive toxicity or carcinogenicity, including by the same mode of action (e.g. DEHP and other phthalates have been identified as ED and for reproductive toxicity caused by the same ED mode of action). EDs might also be persistent, bioaccumulative and toxic (PBT) or very persistent, very bioaccumulative (vPvB). Risk management measures may already have been taken due to the substance's other hazardous properties (e.g. phthalates). If these measures are the maximum that can be taken then there is no further impact of identifying the substance as an ED. However, in other cases, the identification of a substance as ED in addition to other toxicities (e.g. due to different effects or modes of action) may lead to a need to apply further risk management measures. In addition, not all EDs for human health will be identified as CMRs and identification as an ED for the environment may also trigger additional risk management measures. In the future, EDs with adverse effects other than reproductive toxicity or carcinogenicity may be identified once methods to detect different related adverse effects and their modes of action are available.

5.1 Current process of ED identification

In relation to ED identification the critical point is the availability of suitable, relevant and validated methods to test substances for endocrine disrupting properties. The European Commission supports the development of methods at the international level so that the data generated with the methods will be accepted globally under the mutual acceptance of data (MAD) agreement which is both cost efficient for European businesses and prevents the unnecessary repetition of animal tests. The OECD

test guidelines programme has been striving for many years (since the mid-1990s) to develop and validate appropriate tests which investigate possible ways in which the endocrine system can be perturbed and consequently cause an adverse effect. Test guidelines have been developed in laboratory animals (fish, amphibians and mammals) as well as *in vitro* assays in mammalian cells. The OECD Conceptual Framework for the testing and assessment of endocrine disruptors currently refers to over 30 test guidelines which can be used (together) to investigate endocrine disrupting properties of a substance (OECD, 2018). The methods focus on interference with estrogen (E) and androgen (A) pathways including the process of steroidogenesis (S) (production of steroid hormones such as estrogen and testosterone) and some tests can also identify thyroid (T) hormone disruption, together often referred to as the EATS pathways or modes of action. It is recognised that the toolbox of available tests is not yet complete and intensive work is ongoing through EU-funded research programmes such as the current 5-year EURION project[48]. EURION is a cluster of eight research projects funded with €50 million by the European Commission's Horizon 2020 Research and Innovation Programme, the largest public funding of this type of research in Europe. Each project in the cluster is focusing on a different aspect of new testing and screening methods identifying EDs. The projects focus on improving methods for the identification of thyroid hormone disruptors, as well as developmental, metabolic disorders and female reproductive disorders caused by endocrine disruption. There is also a project specifically exploring cross-species extrapolation of thyroid effects from fish to mammals.

The Commission is also promoting the adoption of the methods (once validated) as OECD Test Guidelines and has contributed to the development of standardised and internationally agreed test methods through grants to the OECD test guideline programme. For the periods 2015/2016 and 2017/2018 a contribution of around €1 million was given twice towards the development of guidelines for the testing of endocrine disruptors either through grants to the OECD or through framework contracts. The contribution also benefitted the work on Integrated Approaches to Testing and Assessment (IATA) and Adverse Outcome Pathways (AOP), which are expected to play an important role in defining future alternative testing approaches[49]. In addition, the JRC's EURL ECVAM in collaboration with the network of validation laboratories in the EU Member States (EU NETVAL)[50], is carrying out the validation of 17 *in vitro* methods drawn from the OECD scoping document 207 (OECD, 2017) which can then be used to identify substances that interfere with thyroid hormone production and action.

In summary, some endocrine disruptors can be identified using regulatory test guidelines whilst for others, methods are still under development and require validation. These tests are the basis for ED identification (where required) under any existing EU regulatory instruments related to chemical safety assessment. In practice, to date, identification of endocrine disruptors has also relied on information derived from non-regulatory studies in the published scientific literature. In 2016, the European Commission commissioned a study on commonalities and differences in approaches for testing and assessment of endocrine disruptors within the EU and among relevant international trading partners (Brunel University London and DTU Food National Food Institute Denmark, 2016). The study compared the approaches for the regulatory screening, testing and assessments of substances between the legal frameworks, and used cases studies to demonstrate commonalities/differences. The analysis confirmed that the current approach of considering data from scientific literature alongside

[48]EURION project: https://eurion-cluster.eu
[49]SWD(2018) 58
[50]https://ec.europa.eu/jrc/en/eurl/ecvam/alternative-methods-toxicity-testing/eu-netval

those obtained by regulatory testing was needed (5 out of the 8 EDs used as case-studies were discovered through research activities, and not regulatory assessment).

Many of the current activities at OECD level and EC level are addressing the concerns of the stakeholders who replied to the survey (**Box 5.1**).

Box 5.1 Stakeholder views on available regulatory test methods*

Regarding **available regulatory test methods**, the need of test methods for assessment of endocrine pathways beyond 'EATS' was highlighted most often by respondents (49% of the responses). The second most commonly highlighted point was about the need to develop non-animal tests (32% of the responses), particularly in relation to the animal testing ban for cosmetic products. The need for methods investigating pathways beyond 'EATS' was the main concern of academic/research institutions, civil society organisations, public authorities and trade unions. Business associations and companies/business organisations would focus on the need for non-animal tests.

The examples of endocrine modalities beyond EATS included; adrenal and retinoid pathways; the neuroendocrine axis; and the immune system and interference with hormones associated with metabolism disorders (obesity, diabetes) or developmental neurotoxicity.
Some respondents referred to the need for specific types of test including:

- Tests covering the whole life cycle of organisms including impact of EDs on aging
- Tests on thyroid effects
- Tests on species representing more widely environmental species including invertebrates
- Tests on Absorption, Distribution, Metabolism and Excretion (ADME)
- Several stakeholders also mentioned that current tests are not sensitive enough and should be further developed to include more sensitive endpoints. There was also reference to the doses at which tests are run, cautioning against running tests at too low doses such that important effects are missed, whereas others are suggesting that tests also be run at low doses in order to detect low dose effects (which might be different from effects at high dose).
- Some respondents mentioned that tools such as Integrated Testing Strategies, Defined Approaches, Integrated Approaches to Testing and Assessment, or Adverse Outcome Pathways should be developed.

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

As described in the state of play (**Annex 4**), there are currently five regulatory instruments that contain provisions related to endocrine disruptors. These are REACH, the BPR, the PPPR, the WFD and the medical devices Regulation.

Criteria for ED identification are laid down for Biocidal Products and Plant Protection Products but not under REACH, which relies directly on the IPCS/WHO definition. The ability to detect endocrine disrupting properties under the three pieces of legislation is limited by the requirements for data generation (see 4.1), which are in the process of being updated for ED endpoints, in particular to include the mechanistic assays (addressing stakeholders concerns (**Box 5.2**).

Box 5.2: Stakeholder views on data requirements*

Over 70% of respondents consider the available regulatory tests insufficient to identify EDs and that the data requirements laid down in relevant legislation (REACH, Biocidal Products Regulation, Plant Protection Products Regulation) are also insufficient. This view point was shared amongst all the stakeholder groups.

Regarding data requirements, many respondents to the stakeholder survey (from public authorities and academic/research institutions) stated that they have to be adapted to include mechanistic data. Some respondents primarily from civil society organisations also suggested to make full use of "independent" research, including when it does not follow OECD guidelines or GLP, as a way to improve the effectiveness of the BPR, PPPR and REACH in identifying EDs.

Regarding the BP and PPP Regulations views expressed by public authorities in the stakeholder survey included:

- Data requirements should be updated to require the most modern test guidelines including the ED-sensitive endpoints
- Investigations should go beyond the EATS modalities, for example including immunotoxicity as a core data requirement.
- For PPPs, thyroid effects should be addressed in non-target organisms and there should be requirements for top tier definitive studies in fish (MEOGRTS) and amphibians (LAGDA) at level 5 of the OECD Conceptual Framework.
- Data requirements for co-formulants of PPPs should be specified in a simpler way.

Regarding the REACH Regulation views drawn from the stakeholder survey included the following:

- The development of screening strategies and a better integration of the latest test methods was recognised as a need by civil society organisations
- Several respondents (from public authorities, civil society organisations and business associations) suggested the inclusion of mechanistic data for low tonnage substances
- With regard to data requirements for the environmental assessment, one respondent pointed out that there are no explicit data requirements for ED relevant aquatic vertebrate tests
- A public authority mentioned that thyroid-specific endpoints only exist for amphibians and should also be included in the fish tests (FELS/FSDT),
- A business association stressed that applying the same test strategy as for PPPs and BPs to REACH would lead to an enormous amount of animal testing, with also severe delays and economic burdens.
- Several civil society organisations suggested that peer-reviewed scientific literature should be given as much weight as validated tests

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Moreover, the adaptive nature of the endocrine system requires a combination of tests for ED identification, which currently mostly rely on animal testing and require considerable cost and time to produce the necessary data (Browne et al., 2020). Most of the available *in vivo* toxicity test guidelines currently required, although not specifically designed for the purpose of investigating endocrine disrupting properties, do include some endocrine-related parameters. These tests have to be carried out for biocides and pesticides and higher tonnage REACH substances to investigate toxicity in

general, independent of endocrine disruption. However, to reach a conclusion on endocrine disruption, additional tests will likely be required, covering additional evidence of specific interactions with the endocrine system (so-called mechanistic studies). Sometimes this may also include the need to repeat an old study in accordance with updated test guidelines incorporating more sensitive markers of endocrine disruption. The amount of additional testing to be carried out thus depends on the amount of reliable data available for the substance and the data gaps that need to be filled to draw a conclusion.

An example of a potential increased cost due to ED testing would be the difference between the cost of the basic design of an Extended One Generation Reproductive Toxicity Study (OECD TG 443) compared with the additional cost of extending the study to two generations and/or including additional groups of animals to investigate effects of the substance on neurological development. The basic design of the EOGRTS was included in the REACH data requirements in 2015. Extensions are triggered in case of a concern, e.g. for endocrine disruption. In a study commissioned by ECHA on the analysis of capacities and capabilities of laboratories to conduct the OECD TG 443, contract research organisations stated that the cost of the basic study design in 2015 to be on average around 430,000€ (Risk & Policy Analysts Limited, 2015). Extension of cohort 1B (to test for reproduction/development) increases the cost by 20% (median value) compared to the basic study design, the developmental neurotoxicity cohorts 2A & 2B increase the cost by 30%, the developmental immunotoxicity cohort 3 by 15%, and a full study design by 60%. Examples of costs of mechanistic methods specifically designed for endocrine testing, are in 2020, about 170,000 € for the uterotrophic and Hershberger assays (combined). For the Amphibian Metamorphosis Assay an estimation of 75,000 USD is given in OECD GD 150 (version 2012). Regarding *in vitro* testing (OECD TG 455, 456, 458, OPPTS 890.1200), the average cost in 2020 of each test goes from 2000 to 20,000€ depending on the test or service provider. In relation to the time taken to conduct the test, contract research organisations have recently indicated durations of around 9 months to conduct the mechanistic *in vitro* tests and around 20 to 24 months for the *in vivo* assays such as the uterotrophic and extended one generation study in rodents and up to 28 months for an extended one generation reproductive toxicity test in fish (medaka) (MEOGRTS) or a larval amphibian growth and development study (LAGDA)[51]. However, the estimated time periods do not consider possible limitations of testing capacity of laboratories, which is an important factor to take into account when updating data requirements.

Regarding the REACH data requirements for environmental assessment, chronic toxicity data on fish are required for tonnages above 100 tonnes, but will often be based on a fish early life-stage (FELS) test which does not allow for ED identification, as it does not include any ED-related endpoints. Therefore, additional testing would be required for ED identification. In addition, for thyroid-specific effects, an amphibian test would be needed as there is no thyroid-related endpoint in the fish test guidelines. However, this should change as several research projects funded by the European Commission are investigating the possibility to add thyroid-related endpoints to the fish tests.

Although data requirements under the PPPR, BPR and REACH are still in the process of being updated, available or newly generated data sets, including studies reported in the published scientific literature, have allowed some substances to be identified as EDs under each of these regulations as explained further below.

[51]Response to request for information from EFSA provided on 30th June 2020

Box 5.3: Stakeholder views on animal testing*

With regard to the use of *in vitro* and/or *in silico* methods, a majority of stakeholders think that they are not used systematically enough to prioritise further investigations (80 agree, 7 disagree, and 38 neither agree nor disagree). In particular, they commented that:

- *in vitro* and/or *in silico* methods are not easily accepted by competent authorities
- there are not enough *in vitro* and/or *in silico* methods available (they would be easier to use if more were available and could be combined), and available ones are not reliable or predictive enough. Some stakeholders also mentioned the lack of expertise in these methods as a limiting factor for their use. Several stakeholders call for the development of guidance for the use of such methods.
- if *in vitro* and/or *in silico* methods are used for prioritisation purposes, they might not need to be OECD Test Guidelines. It might be sufficient for the methods to meet some acceptance criteria.
- *in vitro* and *in silico* methods should also be used more systematically to support the development of grouping approaches
- *in vitro* and/or *in silico* data cannot outweigh *in vivo* data to identify ED potential (not used to discard evidence of adverse effects)

A bit more than half of the stakeholders expressing an opinion (54%) think that the impact of assessing chemicals for endocrine disrupting properties on animal welfare is minimised in the EU to the extent possible. This opinion is globally shared by all the stakeholder groups, except the civil society organisations which mostly think it is insufficiently minimised. Amongst the citizens, 37% think that animal testing for endocrine disrupting properties in the EU is insufficiently minimised, whereas 28% consider animal testing to be fully minimised (5%) or minimised to the extent possible (23%).

- Many stakeholders mentioned that the best way to minimise the use of animals would be to apply the one substance –one assessment approach, allowing data to be used across regulatory sectors. Moreover, this could be made more efficient and transparent through a more centralised approach to testing (based on industry fees but managed by independent authorities).
- A common data base of registration data covering all regulatory regimes, accessible to both applicants and regulatory bodies was mentioned as another tool to reduce animal testing.
- A stakeholder suggested to allow cross-class extrapolations among vertebrates, highlighting that the endocrine system is highly conserved among vertebrates.
- Some stakeholders suggested that the creation of a suspected category for EDs would lead to minimization of exposures and less use of animal tests, stating that today many tests are carried out to defend continued use of a chemical.
- A stakeholder suggested to further develop models such as the ToxCast ER bioactivity model

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Regarding the stakeholder statement that "the best way to minimise the use of animals would be to apply the one substance–one assessment approach, allowing data to be used across regulatory sectors", it should be highlighted that under REACH and the Biocidal Products and Plant Protection Products Regulations, the sharing of data from vertebrate animal tests is an obligation.

5.2 Biocidal Products and Plant Protection Products Regulations

The PPPR and BPR introduced, in 2009 and 2012 respectively, an approach that active substances identified as EDs cannot be approved – unless very limited derogation possibilities are met. Such an approach is already applied to substances with CMR properties (the so-called exclusion or cut-off criteria; see **Section 3** and **Annex 4**).

According to EFSA[52], seven of the 57 ED assessments of active substances conducted so far under the PPPR resulted in the active substances being identified as EDs with respect to human health (**Table 5.1**). Of the remaining 50, there was no evidence of endocrine disruption for 17, further information was requested for 20 substances, the ED assessment was waived for 12 substances for different reasons and one assessment is still in progress. The 55 assessments conducted with respect to the environment (non-target organisms) concluded that three active substances had endocrine disrupting properties whereas five did not, eight assessments were waived and 39 required further testing.

According to ECHA[53], the Biocidal Products Committee (BPC) has delivered 17 opinions on biocidal active substances since the criteria came into action (June 2018). In these opinions, three substances were concluded to meet the ED criteria for human health and/or non-target organisms, and three substances were concluded not to meet the ED criteria. Of the remaining 11 substances, the BPC could not conclude due to the absence of sufficient data. However, for assessment reports submitted before 1 September 2013, the evaluating Competent Authority has to conclude based on the already available data and/or the data provided by the applicant. Where this data is insufficient to reach a conclusion, the BPC may conclude in its opinion that no conclusion could be drawn[54]. In addition, when the substance is already non-approved (due to meeting other exclusion criteria) no additional data are requested for the ED assessment.

An additional 12 substances have already been discussed by the BPC Working Groups without having progressed to the BPC. In the Human Health working group, 11 substances have been discussed: 4 substances were concluded to not meet the criteria. For the remaining 7 substances no conclusion could be drawn, although in some cases there could be technical limitations to providing additional data. In the Environment Working Group, 10 substances have been discussed: for 1 substance the ED assessment was waived, while for the remaining 9 substances no conclusion could be drawn due to the absence of sufficient data. In most cases, additional data will need to be generated in order to conclude on the ED properties for non-target organisms, particularly for non-mammals.

Table 5.1: Outcomes of active substance assessments for endocrine disrupting properties under the PPPR (as of August 2020)

Properties	Substances assessed for ED properties	Substances identified as ED	Substances not meeting the ED criteria	No conclusion possible (further data may be required)	Assessment waived	Assessment in progress
Human Health	57	7	17	20	12	1
Environment	55	3	5	39	8	

[52]Response to request for information from EFSA provided in August 2020
[53]Response to request for information from ECHA provided in September 2020
[54]CA-March18-Doc.7.3a-final- EDs- active substances under assessment

Table 5.2: Outcomes of active substance assessments for endocrine disrupting properties under the BPR (as of September 2020)

	Substances assessed for ED properties	Substances identified as ED	Substances not meeting the ED criteria	No conclusion possible (further data may be required)	Assessment waived
BPC Opinions (Human Health and Environment)	17	3	3	11	
BPC Human Health WG	11		4	7	
BPC Environment WG	10			9	1

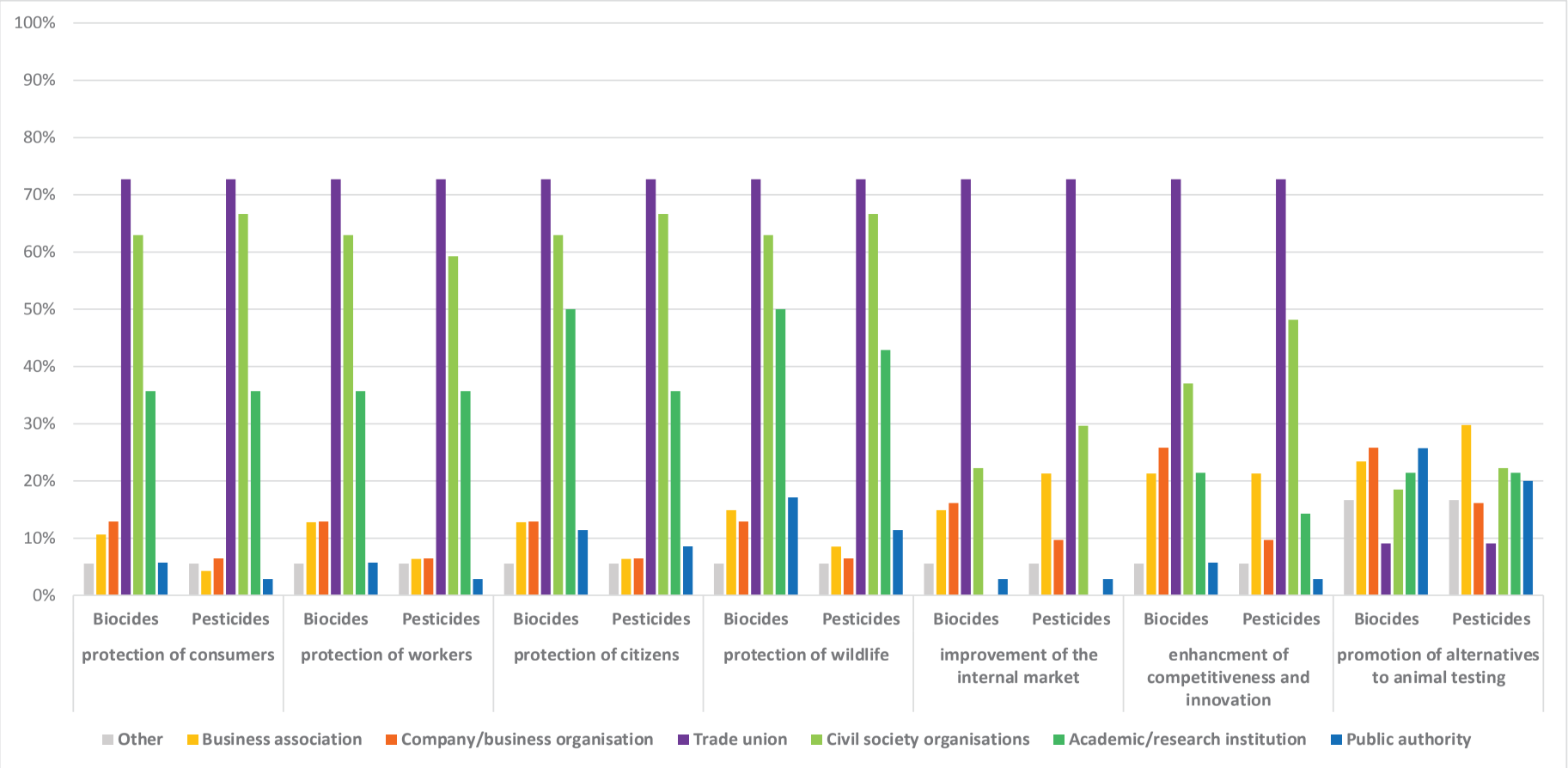
The experience gained so far demonstrates that for some substances the existing data were sufficient to reach a decision but for many the existing data were insufficient. This confirms that the data requirements for the Regulations need to be updated in order to increase the likelihood that a decision on endocrine disrupting properties can be made on the basis of the data package presented as part of the approval or renewal applications. This should significantly reduce the frequency of the necessity to 'stop the clock' to request further information related to ED properties which slows down the regulatory process. An update of the data requirements has been initiated under the BPR and the PPPR as described in the state of play (**Section 3** and **Annex 4**). Since the criteria only came into effect in 2018 it may be considered too early to assess the effectiveness of the ED criteria for the BP and PPP Regulations (a view supported by many of the respondents to the stakeholder survey) – in fact, the Regulations establishing the criteria foresee a review by 2025 (i.e. 7 years after they start to apply). However, 44 PPP active substances considered as EDs according to the WHO-UNEP Report of 2012 have been already withdrawn from the market due to other hazardous properties leading to unacceptable risks to human health and the environment[55]. In addition, many active substance renewal/non-renewal regulations already include consideration of the ED aspect in light of the submitted dossier and criteria.

In summary, since the criteria came in force in 2018 any pending or new request for approval of a new active substance under the BP and PPP Regulations require an evaluation of endocrine disrupting properties. In addition, for active substances currently on the market, renewal of approvals is required on a regular basis (every 7 to 15 years), ensuring that all substances will be re-evaluated in light of new scientific information. This also covers the assessment of endocrine disrupting properties, according to the new criteria, and renewal processes which were already ongoing when the new criteria entered into force but were still pending. Furthermore, re-assessment is also required when new evidence emerges[56]. The data requirements under both regulations are currently being updated to enhance the possibility to identify EDs based on relevant OECD test guidelines within the OECD Conceptual Framework. A (systematic) review of the literature is also required to identify relevant studies from the published scientific literature. Evaluations conducted since 2018 have demonstrated that it is possible to identify EDs, or the absence of ED properties, for a number of substances based on data already available within the dossiers supported by the published scientific literature, which is always considered since evaluations must be based on all available data (see **Table 5.1**).

[55]SWD(2016) 211, Annex 9, p214
[56]SWD(2019) 199, p64

Box 5.4: Stakeholder views on effectiveness of BP and PPP Regulations as regards EDs*,**

The proportion of each stakeholder group responding that the Regulations are not effective is presented in the graph below:



- A viewpoint from companies/business organisations and business associations is that restrictions on use of some biocides based on their ED properties will decrease the availability of products and may increase the risk of an outbreak of resistant microbes. Similarly, for pesticides with the risk of pest resistance. This could have major adverse impacts on food production and price, with associated negative consequences on health, the environment and society as a whole.

• According to civil society organisations, slowness of the procedures is leaving many substances un-assessed (and thus still on the market). • Effectiveness of the BPR/PPPR is reduced by the (too) high level of evidence required to demonstrate endocrine properties of a substance. • There is a risk to buy on-line products from outside of the EU which may not comply with EU regulations which is a factor limiting the effectiveness of the regulations. • The same assessment strategy for identification of ED properties cannot be applied to the non-active substances in biocidal products or co-formulants under PPPR as data are not available and cannot be requested from applicants.
*Answers are given as a percentage of respondents from each stakeholder group. For more details see Annex 2. **Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

5.3 REACH

Under REACH there are provisions for restricting or authorising the use of substances with endocrine disrupting properties. The REACH registration database contains 22,877 substances (as of 11 July 2020)[57]. One of the principles of REACH is an increasing requirement for information on hazardous properties in accordance with potential for exposure, based on uses and production levels. The process of substance evaluation, however, allows for the evaluation of any substance based on concerns from existing data.

The ED-related provision is introduced through Article 57(f), which allows endocrine disruptors to be identified as substances of very high concern (SVHCs) if they exhibit serious effects that are of equivalent concern to other substances of very high concern such as carcinogens, mutagens and reproductive toxicants (CMRs) (Category 1A/1B) or persistent, bioaccumulative and toxic substances (PBTs/vPvBs).

Although criteria for the identification of EDs are not defined in the legal text of REACH, this has not prevented substances from being identified as EDs. This has been achieved through agreements by Member State competent authorities to follow the IPCS/WHO definition and use the OECD guidance document 150 on the testing and assessment of endocrine disruptors (OECD, 2018) with their own expertise to evaluate existing data (including non-regulatory studies in the scientific published literature). Through the substance evaluation procedure of REACH, it is also possible to request the registrant to conduct additional studies listed in the OECD Conceptual Framework in order to clarify concerns on toxicity, including endocrine disrupting properties.

As an action under the Community Strategy for EDs from 1999 a study was contracted by DG ENV in which an extensive literature search was carried out to identify substances that had been reported in the literature to be associated with endocrine activity either from *in vitro* or *in vivo* studies. Around 500 substances were identified and a process of verification of the validity of the studies was undertaken through expert workshops. Substances were categorised according to the presence of endocrine activity *in vitro* or *in vivo* in at least one positive test. Further analysis revealed that many of the uses of these substances were already restricted under EU legislation in relation to their other hazardous properties (e.g. CMRs or PBTs/vPvBs).

This list of substances along with other information (e.g. from the ChemSec SIN list[58]) fed into the ECHA screening approach[59, 60] for REACH registered substances, which serves as a starting point for further investigation of ED properties under REACH substance evaluation or for regulatory action such as a restriction or SVHC-identification/authorisation. The starting pool of substances for all ECHA's screening activities comprises approximately 130 000 substances in ECHA's database. The screening approach also uses computational tools to identify substances with chemical structures or sub-structures/functional groups related to the structures of known endocrine disruptors as well as searches in registration dossiers of endocrine-related terms including potentially endocrine-related (adverse) effects.

[57] https://echa.europa.eu/information-on-chemicals/registered-substances
[58] https://echa.europa.eu/documents/10162/19126370/sin-list_analysis_en.pdf/6248cac0-ffa8-5a14-ae55-93ace7ee9017
[59] https://echa.europa.eu/documents/10162/19126370/common_screening_approach_en.pdf/b195b928-25ce-4a1c-9eec-8f58ca724f58
[60] https://echa.europa.eu/documents/10162/19126370/screening_definition_document_en.pdf/e588a9f8-c55e-4412-a760-49ddbf7ac687

In this manner, substances in ECHA's database have been screened for potential endocrine activity based on existing data in REACH registration dossiers but also, in some cases, the published scientific literature and those with indications of activity have been taken up by REACH competent authorities for further regulatory action.

Screening information on potential ED properties of pre-registered substances in the tonnage range of 1-10 tonnes per year was also made available by ECHA on their dissemination portal as part of the REACH Annex III inventory. Registrants of low tonnage substances could check prior to registration whether their substances were considered likely to have hazardous properties. Lower numbers of low tonnage substances were registered at the last registration deadline (end of May 2018) than originally expected. While reasons for a lower number of registrations are unknown, it could be hypothesised that the screening information provided by ECHA may have discouraged industry from registering such potentially hazardous substances.

To support the effectiveness of the process of ED assessment an ED Expert Group has been set up to provide an informal consultation body for the Member States, the Commission and ECHA on all regulatory assessments related to EDs under REACH and the BPR. The ED Expert Group helps define the best testing strategy and data to be requested in a substance evaluation decision before a substance enters the formal substance evaluation decision-making process. This happens during the 12-month period given to Member States to evaluate the substance, and therefore does not affect the duration of the overall process. Besides the MS experts, the ED Expert Group includes stakeholder organisations as observers (representing industry, consumer and environmental protection groups, trade unions and animal welfare organisations). According to the endocrine disruptor assessment list on ECHA's website[61], the ED Expert Group has discussed 92 substances or group of substances under REACH or the BPR. Many substances are brought to the expert group before being moved to SVHC identification, which has resulted in improved dossier quality and less need for discussion at Committee level. Member State Competent Authorities responsible for drafting the Annex XV dossier can decide to focus on either ED for the environment or ED for human health (or both) since often different agencies with different expertise carry out each type of assessment. This allows Member States some flexibility in deploying their resources. In principle, this could lead to a lack of coherence on the data sets used and reduce the possibility for effective read-across between the human health and environmental data, which should be used together in a weight of evidence approach to reach decisions. However, in most cases Member State authorities consider human health data when assessing environmental properties and vice versa, and there is no evidence showing that separating the assessments is affecting the assessments.

Substances with endocrine disrupting properties are identified as SVHC if the substance is of an equivalent level of concern (ELoC) to CMRs Cat. 1A/1B or PBT/vPvBs as specified in Article 57 (f) of the REACH Regulation. Lack of unanimous agreement in the REACH Member State Committee (MSC) of ECHA on identifying a substance as an SVHC under REACH and the need to refer such cases to the Commission can be seen to have slowed down the process (as highlighted by some stakeholders). However, through the decisions taken by the Commission (after a vote in the REACH Committee) on these disputed cases and by judgements of the Courts in Luxembourg, a common interpretation has started to emerge, which can be applied by the MSC in future cases and should increase the efficiency of the overall process. As of July 2020, 17 substances have been identified as endocrine disruptors of equivalent concern to SVHCs for either human health (5 substances) or the environment (10 substances), plus 2 identified as ED for both human health and the environment. All

[61] https://echa.europa.eu/ed-assessment

the substances that have been agreed to be endocrine disruptors by ECHA's Member State Committee have also been identified as SVHCs (i.e. ELoC) except for resorcinol. In the case of resorcinol, the MSC opinion that the substance is an ED of ELoC has recently been referred to the European Commission's REACH Committee, along with the minority position disagreeing with the opinion. Some of these substances were already listed as SVHCs and undergoing authorisation due to their other hazardous properties. Of those EDs placed on the candidate list, 6 have been transferred to the authorisation list (Annex XIV). Applications for authorisations are undergoing or have undergone evaluations by ECHA's Committee for Risk Assessment (RAC) and Committee for Socioeconomic Analysis (SEAC) leading to the granting of authorisations for certain specific uses while other uses have been restricted following the restriction procedure (see **Annex 5** – Case studies).

Substances identified as endocrine disrupting substances of an equivalent level of concern to CMRs or PBT/vPvBs include the phthalate esters DEHP, DIBP, DBP and BBP (see **Annex 5B**, DEHP case study). In fact, regulatory action on DEHP and other phthalates started in relation to the reproductive toxicity of the substances before ED-specific provisions were in place. The additional inclusion of a concern for endocrine disrupting effects on human health in the SVHC list did not directly affect REACH authorisation and restriction procedures since they are based on the same effects that led to the inclusion due to toxicity for reproduction. However, it triggered additional risk provisions for risk assessment (Chemical Safety Report) and risk communication (Safety Data Sheets) and required specific consideration of endocrine effects in reviews of authorisation. DEHP was also identified as an SVHC for endocrine effects on the environment and was added to the Candidate list for authorisation under REACH which also leads to an obligation to obtain authorisations in other sectors (food contact materials, medical devices). It also prompted the re-designation of DEHP from a Priority Substance to a Priority Hazardous Substance under the Water Framework Directive which requires that emissions be phased out.

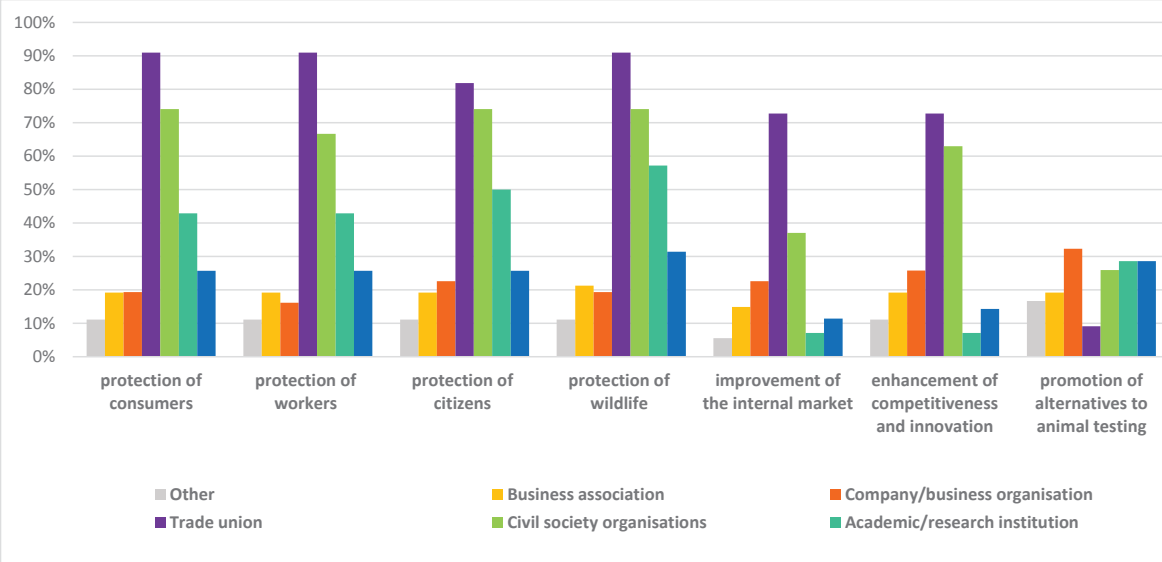
Other substances identified as SVHCs for the environment due to endocrine disrupting properties and placed on the REACH Candidate list include a number of alkylphenols and alkyl phenol ethoxylates. One of these, nonylphenol (NP), is an intermediate in the production of various derivatives including nonylphenol ethoxylates (NPnEOs) which were used as surfactants and emulsifiers in many different applications including detergents with consequent widespread emissions to the aquatic environment (see **Annex 5C**, NP case study). They have been progressively restricted over many years due to risks to the aquatic environment, firstly via the 1992 PARCOM[62] convention and then through REACH restrictions together with setting of Environmental Quality Standards (EQSs) and actions taken under the WFD. NP and NPnEOs were identified as SVHCs of equivalent concern under REACH due to endocrine disrupting effects on the environment in 2012 and 2013 respectively and further restrictions were introduced in 2016. They are widely restricted in the EU, with a few speciality biomedical applications currently subject to the authorisation requirements after NPnEOs were placed on the Authorisation List (Annex XIV) of REACH. In recent years increasing scientific knowledge has led to updates of predicted no effect concentrations (PNEC) and EQS values for the aquatic environment. With respect to human health concerns, NP was classified as a category 2 reproductive toxicant in 2001 and consequent restrictions included the addition to the list of prohibited substances in cosmetic products. The closely related octylphenol and their ethoxylates were also identified as SVHCs due to endocrine disrupting effects on the environment in 2011 and 2012, respectively, and are similarly subject to authorisation requirements.

[62]Convention for the prevention of marine pollution from land-based sources (Paris Convention) PARCOM Recommendation 92/8 on nonylphenol ethoxylates. https://www.ospar.org/convention/agreements/page13

Box 5.5: Stakeholder views on effectiveness of REACH Regulation as regards EDs*

Of the stakeholders expressing an opinion on the effectiveness of REACH, there is a roughly even split between those that consider the regulation is effective in protecting human health and those that do not when considering consumers (57 agree, 62 disagree, and 17 neither agree nor disagree) or workers (56 agree, 59 disagree, and 18 neither agree nor disagree). A smaller proportion of respondents consider that the regulation is effective in protecting citizens exposed via the environment (46 agree, 63 disagree, and 26 neither agree nor disagree) or wildlife (43 agree, 67 disagree, and 23 neither agree nor disagree).

The proportion of each stakeholder group answering that the Regulation is not effective is presented in the graph below:



Answers are given as a percentage of respondents from each stakeholder group. For more details see Annex 2.

Regarding human health and environmental protection, some respondents (from academia, or civil society organisation) declared that the risk-based control of ED substances in REACH may lead to insufficient protection, while others (representing Industry) stated that there is a high level of protection of consumers, workers, citizens and the environment.

Motivations for respondent's replies include the following:

- the process to identify substances as EDs is too slow, with only 16 substances identified so far as ED. Application of a grouping approach could be a way to speed up the process.
- some respondents suggested to extend the simplified restriction procedure (art.68, §2) for CMR cat1A or 1B in consumer products to endocrine disruptors.
- there were some suggestions to remove the "equivalent level of concern" (ELoC) step so that the new horizontal criteria would automatically fulfil Art. 57(f) or by creating an additional category as Art.57(g). Another option could be to develop a guidance on the interpretation of 'ELoC'.
- inclusion on the Candidate List should be automatic for substances with known ED properties (whether classified or not). SVHCs not registered under REACH should immediately be moved to Annex XIV and if no authorisation applications are made before the sunset date, all uses should be automatically restricted (i.e. the substance should be included in Annex XVII).

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Apart from SVHC identification and authorisation, REACH contains the restriction procedure as a powerful tool for imposing risk management measures including the complete ban of a substance.

A restriction can be put in place if there is an unacceptable risk to human health or the environment that arises from the manufacturing, use or placing on the market of a substance. Examples of restricted substances with confirmed or suspected endocrine disrupting properties are multiple organo-tin compounds, the mentioned octylphenol, nonylphenol as well as their ethoxylates, phthalates, perfluorooctanoic acid and related substances, or substances that are now regulated under the Regulation (EU) 2019/1021 (e.g. decabromo diphenylether). However, only octylphenol, nonylphenol and their ethoxylates are restricted due to their ED properties.

In the targeted stakeholder survey comparing BPR, PPPR and REACH, the large majority of respondents with an opinion stated that REACH is the regulation with the lowest likelihood of identifying a substance as an endocrine disruptor. This view was mainly coming from respondents from public authorities, as well as respondents from academia and civil society organisations. The main two reasons for this ranking were: 1) the few data requirements for low tonnage substances, and 2) the lack of specific information requirements for EDs. Testing for endocrine properties is triggered based on observations coming from repeat dose and reproductive/developmental testing, and chronic tests in aquatic organisms, however, these tests may not be available since REACH applies a tiered approach for information requirements, based on production tonnage. Thus such tests would not be required for low tonnage substances, limiting the possibility to detect toxicological effects (this aspect is not ED specific). In contrast, investigation of endocrine disrupting properties is mandatory under the BPR and PPPR, irrespective of tonnage level.

Some respondents also mentioned that the REACH process could be strengthened by making the BP and PPP ED-identification criteria applicable and formally used by the REACH-SVHC process. This option would be in line with the Commission's aim to develop a horizontal approach to ED identification. However, it should be noted that the BP and PPP criteria were developed specifically for these two regulations and it needs to be examined whether they can be applied directly for REACH processes. It was also mentioned that the additional requirement within REACH to demonstrate an equivalent level of concern as for CMRs or PBTs/vPvBs when identifying an ED as a substance of very high concern (SVHC) also decreases the likelihood of an identification.

A point was also made in favour of the creation of a European mechanism to enable the European and national agencies, to carry out independent studies on potential EDs. It was suggested that the work should be financed by an increase in the fees charged by the agencies to companies.

5.4 Other sector-specific and product-specific legislation

Many pieces of sector-specific and product-specific legislation have provisions to address risks posed by hazardous substances, but do not require the necessary toxicity data to be generated to allow the identification of the hazard. Substances used in some sectorial legislation, such as the Toy Safety Directive, Detergents Regulation, Fertilisers Regulation, Food Contact Materials Regulation, the Cosmetic Products Regulation and the Medical Devices Regulation, are required to be registered under REACH (unless produced/imported at <1 tonne/annum). Some pieces of sectorial legislation rely primarily on REACH for ED identification, others such as food contact materials, cosmetic

products and food additives have further requirements for products or sectors they regulate but these do not, as yet, specifically address endocrine disruption.

It is important to bear in mind that many substances may have more than one hazardous property and indeed this is often the case with EDs since the adverse effect associated to the endocrine mode of action might also be classified as e.g. a carcinogen, mutagen or reproductive toxicant (CMR). EDs might also be persistent, bioaccumulative and toxic or very persistent and very bioaccumulative (PBTs/vPvBs). For substances where the adverse effect caused through disruption of the endocrine system has already been identified and appropriate risk management measures have been applied, the effective measures to minimise exposure may already be in place and identification of a substance as an ED would not bring any additional measures. However, this may not always be the case and knowledge that a substance is an ED can increase the level of concern, which may lead to stricter risk management measures being applied.

In product or sector specific legislation with no ED-specific provisions, there are possibilities to evaluate the risks and apply appropriate risk management measures on a case-by-case basis. This may occur when endocrine disrupting properties of a substance become known through other regulatory processes e.g. under REACH or through publication of scientific papers.

When asked for which sectors they think ED identification should be more specifically introduced some stakeholders referred to the WFD (any Priority Substance with known ED properties should be identified as a Priority Hazardous Substance), the Detergents Regulation (identification of EDs especially for the environment should be emphasized), and the toy safety directive.

Several respondents also proposed to adopt a "one substance-one assessment" approach, which would, in their opinion, increase the effectiveness of regulatory procedures while avoiding discrepancies in ED identification. Under this scenario, there would be no need for specific provisions in each of the legislative pieces, but rather a reference could be made to an overarching regulation like REACH which already has provisions allowing for ED identification.

Pieces of legislation where some stakeholders consider that risk management measures for EDs should be more explicitly described include occupational safety and health Regulations, indoor air pollution, industrial emissions, waste and water Regulations. Several stakeholders suggested that ED identification under one regulation should automatically trigger risk management measures for the same substance under other regulations.

When asked about the impact on human and environmental health of either hazard-based or risk-based approaches[63] to decision making, both were viewed positively by the majority of respondents in the stakeholders survey with slightly more support for risk-based approaches. However, some differences emerge when looking at specific stakeholder groups. Representatives from industry (business association and company/business organisation) have a marked preference for risk-based decision making while civil society organisations favour a hazard-based approach. Similar responses were received with respect to both environment and human health.

Water Framework Directive and Medical Devices Regulation

[63]The terminology "hazard-based" and "risk-based" approaches is used in the context of consultation activities of this Fitness Check. The terms are equivalent to "generic risk" and "specific risk" approaches used elsewhere in the document.

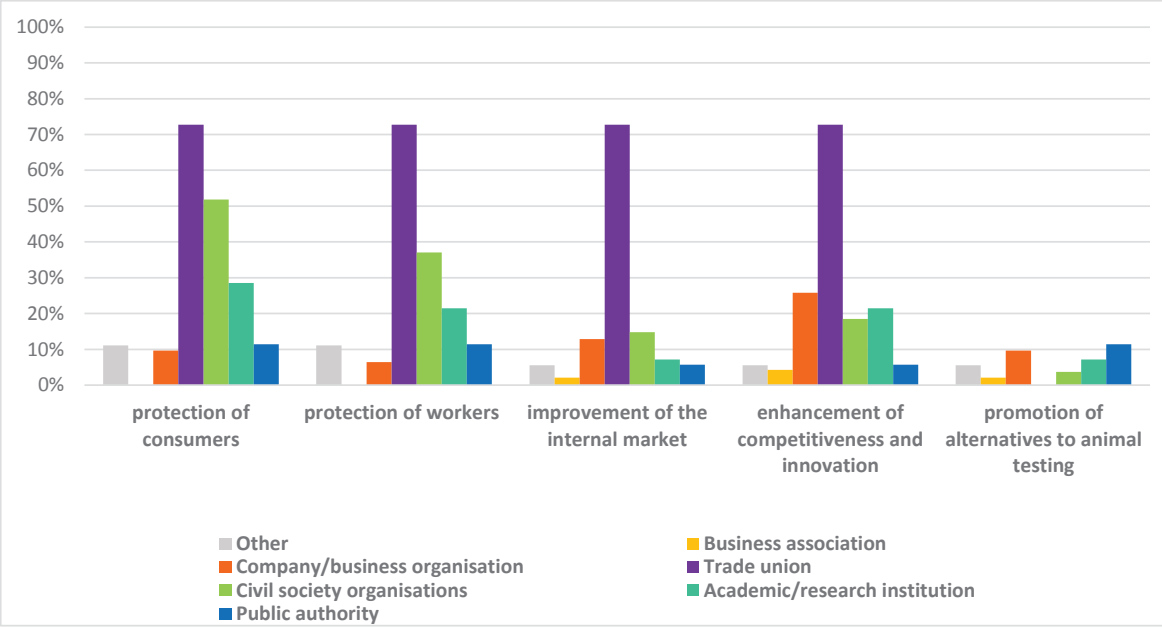
The provisions on EDs in the Water Framework Directive and the Medical Devices Regulation refer to the steps to follow once a substance is identified as an ED but there are no mechanisms within either piece of legislation for ED identification. The Medical Devices Regulation relies on REACH and on the BPR for ED identification. However, there is no provision that requires all substances used in medical devices to be evaluated under REACH for ED properties. Only if the medical device manufacturer is also considered a manufacturer, an importer or a downstream user under REACH, would the related REACH obligations apply (i.e. a chemical safety assessment). The Water Framework Directive (WFD) has also relied largely on REACH for ED identification.

Box 5.6: Stakeholder views on effectiveness of Medical Devices Regulation and WFD as regards EDs*

Regarding the **Medical Devices Regulation**:

A large proportion of stakeholders who replied to the closed questions say they do not know about the effectiveness of the regulatory process of the Medical Devices Regulation. Of those expressing an opinion, more respondents disagree than agree that it is protecting consumers, protecting workers or enhancing competitiveness and innovation.

The proportion of each stakeholder group answering that the Regulation is not effective is presented in the graph below:



Answers are given as a percentage of respondents from each stakeholder group. For more details see Annex 2.

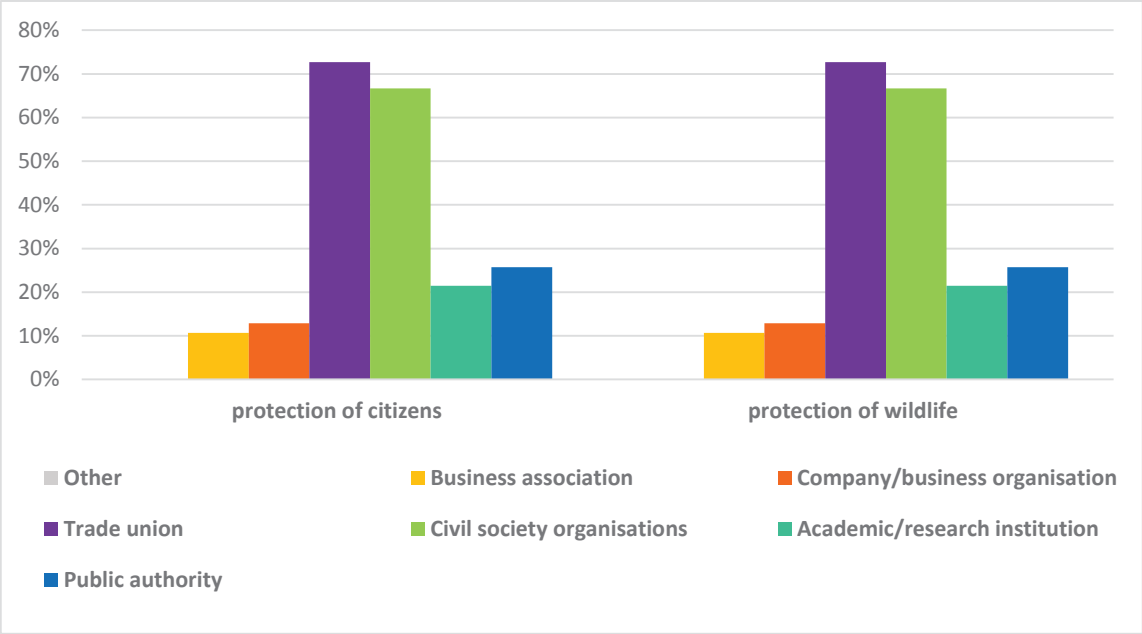
Reasons given in support of their views were as follows:

- regarding human health protection, some respondents (from civil society organisations and academic/research institutions) stated that while the Medical Devices Regulation introduces new provisions with regard to EDs, the provisions are considered too weak to allow the proper identification of EDs, since the dependency on REACH (for data) hampers the effectiveness of the regulation and makes the horizontal approach for EDs critical.
- these respondents called for a systematic testing of the substances used in medical devices for possible ED concern.
- some stakeholders (from civil society organisations) considered that patients are still exposed to EDs via medical devices even if in many cases safer alternatives exist
- the effectiveness of the Medical Devices Regulation is limited by the possible exemptions.

Regarding the **Water Framework Directive**:

More respondents disagreed than agreed that the directive is effective in minimising the exposure of citizens (22 agree, 47 disagree, and 12 neither agree nor disagree) or wildlife (27 agree, 47 disagree, and 12 neither agree nor disagree) to endocrine disruptors via the environment. However, the numbers of "don't knows" were relatively high.

The proportion of each stakeholder group responding that the Regulation is not effective is presented in the graph below:



Answers are given as a percentage of respondents from each stakeholder group. For more details see Annex 2.

Reasons given in support of their views were as follows:

- WFD is ineffective at protecting consumers and the environment from exposure to EDs because of the lack of coordination between the WFD and upstream chemicals legislation.
- Only a few EDs are monitored in surface waters, and it is difficult to update the list of priority substances.
- WFD does not succeed to apply the 'polluter pays' principle. While companies releasing chemicals into the environment have virtually no obligations regarding ED assessment, the burden of monitoring and follow up action falls mostly on public authorities and taxpayers.

