

Review

Endocrine Disruptors in Cosmetic Products and the Regulatory Framework: Public Health Implications

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Abstract: Endocrine disruptors (EDs) are molecules capable of mimicking the natural hormones of the body and interfering with the endocrine system in both humans and wildlife. Cosmetic products are one source of EDs; these include an extensive variety of personal care and beauty products designed for the skin and hair, as well as makeup. The widespread use of such products has raised concerns about the presence of EDs within them. In this study, we highlight the issue of EDs and analyze the functioning of the EU regulatory framework for chemicals, specifically those which act as EDs in cosmetic products. We also highlight issues related to the interface between science and policy in the critical area of risk regulation within the EU. In addition, we investigate how chemical substances that act as EDs are identified based on specific criteria and conditions, a process which involves the production and adoption of particular scientific opinions. Finally, we assess the efficiency, suitability, and effectiveness of the regulatory framework in this sensitive area of human exposure to chemicals, especially those that function as EDs.

Keywords: cosmetics regulation; endocrine disruptors; risk assessment; risk regulation; health risk; public health



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1. Introduction

Endocrine disruptors (EDs) are not a new phenomenon in the EU. In recent years, they have been a source of concern to the public and to stakeholders who have sought to identify these chemical substances, which are found in many everyday products such as pesticides, biocides, cosmetics, and children's toys [1,2]. EDs cause serious disruptions to the endocrine system, with equally serious implications for human health and overall well-being [3]. Long-term exposure to these substances, especially during the embryonic period, is believed to contribute to the development of various diseases, including fertility disorders, certain cancers, neurological disorders, obesity, and reproductive problems. It should be emphasized that the majority of chemicals used have not been adequately assessed for their safety [4]. It is essential to evaluate the potential adverse impacts of EDs within the context of regulating hormone synthesis, secretion, and functionality, while also accounting for the variations in these regulatory processes throughout the various stages of life. An important factor to emphasize is the developmental stage during which exposure to EDs takes place, as this plays a pivotal role in comprehending outcomes [3,4].

Absorption of chemicals from cosmetics is possible, with the skin being the main route of exposure. The health of the skin represents a critical determinant in the efficiency of the skin's protective barrier. Exposure is also possible through inhalation and through ingestion. The scientific debate regarding the appropriate criteria for identifying chemical substances as EDs continues unabated, with strong disagreements within the scientific community. The operation of the EU regulatory framework for EDs, as part of the broader field of EU risk regulation, is primarily characterized by the intersection of science and

policy [5]. Within this framework, however, it can be a challenging task to determine where science ends and policy begins, as the boundaries are often blurred. Another key aspect of this framework which is characterized by scientific uncertainty is the wide discretionary power of EU institutions in the decision-making process [6]. Specifically, concerning EDs, the method and procedure for determining chemical substances with ED properties has become a matter of particular importance.

A major research issue which the scientific community concerns the question of whether the regulations in this sensitive area of human exposure to chemicals, especially those that act as EDs, serve the EU's goal of providing a high level of environmental and human health protection [7]. The EU directed its attention towards EDs quite early on. In 1999, the European Commission published a strategy for EDs, outlining specific EU actions of a short-term (research and international cooperation), medium-term (testing methods), and long-term (regulatory measures) nature, all of which were aimed at reducing exposure to the lowest possible levels [8,9].

Since then, in addition to funding research [10], the EU has adopted regulatory measures to identify these substances, enabling a reduction in exposure in various sectors such as water [11], cosmetics [12], and chemical products [13]. Under the REACH Regulation, ECHA included substances with endocrine-disrupting properties in the "substances of very high concern" list which were subject to authorization [14]. Finally, it was stipulated that the Commission would initiate "a review to assess, taking into account the evolution of scientific knowledge, whether to broaden the scope" of the more stringent procedure (i.e., authorization) to include EDs [15].

2. Risk Regulation

Science plays a dual role as both the primary creator of environmental problems and as the essential tool for identifying and solving them. This dual role reflects the absolute dependence of our societies on science on the one hand, and skepticism towards it on the other, leading to scientific uncertainty [16].