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Cosmetic Products Regulation (CPR)

In the case of the Cosmetic Products Regulation (CPR), which does not have specific provisions for EDs, the environmental risks of endocrine disruptors are explicitly covered by REACH but the human health assessments are dealt with under the CPR. Under the CPR, substances classified as carcinogens, mutagens and reproductive toxicants (CMRs) category 1A/1B or 2 are prohibited unless specific derogations are applied (see **Annex 4**). EDs that are also CMRs would fall into the same

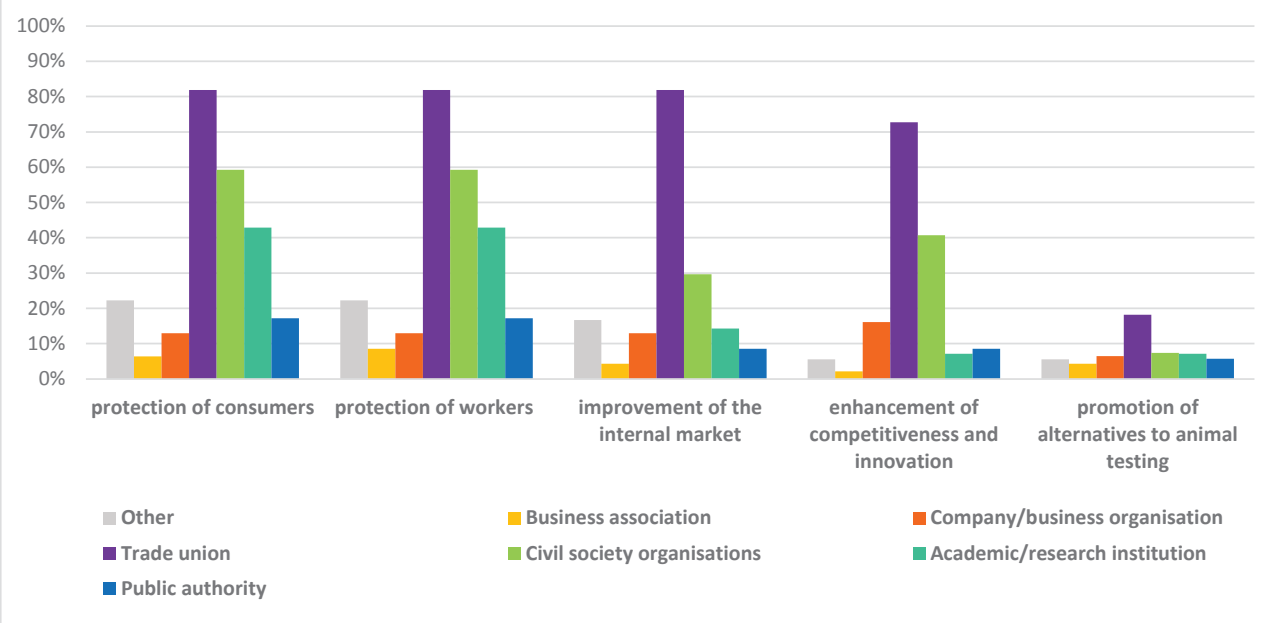
category. The SCCS also proposes to follow a specific risk approach for identified or potential endocrine disruptors which might cause other types of adverse effects. The question still arises how to ensure the systematic consideration of endocrine disrupting properties in cosmetic ingredient assessments. Following the review of the CPR[64] the Commission committed to establish a priority list of potential EDs not already covered by bans or restrictions in the CPR for their subsequent safety assessment. A priority list of 28 potential EDs in cosmetic products was consolidated in early 2019 based on input provided through a stakeholder consultation. The list was prioritised and 5 substances are currently under risk assessment by the SCCS. Due to the animal testing ban in the cosmetics sector, a specific issue arises concerning the identification of EDs (see **Annex 4**) and in particular the need to demonstrate the adverse effect for an ED, which currently requires *in vivo* testing. This raises a fundamental question about the interpretation of the IPCS/WHO definition, namely whether it is strictly necessary to observe adverse effects in animals, or whether the likelihood of adversity can be extrapolated from effects in non-animal methods. However, the difficulty to conclude on adverse effects due to the animal testing ban is not restricted to endocrine disruption but is also relevant to other endpoints (such as reproductive toxicity). Respondents to the stakeholder survey propose some possible solutions (see **Box 5.7**).

[64]COM(2018) 739

Box 5.7: Stakeholder views on effectiveness of the Cosmetic Products Regulation as regards EDs*,**

For cosmetic products, more respondents disagree than agree that the regulation with respect to EDs is protecting consumer health (31 agree, 48 disagree, and 23 neither agree nor disagree) or worker health (professional users) (24 agree, 49 disagree, and 28 neither agree nor disagree).

The proportion of each stakeholder group answering that the regulation is not effective is presented in the graph below:



- Some stakeholders (from public authorities, civil society organisations, academic/research institutions) mentioned that the SCCS is currently risk assessing EDs without taking all the uncertainties in relation to assessment of EDs into account (e.g. low dose effects, non-threshold issue, lack of knowledge, lack of adequate test methods), limiting the effectiveness of the regulation. Others (mainly from business associations and companies/business organisations) think that the fact that these substances can be subject to restriction or prohibition is a conservative approach for consumer safety.
- Some stakeholders (from civil society organisations) challenged the viewpoint that the data necessary for the SCCS to identify and assess possible endocrine disrupting effects are available. They report that five of the parabens that were banned in 2014 were so because industry chose not to support the substances (limited or no data were submitted by industry to the SCCS which therefore could not evaluate their risk to human health).
- Some stakeholders (from public authorities, trade unions and civil society organisations) consider that the effectiveness of the CPR for EDs is decreased by the lack of automatic risk management measures (i.e. automatic ban of CMRs).
- Many respondents (from public authorities, civil society organisations, academic/research institutions) acknowledge that the ban of animal testing without suitable alternatives with equivalent value to identify ED makes it difficult to properly identify hazard related to ED. However, use of animal data for ED identification is possible for substances also assessed under REACH.
- Some respondents (mainly from civil society organisations) stated that the integration of all available information (such as physicochemical properties, literature, *in vitro*, *in silico* data) in a weight of evidence can be used to exclude the potential toxicity of a cosmetic ingredient through the endocrine related effects
- Some stakeholders suggested to define a "potential endocrine activity" as a way to address the challenge raised by the ban of animal testing in the cosmetics sector.
- Some stakeholders from civil society organisations and public authorities suggest that in the context of the CPR, the precautionary principle should be applied for all substances suspected to be endocrine disruptors in the absence of animal data, in order to increase the effectiveness of the regulation.
- Some stakeholders mentioned that the lack of clear identification of the presence/absence of EDs in

*Answers are given as a percentage of respondents from each stakeholder group. For more details see Annex 2.

**Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Stakeholder views regarding the effectiveness of the Cosmetic Products Regulation reflect the differences in risk assessment and management where a specific risk approach is advocated by the SCCS compared with a hazard-based approach under the Biocidal Products and Plant Protection Products Regulations, or REACH. This aspect is further analysed in **Sections 4.3 and 4.4**.

Viewpoints of SMEs and citizens have also been gathered regarding the effectiveness of EU legislation.

In general, respondents to the SME survey consider the regulatory process to identify and control chemicals with endocrine disrupting properties to be effective in protecting people (40-45 agree, 9 disagree, 6-9 neither agree nor disagree) and wildlife (38 agree, 9 disagree, 11 neither agree nor disagree), in improving the functioning of the internal market, and enhancing competitiveness and innovation (30 agree, 10 disagree, 10 neither agree nor disagree).

With regard to the views from the citizens, the majority of respondents (54% to 74%) consider that EU laws do not protect them at all or only to a small extent from exposure to endocrine disruptors across all of the potential exposure sources listed in the survey. The four exposure sources where respondents consider that EU laws protect them the least are personal care products, food contact materials, clothing, and home or office furnishings, floors and paints. Moreover, when respondents were asked which other sources of exposure to endocrine disruptors were of particular concern, the most often mentioned were pesticides, toys, as well as effects due to combined exposure to EDs.

5.5 Communication

Current mechanisms are in place to inform consumers and recipients of articles in general about the presence of substances of very high concern (SVHCs) with ED properties (REACH Article 33). Furthermore, producers and importers of articles containing SVHCs must notify ECHA under certain conditions (e.g. if the SVHC is intended to be released from the product (REACH Article 7). Safety Data Sheets (REACH Annex II) are required to include information on whether a substance has been identified as an endocrine disruptor or whether such a substance is present in a mixture. An update of the provisions for Safety Data Sheets that includes further obligations to report on EDs was recently agreed in the Commission's REACH Committee and will apply from 1 January 2021. Similarly, under the Biocidal Products Regulation, safety data sheets for active substances and biocidal products shall be prepared and made available in accordance with REACH (Art 70). Moreover, articles treated with a biocidal product shall display a list of the active substances on the label (Art 58).

The respondents to the citizens' survey feel they lack information on the presence of EDs in products, or that the information is difficult to understand. Moreover, the respondents called for more and better information on EU activities regarding EDs. The European Commission has recently launched a web portal[65] providing a single point of access to all EC activities related to EDs.

[65]https://ec.europa.eu/info/policies/endocrine-disruptors_en

5.6 Monitoring data

Environmental and human monitoring data are useful for providing evidence on the effectiveness of a risk-reduction measure, as well as providing alerts to rising levels of substances of potential concern and in understanding actual human and environmental exposures including combined exposures to mixtures of substances. EU Member States monitor several EDs in surface waters under the WFD, either because Environmental Quality Standards already exist or to determine whether the substances pose a risk and should be regulated. The European Human Biomonitoring Initiative (HBM4EU[66]), is a 5-year project which was launched in 2017 to respond to the need for harmonised information at European level concerning human exposure to chemicals in order to support reliable risk assessment and management. HBM4EU is a joint effort of 30 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. The initiative is coordinating and advancing human biomonitoring in Europe. HBM4EU is generating evidence of the actual exposure of citizens to chemicals and the possible health effects in order to support policymaking. A number of EDs such as bisphenols, phthalates and flame retardants have been prioritised under the programme, and data are being made available via the Information Platform for Chemical Monitoring[67]. A similar initiative, albeit smaller in scale, for terrestrial and aquatic wildlife is the LIFE APEX project[68] which focuses on chemical monitoring in apex predators and their prey. A more regular screening of 'unknowns' (i.e. sampling and testing designed to detect unsuspected hazardous chemicals) in humans and the environment is also missing.

Such monitoring was done in the US after the ban on PBDEs at the beginning of 2004. Blood measurements in pregnant women (111) showed a decline in the PBDE concentrations between 2008/09 and 2011/12, but appeared to plateau between 2011/12 and 2014 (possibly due to persistence and bioaccumulation, from dust and food) (Parry 2018). Another study on 334 children, with repeated sample collection from birth to 9 years of age over a 15-year period, found a significant decrease of PBDEs between 1998 and 2013 (Cowell, 2019).

However, an aspect which is not adequately considered with regard to the regulation of EDs is combined exposure, although this issue is not unique to EDs. Provisions for the assessment of cumulative exposure/effects exist in the Maximum Residue Levels of Pesticides, the Biocidal Products and Plant Protection Products Regulations. Two retrospective cumulative risk assessments of dietary exposure to pesticide residues have been recently carried out by EFSA: one considering two chronic effects on the thyroid system and another looking at two acute effects on the nervous system (EFSA, 2020a, b). In both cases, it was concluded that cumulative exposure to pesticide residues did not exceed the threshold for regulatory consideration established by risk managers on the basis of individual substance assessments. Under REACH, four phthalates (DEHP, DBP, BBP and DIBP) have recently been further restricted based on combined exposure estimates, with diet indicated as a signficant source of exposure to DEHP. While EFSA concluded that there is no risk from the three of these phthalates that are authorised in Food Contact Materials, consequential risk management takes into account both combined exposure to the phthalates with the same mode of action and cumulative exposure from other sources. In water legislation, the application of effect-based methods (European Commission, 2014) is a promising development.

[66]https://www.hbm4eu.eu/about-hbm4eu/
[67]IPCHEM: https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html
[68]https://lifeapex.eu/

Considering the possible non-monotonic dose-response of EDs, it is difficult to predict combined effects from exposure to multiple EDs using standard additivity-based approaches (which assume monotonic behaviour) using information on individual chemicals, and the potential for combined effects adds to the overall uncertainties of a risk assessment (Bopp et al., 2019; Munn and Goumenou, 2013b).

Box 5.8: Stakeholder views on aggregate exposure and combined effects of endocrine disruptors*

- Amongst the respondents giving an opinion, about 60% (145-160 of 183 respondents) disagree that the current regulatory framework protects humans or wildlife from the risks associated with the aggregate exposure to one substance with endocrine disrupting properties from all exposure sources. Similar results were obtained regarding protection to combined exposure to different substances with endocrine disrupting properties. Similar comments were made by respondents to the citizens survey.
- Several stakeholders (mainly from public authorities) highlighted the fact that in order to take into account aggregate exposure and combined effects for EDs, a horizontal definition/identification would be needed. Cross-agency initiatives should be developed to deal with aggregate exposure and combined effects.
- Some stakeholders mentioned that aggregate exposure and combined effects are particularly relevant for EDs because of their no/low threshold.
- Some stakeholders mentioned that several pieces of legislation consider aggregate exposure to a certain extent (such as REACH), however it is never considered across regulations
- Some stakeholders suggested that the aggregate exposure assessment methodology under REACH could be further developed to cover all sectorial uses.
- Several respondents (from civil society organisations) suggested that where health concerns are raised in one sector, it should automatically trigger risk evaluation across legislative sectors to fully assess the impact of combined exposure.
- Some stakeholders stated that combined effects are relevant only if substances have the same adverse outcome pathway.

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Although only a few substances have been formally identified and controlled due to their endocrine disrupting activity, many substances with endocrine disrupting properties have already been identified due to other hazardous properties which may or may not be related to endocrine disruption (e.g. reproductive toxicity or persistent, bioaccumulative and toxic (PBT)/very persistent, very bioaccumulative (vPvB) properties). Consequently, regulatory measures to reduce exposures to some of these substances have already been taken and environmental monitoring and human biomonitoring have been used to follow the trends in exposure to such substances over time.

The case study on DEHP (**Annex 5B**, DEHP case study) illustrates through human biomonitoring data (levels of phthalate metabolites in the urine) how the successively increased restrictions on DEHP and other low molecular weight phthalates over time have been successful in reducing exposure of the human population in the EU. With respect to nonylphenol (**Annex 5C**, NP case study) there is evidence of substantial decreases in aquatic concentrations in EU wastewater, surface waters and biota in the last two decades. For instance, concentrations in fish (bream, muscle tissue) caught in Germany diminished by 67% between 1995 and 2001. However, reduced concentrations of NP in the

aquatic environment cannot be linked to changes in estrogenic activity of water bodies because this is mainly driven by more potent natural and synthetic estrogens.

One concern is that of 'regrettable substitution' where the restricted substance is replaced by another substance able to provide a comparable technological function but which might also be similarly hazardous, although the substance is not so well tested so these properties are not known at the time of the replacement. This could reduce the effectiveness of the measures. To reduce the possibilities of this occurring there is a move towards group assessments, where substances with similar molecular structure, with similar properties or with similar functions are assessed together. This requires either the generation of comparable data for each substance in the group or the use of 'read across' approaches. Indeed, regulatory action on phthalates did follow a group approach whereby a group of low molecular weight phthalates (DEHP, DBP, DIBP and BBP) were assessed together.

A number of Persistent Organic Pollutants (POPs) have endocrine disrupting properties and inclusion in the POPs Regulation defines requirements for reporting environmental release inventories (Article 6), environmental monitoring (Article 10) and production volumes (Article 12). Release should be minimised or eliminated from all sources (Article 6) including waste (Article 7). Waste containing or contaminated with POPs should be handled to ensure no release or recirculation in recycled/reused material flows. Recent reviews describing spatial and temporal trends of some of these substances in the environment provide an opportunity to evaluate the effectiveness of the regulatory measures in relation to exposure reductions. One example looking at levels of flame retardants (PBDEs) in human breast milk, cord blood and placentas found levels of PBDEs in North America were substantially higher than those in many regions of Europe, Asia, Oceania or Africa. One possible explanation given for this was the higher use of flame retardants in furniture in North America (Tang and Zhai, 2017).

5.7 Human health and environmental impact evidence and indicators

The trends in the main health and environmental impact parameters that are known, or suspected, to be associated with exposures to endocrine disrupting substances are important considerations when examining the effectiveness of EU chemicals policy. These trends include upward trends in the incidence rates of certain hormone-related cancers and reproductive diseases, decreasing fertility rates in females and males and decreasing sperm counts, and on the environmental side reduction in species diversity and eco-system health/resilience. However, caution needs to be exercised when using human health and environmental adverse effects as direct and reliable indicators of chemicals policy performance. This is because of the attribution challenge: many of the observed health and environmental adverse effects may derive from multiple causes (life-style, genetics, habitat destruction/degradation, etc.) and it is difficult to determine to what extent exposure to endocrine disrupting substances contributes to the observed adverse effects[69]. Statistical approaches exist and have been applied in (eco)epidemiology with the aim of separating the contribution of (mixtures of) chemicals from other contributing or confounding factors (Gennings et al., 2018; Slama et al., 2017). Differences in study design and low reproducibility of findings, however, remain a major challenge for use in a regulatory context.

Complicating things further is the fact that observable adverse effects in human health and the environment often do not materialise immediately after exposure. For example, the effects of early life exposure to endocrine disruptors may not materialise until many years later. Moreover, the

[69]SWD(2019) 199

involvement of the endocrine system in the control of processes such as embryonic development and puberty means that young people are at higher risk regarding endocrine disruption.

Indeed, developing organisms are extremely sensitive to perturbation by chemicals with hormone-like activity, and adverse effects may be most pronounced in the developing organism and occur at concentrations of the chemical that are far below levels that would be considered harmful in the adult. The continued maturation of key endocrine systems during childhood and adolescence, make these life periods also particularly sensitive to endocrine disruption, beyond foetal development (Schug et al., 2011). Many of the adverse effects on development in late pregnancy and early childhood are expressed as functional deficits in organs or systems, instead of overt malformations or growth retardation (Schug et al., 2011). Evidence from many studies support the hypothesis of a relationship between exposure to EDs and early maturation of secondary sexual characteristics (e.g. precocious puberty) (Lee et al., 2019; Lucaccioni et al., 2020) or predisposition to breast cancer (occurring later in life after exposure during puberty) (Lucaccioni et al., 2020). Exposure to EDs during early development have also been associated with non-reproductive effects such as obesity and related diseases (Petrakis et al., 2017). It is important when considering these vulnerable groups to ensure that the sensitive life stages are covered by the methods used to investigate toxicity and endocrine modes of action.

Box 5.9: Stakeholder views on protection of vulnerable groups*

When asked whether various groups of the population are sufficiently protected from endocrine disruptors, stakeholders replied that the level of protection is generally insufficient (ranging between 56% of respondents considering adults in general, to 66% for the unborn exposed during pregnancy). Similar views were shared by respondents to the citizens survey, with over 60% of respondents considering that EU laws offer a low level of protection for one or more life stages, with highest concern for adolescents (75%) and the lowest for pregnant women, foetuses and newborns (62% to 66%).

However, it should be noted that viewpoints differed among stakeholder groups, with only 14% to 30% of representatives from business associations and companies/business organisations stating that the various sub-groups within the population are insufficiently protected.

Stakeholders mentioned that:

- Clear definitions of children and vulnerable groups are missing in most EU chemical laws and there was a perception of a lack of consistency in treatment of vulnerable groups across EU legislation.
- The current data requirements and available test methods do not adequately cover vulnerable groups.

Suggestions were made to increase the protection of children by:

- Adding the possibility in the Toy Safety Directive to set new concentration limits for harmful substances in toys intended for children above 3 years.
- Applying the same risk management for EDs as for CMR substances, i.e. the automatic ban of EDs in toys.

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

A few attempts have been made to estimate the costs of endocrine-related diseases/disorders in humans and the proportion that might be attributable to exposure to endocrine disrupting substances.

Four studies published in 2015 (Bellanger et al., 2015; Hauser et al., 2015; Legler et al., 2015; Trasande et al., 2015) estimated the costs associated to the use of several endocrine disruptors for a subset of health effects to be hundreds of billion euros per year. Those studies subsequently received criticism from other scientists, claiming their aim would be to shape policy (Middelbeek and Veuger, 2015). Further criticism related to alleged methodological flaws and the hypothesis on which the studies were based (Bolt, 2017; Bond and Dietrich, 2017a, b; Middelbeek and Veuger, 2015). The main problem with such studies is the attribution challenge (i.e. that EDs are responsible for causing several diseases for a certain minimal percent factor of probability). The Commission reviewed the four studies when carrying out an impact assessment in the context of setting criteria for endocrine disruptors under the BPR and PPPR[70]. Other studies have tried to estimate costs linked to effects of endocrine disruptors on male reproductive health (Olsson and al., 2014).

Nevertheless, there are examples of non-approval of substances with endocrine disrupting properties resulting in significant benefits to human health and wildlife. For instance, the restriction of the use of the endocrine disruptor tributyltin (TBT, REACH Annex XVII, entry 20) as an antifoulant in marine paints has resulted in the recovery of mollusc populations in many ports and coastal areas in Europe[71].

5.8 Market surveillance

An aspect which could weaken the effectiveness of EU legislation is differences compared with laws in non-EU countries. The potential import of substances banned in the EU from non-EU countries raises the issue of EU market surveillance.

The respondents to the stakeholder survey mentioned that some substances banned in the EU but still allowed in other countries can still be found in products imported and marketed in the EU. Such statements are supported by an enforcement project conducted by ECHA's Forum, which is a network of national authorities responsible for the enforcement of REACH as well as the CLP, Biocidal Products and PIC Regulation. The project investigating compliance with the REACH restriction on phthalates in toys and child-care articles found that 19.7 % of the inspected toys and 3.6% of childcare articles contained one of the phthalates above the permitted level. Most products found to be non-compliant came from countries outside of the European Economic Area or were of unknown origin (**Annex 5B**, DEHP case study).

Moreover, these substances can be found in the environment (e.g. water bodies, including by transboundary flow). Regarding the residues of pesticides found in imported products, some stakeholders suggested to set the maximum residue levels (as a general principle) at the level of quantification for substances falling under the cut-off (exclusion) criteria.

Respondents to the stakeholders' survey consider that all sectors would benefit from an increased market surveillance. In particular, the fields of: feed and food (environmental contaminants, natural toxins, flavouring agents); water, including drinking water; industrial emissions; the General Product

[70]SWD(2016) 211
[71]Non-REACH FC CuBA Study, p. 204

Safety Directive (GPSD); products in contact with vulnerable groups, and online sales were listed by stakeholders as those where market surveillance authorities should focus their activities. However, this aspect is not specific to endocrine disruptors and it has been recognised that its implementation depends on the resources available in Member States[72].

5.9 Functioning of the internal market, competitiveness and innovation

Box 5.10: Stakeholder views on the efficient functioning of the internal market, and enhancement of competitiveness and innovation*

For Biocidal Products:

- The possibility of derogation according to Art 5(2) makes it difficult to assess the functioning of the internal market since derogation conditions may be met in some, but not all Member States.
- Some comments suggested that the complexity of the regulation does not facilitate innovation and the uncertainties/moving goalposts were negatively impacting innovation.

For Plant Protection Products:

- Some respondents mentioned that the costs incurred by the additional studies necessary to comply with the "data sufficiency" of the ED criteria inevitably compromise investment in research on new substances and innovative products.
- Substances withdrawn are not likely to be replaced easily. According to one respondent there are two reasons for this: first, the development of new active ingredients up to market introduction takes about 11 years and costs over €280 million. Secondly, the pipeline of products waiting for approval for the European market is also getting emptier due to rising Research and Development time and costs.

For REACH:

- The lack of coherent criteria to identify endocrine disruptors may impede the functioning of the internal market and could reduce competitiveness and innovation.
- The risk-based regulation of EDs under REACH provides a more nuanced approach accelerating the potential for innovations and more rapid substitution of 'old' substances with new better alternatives, while still ensuring protection of human health and the environment.
- The fact that non-EU countries can still use substances restricted/banned in EU is a competitive disadvantage for the European industry
- The additional requirements to understand mode of action and the link with the adverse effects mean additional resource and cost requirements compared to non-EU competitors which can undermine competitiveness of EU producers.
- The introduction of the REACH Regulation has resulted in a notable reduction in the number of chemicals used on the European market as manufacturers must balance registration costs against possible revenues, while also taking into account requirements on substance authorisation and restrictions.

[72]SWD(2019) 199

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

6 EFFICIENCY

- Inefficiencies in the assessment and management of endocrine disruptors can result from situations where a given substance falls under multiple pieces of legislation and thus within the mandate of multiple agencies and expert groups.
- Inefficiencies may also result from the absence of a common interpretation of certain regulatory provisions, such as "equivalent level of concern" under REACH.
- EU agencies are stepping up their efforts to coordinate assessment work. However, additional efficiencies could be obtained by developing further a horizontal approach to EDs, including an increased use of new approach methodologies and grouping approaches.
- The need to carry out testing and assessment for additional ED-related effects for a larger number of chemicals will inevitably lead to increased workload and costs. Some industry stakeholders are concerned that this will put economic operators in the EU at a competitive disadvantage, while some public authority stakeholders are concerned that this will result in delays to other areas of regulatory assessment work.
- The costs and benefits for human health and the environment resulting from regulatory requirements to assess and risk manage chemicals, including endocrine disruptors, are difficult to quantify and compare. There is a need to further develop and harmonise risk-benefit methodologies, such as socioeconomic analysis.
- It was difficult to perform conclusive economic assessments on the possible impacts of regulatory interventions on trade. This is partly because there is a lack of trade flow data at the level of specific chemicals and the commodities containing these chemicals, as well as data on the market share of a chemical in a given commodity. Two case studies illustrate the methodological challenges involved.

Q4. To what extent has EU legislation been efficient in identifying EDs and managing risks related to their exposure across different legal frameworks, ensuring the protection of human health and the environment?

There is evidence that a lack of coherence across regulatory sectors has had an impact on efficiency. This is particularly the case when multiple regulatory assessment and management procedures have focused on the same substances. Examples are given in the case studies (**Annex 5**).

In other cases, a lack of efficiency can be attributed to differences in the interpretation of terms in legislation. For example, under REACH, different views of Member States in ECHA's Member State Committee (MSC) on the interpretation of 'equivalent level of concern' (Art. 57(f)) has resulted in a number of cases[73] where the MSC could not reach unanimity on the identification of a substances as substance of very high concern, meaning that the decision had to be referred to the Commission via its REACH Committee (EC 2018a, part 1/7).

The targeted stakeholder survey revealed a range of opinions on the efficiency of current regulatory procedures for assessing and managing EDs (see **Box 6.1**). A slight majority of respondents (53%)

[73]As of May 2020, this applied to nine substances for different hazard endpoints, out of which seven related to EDs.

thought that the regulatory framework is not flexible enough to take into account new scientific information and methods in the assessment of endocrine disrupting properties. Some commented on the need to give more weight in the evaluation process to non-standard sources of information (e.g. non-guideline methods, scientific literature findings). Others argued that the substance-by-substance approach is hampering the assessment process, which would be more efficient if grouping approaches were more widely implemented. Several respondents referred to the time lag between hazard identification and risk management, as well as perceived inefficiencies resulting from the time taken to officially adopt test methods, to update standard information requirements, or to update guidance documents.

The costs and benefits for human health and the environment resulting from regulatory requirements to assess and risk manage chemicals, including endocrine disruptors, are difficult to quantify and compare. Regulatory decision making requires that besides impacts on human health and environment, economic and social impacts are assessed and considered. This is to provide regulation at minimum cost but with maximum benefits to citizens, businesses and workers, as outlined in the Commission Better Regulation guidelines[74]. Costs of regulatory testing are discussed in **Section 5.1**.

REACH incorporates these principles by requiring a socioeconomic analysis for applications for authorisations as well as for restriction proposals. Socioeconomic analysis is a tool to provide decision-makers with the necessary evidence and analysis on the socioeconomic impacts of different options for how to regulate chemicals. The REACH authorisation procedure requires applicants to submit a socio-economic analysis (ECHA, 2011). The ECHA Committee for Socio-economic Analysis (SEAC), which consists of experts nominated by Member States, scrutinises the socioeconomic analysis carried out in the authorisation and restriction processes. Stakeholder organisations participate in SEAC meetings as observers. Some stakeholders have claimed that the socioeconomic analysis for authorisations does not yield satisfying results and has methodological limitations, such as the choice of discounting rate (Chemsec, 2019)[75]. However, the socioeconomic analyses applied in regulatory processes use sensitivity analyses to assess the impact of different discount rates. These sensitivity analyses have shown that use of lower discount rates would not have resulted in a different policy choice for any of the REACH restrictions or authorisations reviewed.

In view of the challenge of conducting cost-benefit analyses, one recommendation voiced in the stakeholder survey was that the EU should establish a population-based monitoring scheme to assess the long-term benefits of regulatory action.

In the targeted stakeholder survey, 88% of respondents (53 out of 60) representing companies reported an increase in costs related to compliance with regulatory requirements for EDs (Targeted Stakeholder Survey). The additional costs were most often (21 out of 68 respondents) attributed to the provision of test data on endocrine disrupting properties. Costs related to substitution efforts were reported by 19 out of 65 respondents. According to some stakeholders, such efforts have been hampered by a lack of voluntary (non-regulatory) incentives, as well as lack of expertise, tools and guidance for avoiding regrettable substitutions (Ministère de la Transition Ecilogique et Solidaire,

[74]https://ec.europa.eu/info/law/law-making-process/planning-and-proposing-law/better-regulation-why-and-how_en

[75]The above-mentioned Chemsec report was presented at the 42nd meeting of SEAC. According to the minutes "*Different views by members were expressed, some technical inaccuracies were noted. It was observed the aim of the document was to spur a political discussion*.": https://echa.europa.eu/about-us/who-we-are/committee-for-socio-economic-analysis/meetings-of-the-seac/2019

2019). Other costs reported by stakeholders were related to the development of new testing methodologies and the regulatory reporting of ED properties. According to one industry stakeholder, the lack of a globally consistent approach to assessment can lead to additional costs exceeding 10%. In general, however, most respondents did not specify the origin or magnitude of additional costs.

In the SME survey, an increase in total operating costs was reported by 25 out of 70 respondents, whereas 12 respondents reported no effect on operating costs. For the remaining 33 respondents, this question was either not applicable (30) or no answer was provided (3). Costs were attributed to: a) the replacement of substances (21 respondents); b) the preparation of registration or authorisation dossiers (14 respondents); c) the provision of test data (14 respondents); and d) the development of new testing methodologies (13 respondents).

Stakeholder opinions on whether the additional costs are justified varied. Governmental and civil society organisations typically considered the costs justified, in the overall interest of public health and environmental protection. Conversely, industry organisations and associations expressed concerns that the hazard-based management of chemicals results in a competitive disadvantage for EU operators, which is unjustified in exposure scenarios where the substance poses a low risk.

In the SME survey, the additional costs were considered justified and proportionate for the benefits obtained by 23 respondents, not at all justified or proportionate by 8 respondents, while 38 did not know.

Overall, stakeholders who expressed an opinion considered the impacts of regulatory provisions for EDs on their sectors to be negative (Targeted Stakeholder Survey). Among the regulators, 80% of respondents (51 out of 64) reported that assessing substances for endocrine disrupting properties resulted in a delay in their assessment work in other areas of human health or environmental protection.

In the SME survey, impact of the provisions for endocrine disruptors on innovation, productivity, profitability and international trade within their sectors was perceived as negative by a minority of respondents (between 1 to 6) while another minority (7 to 10 respondents) considered the impact as positive.

In the public survey, 26% of the 474 respondents considered that the costs of EU laws on endocrine disruptors are fully proportionate for the benefits accrued, 18% to a moderate extent, 15% to a small extent only, and 11% not at all. Thirty percent replied that they do not know. In addition, there was a general perception that slightly higher costs are borne by the agricultural and industrial sectors compared with costs to citizens or ethical costs.

In principle, differences in regulatory assessment and management procedures between the EU and non-EU countries could have (positive or negative) impacts on trade. However, it is very difficult to predict such impacts. Retrospective assessments using economic methodology can analyse trade flows before and after regulatory interventions, but the results must be interpreted with caution, as illustrated by two case studies carried out by the JRC (see **Box 6.2** and Canzian et al., 2020).

Box 6.1: Stakeholder views related to efficiency*

- The categorisation of EDs including a suspected category would increase efficiencies in assessment and risk management and would also stimulate substitution efforts.
- Concerns from industry that a hazard-based approach to risk management could result in substances posing low risk being removed unnecessarily from the market as well as regrettable substitutions.
- Concerns from an industry association that lack of coherence between the BPR and REACH regarding co-formulants is placing a disproportionate cost burden on industry and authorities.
- Under REACH, the need to prove EDs are substances that give rise to an equivalent level of concern as CMRs to identify them as Substances of Very High Concern (SVHC) is inefficient.
- The perception that the listing, at different points in time, of multiple properties of concern (e.g. reproductive effects and endocrine disruption) for the same substance (e.g. DEHP) on the REACH Candidate List is inefficient.
- Concerns from civil society organisations that lack of coherence across regulatory sectors results in animal tests being performed unnecessarily, with slight variations in the endpoints included.
- Differences in how endocrine disruptors are regulated in the EU compared with non-EU countries can result in a competitive disadvantage. An industry association gave the example of isophorone, with ECHA and US EPA having different data requirements.
- A non-EU business association considered that EU regulations are more cost-intensive than other regions.
- Concerns from governmental and civil society organisations about the time taken for regulatory action from ED identification to risk management, with examples from BPR, PPR and REACH.
- Concerns from industry that financial losses could result from "stigmatisation" of substances with endocrine activity (Mode of Action).
- Concerns from an industry association that restricting the number of biocidal active substances according to hazard-based criteria could have negative effects on sustainability goals, such as increased health burden due to insufficient control of infectious diseases, and increased food waste due to decreased variety of preservatives.
- An industry and a civil society organisation expressed the need for a broad approach to sustainability assessment, including the need to improve the circular economy.
- For research to be efficient and cost-effective, cooperation and co-ordination is required among the key stakeholders, within the EU and globally, to pool knowledge and avoid duplication of efforts.

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Box 6.2: Trade impact case studies

As a contribution to the Fitness Check, the JRC carried out two case studies aimed at exploring the feasibility of economic analysis to identify associations between the implementation of risk management measures on selected chemicals and trade flows, both within the EU and between the EU and non-EU countries. The first case study considered four low molecular weight (LMW) phthalates commonly used as plasticisers (DEHP, DBP, BBP and DIBP), which have been *inter alia* subjected to a series of restrictions since 1999. The second case study focused on 3-Benzylidene Camphor (3-BC), a UV filter used in sunscreen products, which has been subject to a ban under the Cosmetic Products Regulation since 2015 and was identified as SVHC under REACH in 2018.

The approach applied the "gravity model" which is a well-established methodology in economics. A particular challenge, however, was due to the level of aggregation of the input trade data (in the UN Comtrade database). Since the trade flow data relate to baskets of commodities, rather than the specific chemicals of interest, it was necessary to choose a proxy for the chemicals of interest (namely plasticisers for LMW phthalates, and cosmetic/toilet preparations for 3-BC).

The results showed a downward trend in the trade flows of plasticisers which started before the 1999 intervention, making it difficult to judge whether the intervention contributed to this trend. Conversely, the results showed increased trade flows of cosmetic/toilet preparations following the 2015 intervention on 3-BC. While this is consistent with the conclusion that the ban of the UV filter positively impacted on the trade cosmetic/toilet preparations, uncertainties relate to the extent to which 3-BC was present in those products, as well as confounding socioeconomic factors.

These case studies illustrate some of the challenges in using economic analysis to identify the trade impacts of regulatory interventions. They also point to the need for higher resolution trade data, closer to the chemical and commodity of interest, as well as information on the market share of the chemical of interest in various commodities or baskets of commodities. However, obtaining such data could be problematic as they are typically commercially sensitive.

The two case studies, including methodological details of the economic analysis and associated uncertainties, are further described in (Canzian et al., 2020).

7 RELEVANCE

- Societal concerns about chemicals in general are high. Concerns on EDs have received societal attention, especially in certain MS (France, Nordic countries), and political support from EU-level institutions including the European Parliament, the EU Committee of the Regions, as well as the Commission. Citizens engaged in the topic lack trust in the ability of EU legislation to achieve its objectives of human health and environmental protection. Economic stakeholders are concerned that the lack of trust in EU regulatory processes undermines science-based decision making.
- A sustained global increase in chemical manufacturing is expected, primarily in Asia. Imports of chemicals and products into the EU are increasing. Assessing and ensuring the safe use of hazardous chemicals including EDs in global material streams through subsequent life cycles is essential to achieve the benefits of a more circular economy.
- The next generation of EU funded research strives to address realistic mixture (combined) exposure scenarios and to embrace the multi-factorial nature of certain indicators of concern, such as the increase in certain non-communicable diseases and the decline in biodiversity. To improve the chance of establishing (or ruling out) causal links, exposure to environmental mixtures of EDs need to be assessed, ideally in conjunction with other stress factors. Building on the currently available methods developed in key research areas (e.g. use and interpretation of human biomonitoring data, effect-based methods in water quality assessments) the Commission is exploring new mechanisms to use emerging knowledge in the policy cycle (e.g. the candidate European Partnership for Chemicals Risk Assessment).

Q5. To what extent do the EU legal provisions on and approaches to EDs take into account health and environmental concerns, and social and economic consequences that are relevant to citizens and stakeholders?

7.1 Relevance to citizens and stakeholders

The overall objectives of human health and environmental protection enshrined in EU chemical legislation remains relevant to EU citizens. According to a Eurobarometer survey conducted in December 2019[76], nine in ten Europeans are worried about the impact of chemicals present in everyday products on the environment; a slightly smaller proportion (85%) is worried about impacts on their health (the survey question concerned the overall impact and did not query ED effects specifically). Societal concerns on EDs have received attention and political support in the recent resolution by the European Parliament[77] and the opinion of the European Economic and Social Committee[78] and the European Committee of the Regions[79].

[76]Eurobarometer 2020: https://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/survey/getSurveydetail/instruments/special/surveyky/2257
[77]European Parliament resolution 2019/2683(RSP)
[78]European Economic and Social Committee NAT/754-EESC-2018-05760

Perspectives on the importance of regulating EDs are polarised between stakeholders representing citizens and civil society organisations and those representing business organisations (see **Box 7.1**). The discrepancy between the views of citizens engaged on the topic and business organisations appear to reflect different opinions about how to apply the precautionary principle and how to deal with the uncertainties in quantifying risks associated with exposure to EDs (such as the issue of whether EDs have a threshold effect or not). All parties, however, agree on the need to enhance the exchange on the latest science (e.g. ED stakeholders forum) and the collaboration among authorities and between authorities and stakeholders.

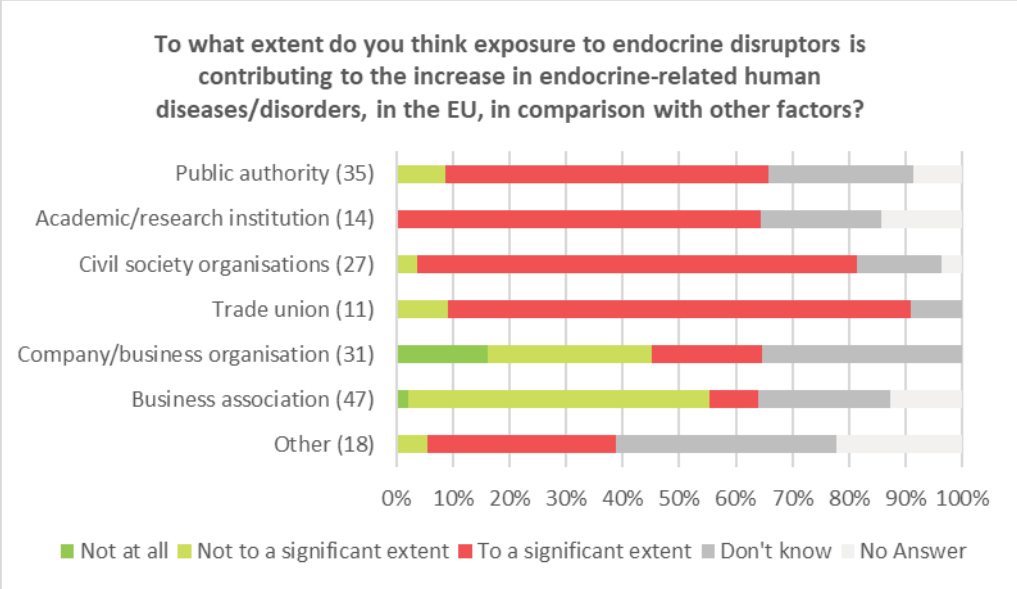
The Commission and the European Agencies regularly involve citizens and other stakeholders through public consultations at different steps of the policy cycle from new legislative proposals, to scientific evaluation and decisions, including EFSA opinions, biocide evaluations, REACH SVHC proposals, restriction regulations, and authorisations decisions.

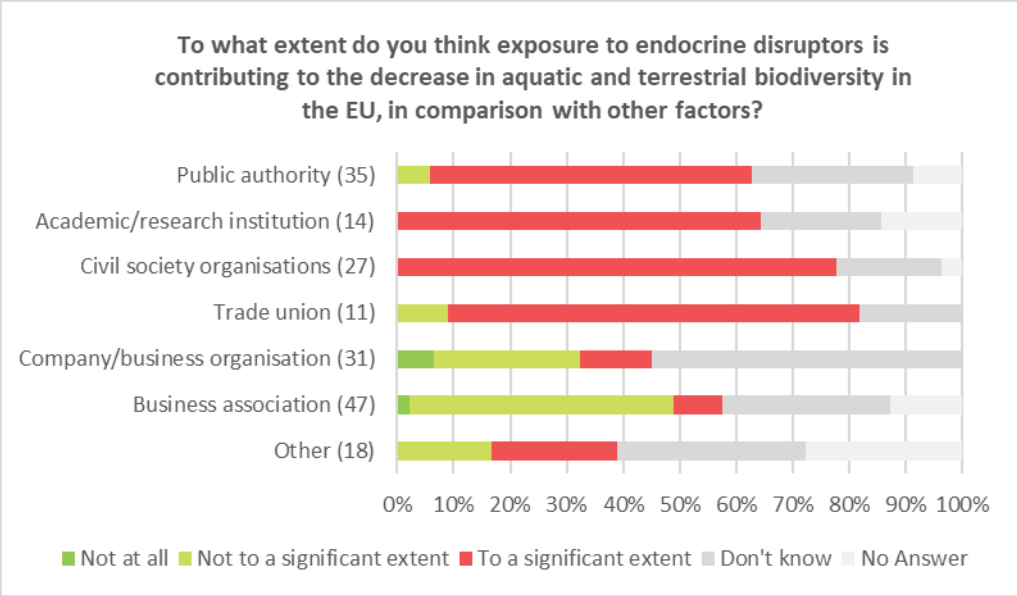
Box 7.1: Stakeholder views on the relevance of EU legislation on endocrine disruptors*

Among respondents to the public consultation, 61% think they are less protected from EDs compared to other toxic chemicals. Despite the EU laws' ambition to achieve a high level of protection including for all vulnerable groups, the percentage of respondents who think that a high or a moderate level of protection is achieved range between 15% (for adolescents) to 30% (for new-borns up the age of 3) with relatively small differences between the general population (adults in general, 20%) and other sub-populations (elderly, children in puberty, people at work, people with illness, unborn through exposure during pregnancy and pregnant women). Even lower is the percentage of respondents who think that EU legislation achieves a high level of protection for wildlife, with small differences among categories of wildlife, ranging between 6% (invertebrates such as snails, shrimps and worms) and 14% (mammals). Seventy-five percent of respondents to the public survey believe that EDs contribute to a large extent to some human diseases/health conditions such as infertility, cancer or obesity (and 18% to a moderate extent).

The perspectives of different stakeholders about the relative importance of EDs as a stress factor contributing to human health condition/disease and to the observed decrease in biodiversity is illustrated in the figures below. In both cases, the vast majority of public authorities, academic/research institutions, civil society organisations and trade unions think that EDs contribute to a significant extent, in comparison with other factors. The majority of companies/business organisations and business associations think that EDs do not make a relatively large contribution. The different opinions by companies and business associations compared to the other stakeholder groups may be explained by their positive opinion about the effectiveness of legislation or by different interpretations of the question (i.e. company or sector specific).

[79]European Committee of the Regions 2019/C 404/07





The scientific debate has polarised perspectives from different stakeholder groups, with all sides arguing that science supports their opinions. On one side, respondents from civil society organisations and most scientific stakeholders state that legislative developments do not match the "*unanimous call from the scientific community"*. On the other side economic stakeholders (business organisations, EU trading partners) are concerned that "*legislation begins to be based on societal concern rather than on science*".

Some citizens, civil society organisations, trade unions and academics/research institutions claimed that there is limited information available on ED in products, while human and environmental exposure to EDs is ubiquitous. Some respondents from these stakeholder groups expressed concerns about their potential association with the increase of non-communicable disease and the related high health costs, as reported for example by the Endocrine Society (Gore et al., 2015). According to some

NGOs, the current situation makes it "*almost impossible for consumers to avoid these harmful chemicals*". Most civil society organisations are concerned that the current legislative framework provides an uneven level of protection across regulated sectors and therefore fails to achieve a high level of protection by minimisation of exposure, as laid down in the EU 1999 strategy. Almost 90% of respondents to the public consultation think that the EU needs to step up its efforts to reduce human exposure; the percentage is only slightly lower (86%) for environmental exposure.

Respondents to the stakeholders consultation from business organisations expressed concern about the trade-offs of hazard-based risk management, including economic impacts (e.g. disproportionate increase in production costs, such as due to regulatory-induced substitution), societal impacts (e.g. reduced shelf life of blood bags without DEHP), environmental impacts (e.g. increased waste due to reduced product lifetime without effective preservation, regrettable substitution). They are also concerned about the lack of citizens' trust in EU regulatory decision-making, the gaps in the market surveillance activities especially at the EU border, the consequences of *"stigmatising" substances that are undergoing risk assessment*, and the difficulty in operating in a framework with a "*continuously moving goal target*".

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Q6. To what extent do the EU legal provisions on and approaches to EDs take into account evolving needs (e.g. transition to circular economy) and the latest scientific findings (e.g. developments in chemical mixtures and grouping assessments, biomonitoring, effect based methods, etc.)?

7.2 Ability to adapt to the evolving societal and economic context

Societal concerns on chemicals in general and on EDs reflect the high expectations of Europeans for ambitious health and environmental policies. The EU is a global leader in environmental and consumer protection policy. The political agenda set by the Von der Leyen Commission aims at firmly setting the EU on a new path of sustainability, inclusive growth and healthy lifestyles. The action plan outlined in the European Green Deal[80] comes with significant economic and societal transformations. Many core elements of the Green Deal, including the zero-pollution ambition for a toxic-free environment, the farm to fork strategy, clean and circular economy[81], and the protection of ecosystems and biodiversity are interlinked with the chemical policy agenda in general and with EDs in particular. Another societal trend relevant to ED management is the decline in population growth due to low fertility rates across much of the EU[82]. In parallel to these trends, changes in global patterns of production and consumption have accelerated in recent years. Global chemical production has grown in recent years and is expected to almost double from 2017 to 2030 (UNEP, 2019). Projected growth will be highest in Asia, with China estimated to account for almost 50 percent of global sales by 2030. The imports of consumer goods and other articles into the EU have tripled

[80]COM(2019) 640
[81]EU Circular Economy Action Plan. https://ec.europa.eu/environment/circular-economy/index_en.htm
[82]https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Fertility_statistics

between 2000 and 2015 creating additional challenges for managing the risks associated with the presence of hazardous substances in articles[83].

Many functional chemicals that have raised concerns for their negative impact on the circular economy, including plasticisers (e.g. DEHP and other low molecular weight phthalates), flame retardants (e.g. polybrominated diphenyl ethers), water repellents (e.g. perfluoroalkyl substances), preservatives and other biocides, have been assessed for their endocrine disrupting properties (Milieu Ltd et al., 2017) (sub-study b). The intentions to strengthen the single market for secondary raw materials and in general the inclusion of circular economy considerations into chemicals risk management will require a transformation of the life cycle stages and timescales considered in risk assessment[83]. Exposure data in REACH dossiers fail in many cases to cover all relevant exposure situations along the supply chain[84]. Exposure information on substances in waste and in recycled material streams is even more limited. Both information gaps are evidently at odds with the circular economy ambitions: it is difficult to conclude on long-term safety and sustainability of substances of concern (e.g. SVHC) without the ability to track their mass flows in material cycles and in the environment.

Hence, efforts to control hazardous chemicals (e.g. SVHC) in materials and products and recycled material streams need to step up to achieve the objectives of the circular economy[85]. The scale of the problem is significant and regards both legacy chemicals present in recycled material streams (Milieu Ltd et al., 2017) (sub-study b) and chemicals produced and used today, specifically those authorised for specific uses, if they are not managed in closed and controlled material cycles. The problem is also likely to increase, considering that the amount of recycled materials used in the EU needs to increase substantially from the current 12%[Error! Bookmark not defined.]. The EU Circular Economy Action Plan further stresses the need for action to ensure that the EU does not export its waste challenges to third countries and to facilitate preparing for re-use and recycling of waste in the EU[86]. SVHCs in recycled materials have been regulated through REACH authorisation and restrictions, as was the case for authorised uses of recycled PVC containing DEHP and for the exemption of recycled textiles from the restriction of nonylphenol ethoxylates (**Annex 5B and 5C**, DEHP and NP case studies). In other cases, however, and especially for heterogeneous waste, information on the presence of substances of concern is lost or not available to waste operators by the time products become waste. The establishment of the SCIP database on "Substances of Concern In articles as such or in complex objects (Products)" under the waste framework directive is an important first milestone in this direction as it intends to help waste operators in waste separation[87].

7.3 Ability to adapt to scientific progress

Recent policy evaluations concluded that the framework has generally been able to adapt to the evolving scientific progress[88] [89]. The question is particularly important in the context of EDs, considering the increasing resources dedicated to scientific research on EDs over the last two

[83]SWD(2019) 199
[84]SWD(2018) 58
[85]SWD(2019) 199
[86]EU Circular Economy Action Plan. https://ec.europa.eu/environment/circular-economy/index_en.htm
[87]Directive (EU)2018/851 amending Directive 2008/98/EC on waste
[88]SWD(2018) 58
[89]SWD(2019) 199

decades[90]. All three case studies (**Annex 5**) provide examples of recent regulatory assessments including reviews of all available evidence in the open scientific literature. Academic studies, however, often miss to include critical parameters as described in standard guidelines and are consequently given a lower consideration in weight of evidence assessments (e.g. **Annex 5A**, 3-BC case study).

The consideration of new scientific evidence is usually more problematic for academic studies on human biomonitoring, (eco)epidemiological studies, studies addressing exposure to mixtures, biomarkers of effects, or effect-based methods in ecotoxicology. Current standard test and assessment methods typically on single substance assessments which do not fully exploit the value of these types of studies[91].

Long-term low dose exposure to ED mixtures is a well-recognised challenge in both regulatory toxicology and ecotoxicology[92]. The scope of mixture assessment and management within the existing framework is mostly limited to intentional mixtures within single policy domains, even though the potential for aggregate and combined (mixture) exposures across policy domains is well known (**Figure 3.1**).