The identification of a chemical substance as an ED by the Commission is indeed based on scientific data. However, due to existing scientific uncertainty, a significant role is given to the precautionary principle, which is a fundamental principle in EU risk governance [17]. In the EU, the precautionary principle is a cornerstone legal and policy principle with significant application in the field of chemical substances [18].

Specifically, it is at the core of the institutional architecture of EU risk regulation, and it is applied at both the risk assessment stage and the risk management stage. During the risk management stage, in line with this principle, the decision-making political body is obligated to establish measures aimed at achieving a high level of environmental and human health protection. This principle allows for action to be taken even in cases where scientific evidence is uncertain or incomplete in order to prevent potential harm to the environment and/or human health [19]. It emphasizes the importance of acting cautiously when there are indications of potential harm, even in the absence of conclusive scientific evidence [20]. In particular, it allows for the adoption of precautionary measures when scientific data concerning risk to the environment or human health is uncertain and not definitive [21]. This means that in cases where the assessment of the risk level (risk assessment) for certain substances with regard to human health or the environment is uncertain, precautionary actions can and should be taken to mitigate potential risks [22].

Risk regulation is a process that involves a set of parameters which include the legislative framework, regulatory provisions of the administration, scientific knowledge, and specific policy objectives. The apparent complexity of risk regulation, the core of which is interdisciplinarity, is the reason for the difficulty in scientific or political analysis [23]. The regulatory framework of risk analysis or risk regulation is a decision-making process under conditions of uncertainty that includes three stages, as listed in Table 1 [24].

Table 1. Risk regulation parameters [25].

Risk assessment:	The nature and severity of the risk associated with a specific activity or substance are assessed. This involves gathering scientific data and analyses to understand the risk.
Risk management:	After analyzing the risks, measures are taken to reduce, control, or limit these risks. This includes establishing legislation, regulations, and policies to protect health and the environment.
Risk communication:	It is crucial to inform the public and stakeholders about the risks, management measures, and the scientific basis of decisions. This contributes to transparency and public awareness.

3. Risk Assessment

The scientific process of risk analysis consists of four steps, as listed in Table 2 [26,27].

Table 2. The four steps of risk assessment [26,27].

Hazard identification:	Determining the adverse effects, if there is a potential cause for concern regarding health when individuals are exposed to biological, chemical, or physical agents [28]; collecting and evaluating toxicity data from testing systems, epidemiological studies, incident reports, and field observations [29].
Dose–response assessment:	Defining how the level of exposure to a substance relates to the likelihood or seriousness of harmful effects occurring in a population exposed to that substance. This entails analyzing how the risk of adverse effects varies with varying levels of exposure to a specific substance or agent. This assessment is essential in establishing safe exposure thresholds and offers vital insights in order to make decisions related to risk management and regulations [30].
Exposure assessment:	Identifying chemical substances that raise concerns for the exposed population, determining the route through which exposure occurs, and evaluating the magnitude, duration, and timing of doses individuals may have received during their exposure. In other words, it assesses the intensity, frequency, and duration of human exposure to a specific agent [31].
Risk characterization:	Synthesizing information gathered in the previous three stages of risk assessment to assess the potential health impacts on the exposed population under various conditions. The goal is to make the risk understandable to relevant authorities and stakeholders, facilitating their understanding of the risk and its implications [32].

4. The Stages of Risk Assessment

Despite the fact that the general approach to quantitative risk assessment (QRA) has remained largely unchanged since the early 1980s, it is continually evolving in various forms, and its fields of application have significantly expanded. Several organizations and research groups have developed or adopted systematic reviews in the assessment of chemical substances. Moreover, there is a growing body of research which focuses on dynamic risk assessment and risk management, rather than static or traditional risk assessment [33]. The use of systematic reviews can identify differences in how questions are formulated, searches are conducted, or studies are evaluated [34]. The application of these methods can lead to improved transparency, objectivity, and communication in risk assessment [35]. On the other hand, the process also involves disadvantages, mainly uncertainty resulting from contentious comparative results, such as the assumption that exposure to high doses applies equally to low doses, and that short-term exposures apply equally to long-term ones. Additionally, it often disregards the synergy of multiple sources of exposure (e.g., chemical substances and their mixtures in real-life exposures). Factors such as these which lead to uncertainty in the risk assessment process are illustrated in Figure 1 [36,37]. While scientific knowledge is essential, it is not always adequate for the assessment of risks. In any case, the management of risks falls under the jurisdiction of the competent political bodies of the community, which determine whether a risk is acceptable or not [38].

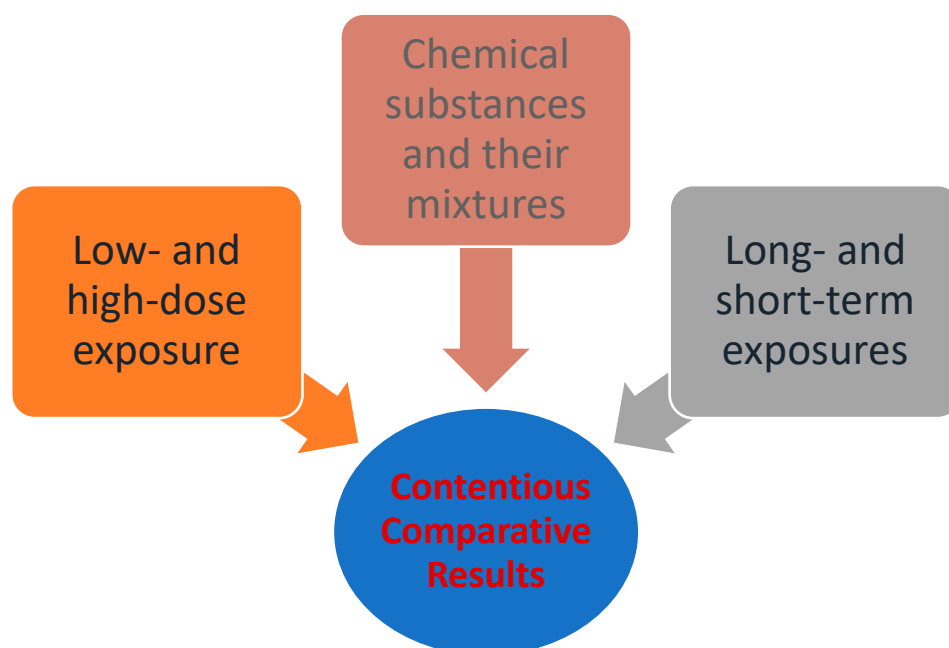


Figure 1. Factors that lead to uncertainty in the risk assessment process [39] (modified by Dr. P.Kalofiri).

5. The Criteria for Determining ED

The criteria for identifying and determining EDs can be found in the regulations for Biocides 2100/2017 [40] and Plant Protection Products 2018/605 [41], and in the REACH Regulation [42]. Substances that pose endocrine disruption risks should not be placed on the market.

The criteria for determining the properties of EDs in humans are different from those that apply to non-target organisms. Both sets of criteria are further subdivided into two sections: one section for defining an ED, and one section regarding the information that must be taken into account for the determination of the properties of EDs [43].

In March 2019, the European Parliament published a study that examined the scientific evidence related to the concept of endocrine disruption, the extent of exposure, the relevant health impacts, and the associated costs [44]. It called on the EU to establish regulations governing all types of chemicals that cause endocrine disruptions in order to minimize human exposure. The conclusions included several recommendations to EU political bodies regarding goals, the definition of endocrine disruptors, guidance documents, test development and requirements, the management of endocrine disruptors in specific sectors and various areas, production, use, exposure to endocrine disruptors, and research priorities. The Endocrine Society praised the report. It stated that “the report demonstrates that chemicals causing endocrine disruption pose a serious threat to the health of current and future generations and highlight the need for additional action by policymakers in the EU to address this issue” [45].

In October 2020, a significant milestone was reached when the European Commission initiated the process of revising the requirements related to the identification of endocrine-disrupting substances. This important development was achieved by amending the Biocidal Products Regulation (Regulation 2021/525) [46]. The modifications take into account the “need to reduce testing on vertebrate animals and the need of a testing strategy and methods for the determination of endocrine disrupting properties of substances” [47].