Unintentional mixtures are considered in some legislation, including for pesticide residues (MRLs) plant protection products and biocidal products. However, practical examples are mostly limited to the legislation on MRLs, where methodology is so far established for two cumulative assessment groups (effects on nervous system and on thyroid) and some recent examples of grouping assessments and management processes (e.g. phthalates regulated under REACH and FCMs, PFAS, etc.) (**Annex 5B**, DEHP case study). An increasing number of academic studies explore how to incorporate assessments of complex and realistic ED mixture exposure scenarios in regulatory assessments (Bopp et al., 2019; Ganzleben et al., 2017; Gennings et al., 2018).

Translating new scientific findings about the effects of combined exposure to EDs into regulatory action conflicts with a framework designed to assess one substance at a time and to implement risk management measures across multiple regulated sectors. Addressing this challenge might require a complete rethink of the way in which risk assessment and management of chemicals mixtures is currently performed (Bopp et al., 2019). One promising advancement in the monitoring field is the development of effect-based methods, which might be used in combination with effect-directed analysis in water quality assessment under the WFD (Brack et al., 2017; Hamers et al., 2018). The oestrogen receptor transactivation assay has been recommended by the JRC as a suitable *in vitro* method to determine estrogenic activity of water samples (European Commission, 2014). Other *in vitro* assays to determine (anti)androgenic and thyroid hormone disruption have been also proposed for both environmental (Hamers et al., 2018) and human health applications (Hamers et al., 2020). The method opens potential synergies between the water and chemicals legislation in the assessment of environmental effects of EDs. Similarly, in human biomonitoring some integrative biomarkers of effect have been proposed as an early marker of endocrine-mediated health effects (Baken et al., 2019).

[90]RTD Factsheet: EU Research on Endocrine Disruptors: https://ec.europa.eu/info/files/eu-research-endocrine-disruptors-factsheet_en
[91]COM(2019) 199
[92]COM(1999) 706

A major scientific challenge in estimating the impact of chemical stress is the multi-factorial nature of negative trends of concern such as the increase of non-communicable diseases (Slama et al., 2017) and the decline in biodiversity (Posthuma et al., 2016). To disentangle the contribution of multiple stress factors, chemical mixture exposure must be assessed in combination with other factors, referred to as confounding factors in (eco)epidemiological research. Statistical methods to account for confounding factors have been developed and applied in recent (eco)epidemiological research addressing EDs exposure (Demeneix and Slama, 2019; Gennings et al., 2018; Slama et al., 2017).

The next generation of EU funded research is taking a more holistic consideration of environmental stressors on disease burdens. Examples include the Health Environment Research Agenda for Europe (HERA[93]) and the candidate European Partnership for Chemicals Risk Assessment[94]. The Commission is exploring new mechanisms to distil emerging streams of scientific evidence into the policy cycle (e.g. HBM4EU[95] and the candidate European Partnership for Chemicals Risk Assessment). The issue goes beyond the well-known obstacles encountered in the development and validation of novel test methods.

Box 7.2. Stakeholder views on the ability of the framework to adapt to scientific progress*

Stakeholders are split between those who think the framework is able to consider the latest scientific developments (46%) and those who think it is not (54%).

Several business organisations and public authorities consider that processes embedded in the policy cycle allow for updates of regulations and guidance to account for new scientific knowledge and methods. Many stakeholders, however, complain about the lengthy process of validation and regulatory uptake of new test methods developed under the OECD programme. Several stakeholders suggest that building on the ECHA and EFSA experience, enhanced collaboration between agencies and stakeholders can spearhead uptake of new scientific methods. According to some stakeholders, the implementation of the criteria adopted in 2018 and the related joint EFSA and ECHA guidance is currently too rigid and does not encourage the uptake of new information and the evaluation of its relevance. Some stakeholders call for revisions of the guidance to adapt it for specific considerations (e.g. metal characteristics) and in general to ensure additional data requirements bring added value to the assessment and do not result in unnecessary animal testing.

Stakeholders widely recognise that provisions exist in regulatory assessments that require in principle the consideration of all available scientific evidence. The extent to which such provisions are applied in practice is debated. Regulators place higher confidence on standard, validated test methods because of easier interpretation and reproducibility of results. According to several civil society organisations, scientific stakeholders and some public authorities, regulators are reluctant to consider information from non-standard methods. One respondent pointed out that *"with the current gaps in the data requirements, dismissing such information from the academic literature risks to misclassify a dangerous substance as a non-ED"*.

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

[93] https://www.heraresearcheu.eu/key-objectives
[94] https://ec.europa.eu/info/files/european-partnership-chemicals-risk-assessment_en
[95] https://www.hbm4eu.eu/

8 EU ADDED VALUE

- Regulating EDs at EU level contributes to ensuring an equal level of protection across the EU Member States regarding human and environmental health.
- Furthermore, better scientific consistency in the assessments and more efficiency can be achieved by joining forces in testing capacities, experience and knowledge across the Member States.
- There have been cases of unilateral measures at Member State level for a few ED substances, such as Bisphenol A and DEHP.
- Stakeholders expressed a strong wish to avoid unilateral measures where possible, but also agreed that if individual Member State level decisions are taken, e.g. to avoid delays in finding agreement at EU level, such decisions should be followed up at EU level to come to a harmonised approach.
- EU-level follow up to unilateral decisions should happen in a timely manner, to minimise disruption to the single market and to ensure an equal level of protection throughout the Member States.

Q7. What is the added value of regulating EDs at EU rather than Member State level?

Regulating EDs at EU rather than Member State level is adding value in various ways. The Commission evaluations, carried out recently across various pieces of legislation for different sectors (e.g. REACH, non-REACH chemical legislation, plant protection products, etc.), have all concluded that a unique chemicals legislation centralised at the EU level has in general proven largely successful in terms of the protection of human health and the environment as well as the functioning of the internal market[96].

8.1 Joining forces and efficient use of resources

The assessment of EDs requires a high level of scientific expertise and experience. The sharing and pooling of knowledge and resources and the application of common rules and standards across the EU has resulted in significant positive economic, health and environmental impacts that would not have been possible to achieve on the basis of legislation at the Member State level alone, as concluded for chemicals in general in the Fitness Check of non-REACH Chemicals legislation[97]. Thus, regulating the risk assessment and management of EDs at EU level also increases efficiency. It helps to avoid duplication of efforts at Member State level and improve the state of knowledge, quality and availability of data needed for risk management decision making. It also provides a clearer overarching framework for companies operating across different Member States, so that they do not need to adapt to multiple potentially diverging national rules. An EU level approach offers advantages

[96]SWD(2019) 199
[97]SWD(2019) 199

in terms of effectiveness by avoiding a fragmented approach in a market where firms are increasingly cross-border in their outlook[98]. The costs of achieving the objectives to protect human health and the environment are considered to be lower than in a system where each Member State conducts the risk assessments on its own (Ecorys, 2018). A uniform EU approach also strengthens the EU's position in chemicals regulation worldwide, which also has benefits for the EU chemical industry.

Reaching a consensus at EU level in regulating EDs also plays a role in preventing unfair competition between Member States and leads to an equal level of protection for citizens and the environment throughout all Member States. Since the adaptation of sector-specific legislation to new scientific evidence regarding risks of endocrine disruptors requires a certain amount of time, measures for protecting health and the environment can be taken by more general provisions in EU legislation, namely under the General Product Safety Directive in the case of products, and under the General Food Law in the cases of food and feed.

8.2 Preserving the functioning of the single market

There have been cases of unilateral measures at Member State level for a few ED substances. Bisphenol A is the most relevant example; its use has been banned in specific consumer products aimed at babies or young children in France, Denmark, Austria, Belgium and Sweden – and for all age groups in France. Some Member States, such as Italy and Denmark, have also taken 'soft' measures at the national level, such as providing advice to the public, creating incentives for industry for the development of safer alternatives or the promotion of voluntary agreements (Brunel University London and DTU Food National Food Institute Denmark, 2016; UNEP IPCP, 2017). In 2011, Denmark proposed to restrict the use of four phthalates (DEHP, BBP, DBP, DIBP) in consumer articles in the EU. However, ECHA's Risk Assessment Committee concluded that the "available data does not indicate that there is currently a risk from combined exposure to the four phthalates" and did not support the restriction[99]. In the following, Denmark subsequently planned to ban the four phthalates unilaterally. However, it dropped the plan in 2015 since it was not in line with the rules set by REACH (ECPI, 2014). The safeguard clause of REACH stipulates that a Member State can take unilateral measures if it has grounds for believing that urgent action is needed to protect human health or the environment. This triggers a decision taken via Comitology procedure on whether the unilateral measure should be revoked or authorised for a certain time period. This decision has to be taken within 60 days. If the measure is a restriction and if it is authorised, the Member States which took the unilateral decision should initiate the procedure for an EU-wide restriction under REACH. Similarly, unilateral action by MSs that contradict EU rules must be followed up at EU level for FCMs, for example in the case of bisphenol A.

Moreover, after considering results from FCMs inspection and control project, on September 2019, the Danish Ministry of Environment and Food announced that the Danish government will ban the use of any per- and polyfluoroalkyl substances (PFAS) in paper and cardboard used in food contact

[98] SWD(2018) 58, part 1/7

[99] https://newsletter.echa.europa.eu/home/-/newsletter/entry/2_14_denmark-advises-on-how-to-limit-phthalates-of-concern

materials by July 2020[100] due to inter alia the concerns on the suspected endocrine disrupting properties for human health and the environment and evidence of bioaccumulation. The European Commission published a recommendation on a coordinated control plan to determine the prevalence of certain substances migrating from or present in FCMs—including the fluorinated compounds per- and polyfluoroalkyl substances (PFAS)—into food, in May 2019[101]. Notably, PFOA has been restricted for use in the production and placing on the market of articles, including FCMs from July 4, 2020 under REACH. Regulatory action on multiple other PFAS has been launched or already been concluded (REACH Regulation, Regulation (EU) 2019/1021).

More recently, France has also launched, based on its Second National Strategy on Endocrine Disruptors key measures (Ministère de la Transition Ecologique et Solidaire et Ministère des Solidarités et de la Santé", 2019) (Annex 1), a project to draw up a list of chemicals that may present ED-properties to better manage risks depending on the degree of proof and the level of uncertainties (to be ready by 2021). This is intended to inform recommendations for appropriate management (for example, by considering a recognition in European regulation, by reducing use as a precaution, or by pursuing more in-depth assessment) of suspected or presumed EDs. This includes also a recommendation to inform citizens about the chemicals, notably endocrine disruptors, to be found in everyday consumer products.

Unilateral measures are triggered by provisions (safeguard clauses) that are included on purpose in legislation to allow Member States to act first. There is insufficient evidence to estimate the overall impact of the unilateral measures described above. However, such unilateral measures should be followed up at EU-level as fast as possible to minimise any disruptive effects on the single market.

The stakeholders answering the survey expressed a strong wish to avoid unilateral measures where possible. If they are taken by individual Member States as a precautionary measure, e.g. to avoid delays in finding agreement at EU level, such measures should be followed up at EU level. Even soft measures such as publishing advice on the use of products containing certain chemicals can have a strong influence on consumer behaviour. However, a Eurobarometer survey (Nr. 456) on Chemical Safety of 2019[102] showed that EU citizens consider products manufactured in the EU to contain safer chemicals than those imported from outside the EU. This indicates a higher level of confidence in the EU regulatory framework for manufactured products compared to regulatory regimes abroad[103] (EC 2019).

Also in the public consultation related with this Fitness Check, 6 out of 474 respondents[104] provided free text comments related to the EU added value. Even if they are mostly in favour of regulating EDs at EU level in a uniform way across Member States, they raised two issues. Firstly, they state that there is no full implementation of EU rules in each Member State and putting EU legislation into practice need to be accelerated. Secondly, citizens seem to be worried about imported products from non-EU countries with less stringent rules and ask for more controls and enforcement to ensure imported products comply with EU requirements.

[100] https://mfvm.dk/nyheder/nyhed/nyhed/foedevareministeren-er-klar-til-at-forbyde-fluorstoffer/
[101] Recommendation on Coordinated Control Plan for Certain Substances Migrating from FCMs. (EU) 2019/794
[102] http://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/resultdoc/download/documentky/78786
[103] SWD(2019) 199
[104] Four comments were from individual citizens, two from NGOs

8.3 Legislative measures alignment between Europe and global regimen

The EU chemicals legislation has become a reference point for international standards in several areas, which helps to reduce potential trade frictions as well as address transboundary chemical related issues. REACH for example has influenced legislation in a few third countries (e.g. South Korea), although significant differences exist and there is room to further exploit the potential of REACH to serve as a global model for chemicals legislation[105].

European companies also benefit from the perceived quality of EU products in non-EU country markets, which has brought important advantages in terms of international trade. The EU chemicals legislation has also helped to decrease the barriers to, and costs, of intra-EU trade by limiting the application of multiple and potentially diverging national rules with limited territorial coverage and existing only in the applicable national language(s)[106].

However, there are also concrete examples of problems at international level, e.g. in the area of Plant Protection Products and Maximum Residue Levels (MRLs). Non-EU countries often remind the Commission that non-approval decisions and setting of MRLs need to respect WTO principles. The issue of cut-off criteria, including the criteria to identify endocrine disruptors, has been the subject of acrimonious discussion in the WTO-TBT and WTO-SPS Committees since 2013. Between 2015 and 2017, in the WTO Committees, non-EU countries raised specific trade concerns on pesticides 208 times against the EU. This should be compared with two specific trade concerns on pesticides raised by the EU against other countries. Although decisions under the MRL Regulation are based on assessments of risk only, the effects of the cut-off criteria applied under the PPP Regulation with subsequent lowering of MRLs, is perceived by third countries to result in inconsistency between the EU and WTO. However, the extent of this inconsistency is currently unproven as so far no active substance has not been approved (or approval not renewed) based solely on the cut-off criteria[107].

[105]SWD(2018) 58
[106]SWD(2018) 58, part 5
[107]SWD(2020) 87

Box 8.1: Stakeholder views on reasons for regulating EDs at EU level*

EU level regulation of EDs is needed in order to:

- achieve an equal level of protection across the EU Member States for human health and the environment in accordance with the precautionary principle;
- react to the knowledge gaps around EDs, such as epigenetic and transgenerational effects, combined effects, limitation of assessing specific modes of actions in particular beyond EATS;
- share capacities in testing and assessment, experience and knowledge across the EU to guarantee consistency, predictability, efficiency and credibility and thus avoid disputes;
- support achieving the overall Commission Priorities of e.g. Zero Pollution ambition, biodiversity strategy and farm to fork strategy and facilitate the circular economy;
- ensure competitive industry, preserve the EU single market, and stimulate EU wide safe innovation initiatives;
- allow more efficient implementation of control measures and improve overall enforcement;
- provide stronger signal to non-EU countries to support globally safer use of chemicals and setting a global example.

*There were no clear trends according to stakeholder group. This is a summary of the most frequently mentioned free text comments.

Box 8.2: Stakeholder and SME views on the impact of unilateral actions at national level*

In the **stakeholder survey**, the question of impacts of unilateral actions at national level was asked only to business associations and company/business organisations. Of those who answered the questions, 48% stated that their organisation had been impacted, while 52% stated they had not been impacted.

Several business associations and company/business organisations highlighted examples of unilateral Member State actions that had a direct or indirect impact on their business. Examples are:

1) the French Ban of BPA in Food Contact Materials
2) the Danish ban of propyl and butyl paraben in cosmetic products
3) the ban of some Plant Protection Products in MSs even if the product is approved by mutual recognition in the respective regulatory zone.

One direct impact is the direct pressure to eliminate substances from the production sometimes without the availability of appropriate alternatives.

In addition, unilateral bans may also create shifts in wider consumer behaviour. For example, even if bans are limited to specific uses, consumers' concerns lead to avoid the use of the limited substance in all types of products thus reducing trust in the safety of a chemical EU wide. This can also occur when MS authorities draw up lists of chemicals of concern or with suspected ED properties.

In the **SME survey**, only three of 70 SMEs answered that individual Member State initiatives have affected their companies. Sixty-five stated there were no effects on their companies, two did not reply

to the question. The three SMEs stating they were affected were two large enterprises (with more than 250 employees) and one medium size enterprise (with 50-249 employees).

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

Box 8.3: Stakeholder views: Are national level unilateral actions by Member States on specific EDs justified?*

In order to achieve an equal level of protection of humans and the environment throughout Europe, endocrine disruptors should be regulated centrally at EU level. This is with the intent to ensure and preserve the single market within the European countries, avoiding the introduction of non-tariff trade barriers. However, unilateral actions at national level, aimed to restrict or ban substances with ED properties, have been recently taken in some of the Member States.

The Stakeholder Survey revealed that 36% of the stakeholders agreed that unilateral actions by individual Member States, such as banning chemicals because of ED properties, are not justified. However, 26% of stakeholders replied that this is justified since the protection of human health or the environment is more important than preserving the integrity of the single market. Another 36% stated that unilateral actions are justified in certain circumstances when those are followed by wider actions at EU level to preserve the single market. Very few (4 out of 165) respondents believed regulating EDs at EU level is not justified.

Many stakeholders indicated that ideally all measures taken to protect humans and the environment from EDs should be agreed and implemented at EU level. It was pointed out, however, that individual Member State actions are justified in case of sound scientific evidence of concern, in line with the precautionary principle, when follow-up action at EU level cannot be agreed in an appropriate time frame.

Many stakeholders referred to past examples where individual MS-level actions have led to EU-level action, thus positively contributing to the protection goals and reduction of societal costs. To provide equal level of protection to all citizens in the EU and to preserve the single market, EU-level actions should follow in a timely manner.

Some stakeholders proposed to introduce legal mechanisms that automatically trigger a follow-up assessment centrally at EU-body-level in case relevant actions are taken at the level of Member States.

*Respondents to all three surveys (citizens, stakeholder and SME surveys) were self-selected and thus not necessarily representative of the full range of views of these groups.

9 CONCLUSIONS

Endocrine disruptors (EDs) are chemical substances of synthetic or natural origin that adversely affect the health of humans and animals by altering the functioning of the endocrine system. Exposure to EDs can occur from different sources, such as pesticide residues in food or everyday consumer products. Different regulatory approaches for managing the risks posed by EDs exist because sector-specific regulations have been developed at different points in time and in some cases incorporate different specific considerations. This raises questions about the overall coherence of the EU's legal framework in relation to EDs.

In this Fitness Check, the current ED-relevant provisions have been mapped across the EU Chemicals Acquis, and the overall regulatory framework has been analysed in terms of its coherence, effectiveness, efficiency, relevance and EU-added value.

Knowledge about endocrine disruptors

Significant progress has been made in understanding EDs since the adoption of the 1999 Community Strategy for Endocrine Disruptors. Much of this knowledge relates to chemicals that affect the estrogen, androgen or thyroid axes or that interfere with steroidogenesis. The need to elucidate additional mechanisms of endocrine disruption is being addressed via EU-funded research projects, such as those in the EURION cluster.

The next generation of EU funded research will aim to address realistic mixture (combined) exposure scenarios and to embrace the multi-factorial nature of certain indicators of concern, such as the increase in certain non-communicable diseases and the decline in biodiversity. Building on the currently available methods developed in key research areas (e.g. use and interpretation of human biomonitoring data and effect-based methods in water quality assessments) the Commission is exploring new mechanisms to use emerging knowledge in the policy cycle (e.g. the candidate European Partnership for Chemicals Risk Assessment).

There is also a need to share information on chemicals with all stakeholders, preferably via an open platform.

Coherence

The coherence of the regulatory framework was assessed by focusing on the definition for EDs, information requirements, hazard and risk assessment practices, and consequences for risk management.

The World Health Organization definition of endocrine disruptors is broadly accepted in EU legislation. The criteria for the identification of EDs under the Plant Protection Products Regulation and Biocidal Products Regulation, and as substances of very high concern under REACH, are based on this definition. EU Agencies (EFSA, ECHA) and the Commission's Scientific Committee on Consumer Safety (SCCS) have endorsed the definition and apply it in their assessments. Cross-sectorial (horizontal) criteria for EDs in EU legislation would facilitate consistent identification across sectors.

Based on the limited number of chemicals examined for endocrine disrupting properties (mainly under the BPR or PPPR, and REACH), this Fitness Check did not identify any cases of inconsistent identification.

However, the current data requirements limit the opportunity to identify EDs. The update of data requirements to include further tests relevant for the detection of ED properties has started under the Biocidal and Plant Protection Products Regulations, as well as REACH.

EU agencies have been stepping up their efforts to coordinate assessment work, with a view to ensuring consistency as well as increased efficiency in the assessment process. These efforts will continue, as the European Green Deal commits the Commission to "*review how to use better the EU's agencies and scientific bodies to move towards a process of 'one substance – one assessment' and to provide greater transparency when prioritising action to deal with chemicals*."[108]

There are only a few examples of risk assessments based on endocrine disrupting properties. In this limited number of cases, risks were identified following the standard risk assessment approach based on exceedance of a safe threshold (derived no-effect levels) for endpoints which were not necessarily ED-specific. The uncertainties associated with the possible peculiarities of endocrine disrupting effects (i.e. non-threshold, non-monotonic behaviour) are recognised and in some cases have been taken into account through the use of uncertainty factors defined on a case by case basis.

Not all pieces of legislation have information requirements for the toxicological properties of chemicals, and nor do they need to, provided that mechanisms are in place to exploit data generated under other pieces of legislation. Differences in data requirements for the identification of EDs exist across different sectors, reflecting differing intended uses and exposure scenarios contributing to the risk, as well as the need to consider proportionality with respect to socioeconomic and laboratory animal welfare considerations. Where information requirements do exist, they need to be updated to include the latest validated methods relevant to ED identification.

Information requirements also need to address the effects of chemicals on vulnerable groups. In this respect, there is an opportunity to introduce and improve the consistency of definitions of vulnerable groups across legislation, and to clarify the scientific rationale for triggering specific provisions for vulnerable groups (such as the unborn, children and the elderly).

Across the chemicals acquis, the co-legislators have opted for different approaches to risk management (namely, generic risk approaches *vs* specific risk approaches *vs* risk/impact-benefit-based) according to specific policy considerations. This situation has been criticised by many stakeholders, who expressed concerns that differences in risk management measures may not be justified. Indeed, the rationale for some of the differences should be made more transparent. A case in point concerns the possibilities for derogation from the exclusion or cut-off criteria for biocidal and plant protection products, respectively. Under BPR, a derogation can be granted based on negligible risk, essentiality or risk-benefit considerations, while under the PPPR, it can only be granted when exposure is negligible or for essential uses.

Despite differences in risk management approaches, this Fitness Check found no cases of inconsistent risk management for specific substances based on the lack of a horizontal approach to ED identification or any other ED-specific considerations. This finding has to be qualified, however, by the limited number of EDs risk managed due to their ED properties as examined in this Fitness Check.

The difficulty in deciding between the generic risk approach and the specific risk approach is partly related to a fundamental scientific uncertainty – whether the effects of an ED are considered to have a threshold or not. In the absence of scientific consensus, legislation can either opt for an approach that does not require an answer to the question (e.g. generic risk approach with derogations as done for

[108]COM(2019) 640

plant protection products and biocidal products) or it can determine case by case whether or not a safe (or acceptable) threshold can be quantified and consequently apply an appropriate risk management approach, as done in REACH. In certain pieces of sectorial legislation (e.g. Cosmetic Products Regulation, Food Contact Materials Regulation), existing guidance and examples do not as yet provide a clear indication about how to deal with EDs, for which it is not possible to quantify a safe (or acceptable) threshold. In practice, in cases where a threshold cannot be established, the regulatory approach followed under EU legislation is to minimise exposure as far as possible including the option to prohibit the use of a substance. Application of the generic risk approach is combined with derogations allowing essential uses or risk-benefit options tailored to specific policy contexts.

In view of the Commission's ambition to develop a process of "one substance-one assessment", including a horizontal approach to EDs, consolidation and simplification options should be explored, as well as better communication of the approach to citizens and stakeholders. This ambition would also provide an opportunity to systematically assess and manage the risks resulting from the aggregate exposure to the same ED across sectors and from the combined exposures to different EDs, which is a concern expressed by stakeholders. A "one substance-one assessment" approach was seen by many stakeholders as a way of avoiding discrepancies in ED identification while also increasing the effectiveness of regulatory procedures and improving communication with citizens.

The principle of a horizontal approach to ED identification and assessment is broadly supported by stakeholders. However, it needs to be better defined what this means in practice. Elements to consider are: a) the common criteria for ED identification, based on the International Programme on Chemical Safety/World Health Organization definition, which may be implemented via the CLP Regulation (and GHS at the international level); b) a common basic set of information requirements, including screening level information based on new approach methodologies, that provide the basis for applying the criteria; c) a common toolbox to fulfil the information requirements; d) guidance on the application of the toolbox and interpretation of the data generated; and e) a coordinated approach to ED identification and risk assessment, including whether an existing piece of legislation, such as REACH, should serve as the basis for filling data gaps, where necessary.

The International Programme on Chemical Safety/World Health Organization definition of endocrine disruptors is broadly accepted in the implementation of EU legislation. However, in view of the Commission's ambition to develop a horizontal approach to ED identification, there will be a need to provide practical guidance on how this definition should be interpreted. A particular question will be whether evidence of an adverse effect can only be based on the observation of effects in living animals, or whether adversity can be concluded on the basis of scientific reasoning and extrapolation from the results of new approach methodologies that avoid the need for animal testing. This has implications not only for effectiveness (most available animal tests listed under legislative data requirements have not been specifically designed to detect endocrine effects), but also coherence (animal testing for all endpoints, including endocrine-related ones, is banned for cosmetic products, but not under other legislation) and efficiency (animal testing is costly, time-consuming and ethically questionable).

Effectiveness

Increasing trends in some adverse health and environmental impacts associated with EDs are a matter of societal concern. In this Fitness Check, however, it was not possible to draw firm conclusions on the effectiveness of EU legislation in reducing the potential impact of EDs on these trends.

The assessment of effectiveness is very challenging, mainly because of the attribution challenge. Since there are multiple causes of these effects, it is difficult to determine to what extent exposure to

EDs contributes to the observed adverse effects. A further complication is that observable adverse effects on human health and the environment often do not materialise immediately after exposure. In particular, the effects of early life exposure to EDs may not materialise until many years later.

Nevertheless, for some EDs, environmental monitoring data and/or human biomonitoring data have provided evidence that restriction measures (although taken in relation to other hazardous properties) have been successful in reducing exposure levels. There are examples of non-approval of substances with endocrine disrupting properties resulting in significant benefits to wildlife. For instance, international bans on the use of the endocrine disruptor tributyltin as an antifoulant in marine paints has resulted in the recovery of mollusc populations in European coastal waters.

The methodological challenges in assessing effectiveness point to a need to develop and apply a more extensive suite of indicators.

It is too early to assess the effectiveness of the BPR and PPPR, since only a limited number of substances have been identified as EDs or as not being EDs, according to the criteria adopted in 2018. Reflecting the need to gain experience, the Regulations setting out the criteria foresee a review after 7 years, i.e. by 2025.

Under REACH, 17 substances have been identified as Substances of Very High Concern (SVHC) due to endocrine disrupting properties with respect to human health and/or the environment. However, only octylphenol, nonylphenol and their ethoxylates are subject to authorisation specifically due to their endocrine disrupting properties. The inclusion of a substance in the Candidate List for authorisation due to concerns for endocrine disrupting effects triggers additional provisions for risk assessment (Chemical Safety Report) and risk communication (Safety Data Sheet).

CMRs cat. 1A/1B can be identified as SVHCs under REACH and fulfil the cut-off/exclusion criteria for non-approval under the plant protection products and biocidal products regulations. Identification of a CMR as an ED for human health will probably not lead to any additional risk management measures, where they are already the strictest, but may nevertheless contribute to the overall evaluation within a risk-benefit context.

CMR classification is not, however, sufficient to capture all EDs for human health, since other effects are potentially mediated by endocrine disruption, such as certain neurodevelopmental and metabolic disorders. As methods for less studied modalities of endocrine disruption become available, it is expected that more substances will be identified as EDs beyond CMRs.

Data requirements for the identification of EDs are being updated under the PPPR, BPR and REACH to include already existing OECD test guidelines relevant to ED assessment, in particular to include the so-called ‘mechanistic’ tests, which can pinpoint a specific endocrine modality.

Some pieces of sectorial legislation rely primarily on REACH for ED identification. Others such as food contact materials, food additives and cosmetic products have further requirements for products or sectors they regulate but these do not, as yet, specifically address endocrine disruption. Due to the animal testing ban in the cosmetics sector, a specific issue arises concerning the identification of EDs given the need to demonstrate an adverse effect in intact organisms, which currently requires *in vivo* testing.

There may be a need to strengthen the interconnections between legislation, such as REACH, that have provisions for data generation with sector and product-specific legislation that rely on such data for assessment and management purposes. This may require that ED risk management provisions are introduced into certain pieces of legislation, which currently do not contain any reference to EDs, respecting the special case of cosmetics where *in vivo* tests should not be generated solely for the

purposes of cosmetic ingredient evaluation. Effective sharing of data across legislation should ensure that the information eventually generated is made available for assessing potential EDs falling under sectorial legislation where information is not specifically required.

Irrespective of regulatory provisions for identifying EDs, there is a technical challenge concerning the ability to identify EDs. While progress has been made in developing standardised test methods for identifying EDs and characterising their hazards, the current assessment toolbox is still mainly based on animal tests. The toolbox is incomplete in terms of its coverage of all adverse outcomes and is also limited to a few modes of endocrine action. Another limitation is the ability to detect possible effects of EDs in sensitive life stages. The involvement of the endocrine system in the control of processes such as embryonic development and puberty means that foetuses, infants and adolescents are at higher risk regarding endocrine disruption.

Given the limitations of the current assessment toolbox, new approach methodologies, not involving the use of animals, need to be developed and integrated into the regulatory assessment process. The Commission is addressing this challenge on multiple fronts, from funding research into the development of new methods, to assessing their scientific validity, to promoting their adoption (once validated) as OECD Test Guidelines.

Communication on the presence of EDs in products (articles and mixtures) is required under REACH (when identified as SVHCs) and the BPR. However, there is scope to improve the availability of information on EDs across sectors.

Efficiency

Inefficiencies in the assessment and management of endocrine disruptors can result from situations where a given substance falls within the mandate of multiple agencies and scientific committees, but also from certain regulatory provisions, such as “equivalent level of concern” under REACH. EU agencies have been stepping up their efforts to coordinate assessment work. However, efficiencies could be gained by developing a horizontal approach to EDs, including an increased use of grouping approaches and new approach methodologies that avoid the use of animal tests.

The need to carry out testing and assessment for additional ED-related effects for a larger number of chemicals will inevitably lead to increased workload and costs. Some industry stakeholders are concerned that this will put economic operators in the EU at a competitive disadvantage, while some public authority stakeholders are concerned that this will result in delays to other areas of regulatory assessment work.

The costs and benefits for human health and the environment resulting from regulatory requirements to assess and manage risks of chemicals, including endocrine disruptors, are difficult to quantify and compare. There is a need to further develop and harmonise risk-benefit methodologies, such as socioeconomic analysis. In this Fitness Check, two case studies illustrated the methodological challenges in performing conclusive macroeconomic assessments on the possible impacts of regulatory interventions on trade. This is partly because there is a lack of trade flow data at the level of specific chemicals and the commodities containing these chemicals, as well as data on the market share of a chemical in a given commodity.

EU-added value

Regulating EDs at EU level contributes to ensuring an equal level of protection across the EU Member States regarding human and environmental health. The need for the EU to act in this area is broadly supported by the public and stakeholders, and at the political level by EU institutions such as European Parliament and the EU Committee of the Regions.

There is an opportunity for the Member States to join forces in testing capacities, experience and knowledge sharing. This should lead to greater efficiency and scientific consistency in the assessment of EDs. A uniform EU approach also strengthens the EU's position in chemicals regulation worldwide, which also has benefits for the EU chemical industry.

Safeguard clauses in EU legislation allow unilateral risk management measures to be taken at Member State level, in cases where an individual Member State has concerns regarding human health or the environment. Such measures have been taken for a few ED substances, such as Bisphenol A and DEHP, and are usually followed by EU-level intervention or withdrawal of unilateral action, to ensure an equal level of protection throughout the EU.

Relevance

Societal concerns about the health and environmental impacts of EDs are high, consistent with concerns about chemicals in general. Perspectives on the importance of regulating EDs are polarised between different stakeholder groups. Citizens engaged in the topic generally lack trust in the ability of EU legislation to achieve its objectives of human health and environmental protection, while economic stakeholders are concerned that decisions may ultimately be based on societal concerns rather than science-based evidence.

A particular challenge over the coming decades is the expected global trend towards increased chemical manufacturing outside the EU, primarily in Asia. The successful implementation of the EU Circular Economy Action Plan will promote innovation and give proper incentives to chemical suppliers, wherever they are located, as regards the safe use and life cycle management of chemicals.

Overall conclusions

The need to address the impacts of EDs on human health and the environment is highly relevant to EU citizens, who also favour regulatory action at the EU level.

Based on the limited number of chemicals examined for ED properties under the BPR or PPPR, or as SVHCs with ED properties under REACH, this Fitness Check did not identify any cases of inconsistent identification across sectors. However, the need for a horizontal approach for identification of EDs has been recognised that is based on the definition of the World Health Organization and builds on the criteria developed for plant protection products and biocidal products while ensuring that it is fit for purpose for other relevant legislation, particularly for REACH but also legislation on cosmetic products, toys and food contact materials. This is also an opportunity to simplify and rationalise current parallel identification procedures.

A horizontal approach for the identification of EDs would also feed into the development of a 'one substance-one assessment' approach across legislation and facilitate the management of risks to humans and wildlife resulting from combined exposures to different endocrine disruptors regulated under different pieces of legislation. Current data requirements limit the opportunity to identify EDs. The strengthening of information requirements in the relevant legislation is key to improving the identification of EDs.

This Fitness Check could not conclude on the effectiveness of the chemicals acquis in protecting health and the environment from EDs. However, there is a need to explore options to strengthen the legislative framework to further minimise exposure to EDs, both for consumers and for the environment

Overall, there are opportunities for simplification, consolidation, burden reduction and better communication of the principles guiding risk management of EDs. The findings of this Fitness Check

will provide an input to the Chemicals Strategy for Sustainability being developed in the context of the European Green Deal.

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11 GLOSSARY

Term	Definition / Explanation
Adverse effect	A change in the morphology, physiology, growth, development, reproduction, or, life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.
Adverse Outcome Pathway (AOP)	An AOP is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organisation that lead to an adverse health or ecotoxicological effect.
Alternative method	A method that replaces, reduces or refines the use of animals in toxicity testing
Apical Endpoint	An observable outcome in a whole organism, such as a clinical sign or pathological state that is indicative of a disease state that can result from exposure to a toxicant. As such, the apical endpoint is representing a measurable outcome responding to multiple different toxicity pathways/MoAs and can potentially be indicative of adverse effects.
Biomarker	A biological parameter that is objectively measured and evaluated as an indicator of normal biological state or pathological processes.
Dose-response relationship	The dose–response relationship describes the change (in nature, incidence, magnitude and/or severity) in an effect on an organism caused by different levels of exposure (or doses) to a stressor (usually a chemical) after certain exposure duration. This definition includes the following assumptions: the response observed is due to the chemical administered, the magnitude of the response is in fact related to the dose and the observed effect is quantifiable.
EATS parameters	Parameters measured in vivo that may contribute to the evaluation of adversity, while at the same time (due to the nature of the effect and the existing knowledge as described in OECD GD 150) they are also considered indicative of an EATS MoA and thus (in the absence of other explanations) also imply underlying in vivo mechanistic information. This group includes the parameters mainly from OECD Conceptual Framework Level 4 and 5 tests labelled in OECD GD 150 as ‘endpoints for estrogen-mediated activity’, ‘endpoints for androgen-mediated activity’, ‘endpoints for thyroid-related activity’ and/or ‘endpoints for steroidogenesis-related activity’.
ED criteria	The criteria are legally defined in Commission Delegated Regulation (EU) No 2017/2100 and Commission Regulation (EU) No 2018/605 for biocidal products and plant protection

Term	Definition / Explanation
	products, respectively. They are based on the 2002 WHO/IPCS definition of an endocrine disruptor. They ask for consideration, in a weight of evidence approach, of all relevant scientific information including human and/or animal evidence, therefore allowing for the identification of both known and presumed endocrine disrupting substances.
Endocrine activity	Interaction with the endocrine system that can potentially result in a response of the endocrine system, target organs and tissues. A substance that has an endocrine activity it has the potential to alter the function(s) of the endocrine system.
Endocrine disruptor	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.
Endocrine modality	A modality is an axis, pathway, signalling process, in this case within the endocrine system.
Endocrine system	The endocrine system is a highly integrated and widely distributed group of organs that orchestrates a state of metabolic equilibrium, or homeostasis, among the various organs of the body. In endocrine signalling, molecules, i.e. hormones, act on target cells that are separate from their site of synthesis.
Group of substances	Substances that have physicochemical, toxicological and ecotoxicological properties that are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances.
Hormone	Substances which are produced by endocrine glands and secreted into the circulation, and which exert a regulatory effect elsewhere in the body.
In silico model	The technique of performing experiments via computer simulations. Examples include Structure-Activity Relationships (SAR) and Quantitative Structure-Activity Relationships (QSAR).
In vitro test	The technique of performing a given experiment in a test tube, or, more generally, in a controlled environment outside of a living organism.
Integrated Approach to Testing and Assessment	A structured approach used for hazard identification (potential), hazard characterisation (potency) and/or safety assessment (potential/potency and exposure) of a chemical or group of chemicals, which strategically integrates and weights all relevant data to inform regulatory decision regarding potential hazard and/or risk and/or the need for further targeted and therefore minimal testing.
Mechanism of action	A detailed molecular description of the mechanistic interaction through which a substance/molecule produces its effect.
Mode of action (MoA)	A biologically plausible sequence of key events at different levels of biological organisation, starting with the exposure to a chemical and leading to an observed (adverse) effect.
New Approach Methodology (NAM)	A recently coined term referring to any technology, methodology or combination thereof, that can be used to provide information on chemical hazard and risk assessment

Term	Definition / Explanation
	that avoids the use of intact animals.
Non-animal method	An alternative method that avoids testing in intact animals. The more traditional phrase for New Approach Methodology
Uncertainty	Uncertainty refers to all types of limitations in the knowledge available to assessors at the time an assessment is conducted and within the time and resources agreed for the assessment.
Weight of evidence (WoE)	A stepwise process/approach of collecting and weighing evidence to reach a conclusion on a particular problem formulation including assessment of the degree of confidence.

Annex 1. Procedural information

1 Lead DG and internal references

The "Fitness Check on the relevant EU legislation on Endocrine Disruptors" was led by DG Joint Research Centre (JRC). The mandate was established in the Communication "Towards a comprehensive European Union framework on endocrine disruptors"[109].

Issues relevant to endocrine disruptors (EDs) were included in recent Fitness Checks and evaluations of chemical legislation, including the REACH REFIT evaluation, the REACH Review on the authorisation route of substances with endocrine disrupting properties according to REACH Art. 138(7), the Fitness Check of the chemicals legislation other than REACH, the review of the legislation on cosmetics with regard to endocrine disrupting substances, and the evaluation of the 7th Environment Action Programme. Among legislation regulating downstream uses of chemicals in products, the evaluation of the legislation on food contact materials and the evaluation of the legislation on toy safety were also considered relevant to this FC. Among pieces of environmental legislation, the Fitness Check of the water legislation was considered for potentially ED-relevant aspects.

Also relevant was Annex 9 of the impact assessment on the definition of criteria for identifying EDs in the context of the Plant Protection Products Regulation and Biocidal Products Regulation. This provides a multi criteria analysis of impacts (on health, environment etc.) based on a scientific review of the evidence linking endocrine disrupting chemicals to hormone-related diseases and the estimated related costs to society attributed to exposure to EDs.

The findings of this Fitness Check formed an important contribution to the Chemicals Strategy for Sustainability under the European Green Deal[110]. This strategy was part of the Commission's Work Programme for 2020[111].

2 Organisation and timing

The pre-existing Inter-service Steering Group (ISG) on endocrine disruptors was used to steer the process and provide input. The ISG comprised representatives from the Directorate Generals for Agriculture and Rural Development (AGRI), Environment (ENV), Internal Market, Industry, Entrepreneurship and SMEs (GROW); Health and Food Safety (SANTE), Employment, Social Affairs and Inclusion (EMPL), Maritime Affairs and Fisheries (MARE), Research and Innovation (RTD), Justice and Consumers (JUST), Trade (TRADE), Legal Service (SJ), Joint Research Centre (JRC) and the Secretariat General (SG).

A meeting with DGs directly responsible for the implementation of the Commission communication (DGs ENV, GROW, SANTE, EMPL, JRC and SG) was held to kick-off the Fitness Check. The ISG

[109] COM(2018) 734
[110] COM(2019) 640
[111] https://ec.europa.eu/info/publications/2020-commission-work-programme-key-documents_en

met twice during the evaluation process and provided feedback through two written consultations (**Table 12.1**).

Table 12.1 Meetings of the Endocrine Disruptor Inter-service Steering Group and informal task force

Date	Nature of meeting
13 March 2019	Inter-DGs meeting to discuss operational plans
19 July 2019	Agreement of ISG on draft methodology, evaluation questions and stakeholder consultation strategy
08 April 2020	Written consultation of ISG on the draft evaluation report (SWD) for submission to the RSB
05 May 2020	Meeting of ISG to discuss comments on the draft evaluation report (SWD)
22 May 2020	Written consultation on the revised draft evaluation report (SWD) for submission to the RSB

3 Exceptions to the better regulation guidelines

No exceptions were made to the Better Regulation Guidelines[112] during this Fitness Check.

4 Consultation of the Regulatory Scrutiny Board

An upstream consultation of the Regulatory Scrutiny Board (RSB) of the European Commission on the planned methodology for the Fitness Check was held on 3 October 2019. A draft version of the evaluation report (Staff Working Document) was submitted to the RSB on 26 May 2020. The RSB issued its positive opinion on 24 June 2020. The Board made a number of recommendations to further improve the report. These were addressed in the revised report as follows:

RSB recommendations	Modification of the report
(B) Summary of findings The Board appreciates the efforts put in analysing the wide range of legislation dealing with the sensitive issue of regulating endocrine disruptors. The Board notes the additional information provided in advance of the meeting. The Board gives a positive opinion. The Board also considers that the report should	(1) Efforts were made to remove or better explain technical terms and to use fewer abbreviations or re-state them in full at the beginning of each section. The section on the State of Play of the 34 regulatory instruments within the scope of the Fitness Check was moved to an annex and replaced by a table shortly stating the intervention logic and most relevant points related to the presence or absence of

[112] https://ec.europa.eu/info/better-regulation-guidelines-and-toolbox_en

RSB recommendations	Modification of the report
further improve with respect to the following aspects: (1) While acknowledging that the subject matter of the fitness check is very technical, the report is not sufficiently accessible to the non-expert reader. (2) The report does not clearly explain the uncertainties and the political sensitivities relating to regulation in this area. (3) The conclusions of the analysis are not sufficiently clear to inform future policy intervention(s).	ED-specific provisions. (2) The introduction was extended to include reference to the specific uncertainties surrounding the assessment of EDs and the related political sensitivities with respect to the possibilities to set a 'safe threshold' and throughout the text more focus was put on the consequent impact on risk assessment/management options. (3) The conclusions were reinforced to include more concrete takeaway messages from the findings of the Fitness Check, which could inform future policy interventions.
(C) What to improve (1) To make the report more accessible, the introduction should succinctly present the landscape of endocrine disruptors in the EU. It should give basic information, such as the number of tested, identified and banned substances per type of legislation, the length of the testing procedure, costs, etc. It should better explain how the results of this fitness check could feed into policy-making. The report should avoid overlaps and could move much of the information provided on the 'state of play' to an annex. (2) On the methodology, the report should better explain how the case studies were selected and assess how representative they are. The report should present the views of stakeholders in a more nuanced way. It should clearly break down responses according to stakeholder groups and be more explicit about their opinions on particular issues raised in the consultations. To the extent possible, it should assess stakeholder views against other available evidence. (3) The report should draw clearer conclusions, both in the sub-sections and in the concluding chapter. Firstly, it should better distinguish between issues where	(1) More background information on the landscape of EDs in the EU was added to the introduction including a table of EDs identified at EU level. Costs and duration of testing was introduced in the effectiveness section. Sections summaries and the conclusions were made more concrete with respect to findings that could support future policy interventions. The 'state of play' was moved to the annex (2) An additional description of how the case studies were selected was included in the methodology. A breakdown of responses according to stakeholder groups has been added and for some of the survey questions an assessment of the differing views has been added. (3) The body of the text was checked and some additional points were added to the summaries of each sub-section addressing the evaluation criteria.

RSB recommendations	Modification of the report
policy conclusions can be drawn with some degree of certainty and where further assessment is necessary. Secondly, the conclusions on the different evaluation criteria should be coherent with the presented analysis and should cover all identified issues. Thirdly, being a fitness check, the conclusions should put a greater focus on the potential for simplification and reduction of regulatory burdens. Finally, the report should more clearly bring out the main takeaways for future policy-making, without formulating concrete solutions as this should rather be dealt with in a potential future impact assessment.	The conclusion section has been rewritten, checking for coherence with the summaries in each sub-section, focusing on issues that could inform future policy interventions. The aspect of simplification was considered further and some of the conclusions are strengthened with respect to this point. Some additional points were taken forward to the Executive Summary.
(4) While the report focuses primarily on the science-based assessment of endocrine disruptors, it is apparent from the analysis that there are also important policy choices involved. It should better explain that the choice between different approaches (e.g. applying a generic vs. specific risk approach to regulating endocrine disruptors) concerns uncertainty about the likelihood of damages and the value judgement on acceptable risks. The report should elaborate on this issue and any implications for the conclusions. Some more technical comments have been sent directly to the author DG.	(4) The scientific uncertainty ("threshold question") underlying the choice between the generic risk and the specific risk management approach is now explained in the coherence section, as well as the conclusions. The implications of this distinction are also used to draw a conclusion on the need for consistent risk management principles. The coherence section explains the different risk management approaches in the context of the precautionary principle, as well as the need to consider trade-offs and to apply the risk-benefit approach in certain sectors. Specific comments to the authors were also addressed.

5 Evidence, sources and quality

The sources of evidence and their quality are described in **Annex 3**. These included the findings of previous fitness checks and evaluations, a series of case studies, and the results of public, stakeholder and SME consultations. No external expertise was used, apart from *ad hoc* consultations with EU agency staff related to EU chemical safety assessments. All of the work was conducted by Commission staff, with no external studies being performed.

Annex 2. Synopsis report: stakeholder consultation activities

1 Summary

An important element of the Fitness Check is a consultation strategy aimed at citizens, stakeholders and companies.

In the **public consultation**, 474 responses were received over a twelve-week period from 16/12/2019 to 09/03/2020. The survey, which was translated into all official EU languages, was designed to gain the perspective of the citizen, rather than stakeholders or companies, who were targeted via separate surveys. In total, 431 of the 474 responses (91%) came from citizens. A majority of citizens felt informed about endocrine disruptors and considered that their effects on health and wildlife, while poorly understood, do represent a concern. Similarly, a majority felt informed about the regulation of endocrine disruptors, but do not feel that the current regulatory framework is sufficiently protective. A majority of respondents also expressed the view that the EU should have the same approach or more consistent approach for both identifying and managing the risks of exposure to endocrine disruptors. Opinions were divided on whether animal testing is minimised in the assessment process. Similarly, there were mixed views on whether the cost of regulatory action is proportionate to the benefits accrued for human health, wildlife and the economy. In general, the respondents considered that EU laws on endocrine disruptors are relevant to societal concerns, and that regulatory action should be taken at the EU level.

In the **stakeholder consultation**, 183 responses were received over an eight-week period from 06/12/19 to 31/01/20. The respondents were businesses, public authorities, academics, research organisations, and civil society organisations. A large majority (93%) of the respondents considered that the absence of harmonised criteria for identifying endocrine disruptors across sectors is problematic. A smaller majority (53%) considered that this harmonisation should be achieved by introducing an endocrine disruptor category under the classification and labelling legislation. Around three quarters said they were aware of inconsistencies, gaps or overlaps in the regulatory framework, and a similar proportion were aware of inadequacies in the availability of regulatory test methods. A large majority (88%) reported an increase in costs to comply with EU laws on endocrine disruptors.

The results of the stakeholder consultation also give a detailed breakdown of stakeholder views on the effectiveness of legislation in specific sectors (REACH, cosmetics, biocides, plant protection products). This includes the perceived effectiveness in protecting people and wildlife, improving the functioning of the Single Market, enhancing competitiveness and innovation, and promoting alternatives to animal testing. Opinions were typically divided on these issues. However, in relation to exposure to chemical mixtures, there was a tendency to consider the regulatory framework as insufficiently protective.

The answers to additional questions confirmed that a majority of stakeholders consider the objectives of the regulatory framework to be relevant in addressing health and environmental concerns. Moreover, the prevailing view was that regulatory actions should be taken at the EU rather than Member State level.

An additional survey, targeting **micro, small and medium-sized enterprises** (SMEs), was conducted through the Enterprise Europe Network and was open from 01/02/2019 to 09/03/2020. Responses

were received from 70 SMEs. In general, opinion was divided, or not expressed, across a range of questions. However, many respondents considered the regulatory process to identify and control chemicals with endocrine disrupting properties to be effective in protecting people and wildlife, in improving the functioning of the internal market, and enhancing competitiveness and innovation. A majority considered that the lack of a hazard category for the classification and labelling of endocrine disruptors poses a problem for their consistent identification and risk management. On the question of EU-added value, most respondents reported that unilateral Member State actions had not affected their company.

2 Introduction and approach

Stakeholder consultation was a key component of this Fitness Check to collect views and factual information in response to the evaluation questions and to ensure a balanced and comprehensive assessment of the legislative framework.

The objectives of the consultation activities were to:

- Assess public concerns and needs with respect to endocrine disruptors in the EU.
- Evaluate to what extent current EU legislation meets the concerns and needs of citizens.
- Collect views on possible lack of legislative coherence of EU legislation with respect to EDs and possible impacts on stakeholders.
- Identify any inconsistencies in the legal framework for endocrine disruptors and their consequences for small companies
- Collect information on the effectiveness of the current EU legislation for the identification and risk management of endocrine disruptors.
- Collect information on the efficiency of the current procedures for the identification and risk management of endocrine disruptors.
- Identify opportunities for improving the way endocrine disruptors are assessed, managed and potential risks communicated

The consultation strategy developed for the purpose of this Fitness Check[113] comprised:

- presentation of the methodological approach at the First Annual Forum on Endocrine Disruptors on 8 November 2019;
- an open public consultation from 16/12/2019 to 09/03/2020;
- a stakeholder consultation from 06/12/19 to 31/01/20;
- an SME panel through the Enterprise Europe Network from 01/02/2019 to 09/03/2020.

The open public consultation and SME panel were conducted in all official EU languages, while the stakeholder consultation was conducted in English. Reports on the results of open public consultation[114] and stakeholder consultation[115] are available via the JRC Publications Repository. The public consultation report is also available via the Better Regulation (Have Your Say) website[116].

[113] https://ec.europa.eu/info/sites/info/files/food-farming-fisheries/key_policies/documents/20191120_ed_consultation_strategy.pdf
[114] https://publications.jrc.ec.europa.eu/repository/handle/JRC120369
[115] https://publications.jrc.ec.europa.eu/repository/handle/JRC120148
[116] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/2142-Fitness-Check-on-endocrine-disruptors/public-consultation

3 Stakeholder groups covered by the consultation activities

In line with the consultation strategy, input from a wide range of stakeholders was collected:

- Public authorities, notably competent authorities and relevant EU Agencies responsible for the implementation of relevant EU legislation
- Industry associations covering both the chemicals industry and downstream sectors (manufacturers and importers of chemicals, distributors of substances and mixtures, formulators, downstream users, manufacturers and importers of products/articles, retailers)
- Companies in the chemicals industry and downstream sectors, including Small and Medium-sized Enterprises (SMEs) (manufacturers and importers of chemicals, distributors of substances and mixtures, formulators, downstream users, manufacturers and importers of products/articles, retailers)
- Consultants – professional consultancies, law firms, compliance testing companies
- Civil society organisations – with the objective to protect human health and the environment from exposure to harmful substances via the workplace, consumer products or environmental media.
- Civil society organisations – with animal welfare objectives aimed at reducing use of animals for scientific purposes (i.e. testing for ED properties)
- Trade unions that represent workers that manufacture or use chemicals within the chemical industry, downstream sectors or use chemicals, as substances, mixtures or articles, as industrial/professional users
- Academics/research institutes/think tanks/scientific societies contributing to the development of methods and methodologies for the identification and assessment of endocrine disrupting substances.
- Consumers / workers /citizens
- International partners and stakeholders of third countries

Error! Reference source not found. demonstrates how each of the tools mentioned above was used to collect information from different categories of stakeholders.

Table 13.1 Different stakeholder groups consulted

	Public consultation	SME panel	Stakeholder consultation
Public authorities			✓
Industry associations			✓
Companies / SMEs		✓	✓
NGOs			✓
Consumer associations			✓
Trade unions			✓
Academia / research institutes			✓
Consumers / workers / citizens	✓		

These different consultation activities and tools allowed receiving feedback from all stakeholder groups. A summary of the views expressed in each consultation is provided below. It is recognised

that the results of any survey are associated with an inevitable bias towards those who have an interest in responding. Therefore, observations are stated in terms of numbers or percentages of the respondents.

4 Outcome of the public consultation

4.1 Respondents

A total of 474 respondents provided an answer, of which 90% are EU citizens, 3% are academic/research institutions and 2% non-governmental organisations.

As regards the origin of the respondents participating to the survey, most answers were received from France (40%), Germany (17%), Spain (14%), Belgium (5%) and Finland (5%).

Analysis of the survey results for attempts to bias the conclusions revealed no obvious re-occurring pattern across the answers. Ten percent of the responses were from non-citizens, but these show no alignment to a common position and do not influence significantly the results.

4.2 How well informed do citizens feel?

A majority of the respondents consider themselves to be very well informed (14%) or reasonably well informed (49%) about endocrine disruptors, as opposed to feeling poorly informed (31%) or not informed at all (6%).

The main sources of information on endocrine disruptors used by the respondents are specialised scientific sources (246), general news coverage (222), social media (178), education and training sources (131) and other sources (118).

A majority of the respondents feel informed about the decisions made in the EU with regard to endocrine disruptors (11% very well informed; 57% somewhat informed). A minority (21%) do not feel informed, but trust regulators to keep them safe, while 11% replied that they do not know.

Fifty-four percent of the respondents do not think that the effects on endocrine disruptors on public health and the environment are understood and 38% think the effects are understood to a certain extent as opposed to 5% that think effects are not understood.

Twenty-five percent of respondents (118) gave details on the source of information they mainly consult (open question Q2) (**Figure 13.1**).

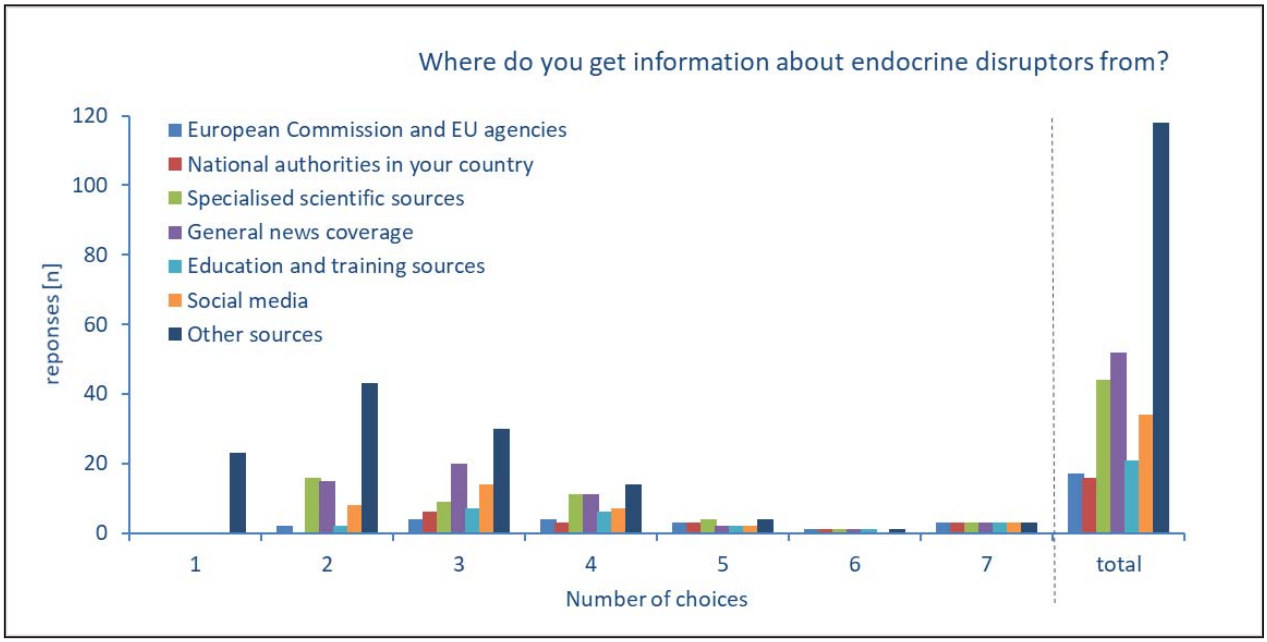

Figure 13.1. Distribution of responses for Q2. Multiple answers were possible. Total number of responses (n=118).

From the open box 'other: please specify' (**Figure 13.2**), data and reports from NGOs, environmental and human health associations (e.g. Greenpeace, PAN, Free Europe etc.), non-profit networks for consumers and specific consumer products represent the main source of information across all respondents. Specialised scientific sources include scientific and academic reviews (Pubmed search), books and publicly available databases. This type of information is also enriched by online search on the subject of endocrine disruptors, specialised and general websites (NGOs portals, documentaries, Wikipedia, Google) together with newspapers consultation. One third of all respondents, mainly involved in education or health professions (academia, physicians) reported to attend trainings and to participate to conference or meetings.

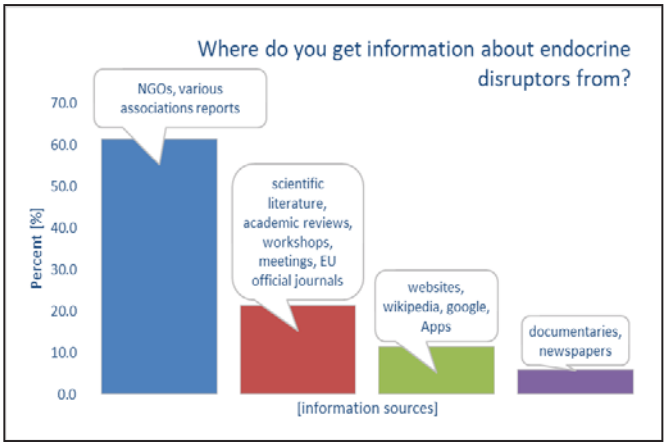

Figure 13.2. Distribution of responses for Q2. Other sources of information

4.3 Public views on effectiveness

The majority of respondents (54% to 74%) considered that EU laws did not protect them at all or only to a small extent from exposure to endocrine disruptors across all of the potential exposure sources listed in the survey. The four exposure sources where respondents consider that EU laws protect them the least are personal care products, food contact materials, clothing and home/office.

Sixty-one percent of the respondents consider that they are less protected by EU laws from endocrine disruptors than from other toxic chemicals, such as carcinogenic or mutagenic substances, or substances toxic to reproduction with 20% considering that they are protected to the same extent.

In general, over 60% of respondents consider that EU laws offer a low level of protection for one or more life stages with the highest number of respondents concerned about adolescents (75%) and the lowest numbers concerned about pregnant women, foetuses and newborns (62% to 66%).

In their free text replies, 70 respondents (open question Q5) considered not be protected at all or only to a small extent (56% and 11%) from combined exposures, mixtures and cocktail effects of potential endocrine disruptors and their presence in toys, industrial chemicals, thermo-paper, pesticides, biocides, perfumed products, medicinal products. Other concerns, to a lesser extent, were indoor air, car air filters, nanoparticles, construction materials, plastics and utensils.

Ninety-three percent of respondents believe that endocrine disruptors contribute to a large or moderate extent to some human diseases or health conditions such as infertility, cancer or obesity.

From 72% to 81% of respondents consider that EU laws offer a low level of protection for wildlife such as insects, including bees and other pollinators (81%), fish and amphibians (80%), other invertebrates, such as snails, shrimps or worms (79%), birds and reptiles (76%), mammals (74%) and plants (72%).

A majority of respondents expressed the view that the EU should have the same approach or the same approach to the extent possible across regulatory sectors for both identifying endocrine disruptors (86%) and managing the risks of exposure to endocrine disruptors (84%).

Many of the respondents are of the opinion that endocrine disruptors are insufficiently identified across a range of sectors, particularly in furnishing and electrical and electronic equipment (see figure below).

The majority of respondents are also of the opinion that EU laws insufficiently manage the risks linked to endocrine disruptors across all sectors. For example, the number of respondents considering that endocrine disruptors are not well managed in the pesticide sector is 73% compared with 15% who think endocrine disruptors are well managed or fairly well managed and 12% who do not know or did not reply. For medical devices, 53% of respondents consider that endocrine disruptors are not well managed compared with 22% who think that they are well managed or fairly well managed and 25% who do not know or did not reply.

4.4 Public views on efficiency

Forty-four percent of the respondents consider that the costs (e.g. time, resources, use of laboratory animals) of EU laws on endocrine disruptors are proportionate for the benefits accrued compared with 26% who consider costs are only to a small extent or not at all proportionate. Thirty percent replied that they do not know.

In general, the respondents consider that EU laws on endocrine disruptors generate slightly more costs for the agricultural and industrial sectors compared with costs to citizens or ethical costs.

In their free text replies, 40 respondents gave further insights regarding the costs to which extent EU laws generate on endocrine disruptors (open question Q15). The majority (75%) highlighted high costs in terms of healthcare, diseases and environmental health and finally for citizens which the EU is generating by means of inaction. Other costs are generated by unnecessary use of animals and lobbying. Many respondents (20%) while declaring not to be aware of costs, suggested water treatment and soil.

EU laws on endocrine disruptors are believed to generate benefits for the EU market by about half of the respondents (49% agree fully or to a moderate extent, while 24% agree to a small extent or don't agree at all and 27% don't know or did not reply). Opinion is also divided on the extent to which EU laws on endocrine disruptors are seen to benefit human health and wildlife.

4.5 Summary of public views on regulatory testing and animal welfare

Thirty-seven percent of the respondents think that animal testing for endocrine disrupting properties in the EU is insufficiently minimised, whereas 28% consider animal testing to be either minimised to the extent possible (23%) or fully minimised (5%). Thirty-five percent replied that they do not know.

4.6 Public views on EU-added value

In terms of which bodies should regulate to protect people and wildlife from harm caused by endocrine disruptors, most respondents expressed the view that this should be done by EU authorities (432), and many respondents considered that national authorities (356), international organisations (292) and local/regional authorities (238) should act. For this question, the numbers of respondents are given, rather the percentage values, since it was possible to select more than one option.

4.7 Public views on relevance

In terms of areas where the EU needs to significantly step up its efforts, the respondents prioritised as follows: reducing exposure of humans (88%), reducing exposure to wildlife (84%), identifying endocrine disruptors (80%), and adopting a coherent approach to identification and management of endocrine disruptors (79%). Fewer respondents consider that a lot of efforts are needed by the EU to reduce the burdens and costs to business (30%).

4.8 Additional comments made by citizens

There were 196 responses to the final question (Q19) which asked respondents to provide any additional comment or suggestion that they considered relevant for the endocrine disruptors Fitness Check.

Ten of the respondents were on behalf of NGOs (advocacy for environment, justice, animal welfare), two were representing cancer prevention associations, and one spoke on behalf of electronic equipment industry association. The responses from stakeholders (NGOs, industry association and cancer associations) were removed from the summary of citizens' responses, thus leaving 183 responses. This did not affect either the contribution to the public consultation, by means of percentages, or main key messages.

In addition, five respondents were researchers from (academia, research institutes), six were health professionals, such as doctors (general medicine, endocrinology, paediatrics) and one was from a private law firm. These responses were included in the following analysis, on the basis that these respondents were experts replying as citizens,

Twenty eight percent of these respondents (52 out of 183) expressed their concerns about the presence of endocrine disruptors in the environment and many products they might be in contact with. Respondents in this group asked for more attention and immediate actions to prevent potential toxic effects of EDs on humans and the environment. Many advocated for an immediate ban of such substances, stricter measures for their identification on the basis of precautionary principle, more stringent control and regulation by authorities. Many fear the presence of endocrine disruptors in consumer goods (such as personal care products, toys, food contact materials, and children's products) where they consider EDs should be forbidden. Despite acknowledging the difficulties in the identification of chemicals as potential EDs, respondents asked for limited use of any chemical showing concern either for human health or environment. In addition, industry was asked to develop safer alternatives.

Fifteen percent of respondents (28 out of 183), expressed concerns about the role of companies and their potential lobbying of EU institutions. This group feared that economic interests are politically favoured over human and environment health. Independent assessment of substances was also requested together with independent research through public funds. In this regard, 12% of respondents (22 out of 183) asked for more information on industry activities, on production and safety assessments of substances. They asked for better information about marketed products; more transparency on product labelling; greater awareness of the EU policies, better information and training offerings for health professionals; more instructions and advice to consumers; multiplication of the information channels on research, diagnostics and regulatory decisions on endocrine disruptors.

Approximately 10% of respondents highlighted the need for stronger action in response to the increased evidence of ED-related diseases (e.g. obesity, cancer, infertility etc.). They asked for more studies on biomonitoring and exposure to endocrine disrupting chemicals, including requests to further the knowledge on mixtures, combined exposures and cocktail effects. This group advocated for attention to vulnerable groups, especially children, including more stringent measures on the exposure to EDs, considering the evidence of neurobehavioral disorders and IQ impairment. Two respondents claimed that they suffered adverse health effects resulting from exposure to endocrine disruptors.

Citizens (3.8% of respondents) commented on the need to identify endocrine disruptors in consumer products, especially detergents, sanitizers and medicines, alongside the promotion of research activities to develop better bioanalytical methods (1.6%) and application of novel methodologies for ED identification and safety testing of substances which would ultimately reduce the use of animals (2%).

According to approximately 3% of respondents, clear identification criteria and eventually hazard categories for endocrine disruptors are still needed, including harmonisation across different product sectors, to reach the highest level of protection for humans and the environment. Another 0.5% of respondents considered that new hazard categories for classification and labelling is scientifically questionable, may lead to unnecessary administrative burden in regulatory decision making, and it would have questionable value in terms of risk communication and management.

Citizens (2.7%) also considered it essential that endocrine disruptors are regulated and monitored consistently across the EU, and that measures are implemented in each Member State. The EU should monitor and impose heavy sanctions on the Member States that do not comply with the rules or make it difficult to comply with them. Where unilateral actions are taken by single Member States those actions should be quickly adopted at EU level. This group expressed concerns about the safety of products imported from non-EU countries that do not have similar standards.

According to 4.4% of respondents further studies are also needed on the quality of soils, water, tap water, in particular surface water installations but also aquatic ecosystems.

Seventeen percent of respondents (29 out of 183) expressed their scepticism about the ability of the EU to act and the poor measures taken so far. They lamented delays and inadequacies of current EU regulations, which do not protect people and the environment against exposure to EDs. In particular, the following were mentioned: delays in the implementation of the REACH regulation and failure to implement a number of recommendations from the EU Parliament and Council; delays in the substitution of harmful chemicals or their complete ban; and delays of the application of measures despite evidence being available for the past twenty years. In general, this group thought that little or nothing has been done and too many chemicals were left on the market without proper testing and controls. Moreover, the identification of EDs was considered insufficient. Negative comments from 44% of this group were also about the questionnaire itself which was considered unclear (Q11, Q14, Q16) and unsuitable for the general public. It was also noted that questions 15 and 16 could only be answered hypothetically as none of pesticides or biocides have been identified based on new test procedures (implemented in 2018).

5 Outcome of the stakeholder consultation

5.1 Structure of survey

The survey was structured into different parts. The first section concerned information about the respondents such as category of stakeholder, country of origin and residency, and regulatory sector of interest. The second section asked about the level of familiarity with the different pieces of legislation within the scope of the Fitness Check and then went on to ask questions, seeking views and information on different aspects of coherence, effectiveness, efficiency, relevance and EU-added value of the current approaches to identification, assessment and management of endocrine disruptors in the EU legislation.

Apart from the introductory section related to respondent characteristics, the survey did not include any mandatory fields. It was therefore possible for respondents to leave one or more of the 36 questions unanswered. As a result, the total number of responses to each question varied.

Some questions were aimed at specific categories of stakeholders: questions 25, 26 and 29 were intended for business associations, company/business organisations and public authorities; questions 27, 28 and 35 were intended for business associations and company/business organisations. These questions did not appear to respondents identifying themselves in other categories.

5.2 Respondents

Overall, 183 replies were received in the stakeholder consultation. A quality check of the responses revealed the presence of 11 replicates in the answers. Analysis the origin of these replicates showed that some respondents replied more than once by mistake (twice, and in once case trice) and covered evenly all categories of stakeholders. Removal of these replicates leads to a variation of no more than one percent for each question.

Analysis of the survey results for attempts to bias the conclusions indicated five clusters of similar patterns of answers for both closed or open types of questions. Nevertheless, the fact that these clusters represent fewer than six respondents shows that they are probably coordinated groups sharing similar positions. Furthermore, they cover evenly all categories of stakeholders. Removal of these similar types of responses (keeping only one per identified cluster) leads to a variation less than five percent in all cases.

Taking into account these two points, the survey responses were analysed without removing any of the 183 answers.

Replies provided to the survey cover all categories of respondents with respect to their stakeholder category (**Table 13.2**).

Table 13.2 Respondents from different stakeholder groups consulted

Stakeholder group	No of responses
Business associations	47
Public authorities	35
Company or business organisations	31
Civil society organisations	27
Academic/Research institutions	14
Trade unions	11

The most represented country is Belgium with 48 respondents, followed by France (27), Germany (18) and Spain (11).

Respondents outside of the EU come from Switzerland (6), USA (3), Norway (2), Japan (1) and Turkey (1).

The geographical scope of the respondents is 61% international and 39% national, regional or local.

Country	Answers	Percentage
Belgium	48	26%
France	27	15%
Germany	18	10%
Spain	11	6%
Denmark	8	4%
Italy	7	4%
United Kingdom	6	3%
Sweden	5	3%
Austria	4	2%
Bulgaria	4	2%
Luxembourg	4	2%
Finland	3	2%
Hungary	3	2%
Ireland	3	2%
Portugal	3	2%
Latvia	2	1%
Netherlands	2	1%
Poland	2	1%
Romania	2	1%
Slovenia	2	1%
Croatia	1	1%
Cyprus	1	1%
Lithuania	1	1%
Malta	1	1%
Slovak Republic	1	1%
Other (Please specify)	13	7%

Among economic operators (companies and business associations) and public authorities, the main sectors of interest are General Chemicals (14%), Biocidal Products (12%) and Cosmetics (11%).

Sector	Answers	Percentage
General chemicals	51	14%
Biocidal products	43	12%
Cosmetics	40	11%
Plant Protection Products	33	9%
Food contact materials	30	8%
Detergents	28	8%
Food additives	25	7%
Medical devices	24	6%
Human and veterinary medicines	20	5%

Sector	Answers	Percentage
Fertilisers	16	4%
Water industry	16	4%
Waste/recycling industry	16	4%
Electric and electronic equipment	15	4%
Toys	14	4%

5.3 Familiarity of stakeholders with relevant legislation

Q1. How familiar are you with the following pieces of legislation?

The familiarity of the respondents with the pieces of EU legislation included in the scope of the Fitness Check may be relevant to the interpretation of the replies.

Among the listed legislative instruments, the respondents are most familiar with the following pieces of legislation:

Legislation	Very familiar	Fairly familiar	A little familiar	Not at all familiar
REACH Regulation (EC) 1907/2006	122	32	20	2
CLP: Classification, Labelling and Packaging of substances and mixtures (EC) 1272/2008	113	35	17	10
Biocidal Products Regulation (EU) 2012/528	60	57	42	13
Cosmetic Products Regulation (EC) 1223/2009	59	35	35	40
Plant Protection Products Regulation (EC) 1107/2009	51	41	42	38

The respondents are least familiar with the following legislative instruments:

Legislation	Very familiar	Fairly familiar	A little familiar	Not at all familiar
Fertilisers Regulation (EC) 2003/2003 and Regulation (EU) 2019/1009	21	18	36	91
Medicinal Products for Humans Directive 2001/83/EC	15	23	52	77
Marine Strategy Framework Directive 2008/56/EC	15	16	48	85
Urban Waste Water Directive 91/271/EEC	21	9	44	90
Veterinary Medicinal Products Regulation (EU) 2019/6	16	14	40	97
In vitro Diagnostic Medical Devices Regulation (EU) 2017/746	14	12	45	94

5.4 Stakeholder views on coherence (overall statistics)

Q2. To what extent does the absence of harmonised criteria pose a problem to a coherent approach for the identification of endocrine disruptors?

Overall, 150 (93%) of the respondents consider that the absence of harmonised criteria poses a problem to the identification of endocrine disruptors across sectors, while 11 (7%) think it is not a problem, the criteria should be sector specific.

Q3. Do you think that the lack of a hazard category covering endocrine disrupting properties in the CLP Regulation and/or GHS poses a problem for the coherent identification of endocrine disruptors?

Opinion is divided on this topic with 94 of the respondents (53%) thinking that this is a problem for coherent ED identification, and 83 (47%) thinking it is not.

Q4. Do you think that the lack of a hazard category covering endocrine disrupting properties in the CLP Regulation and/or GHS poses a problem for the coherent risk management of endocrine disruptors?

Opinion is divided on this topic with 86 of the respondents (51%) thinking that the lack of a hazard category is a problem for coherent risk management, and 84 (49%) thinking it is not a problem.

Q5. Do you think that a category of suspected endocrine disruptor should be introduced?

Some stakeholders have suggested to classify endocrine disruptors in one of three categories based on the level of evidence: i.e. known, presumed or suspected.

With regard to the need of a category of suspected endocrine disruptors, opinion is again divided with 89 respondents (53%) being in favour of introducing a category for suspected endocrine disruptors, while 79 (47%) are not in favour.

Q6. Are you aware of any inconsistencies in the way chemicals are identified and controlled with regard to endocrine disrupting properties across regulated areas in the EU?

Overall, 123 respondents (73%) are aware of inconsistencies in the way endocrine disruptors are identified and controlled in the European Union, while 45 (27%) are not.

Q7a. In your opinion, how do hazard-based criteria for identifying endocrine disruptors in combination with a hazard-based approach[117] to decision-making affect the following objectives?

[117]The terminology "hazard-based" and "risk-based" approaches is used in the context of consultation activities of this Fitness Check. The terms are equivalent to "generic risk" and "specific risk" approaches used elsewhere in the document.

A majority of respondents consider that the use of hazard-based criteria for identifying endocrine disruptors in combination with a hazard-based approach to decision making would affect (very) positively[118] human health protection (93), and environmental protection (92) compared with 58 and 54 who viewed these impacts (very) negatively[119].

The effects on "competitiveness and innovation" and on the "functioning of the internal market" are viewed more negatively than positively, although higher numbers of respondents indicate “no effect” or “don’t know”.

	Very positively	Positively	No effect	Negatively	Very negatively	Don't know
Human health protection	60	33	5	24	34	15
Environmental protection	62	30	9	26	28	15
Competitiveness and innovation	33	16	10	21	46	45
Functioning of the internal market	34	9	19	29	23	56

Q7b. In your opinion, how do hazard-based criteria for identifying endocrine disruptors in combination with a risk-based approach to decision-making affect the following objectives?

Of those respondents expressing an opinion the majority view positively or very positively a risk-based approach to decision making in relation to human health and environmental protection.

The effects on "competitiveness and innovation" and on the "functioning of the internal market" are also viewed more positively than negatively, although higher numbers of respondents indicate “no effect” or “don’t know”.

	Very positively	Positively	No effect	Negatively	Very negatively	Don't know
Human health protection	60	51	3	32	10	14
Environmental protection	60	49	4	33	10	13
Competitiveness and innovation	37	42	15	29	4	43
Functioning of the internal market	32	28	18	28	5	56

Q8. Are you aware of any gaps or overlaps in the way endocrine disruptors are regulated in the EU?

[118]Sum of respondents agreeing very positively or positively
[119]Sum of respondents agreeing very negatively or negatively

Overall, 127 respondents (73%) consider that there are gaps or overlaps in the EU legislation on endocrine disruptors, while 46 (27%) do not.

Q9. Have you experienced issues or problems because endocrine disruptors are regulated differently in the EU compared with non-EU countries?

Opinion is divided with 81 respondents (51%) not experiencing issues or problems due to endocrine disruptors being regulated differently in the EU compared to non-EU countries, while 81 (49%) reported problems.

Q10. Do you have further comments on the coherence of the EU legislation with regard to endocrine disruptors?

Ninety-four respondents provided answers to this open question. The results are summarised in the respective sections of the Staff Working Document.

5.5 Stakeholder views on effectiveness (overall statistics)

*Q11a. In the case of **Biocidal Products**, do you agree that the regulatory process to identify and control substances with endocrine disrupting properties is effective in: protecting consumers, workers, citizens and wildlife; improving the functioning of the internal market ; enhancing competitiveness and innovation; and promoting alternatives to animal testing.*

With regard to biocidal products, of those expressing an opinion there is a roughly even split between those that consider the regulation is effective in protecting human health and those that do not: consumers (51 agree , 42 disagree, and 18 neither agree nor disagree), workers (46 agree, 43 disagree, and 19 neither agree nor disagree) and citizens exposed via the environment (43 agree, 47 disagree and 21 neither agree nor disagree).

When it comes to protecting wildlife the number of respondents agreeing that the regulation is effective decreases (35 agree, 50 disagree and 22 neither agree nor disagree).

Of those expressing an opinion, more respondents disagree than agree that the provisions related to EDs have a positive effect on the functioning of the internal market (19 agree, 28 disagree and 34 neither agree nor disagree), on enhancing competitiveness and innovation (22 agree, 42 disagree and 27 neither agree nor disagree) and on promoting alternatives to animal testing (24 agree, 40 disagree and 33 neither agree nor disagree). However, to these questions there are many respondents choosing "neither agree nor disagree" or "don't know".

*Q11b. In the case of **Plant Protection Products**, do you agree that the regulatory process to identify and control substances with endocrine disrupting properties is effective in: protecting consumers, workers, citizens and wildlife; improving the functioning of the internal market ; enhancing competitiveness and innovation; and promoting alternatives to animal testing.*

With regard to plant protection products, of those expressing an opinion there is a roughly even split between those that consider the regulation is effective in protecting human health and those that do not: consumers (41 agree, 37 disagree, and 24 neither agree nor disagree), workers (37 agree, 36

disagree, and 19 neither agree nor disagree) and citizens exposed via the environment (36 agree, 40 disagree and 26 neither agree nor disagree).

When it comes to protecting wildlife the number of respondents agreeing that the regulation is effective decreases (34 agree, 43 disagree and 23 neither agree nor disagree).

Of those expressing an opinion, more respondents disagree than agree that the provisions related to EDs have a positive effect on the functioning of the internal market (21 agree, 31 disagree and 22 neither agree nor disagree), on enhancing competitiveness and innovation (23 agree, 38 disagree and 18 neither agree nor disagree) and on promoting alternatives to animal testing (22 agree, 39 disagree and 24 neither agree nor disagree). However, to these questions there are many respondents choosing "neither agree nor disagree" or "don't know".

*Q11c. In the case of **REACH**, do you agree that the regulatory process to identify and control substances with endocrine disrupting properties is effective in: protecting consumers, workers, citizens and wildlife; improving the functioning of the internal market ; enhancing competitiveness and innovation; and promoting alternatives to animal testing.*

With regard to the effectiveness of REACH in protecting human health and the environment there are fewer respondents selecting 'neither agree nor disagree' or choosing to select 'don't know', than is the case for biocides or PPPs.

Of those expressing an opinion there is a roughly even split between those that consider the regulation is effective in protecting human health and those that do not (consumers (57 agree, 62 disagree, and 17 neither agree nor disagree), workers (56 agree, 59 disagree, and 18 neither agree nor disagree). A smaller proportion of respondents consider that the regulation is effective in protecting citizens exposed via the environment (46 agree, 63 disagree, and 26 neither agree nor disagree) or wildlife (43 agree, 67 disagree, and 23 neither agree nor disagree).

More respondents disagree than agree that the regulation (with respect to EDs) improves the functioning of the internal market (31 agree, 48 disagree, and 36 neither agree nor disagree) or enhances competitiveness and innovation (24 agree, 50 disagree, and 34 neither agree nor disagree) or promotes alternatives to animal testing (32 agree, 44 disagree, and 38 neither agree nor disagree). Again, there are many respondents choosing "neither agree nor disagree" or "don't know" to this group of questions.

*Q11d. In the case of **Cosmetics**, do you agree that the regulatory process to identify and control substances with endocrine disrupting properties is effective in: protecting consumers, workers, citizens and wildlife; improving the functioning of the internal market ; enhancing competitiveness and innovation; and promoting alternatives to animal testing.*

For cosmetics, more respondents disagree than agree that the regulation with respect to EDs is protecting consumer health (31 agree, 48 disagree, and 24 neither agree nor disagree) or worker health (24 agree, 49 disagree, and 28 neither agree nor disagree).

Few respondents agree that it is improving the functioning of the internal market (13 agree, 31 disagree, and 44 neither agree nor disagree) or enhancing competitiveness and innovation (17 agree, 30 disagree, and 37 neither agree nor disagree). However, the agree to disagree ratio changes around

with respect to promoting alternatives to animal testing, where 34 moderately or strongly agree compared with 12 that strongly or moderately disagree. The number that "don't know" or "neither agree nor disagree" is rather high.

*Q11e. In the case of **Medical Devices**, do you agree that the regulatory process to identify and control substances with endocrine disrupting properties is effective in: protecting consumers, workers, citizens and wildlife; improving the functioning of the internal market ; enhancing competitiveness and innovation; and promoting alternatives to animal testing.*

For medical devices, a large proportion of respondents say they do not know about the effectiveness of the regulatory process (ranging from 59 to 72). Of those expressing an opinion, more respondents disagree than agree that it is protecting consumers (25 agree, 35 disagree, and 15 neither agree nor disagree), protecting workers (23 agree, 29 disagree, and 19 neither agree nor disagree) or enhancing competitiveness and innovation (13 agree, 29 disagree, and 23 neither agree nor disagree).

More respondents neither agree nor disagree that it is improving the functioning of the internal market (9 agree, 21 disagree, and 31 neither agree nor disagree) or promoting alternatives to animal testing (11 agree, 11 disagree, and 39 neither agree nor disagree) compared with those that agree or disagree.

*Q11f. In the case of the **Water Framework Directive**, do you agree that the regulatory process to identify and control substances with endocrine disrupting properties is effective in: protecting consumers, workers, citizens and wildlife; improving the functioning of the internal market ; enhancing competitiveness and innovation; and promoting alternatives to animal testing.*

Regarding the Water Framework Directive, more respondents disagree than agree that the directive is effective in minimising the exposure of citizens (22 agree, 47 disagree, and 12 neither agree nor disagree) or wildlife (27 agree, 47 disagree, and 12 neither agree nor disagree) to endocrine disruptors via the environment. However, the numbers of "don't knows" are relatively high.

Q12. Aggregate exposure to one substance from all exposure sources

More respondents disagree than agree that the current regulatory framework protects humans (60 agree, 96 disagree, and 6 neither agree nor disagree) or wildlife (39 agree, 91 disagree, and 14 neither agree nor disagree) from the risks associated with the aggregate exposure to one substance with endocrine disrupting properties from all exposure sources.

	Strongly agree	Moderately agree	Neither agree nor disagree	Moderately disagree	Strongly disagree	Don't know
Humans are protected by the current regulatory framework	25	35	6	33	63	8

Wildlife is protected by the current regulatory framework	19	20	14	23	69	24

Q13. Combined exposure to multiple substances from all sources

Compared with Q12, a larger proportion of respondents disagree that the current regulatory framework protects humans (46 agree, 100 disagree, and 14 neither agree nor disagree) or wildlife (27 agree, 95 disagree, and 23 neither agree nor disagree) from the risks associated with the combined exposure to different substances with endocrine disrupting properties (combined effects).

	Strongly agree	Moderately agree	Neither agree nor disagree	Moderately disagree	Strongly disagree	Don't know
Humans are protected by the current regulatory framework	14	32	14	24	76	9
Wildlife is protected by the current regulatory framework	9	18	23	15	80	21

Q14. Do you think that the following groups are sufficiently protected from exposure to substances with endocrine disrupting properties?

For all population categories, the level of protection is regarded as insufficient by about two thirds of respondents (ranging between 56% for adults in general to 66% for the unborn exposed during pregnancy).

Population category	Yes	No	Don't know
Unborn through exposure during pregnancy	47	90	34
Newborn up to the age of 3	49	90	30
Children until puberty	49	90	30
Young persons around the age of puberty	48	91	30
Pregnant women	52	87	29
Adults in general	63	80	26
People at work	54	85	30

Population category	Yes	No	Don't know
Elderly	56	78	34
People with illnesses	46	81	43

Q15. Are available regulatory tests sufficient to identify endocrine disruptors for humans (including vulnerable groups) as well as wildlife?

Overall, 116 respondents (74%) consider the available regulatory tests insufficient to identify EDs, while 41 (26%) consider the tests sufficient.

Q16. Are current provisions for data requirements laid down in relevant legislation (REACH, Biocidal Products Regulation, Plant Protection Products Regulation) sufficient to identify endocrine disruptors for humans (including vulnerable groups) as well as wildlife?

Similarly, 114 respondents (71%) consider that the data requirements laid down in relevant legislation (REACH, Biocidal Products Regulation, Plant Protection Products Regulation) are insufficient, while 46 (29%) consider the requirements sufficient.

Q17. Considering the information requirements of REACH, the Biocidal Products Regulation and the Plant Protection Products Regulation, do you think the likelihood of identifying a substance as an endocrine disruptor is lower under one of these regulations compared to the others?

The likelihood to identify an endocrine disruptor under REACH, the Biocidal Products Regulation and the Plant Protection Products Regulation is about the same, according to 74 respondents (53%), and not the same according to 65 respondents (47%).

Q18. Do you have any further comments on available regulatory test methods and data requirements under REACH, the Biocidal Products Regulation, the Plant Protection Products Regulation, and other sector specific legislation?

Sixty-three respondents answered to this open question. The results are included in the relevant section of the Staff Working Document.

Q19. Do you agree with the following statement? In vitro and/or in silico methods are not used systematically enough to prioritise further investigations.

Among those who expressed an opinion, a majority of respondents think that in vitro and/or in silico methods are not used systematically enough to prioritise further investigations (80 agree, 7 disagree, and 38 neither agree nor disagree).

	Answers
Strongly agree	39
Moderately agree	41
Neither agree nor disagree	38

Moderately disagree	5
Strongly disagree	2
Don't know	41

Q20. In your opinion, is the impact of assessing chemicals for endocrine disrupting properties on animal welfare minimised in the EU?

A bit more than half of the respondents expressing an opinion (54%) think that the impact of assessing chemicals for endocrine disrupting properties on animal welfare is minimised in the EU to the extent possible.

	Answers
Not at all	12
Insufficiently minimised	43
Minimised to the extent possible	64
Don't know	51

Q21. Do you have recommendations on how to further minimise the impact of assessing chemicals for endocrine disrupting properties on animal welfare?

Overall, 108 respondents answered to this open question. The results are included in the relevant section of the Staff Working Document.

Q22. Are you aware of issues that result from the lack of specific provisions for identifying endocrine disruptors in sector-specific legislation for the following areas:

A majority of respondents are not aware of issues resulting from the lack of specific provisions for identifying endocrine disruptors in sector-specific legislation (from 60% to 70%).

Sector	Yes	No
Human and veterinary pharmaceuticals (only for effects on the environment)	39	80
Electrical and electronic equipment	40	81
Other (please specify)	33	65
Medical devices and in vitro diagnostic medical devices (only for effects on the environment)	42	81
Waste/recycling	42	81
Food additives	43	78

Sector	Yes	No
Toys	45	77
Workers protection	47	78
Detergents	46	75
Fertilisers	46	74
Cosmetics	52	83
Food contact materials	52	79
Water	51	77

Q23. Are you aware of issues that result from the lack of specific provisions for managing endocrine disruptors in sector-specific legislation for the following areas:

A majority of respondents are not aware of issues resulting from the lack of specific provisions for managing endocrine disruptors in sector-specific legislation (from 60% to 67%).

Sector	Yes	No
Electrical and electronic equipment	39	81
Food additives	40	80
Fertilisers	41	79
Human and veterinary pharmaceuticals (only for effects on the environment)	41	79
Medical devices and in vitro diagnostic medical devices (only for effects on the environment)	43	82
Waste/recycling	42	78
Detergents	44	76
Workers protection	45	77
Toys	45	75
Water	49	76
Cosmetics	53	81
Food contact materials	51	76
Other (please specify)	32	72

Q24. In your view, on which areas should market surveillance authorities focus their activities to effectively enforce chemical safety of products as regards endocrine disruptors?

A majority of respondents (80 to 90% of those who expressed an opinion) indicated that authorities should focus on market surveillance across all sectors listed.

	Yes	No	Don't know
Toys	88	10	44
Food contact materials	99	12	37
General chemicals	93	13	40
Cosmetics	92	13	37
Human and veterinary pharmaceuticals (only for effects on the environment)	75	11	52
Food additives	90	14	40
Waste/recycling	80	13	50
Plant Protection Products	87	16	39
Fertilisers	74	14	49
Biocidal products	88	17	38
Detergents	76	16	48
Medical devices and in vitro diagnostic medical devices (only for effects on the environment)	71	15	53
Electrical and electronic equipment	65	15	61
Other (please specify)	27	13	63

5.6 Stakeholder views on efficiency (overall statistics)

Benefits of regulatory intervention include human health and environmental protection, smooth functioning of the internal market, innovation and competitiveness. Costs can be economic (time, resources) as well as ethical (e.g. use of laboratory animals for testing). Efficiency considers the benefits in relation to costs.

Q25. Has the implementation of regulatory requirements for endocrine disruptors increased your total operating costs?

Eighty-eight percent of the concerned respondents report an increase of costs related to regulatory requirements for endocrine disruptors. Forty-eight percent consider the increased costs to be significant.

	Answers

Yes, to a significant extent	29
Yes, but not to a significant extent	24
No	7
Not applicable	42

Q26. Has the assessment of substances for endocrine disrupting properties delayed your assessment work in other areas of human health or environmental protection?

Eighty percent of concerned respondents report a delay in their assessment work in other areas of human health or environmental protection. Thirty-eight percent consider the delay to be significant.

	Answers
Yes, to a significant extent	24
Yes, but not to a significant extent	27
No	13
Not applicable	40

Q27. What is the cost increase for your company (companies your association is representing) to comply with the regulatory requirements (e.g. testing, restriction or ban) specifically related to endocrine disruptors?

Few respondents replied to this question. The type of costs incurring the highest cost increase was most commonly reported to be related to the provision of test data on endocrine disrupting properties.

	More than 10%	Between 5 and 10%	Between 1 and 5%	Below 1%	Don't know	Not applicable
Costs related to the provision of test data on endocrine disrupting properties	14	2	4	1	27	20
Cost to replace substances due to endocrine disrupting properties (e.g. as a producer or user)	7	4	7	1	27	19
Investment in the development of new testing methodologies for endocrine disrupting properties	6	8	3	0	25	26
Costs related to the preparation of registration or authorisation dossiers covering endocrine	5	7	6	4	22	24

disrupting properties						

Q28. What has been the impact of the provisions for endocrine disruptors on the sector you represent?

More of the respondents expressing an opinion report the impact to be negative rather than positive, impacting productivity (0 positively, 22 (very) negatively, and 9 no impact), profitability (1 very positively, 28 (very) negatively, and 3 no impact) and international trade (1 very positively, 25 (very) negatively, and 6 no impact) and to a lesser extent innovation (6 (very) positively, 22 (very) negatively, and 14 no impact).

Q29. Are the costs of the provisions for endocrine disruptor identification and management, for the sector(s) you operate in, justified and proportionate to the benefits accrued for society and the environment?

Of those respondents expressing an opinion, 79% consider the costs for endocrine disruptor identification and management justified and proportionate to the benefits accrued for society and the environment in their sectors (fully or to some extent). Thirty percent fully agreed with the statement.

	Answers
Not at all	12
To some extent	28
Fully	17
Don't know	40

5.7 Stakeholder views on relevance (overall statistics)

Q30. To what extent do you think exposure to endocrine disruptors is contributing to the increase in endocrine-related human diseases/disorders, in the EU, in comparison with other factors?

Sixty-two percent of respondents who expressed an opinion think that exposure to endocrine disruptors is contributing to a significant extent to the increase in endocrine-related human diseases/disorders in the EU, in comparison with other factors.

	Answers
To a significant extent	75
Not to a significant extent	40
Not at all	6
Don't know	46

Q31. To what extent do you think exposure to endocrine disruptors is contributing to the decrease in aquatic and terrestrial biodiversity in the EU, in comparison with other factors?

Sixty-four percent of respondents who expressed an opinion think that endocrine disruptors are contributing to a significant extent to the decrease in aquatic and terrestrial biodiversity in the EU, in comparison with other factors.

	Answers
To a significant extent	70
Not to a significant extent	36
Not at all	3
Don't know	57

Q32. Is the regulatory framework flexible enough to take into account new scientific information and methods in the assessment of endocrine disrupting properties (e.g. new toxicological tests, (bio)monitoring data, (eco)epidemiology)?

Overall, 84 respondents (53%) think that the regulatory framework is not flexible enough to take into account new scientific information and methods in the assessment of endocrine disrupting properties, while 73 (47%) think it is.

Q33. Do you have any further comments on the adequacy of legislation to address societal needs and concerns on endocrine disruptors?

Sixty-four respondents answered this open question. The results are included in the relevant section of the Staff Working Document.

5.8 Stakeholder views on EU-added value (overall statistics)

Q34. Do you think unilateral action on endocrine disruptors by Member State Authoritie is justifiable?

Thirty-two percent of the respondents think it is not justifiable at all. Another thirty-two percent thinks it is justifiable but should be followed by an EU wide action. Twenty-four percent think that this is justifiable in some cases, while 2% consider EDs should not be regulated at EU level.

	Answers
This is not justifiable – decisions should be taken at EU level and all citizens of the EU should be protected in an equal way, while preserving the integrity of the single market.	59
This is justifiable, but it should be followed by an EU wide action to preserve the integrity of the single market.	59
This is justifiable in some cases – protection of human health or the environment is more important than preserving the integrity of the single market.	44
This is justifiable – endocrine disruptors should not be regulated at EU level.	4

Q35. Has your organisation been impacted by unilateral actions at national level?

Of the 66 responses to this question, 30 (48%) consider that their organisation has been impacted by unilateral actions at national level, while 33 (52%) do not.

Q36. Do you have any further comments on the added value of regulating endocrine disruptors at EU level?

Seventy-eight respondents answered this open question. The results are included in the relevant section of the Staff Working Document.

5.9 Breakdown of stakeholder views according to stakeholder group

For selected questions, the distribution of responses according to stakeholder group was analysed, to see if there are notable differences in the views between groups.

Q2. To what extent does the absence of harmonised criteria pose a problem to a coherent approach for the identification of endocrine disruptors?

Overall, 150 (93%) of the respondents consider that the absence of harmonised criteria poses a problem to the identification of endocrine disruptors across sectors, while 11 (7%) think it is not a problem, the criteria should be sector specific.

The breakdown shows that academic/research institutions, civil society organisations, public authorities and trade unions are more likely to see this as a problem, compared with business associations and companies.

Stakeholder group	No Answer	It is an important problem, leading to incoherent identification of endocrine disruptors across sectors	It is not a problem, the criteria should be sector specific
Academic/research institution	1	13	0
Business association	11	33	3
Civil society organisations	1	25	1
Company/business organisation	5	21	5
Other	3	15	0
Public authority	1	32	2
Trade union	0	11	0
TOTAL	22	150	11

Q3. Do you think that the lack of a hazard category covering endocrine disrupting properties in the CLP Regulation and/or GHS poses a problem for the coherent identification of endocrine disruptors?

Opinion is divided on this topic with 94 of the respondents (53%) thinking that this is a problem for coherent ED identification, and 83 (47%) thinking it is not.

The breakdown shows that academic/research institutions, public authorities and trade unions are more likely to see this as a problem, compared with business associations, companies and civil society organisations.

Stakeholder group	No Answer	No	Yes
Academic/research institution	0	7	**7**
Business association	2	34	11
Civil society organisations	1	14	12
Company/business organisation	0	18	13
Other	3	4	11
Public authority	0	4	**31**
Trade union	0	2	**9**
TOTAL	6	83	94

Q4. Do you think that the lack of a hazard category covering endocrine disrupting properties in the CLP Regulation and/or GHS poses a problem for the coherent risk management of endocrine disruptors?

Opinion is divided on this topic with 86 of the respondents (51%) thinking that the lack of a hazard category is a problem for coherent risk management, and 84 (49%) thinking it is not a problem.

The breakdown shows that academic/research institutions, public authorities and trade unions are more likely to see this as a problem, compared with business associations, companies and civil society organisations.

Stakeholder group	No Answer	No	Yes
Academic/research institution	1	4	**9**
Business association	5	31	11
Civil society organisations	4	16	7
Company/business organisation	0	20	11
Other	3	4	11
Public authority	0	7	**28**
Trade union	0	2	**9**
TOTAL	13	84	86

Q5. Do you think that a category of suspected endocrine disruptor should be introduced?

Some stakeholders have suggested to classify endocrine disruptors in one of three categories based on the level of evidence: i.e. known, presumed or suspected.

With regard to the need of a category of suspected endocrine disruptors, opinion is again divided with 89 respondents (53%) being in favour of introducing a category for suspected endocrine disruptors, while 79 (47%) are not in favour.

The breakdown shows that academic/research institutions, public authorities, trade unions and civil society organisations are more likely to be in favour, compared with business associations and companies.

Stakeholder group	No Answer	No	Yes
Academic/research institution	0	5	**9**
Business association	3	38	6
Civil society organisations	3	1	**23**
Company/business organisation	1	22	8
Other	6	8	4
Public authority	2	4	**29**
Trade union	0	1	10
TOTAL	15	79	89

Q30. To what extent do you think exposure to endocrine disruptors is contributing to the increase in endocrine-related human diseases/disorders, in the EU, in comparison with other factors?

Sixty-two percent of respondents who expressed an opinion think that exposure to endocrine disruptors is contributing to a significant extent to the increase in endocrine-related human diseases/disorders in the EU, in comparison with other factors.

	Answers
To a significant extent	75
Not to a significant extent	40
Not at all	6
Don't know	46

The breakdown shows that academic/research institutions, public authorities, trade unions and civil society organisations think that exposure to endocrine disruptors is contributing to a significant extent, compared with business associations and companies.

	No Answer	Don't know	Not at all	Not to a significant extent	To a significant extent
Academic/research institution	2	3	0	0	**9**

	No Answer	Don't know	Not at all	Not to a significant extent	To a significant extent
Business association	6	11	1	25	4
Civil society organisations	1	4	0	1	**21**
Company/business organisation	0	11	5	9	6
Other	4	7	0	1	6
Public authority	3	9	0	3	**20**
Trade union	0	1	0	1	**9**
TOTAL	16	46	6	40	75

Q31. To what extent do you think exposure to endocrine disruptors is contributing to the decrease in aquatic and terrestrial biodiversity in the EU, in comparison with other factors?

Sixty-four percent of respondents who expressed an opinion think that endocrine disruptors are contributing to a significant extent to the decrease in aquatic and terrestrial biodiversity in the EU, in comparison with other factors.

	Answers
To a significant extent	70
Not to a significant extent	36
Not at all	3
Don't know	57

The breakdown shows that academic/research institutions, public authorities, trade unions and civil society organisations think that exposure to endocrine disruptors is contributing to a significant extent, compared with business associations and companies.

	No Answer	Don't know	Not at all	Not to a significant extent	To a significant extent
Academic/research institution	2	3	0	0	**9**
Business association	6	14	1	22	4
Civil society organisations	1	5	0	0	**21**
Company/business organisation	0	17	2	8	4
Other	5	6	0	3	4
Public authority	3	10	0	2	**20**

	No Answer	Don't know	Not at all	Not to a significant extent	To a significant extent
Trade union	0	2	0	1	**8**
TOTAL	17	57	3	36	70

6 Outcome of the SME consultation

6.1 Respondents

A total of 70 replies were received during the SME consultation. Eighty-one percent of the respondents have micro enterprises (23), small enterprises (13) or medium enterprises (19); four percent are self-employed (3), and fifteen percent have large enterprises (10).
An analysis of the responses received from large companies shows that they are usually more informed about EU regulations and less affected by them, but their contribution does not affect significantly the overall results (less than ten percent). Consequently, the contribution of large companies was kept in the following analysis.

Most answers were received from respondents in Romania (27%), Bulgaria (20%), Poland (14%) and Portugal (11%). The other respondents are based in Italy (7%), Greece (6%), France (4%), Latvia (4%), Czech Republic (3%), Belgium (1%) and Spain (1%).