In the context of the regulatory procedure, if the Regulatory Committee does not agree with the draft decision submitted by the Commission, the matter is referred to the Council where, if a majority is not achieved, the decision is ultimately taken by the Commission [48]. In this process, there are advantages in avoiding deadlock, but there are also disadvantages. The first is that the right of each member state to determine the level of

protection it desires is disregarded; the second is that achieving a majority in the Council is difficult, especially in highly sensitive political issues, so that political decisions are finally made by a body which is not democratically legitimized, such as the Commission. While Regulatory Committees are not considered political committees, in practice they often take on a political character because the delineation between political decisions and techno science assessments is ambiguous [49]. A notable example is the case of EDs, in which many legal, political, and ethical controversies arise.

The absence of a universally accepted definition makes the risk assessment of EDs more challenging. Relevant public authorities, stakeholders, and the public should all examine the extent of uncertainty as well as its sources and nature, and consider whether it is due to inherent random occurrences or a lack of knowledge [50]. Although consultation and public participation play a crucial role in clarifying elements of uncertainty or ignorance, and lead to more informed decisions, the established criteria are highly restrictive and make it very difficult if not impossible to prove that a substance disrupts the endocrine system, as the high degree of uncertainty does not allow for complete proof. Because of the greater burden of proof of harm, more products will remain on the market, resulting in citizens being exposed to dangerous substances and creating a significant burden on the public health budget [51]. In other words, the definition requires such a high level of evidence that it ultimately leads to very few substances being considered EDs [52].

6. Cosmetics

Cosmetics have been used for centuries, not always with safe ingredients. Even in ancient times, when all ingredients were natural, the toxicity of cosmetics was often high, especially when ingredients such as mercury and lead were used. In addition, there was ignorance about their effects [53]. Today, Regulation 1223/2009 for Cosmetics defines a “cosmetic product” as “any substance or mixture intended to come into contact with various external parts of the human body (skin, hair, scalp, nails, lips, and external genital organs) or with the teeth and the mucous membranes of the oral cavity, with the exclusive or main purpose of cleaning them, perfuming them, changing their appearance, and/or correcting body odors and/or protecting them or keeping them in good condition” [54]. Cosmetic products contain active substances, preservatives, and also so-called “fragrances” [55].

6.1. Exposure Pathways

Human exposure to EDs occurs through ingestion of food, dust, and water, inhalation of airborne particles, dermal contact, and maternal exposure [56,57]. The primary exposure route for cosmetics is the skin; most cosmetic products are applied directly to the skin, and their ingredients, or molecules, can penetrate the skin barrier and enter the systemic circulation through various pathways [58]. Additionally, exposure can occur through inhalation, as in the case of fragrances and hair sprays, as well as through ingestion, as in the case of lipsticks [59]. These means of exposure are illustrated in Figure 2. Furthermore, though the environmental risk is not fully understood, it is nonetheless known to exist. Many substances found in cosmetics end up in natural ecosystems through wastewater treatment facilities, water used for personal hygiene, and seawater used by swimmers using sunscreen, as well as through sanitary landfills where residues from cosmetic product packaging may enter the soil [60]. The potential for cosmetic ingredients to bioaccumulate in the fatty tissue of fish [61], the presence of such ingredients in marine mussels [62], and the ability of UV filters to cause coral bleaching [63] are all important environmental concerns [64]. However, there are limitations in scientific evidence, and it is challenging to establish absolute certainty, as some EDs can have adverse effects even at low doses. Moreover, establishing a causal relationship between exposure and the outcome of a disease is nearly impossible to confirm [65,66].