Sixty-five respondents regularly sell products in all the EU with the exception of Ireland and Luxembourg. The main countries where products are sold are Romania (26), Germany (17), Bulgaria (16), Italy (14), Poland (13) and the United Kingdom (12).

Most of the respondents describe themselves as downstream users (29), followed by suppliers (19), distributors (12), formulators (9), importers (8), manufacturers of chemical substances (6) or only representatives (2). Six respondents declared another role (e.g. water treatment, security service provider, construction works).

Respondents are involved in almost all of the chemical sectors listed with the exception of aerosols and cleaning services. The sectors most reported are metals (12), paints, inks and coatings (12), plastics (11), dyes and pigments (11), and polymers (10).

6.2 Legislation affecting respondents

The five pieces of EU legislation affecting most respondents are: Directive 2008/98/EC on Waste (34 being familiar with its content *vs.* 14 being not familiar); REACH Regulation (EC) No 1907/2006 (33 familiar *vs.* 5 not); Classification, Labelling and Packaging of substances and mixtures (EC) No 1272/2008 (32 familiar *vs.* 3 not); Chemical Agents Directive at Work (98/24/EC) (25 familiar *vs.* 10 not); and Pregnant Workers Directive (1992/85/EEC) (24 familiar *vs.* 6 not).

The five pieces of EU legislation affecting the least respondents are: Veterinary Medicinal Products Regulation ((EU) 2019/6) (54 not being familiar with its content *vs.* 6 being familiar); Regulation (EU) 2017/746 on in vitro Diagnostic Medical Devices (56 not familiar *vs.* 4); Medicinal Products for Humans (Directive 2001/83/CE) (54 not familiar *vs.* 4); Regulation (EU) 2017/745 on Medical Devices (53 not familiar *vs.* 6); and Toy Safety Directive 2009/48/EC (53 not familiar *vs.* 6).

6.3 Information in the company about endocrine disruptors

The five sources of information most used by the respondents are safety data sheets from business partners (43 often use this source and 7 sometimes); manufacturers or suppliers of chemicals (32 often, 6 sometimes); national authorities (16 often, 12 sometime); customers (16 often, 11 sometimes); and industry associations (16 often, 10 sometimes).

The five sources of information least used by the respondents are: EU Agencies (18 never use this source and 7 rarely); European Commission (20 never, 9 rarely); authorities at local level (19 never, 8 rarely); authorities at regional level (19 never, 9 rarely); and consultants including law firms (14 never, 10 rarely).

The respondents are divided in their views on whether the information at their disposal helps their company to comply with legal requirements for endocrine disruptors, with 12 replying not at all and 25 to a small extent; 23 to a large extent and 8 completely.

One respondent referred to the use of scientific literature, while another made use of several databases (Toxnet, ACGIH, HHS, AIDII).

6.4 SME views on coherence

Twenty seven percent of respondents consider the lack of horizontal criteria to be problematic, while 22% do not consider it a problem. The remainder either did not know or did not reply. In the free text comments, respondents highlighted problems in the following areas: non-stick coatings, the food sector generally, stabilised aqueous mixtures for different industrial sectors, as well as perfumery and cosmetics. One respondent who did not consider it a problem said that EDs can be identified using various information sources (ECHA, European Council of Paintings), noting that the real problem is the risk assessment.

The lack of a hazard category covering endocrine disrupting properties in the Classification, Labelling and Packaging (CLP) Regulation and/or GHS poses a problem for the coherent identification of endocrine disruptors according to 82% of respondents, and also causes a problem for the coherent risk management of endocrine disruptors according to 84% of respondents.

Sixteen percent of the respondents reported being aware of inconsistencies in the way chemicals are addressed with regard to endocrine disrupting properties across regulated areas in the EU. In the free text comments, respondents cited inconsistencies related to bisphenol A, phthalates, and water-based textile auxiliaries vs biocidal products/pesticides.

Differences in the ways EDs are regulated between the EU and other jurisdictions (e.g. USA, China) affect five respondents to a significant extent, ten to some extent, five to a minor extent, sixteen not at all, while thirty-four respondents indicated that they did not know. In the free text comments, respondents commented on unfair competition (e.g. toys) and the fact that some suppliers are selling raw materials to a less restrictive market, accompanied by an increase in the costs and availability of products in Europe.

6.5 SME views on effectiveness

In general, respondents consider the regulatory process to identify and control chemicals with endocrine disrupting properties to be effective in protecting people and wildlife, in improving the functioning of the internal market, and enhancing competitiveness and innovation. This can be seen in **Figure 13.3** since respondents more often agree than disagree.

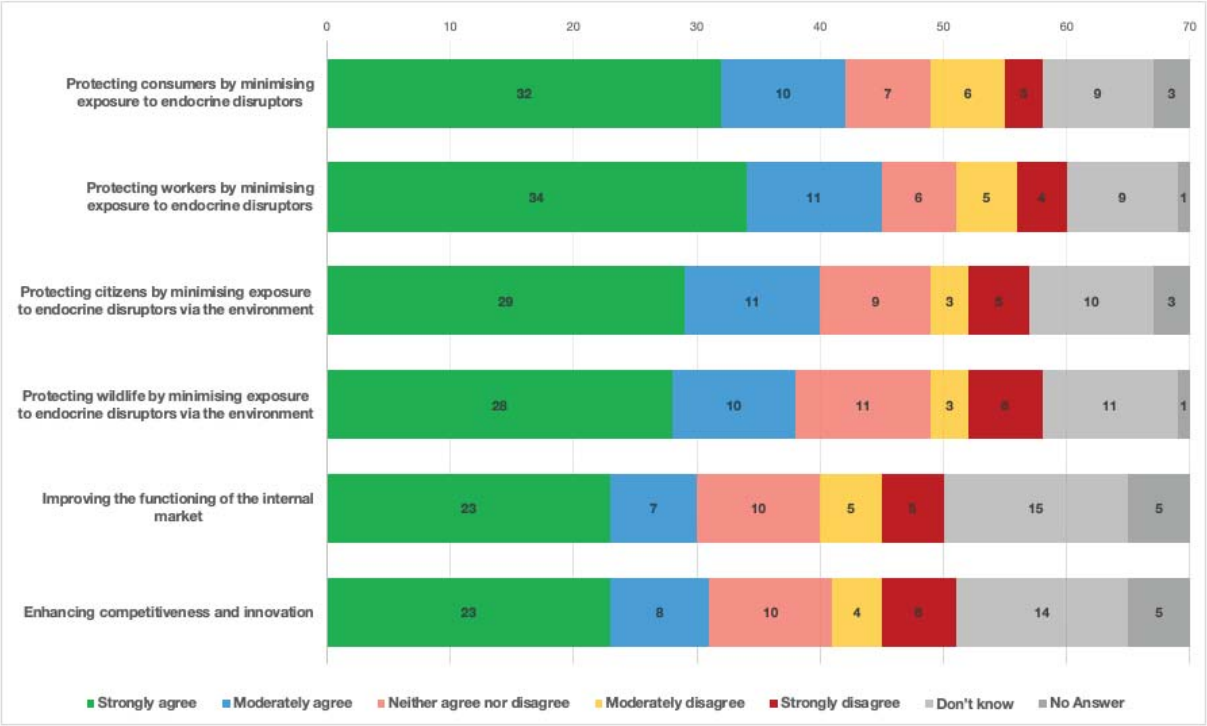

Figure 13.3. SME views on effectiveness

6.6 SME views on efficiency

Out of 70 respondents, the need to implement regulatory requirements for endocrine disruptors was reported to increase total operating costs by 25 respondents (3 to a significant extent, and 22 not to a significant extent), whereas 12 respondents reported no effect on operating costs. For the remaining 33 respondents, this question was either not applicable (30) or no answer was provided (3). Costs are related to: a) the replacement of substances (21 respondents); b) the preparation of registration or authorisation dossiers (14 respondents); c) the provision of test data (14 respondents); and d) the development of new testing methodologies (13 respondents).

In terms of the perceived impact of the provisions for endocrine disruptors on innovation, productivity, profitability and international trade within their sectors (**Figure 13.4**), few respondents (between 1 to 6) regarded the impact as negative or very negative and another minority (7 to 10) considered the impact as positive or very positive. The rest considered there was no impact (8 to 13), did not answer or did not know (14 to 17), or considered the question not applicable to them (26 to 32).

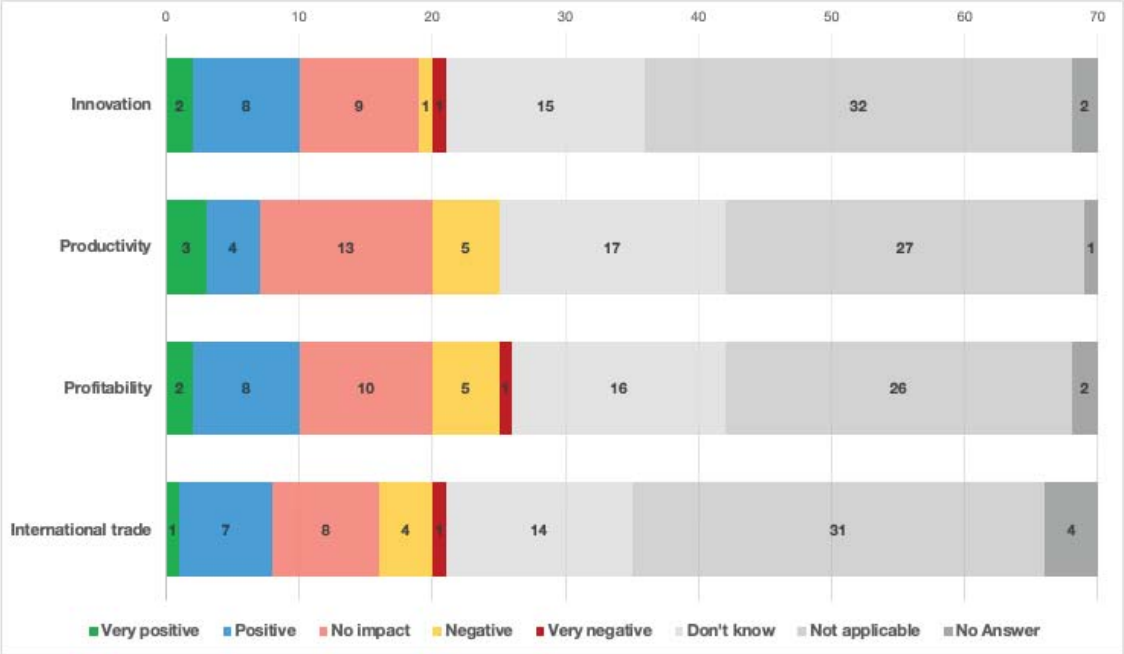

Figure 13.4. SME views on efficiency

The costs of the provisions for ED identification and management in each respondent's respective business sector were considered justified and proportionate for the benefits accrued by 23 respondents (3 fully and 20 to some extent), not at all justified or proportionate by 8 respondents, while 38 did not know.

6.7 SME views on EU added value

In some instances, Member State authorities have taken unilateral action on endocrine disruptors, before the EU made a decision on them. For example, in October 2012, the French authorities introduced a ban of Bisphenol A in all food contact materials, applicable from July 2015. One respondent commented on the need to treat products destined for France as a special case. Another expressed concerns about the implications of a Scandinavian SIN list.

Ninety-six percent of the respondents reported that unilateral Member State actions did not affect their company.

6.8 Additional comments made by SMEs

In the free text field for the final question (Q19; "Please provide any additional comment or suggestion that you consider relevant for the ED Fitness Check"), respondents raised the following points:

- Need to align legislation for cosmetics, chemicals, medical and surgical products and detergents
- Difficulty in moving from hazard identification to risk management.
- Difficulty in establishing a safe exposure threshold: " there is a big difference between injecting an isothiazolinone into a living being, and the exposure of an individual to a dry painting containing 0.00015%."

- Elimination of new ED substances is complicated and costly.
- The precautionary principle should be applied based on scientific evidence.
- Need for better information and tools (e.g. databases) for SMEs
- Need for SME support and private-public co-financing programmes

One respondent made reference to the fact that water companies do not seek information on endocrine disruptors, because the Drinking Water Directive does not impose an obligation to do so. It was also noted that some larger water companies are conducting research, such as into the feasibility of an effective extended producer responsibility (EPR) scheme on products that release micropollutants and microplastics into the aquatic environment during their life cycle[120].

Another respondent proposed to replace the plastic packaging materials with glass, and to replace juices containing dyes and synthetic chemicals with natural ones, which should also be favourably priced.

[120]http://www.eureau.org/resources/publications/4380-deloitte-eureau-report-extended-producer-responsibility-modules-1-2-3/file

Annex 3. Methodology

1 Summary

The methodology for the Fitness Check was developed by the JRC and agreed with the Interservice Steering Group. The methodology identified the legislation considered to be in the scope of the Fitness Check, and a series of questions were formulated to guide the interpretation of the five evaluation criteria, namely coherence, effectiveness, efficiency, relevance and EU-added value.

Four main evidence streams were generated to inform the findings: a) mapping of regulatory provisions related to the identification or risk management of endocrine disruptors; b) review of key policy and scientific documents; c) chemical specific case studies to illustrate the interplay between different pieces of legislation; and d) the results of consultations with the public, stakeholders and SMEs.

2 Workflow

The horizontal nature of the Fitness Check required a broad scope, covering many legal acts addressing chemicals that are relevant to human health and the environment. For much of the chemicals acquis, Fitness Checks and other 'Better Regulation' activities addressing specific pieces of legislation had been completed or are ongoing.

To make optimal use of the extensive work already completed under regulatory review activities, a stepwise approach was adopted (**Figure 14.1**). In the first phase (blue), a preliminary analysis of the current situation defined the scope of the Fitness Check and led to the formulation of the evaluation questions. In the second phase (orange), factual evidence was extracted from existing fitness checks, in-scope legislation and relevant literature reviews. Additional information relating to the evaluation questions was sought in the third phase (green) through a series of consultations.

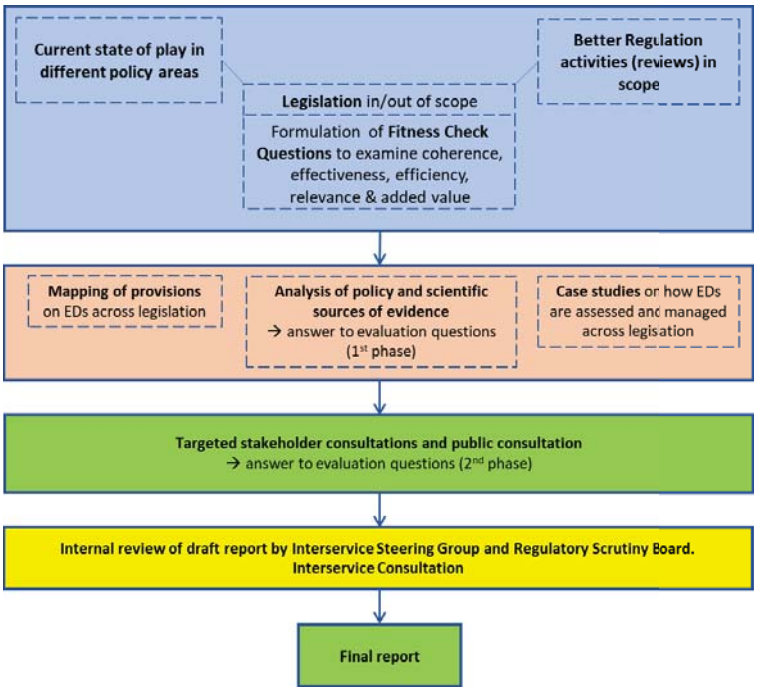

Figure 14.1 Workflow of the Fitness Check

3 Preliminary analysis of current situation

3.1 Questionnaire to policy DGs

A questionnaire was prepared by JRC to solicit initial inputs from policy DGs (ENV, GROW and SANTE) with experience in managing ED-relevant legislation on the current policy and regulatory state of play and the practical implementation of policy and legal instruments. Information was collected on the specific and generic provisions for ED identification, risk assessment and risk management, and on the chemicals that have been regulated based on identification as ED across the different pieces of (in-scope) legislation. This input informed the definition of the scope of the FC and the formulation of evaluation questions. It also provided an initial basis for a systematic mapping of provisions in the different pieces of legislation that are relevant for the identification, assessment and regulation of EDs.

3.2 Identification of Regulatory Reviews/Better Regulation activities

The evaluation of the 7th Environment Action Programme mentions ED risks as an emerging concern. ED-related issues are addressed at different levels of detail in recent Fitness Checks and evaluations of chemical legislation, including the REACH REFIT evaluation[121], the REACH Review on the authorisation route of substances with endocrine disrupting properties according to REACH Art. 138(7), the Fitness Check of the chemicals legislation other than REACH and the review of the legislation on cosmetics with regard to endocrine disrupting substances. Among legislation regulating downstream uses of chemicals in products, the evaluation of the legislation on food contact materials and the evaluation of the legislation on toy safety were also considered relevant to this FC. Among pieces of environmental legislation, the Fitness Check of the water legislation was considered for potentially ED-relevant aspects.

Also relevant was Annex 9 of the impact assessment on the definition of criteria for identifying EDs in the context of the Plant Protection Products Regulation and Biocidal Products Regulation. This provides a multi criteria analysis of impacts (on health, environment etc.) based on a scientific review of the evidence linking endocrine disrupting chemicals to hormone-related diseases and the estimated related costs to society attributed to exposure to EDs.

3.3 Definition of scope

On the basis of the mandate of the FC described in the Commission Communication "Towards a comprehensive EU framework on endocrine disruptors", in-scope legislation was defined as legislation including provisions for the identification, hazard assessment, risk assessment or risk management of chemicals with endocrine disrupting properties for human health and the environment. In-scope legislation includes:

[121] Second REACH review. COM(2018) 116 and SWD(2018) 58

a) Legislation that specifically identifies EDs with regulatory consequences following such identification (ED-specific provisions)
b) Legislation that does not specifically identify EDs but regulates chemicals according to the risk identified and which may include adverse effects on the endocrine system (general provisions)
c) Legislation which is interconnected with a) or b) with implications for the identification, hazard assessment, risk assessment or risk management of chemicals

Based on these criteria legislation considered in scope is listed in **Table 14.1.**

Table 14.1 Legislation in scope for this Fitness Check

Legislation
Plant Protection Products Regulation (EC) No 1107/2009
Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties (plant protection products)
Regulation (EU) No 283/2013 setting out the data requirements for active substances in accordance with Regulation (EC) No 1107/2009
Maximum Residue Levels of Pesticides Regulation (EC) No 396/2005
Biocidal Products Regulation (EU) No 528/2012
Commission Delegated Regulation (EU) 2017/2100 of 4 September 2017 setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council (biocidal products)
REACH Regulation (EC) No 1907/2006
CLP: Classification, Labelling and Packaging of substances and mixtures (EC) No 1272/2008
Persistent Organic Pollutants Regulation (EU) 2019/1021
Food contact materials legislation Regulation (EC) No 1935/2004*
Contaminants in food Regulation (EEC) No 315/93 and in feed Directive 2002/32/EC
Food Additives Regulation (EC) No 1333/2008
Cosmetic Products Regulation (EC) No 1223/2009
Medical Devices Regulation (EU) 2017/745
In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746
Toy Safety Directive 2009/48/EC
Fertilising Products Regulation (EU) 2019/1009
Detergents Regulation (EC) No 648/2004
Medicinal Products for Human Directive 2001/83/EC ** Coverage here limited to unintended exposure via the environment (see also 3.10)
Veterinary Medicinal Products Regulation (EU) 2019/6 ** Coverage here limited to unintended exposure via the environment (see also 3.10)
General Product Safety Directive 2001/95/EC
Water Framework Directive 2000/60/EC
Priority substances Directive 2013/39/EU
Drinking Water Directive 98/83/EC
Groundwater Directive 2006/118/EC
Marine Strategy Framework Directive 2008/56/EC
Urban Waste Water Directive 91/271/EEC

Legislation
Chemical Agents at Work Directive 98/24/EC
Carcinogens and Mutagens at Work Directive 2004/37/EC
Pregnant Workers Directive 92/85/EEC
Young People at Work Directive 94/33/EC
Waste Directive 2008/98/EC
Commission Decision 2014/955/EU on the list of waste pursuant to Directive 2008/98/EC
Restriction of the use of certain hazardous substances in electrical and electronic equipment Directive 2011/65/EU
Industrial emissions (integrated pollution prevention and control) Directive 2010/75/EU
Seveso-III-Directive 2012/18/EU
Ambient Air Quality and Cleaner Air for Europe Directive 2008/50/EC
EU Ecolabel Regulation (EC) No 66/2010

*Evaluation ongoing

**EU Pharmaceuticals Strategy is under development

3.4 Formulation of Fitness Check questions

Based on the preliminary analysis of the current situation, evaluation questions were drafted by JRC, with emphasis on coherence issues across the different in-scope regulatory instruments in **Table 14.1**. The questions were refined and endorsed by the inter-service steering group (ISSG).

To apply the FC questions, it was necessary to establish a baseline for comparison. When a temporal reference needs to be established, the baseline is the situation with no specific provisions in EU legislation, corresponding to the year of adoption of the first strategy on endocrine disruptors (1999). The evaluation questions relate to the specific policy interventions or non-interventions across the different regulatory sectors from 1999 to date (e.g. implementation of REACH or the establishment of ED criteria for pesticides and biocides). Other points of reference, such as non-EU jurisdictions, were considered when appropriate.

4 Extraction and review of available evidence

4.1 Mapping of provisions

The FC required analysis of the provisions that are relevant for the identification, assessment and management of EDs across in-scope legislation. ED-specific and general provisions on hazard assessment, risk assessment and management were mapped with inputs from policy DGs on the respective areas of competence. The mapping exercise identified the main regulatory instruments and the relevant implementing measures. Legislative instruments are to some extent interconnected. This is the case for substances with endocrine disrupting properties regulated both via the horizontal chemical legislation (e.g. REACH & CLP Regulations) and by sectorial legislation (e.g. cosmetic products, toys, food contact materials). The objective of this step was thus to provide a complete picture of how substances with endocrine disrupting properties are regulated in the EU, illustrating the current logic of legislative intervention across regulated sectors.

4.2 Policy and scientific sources of evidence

Regulatory reviews/Better Regulation activities

The outcome of recent and ongoing Better Regulation activities (**Section 2.1.2**), was expected to be a major source of information, together with the mapping of provisions (**Section 2.2.1**). Factual evidence was therefore extracted and synthesised to help address the evaluation questions.

EU institutions and stakeholder reviews

Numerous scientific studies and reports have been published in recent years. A selection of studies of policy and scientific relevance were identified and screened for relevant input to the evaluation questions. These studies (cited throughout this document) were studies by EU institutions; studies commissioned by EU institutions, national and international organisations; and studies by stakeholder organisations.

4.3 Evidence base and limitations

Details on the sources of evidence in previous Commission fitness checks and evaluations, including their limitations, are given in the respective reports.

Reviews in the scientific literature were used where they refer to general scientific background. Scientific studies and stakeholder reports were only used to refer to an important stakeholder point of view. The citation of these sources does not necessarily imply that the Commission agrees with the findings, or shares the same views.

4.4 Case studies

Case studies were developed for specific chemicals, which are regulated under different and interconnected legislative instruments, with the aim to provide representative examples illustrating how EDs are identified, assessed and managed across legislation for their effects on human health and the environment. Any differences or inconsistencies were analysed with inputs from the ISSG. The case studies were used as an additional source of evidence for the evaluation questions.

Substances selected for the case studies:

- 3-Benzylidene camphor (3-BC; under assessment under REACH and the Cosmetics Regulation; endocrine disruptor with human health and environmental concern)
- Diethylhexyl phthalate (DEHP; regulated under several pieces of legislation: REACH, cosmetic products, medical devices, food contact materials, toys, Water Framework Directive; endocrine disruptor with human health and environmental concern):
- Nonylphenol (NP; regulated under REACH (covering many sectors: detergents, biocides, plant protection products, cosmetic products, medical devices), Water Framework Directive; endocrine disruptor with environmental concern)

4.5 Evidence base and limitations

The main criterion for selecting case studies was that the substances should be identified as EDs, relevant to more than one policy area, thereby enabling an analysis of the coherence of the assessment and risk management approaches applied. The number of SVHCs with endocrine disrupting properties under REACH were limited at the time of selection to 14, with several being from the same chemical family. DEHP, 3-BC and nonylphenols and their ethoxylates are regulated by various pieces of analysed legislation, including the ones specifically mentioned in the FC mandate. DEHP and

nonylphenols are representative of two main groups of substances which have been formally identified as EDs (phthalates, alkylphenols). Thus, case studies were chosen to be as representative and informative as possible.

4.6 Economic case studies

Two economic case studies were also carried out to explore possible associations between the implementation of risk management measures on selected chemicals and trade flows, both within the EU and between the EU and non-EU countries (Canzian et al, 2020).

The first case study considered four low molecular weight (LMW) phthalates commonly used as plasticisers (DEHP, DBP, BBP and DIBP), which have been inter alia subjected to a series of restrictions since 1999. The second case study focused on 3-Benzylidene Camphor (3-BC), a UV filter used in sunscreen products and other whitening skin care cosmetic products, which has been subject to a ban under the Cosmetic Products Regulation since 2015 and was identified as SVHC under REACH in 2018.

The approach applied the "gravity model" including the Difference-in-difference (DiD) approach. Gravity models relate the magnitude of trade between countries to a series of country-specific characteristics - notably, their economic size and level of economic development - and to factors stimulating or discouraging the movement of products between countries. The latter include transportation costs, usually proxied by the presence or absence of a shared land border and by geographic distance, and informal and formal trade barriers, often proxied by the existence of a common language and by the presence of free trade agreements. Among other applications, gravity models have been used to evaluate trade under Non-Tariff Measures, such as the above-mentioned restrictions on chemicals.

The Difference-in-difference (DiD) approach is an econometric method for non-experimental causal inference.

In this study, it was used to compare the change in trade flows before and after the intervention of a treated group of units/countries relative to the change in trade flows before and after the intervention of a control group of units/countries considered to be a suitable counterfactual. The DiD approach aims to account for confounding variables.

As inputs to the methodology, worldwide import trade data were retrieved from the United Nations Commodity Trade Statistics Database (UN COMTRADE) for the years running from 1995 to 2018. Additionally, data were collected for control variables that are typically included in standard gravity models, such as the GDP, the size and the population levels of both countries, the geographical distance between them, whether they share a common language or (past or current) colonial ties. These variables were collected from CEPII (Centre d'Études Prospectives et d'Informations Internationales) and the World Bank.

In the case study on LMW phthalates, the analysis of trade flows focused on plasticisers, the actual material subject to the intervention. For the analysis of intra-EU trade flows, the control commodity was polyethylene polymer (PET), the most commonly used plastic not containing plasticisers.

In the case study on 3-BC, the analysis of trade flows focused on the commodity of "cosmetic and toilet preparations", while the control commodity for the analysis of intra-EU trade flows was "oral and dental hygiene preparations". The rationale for selecting the control commodity was that it

belongs to the same broader category as the treated good (cosmetic and toilet preparations) but excludes products containing UV filters.

To compare EU vs non-EU trade flows, there was no need for a control commodity, since the trade flows of the case commodity could be compared directly.

The use of the gravity model with difference-in-differences is a well-established econometric approach. The major source of uncertainty in these case studies was therefore linked to the nature of the input data. Since the trade flow data in the UN Comtrade database relate to baskets of commodities, rather than the specific chemicals of interest, it was necessary to choose proxies for the chemicals of interest (namely plasticisers for LMW phthalates, and cosmetic/toilet preparations for 3-BC). The actual market share of the chemical of interest in the chosen commodities was not known.

Thus, the two case studies illustrated some of the challenges in using economic analysis to identify the trade impacts of regulatory interventions. They also point to the need for higher resolution trade data, closer to the chemical and commodity of interest, as well as information on market shares.

5 Consultation activities

5.1 External consultation activities

Consultation activities were carried out to gather inputs from a broad range of stakeholder groups as well as citizens to ensure that views from all interested parties were considered in the evaluation. The consultation activities relied primarily on the results of three surveys aimed at the general public, stakeholders and SMEs. The targeted stakeholder consultations were also used to solicit information from companies on financial and other consequences of implementing ED-related legislation. Further information on the approach and findings is given in **Annex 2**.

5.2 Evidence base and limitations

The consultation activities were used as an additional source of evidence, recognising that survey results are associated with an inevitable bias towards those who have an interest in responding. Therefore, the results in **Annex 2** are presented in terms of the numbers and percentages of responses received. It is not implied that these statistics are representative of the population being surveyed.

In the **public consultation,** a total of 474 respondents provided an answer, of which 90% were EU citizens, 3% were academic/research institutions and 2% non-governmental organisations. Analysis of the survey results for attempts to bias the conclusions revealed no obvious re-occurring pattern across the answers. Ten percent of the responses were from non-citizens, but these showed no alignment to a common position and did not influence significantly the results.

In the **stakeholder consultation**, 183 responses were received. The respondents were businesses, public authorities, academics, research organisations, and civil society organisations.

In the survey targeting **micro, small and medium-sized enterprises** (SMEs), responses were received from just 70 SMEs. In this case, while individual free responses were informative of some SME views, the sample size was too small to draw firm conclusions.

Annex 4. Mapping of provisions and regulatory processes for identifying and managing Endocrine Disruptors

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1 Biocidal Products

The Biocidal Products Regulation ((EU) No 528/2012) aims to improve the functioning of the internal market through the harmonisation of the rules on the marketing and use of biocidal products, whilst ensuring a high level of protection of both human and animal health and the environment. The provisions of this Regulation are underpinned by the precautionary principle and pay attention to the protection of vulnerable groups.

All biocidal products require an authorisation before they can be placed on the market, and the active substances contained in the biocidal product must have been previously approved. The approval of active substances takes place at EU level and the subsequent authorisation of the biocidal products at Member State level (with possible extension to other Member States by mutual recognition). An authorisation of products at EU level (Union authorisation) is also possible.

The Biocidal Products Regulation is interlinked with other regulations and directives including: REACH, CLP, Chemical Agents at Work Directive, Carcinogens and Mutagens at Work Directive, POPs Regulation, Drinking Water Directive, and the Water Framework Directive.

This Regulation contains specific provisions for substances with endocrine disrupting properties. Regarding the identification of EDs, the Regulation states that "no later than 13 December 2013, the Commission shall adopt delegated acts in accordance with Article 83 specifying scientific criteria for the determination of endocrine-disrupting properties". The Commission conducted a public consultation and an impact assessment evaluating different options as included in the roadmap for supporting the process of developing the criteria. In addition, the regulatory process for setting the scientific criteria for the determination of endocrine disrupting properties under the Biocidal Products Regulation and the Plant Protection Products Regulation (EC) 1107/2009 was coordinated and aligned as far as possible. The Delegated Regulation setting out scientific criteria for the determination of endocrine-disrupting properties ((EU) 2017/2100) was adopted by the Commission in September 2017 and entered into application in June 2018. The criteria are based on the IPCS/WHO definition of an endocrine disrupter, and state that:

"A substance shall be considered as having endocrine disrupting properties that may cause adverse effect [in humans]/[on non-target organisms] if, based on points (a) to (d) of point (2), it is a substance that meets all of the following criteria, unless there is evidence demonstrating that the adverse effects identified are not relevant [to humans]/[at the (sub)population level for non-target organisms]:

(a) it shows an adverse effect [in an intact organism or its progeny]/[in non-target organisms], which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;

(b) it has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system;

(c) the adverse effect is a consequence of the endocrine mode of action"

Member State competent authorities evaluate the dossiers submitted by applicants in view of the approval (or renewal of approval) of active substances, and draft a Competent Authority Report which

is sent to ECHA for peer-review by the Agency and the other Member States. The Biocidal Products Committee (on behalf of ECHA) prepares an opinion which is the basis for decision on the approval by the European Commission, following a vote in the Standing Committee on Biocidal Products. The Endocrine Disruptor Expert Group set up by ECHA can be consulted for scientific advice, by the Competent Authority during its evaluation, or by the Biocidal Products Committee.

The guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 (and (EC) No 1107/2009) (developed jointly by ECHA and EFSA and published in June 2018; (ECHA et al., 2018)), describes how to perform hazard identification for endocrine-disrupting properties. As required by the criteria, the identification is based on the gathering, evaluation and consideration of all relevant information for the assessment, mode of action analysis, and application of a weight of evidence approach, to establish whether the ED criteria are fulfilled.

The Biocidal Products Regulation states that active substances which are considered as having endocrine-disrupting properties that may cause adverse effects shall not be approved. Derogations exist if (a) the risk to humans, animals or the environment from exposure to the active substance in a biocidal product, under realistic worst case conditions of use, is negligible, (b) it is shown by evidence that the active substance is essential to prevent or control a serious danger to human health, animal health or the environment; or (c) not approving the active substance would have a disproportionate negative impact on society when compared with the risk to human health, animal health or the environment arising from the use of the substance. However, the use of a biocidal product containing such active substances shall be subject to appropriate risk-mitigation measures to ensure that exposure of humans, animals and the environment is minimised. Moreover, such biocidal products shall not be authorised for making available on the market for use by the general public. They can also not be authorised via a Union authorisation.

The information requirements for active substances and biocidal products are listed in Annexes II and III to the Regulation. Currently, specific information requirements for endocrine disrupting properties are not part of the core data set (they are “additional” information requirements). However, applicants need to submit the relevant data to determine whether a substance can be considered to have ED properties as a competent authority shall have all the necessary information to carry out the evaluation of a substance. Studies shall be required in accordance with the Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009, among others, to elucidate the mode/mechanism of action, and provide sufficient evidence for relevant adverse effects. The guidance referred to above clearly states that the Test guidelines (TGs) are able to identify only certain endocrine modes of action related to the EATS pathways but that on a case-by-case basis specific investigations of evidence of other types of endocrine activity (non-EATS) may be requested. Although these TGs are not specifically designed to allow for the identification of EDs they do permit the identification of possibly endocrine-related adverse effects. The guidance is based on the OECD GD150 (OECD, 2018)[122] and the test guidelines within the OECD Conceptual

[122]This Guidance Document, originally published in 2012 and updated in 2018, is intended to provide guidance for evaluating chemicals for endocrine disrupting properties using standardised test guidelines. Specific objectives include providing a description of the OECD conceptual framework for evaluating chemicals for endocrine disruption, background on the standardised test methods used, and guidance for interpreting the outcome of individual tests. The Guidance Document is focused primarily on endocrine modalities included in the conceptual framework; estrogen, androgen, and thyroid mediated endocrine disruption and chemicals that interfere with steroidogenesis.

Framework (CF) from which a stepwise testing strategy is built to identify substances acting through EATS modes of action, in many cases requiring the generation of further data to either confirm or remove concerns for endocrine disrupting properties. A (systematic) review of the literature is also required to identify relevant studies from the published scientific literature.

Data requirements in Annex II and III are currently being adapted to scientific and technical progress including data that are relevant for the determination of ED properties.

2 Plant Protection Products and residues

The purpose of the Plant Protection Products Regulation ((EC) No 1107/2009) is to ensure a high level of protection of both human and animal health and the environment and to improve the functioning of the internal market through the harmonisation of the rules on the placing on the market of plant protection products, while improving agricultural production. The provisions of this Regulation are underpinned by the precautionary principle.

The Plant Protection Products Regulation is interlinked with other Regulations and Directives including: REACH, CLP, Chemical Agents Directive at Work, Carcinogens and Mutagens at work Directive, POPs Regulation, Drinking Water Directive, Water Framework Directive, and the Directive on the Sustainable Use of Pesticides.

The Regulation on maximum residue levels (MRLs) of pesticides ((EC) No 396/2005), ensures a high level of consumer protection and harmonised provisions relating to maximum levels of pesticide residues in or on food and feed of plant and animal origin.

Similar to the Biocidal Products Regulation, the Plant Protection Products Regulation contains specific provisions for substances with endocrine disrupting properties. Regarding the identification of EDs, specific scientific criteria for the determination of endocrine disrupting properties were introduced into the PPPR by the Regulation (EU) 2018/605. These criteria are applicable since November 2018.

The criteria are almost identical to those applicable to the biocidal products (see above). A guidance for the identification of endocrine disruptors in the context of Regulations (EC) No 1107/2009 (and (EU) No 528/2012) is available (published in June 2018, see above under biocides for more details).

The procedure to approve a substance starts with the submission by an applicant of a dossier to a Rapporteur Member State, who prepares an initial risk assessment and a Draft Assessment Report which EFSA, together with the Member States, peer reviews. EFSA then adopts conclusions and the Commission prepares a review report and a draft Regulation on the approval (or renewal of approval), which is presented to the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) for a vote, following which the Commission adopts the Regulation.

Similarly applications for setting or changing Maximum Residue Levels (MRLs) can be submitted by an applicant to a Member State which carries out an initial risk assessment and prepares an Evaluation Report, followed by an assessment of the application and the Evaluation Report by EFSA, which adopts a reasoned opinion on the risk to the consumer and where relevant to animals associated with the setting, modification or deletion of an MRL. The Commission then prepares a draft Regulation to set (amend or remove) MRLs, which is presented to the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) for a vote, followed by scrutiny of the draft Regulation by the Council and the European Parliament. If neither of them objects, the Commission adopts the Regulation.

The Plant Protection Products Regulation states that an active substance, safener or synergist shall only be approved if it is not considered to have endocrine disrupting properties that may cause an adverse effect in humans or non-target organisms, unless the exposure of humans/non-target organisms to that active substance, safener or synergist, under realistic proposed conditions of use, is negligible, or if the substance is necessary to control a serious danger to plant health, which cannot be contained by other available means including non-chemical methods. If an active substance is considered to have endocrine disrupting properties that may cause an adverse effect in humans, and the derogation possibilities are fulfilled, it can only be approved as a candidate for substitution in accordance with Article 24 of the Regulation.

According to Recital (27) of the MRL Regulation, it is necessary that endocrine disrupting properties are taken into consideration when setting an MRL.

The data requirements for active substances and plant protection products are described in Regulations (EU) No 283/2013 and (EU) No 284/2013 respectively. Regarding the toxicological assessment, if there is evidence that an active substance may have ED properties, additional information or specific studies are required to elucidate the mode/mechanism of action, and to provide sufficient evidence for relevant adverse effects. The ecotoxicological assessment should consider mammalian data. The list of test methods and guidance documents relevant to the implementation of these Regulations are presented in Commission Communications 2013/C 95/01 and 2013/C 95/02. The Commission Communications are currently being revised in order to include methods that are relevant for the determination of ED properties.

3 REACH

Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) aims at improving the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances while promoting alternative methods for the assessment of hazards of substances**Error! Bookmark not defined.**. This is done by the four processes of REACH, namely the registration, evaluation, authorisation and restriction of chemicals. REACH also aims to ensure free circulation of substances while enhancing innovation and competitiveness of the EU chemicals industry.

A brief overview of REACH can be found in the Staff Working document of the last REACH review[123].

In general, all provisions of REACH, including those of registration, evaluation, SVHC-identification, authorisation and restrictions, apply to chemical substances used in other sectors for which specific legislation exist with references to REACH provisions, unless there is a specific exemption mentioned in REACH.

Manufacturers or importers of chemicals must register their substances with ECHA. Registration requires to provide data on the substance properties. The obligatory information requirements increase with the tonnage range. The underlying assumption for requesting less data for lower tonnage substances is that tonnage is a placeholder for exposure, and that due to that the risk from substances

[123]SWD(2018) 58, part 1, section 2.1.3.

manufactured or placed on the market in lower tonnages is also lower. Substances registered in quantities above 10 tonnes per year must undergo a chemical safety assessment (REACH Annex I).

Provisions of the Substance Evaluation procedure allow ECHA, based on an evaluation by Member States, to oblige registrants to provide further data not listed in the information requirements. Any test that is based on a Test Guideline that is accepted by the Commission or ECHA can be requested, including all methods listed in the OECD GD 150 (OECD, 2018).

ECHA implemented an approach to screen substances in the REACH database using computational tools to identify substances that require further regulatory action. The screening includes indications of ED properties and allows prioritising substances for further assessments.

Only a part of the information and tests described in the Conceptual Framework of the OECD GD 150 for evaluating chemicals for endocrine disruption within a tiered approach, are included in the REACH Annexes on standard data requirements. However, as described above, further data can be requested from registrants via the Substance Evaluation procedure. The European Commission, as part of its activities outlined in the Commission Communication "Towards a comprehensive European Union framework on endocrine disruptors", has proposed an update of REACH Annexes for inclusion of data requirements relevant to endocrine disruption.

Provisions under REACH for identifying substances with endocrine disrupting properties are in Article 57 (f) and Article 59. The IPCS/WHO (IPCS, 2002) definition of endocrine disruptors is used as a basis for identifying substances of very high concern (SVHCs) with endocrine disrupting properties. However, not all substances with endocrine disrupting properties necessarily qualify as SVHCs under REACH. It has to be additionally demonstrated that there is scientific evidence that the effects of the substance give rise to equivalent level of concern to those mentioned in Article 57 (a) to (e) (substances meeting the criteria for classification as CMRs cat. 1A/1B or to persistent, bioaccumulative and toxic (PBT) substances, or to very persistent and very bioaccumulative (vPvB) substances). As for other regulations, REACH distinguishes when identifying endocrine disruptors between substances having effects on human health and substances having effects on the environment.

To be identified as a SVHC, it is not required that a substance is registered under REACH or that it is manufactured in the EU, imported or used. The identification of SVHCs with endocrine disrupting properties can apply in principle to all chemical substances, irrespective of whether sectorial legislation is regulating the use of a chemical. *Inter alia*, REACH can identify substances as SVHCs when they are used e.g. in cosmetic products, toys, food contact materials, or as co-formulants in biocidal and plant protection products.

Member States or ECHA (on behalf of the Commission) assess whether a substance exerts potentially endocrine-related adverse effects, whether scientific evidence allows establishing an endocrine activity and whether a scientifically plausible link between endocrine activity and adverse effects can be shown. The assessment is documented in a dossier following the requirements of REACH Annex XV[124]. The Member State Committee (MSC) at ECHA decides by unanimity whether a substance is identified as an SVHC with endocrine disrupting properties. If there is not unanimity within the MSC,

[124]Annex XV: Dossiers – general principles of preparing dossiers to propose and justify the identification of CMRs, PBTs, vPvBs or a substance of equivalent concern (such as EDs) as well as restrictions on the manufacture or placing on the market or use of a substance within the community.

the responsible comitology Committee (REACH Committee) votes on a draft decision prepared by the Commission.

The use of substances identified as SVHCs with endocrine disrupting properties can be subjected to the REACH authorisation procedure as described in REACH Title VII (authorisation). Substances regulated via some of the sectorial pieces of legislation are partially or totally excluded from the authorisation requirement under REACH. This is based on the rationale that sectorial legislation is providing provisions for risk assessment and risk management of the use of substances in the sectorial areas. Several pieces of legislation already cover the assessment of risks to human health, but not risks to the environment. In these cases, REACH authorisation applies to substances that have been identified as SVHCs with endocrine disrupting properties having effect on the environment. This is the case for substances used in a) cosmetic products, b) medical devices and c) food contact materials. REACH does not exclude substances used in toys from the authorisation requirement, for either SVHC with effects to the environment or to human health.

The identification of a substance as SVHC with endocrine disrupting properties is not a precondition for taking regulatory risk management measures under REACH other than authorisation. The restriction process addresses unacceptable risks to human health or the environment posed by any substance that requires Union-wide action. The manufacture, use or placing on the market of those substances on their own, in mixtures or in articles may be restricted for some uses or even completely banned, if necessary. Several substances which are endocrine disruptors have been restricted (**Error! Reference source not found.**). The standard restriction procedure can be launched on the initiative of a Member State or by ECHA (acting on a request from the Commission). It requires the preparation of an Annex XV dossier, which should include information on hazard and risk, information on alternative substances, justification for restrictions, and socio-economic information. Relevant information is further gathered via a public consultation and by consulting the Forum for Exchange of Information on Enforcement (Forum). The scientific committees at ECHA (RAC and SEAC) assess the information in the dossier and gathered via the consultations and provide opinions to the Commission, which drafts then a decision and submits it to the responsible Comitology committee (REACH Committee). REACH restrictions apply in general to uses of substances or to the placing on the market of substances or articles in other sectors unless exempted by specific REACH provisions. This includes *inter alia* substances used in cosmetic products (only with regard to addressing risks to the environment), toys, food contact material, medical devices, detergent substances used in biocidal products (active substances, co-formulants), and substances used in plant protection products (active substances, co-formulants) etc.

4 Classification, Labelling and Packaging (CLP)

The Regulation (EC) N° 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures (CLP Regulation) determines whether a substance or mixture displays properties that lead to a hazard classification and ensures that such hazards are communicated through consistent labelling along the supply chain including workers and consumers. Manufacturers, importers and downstream users must evaluate (Article 5) and classify (Article 13) substances according to classification criteria laid out in Annex I.

In the CLP Regulation, the EU implements almost completely the United Nations Globally Harmonised System (GHS) for classification and labelling of chemicals. Classification categories in Annex I include *inter alia* germ cell mutagenicity (section 3.5), carcinogenicity (section 3.6) and reproductive toxicity (section 3.7) and specific target organ toxicity (STOT), single and repeated

exposure (sections 3.8 and 3.9). For ecotoxicity, a generic hazard category for the aquatic environment is listed (short and long term). Classification takes into account the total weight of evidence, (Article 5 and section 1.1.1 of Annex I). This means that all available information that bears on the determination is considered together (Article 5).

There are no classification criteria for EDs, however effects on endocrine organs are explicitly mentioned as relevant to reproductive toxicity: relevant information includes epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs (CLP, Annex I, 3.7.2.3.1)

Generic and specific concentration limits are established (Article 10) for the classification of substances and mixtures. The Regulation applies, as a general principle, to all substances and mixtures supplied in the EU but not to chemicals that are in the finished state intended for the final user: medicines, medical devices, cosmetic products, veterinary medicines, food and feeding stuff such as food additives, food flavouring and feeding stuffs used in animal nutrition (Article 1.2). CLP acts as a horizontal reference point for a large number of the EU chemicals and chemical-related legislation designed to ensure consistency in chemical hazard identification and classification.

The REACH Regulation, the Regulation on Biocidal Products (BPR), the Regulation on Plant Protection Products (PPPR) and the CLP Regulation are closely interlinked. The obligation to classify is based on the CLP Regulation (Article 4). The provisions of the CLP Regulation apply in full to any substance or mixture whose marketing and use are controlled by the BPR or the PPPR.

Many other pieces of legislation refer to CLP hazard classes and categories in their provisions, often with direct implications for risk management. Examples of legislation including such references include REACH, cosmetic products, food contact materials, toys, medical devices and *in vitro* diagnostic medical devices, occupational safety and health (OSH) legislation (including chemical agents at work, carcinogens and mutagens at work, young people at work, pregnant and breastfeeding women at work directives), ecolabel, industrial emissions directive, detergents, hazardous waste.

5 POPs Regulation

The Persistent Organic Pollutants (POPs) Regulation (EU) 2019/1021 implements two worldwide agreements, the Stockholm Convention[125] and the Aarhus Protocol[126] to the Convention on Long-Range Transboundary Air Pollution, without including specific provisions for ED identification. Its aim is to protect human health and the environment from the risk posed by organic substances that persist in the environment, accumulate in living organisms.

Under the Stockholm Convention, POPs are defined by criteria of persistence, bioaccumulation, long-range transport and adverse effects (paragraph 1 of Annex D to the Convention). Adverse effects are demonstrated by toxicity or ecotoxicity data indicating the potential for damage to human health or the environment. If a substance fulfils the Annex D criteria, a risk profile in accordance with Annex E to the Convention is prepared. If it is concluded on the basis of the risk profile that a substance leads to significant adverse human health and environmental effects such that global action is warranted, a risk management evaluation is prepared, which considers socio-economic aspects in accordance with

[125] http://www.pops.int
[126] https://www.unece.org/env/lrtap/pops_h1.html

Annex F to the Convention. On the basis of the risk management evaluation, a recommendation is made to include the substance in Annex A (ban with or without specific exemption), Annex B (restriction with or without acceptable purpose or specific exemption) or Annex C (in case of unintentional production) to the Convention. Following the inclusion of a substance in the Convention, the substance is listed in the POP regulation.

The Regulation defines requirements for the reporting on environmental release inventories (Article 6) environmental monitoring (Article 10) and production volumes (Article 13) of POPs. Release should be minimised or eliminated from all sources (Article 6) including waste (Article 7). Waste containing or contaminated with POPs should be handled to ensure no release or recirculation in material flows.

When a substance is prohibited or restricted in the POPs Regulation, the Commission withdraws the authorisation for that use under REACH. When a substance restricted under REACH is subsequently listed under the Stockholm Convention, the practice is to implement the listing in the Stockholm Convention by amending the appropriate Annex(es) to the POPs regulation and to remove the restriction from REACH (examples of this are decaBDE, pentaBDE and PFOAs).

6 Toys

The Toy Safety Directive (2009/48/EC) aims to ensure that "*toys including the chemicals they contain, shall not jeopardise the safety or health of users or third parties when they are used as intended or in a foreseeable way, bearing in mind the behaviour of children*". Regarding chemicals the directive sets a number of limitations, such as for metals or allergenic fragrances. It is closely interconnected with the CLP regulation, such as concerning the prohibition of CMR substances, and the REACH regulation, such as concerning the restriction of phthalates. In general, all provisions of REACH apply to chemical substances used in toys.

The directive does not have specific provisions for EDs. However, it allows to establish specific limit values for any chemical (including EDs) in toys for children under 36 months of age and for toys intended to be placed in the mouth (Appendix C). So far, this approach has been used for CMR substances such as bisphenol A but also for strongly sensitising substances.

CMR substances cat. 1A, 1B or 2 are prohibited in principle (Annex II, Part III, point 3). However, by derogation CMRs may be used in toys up to the relevant limits in the CLP regulation. CMRs may also be permitted by the Commission if certain criteria are fulfilled (Annex II, Part III, point 4 for cat. 1 CMRs, Annex II, Part III, point 5 for cat. 2 CMRs). The criteria include a safety evaluation with an opinion of the relevant Scientific Committee that the use of the CMR in toys is safe.

7 Food legislation

7.1 Food Contact Materials

Alongside EU food law (EC) No 178/2002, Regulation (EC) No 1935/2004 aims to protect consumers from exposure to substances migrating from food contact materials and articles (FCM) into food. FCM are either intended to be brought into contact with food, are already in contact with food, or can reasonably be brought into contact with food or transfer their constituents to the food under normal or foreseeable use and includes direct or indirect contact. Examples include containers for transporting food, machinery to process, store food, packaging materials as well as kitchenware and tableware.

The objectives of the FCM Regulation are to ensure *the effective functioning of the internal market in relation to the placing on the market in the Union of materials and articles intended to come into contact directly or indirectly with food, whilst providing the basis for securing a high level of protection of human health and the interests of consumers.* Specific rules have been introduced at EU level mainly on the composition of plastic FCMs, including an authorised list of substances and associated restrictions. However, rules also exist on active and intelligent packaging (AIM), ceramic-ware, regenerated cellulose film, some specific substances and processes to recycle plastic, all focussed on chemical safety.

The use of chemicals in FCMs in relation to protection of the environment is regulated under REACH. As FCMs are already regulated in relation to human health by the Regulation (EC) No 1935/2004, FCMs are exempted from some of the requirements in REACH. This means that the REACH authorisation procedure does not apply to FCMs, unless the chemical enters the authorisation process under REACH due to environmental health concerns (Article 56(5)(b) of REACH) and the chemical safety report is not required to include an evaluation of human health risks (Article 14(5)(a) of REACH). However, for certain substances, the restrictions laid down in Annex XVII to REACH apply equally to those found in FCMs, such as phthalates in articles used for feeding children, polycyclic aromatic hydrocarbons (8 PAHs) in all articles where oral exposure occurs, and perfluorooctanoic acid (PFOA).

The FCM Regulation does not contain specific provisions for EDs. However, substances for which an authorisation is required, such as monomers and additives in plastic FCM, require an evaluation by the European Food Safety Authority (EFSA). EFSA requires specific studies depending on the migration level to food based on a tiered-approach. For example, in the case of plastic FCM, where migration is relatively high (i.e. migration 5 – 60mg/kg food) studies investigating reproductive and developmental toxicity are required (EFSA Panel on Food Contact Materials et al., 2008). In its work, EFSA evaluates hazardous properties and risks of substances by examining data on migration and potential exposure. The resulting risk management action is therefore based on the risk from the substance, rather than purely intrinsic hazardous properties. Legal reference is only made to CMR substances, which require assessment even if they are used behind a functional barrier (to avoid migration) according to specific EU rules on plastics and AIM.

In addition, EFSA may evaluate or re-evaluate substances considering additional information that becomes available since the initial assessment. Such is the case for bisphenol A (BPA) where EFSA continues to date, to assess scientific information on the endocrine disrupting properties of BPA. However, the 2015 EFSA opinion on BPA (EFSA Panel on Food Contact Materials et al., 2015) has already resulted in increased risk management action by the Commission[127], including further restrictions based on the precautionary principle. More recently, EFSA has assessed the risk from phthalates from the diet (EFSA Panel on Food Contact Materials et al., 2019), taking into account new information available on the toxicity to reproduction of these substances assessed by ECHA under REACH and for which the Commission is taking follow-up action concerning their use in plastic FCM (see also Annex 1, DEHP case study).

[127]Commission Regulation (EU) 2018/213 - on the use of bisphenol A in varnishes and coatings intended to come into contact with food and amending Regulation (EU) No 10/2011 as regards the use of that substance in plastic food contact materials

EFSA has also recently published a scientific opinion which describes recent developments in the safety assessment of chemicals in food and explores their potential impact on its evaluations of FCM (EFSA Panel on Food Contact Materials et al., 2016). The opinion indicates that the use of the most recent updated versions of test guidelines and new methodologies which includes potential endocrine disruptors (as from OECD GD150, 2018), as well as immunotoxicity and neurotoxicity effects identification may be needed depending first on the initial testing strategy.

Currently, the European Commission is carrying out an evaluation to assess to what extent the current EU legislative framework for FCMs is fit for purpose and delivers as expected. The evaluation has been examining, *inter alia*, the coherence with other legislation, such as REACH. Whilst the evaluation is still ongoing, the Commission is also in the process of preparing an impact assessment on new FCM rules, taking into account the information already collected from the FCM evaluation and other initiatives, such as this ED Fitness Check, whilst complementing the already established information.

7.2 Contaminants in feed and food

Under the European framework legislation, Council Regulation (EEC) No 315/93 lay down procedures for contaminants in food and Directive 2002/32/EC provides for the establishment of regulatory levels on undesirable substances (contaminants) in feed. Contaminants in food are *any substance not intentionally added to food which is present in such food as a result of the production (including operations carried out in crop husbandry, and animal husbandry), manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food or as a result of environmental contamination*. In feed, undesirable substances (contaminants) are defined as *any substance or product which is present in and/or on the product intended for animal feed and which presents a potential danger to animal or human health or to the environment or could adversely affect livestock production*. With regard to residue levels of pesticides in food or feed, those are covered by Regulation (EC) No 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin (see paragraph 3.2). With regard to residue levels of veterinary medicinal products administered to food-producing animals and present in food, those are covered by Regulation (EC) No 470/2009.

Council Regulation (EEC) No 315/93 provides the basis for establishing maximum levels or maximum tolerances for certain contaminants but does not identify specific substances for which maximum levels are to be established. Maximum levels are set in Commission Regulation (EC) No 1881/2006 for e.g. nitrates, mycotoxins, metals, dioxins and PCBs, polycyclic aromatic hydrocarbons.

As such, Commission Regulation (EC) No 1881/2006 does not contain specific provisions for the identification, risk assessment and risk management of endocrine disruptors. However, potential effects of endocrine disruptors are also covered by Annex XVII to REACH, on restriction of use, and several substances listed in that Annex fall within the scope of the contaminants legislation when present in food. Restriction of use of these substances can effectively result in preventing or minimising their presence in food.

Indirect protection to potential endocrine disrupting effects related to the presence of contaminants in food is also ensured by Directive 2002/32/EC on undesirable substances in animal feed which, in Article 3 states that: *products intended for animal feed may enter for use in the Community from third countries, be put into circulation and/or used in the Community only if they are sound, genuine and of merchantable quality and therefore when correctly used do not represent any danger to human*

health, animal health or to the environment or could adversely affect livestock production. Hence, in case the presence of a potential endocrine disrupting chemical in food of animal origin is the result of the transfer from feed into food of animal origin, the presence of this potential endocrine disrupting chemical in food has to be minimised by regulating this chemical in feed.

7.3 Food additives

Regulation (EC) No 1333/2008 covers food additives and Regulation (EC) No 1331/2008 establishes a common authorisation procedure for food additives, food enzymes and food flavourings.

The most recent implementation (Commission Regulation (EU) No 234/2011) describes a common authorisation procedure for food additives, food enzymes and food flavourings including data required for safety assessment. The regulations do not specifically address endocrine disrupting properties however, some of the data required (by Article 6 of Regulation (EU) No 234/2011), such as sub-chronic toxicity; chronic toxicity/carcinogenicity; reproductive and developmental toxicity are able to provide information on endocrine properties, particularly where additional endocrine-related parameters have been recently included (e.g. thyroid hormone levels in subchronic toxicity tests) to place more emphasis on endocrine-related endpoints. The EFSA Guidance for submission of food additive evaluations (EFSA Panel on Food Additives and Nutrient Sources added to Food, 2012) describes a tiered-approach for the safety assessment requiring subchronic toxicity testing within Tier 1 that also includes additional parameters on endocrine-related endpoints, (e.g. determination of thyroid hormones, gross necropsy and histopathology of tissues that are indicators of endocrine-related effects) allowing for the identification of effects that may warrant further in-depth investigation. In addition, Commission Regulation (EU) No 234/2011 lays down specific data required for risk assessment and data required for risk management of food additives (Articles 6 and 7) as well as food enzymes (Article 8 and 9) and flavourings (Articles 10-11). For food additives, these contribute to establishing normal and maximum use levels of food categories included in the Union list of approved food additives (Regulation (EC) No 1333/2008 Annex II) with related management measures and provide coverage of potential endocrine disruptors by using the most recent updated versions of the Test Guidelines.

8 Cosmetic Products

Regulation (EC) No 1223/2009 on cosmetic products (CPR or "Cosmetics Regulation") aims to ensure a high level of protection of human health by providing a framework for assessing and managing cosmetic ingredients. Its scope is limited to the functioning of the internal market and a high level of protection of human health, whereas environmental concerns, including the identification and regulation of environmental EDs, are addressed under the REACH regulation. Within the human health domain, the regulation establishes its own framework for risk assessment and risk management. However, substances used in the cosmetics sector over 1 tonne per year are subject to the REACH registration, which includes data generation as laid down in the standard information requirements of (Chapter 3.2 of REACH). REACH, however, exempts substances used in cosmetics specifically from the chemical safety report/chemical safety assessment for human health. Instead, the CPR requires evaluation of the finished cosmetic product through the Cosmetic Product Safety Report.

Annex II to the CPR lists substances prohibited in cosmetics products. Annex III lists restricted substances that shall be used in accordance with the restrictions laid down therein. Certain categories of ingredients, namely colorants, preservatives and UV-filters, can only be used in cosmetic products

if they have been authorised through their inclusion in the so-called “positive lists” of the CPR (Annexes IV, V and VI).

For all cosmetic products made available on the EU market, the operator designated as the responsible person shall ensure that the cosmetic product undergoes a safety assessment and that a cosmetic product safety report is set up. In case of identified potential risk to human health or for adaptation to technical and scientific progress the Commission can prohibit or restrict ingredients from use in cosmetic products by amending the relevant Annexes to the CPR. Amendments to the Annexes of the CPR (inclusion of new substances or revision of existing entries) are preceded by a scientific risk assessment conducted by the Scientific Committee on Consumer Safety (SCCS). According to the SCCS Notes of Guidance (SCCS, 2018), in the risk assessment procedure for substances used as cosmetic ingredients, the SCCS considers, among other factors, the exposure assessment for specific vulnerable groups, such as children and pregnant women.

Article 15 of the CPR governs the use in cosmetic products of substances which have been classified as carcinogenic, mutagenic or toxic for the reproduction (CMR) under the CLP regulation. CMR substances of category 1A or 1B and of category 2 under Part 3 of Annex VI to Regulation (EC) No 1272/2008 shall be prohibited from use in cosmetic products unless a derogation is granted. Article 15(1) governs the derogations that might apply to CMR substance classified in category 2. This requires that the substance is evaluated by the SCCS and found safe for use in cosmetic products, while Article 15(2) governs the derogations that might apply to substance classified as CMR 1A or 1B.

The CPR does not have any specific provisions for EDs. For substances that have been identified or have potential endocrine disrupting properties, but are not classified as CMRs, the assessment of potential risk to human health is governed by the general provisions of Article 31. Article 31 provides that where there is a potential risk to human health, arising from the use of substances in cosmetic products, which needs to be addressed at EU level, the Commission may, after consulting the SCCS, amend Annexes II to VI accordingly. The ability of the regulation to identify and assess potential endocrine disrupting substances depends on the toxicological data related to potential ED modalities available to the SCCS. The CPR does not set specific toxicity test requirements. However, there are explicit guidelines included in the SCCS Notes of Guidance that follow the recommendations of WHO and OECD on this issue.

Article 18 prohibits animal testing of finished cosmetic products and cosmetic ingredients (“testing ban”) as well as the placing on the EU market of cosmetic products and their ingredients tested on animals in order to meet the requirements of the CPR. Since its enforcement, only *in silico* and *in vitro* methods can be used to evaluate safety. However, *in vivo* studies may still be used if performed before the animal testing ban or if they become available through the requirement of other regulatory processes such as PPPs, biocides and REACH.

Cosmetic ingredients could be assessed for endocrine properties in a stepwise approach using non-animal methods (*in silico* models, read across, *in vitro* assays, other mechanistic techniques such as 'omics') and/or data generated outside the cosmetics sector. Regarding reproductive toxicity three non-animal methods have been developed and validated by ECVAM for embryotoxicity screening purposes. Overall, as recognised in the Memorandum SCCS/1544/14 and in the SCCS Notes of Guidance, the complex endpoint of reproductive toxicity is not covered by the above systems and no alternative methods are currently available covering the whole area. In practice, many recent

evaluations and decisions have relied on historical *in vivo* data generated before the animal testing ban in combination with evidence emerging from non-animal methods.

As per Article 15(4), the Commission has consulted the SCCS when reviewing the regulation regarding substances with endocrine-disrupting properties[128]. The review concluded that "*the experience collected since the entry into application of the Cosmetics Regulation has not revealed elements which would justify deviating from the regime designed by the legislator to address the safety concerns related to the use of endocrine disruptors in cosmetics*". In the same Communication, the Commission committed to establish a priority list of potential EDs not already covered by bans or restrictions in the CPR for their subsequent safety assessment. A priority list of 28 potential EDs in cosmetic products was consolidated in early 2019 based on input provided through a stakeholder consultation[129]. In 2019 the Commission organised a public call for data on 14 of the 28 substances (to be treated with higher priority) to enable the preparation of the safety assessment of these substances. In February 2020 the Commission mandated the SCCS to carry out the risk assessments with an updated evidence base for five substances, including one hair dye (resorcinol), one preservative (propylparaben) and three UV-filters (octocrylene, homosalate and benzophenone-3). The mandate set a nine-month deadline for the SCCS to adopt the preliminary opinions. Concerning the remaining nine substances with suspected endocrine disrupting properties, the Commission has requested additional data to proceed with the risk assessment. Provided that new scientific data are submitted, the Commission will proceed in mandating the SCCS in the first half of 2021.

9 Medical devices and *in vitro* diagnostics

The Medical Devices Regulation (MDR) (EU) 2017/745 and the Regulation (EU) 2017/746 on *In Vitro* Diagnostics (IVDR) adopted in May 2017 will apply from May 2021[130] and May 2022, respectively.

Medical devices are critical for health and safety of patients and are often lifesaving. Therefore, the special and fundamental feature of the regulatory framework on medical devices is the principle of benefit-risk ratio, i.e. the benefit of the device must outweigh the risks for it to be compliant.

Both Regulations have specific provisions (Annex I) on substances with endocrine disrupting properties with effects on human health. With reference to the MDR and only for certain types of devices the manufacturer is required to perform a thorough justification for the presence of such substances at a concentration above 0.1% w/w. This justified exemption procedure is not included in the IVDR. Such justification shall be based, among others, on an analysis of possible alternative substances. For identification of substances with endocrine disrupting properties for human health, reference is made to REACH, and only for the MDR, to the Biocidal Products Regulations, which have processes in place to update the list of these substances.

To satisfy the requirements of MDR and IVDR Regulations, the manufacturer must demonstrate that the benefit of the device placed on the market offsets the risks from use of substances with endocrine disrupting properties to human health. Regarding possible benefit, SCHEER was mandated by the Commission to draft Guidelines for the benefit/risk assessment on the presence of phthalates having endocrine disrupting properties in certain medical devices (SCHEER, 2019).

[128]COM(2018) 739
[129]https://ec.europa.eu/growth/sectors/cosmetics/products/endocrine_en/
[130]http://data.europa.eu/eli/reg/2020/561/oj

10 Human and veterinary medicines

Human and veterinary medicines are regulated respectively by Directive 2001/83/EC and by Directive 2001/82/EC, to be replaced as of January 2022 by Regulation 2019/6. The regulatory framework for human and veterinary medicines follows a different logic than for other chemicals, with the main emphasis on the therapeutic benefit for the target group evaluated in the context of possible adverse side effects and risks to target organisms (patients and treated animals). The rationale for including this policy area in this FC is primarily related to those provisions aiming at protecting non-target organisms in the environment[131]. The forthcoming Commission EU Pharmaceutical strategy will further consider the environmental aspects of medicinal products, including effects of EDs as part of the implementation of the Commission Communication on the EU strategic approach of pharmaceuticals in the environment (COM(2019) 128).

Whereas there is no formal requirement for ED identification for pharmaceuticals and veterinary medicines, in both cases concerns related to the environmental impact of endocrine properties can be addressed through environmental risk assessment. It can be expected that information relevant to the assessment of endocrine disrupting properties in these sectors comes from data generated in the context of safety to target organisms. It should always be kept in mind that the intended purpose and mechanism of action of the medicine concerned may target the hormonal system of the body. These medicines may be life-saving and used in treatment of severe chronic diseases

Directive 2001/83/EC requires that the application for marketing authorisation of a medicine for human use should include an environmental risk assessment to evaluate the risks due to the use and/or disposal of the medicinal product on the environment. Reproductive and developmental toxicity is investigated as part of the toxicological assessment. In addition, the environmental risk assessment of medicinal products for human use, requires a tailored evaluation of a potential endocrine effect on the environment if a direct mechanism of action is affecting reproduction. This tailored assessment is necessary in order to ensure that the most sensitive and appropriate tests with specific groups of organisms are used in the assessment and a phase II ERA always needs to be performed irrespective of the predicted exposure in surface water. The EMA guideline on the ERA is currently under revision. In the draft revision[132] published for public consultation, the identification of endocrine active substances has been broadened compared to the current guideline in order to include all active substances which may affect development or reproduction through effects linked to steroid hormone pharmacology, and does not address potential thyroid disruptors. The rationale for this is that compounds acting on steroid receptors are known to have pharmacological activities at concentrations below the current action limits and some have shown to have effects on aquatic organisms at the population level at very low concentrations. This level of evidence is currently not available for compounds acting on the thyroid system. Nevertheless, if for a substance acting on the thyroid system the action limit is exceeded, it would be expected that a tailored risk assessment would be performed as recommended in the draft guidance document. This draft guidance also includes a list of recommended tests to address (anti)estrogenic, anti(androgenic) and thyroid effects. These aspects will be further considered under the forthcoming EU Pharmaceutical Strategy.

[131]The 2019 Commission Fitness check (COM(2019) 264 final) of the chemicals legislation excluded from its scope the pharmaceuticals, veterinary and food additives legislation "*because their hazard and risk assessment is based on different considerations (i.e. an assessment of the risk trade-offs between the health benefits of the medical product versus potential undesired side-effects).*

[132]EMEA/CHMP/SWP/4447/00 Rev. 1, draft version published in 2018

Regarding medicines for veterinary use, the straightforward application of the environmental risk assessment (guidelines and tests) (EMA, 2016) does not address endpoints relevant to endocrine disruption, and hence recommended tests (i.e., OECD TGs) are not suitable for identifying if the substance is a potential ED. However, endocrine disrupting effects can be addressed within an environmental risk assessment when there is an underlying concern that the substance is a potential ED, based on changes indicative of endocrine dysfunction reported in the repeated dose toxicity study, or other evidence available (e.g., QSAR data, presence of structural alert, literature studies). In this case, the applicant can be requested to conduct special studies as part of the authorisation application, even when environmental exposure is predicted to be very low.

The outcome of the environmental risk assessment does not influence the approval of human medicines but is considered for veterinary medicines. In this case, evidence of an environmental risk, which cannot be controlled with risk management/mitigation measures, can prevent the granting of the authorisation, if the risk is considered to outweigh the benefits of the product.

In addition, Regulation 2019/6 on medicinal products for veterinary use highlights the need to examine a substance of concern in the broader context of the EU environmental legislation, e.g. to identify during the authorisation procedure if such substances should be included in the 'Watch list' of Directive 2000/60/EC, in order to gather monitoring data on them. If an environmental quality standard is requested and it is necessary to identify measures to reduce its emissions to the environment, such as measure to reduce emissions from manufacturing by following Best Available Techniques (BAT), a substance will be included in the Priority Substances list.

11 Occupational Safety and Health legislation (OSH)

The EU OSH legislation comprises the Framework Directive 89/391/EEC, which lays down the main principles of prevention and protection of occupational risks, and amongst others includes the following individual and related Directives: the Chemical Agents at Work Directive, the Carcinogens and Mutagens at Work Directive, the Pregnant Workers Directive and the Young People at Work Directive.

The Chemical Agents at Work Directive (98/24/EC) covers all chemical agents that present a risk to the safety and health of workers, which includes chemicals toxic to reproductive health as well as substances with endocrine disrupting properties if there is a risk for workers.

A hazardous chemical agent according to Article 2 of this Directive is any chemical that meets the CLP classification criteria whether or not the chemical is classified under the CLP Regulation. If a chemical does not meet the criteria for classification as hazardous according to CLP, it may still present at risk to the safety and health of workers, due to its physicochemical, chemical or toxicological properties and the way it is used or is present in the workplace including any chemical agent that is assigned an occupational exposure limit value under Article 3 of the Directive.

The employer assesses any risk to the safety and health of workers arising from the presence of hazardous chemical agents at the workplace and takes preventive and protective measures to protect workers. The Directive provides a hierarchy of risk management measures to protect workers from the risks.

The Carcinogens and Mutagens at Work Directive (2004/37/EC) aims to protect workers against risks to their health and safety, including the prevention of such risks, arising or likely to arise from

exposure to carcinogens or mutagens at work. As such, substances toxic for reproduction and substances with endocrine disrupting properties are within the scope of this Directive if they are also carcinogenic or mutagenic. The prevention and protection of workers is ensured through a comprehensive system of measures including binding occupational exposure limit values, which are established and when necessary revised in the light of the most recent and relevant scientific data.

The Pregnant Workers Directive (92/85/EEC) aims to implement measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or who are breastfeeding. As regards all activities involving exposure to the agents, processes or working conditions referred to in the non-exhaustive list of Annex I (covering reproductive toxicity, category 1A, 1B or 2 as defined under the CLP Regulation as well as endocrine disrupting properties as this list is non-exhaustive), employers shall assess the risks and any possible effect on the pregnancies or breastfeeding of the concerned workers and decide what measures should be taken - starting by avoiding exposure by temporarily adjusting the working conditions and/or the working hours of the worker concerned. If this is not technically and/or objectively feasible, or cannot reasonably be required, the employer shall take other required measures mentioned in the Directive.

The Young People at Work Directive (94/33/EC) aims to protect young workers (under 18 years of age) and their health and safety at work. The Directive states the obligations of the employer to protect health and safety at work of young workers. It also mentions that work involving harmful exposure to the physical, biological and chemical agents referred to in point I of the Annex is likely to entail specific risks for young people. The non-exhaustive list of agents included in the Annex of the Directive covers reproductive toxicants of category 1A and 1B, and the three carcinogenicity and mutagenicity categories 1A, 1B and 2, which then could cover substances with endocrine disrupting properties.

12 Water

The central piece of water-related legislation in Europe is the Water Framework Directive (WFD, 2000/60/EC), which aims at protecting and enhancing freshwater resources with the aim of achieving good status of European water. This directive has two daughter directives: the Groundwater Directive (GWD, 2006/118/EC) and the Environmental Quality Standards Directive (EQSD, 2008/105/EC) which follow from obligations under the WFD and are directly relevant to the determination of the environmental objectives and standards specified under the WFD.

The GWD sets groundwater quality standards and requires measures to be taken to prevent or limit inputs of pollutants into groundwater and reverse upward trends. The directive refers to the indicative list of the main pollutants of the WFD (Annex VIII to Directive 2000/60/EC).

The EQSD[133] has been used to update the list of priority substances (PS), including priority hazardous substances (PHS), in Annex X to the WFD, for which Member States should implement necessary measures to reduce (PS) or to phase out (PHS) discharges, emissions, and losses. Some EDs are included. The directive (Annex I) establishes Environmental Quality Standard (EQS) for PS, PHS and certain other pollutants representing limit values for acceptable concentrations in water or biota for each substance for inland and other surface waters in Europe. It also requires MS to establish an inventory of emissions, discharges and losses of the substances listed in the Annex. The 2013

[133]Directive 2008/105/EC as amended by Directive 2013/39/EU

amendment not only revised the list of PS, which now includes 45 chemicals (of which 21 PHS), but also introduced a watch-list mechanism; the list itself was published in 2015 and updated in 2018 and 2020[134]. The watch list is a list of potential water pollutants that should be monitored by the Member States to determine the risk they pose to the aquatic environment and whether EQS should be set for them. Until recently it included[135]. It now includes a number of other substances that are suspected or designated EDs.

The Marine Strategy Framework Directive (2008/56/EC) aims at achieving or maintaining a good environmental status in the marine environment, including as regards contaminants. It does not address EDs specifically, but Member States are obliged to assess, in particular, the PS listed in the WFD, which include some EDs, and to meet the EQS for relevant PS in territorial waters (at least). In those waters, Member States may select additional contaminants, and beyond territorial waters they must define the contaminants to be assessed, taking account of the PS. The MSFD thus allows Member States some freedom to decide which contaminants should be monitored. Decision 2017/848 lays down criteria and methodological standards for good environmental status. The standards for contaminants are set through cooperation in the Regional Seas Conventions, when not already set under the WFD.

The Urban Waste Water Treatment Directive (UWWTD, 91/271/EEC) aims at protecting the environment from the adverse effects of urban waste water discharges and discharges from certain industrial sectors. It concerns the collection, treatment and discharge of domestic wastewater, mixed wastewater, and wastewater from certain industrial sectors. The directive mainly focuses on parameters such as suspended solids, oxygen demand, and some chemicals responsible for eutrophication such as phosphorus and nitrogen but does not mention chemical micropollutants (and all the more does not specifically mention EDs), although some treatments are effective at removing some chemicals (Pistocchi et al., 2019). The directive has recently been evaluated[136] and the follow-up is likely to include consideration of a wider range of chemical pollutants, such as pharmaceutical residues and microplastics.

Finally, the Drinking Water Directive aims at regulating the quality of water intended for human consumption. The first DWD was adopted in 1998, and in 2018 the EC adopted a proposal for a recast of the DWD to improve the quality of drinking water and provide greater access and information to citizens, as a direct follow-up to the Right2Water European Citizen's Initiative and of the REFIT of the DWD[137]. This proposal is politically agreed by the European Parliament and the Council, to be adopted and published by the end of 2020. To address growing public concern about the possible effects of "emerging pollutants" (including EDs) on human health through drinking water, the proposal includes provisions for certain substances. It introduces standards for Bisphenol A and PFAS in drinking water, and a watch-list mechanism designed to ensure that MS pay particular attention in their risk assessment to endocrine-disrupting substances, such as nonylphenol and 17-beta-estradiol, and that, where necessary, water suppliers monitor those substances and treat the water accordingly if its quality is considered to pose a risk to human health. Based on the risk assessments, management measures to prevent or control the risks identified should be taken to ensure the good quality of the water intended for human consumption.

[134]Commission Implementing Decisions (EU) 2018/240 and (EU) 2020/1161, respectively
[135]https://ec.europa.eu/jrc/en/science-update/updated-surface-water-watch-list-adopted-commission
[136]https://ec.europa.eu/environment/water/water-urbanwaste/evaluation/index_en.htm
[137]SWD(2016) 428

All pieces of water related legislation are closely interconnected, due to the water cycle: surface water quality is directly influenced by waste water quality and in turn has a direct impact on the quality of drinking water. A water FC was finalised in 2019[138] which covered the WFD, the GWD, the EQSD as well as Directive 2007/60/EC on the assessment and management of flood risks. This FC is linked to the evaluation of the UWWTD, as the measures under the UWWTD are essential for the achievement of the WFD objectives.

Many of the actions being taken, planned or considered in the water policy area serve to support the objectives of the Commission Communication "A European Union Strategic Approach to Pharmaceuticals in the Environment"[139], the Commission Communication "Towards a Comprehensive European Union Framework on Endocrine Disruptors"[140] and the Council Conclusions "Towards a Sustainable Chemicals Policy Strategy of the Union"[141]. They will also allow following up on new knowledge about the relevance of EDs for human health and new knowledge on the most appropriate monitoring approaches and methodologies.

13 Chemical-product-waste interface

Two boundaries define the interface between, on the one hand, horizontal chemicals and product-specific legislation and, on the other hand, waste legislation: the first boundary is crossed when products become waste (end-of life); the second when waste is recycled into secondary materials and products (end-of-waste). As long as substances are part of waste, they are regulated under the Waste Framework Directive. Directive 2008/98/EC on waste (i.e. Waste Framework Directive) defines the hierarchy of waste management, which prioritises waste prevention, including reduction of the hazardousness of wastes. According to the waste hierarchy, waste generation cannot be prevented, material recycling should have priority over thermal recovery and the last option should be the (safe) disposal of wastes (incineration or landfilling). Reuse and recycling of wastes closes the material cycles are therefore a core element of the circular economy. From the point of view of waste legislation, the potential negative impacts of hazardous substances in material cycles are controlled by product-level restrictions, waste management rules (e.g. treatment requirements, traceability of waste streams) and provisions for end-of-waste criteria. Restrictions in products belong to the chemical (e.g. REACH) and to product-specific legislation (e.g. Restriction of Hazardous Substances – RoHS Directive). The RoHS Directive 2011/65/EU sets restrictions on the use of certain hazardous substances in electrical and electronic equipment. In the prioritisation of substances for inclusion in the Annex II of the RoHS, EDs are given equally high priority as category 1 CMRs, to the extent they are listed as SVHC under REACH[142]. They are the only piece of product-level legislation restricting specific substances (e.g. Annex II to RoHS) with the main objective of facilitating waste treatment and recycling. Other product-level legislation mainly aims to ensure safety for human health and the environment during (primary) use of the product.

Directive 2008/98/EC (Waste Framework Directive) establishes waste management and end of waste provisions. Provisions for waste management act as a filter that aims to clean/regenerate material flows by separating unwanted compounds so that they can be re-used or re-purposed according to the

[138] SWD(2019) 439
[139] COM(2019) 128
[140] COM(2018) 734
[141] https://www.consilium.europa.eu/en/press/press-releases/2019/06/26/council-conclusions-on-chemicals
[142] https://rohs.exemptions.oeko.info/fileadmin/user_upload/RoHS_Pack_15/4th_Consultation/Pack_15_Substance_Review_Draft_Manual_Methodology_second_version_20190926.pdf

needs of new production processes or products, all while considering potential human health (workers) and environmental implications.

The properties which render waste hazardous are laid down in Annex III of the directive, which refers to CLP categories including specific target organ toxicity (HP5), acute toxicity (HP6), carcinogenic (HP7), mutagenic (HP11), reproductive toxicants (HP10) and ecotoxicity (HP14), with specified concentration limits referring to the waste material for sub-hazard classes. For CMRs category 1A, 1B and 2 the classification of mixtures in CLP corresponds to the concentration limits for the classification of waste as hazardous. However, multiplying factors for mixture classification (M-factors) applied in the CLP are not reflected in the classification of hazardous waste. The identification of hazardous waste is further specified in the list of waste established by Decision 2014/955/EU, although the list does not specify the hazardous property motivating the classification.

Hazardous waste is subject to stricter controls including cradle-to-grave traceability and the prohibition to dilute with other waste streams (Directive 2008/98/EC, Article 17 and 18). The quality of recycled materials can be controlled by setting specific end-of-waste criteria for placing secondary materials on the market. These are established at EU level or alternatively by Member States, in line with the general principles of Article 6, including no adverse environmental or human health impact. Specific end-of-waste criteria have been agreed for a few waste types (EC decisions), but not yet for major materials such as paper or plastics. In the absence of specific EU-level or national end-of-waste criteria, case-by-case decisions are made by competent authorities on whether a certain waste has ceased to be waste (Article 6(4)) with implications for its handling.

The Commission has identified four main issues at the interface between chemical, product and waste legislation, which act as barriers to the achievement of the objectives of the circular economy package: the presence of substances that are no longer allowed in waste and recycled products; the lack of information available to waste operators on substances of concern in waste; the lack of harmonised rules for the hazard classification of chemical mixtures and waste; and the lack of harmonised rules on end-of-waste. While these problems relate to all substances of concern and not specifically to EDs, several potential and identified EDs have been mentioned when illustrating those issues, owing to their widespread presence in articles and material flows, such as plastics, paper and textiles (Milieu Ltd et al., 2017) (sub study b).

In response to the need to improve the information flow on the presence of SVHC in materials and waste streams, the Commission has introduced new obligations to Member States under the Waste Framework Directive. Member States are required to ensure that suppliers of an article, as defined under REACH Article 33, provide information to ECHA on the presence of SVHC, as from 5 January 2021. The information shall be stored in a database maintained by ECHA and made accessible to waste treatment operators[143].

14 Other in-scope legislation

14.1 Detergents

The Detergents Regulation ((EC) No 648/2004) establishes rules designed to achieve the free movement of detergents and surfactants for detergents in the internal market while, at the same time, ensuring a high degree of protection of the environment and human health. The regulation focuses on

[143]Directive (EU)2018/851 amending Directive 2008/98/EC on waste

the biodegradability of surfactants, their restrictions or bans on grounds of biodegradability, the labelling of detergents, including fragrance allergens, the limitations on the content of phosphates and other phosphorus compounds in detergents, and the type of information held at the disposal of the Member States' competent authorities and medical personnel.

According to the Detergents Regulation, surfactants and detergents containing surfactants that meet the criteria for ultimate aerobic biodegradation (primary biodegradability of at least 80 %) may be placed on the market without further limitations relating to biodegradability. If this criterion is not met, manufacturers of industrial or institutional detergents containing surfactants, and/or of surfactants for industrial or institutional detergents, may ask for derogation.

The Regulation is interconnected with CLP, REACH, Biocidal Product regulation and the Cosmetic Products Regulation.

It does not have specific provision for the identification of EDs, however, provisions under REACH and the Biocidal Products Regulation apply. Moreover, Annex IV on the complementary risk assessment for surfactants in detergents (applicable to Industrial and Institutional detergents that contain surfactants not meeting the criterion of ultimate biodegradability set in the Regulation, and needing a derogation) states that if some metabolites are suspected for endocrine disrupting activity, it is recommended to determine if these have potential to result in adverse effects.

14.2 Fertilising Products

The Regulation (EC) No 2003/2003 on Fertilisers has been repealed by the new Fertilising Products Regulation (EU) 2019/1009, which will apply from 16 July 2022. The new Regulation maintains the rules of optional harmonisation, where a manufacturer can choose to comply with the Fertilising Products Regulation or with national standards based on the principle of mutual recognition. Both Regulations interconnect with the REACH, CLP, PPP and Waste Regulations.

The Regulations do not have specific provisions for EDs. Fertilising products will only be approved if under normal conditions of use they do not adversely affect human, animal, plant health, or the environment. The safety of the constituent of the product should comply with the REACH regulation.

Different fertilising product functions warrant different product safety and quality requirements adapted to their different intended uses. EU fertilising products are therefore divided into different product function categories (PFCs), each of which are subject to specific safety and quality requirements.

The information requirements should ensure that the safety of the intended use of the fertilising product is demonstrated in a manner comparable to that of Regulation (EC) No 1107/2009 (PPP).

In the event manufacturers have reason to believe that an EU fertilising product which they have placed on the market presents a risk to human, animal or plant health, to safety or to the environment, they shall immediately inform the competent national authorities of the Member States in which the EU fertilising product is placed on the market, and shall cooperate with that authority to eliminate the risks posed by the product. Similarly, where a Member State has justifiable grounds for believing that a specific EC fertilising product, although satisfying the requirements of the Regulation, constitutes a risk to safety, health of humans, animals, plants, or risk to the environment, it may temporarily prohibit the placing on the market of that fertilising product in its territory or make it subject to

special conditions. It shall immediately inform other Member States and the Commission thereof, giving the reasons for its decision, and the Commission shall adopt a decision on the matter.

14.3 Ecolabel Regulation

The objective of Regulation (EC) 66/210 is to recognise through a voluntary scheme products and services meeting high environmental standards throughout their life-cycle. The ecolabel is in principle not awarded to goods containing substances meeting the criteria for classification as toxic, hazardous to the environment, carcinogenic, mutagenic or toxic for reproduction (CMR), in accordance with the CLP regulation and not to goods containing substances referred to in Article 57 of REACH (Article 6(6)). If substitutions are not technically feasible, derogations are possible, but may not be granted to substances listed in the REACH Candidate List (established via REACH Article 59(1)) present in mixtures or in (homogeneous parts of) articles at > 0.1% w/w (Article 6(7)). There is no explicit reference to EDs, but EDs may be addressed by Article 6(6) and 6(7). Specific ecolabel criteria are developed per product category following procedures involving the European Union Ecolabelling Board, the Commission, Member States, Competent Bodies and other stakeholders. Most product categories set specific provisions for the restriction of hazardous substances defined according to CLP and SVHC criteria. Products associated with domestic wastewater emissions (e.g. detergents, cosmetic products) include criteria for chronic aquatic toxicity.

14.4 General Product Safety Directive

In principle, under Directive 2001/95/EC producers are obliged to only place safe products on the market. To ensure consumer safety and health protection, market surveillance activities are established by Member States authorities and measures taken against products posing risk are to be notified in the Rapid Alert System for dangerous non-food products (Safety Gate/RAPEX). Notifications in the system also cover chemical risk. The Guidelines of the system (Decision 2019/417) include a chapter on risk assessment. For chemicals there are specific instructions on how to prepare a risk assessment, and therefore they are not dealt with in detail in these guidelines. Nevertheless, they follow the same principles as for 'normal' consumer products. For products posing chemical risks, the Guidelines also indicate that the risk level of a product may be considered serious if it contains a chemical substance either banned or in a concentration above the limit established by European legislation. Therefore, in cases where measures are taken against products containing a chemical substance subject to a restriction contained in EU Legislation, a notification may be submitted without a detailed risk assessment.

In general terms, the GPSD requires producers and distributors to take action to prevent risk to consumers when they become aware that a product that they have placed on the market poses risks and to inform competent authorities of the Member States thereof. Market surveillance authorities can seek to limit the marketing or use of a chemical substance or preparation.

Where measures are taken against products for the presence of a chemical risk in one Member State, these are to be notified in Safety Gate/RAPEX. Except in justified cases as explained above notifications must be accompanied by sound risk assessment considering the risks posed by the product over its lifetime. Risk management is also paramount and should take account of the quantities placed on the market. For all notifications made, all countries of the network (EU + Norway, Iceland and Liechtenstein) are required to take appropriate follow up action and screen their market on the possible presence of the same product so as to ensure a safe single market.

As of August 2020, phthalates and bisphenol A are the only substances with endocrine disrupting properties that have been referred to in RAPEX for their restriction under REACH.

14.5 Seveso III Directive and Industrial Emission Directive

The Seveso III directive (2012/18/EU) aims at laying down the rules for the prevention of major accident involving dangerous substances, and the limitation of their consequences for human health and the environment. It does not contain provisions specific to EDs, and defines "dangerous substances" based on classification and volume: for human health, a substance classified based on acute toxicity and specific target organ toxicity (single exposure) might be considered as hazardous, depending on the volume, whereas for environmental health, a substance classified as hazardous to the aquatic environment (categories acute 1 or chronic 1, above 100 tonnes; chronic 2 above 200 tonnes) might be considered as hazardous. Therefore, the limitation to prevent and manage exposure to EDs linked to major accident are both linked to the limitation of the above-mentioned CLP categories to identify EDs and the missing specific provisions in the Directive.

The Industrial Emission Directive (2010/75/EU) aims at ensuring a high level of environmental protection and the improvement of environmental quality by laying down rules to prevent or to reduce emissions into air, water and land and to prevent the generation of waste through requiring the application of Best Available Techniques (BAT) in installations. BATs are identified on a sector-by-sector basis in what are called BAT reference documents (BREFs). One of the first steps in preparing a BREF is to agree what are the Key Environmental Issues to be addressed. The Directive does not specifically address EDs, although if EDs are identified as a Key Environmental Issues they could be included in the BREFs. inclusion of hazardous substances as Key Environmental Issues is not based on explicit criteria but rather refer to existing regulatory intervention under chemical (e.g. REACH restrictions) and water legislation (e.g. priority substances under the WFD)[144]. It is important to note that emission limit values set in this directive are only based on the BAT, not on health or ecotoxicity criteria. Moreover, to detect possible soil and groundwater pollution and to take appropriate corrective measures, the monitoring of soil and groundwater for relevant hazardous substances is also required.

14.6 Directive on air quality

Two directives are focusing on air quality, Directive 2008/50/EC and Directive 2004/107/EC. The first one aims at defining and establishing objectives for ambient air quality in order to avoid, prevent or reduce harmful effects on human health and the environment, whereas the second one relates to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air. None have specific provisions for EDs, but address air pollutants of toxicological concern. In the case of arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons, their carcinogenic potential, not their endocrine disrupting potential, is the main source of concern.

Ambient air quality standards (i.e. maximum allowed concentration) are established for sulphur dioxide, nitrogen, dioxides and oxides of nitrogen, particulate matter (PM_{10} and $PM_{2,5}$), lead, benzene, ozone and carbon monoxide in the context of Directive 2008/50/EC, and arsenic, cadmium, nickel and benzo(a)pyrene in the context of Directive 2004/107/EC. Member States should monitor air quality in their territory and should take measures to ensure that concentrations do not exceed the limit or target value.

[144]See for example draft BREF for textile industry: https://eippcb.jrc.ec.europa.eu/sites/default/files/2020-01/TXT_bref_D1_1.pdf

Those air quality standards are based on WHO guidelines (WHO, 2005), which collect available scientific evidence about air pollution and its health consequences and provide indicative levels as guidance for reducing the health impacts of air pollution. Member States are required to take measures whenever there is exceedance of those air quality standards and to establish air quality plans to keep the exceedance period as short as possible.

14.7 WTO rules

With respect to setting rules that restrict the imports of chemicals, materials and products, the EU must adhere to WTO rules, namely the Agreement on Technical Barriers to Trade (TBT agreement[145]) and, regarding pesticides, the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement[146]). The aim of both agreements is to maintain the sovereign right of any government to provide the level of health protection it deems appropriate, but to ensure that these sovereign rights are not misused for protectionist purposes and do not result in unnecessary barriers to international trade. Regulatory measures must not create technical barriers to trade, unless justified by legitimate objectives, which include the protection of human health or safety, animal or plant life or health, or the environment. Under the SPS agreement, WTO members shall ensure that their sanitary or phytosanitary measures are based on a scientific assessment, as appropriate to the circumstances, of the risks to human, animal or plant life or health, taking into account risk assessment techniques developed by the relevant international organizations. For example, the Codex Committee on Pesticide Residues is responsible for establishing Codex Maximum Residue Limits (MRLs) for pesticide residues in specific food items or in groups of food or feed that move in international trade.

Upon implementing regulatory measures that create a technical barrier to trade, members are obliged to submit at draft stage to the other members any legislation that could potentially contain technical barriers to trade and to allow a reasonable interval between the publication of technical regulations and their entry into force.

WTO rules establish a procedure for members to raise specific trade concerns (STCs) to challenge measures deemed unnecessary barriers to trade. Most STCs raised before the WTO Committee on Technical Barriers to Trade (TBT Committee) are discussed without escalating into formal disputes. A relatively small number of disputes have been subject to the WTO dispute settlement procedures (Holzer, 2018).

[145] https://ec.europa.eu/growth/tools-databases/tbt/en/documents
[146] https://www.wto.org/english/tratop_e/sps_e/spsagr_e.htm

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Annex 5A. Case Study: 3-benzylidene camphor (3-BC)

1 Case study factsheet: overview of concerns for human health and environment and main regulatory intervention

Product types (possible exposure sources)	Cosmetic products (e.g. sunscreens)* * the use has been restricted or otherwise regulated in the EU.
Exposure pathways of concern (human and environment)	Human exposure through skin absorption. Environmental exposure through domestic wastewater discharges, wash-off from bathers, and direct emissions from cosmetics production sites.
Concerns for human health and/or the environment	In humans: developmental (teratogenicity) effects, likely mediated by estrogenic activity. In wildlife: endocrine mediated reproductive toxicity with serious and long-lasting effects on aquatic species.
Regulatory hazard and risk assessment	• 1998 - SCCNFP favourable opinion on use in cosmetics at a maximum concentration of 2% as proposed by submitter. No ED specific assessment was required. • 2013 (June) – SCCS opinion: not safe for use in cosmetics based on risk assessment with insufficient margin of safety due to teratogenic effects. Studies showing effects likely caused by an ED mode of action (MoA) and relevant for human health used as supporting evidence. • 2016 (February) –Proposal from Germany for identification SVHC for ED effects in the environment. • 2018 (December) – Identification as a substance of very high concern due to its endocrine disrupting properties in the environment in line with the WHO definition of an endocrine disruptor and REACH Article 57(f), based on a dossier submitted by Germany
Risk management measures	• 1988 - Submitted for assessment for cosmetics use • 1998 - Listed in the Cosmetics Directive Annex VII for use up to 2% based on SCCNFP opinion (removed in 2015) • 2011 France bans use in cosmetics based on developmental effects and

	potential endocrine MoA • 2015 (July) Cosmetics use (UV filter and UV absorber) banned EU-wide[147], with effect from 18 February 2016 2019 (February) Added to REACH candidate list, but no further regulatory management measures proposed for the time being since the substance is not registered under REACH and there is no information on uses falling under REACH. As from 16 July 2019, obligation for producers and importers to notify ECHA if an article contains > 0.1% of 3-BC and to inform downstream users and consumers.

2 Substance profile

The main use of 3-Benzylidene camphor was in cosmetics as an effective UV absorber previously used in sunscreen and whitening products. It is highly hydrophobic and insoluble in water. There is no evidence about other uses in the EU since the substance is not registered under REACH or other regulations.

2.1 Exposure pathways of concern

Human Exposure

As a UV filter used in sunscreen and skin whitening products, dermal absorption is the main human exposure pathway of concern.

Environmental Exposure

UV filters can enter the aquatic environment indirectly via wastewater treatment plants (washing, bathing, laundering), and directly from recreational activities such as swimming and bathing. Due to its hydrophobicity it has high potential to accumulate in organic matter and in organisms' lipid tissues. It is considered to be not readily biodegradable based on available QSAR predictions (ECHA 2016).

2.2 Effects on human health and the environment

Human Hazard

Multiple hormonal activities of 3-BC have been reported *in vitro*: estrogenic and anti-estrogenic effects as well anti-androgenic activities. Estrogenic activity has been observed *in vivo* in rats and fish and the likely cause of developmental (teratogenicity) effects observed in rats (SCCS 2013).

Environmental Hazard

In vivo fish assays indicate that 3-BC or its metabolites cause serious, irreversible and long-lasting adverse effects (decreased fertility and fecundity) in fish (that are population-relevant) due to an endocrine mode of action (ECHA 2016).

[147]Commission Regulation (EU) 2015/1298 of 28 July 2015 amending Annexes II and VI to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products

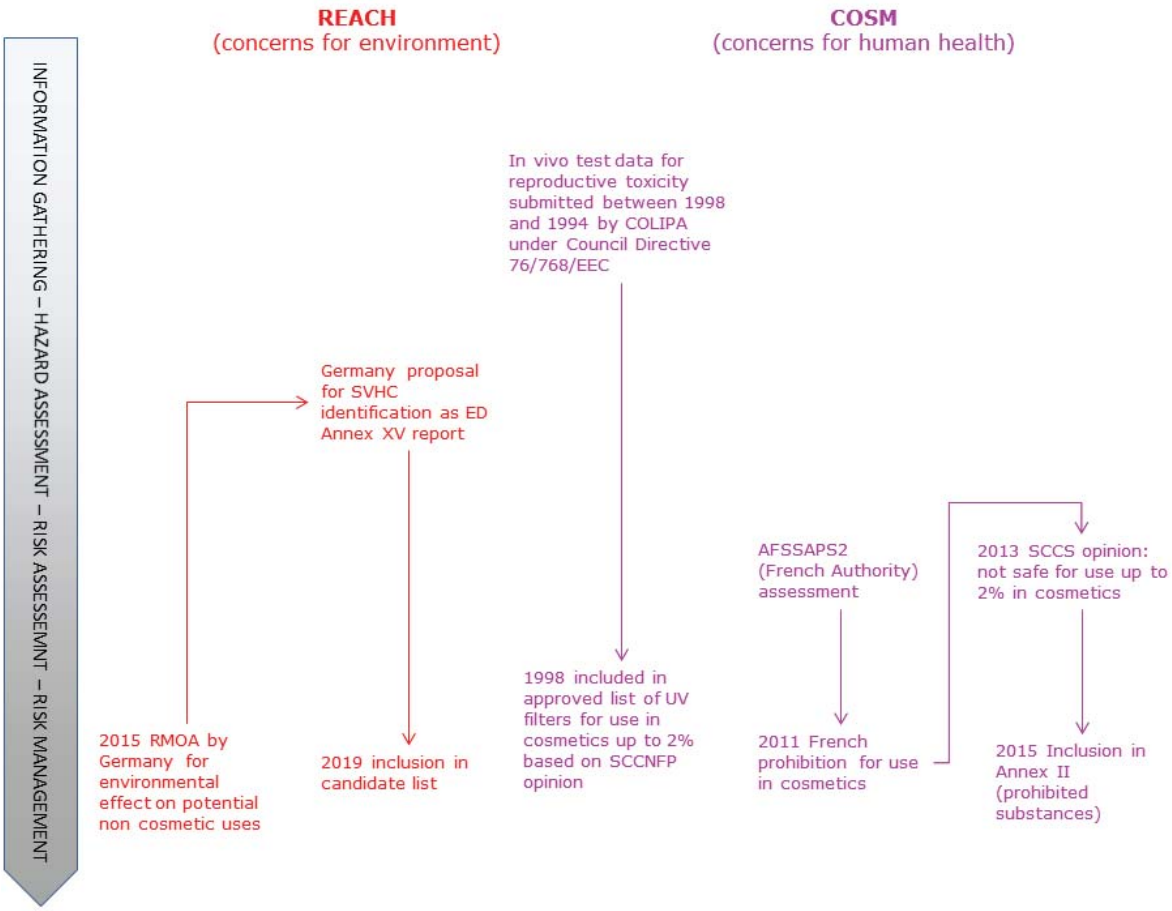

Figure 16.1. 3-BC case study: illustration of applied provisions across legislation

3 3-BC and structurally similar UV filters in EU legislation

3.1 Regulating 3-BC in cosmetics legislation

Submission I on the UV-filter 3-benzylidene camphor with the chemical name 3-benzylidenebornan-2-one was submitted by COLIPA in 1988. The Scientific Committee on Cosmetic Products and Non-Food products intended for consumers (SCCNFP) adopted an opinion in January 1998 (1374/1998). Data on toxicological endpoints specifically related to potential endocrine effects were not available at that time and consequently not assessed. The SCCNFP evaluation was carried out for a proposed maximum concentration of 2% indicated by the dossier submitter. The favourable opinion was justified by a sufficient margin of safety determined based on a NOAEL of 20 mg/kg/day from a 90-day oral toxicity study in rats. The corresponding adverse effect was an elevated level of plasma lipids in female rats (SCCNFP opinion)

The substance was then included in Annex VII, part 1 n.19 of the Cosmetics Directive ("List of permitted UV filters which cosmetic products may contain") in a concentration up to maximum 2%.

In October 2011, the French authorities notified the Commission that the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS), had adopted a decision prohibiting cosmetic products containing 3-BC as a safeguard measure in accordance with the provisions of Article 12 of the Directive 76/768/EEC, which preceded the Cosmetic Products Regulation currently in place. The safeguard measure requires the Member State, if it considers that a hazard to health from the use of a cosmetic product exists although complying with the requirements of the Directive, to inform immediately the Commission and other Member States. If the measure is justified, the Commission proposes to extend the measure to the whole of the EU. If it is not justified, the action taken by the Member State has to be revoked.

The AFSSAPS considered the hazard characterisation for this substance incomplete. In addition, it questioned assumptions in the exposure characterisation and the determination of the no observed adverse effect level (NOAEL). Using a higher cutaneous absorption rate and a lower NOAEL (15 mg/kg/day) from an existing teratogenicity study, the risk assessment resulted in an insufficient margin of safety. Finally, as endocrine disrupting effects were observed in new studies published in the scientific literature after 1998, the French authorities considered that it was not possible to conclude that there was no risk to humans from the use in cosmetics.