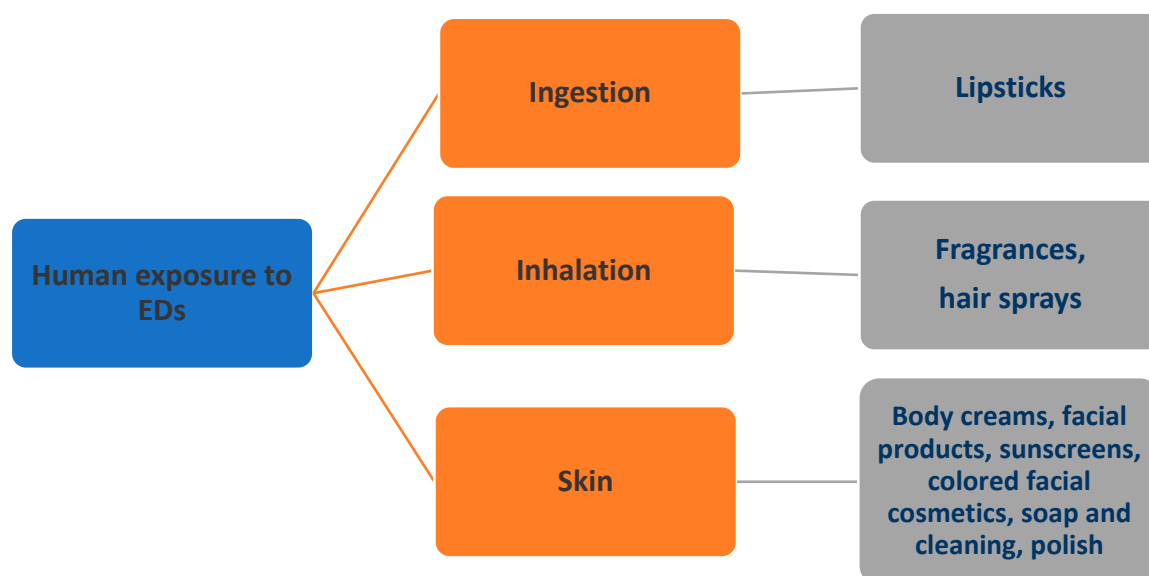


Figure 2. Human exposure to EDs in cosmetics (modified by Dr. P.Kalofiri) [56,57].

The use of alternative natural substances should not be considered absolutely safe. Many of these substances have estrogenic activity and can also function as EDs [67].

The absence of a systematic method for integrating data to help identify risks from EDs has recently led to the recognition of ten key characteristics (KCs) of EDs. These are known as “Key Characteristics (KCs) of EDs”, and provide a framework for searching and organizing relevant literature regarding the mechanistic information required to support the assessment of an ED [68]. Given the incomplete nature of knowledge, the suggested KCs for EDs can methodically pinpoint areas of missing data. As a result, they can guide the establishment of research priorities during the risk identification process [69,70].

6.2. Approval Process for Ingredients in Cosmetic Products

Certain categories of ingredients (colorants, preservatives, and UV filters) can only be used in cosmetic products if they have been approved through their inclusion in the relevant positive lists set out in cosmetics regulations [71]. Other ingredients can be used in cosmetic products without a permit, provided they are safe for human health [72,73].

Before substances are included in these annexes, a scientific risk assessment is carried out by an independent scientific committee, the Scientific Committee on Consumer Safety (SCCS). During the risk assessment process for substances used as ingredients in cosmetics, the SCCS examines exposure assessments for specific vulnerable groups, such as children and pregnant women [74]. This is crucial because cosmetic products are consumer goods used on a wide scale by citizens every day [54].

For substances classified as carcinogenic, mutagenic, or toxic to reproduction (SVHC—Substances of Very High Concern) [75], specific rules apply for labeling and packaging of substances and mixtures. Furthermore, according to Regulation 1272/2008, under Part 3 of Annex VI, the use of SVHC substances of category 1A or 1B and category 2 in cosmetic products is prohibited, based on the SVHC classification of these substances due to their hazardous properties [76]. The European Commission assigns the SCCS to conduct safety assessments of substances used in cosmetic products, including SVHC substances and nanomaterials [77]. A chemical substance may be proposed as an SVHC substance by a member state or by ECHA if it meets the specified criteria [78]. Different regulatory approaches exist in different legislative acts for substances recognized as EDs [79].

As mentioned in the REACH Regulation, chemicals with endocrine-disrupting properties are included. Such substances may be used in cosmetic products and are therefore subject to the REACH Regulation. Under the REACH Regulation, nine substances have been identified as endocrine disruptors with adverse effects on the environment [80].