In response to the initiative taken by the French authorities and as foreseen in Directive 76/768/EEC, in 2013 the Commission tasked the SCCS with re-evaluating the safety of 3-BC for use as a UV filter in cosmetic products at a concentration of up to 2.0%. The task had to take into account the scientific data provided as well as any additional scientific concern related to its potential endocrine disrupting properties for humans. The toxicological evaluation was based on the previous SCCNFP opinion from 1998 (1374/96) and on the dossiers I, II, III and IV on the UV-filter 3-benzylidene camphor with the chemical name 3-benzylidenebornan-2-one submitted by COLIPA respectively in 1988, 1991, 1992 and 1994. The submitted files contained only summaries of the experimental studies; original data were not made available to the scientific committee (Opinion SCCS/1513/13).

The SCCS concluded in its opinion on 3-BC published in 2013 that the use of this substance up to 2 % in cosmetic products is not safe. The opinion in particular re-evaluated a key study from the previous opinion 1374/98. The conclusion was justified by an insufficient margin of safety using a NOAEL derived from an oral study submitted before the 1998 opinion. The NOAEL of 15 mg/kg bw/day as proposed by AFSSAPS was used from evidence of embryo-toxicity at 50 mg/kg bw/day and above in a developmental (teratogenicity) toxicity study with rats very similar to OECD TG 414 (SCCS, 2013). According to the SCCS, the development of the effects may be associated with the maternal toxicity present at 50 mg/kg bw/day. The SCCS did not explicitly link the effects to an endocrine mode of action.

The mandate given by the Commission to the SCCS included the assessment of potential endocrine disrupting properties. The SCCS looked at nine *in-vitro* and *in-vivo* studies published between 2001 and 2009 in the scientific literature. Some of the studies indicated endocrine activity of 3-BC or endocrine-mediated effects. Altered sexual behaviour and modification of the oestrus cycle were observed in one study with rats at dose levels lower than for teratogenicity. The SCCS, however, saw shortcomings in the available studies and a need to confirm the results. In particular, not all parameters necessary to assess comprehensively the results were reported in the academic studies published in scientific journals. Because of that, the evidence for endocrine disruption was used only as supporting evidence in the risk assessment of 3-BC.

Based on the teratogenic effects observed and due to a margin of safety below 100, the SCCS concluded that the use of 3-BC as a UV filter in cosmetic products in a concentration up to 2% is not safe. In February 2015, the Standing Committee on Cosmetic Products voted in favour of the Commission's proposal to prohibit the use of 3-BC as UV filter and UV absorber in cosmetic products by deleting it from Annex VI (authorised list of UV filters) and adding it to Annex II (list of substances prohibited in cosmetic products) to Regulation (EC/1223/2009).

3.2 Regulating 3-BC under REACH

3-BC is not registered under REACH. It is hence should not be manufactured in or imported into the EU in quantities above 1 tonne per year per legal entity. Furthermore, there are no indications that it is imported into, manufactured or used in the EU. Due to the substance not being registered, a registration dossier with test data is not available.

In 2015 Germany submitted its intention to identify 3-BC as SVHC, together with the structurally similar 4-methylbenzylidene camphor (4-MBC). Considering the number of individual notifications in ECHA's C&L Inventory database (as cat. 2 reproductive toxicant) the Risk Management Option Analysis (RMOA) submitted in 2015 concluded that 3-BC might be commercially relevant in the EU. However, notifications for self-classification do not reveal whether a substance is currently on the market in the EU or used. The RMOA hypothesised that uses other than cosmetics could lead to environmental emissions. Therefore, risk management under REACH was judged necessary for other applications than cosmetics (RCOM 2015).

The proposal for identification as an SVHC (Annex XV report) was submitted by Germany in February 2016. However, the Member State Committee (MSC) did not reach unanimous agreement on this proposal. Following the provisions of REACH, in case where there is no consensus in the Member State Committee on the SVHC identification, a decision has to be taken by the European Commission. Hence, the dossier was forwarded to the Commission.

According to Commission Implementing Decision (EU) 2018/2013), the available data from key scientific studies reported in the supporting document of the MSC majority opinion (e.g. Holbech et al 2002, Kunz et al 2006b) demonstrate an endocrine-mediated mode of action of 3-BC causing serious, irreversible and long-lasting effects on fish fecundity relevant for wildlife populations. The decision further concludes that the fact that the adverse effects on fish fecundity were observed in the key study at low concentration levels strengthens the concern.

The minority views in the MSC pointed to the legislative vacuum due to the lack of a Commission definition on EDs for environment (i.e. at that time, the Commission was still working on the criteria for EDs under the BPR and PPPR), to issues of reliability of the key study (i.e. effects observed before exposure in some of the replicates, loss of test substance during the test).

In its decision, the Commission concluded that 3-BC fulfils the criteria for Article 57 (f). In other words it is a substance with endocrine disrupting properties for which there is scientific evidence of probable serious effects for the environment, which gives rise to an equivalent level of concern as substances with properties listed in points [(a) to (e)] of Article 57 of the REACH regulation.

Having obtained a favourable opinion from the REACH Committee by a qualified majority, the decision was adopted in December 2018. In January 2019, 3-BC was included in the candidate list, which triggered the following obligations:

- Producers or importers of articles must notify ECHA if their article contains 3-BC, if it is present in the article above 0,1% and the quantity of 3-BC in the imported or produced article is above 1 tonne per year (REACH Article 7(2))
- Suppliers of 3-BC, or of mixtures containing the substance, must provide their customers with a Safety Data Sheet (REACH Article 31(1) and Article 31(2)).
- Suppliers of articles must inform downstream users, and on request consumers, if the substance is present in an article at a concentration > 0.1 % (REACH Article 33)

Further risk management measures for 3-BC were not considered to be necessary for the time being since 3-BC is not registered under REACH and since there are indications that the substance is not put on the market or used in the EU above the quantity of 1 tonne per year per legal entity. Nevertheless, information resulting from the legal obligations effective as from 16 July 2019 and linked to the SVHC identification of 3-BC and its candidate listing can serve to determine whether further EU-wide risk regulatory measure (e.g. a restriction) is warranted. However, up to now, no notification of an imported or produced article containing 3-BC has been submitted to ECHA.

3.3 Status of structurally similar UV filters

There are five UV filters in Annex VI to the Cosmetic Products Regulation containing a camphor moiety. Considering that some of them have received attention by the scientific community and by regulators for their potential endocrine disrupting activity, it is useful to review their status for the purpose of this case study. However, up to now, no regulatory body has identified them as endocrine disruptor at national or EU level. Furthermore, it is uncertain whether all substances with a camphor moiety have endocrine disrupting propertiess (Axelstad, 2013).

Three of the five UV filters share the benzylidene camphor sub-structure: 4-methyl benzylidene camphor (4-MBC), benzylidene camphor sulphonic acid, and polyacrylamidomethyl benzylidene camphor (entries 9, 11 and 18 of Annex VI to the Cosmetic Products Regulation), although the latter is a polymer. The other two share the camphor groups in their structure: camphor benzalkonium methosulfate and terephthalyidene dicamphor sulfonic acid (entries 2 and 7 of Annex VI).

Only for 4-MBC is there information that the substance is on the EU-market since it was registered under REACH in 2018. No information is available on whether polyacrylamidomethyl benzylidene camphor is used in the EU. The other three UV-filters are not registered under REACH and hence are either not used in the EU or not on the EU market in quantities above 1 tonne per year per legal entity. The database on Substances in Products in Nordic Countries (SPIN[148]) either does not have data on the substances or indicates no use of the substance in products.

4-MBC is listed in Annex VI based on the 2008 opinion of the Scientific Committee on Consumer Products (SCCP) for safe use in sunscreens up to a maximum concentration of 4% w/w as indicated by the dossier submitter. Safety concerns related to endocrine activity were first voiced in 2000. In

[148]http://www.spin2000.net

2001 the SCCNFP was tasked to assess organic UV filters, including 4-MBC, used in cosmetic sunscreen products for their estrogenic activity and concluded that none have the potential to affect human health (SCCNFP 2001). Upon a request of the Danish authorities the dossier for 4-MBC was reopened and additional data were submitted by industry in February 2004. The SCCP considered the information provided incomplete and requested further data with urgency (SCCP 2004 opinion). In the following opinion from 2006, the SCCP then addressed questions related to potential thyroid-related endocrine effects in humans. Once more, the opinion was inconclusive, ending in additional test data requirements, stating that questions raised in 2004 had not been addressed by the additional data provided by the submitter. Finally, in 2008 the SCCS issued a final opinion concluding that presently the safe use of a maximum concentration of 4% of 4-MBC in sunscreens could be established. A sufficient margin of safety for this concentration limit was established from a NOAEL derived from observed thyroid effects in a 90-day oral study with rats and from a revised exposure level based on toxicokinetic information from the submitter in 2004.

Due to the structural similarity, 4-MBC was considered for the SVHC identification due to its effects on the environment together with 3-BC in the RMOA completed by Germany in February 2016. However, the dossier for SVHC identification of 4-MBC was withdrawn in June 2016, pending its further elaboration[149]. Hence, 4-MBC has not been identified as an SVHC with ED properties for the environment. Subsequently, it was registered under REACH in 2018, for use in cosmetic/ personal care products (https://echa.europa.eu/registration-dossier/-/registered-dossier/25426).

The other two benzylidene camphor UV filters listed in Annex VI were approved for use as UV filters up to 6% in cosmetics in 1994 (benzylidene camphor sulphonic acid) and 1996 (polyacrylamidomethyl benzylidene). Similarly, terephthalylidene dicamphor sulphonic acid was approved in 1994 up to 10%. No data addressing endocrine disrupting properties are available for these substances or have been published. In 2013 an assessment by the Danish Centre for Endocrine Disrupters assessing the endocrine disrupting potential of 23 UV-filters with regard to human health and ecotoxicological concerns concluded that for these substances there is no information and no scientific opinion of EC scientific committees addressing endocrine disrupting properties or reproductive toxicity.

The remaining substance containing a camphor group, camphor benzalkonium methosulfate was evaluated by the SCCP in 2006 and in 2008. It is currently approved for use as a UV filter in cosmetic products up to 3% (SCCP 1202/08). The margin of safety was calculated using a NOAEL derived from observed effects on the digestive tract in a 90-day oral study on rats. Reproductive toxicity was assessed but did not drive the risk assessment as minor uterotrophic effects observed *in-vivo* were not considered toxicologically relevant.

In the review of the Cosmetic Products Regulation with regard to substances with endocrine-disrupting properties (COM(2018) 739), the Commission committed to establishing a priority list of potential endocrine disruptors in cosmetics for their subsequent safety assessment in view of possible bans/restrictions. A priority list of 28 potential EDs in cosmetics was consolidated in early 2019 following input provided by stakeholders[150]. Fourteen substances were prioritised into Group A, to be treated with higher priority because substance evaluation under REACH concluded that the substance is an ED or because an evaluation under REACH is ongoing. The list includes 4-MBC.

[149] https://echa.europa.eu/documents/10162/22837890/msc-48_meeting_minutes_en.pdf/314824ca-fd22-4d96-ae8d-3ba2050341f7

[150] https://ec.europa.eu/growth/sectors/cosmetics/products/endocrine_en

The Commission launched a public call for data from May to October 2019 on the 14 Group A substances. In view of the quality of data received and SCCS's capacity, the Commission sent mandates to the SCCS in January 2020 to evaluate 5 substances (3 of which are UV filters[151]). If needed, the Commission will take appropriate action to prohibit or restrict the use of these different substances in cosmetics.

As regards the remainder of the 9 Group A substances, which includes 4-MBC, safety information provided during the call for data was incomplete, thereby stakeholders have been invited to complement their submission during 2020. The Commission will then proceed to mandate the SCCS with a second wave of another 5 substances in 2021, which will include 4-MBC.

4 Comments on fitness check evaluation criteria

Comments on coherence	• Different regulatory approaches applied for human health (Cosmetic Products Regulation) and environmental concerns (REACH Regulation). REACH applied a generic risk approach for identification as SVHC with effects to the environment, which is eventually followed up by risk management measures based on specific risk or risk-benefit approach (REACH authorisation or restriction). The Cosmetic Products Regulation applies risk assessment to conclude on potential risk to human health. • Cosmetics use banned in France in 2011, in the EU from 2016. • There are several structurally similar UV filters in Annex VI to the Cosmetic Products Regulation. These substances have been assessed at some point in time for their safety (human health) but have not been evaluated explicitly for potential endocrine disrupting properties in in the context of the Cosmetic Products Regulation. However, available data indicate only for one of the substances (4-MBC) that it is placed on the EU market. If there is a potential risk to health or should new data be available, Article 31 is triggered, and a new risk assessment has to be carried out for 4-MBC.
Comments on effectiveness	• Since the 1998 favourable opinion of the SCCNFP on 3-BC, new evidence on estrogenic mode of action from *in-vitro* and *in-vivo* studies motivated France to revisit the 1998 assessment. By reconsidering specific assumptions in key studies already reported in the previous assessment (higher absorption factor, lower NOEAL) the result went in the opposite direction. The 2013 SCCS opinion confirmed the new assessment and concluded that 3-BC is not safe for use in cosmetics at 2%. Consideration of endocrine disrupting potential on human health was used as supporting evidence for the conclusion. • Triggering the safeguard clause by French authorities led to an EU wide restriction of 3-BC in cosmetic products as foreseen in legislation. • Evidence of effects of 3-BC from *in-vivo* fish studies was sufficient for the

[151]Octocrylene, Homosalate and Benzophenone-3

	identification of 3-BC as SVHC under REACH with ED properties for the environment. • The SVHC identification under REACH led to notification obligations for importers and producers that allow better monitoring of whether articles with 3-BC are on the market and how the substance is used in articles. • The obligation under REACH to register substances above 1 tonne per year allows to monitor whether a substance is manufactured in the EU or imported and what are the uses of the substance. This information helps to decide on and to prioritise regulatory action. • Data from the scientific domain have been an integral part of and valuable for the ED assessment. However, studies do not always report all parameters necessary to comprehensively assess the results, which hampers their use in regulatory risk assessments. • 4-MBC has been assessed under REACH for ED properties for the environment; however, the responsible committee did not identify the substance as SVHC as the dossier was withdrawn by the dossier submitter. Other structurally similar UV filters, which are either not used in the EU or only in low quantities, have not yet been evaluated as regards their ED properties. This might at least partly due to limited test data in combination with the ban on animal testing, which hampers the ability of SCCS to reach conclusive opinions.
Comments on efficiency	• Procedures for assessing human and environmental safety are in two different pieces of legislation (Cosmetic Products Regulation and REACH, respectively)
Comments on EU added value	• Different risk management measures in place for cosmetics between 2011 to 2016 in France and the rest of the EU. The mechanism for feeding back a conclusion from an MS to the EU has worked and the substance is regulated at EU level since 2016. • Concerning hazard identification, as from January 2019, 3-BC was identified as an SVHC, based on being an endocrine disruptor for the environment, at EU level under the REACH Regulation. Information resulting from the legal obligations linked to this SVHC identification can serve to determine whether further and EU-wide risk regulatory measures (e.g. a restriction) are warranted.

5 References

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Annex 5B. Case Study: bis(2-ethylhexyl) phthalate (DEHP)

1 Case study factsheet: overview of concerns for human health and environment and main regulatory intervention

Product types (possible exposure sources)	- Toys and childcare articles (plasticised material) including food contact materials * - Cosmetic products * - Products containing plasticised materials such as building materials (floor coverings, wall paper, sealants, wiring) and various other articles made of plasticised materials, e.g. bicycle handles, covers for cell phones and tablets, children's wrist watches, gloves, school bags, PVC tape, rubber boots, rain coats, plastic sandals, bags, oilcloth and dinner mats, tools, synthetic leather furniture, sex toys and erasers (some exemptions apply e.g. for industrial or agricultural use) ** - Other food contact materials *** - Medical devices **** * Products for which placing on the market has been restricted in the EU (before May 2020) ** Products for which placing on the market is restricted from 7th July 2020. This restriction targets mainly imports since EU companies would require since 21 August 2013 an authorisation for the use of DEHP. *** Product for which placing on the market is allowed for certain conditions of use and associated restrictions **** Products for which placing on the market will be allowed under new conditions and restrictions, from May 2021 for medical devices and from May 2022 for in vitro diagnostic medical devices.
Exposure pathways of concern (human and environment)	The general population is exposed to phthalates via different routes and from different sources. Oral exposure occurs from ingestion of food and dust, and from mouthing of articles. Exposure also occurs from inhalation of air and dust and from dermal contact with articles and dust. The main sources of exposure are considered to be food, indoor environment and direct contact with articles. According to ECHA's assessment, exposure to DEHP in women and infants appears to be driven by food consumption, indoor environment and direct contact with articles. Emissions to soil and to a lesser extent to the aquatic environment and to air occur over long time periods at all stages of the life cycle, mostly at the end-of-life /waste management stage

Concerns for human health and/or the environment	Laboratory and epidemiological evidence suggesting risks of serious and interlinked developmental effects in human males, and effects to the environment The spectrum of effects caused by suppression of foetal androgen action in the male rat is known as the phthalate syndrome. Observed effects include decreased gene expression related to steroid biosynthesis, inhibition of testosterone production, changes in germ cell differentiation leading to effects on reproductive organs and fertility such as increased nipple retention, increased male mammary gland changes, decreased anogenital distance, increased incidence of genital malformations, delayed puberty onset, reduced semen quality and testicular changes. Evidence from mammalian and aquatic species has also raised concerns over potential risks for metabolic and immune systems and neurological development.
Regulatory hazard and risk assessment	• 1998 The Scientific Committee on Toxicity, Ecotoxicity and the Environment (SCTEE) identifies a risk from the use of DEHP in certain toys and childcare articles • 2001 classified as toxic to reproduction (Cat 1B) • 2001 listed as a Priority Substance under the Water Framework Directive by Decision No 2455/2001/EC • 2005 EFSA established TDI for DEHP (as well as DBP and BBP) and subsequent restrictions in plastic FCM. • 2006 Opinion of the SCCP on phthalates in cosmetic products SCCP/1016/2006 • 2008 SVHC identification due to reproductive toxicity • 2008 Environmental risk assessment published by ECB-JRC • 2008 and 2015 SCHENIHR reviews of 2002 opinion for use in Medical Devices • 2010 – REACH registration • 2010 ECHA's report on the review of the new available information related to DEHP. • 2012 ECHA SEAC and RAC opinions on a proposal submitted by DK to restrict DEHP, DBP, BBP, DIBP based on combined exposure do not identify a risk for human health • 2013 Re-designated as a Priority Hazardous Substance under the Water Framework Directive by Directive 2013/39/EU • 2014 SVHC identification – ED for environment • 2017 SVHC identification – ED for human health • 2017 Based on new data and taking into account combined exposure, ECHA SEAC and RAC opinions on a proposal submitted by ECHA with the support of DK ECHA (on request of the Commission) to restrict DEHP, DBP, BBP, DIBP, identifies a risk for human health • 2017 EC asked EFSA to reassess DBP, BBP, DEHP, DINP and DIDP for

	use in FCMs based on new evidence on exposure and reproductive toxicity used by ECHA in the 2015 assessment based on reproductive toxicity • 2019 EFSA group-based risk assessment of DBP, BBP, DEHP and DINP following draft guidance on mixtures: estimated combined exposure and established group TDI based on reproductive toxicity • 2019 SCHEER guidelines for the benefit-risk assessment of the presence of CMR/ED phthalates in certain medical devices
Risk management measures	• 1999 first restricted in toys and childcare articles made of PVC • 2003 Restriction of the supply of DEHP as substance or in mixtures to the general public (Directive 2003/36/EEC amending the Council Directive 76/769/EEC) • 2004 DEHP included in the list of prohibited substance in cosmetics (Annex II to the Cosmetic Products Regulation) • 2005 Ban extended to all toys and childcare articles at >0.1% w/w of the plasticised material individually or in combination with two other phthalates (Directive 2005/84/EC of the EU Parliament and the Council). • 2007 The restrictions are transposed into the REACH Regulation (Annex XVII entry 30 and 51) • 2007 Authorisations for use in FCMs are laid down (now in Commission Regulation (EU)10/201152), together with restrictions on the use of these substances, such as specific migration limits • 2008 Environmental Quality Standards set for surface waters by Directive 2008/105/EC • 2011 Added to authorisation list (REACH Annex XIV). Latest application date for authorisation 21 August 2013 Sunset date 21 February 2015. • 2015 RoHS restriction at >0.1% by weight of homogeneous material in EEE, applicable from 22 July 2019. Requests for time-limited and application-specific exemptions submitted by industry are under consideration. • 2018 Amendment of REACH Annex XVII (entry 51) by Commission Regulation 2018/2005 restricts DEHP, DBP, BBP and DIBP >0.1% w/w (individually or in combination) in plasticised material with limited exemptions. Restriction takes effect from 7 July 2020. • REACH Authorisation: Industry submitted since 2014 in total 6 requests for REACH Authorisations. Currently, one of the granted authorisations is still active. Other authorisations expired, were withdrawn, are under review or a decision is pending. • 2020 Further restrictions under consideration for FCMs based on new grouping approach and taking into account exposure from other sources

[152]OJ L 12, 15.1.2011, p. 1–89

2 Substance profile

Phthalates are a group of chemical substances used for various technical purposes in plastic, rubber materials and other polymers. Their main use, sometimes up to 50% of plasticised material, is as plasticisers in normally hard plastic materials to make these softer and more flexible. Bis(2-ethylhexyl) phthalate (abbreviated DEHP) is one of the chemicals belonging to this group. DEHP is highly hydrophobic (log Kow = 7.5), poorly soluble although biodegradable in water, soluble in fatty and oily matrix. More than 95% of the total use of DEHP has been as an additive in polymers, mainly in flexible polyvinyl chloride (PVC)[153,154]. Plastic material containing DEHP was reported to be used in a wide variety of articles for consumers as well as for workers and for professionals, including roofing material, cables, coated fabrics, car-under-coatings, toys, medical devices and shoe soles. Reported other uses of DEHP included sealants, adhesives, paints, lacquers, printing inks for paper, plastics including food processing equipment, textiles, rubber and ceramics for electronic components[155]. Several of the above mentioned uses of DEHP in articles have been regulated in the EU during the last two decades.

DEHP has been the most used phthalate plasticiser to date with an estimated tonnage in Europe of 595,000[1] t/y in 1997, of which 78% were used for indoor and 22% for outdoor applications (ECB 2008). Since EU regulatory action started in 1999, its use has decreased significantly as production has gradually shifted to alternative substances including higher molecular weight phthalates such as di-isononyl phthalate (DINP) (ECHA 2017), and declined to below 170.000 t/y in 2014. It is expected that the latest amendment of the restriction on phthalates under REACH will lower the tonnages on the EU market considerably.

2.1 Exposure pathways of concern

Human Exposure

According to ECHA, the main sources of human exposure to DEHP are considered to be food, indoor environment (including occupational exposure) and articles that have a high potential for direct contact. Whilst food was found to be a major source from combined dietary-biomonitoring studies, EFSA has recently estimated that dietary exposure to DEHP and other relevant phthalates that act via the same mode of up action contribute up to 23% of the temporary Tolerable Daily Intake. Direct exposure from articles can arise from contact between articles and the skin or mucous membrane, or from infants mouthing articles. Additionally, medicines and medical devices may contribute through oral intake and skin penetration to exposure of certain population groups. Furthermore, exposure occurs via slow release of phthalates to the indoor environment (ingestion of dust and inhalation of

[153]European Chemicals Bureau (2008): EU Risk Assessment Report - bis(2-ethylhexyl) phthalate (DEHP). Office for Official Publications of the European Communities, 588 p

[154]https://echa.europa.eu/documents/10162/d6e64c7a-8529-bf51-d850-229a8c3abe61

[155]DEHP in sealants, adhesives and paints is restricted for professional and consumer uses under REACH Regulation, Annex XVII, entry #30

air) and through migration from articles that are used in food processing. Young children may be additionally exposed via mouthing and dermal contact with toys and other indoor materials (ECHA 2017).

Environmental Exposure

Exposure of terrestrial and aquatic ecosystems is expected from emissions to soil and to a lesser extent to the aquatic environment and to air from all stages of the life cycle. Most of the environmental emissions from indoor and outdoor products occur over long time periods at the end-of-life /waste management stage, with significant emissions during products' lifetime and minor contributions from the production/processing (ECB 2008).

2.2 Hazard endpoints of concern

Human hazard

It is believed that the most vulnerable exposed groups are those associated with critical windows of exposure, including pregnant women (due to effects on foetal development). According to the ECHA SEAC and RAC 2017 opinion, "there is strong evidence for risks of serious and interlinked developmental effects in males, including with high probability reduction of semen quality, testicular changes, decreased anogenital distance, decreased foetal testosterone and with moderate likelihood at the estimated exposure levels, hypospadias, cryptorchidism and germ cell changes". Moreover, it has been proposed that developmentally impaired germ cells might correspond to precursors of testicular germ cell cancer in humans but overall, it is unclear whether exposure to the four phthalates has a role in testicular germ cell cancer in humans. In addition, experimental and epidemiological studies have suggested other possible effects not associated with reproductive toxicity, including on the immune system, the metabolic system and neurological development. Some of these studies suggest that reproductive toxicity may not be the most sensitive endpoint. Short-term high exposure level within the critical windows of exposure may be sufficient to cause adverse reproductive effects on the developing foetus. Although the foetus is thought to be more sensitive to the effects of this phthalate, children (boys) are also considered a sensitive population because their reproductive system is still developing.

Environmental Hazard

Concerning the effects of DEHP on the environment, based on available information from mammalian and ecotoxicological studies (ECHA 2014), adverse effects concerning development and reproduction are generally regarded as endpoints of particular relevance because such effects are likely to manifest themselves at the population level. The effects observed in rats are of particular concern for mammalian wildlife species with a natural low reproductive output (including endangered species) as negative effects on reproduction have an even higher potential for causing long term negative effects at the population level for such taxa. Exposure to DEHP is reported to affect steroidogenesis (e.g., decreased foetal testosterone production) resulting in adverse effects in the male reproductive system (e.g., effects on sex ratio, ovo-testis) in a range of mammalian and non-mammalian wildlife across taxonomic groups representative of both terrestrial and aquatic ecosystems. Several studies in fish indicate that DEHP has an estrogenic mode of action which may cause the sex reversal of male fish to female fish and / or affect reproductive output. DEHP appears to act via relatively weak anti-androgenic or oestrogenic mechanisms. However, effects that could be

mediated by the thyroid axis have also been noted by some authors for some species of fish and amphibians. Recent evidence from mammalian and aquatic species has also raised concerns over potential risks for metabolic and immune systems and neurological development.

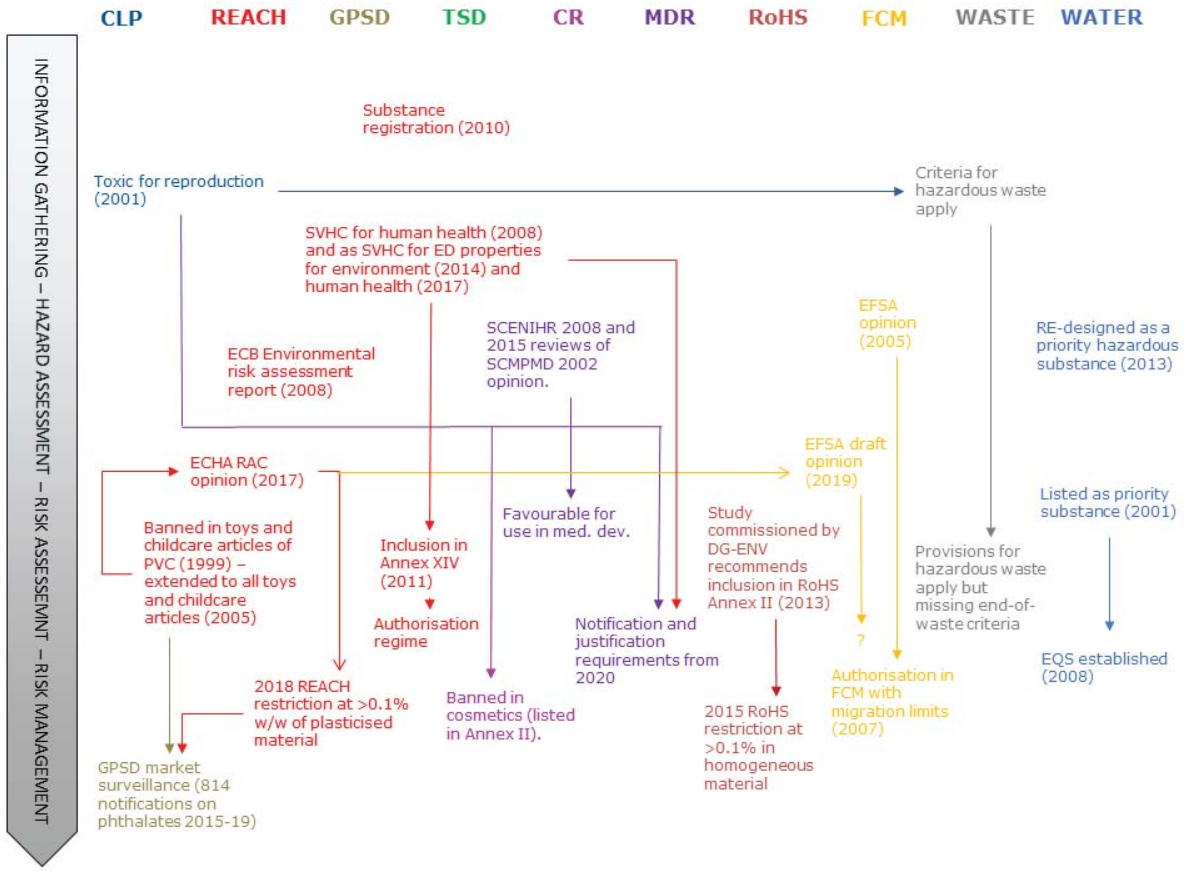

Figure 17.1. DEHP case study: illustration of applied provisions across legislation[156]

[156]CLP: Classification, Labelling and Packaging regulation (including pre-CLP legislation (67/548/EEC, and 1999/45/EC); REACH: Registration, Evaluation and Authorisation and restriction of Chemical substances (including pre-REACH legislation (EEC) No 793/93); GPSD: General Product Safety Directive; TSD: Toy Safety Directive; MDR: Medical Devices Regulation; RoHS: Restriction of Hazardous Substances in electric and electronic devices; FCM: Food Contact Material Regulation; Waste: Waste Framework Directive; Water: Water Framework Directive and Environmental Quality Standards Directive.

3 DEHP and other phthalates in EU legislation

3.1 Regulating phthalates under REACH and preceding legislation

In the 1990s, concerns grew that exposure to DEHP poses a risk especially for infants, while scientific reviews generally concluded that there should be no concerns for the vast majority of adults in relation to toxicity following DEHP exposure[157, 158]. The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE), mandated by the Commission to estimate the risk for children, suggested in 1998 the need to limit the concentration of DEHP in plastics used for toys and childcare articles based on toxic effects on the liver (hepatic peroxisome proliferation). Furthermore, according to the opinion of the CSTEE, laboratory tests with rodents showed adverse effects on kidneys and testicular damage. In 2001, DEHP was classified at the EU level[159] as being toxic to reproduction category 1B due to effects on fertility and the reproductive system. Already in 1999, the Commission restricted[160] under the General product Safety Directive[161] the use of PVC containing phthalates in certain toys and childcare articles for young children made of soft PVC. This restriction, which was based on a scientific assessment carried out by a scientific committee tasked by the Commission[162], was then extended and made permanent in 2005 (Directive 2005/84/EC) in order to cover all toys and childcare articles made of plasticised material. The restriction was later taken over into REACH, after this Regulation entered into force in June 2007.

In 2011, DK proposed to restrict four phthalates (DEHP, DBP, BBP, DIBP) based on their combined exposure. However, the Risk Assessment Committee (RAC) at ECHA concluded that data available could not demonstrate a risk from either of the phthalates or from their combined exposure.

Besides restrictions, REACH foresees the authorisation procedure to assess and control the risks of substances with certain hazardous properties, called Substances of Very High Concern (SVHCs) that are listed in Annex XIV of REACH. This regulatory measure puts the obligation on industry to demonstrate that the risk from the use of a chemical substance is adequately controlled or benefits from the use outweigh the risks and there are no alternative substances or technologies. Only in these cases industry can receive an authorisation to use a substance. However, authorisations cannot be obtained for uses that are already restricted. Authorisations are granted by the Commission and require periodical reviews. Industry is obliged to analyse alternatives to the use of a hazardous substance for which they apply. It is worth to note that the authorisation requirement does not concern imported articles.

The first step of the authorisation procedure is the identification of a substance as SVHC. Identified substances are listed on the REACH Candidate List. Reasons for identification can be that the substance meets the criteria for the classification as carcinogenic, mutagenic or toxic to reproduction category 1A or 1B (CMR Cat. 1A/1B), or that the substance is persistent, bioaccumulative and toxic

[157] SCMPMD/2002/0010
[158] Alternative analysis provided in: http://www.durodie.net/pdf/PoisonousDummies.pdf/
[159] EC (2001): Commission Directive 2001/59/EC of 6 August 2001 adapting to technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. O.J. L225. 21.8.2001, p.1 – 333.
[160] Decision 1999/815/EC
[161] Council Directive 92/59/EEC
[162] Scientific Committee on Toxicity, Ecotoxicity and the Environment (SCTEE)

(PBT), or very persistent and very bioaccumulative (vPvB), and thus hazardous to the environment[163] or a substance has properties that are of an equivalent level of concern to those of the substances of the previous categories. Endocrine disrupting properties with probable serious effects to humans or to the environment qualify a substance as being of very high concern, if the effects give rise to an equivalent level of concern to CMRs Cat. 1A/1B or to PBT/vPvBs.

With the scientific information growing over the years, DEHP was identified as an SVHC for three reasons. In 2008, its toxicity to reproduction, for which DEHP was also classified in 2001, led to its SVHC identification in 2008 and inclusion in the candidate list. The latter triggers the following obligations:

- Producers or importers of articles must notify ECHA if their article contains DEHP, if it is present in the article above 0,1% and the quantity of DEHP in the imported or produced article is above 1 tonne per year (REACH Article 7(2))
- Suppliers of DEHP, or of mixtures containing the substance, must provide their customers with a Safety Data Sheet (REACH Article 31(1) and Article 31(2)).
- Suppliers of articles must inform downstream users, and on request consumers, if the substance is present in an article at a concentration > 0.1 % (REACH Article 33)

The same effects, since caused by an endocrine mode of action, resulted in an additional identification in 2017 as SVHC of an equivalent level of concern due to its endocrine disrupting properties to human health. Three years earlier, in 2014, DEHP's endocrine disrupting properties to the environment were added to the existing SVHC listing. The additional inclusion of ED effects to human health and the environment in the SVHC list triggered provisions for risk assessment of these properties (Chemical Safety Report) and risk communication (Safety Data Sheets). Furthermore, those properties require specific consideration of ED effects in reviews of authorisation.

In 2011 the Commission included DEHP in the authorisation list (Annex XIV of REACH) (Commission regulation (EU) No 143/2011) due to its reproductive toxicity. This inclusion set up the obligation for industry to apply for authorisation by 21 August 2013 (latest application date) for the uses of DEHP it wanted to continue after 21 February 2015 (sunset date). After this date uses of DEHP were not allowed any more unless an authorisation was granted or an application for authorisation had been submitted to the Europeans Chemicals Agency (ECHA) by the latest application date. An update of Annex XIV of REACH is currently in preparation with the view of updating its SVHC properties of DEHP to also list its endocrine disrupting properties for human health and for the environment. Listing of DEHP due to its endocrine disrupting properties for the environment will make authorisation procedures applicable also to uses regulated by sector-specific regulations (e.g. food contact materials, medical devices) as regards environmental risks. Authorisation is also required for DEHP contained in recycled PVC.

Up to November 2019, three applications for authorisation have been granted by the Commission in consultation with Member States and after an in-depth assessment by the responsible scientific committees at ECHA[164]: in 2014 for seven years for a use in the production of aircraft engines, in 2015 for four years for a military use (authorisation expired) and, in 2016, for four years to three companies for two uses of recycled soft PVC containing DEHP to produce PVC blends and certain PVC articles. In the meantime, this authorisation has expired in 2019 for two out of three

[163]REACH Art. 57
[164]https://ec.europa.eu/docsroom/documents/37301

authorisation holders. Two authorisation holders have submitted a review report requesting to continue this use. Due to regulatory pressure for phasing out this substance, one company withdrew their submitted review report and only one company is applying for a review. The Commission decision on the review of authorisation for the latter holder is currently pending. The Commission decision is also pending on one another application on uses of DEHP in PVC.

One example of an authorisation is that granted to the company Rolls-Royce plc for a use in the manufacturing of fan blades for aircraft engines. At the time of applying for authorisation, technically feasible alternatives for the use of DEHP were not available. The risks arising from using DEHP when producing the fan blades are adequately controlled, and the substance is ultimately destroyed by the very high temperature fan blade forming process. Rolls Royce was authorised to use DEHP for this purpose, with a review date in 2022.

Authorisation under REACH does not affect the import of articles containing a SVHC into the EU. REACH however foresees an obligation for ECHA to assess whether further restrictions should be introduced after the sunset date, if there is a risk from use of Annex XIV substances in articles, including those imported. Accordingly, a restriction dossier on DEHP and 3 other phthalates[165] in articles was initiated. Based on the opinions from the scientific committees at ECHA responsible for assessing the risk and the socioeconomic impacts[166] (ECHA 2017), the Commission has adopted a restriction by Regulation (EU) 2018/2005 amending Annex XVII to REACH. The risk assessment considered derived no-effect levels for toxicity to reproduction that were based on N(L)OAELs for anti-androgenic effects seen in developmental studies. A NOAEL for DEHP based on testicular effects (germ cell depletion, reduced testis weight) in male offspring in Wolfe and Layton (2003) was selected for the combined risk assessment. RAC and SEAC considered that DEHP and the other three phthalates have the same mode of action and based the risk assessment on combined exposure and effects of the substances. The exposure assessment considered recent biomonitoring data from the EU funded DEMOCOPHES programme. Consequently, DEHP and the other three phthalates are not permitted to be placed on the market after 7 July 2020 in articles, individually or in any combination in a concentration equal to or greater than 0,1 % by weight of the plasticised material in the article Only few exemptions were introduced in the restriction, namely “for industrial or agricultural use, or for use exclusively in the open air, provided that no plasticised material comes into contact with human mucous membranes or into prolonged contact with human skin” and for other specific uses critical to safety (aircraft, motor vehicles). The restriction also updates the conditions for the ban in toys and childcare articles and extends it to DIBP, setting a limit of 0.1% w/w on the total concentration of the four phthalates in plasticised materials. It is expected that this restriction will considerably lower the quantify of phthalates in articles placed on the EU market.

3.2 Enforcement of regulatory measures under REACH

The Member States, ECHA and the Commission all play a role in enforcement of REACH. The Member States have the legal powers to enforce against duty holders. However, REACH also stipulates some roles related to enforcement to ECHA with the creation of the Forum for Exchange of Information on Enforcement (the Forum)[167] which is a network of national authorities responsible for

[165]Benzyl butyl phthalate (BBP), Dibutyl phthalate (DBP) and Diisobutyl phthalate (DIBP)
[166]The Risk Assessment Committee (RAC) and the Committee for Socio-economic Analysis (SEAC)
[167]REACH Art 76(1)(f)

the enforcement of the REACH as well as the CLP[168], Biocidal Products and PIC[169] Regulation. The Commission's role is to guide on policy issues, provide clarity on the implementation of REACH, facilitating enforcement by Member States.

The Forum coordinates various enforcement projects, which are designed to harmonise enforcement in Member States and check the current level of compliance regarding obligations imposed on industry by REACH, CLP, Biocidal Products and PIC Regulation. The REF-projects[170] are carried out by inspectors based in the national authorities in the participating Member States. The resulting information is collected by ECHA and the Forum Working Group. Findings of the REF projects are them summarised in a final report. Ultimately, the goal of the REF-projects is to improve the quality of enforcement in the Member States but also to improve the compliance of duty holders with REACH and other legislations.

In 2016, the Forum launched an enforcement project to control the compliance with the REACH restriction on phthalates in toys and childcare articles[171,172]. The project consisted mainly of chemical analysis of the restricted phthalates in articles. Toys and childcare articles were purchased by authorities in local shops or via the internet. As normal for enforcement checks, articles were selected by authorities based on their experience on which types of articles are likely to be non-compliant. The selection is hence not representative for the whole toys and childcare market.

In total, 464 toy products were checked for the phthalates DEHP, BBP and DBP in the project. 19.7 % of the inspected toys contained one of the phthalates above the permitted level. Of 193 childcare articles, 7 articles (i.e. 3,6%) were non-compliant. Most products checked during the enforcement project (including other products than toys or childcare articles) and found to be non-compliant come from countries outside of the European Economic Area or are of unknown origin.

The report on the enforcement project concluded that the rate of non-compliance for phthalates in the selected toy articles is rather high and that the findings are a special point of concern considering that those articles are intended to be used by children.

Member States have also been controlling FCMs for phthalates including DEHP in response to Commission Recommendation (EU) 2019/ 794[173]. The findings so far indicate that, for the vast majority of samples analysed, DEHP is not present or is not migrating into food.

3.3 Regulating phthalates under food contact materials (FCM)

Phthalates may be present in several food contact articles, primarily in plastic FCMs for increasing flexibility of PVC or other polymers as well as rubber. Phthalates may migrate into food from processing equipment, such as tubes used in the beverage industries, conveyor belts and vinyl gloves used in the preparation of foods. They may also be present in some types of packaging such as in the

[168]Classification, Labelling and Packaging (CLP) Regulation ((EC) No 1272/2008)
[169]The Prior Informed Consent Regulation (PIC, Regulation (EU) 649/2012) administers the import and export of certain hazardous chemicals and places obligations on companies who wish to export these chemicals to non-EU countries
[170]REACH-EN-FORCE (REF) projects
[171]REACH Annex XVII entry 51 restricting DEHP, BBP and DBP in toys and childcare articles
[172]ECHA (2018): Forum REF-4 Project Report - Harmonised Enforcement Project on Restrictions. ECHA Report ECHA-18-R-03-EN, Helsinki (https://echa.europa.eu/fr/-/inspectors-find-phthalates-in-toys-and-asbestos-in-second-hand-products)
[173]http://data.europa.eu/eli/reco/2019/794/oj

seals between a glass jar and its metal lid although recent information collected by the Commission indicates that these have largely been replaced in the EU by non-phthalate plasticisers[174]. In order to be used in FCM plastics, phthalates must be assessed and authorised according to FCM legislation, including an assessment by the European Food Safety Authority (EFSA).

There are five phthalates listed and authorised as additives in the positive list in Annex I (**Table 1.1**) of Regulation (EC) No 10/2011: (di-butylphthalate (DBP, FCM No 157), butyl-benzyl-phthalate (BBP, FCM No 159), Bis(2-ethylhexyl)phthalate (DEHP, FCM No 283), di-isononylphthalate (DINP, FCM No 728), and di-isodecylphthalate (DIDP, FCM No 729).

In 2005, EFSA published opinions on five phthalate esters, DBP, BBP, DEHP, DINP and DIDP, considering updated toxicological information at that time, relevant to reproductive toxicity. Based on these opinions, these five phthalates are currently authorised for use as plasticisers and technical support agents in plastic FCMs. The authorisations are laid down in Commission Regulation (EU) No 10/2011[175], together with restrictions on the use of these substances, such as specific migration limits (SMLs), taking into account exposure from other sources where necessary, as well as additional restrictions on their use.

On 1 April 2016, ECHA, in cooperation with Denmark, prepared an Annex XV dossier for the four phthalates DBP, BBP, DEHP and DIBP and on 29 August 2017, the Agency submitted the opinions of RAC and SEAC to the Commission. Based on those opinions, the Commission adopted restriction of the four phthalates in articles (Regulation (EU) 2018/2005). Food contact materials are exempted from the restriction, except from childcare articles intended to facilitate the feeding of children, which are covered by the REACH restriction.

In light of the ECHA RAC opinion based on new biomonitoring information which became available only after EFSA's 2005 opinion, the Commission asked EFSA in July 2017 to re-assess the safety of the five authorised phthalates used in plastic FCMs, taking into account in particular new information on reproductive toxicity used in the development of the restriction dossier as well as data examined in a classification proposal for DINP.

Based on its assessment[176], EFSA has set a new safe level – a group Tolerable Daily Intake (TDI) – for four of the five phthalates (DBP, BBP, DEHP and DINP) of 50 micrograms per kilogram of body weight (µg/kg bw) per day based on their effects on the reproductive system. The key effect on which this group-TDI is based is a reduction in testosterone in foetuses. The fifth phthalate in the assessment, DIDP, does not affect testosterone levels in foetuses, therefore a separate TDI of 150 µg/kg bw per day has been set based on its effects on the liver (as per the 2005 evaluation). The new assessment of the five phthalates is in line with the 2005 assessment in terms of their most sensitive effects and the individual tolerable daily intakes.

EFSA improved its estimate of dietary exposure to phthalates and concluded that current exposure to these five phthalates from food is not a concern for public health. Dietary exposure to the group of DBP, BBP, DEHP and DINP for average consumers is 7 µg/kg bw or seven times below the safe level, while for high consumers it is 12 µg/kg bw, which is four times lower. For DIDP, the dietary exposure for high consumers is 1,500 times below the safe level. However, EFSA has set all the TDIs

[174]https://ec.europa.eu/food/sites/food/files/safety/docs/cs_fcm_wg_20200224_pres-02.pdf
[175]http://data.europa.eu/eli/reg/2011/10/2019-08-29
[176]EFSA Journal 2019;17(12):5838

on a temporary basis due to uncertainties about effects other than the reproductive ones and about the contribution of plastic FCMs to overall consumer exposure of phthalates. EFSA identified a need to address these uncertainties by considering the whole body of evidence.

The Commission is currently assessing EFSA's Opinion and the adequacy of existing EU measures and considering what if any changes or additional measures are necessary at EU level[177]. In recognition of the limitations and uncertainties identified in the EFSA opinion and to address its recommendations, the Commission is also mandating EFSA to carry out a full re-assessment of phthalates in FCMs, taking into account all available information to ensure the highest level of protection for consumers.

3.4 Regulating DEHP in cosmetics

The use of DEHP in cosmetic products is prohibited as it was classified as toxic for reproduction (Cat 1B) under the Council Directive 67/548/EEC in 2001. The ban came into force in December 2004 (currently under entry 677 of Annex II to the Cosmetic Products Regulation).

A Greenpeace investigation published in February 2005 examined inter alia the presence of 10 phthalates in perfumes (Greenpeace 2005). It should be noted that the Greenpeace sampling was carried out on products prior to the effective date of the ban of certain phthalates in cosmetics (i.e. between 2003 and 2004, before DEHP was banned in cosmetic products). In this investigation, DEHP was found in some perfumes, usually in low concentrations. The Commission mandated the Scientific Committee on Consumer Products (SCCP 1016/2006) to carry out inter alia a risk assessment using the highest reported concentration of 167 mg/kg of DEHP in perfumes samples. The SCCS concluded '*the inadvertent occurrence of DEHP at trace levels in cosmetics does not seem to be a concern for consumer health* and *'in view of the low concentrations [of phthalates] found in the samples of perfume analysed, there would be no quantifiable risk for the consumer'."*

3.5 Regulating DEHP in medical devices

Medical devices made of PVC, such as blood bags, catheters, and endotracheal tubing, almost always contain DEHP, where its function is to make the material more flexible and durable. Risks associated with DEHP leaching potential have raised concerns among some Member State authorities, particularly for neonates in intensive care units, in view of the relatively high exposure per unit body mass. In 2002, the Commission mandated the Scientific Committee on Medicinal Products and Medical Devices to produce an opinion on "Medical Devices containing DEHP plasticised PVC; Neonates and Other Groups Possibly at Risk from DEHP toxicity"[178]. The Committee concluded that "there is no evidence that any of these groups do experience DEHP related adverse effects". However, the Committee also stated that "a lack of evidence of causation between DEHP-PVC and any disease or adverse effect does not mean that there are no risks". To take account of new information on the safety of DEHP, the Commission mandated the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to carry out two reviews of this opinion, in 2008[179] and in

[177]https://ec.europa.eu/food/sites/food/files/safety/docs/cs_fcm_wg_20200224_pres-01.pdf
[178]SCMPMD/2002/0010
[179]SCENIHR/2008/014

2015[180], which also included an assessment of possible alternative substances. The Committee restated concerns due to the short-term but high exposure of neonates in intensive care, as well as for adult haemodialysis patients, although the currently available data is still inconclusive or inconsistent. The available data on toxicology, leaching and functional efficacy of alternatives was also insufficient. The Committee formulated specific needs for research that would help provide adequate risk assessment for vulnerable groups of patients and inform judgement of the suitability of alternative plasticisers.

In conclusion, although concerns for the use of DEHP-PVC in vulnerable patients cannot be ruled out, bearing in mind that many interventions in question are life-saving, the benefit-risk ratio generally remains favourable for the use of such devices, where no alternatives are available.

Under the new Regulation on Medical Devices, manufacturers will be obliged to re-evaluate the presence of DEHP (classified as toxic for reproduction category 1B and identified as SVHC for endocrine disrupting properties to human health and to the environment under REACH) in their devices at levels above 0,1% weight by weight, providing reasoning why it is indispensable at the concentration used and taking into account guidelines for the benefit-risk assessment of phthalates recently prepared by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER 2019[181]). The forthcoming listing DEHP as SVHC due to its endocrine disrupting properties to the environment will make uses of the substance in medical devices subject to REACH authorisation, requiring the applicant to demonstrate that the benefits from the use outweigh the environmental risks and that there are no alternatives.

In 2015, DEHP was included in Annex II of RoHS based on concerns regarding EEE waste management implications[182]. The restriction took effect in July 2019. Therefore, medical devices covered by the RoHS Directive should follow the specific provisions under RoHS.

3.6 Regulating DEHP at the interface of chemical and waste legislation

The presence of hazardous substances, such as DEHP, in materials and products not only concerns chemical and product safety legislation. It also has profound implications for waste legislation. As society moves towards a circular economy, there are two boundaries between the chemical and the waste legislation: the end-of-life on one side and the end-of-waste on the other. The first boundary is crossed when products reach the end-of-life stage and become waste; the second when waste is recycled into secondary materials and products. As long as hazardous substances are part of waste, they are regulated under the Waste Framework Directive and related policy instruments.

From the point of view of waste legislation, the potential negative impacts of hazardous substances in material cycles can be controlled by restrictions in products, waste management rules (e.g. treatment requirements, traceability of waste streams) and provisions for end-of-waste criteria. Restrictions in products belong to the chemical and product specific domain (e.g. REACH, RoHS). In 2015, DEHP was included in Annex II of RoHS based on concerns regarding EEE waste management implications[182]. The restriction took effect on 22 July 2019. With the increasing regulatory actions on DEHP since 1999 up to the recent regulatory measures (e.g. obligation to obtain an authorisation

[180]SCENIHR/2015/047
[181]https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_015.pdf
[182]https://ec.europa.eu/transparency/regdoc/rep/3/2015/EN/3-2015-2067-EN-F1-1.PDF

under REACH, REACH restriction on plasticised material (applicable from 8 July 2020 on), listing under RoHS), the presence of DEHP in products and recycled materials decreased and will be further minimised. However, its presence in materials and products becoming waste has proved problematic. As a category 1B reproductive toxicant under the CLP regulation, any material containing DEHP above 0.1% is classified as "hazardous" under the waste directive (2008/98/EC). As such it is subject to specific provisions including the need to decontaminate material flows to ensure safety. Technically, treatment of PVC waste to reduce DEHP below 0.1% is expensive and energy intensive and therefore not considered feasible. The quality of recycled materials can be controlled by setting end-of-waste criteria under waste legislation. However, although end-of-waste criteria for plastics were proposed by the JRC in 2012 (JRC 2012), unresolved debate among stakeholders meant that no agreement at the EU level was reached. The lack of agreed EU-wide end-of-waste criteria for plastics constitutes an important regulatory gap for waste operators. It leaves room for different interpretations by operators in the waste recycling industry and in national authorities. The debate remains unresolved to date. As a result of the claim that DEHP is less bioavailable in recycled PVC, some industries have assumed that DEHP-containing recycled PVC meets the generic end-of-waste conditions laid out in Article 6 of Directive 2008/98/EC on waste, thus crossing into the chemical regulatory domain. Directive 2008/98/EC as an EU Directive is however not directly applicable to economic operators. Currently, since no end-of waste criteria have been established at EU or Member State level, national authorities are to take end-of-waste decisions as and if appropriate. So far, no such cases have been notified to the Commission. On this side of the legislative interface, the use of recycled materials that have stopped being waste and that contain substances listed in REACH Annex XIV is subject to authorisation. This applies to DEHP as well as to any other plastic additives included in REACH Annex XIV.

The case of DEHP in recycled PVC illustrates the current situation, as analysed in detail in the "*Study for the strategy for a non-toxic environment of the 7th EAP"* (EC DG ENV 2017). In 2013, three companies submitted an authorisation application for the use of recycled soft PVC containing DEHP in formulations and in industrial processes to produce certain PVC articles. ECHA's RAC concluded that the risk from those uses is not adequately controlled, while its SEAC concluded that the benefits from the formulation of recycled PVC containing DEHP and from its use to produce certain PVC articles outweigh the risk and that there are no suitable alternatives. In view of the RAC and SEAC opinions, in 2016 the EU Commission granted the authorisation based on risk-benefit considerations, with a review period of four years, on the condition that the DEHP content in recycled PVC does not exceed 20 % (w/w). The authorisation is only applicable provided that the recycled PVC material containing DEHP has ceased to be waste. If this is not the case, the waste legislation applies for handling and processing of this material. The granted authorisation does not cover toys and childcare articles; erasers; adult toys (sex toys and other articles for adults with intensive contact with mucous membranes; household articles smaller than 10 cm that children can suck or chew on; consumer textiles/clothing intended to be worn against the bare skin, cosmetics and food contact materials (C(2016)3549). The need to reassess the availability of alternatives and the fact that in the application adequate control of risks to workers during formulation and article production could not be demonstrated justified the review period of the authorisation. Due to regulatory pressure for substituting this substance with alternatives and phasing it out, only one of the three companies is pursuing a review of this authorisation in 2017. A Commission decision on this review is currently pending.

3.7 Regulating DEHP under the Water Framework Directive

DEHP has been listed as a priority substance under the Water Framework Directive (WFD) since 2001. Its inclusion in the priority list was motivated by a relatively high modelling-based ranking (#14) combined with additional evidence of environmental occurrence and endocrine disrupting effects[183]. In 2008 an Environmental Quality Standard (EQS) was set of 1.3 µg/l in surface waters (Directive 2008/105/EC). Its identification as a Substance of Very High Concern under REACH in 2008 motivated a proposal to change the status of DEHP from a Priority Substance to a Priority Hazardous Substance. An impact assessment followed, which analysed the costs and benefits of the modified regulatory status (ENTEC 2011). Annex X to the WFD as amended by Directive 2013/39/EU thus designates DEHP as a Priority Hazardous Substance. In accordance with WFD Article 16(6) all emissions of DEHP to the aquatic environment should be phased out within 20 years.

4 Impact of regulation

4.1 Decline in use and exposure

Since the initial regulatory action in 1999 and with the increasing restrictions coming into force over the following years, DEHP production and use in the EU has declined. Between 2005 and 2013, the estimated combined production of DEHP, DBP and DIBP in the EU28 declined from about 409,000 t to 90,000 (ECHA 2017b). At present, only one company is still manufacturing DEHP, for which an application for authorisation for two uses of this substance is pending. Placing on the market of articles, i.e. manufacturing in the EU as well as import of articles, containing four phthalates (DEHP, DBP, DiBP, BBP) were estimated to equal 179,000 t/y in 2011. It is expected that with the latest amendment of the restriction on phthalates (DEHP, DBP, DiBP, BBP) under REACH imports of articles containing those phthalates will be reduced considerably to well below 10.000 t/y (ECHA 2017b).

Recent studies have reported declining historical trends in urinary concentrations of most phthalates and their metabolites. Biomonitoring data from the EU project DE MO COPHES was used to demonstrate a decline in human exposure to phthalates in the background document supporting the opinions on the REACH restriction proposal (ECHA 2017). Between 2001 and 2011 exposure to the four restricted phthalates including DEHP has decreased by between 30% and 80% depending on the study location and design. Long-term 24h-urine monitoring from the German Eenvironmental Specimen Bank (ESB) reveal a roughly 10-fold decline in internal exposure levels of DEHP metabolites from their peak levels in the late 1980s/early 1990s compared to most recent levels from 2015 (Göen et al 2011, Koch et al 2016). The same study also reports constant or even slightly declining levels of di-isononyl phthalate (DINP), one of the main replacements for DEHP. The authors suggested that probably, non-phthalate alternatives are increasingly taking over from the phthalates in Germany. A comparison with the American NHANES data indicates that this is not the case in the US, where high-molecular-weight phthalates, such as DINP, seem be gaining importance. Overall, internal exposure to most phthalate metabolites monitored in both countries, including those from DEHP, seems to be lower in Germany than in the US. Studies from other EU countries have

[183]https://ec.europa.eu/environment/water/water-dangersub/pdf/commps_report.pdf

consistently reported declining trends in DEHP urinary metabolites. The sum of the concentrations of DEHP metabolites from samples collected from populations in central Italy showed on average a 4-fold reduction between 2011 and 2016 (Tranfo et al 2018); a 3-fold reduction was observed between the 2007-2011 FLEHS II and 2012-2015 FLEHS III monitoring campaigns in Flanders (Schöeters et al 2017).

4.2 Shift to alternatives

The decrease in production volumes in recent years reflects the fact that DEHP for many applications has been replaced by alternative solutions, including higher molecular weight phthalates, non-phthalate plasticisers and alternative materials.

The main alternative plasticisers in PVC have been DINP and di-isodecyl phthalate (DIDP). According to a study commissioned by ECHA in 2008, DINP and DIDP have dominated in marketed PVC flooring, wall coating and carpets with PVC backcoating after 2000 and the publication date of the study (COWI 2009). However, despite the continuous decline in DEHP exposure since the 1990s, no significant increase has been observed in those two substitutes (Koch et al 2016), suggesting that DEHP has not been substituted only by high- molecular-weight phthalates but also by non-phthalate plasticisers and alternative materials. In fact, non-phthalate alternatives have replaced DEHP in uses that raised the biggest concerns as regards human exposure: toys, medical products, food packaging and water beds (COWI 2009). It is likely that the reduction in environmental emissions and exposure from other product types could be significantly slower. Similarly, to other toxic additives in articles and materials, DEHP may remain in the materials cycle for decades, even if measures are taken to prevent the use of those articles/materials or to decontaminate waste streams (Pivnenko et al. 2016).

Several alternative assessment studies have been applied to phthalates to identify and assess alternatives. Studies vary in scope, ranging from alternative phthalates (high molecular volume), non-phthalate plasticisers and alternative materials. The wide variability in the level of information available on alternative solutions makes it difficult to draw definitive conclusions on human and environmental risks of alternatives. Differences in life-cycle attributes add complexity to the problem. According to ECHA's SEAC and RAC opinions, technically feasible alternative plasticisers are available at similar or slightly higher prices for all uses in articles in the scope of the 2018 proposed restriction (ECHA 2018). EFSA has assessed a number of plasticisers, which are known to be used as replacements in food contact materials and which have subsequently been authorised in plastic FCM. Alternatives generally have more benign human health and environmental hazard and risk profiles, although there are some uncertainties regarding the extent to which risks will be reduced following substitution. EFSA will consider in its new work on phthalates whether further assessment is also needed of replacement plasticisers and similar substances. However, based on the current information, it can be concluded that the alternatives will lead to overall risk reduction.

Lifecycle attributes are essential in drawing conclusions on the impact of regulation of DEHP. As regards recycling of PVC containing DEHP, for example, comparing the benefits of reduced overall DEHP exposure with the costs of constraints to PVC recycling involves a high degree of uncertainty. Conclusions on the subject are thus ultimately driven by differences in values and priorities set. Depending on the role of various actors among industry, regulators and NGOs, some stakeholders have prioritised energy and CO_2 saving targets, while others have prioritised reduction in exposure to toxic phthalates. The Commission however needs to balance all the different interests when evaluating impact of regulatory measures.

5 Comments on fitness check evaluation criteria

Comments on coherence	• Under REACH, the use of DEHP contained in recycled PVC to produce certain articles from recycled PVC was authorised in 2016 (currently under review). This authorisation is only applicable if recycled PVC has reached end-of-waste as regulated under legislation on waste. However, no end-of waste criteria have been established so far in the EU, and at Member State level, national authorities are to take end-of-waste decisions as and if appropriate. So far, no such cases have been notified to the Commission. • Restricting articles containing DEHP under REACH in parallel to the REACH authorisation requirement, which is applicable only to EU companies, addressed the issue of imported products. • The scientific opinions issued by ECHA and EFSA on DEHP and other low molecular weight phthalates considered the same hazard, toxicity to reproduction and toxicological data. Both used a dose addition model for the combined risk assessment. ECHA's assessment pointed to evidence of risk to human health from combined exposure using mainly biomonitoring data. Exposure via food contributes to the observed exposure. EFSA's assessment pointed to combined exposure not resulting in exceeding group-based TDIs. EFSA's assessment did not consider DIBP (not authorised in FCM) and focussed on dietary exposure. The two assessments differ in scope (chemicals, exposure sources), exposure information used (e.g. food intake estimates) and to a minor extent to methods (e.g. population age grouping, absorption assessment factor). Differences in results are mainly determined by the specific policy question being addressed but some differences in the assessment exist for the same question (e.g. food intake estimates). • Differences in the risk management approach follow from the different scope of regulations and risk assessments performed. The consequences for the achievement of the objectives (exposure and risk reduction) cannot be quantified at present. • Variations in risk management and approaches taken under different pieces of legislation (REACH, FCM) may be justifiable when considering the objectives and scope of the individual pieces of legislation. However, potential differences in the outcomes of risk assessments of the same substances or group of substances considering the framework as a whole may undermine the science and subsequent risk management action. The situation points to the need for an integrated exposure assessment framework accounting for contributions from different exposure sources in a systematic way. • Regulatory action and risk assessments were launched under the various

	legislations at different points in time by different actors. With the SVHC-Roadmap to 2020[184], a Regulatory Management Option Analysis was introduced under REACH that is looking on potential regulatory measures under all legislations and sectors. However, this coordinative tool did not lead to initiating regulatory action on DEHP outside of REACH since it was developed later and after the first regulation of DEHP under REACH has started.
Comments on effectiveness	• Regulatory assessments included reviews of scientific information available at the time of assessment and took advantage of peer reviewed, quality data (e.g. biomonitoring, non-animal methods). Information from scientific sources often plays a decisive role for high tier assessments and are hence important in regulatory assessments. This was the case for the 2018 REACH restriction when human biomonitoring data was instrumental to support the 2018 phthalates REACH restriction. Similarly, exposure data from the scientific literature was essential for the EFSA 2019 risk assessment because of analytical limitations in measurements from the EFSA chemical occurrence database. • Regulatory action on DEHP and other phthalates started before ED specific provisions were in place. These included the 1999 ban on DEHP in toys and childcare articles, the classification as toxic for reproduction in 2001, the ban to supply DEHP to the general public, the ban in cosmetic products in 2004, restrictions in FCM in 2007 and the inclusion in the REACH authorisation list in 2011. Regulatory assessments and actions followed the increasing knowledge on DEHP over time. • DEHP is tightly controlled by current EU legislation. Under REACH it is subject to authorisation since 2011, to restrictions on toys and childcare articles on the supply to the general public and to a broad restriction in articles since 2018. It is also restricted and subject to authorisation regimes under the RoHS. It is allowed for use in plastic FCMs only for such materials that comply with restrictions including specific migration limits, and in medical devices based on case-by-case risk-benefit considerations and assessment of alternatives. It is banned from use in cosmetics due to its classification as toxic for reproduction under CLP. • The additional inclusion of ED effects on human health and on the environment in the SVHC list triggered risk provisions for risk assessment (Chemical Safety Report) and risk communication (Safety Data Sheets). Once these properties are included also in the DEHP listing in Annex XIV of REACH, the ED effects would need to be considered in applications for authorisations and in reviews of authorisation. Furthermore, listing of ED effects to the environment will trigger an obligation to obtain authorisations in other sectors (FCM, medical devices) that until then were exempted from this obligation. This development also prompted the re-designation of DEHP from a Priority to a Priority Hazardous Substance under the WFD.

[184]https://echa.europa.eu/svhc-roadmap-to-2020-implementation

	• According to ECHA the proposed REACH restriction is capable of significantly reducing the risks to human health of combined exposure (RCRs are expected to be reduced to levels equal to or below 1 at the 95th percentile) within a reasonable period of time, starting from 2020, although some delay is likely to be caused by the service-life of articles in use. • There is evidence of reduced human exposure to regulated low-molecular-weight phthalates including DEHP since the early 2000s. German data indicate that human exposure to di-isononyl phthalate (DINP), one of the most common phthalate alternatives to DEHP has remained constant or even slightly declined in the last years, possibly indicating a move to non-phthalate alternatives, at least in Germany. • DEHP and other low-molecular-weight phthalates are being replaced by high-molecular-weight phthalates, non-phthalate alternatives and other solutions. Yet, analyses by inspecting enforcement authorities have found incompliant products (e.g. toys) especially from imports.
Comments on efficiency	• Hazard assessments of DEHP have been done at various points in time under various pieces of legislation (e.g. CLP, REACH, FCM, WFD). Considering the whole framework, it would be more efficient to do a single hazard assessment per substance or group of substances by fully coordinating the work programme of respective agencies/committees. Despite ongoing efforts in harmonising approaches, the framework is currently not optimised for efficiency.
Comments on EU added value	• DEHP and the other low-molecular-weight phthalates are mostly regulated at EU level under REACH and RoHS. This includes toys and childcare articles, electric and electronic articles using DEHP in plastic material and all other articles restricted under REACH as well as REACH authorisation requirements. • In some Member States, further restrictions apply to DEHP and other phthalates in non-plastic FCMs, such as rubber. These restrictions are inconsistent with each other indicating a possible need for a more coherent EU approach.

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Annex 5C. Case Study: nonylphenol

1 Case study factsheet: overview of concerns for human health and environment and main regulatory intervention

Product types (possible exposure sources)	Nonylphenol (NP) has been used for the following purposes or in the following articles. The listed uses have been restricted or otherwise regulated in the EU, with few authorised uses for specific applications. - Industrial processes - Textiles - Detergents - Pesticides and biocides - Hair care products
Exposure pathways of concern (human health and environment)	Concerns are mainly for exposure of aquatic ecosystems, via domestic and industrial wastewater emissions. Nonylphenol emissions occur during its production and subsequent use as well as from the breakdown of some products containing a nonylphenol group, particularly nonylphenol ethoxylates (NPnEO).
Concerns for human health and/or the environment	Nonylphenols act as estrogen receptor agonists and may have anti-androgenic properties causing adverse effect in fish and amphibians.
Regulatory hazard and risk assessment	• 2001 - Classified as Cat 2 toxic for reproduction and as Cat 1 chronic toxic for the aquatic environment under CLP (Directive 2001/59/EC) • 2001 - Nonylphenol proposed as priority hazardous substance under the WFD (COM/2001/17) • 2002 – European Union Risk assessment report on nonylphenols and nonylphenol ethoxylates under the Existing Substance regulation 793/93 • 2005 Opinions of the Commission Scientific Committee on Consumer Products (SCCP/0888/05 and SCCP/0913/05) related to the listing of NP as prohibited substance in cosmetic products due to its classification as toxic to reproduction • 2005 - EQS established for annual average and maximum exposure under the WFD • 2012 - Identification of NP by ECHA as a substance of very high concern (SVHC) for ED effects in the environment based on a proposal by the Germany

	• 2013 - Identification of NPnEO by ECHA as a SVHC, as a precursor to NP, itself already identified for ED effects in the environment based on a proposal by the Germany • 2014 - ECHA RAC and SEAC opinions on the Annex XV dossier proposing restrictions on NP and NPnEO (branched and linear) in textile clothing, fabric accessories and interior textile articles (including their prints) that can be washed in water if they contain nonylphenol or nonylphenol ethoxylate alone or in combination in concentrations equal or higher than 100 mg/kg textile. • 2016 - Second review of the priority substances list under the WFD, led by JRC leading to JRC proposal to revise NP EQS (2020, pending review and approval). • 2019 Proposal by France for the identification of TNPP as SVHC.
Risk management measures	• 2001 - proposed identification as priority hazardous substance triggers WFD art 16(1) requiring cessation or phasing out of aquatic emissions • 2003 - Restriction for the use of NP and NPnEO at concentrations >0.1% by weight (Directive 2003/53/EC). Restriction incorporated in REACH (Annex XVII entry 46). • 2005 - Included in of the list of prohibited ingredients under the legislation on cosmetic products (however, NP was already restricted in cosmetic products with Directive 2003/53/EC) • 2012 - identification of NP as a substance of very high concern (SVHC) for ED effects in the environment • 2013 identification of NPnEO as a substance of very high concern (SVHC) for ED effects in the environment • 2017 - NPnEO included in REACH Annex XIV → authorisation regime applies: deadline for application July 2019, sunset date January 2021 • 2016 - REACH Restriction of NPnEO in textile articles at concentrations > 0.01% weight which will enter into application after 3 February 2021 (Regulation (EU) 2016/26) • 2020 (ongoing) EQS currently being revised under the WFD, based on new ecotoxicological data

2 Substance profile

Nonylphenol (NP) consists of a family of long-chain alkylphenols composed of a phenol group and an attached linear or branched nine carbon tail, usually in the 4- position (4- or para-nonylphenol). It is structurally related to other long chain alkylphenols and in particular octylphenol. Nonylphenol is a non-ionic amphipathic substance, composed of a hydrophobic and a hydrophilic part, and it acts as a surfactant in aqueous solutions. It has been classified as inherently biodegradable (EC 2002). Biodegradation depends on the isomers with lower degradability at higher degrees of branching. Environmental degradation rates also depend on ecological conditions such as presence and adaptation of microbial communities (EC 2002).

NP is mainly used as an intermediate in the production of various NP derivatives. The derivatives are formulated into mixtures. Nonylphenol ethoxylates (NPnEOs) are the most common substances based

on NP. They are part of the alkylphenol ethoxylate group, a family of non-ionic surfactants. As a surfactant NPnEOs has historically been used as a tenside in household and commercial products (e.g. personal care, laundry products and cleaners) (Kjølholt et al. 2007, in ECHA 2013). Short-chained NPnEOs are used in detergents and other cleaning products. NPnEOs with chains of medium length (between 10 and 30 ethoxylates) are used as emulsifiers, i.e. they help to form stable systems of more fat in less water. Long-chained NPnEOs (with up to 80 ethoxylates) can be used as dispersants; because of their ability to retain small particles in solutions. NP is also used as a catalyst in the curing of epoxy resin and as a binder, e.g. in various alkydes (www.kemi.se/flodessok/floden/kemamne/nonylfenol.htm).

The use of NP and NPnEO in several applications of cleaning products as well as for other applications for end use has been restricted in recent years. Data on market volumes and end use applications are available from the end of the 1990´s. It is difficult to find up-to-date information on market volumes, but one could presume that for all restricted applications the volumes are lower today than they were 10-15 years ago. In the late 1990´s NPnEOs represented 80 to 90% of the alkylphenol ethoxylates used in the EU (by tonnage) (Postle et al 2003, in ECHA 2013). NP and NPnEO are however still used outside the EU as detergents and auxiliaries in the manufacturing of textile articles. According to EU statistics on the import of textiles the annual NP_{equ} release is estimated to be 257 tonnes (ECHA 2013).

Although NP is not used in the manufacturing of the textile it could be unintentionally added to the textile as a contaminant in low concentrations from the degradation of NPnEOs in the manufacturing process. NPnEOs could be unintentionally added to textiles during the manufacturing process by using contaminated water in the washing processes, by leakage from lubricants in the process equipment or by contamination by other fabrics during transport or storage (ECHA 2013).

2.1 Exposure pathways of concern

Human exposure

Consumer exposure is low. Worker exposure may have been significant for certain scenarios such as spray application of speciality paints (EC 2002), before restrictions were put in place. However, these exposures were not the leading reason for regulatory intervention.

Environmental exposure

Environmental exposure of nonylphenol occurs during its production and subsequent use. It may also occur due to the breakdown of some products containing a nonylphenol group, particular NPnEOs (EC 2002). NPnEOs degrade to NP, especially under anaerobic conditions. Even though only about 2.5% of the ethoxylates in influents may be ultimately emitted as NP to surface water (EC 2002), this transformation contributes significantly to the overall NP output of sewage treatment plants.

Uses and emissions have decreased since 2003, when the restriction on uses of 4-nonylphenols and their ethoxylates came into force. Before restrictions were put in place, the majority of emissions to surface water came from urban wastewater treatment plants originating from industrial sites emitting into the public sewage system, from wide dispersive application of products (e.g. paints, painted or printed articles) or from washing of imported textiles where 4-nonylphenols and their ethoxylates are present as contaminants from the production process (EC 2002). The background document to the

opinion on the restriction proposal on NP and NPnEO published in 2014 discusses remaining emission sources in the EU (ECHA RAC and SEAC 2014).

2.2 Effects on human health and the environment

Human Hazard

Some estrogenic activity was observed in *in-vitro* and *in-vivo* studies (EC 2002), which determined it classification as category 2 reproductive toxicant. However endocrine mediated effects on human health have not been the leading reason for regulatory intervention.

Environmental Hazard

Nonylphenols act as estrogen receptor agonists. Competitive ligand-binding studies demonstrated that NPs can displace specifically bound E2 from the ER ligand-binding pocket. The relative potency of NPs compared to 17ß-estradiol ranged from 0.94 10^{-5} to 0.44 10^{-2} for aquatic species (ECHA 2012, Annex XV dossier proposal for SVHC listing). Based on the information for the different isomers, it can be concluded, that the estrogen receptor activation potency is comparable for linear and branched nonylphenols. Binding of NPs to the ER leads to activation of the ER-mediated pathway and consequently to transcriptional activation of typically estrogen-responsive genes.

Moreover, there is some indication that NPs may be able to interfere with other nuclear receptor-mediated pathways. Thus, NPs were demonstrated to inhibit androgen-mediated gene expression *in vitro*.

NPs act as endocrine disruptors in fish i.e. that the substance alters the function of the endocrine system and consequently causes adverse, population relevant effects. *In vivo* data for several fish species show that this holds true for a variety of different species. Overall indication of estrogen activity was observed in all fish species tested. Estrogen activity started at the concentration of 1µg/L (*O.mykiss*) with respect to increased vitellogenin and between 11.6µg/L (*O.latipes*, testis-ova) and 36.8µg/L (*O.mykiss*, sperm stages) with respect to histological changes. In three fish species (*O.latipes*, *P.reticulata*, *D.rerio*) observed effects on apical endpoints are very likely to be estrogen mediated. In another species (*O.mykiss*) and the viviparous fish there is strong evidence for endocrine-mediated apical effects (ECHA 2012).

In-vivo data on amphibians and invertebrate species suggest that organism groups other than fish may be adversely affected by exposure to NP at concentrations in the low µg/L range and below. Effects exerted in two frog species, *R. sylvatica* and *R. pipiens,* on gonadal sexual differentiation and changes in sex-ratio fit to an estrogen-like mode of action (ECHA 2012).

3 Regulating nonylphenols in EU legislation

The environmental risks posed by nonylphenols have been known from the 1980s. In Europe, several initiatives were introduced to reduce emissions. The most significant of these was the 1992 Paris Commission (PARCOM) commitment on the part of members to "take concerted action within the framework of the competent international forums to substitute the use of the NPs and NPnEOs

(among other listed chemicals) by less hazardous or preferably non-hazardous substances where these alternatives are available". Under PARCOM Recommendation 92/8, contracting parties agreed to phase out the use of NPnEOs as cleaning agents for domestic uses by 1995 and for industrial uses by 2000. Hence, significant reductions in use of NPs and NPnEOs had already occurred by 1999 (EC 2016).

At EU level, the use of NPs and NPnEOs is mainly regulated under REACH. In some cases, regulatory assessments and interventions went in parallel with octylphenol. Additional provisions apply under the WFD regarding the identification of nonylphenol as a priority hazardous substance (**Figure 18.1**), which has implications for treatment standards of the Integrated Pollution Prevention and Control (IPPC) Directive.

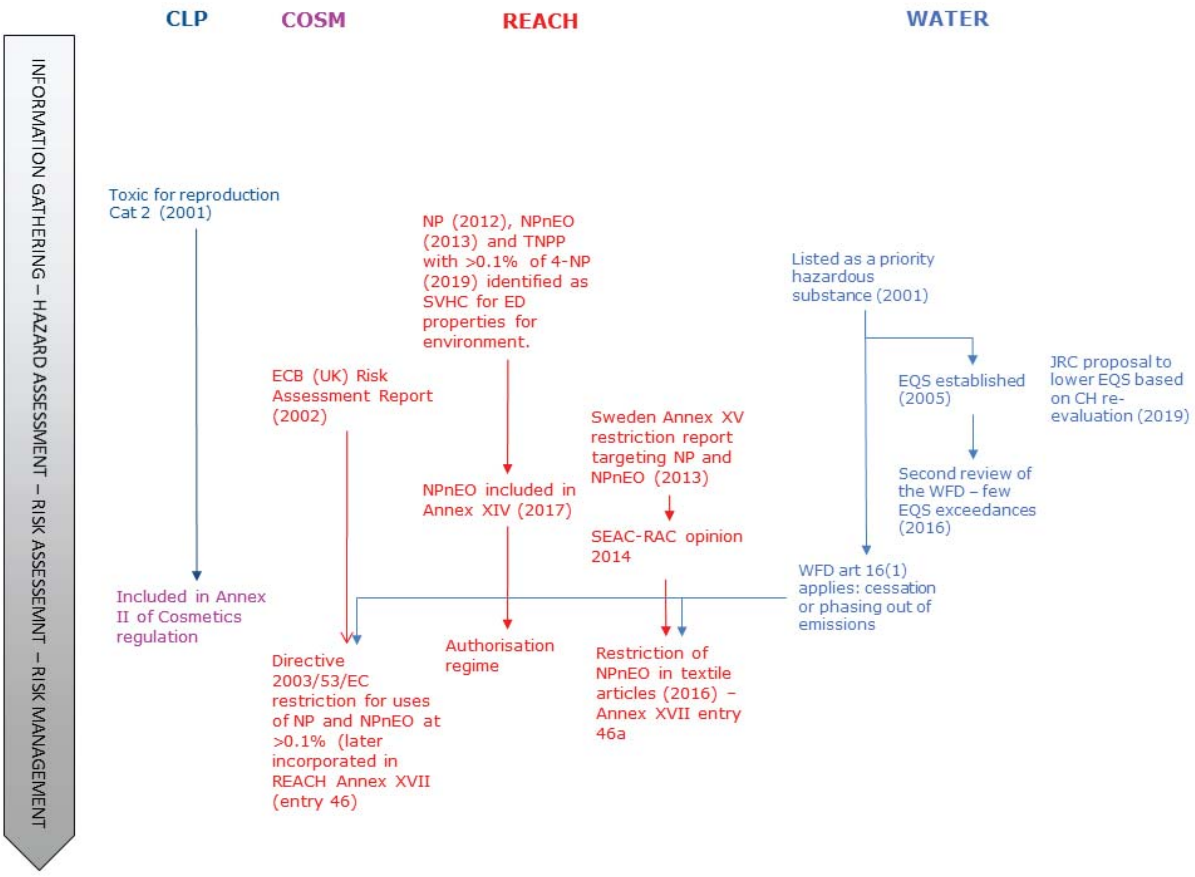

Figure 18.1. Nonylphenol case study: illustration of applied provisions across legislation

3.1 Regulating nonylphenols in REACH

Nonylphenol and its ethoxylates were regulated, before REACH came into force. The UK competent authorities carried out on behalf of the EU a risk assessment covering both environmental and human health concerns under the provisions of Regulation (EC) 793/93 (EC 2002). Results of the risk assessment identified the need to reduce environmental risks at both regional and local scales. Following a conventional approach for the aquatic assessment, a predicted no effect concentration

(PNEC) of 0.33 µg/L was calculated from the lowest NOEC of 3.3 µg/L on the biomass algal growth (*S. subspicatus*). The algal growth study used for the PNEC derivation was not linked to an endocrine modality. Even for other aquatic species including fish, concentrations at which estrogenic effects are observed appeared to be higher than those producing other effects. Therefore, the risk assessment concluded that the derived PNEC should be protective for estrogenic effects in fish as well.

Risks to human health were also assessed for workers and consumers. Furthermore, the risks due to indirect exposure of humans via the environment were evaluated. According to the assessment, the risk from the use of NP was considered to be adequately controlled for consumers as well as for most uses leading to worker exposure. Similar, no risk was identified for human exposure via the environment. The assessment took aggregated exposure into account. The risk assessment report outlines, however, that for certain uses, i.e. the manufacturing of NP, its use as intermediate and the use of speciality paints containing NP, the safety margins were relatively low. This conclusion was based *inter alia* on results of a two-generation-toxicity study that revealed slight effects possibly linked to an estrogenic mode of action (EC 2002).

In its opinion of 6 and 7 March 2001, the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) confirmed the conclusions of the UK assessment. The opinion triggered the restriction of nonylphenol and nonylphenol ethoxylates through entry 46 of Annex I of Directive 76/769/EEC (Directive 2003/53/EC), which became applicable from January 2005. The restriction applied at concentrations equal or higher than 0.1% by mass for use in industrial and institutional cleaning, domestic cleaning, textiles and leather processing, emulsifier in agricultural teat dips, metal working, manufacturing of pulp and paper, cosmetics and other personal care products and as a co-formulant in plant protection and biocidal products. The restriction was later incorporated in Annex XVII of REACH (Regulation 552/2009).

The German competent authority filed an Annex XV dossier proposing the identification of nonylphenol (ECHA 2012) as an SVHC due to serious effects to the environment giving rise to an "equivalent level of concern" to other SVHCs due to meeting the classification criteria for CMRs Cat. 1A/1B or because they are persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) (REACH Article 57(f)).

The SVHC dossier reviewed an extensive list of studies that described over 30 *in vitro* assays on estrogenic activity (e.g. binding assays, reporter gene assays, Yeast estrogenic transactivation (YES) assays and assays analysing vitellogenin induction in primary hepatocytes) as well as 34 *in vivo* assays with various fish species. Collectively, they have provided strong evidence of adverse effects in fish species mediated by an estrogenic modality. Regarding amphibians and invertebrates, no definitive conclusion could be drawn.

The proposal for SVHC identification was agreed by the Member State Committee in December 2012. According to the Support Document of the MSC (ECHA 2012), based on the data mentioned above, NP fulfils the WHO/IPCS definition of an endocrine disruptor. The probable serious effects to the environment were considered of "equivalent concern" to other SVHCs.

According to the MSC the "equivalent level of concern" criterion is fulfilled since effects observed after exposure to NP are considered to impair population stability and recruitment of a wide range of fish species. Effects may occur even after short term exposure and thus may result in impairments in regions other than those where exposure occurred and possibly on a long-term basis. Effects may

influence a wide range of taxa. A safe level of exposure to NP may exist, but it is difficult to estimate it.

Almost in parallel, also NPnEOs were proposed for SVHC identification by Germany (ECHA 2013a). The rationale for inclusion in the candidate list was the fact that 4-Nonylphenol, branched and linear, ethoxylated (4-NPnEO) degrade to 4-nonylphenol, branched and linear, either already in wastewater treatment plants, or via further degradation processes in sediments and soils receiving sewage sludge. In addition, available information reviewed for NPnEO indicate that short chain ethoxylates (NP1EO and NP2EO) possibly show endocrine activity themselves, with *in vitro* and *in vivo* estrogenic activity nearly as high (within a factor of 10) or similar to the endocrine activity of 4-nonylphenol. However, information on endocrine-mediated adverse effects caused by NPnEO was not available, and therefore a conclusion on whether NPnEOs are endocrine disruptors themselves could not be drawn. NPnEOs were identified as SVHCs and included in the candidate list in July 2013.

Nonylphenol ethoxylates were later in 2015 prioritised together with octylphenol ethoxylates (OPnEOs) for inclusion in Annex XIV (authorisation list) and included in that Annex in 2017 with latest application date July 2019 and sunset date January 2021.

The restriction in place since 2005 and the authorisation regime established for nonylphenol ethoxylates through the inclusion in Annex XIV apply to a wide range of substance uses. Starting from the 1990s manufacture, uses, environmental emissions and aquatic exposure of nonylphenol decreased (AMEC 2012 in ECHA 2014b, see also **Section 4.1**).

However, monitoring data obtained from European water bodies between 2006 and 2012 demonstrated that a small proportion of freshwater bodies and some marine waters in more than one MS were at risk due to NP exposure (ECHA RAC and SEAC 2014b). This situation motivated the Swedish competent authority to prepare in 2013 a proposal for restriction for NP and NPnEO at concentrations equal to or higher than 100 mg/kg in textiles (ECHA 2013b). The Annex XV report estimated that release from washing of textiles contributes to approximately half of the estimated aquatic emissions of NP and imported textile articles are identified as a major source.

The Swedish competent authority (CA) presented a section on risk characterisation for environmental compartments of concern (freshwater, marine, sediments and terrestrial). This was done following standard procedures for environmental risk assessment on nonylphenol. Exposure concentrations (PEC) used in the risk assessment were based on the 90th percentile of monitoring data, most of which were obtained under the Water Framework Directive. Several approaches for calculating Predicted No Effect Concentrations (PNECs) were included using data from freshwater or marine organisms and either only classical endpoints not explicitly related to endocrine disruption or applying an additional AF of 10 to take into account 'additional uncertainty' due to endocrine-mediated effects. Another approach was based on species sensitivity distributions (for freshwater or for freshwater and marine species). Risk ratios exceeding 1 were reported when combined effects of nonylphenol, nonylphenol ethoxylates and their degradation products (nonylphenol ethoxycarboxylates) were assessed using a toxicity equivalent approach for the marine compartment at EU level and in freshwater for 8 to 12 EU countries out of a total of 25 EU countries and Norway, but not for freshwater at the EU median level. When introducing the additional assessment factor of 10 the risk characterisation ratios in the combined toxicity assessment exceeded 1 at the EU median level for both the marine and freshwater compartments. It was also noted that, although effects on growth by itself would not lead to a conclusion that a chemical is an ED in fish, together with available *in-vitro and in-vivo* mechanistic data and ED-related adverse effects in certain fish species (e.g. skewed sex ratio) it was reasonable to

assume that the effects are endocrine related. Finally, the Swedish CA concluded that identifying safe concentration limits for all possible endpoints within the endocrine system that can be affected by ED is not possible within the current test method guidelines and would be inconsistent with the objective in REACH to reduce animal testing (ECHA 2013b).

In its opinion (ECHA SEAC and RAC 2014b), the RAC first noted that the derived PNECs based on traditional, apical endpoints are similar independent of the method used or of whether freshwater or marine taxa are considered. Due to that, and based on traditional, apical endpoints, RAC derived a $PNEC_{aqua}$ of 0.4 µg/L for NP covering both freshwater and marine environments.

RAC further noted that compared to traditional apical endpoints, endocrine-mediated effects in fish start at concentrations almost one order of magnitude lower. For other taxa, analogous evidence on relations between apical and indicative endocrine-related effect concentrations is less clear due to the prevalent inconclusiveness regarding endocrine-related modes of action and regarding adversity of available observations at low concentrations. According to RAC, the current knowledge prevents a firm conclusion on a mechanistic endocrine-related link with the observed adverse effects especially in studies with invertebrates. Some observations occurred only at the lowest test concentrations. Uncertainties also derived from the lack of adequate test protocols for some taxonomic groups.

RAC took note that the dossier submitter considered the application of an extra AF when deriving a PNEC for NP as one option to deal with the uncertainties around endocrine-related effects. Limited to fish, RAC believed lowering the PNEC by a factor of 5 might cover adverse endocrine effects. However, RAC explicitly did not offer an opinion about whether such a lowered PNEC would be sufficiently protective for all taxonomic groups.

RAC further pointed to the ongoing discussions at that time on whether, in the context of REACH authorisations, endocrine disruptors should be considered as having a threshold or not. Given that the discussion was still ongoing, RAC considered it premature to provide an opinion on the threshold nature of endocrine disruptors.

As a pragmatic way for assessing the risks of the uses targeted by the restriction proposal RAC based the risk assessment on the PNEC derived from classical endpoints. RAC argued that any risk identified by this approach would already be sufficient for justifying the restriction, and any further consideration of endocrine-mediated effects or of combination effects would likely lead to a greater risk.

The SEAC analysis of the restriction proposal evidenced that NP is not identified as used intentionally in textile processing. Consequently, the inclusion of Nonylphenol in the scope of the restriction was considered not justified because it would be practically difficult to implement and monitor and most likely not necessary to achieve the desired objective. Commission regulation 2016/26 put forward the restriction for certain uses of nonylphenol and nonylphenol ethoxylates in concentrations equal to or greater than 0.1% by weight (Annex XVII, entry 46a) and nonylphenol ethoxylates in textile articles (46a) in concentrations equal to or greater than 0.01% by weight. The proposed restriction is expected to effectively reduce the major part of NP/NPnEO that is estimated to be emitted from textile articles imported to the European Union.

July 2019 marked the deadline for submitting authorisation applications of octyl- and nonylphenol ethoxylates to be able to continue their uses, following their inclusion in Annex XIV (entries 42 and 43). In a notice issued by ECHA to provide advice to applicants for authorisation for uses of octyl phenol ethoxylates (OPEs) and NPnEOs (ECHA RAC 2017) the RAC has elaborated its position on

the feasibility of demonstrating a safe threshold for these substances, in line with the report issued by the Commission on the topic (COM 2016/814). The Commission report concluded that an endocrine disruptor may or may not have a threshold. As for other substances subject to the authorisation requirement, it is the responsibility of the applicant to demonstrate that a threshold exists and to determine that threshold in accordance with Annex I to REACH. Then, it is up to the RAC to assess the validity of the assessment and ultimately decide on the possible existence or not of this threshold. The report also states that, in order to increase predictability and legal certainty for applicants, RAC has set on a case-by-case basis reference DNELs for threshold substances, or reference dose-response curves for non-threshold substances, which industry can use when applying for authorisation and that this practice applies also for EDs.

Based on the above, RAC pointed out that an applicant for authorisation can propose a PNEC or a dose-response relationship. It is then up to the applicant to submit all necessary data, which RAC will assess. RAC indicated on which information it would pay particular attention. RAC also pointed out that applicants may simply choose to follow in their application the same approach as for non-threshold substances. In this case, the assessment of the application for authorisation would follow the approach for non-threshold substances or for PBTs/vPvBs, and the authorisation could, if appropriate, be granted if it is shown that socio-economic benefits outweigh the risks to human health or the environment, and there are no suitable alternative substances or technologies, as provided for in REACH Article 60(3) and 60(4). The authorisation is subject to conditions, including monitoring, to a time-limited review and takes in to account all potential discharges, emissions and losses.

Upon the initiative of the French competent authority, another substance has been identified by ECHA as SVHC due to the presence of 4-nonylphenol as an impurity: tris(4-nonylphenyl, branched and linear) phosphite (TNPP if it contains $\geq$ 0.1% w/w of 4-nonylphenol as impurity (ECHA 2019). TNPP can be produced with or without the occurrence of NP as impurity. It is used as an antioxidant to stabilise polymers and may be present in a variety of applications with a potential of exposure from articles, polymers (including food contact materials) or mixtures (e.g. paints, adhesives). The substance was included in the Candidate List in July 2019.

3.2 Regulating nonylphenols under other chemical legislation

Nonylphenol is restricted under REACH for use in cosmetics since 2003 (date of application: January 2005), it is also included in Annex II of the Cosmetic Products Regulation because it is classified as Cat II toxic for reproduction under the CLP regulation.

Neither nonylphenols, nor their ethoxylates are on the positive list of substances authorised by the Commission Regulation (EU) N°10/2011 of 14 January 2011 relating to the plastic materials and articles intended to come into contact with food.

3.3 Regulating nonylphenols under the Water Framework Directive

The WFD applies a combination of generic and specific risk considerations from both experimental and modelling data for the classification of chemicals as priority substances (PS) and priority hazardous substances (PHS).

Nonylphenol was included in the first list of PS for its relatively high modelling-based ranking (#38) in the prioritisation exercise, combined with additional evidence of environmental occurrence and endocrine disrupting effects (Klein et al 1999).

The criteria for PHS classification consist of both hazard and risk considerations (checks 1 to 6) as well as "additional considerations" (check 7), including the suspected endocrine disrupting potential (EC 2001). In the case of nonylphenol the classification was mainly motivated by evidence for a concern for the freshwater environments from the ECB risk assessment (ECB 4/15/00) under the pre-REACH regulation 793/93 showing a widespread risk to or via the aquatic environment (COM/2001/17).

Identification of a substance as PHS according to art 16(1) of the WFD requires measures aiming at the cessation or phasing out of discharges, emissions and losses within an appropriate timetable not exceeding 20 years.

Environmental Quality Standards were established in 2005 for Annual Average (AA-EQS: 0.33 µg/L) and for Maximum Allowed Concentration (MAC-EQS: 2.1 µg/L) in surface water, together with other specific quality standards for biota (EC 2005). Both AA-EQS and the MAC-EQS were derived following the guidance for the derivation of a PNEC (Predicted No effect Concentrations) using conventional endpoints not explicitly linked with endocrine effects, and an assessment factor of 10. The AA-EQS and the MAC-EQS were calculated from a 72-hours EC_{10} (biomass) with the freshwater alga *Scenedesmus suspicatus*, and from a 96-hour EC_{50} with the freshwater invertebrate *Hyalella Azteca*. Regarding endocrine disrupting potential the report states that "*most of the tests indicate that estrogenic effects may start to occur at around 10-20 µg/l*", therefore the calculated PNECs should be protective for estrogenic effects in fish as well.

The EQS are currently being revised considering additional ecotoxicological data available (Ecotox Centre 2016). Significantly lower EQS values have been calculated in the proposed draft EQS dossier, currently under review (JRC 2020, unpublished draft)

4 Impact of regulation

4.1 Reduced exposure

There have been considerable efforts to phase out alkylphenols since the 1990s. Use of NP was estimated to be 78 500 tonnes per year in 1997 (EC 2002). A decrease of the use of NP in the EU was observed already in the years before due to the phase-out in detergents and for other uses (EC 2016). For 2010, i.e. before further regulatory action was taken, the production volume in the EU was estimated to be in the range of 10 000 to 50 000 tonnes/year (AMEC 2012 in ECHA 2014b). All the above figures include the use of NP as intermediate for the manufacturing of NPnEOs as well as polymers, epoxy resins or other substances. The use as an intermediate appears to be the main use of NP (with roughly 50-60% used for the manufacturing of NPnEO and 30-40% to produce polymers, epoxy resin and other substances) (ECHA 2014b).

Since its listing as a priority substance under the WFD nonylphenol has been subject to routine monitoring in the European wastewater, surface waters and biota. The decline in aquatic exposure is evidenced by analysing long-term temporal trends. For instance, concentrations in fish (bream, muscle tissue) caught in Germany diminished by 67% between 1995 and 2001 (EC 2016).

A recent analysis of monitoring data obtained from 15 MSs (one MS dominates holding about 71.9% from all samples) for the period 2006-2014 demonstrates a reduction of risk posed by NP in European surface water (**Table 18.1**, D. Marinov and T. Lettieri, personal communication).

Table 18.1. Risk quotient (RQ) of NP in European surface water, calculated as the ratio of the 95%ile measured concentrations to the newly proposed EQS (RQ=MEC(p95)/EQS (draft EQS =0.013 µg/l)).

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014
RQ	236.5	53.1	27.7	13.1	4.6	19.2	10.9	0.96	0.77

Another study analysed the concentration of NP in the Lambro River, a tributary of the river Po in Northern Italy, receiving high amounts of industrial and domestic wastewater (Rusconi et al 2015). Two monitoring campaigns in 2003/04 and 2009/10, respectively before and after Directive 2003/53/EC restriction (in force from 2005) as well as the start of operation of three new wastewater treatment plants (WWTPs) in the city of Milan. Data showed that the reduction of the different analytes in the period ranged from 70% to 90%. The reduction was mostly attributed to the substitution of NPnEO in industrial uses as demonstrated by a survey in the textile industrial district, with the entry into operation of the new municipal WWTPs contributing about 10% to total river loads.

Unlike certain steroid oestrogens, there is no strong evidence of the effects of NP on wildlife fish populations (Sumpter 2013). In recent years, the combination of i*n-vitro* bioassays measuring total estrogenic activity in water samples with identification of substances responsible for the observed activity has improved the ability to quantify the contribution of single substances. Recent studies have confirmed that natural and synthetic steroid oestrogens are largely responsible for the observed estrogenic activity in wastewater effluents and freshwater samples (Miege et al 2009, Tusova et al 2019). In conclusion, to date it is not possible to link the observed decline in aquatic concentrations of NP with improved trends in biomarkers of effects or any other biological indicators. Increasing spatial and temporal coverage of effect-based methods, as recommended for chemical water quality assessments under the WFD (JRC 2020) could provide further insights on the link between aquatic exposure ecological effects of mixtures and individual components of estrogenic samples.

4.2 Shift to alternatives

Due to the different functionality of nonylphenol ethoxylates, as a surfactant, emulsifier, etc., several solutions might exist to replace NPEs. A comprehensive analysis of all relevant alternatives and their safety profile is outside the scope of this case study. For the high volume uses restrictions have been successfully implemented with relatively low cost to actors in the supply chains since there are technically feasible alternatives (ECHA RAC and SEAC 2014a). RAC agreed with the dossier submitter (Sweden) that alcohol ethoxylates, glucose-based surfactants (alkyl glucosides and alkyl glucamides), and alcanol fatty acid amines show lower toxicity, no indications of endocrine activity, and pose a lower level of environmental risk when used as alternatives for NPnEO as surfactants or emulsifiers in textile processing. Some limitations in hazard data availability for these alternatives was noticed.

The authorisation applications received by the July 2019 deadline provide an overview of remaining uses, not explicitly banned in Annex XVII entry 46 and 46a[185].

[185] https://echa.europa.eu/applications-for-authorisation-previous-consultations.

5 Comments on fitness check evaluation criteria

Comments on coherence	• In the context of the REACH restriction, the risk assessment applied a PNEC based on traditional, apical endpoints not related to endocrine disruption to demonstrate that risks are not controlled. For that reason, the Risk Assessment Committee (RAC) concluded that in the specific case (restriction of NP) a conclusion on an ED based PNEC was not required. • RAC discussed approaches setting a PNEC for endocrine related effects but pointed also to uncertainties due to the limited knowledge especially for taxa other than fish. • EQS values have been established (and are currently being reviewed) according to the Guidance on EQS setting, which is underpinned by the concept of an overall threshold that protects all receptors and routes. Setting a threshold value is a practical requirement for monitoring and implementation of chemical water quality assessments for priority substances under the WFD. • The study determining the PNEC in the 2002 risk assessment report and the EQS (Kopf 1997 in EC 2005) in the 2005 EQS dossier (PNEC = EQS = 0.33 µ/L), a 72h green algae study, is reported in the 2016 REACH restriction dossier with a different endpoint ($EC_{10,growth}$ instead of $EC_{10,biomass}$ vs). The former value is 8-fold lower than the latter. According to ECHA Guidance on information requirements and chemical safety assessment (Chapter 7.b: Endpoint specific guidance) algae biomass no longer is considered a relevant endpoint, instead the preferred endpoint as regards algae is growth rate. The study determining the $PNEC_{freshwater}$ (0.6 ug/L) in the 2016 REACH Annex XV report, a 91-day study on rainbow trout (Brooke 1993 in ECHA 2013b) is not reported in the 2005 EQS dossier. A $PNEC_{aqua}$ of 0.4 ug/L as chosen by the RAC as representative of marine and saltwater species (ECHA RAC and SEAC 2014). A recent revision of the ecotox dossier of NP under the WFD has led to significantly lower proposed EQS (pending ongoing review and approval procedures).
Comments on effectiveness	• Nonylphenol and nonylphenol ethoxylates have been thoroughly assessed for reproductive toxicity on the aquatic environment. They are widely restricted in Europe, with few speciality biomedical applications subject to authorisation. • The first regulatory intervention was triggered by assessments of reproductive toxicity. In the last years increasing scientific knowledge has led to updates of PNEC and EQS values underpinning risk assessments and their interpretation. • There is evidence of substantial decrease in aquatic exposure of NP in EU wastewater, surface waters and biota in the last two decades. Reduced concentrations of NP in the aquatic environment cannot be linked to changes in estrogenic activity of water bodies because this is mainly driven by more potent natural and synthetic estrogens.

Comments on efficiency	• Monitoring data generated under the WFD have been successfully used to inform environmental exposure assessment in ECHA dossiers (e.g. 2016 restriction report). • Despite some conceptual differences in the approaches to the derivation of PNECs for risk assessment of chemicals and EQS for water quality assessments are similar. The two processes are performed separately by ECHA and by national authorities in the context of the WFD. Resources could be optimised by greater coordination of assessments.

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