In the Cosmetic Regulation, there are no specific provisions for EDs. To address potential risks to human health, the Commission may introduce measures that prohibit or restrict the use of substances. When a substance that is characterized or considered a possible ED has also been classified as a CMR substance (carcinogenic, mutagenic, or toxic for reproduction), then Article 15 of the Cosmetic Regulation applies, and the substance is prohibited unless an exemption from this prohibition is granted under the strict conditions specified in Article 15, paragraphs 1 and 2 (Compliance with the food safety requirements of the general food legislation, restriction of use to a specific category of products, lack of suitable alternative substances, evaluation and positive opinion by the SCCS regarding the safe use of the substance in cosmetic products) [81].

For identified or potential endocrine disruptors that are not classified as CMR substances, their use in cosmetics is governed by the general provisions of Article 31 of the Cosmetic Regulation, which require a scientific opinion from SCCS [54].

In the Memorandum on Endocrine Disruptors (SCCS/1544/14) dated 16 December 2014, the SCCS established the criteria for safety assessment of endocrine disruptors. The SCCS has evaluated cosmetic ingredients suspected of having endocrine-disrupting properties, and has issued scientific opinions on these ingredients, as summarized in Table 3 [82].

Table 3. Substances with endocrine-disrupting properties.

Parabenes	Cosmetic preservatives [83,84]
Homosalad	In sunscreens as a UV filter and skin care products [85]
Benzophenones	To protect cosmetics from the effects of UV radiation [86]
4-methylbenzylidene-camphor and 3-benzylidene-camphor	UV filters [87,88]
Melatonin	Antioxidant [89]
Resorcinol	For hair dyeing [90,91]
Cyclomethicone	It has various properties, it is antistatic, softens and smoothenes the skin and takes care of the hair [92]

Other substances include phthalates (plasticizers, lubricants, solvents etc.) [93–95], aluminum salts (antiperspirant agents) [96], perfluorinated chemicals [97], and nanoparticles [98,99].

These opinions indicate that substances with endocrine-disrupting properties should be investigated based on the safety assessment by the SCCS, taking into account the limitations associated with the bans on animal testing, and considering data from in vitro and in vivo studies [100]. The SCCS has conducted case-by-case safety assessments for various categories of EDs. While it has confirmed the safety of certain types of endocrine disruptors, it has not ruled out the risk to human health from other categories (isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben) [101]. Some parabens have been banned in the cosmetic industry, particularly those intended for use in the diaper region of infants and children under three years of age. Other parabens, including methyl, ethyl, propyl, and butyl parabens, are generally regarded as safe, provided that the combined paraben concentration in cosmetics does not exceed 0.4% for individual parabens or 0.8% for mixtures of various parabens. It is worth noting that parabens can alter the pharmacokinetics of bisphenol A [44]. Substances identified as endocrine disruptors are subject to the general safety assessment by the SCCS. They are treated like other substances that raise concerns for human health and are subject to case-by-case regulatory measures based on the general requirements of legislation [102].

It is important to emphasize that an analysis was conducted on 51 substances used as cosmetic ingredients. This analysis showed that the majority of these substances did not exhibit potential endocrine-disrupting properties based on the applied methodology [103–105]. However, this result may be due to a lack of data regarding the presence of endocrine-

disrupting properties in the subset of the 51 substances examined, rather than evidence of the absence of such properties [54].

7. Discussion

In light of the above, it is evident that the cornerstone of the existing legislative framework is the scientific risk assessment of cosmetic ingredients conducted by the SCCS [106]. The SCCS can assess the safety of cosmetic ingredients with respect to their endocrine-disrupting activity, with the exception of limitations imposed by the ban on animal testing for cosmetics [107]. The most important knowledge gaps derive from the non availability of a validated set of tests for EDs, as well as an inadequate understanding of the mechanisms of action of EDs, exposure and effects during sensitive developmental periods, and the validated dose response relationship for the outcomes induced by ED [108]. These knowledge gaps form the basis for the ongoing debate concerning the need for regulating EDs [109].

Specifically, the existing framework for the detection of EDs needs to be further developed to ensure the detection of effects on human health [110,111]. For example, it is impossible to prove that a pathology is related to the action of a substance to which the population was exposed years ago. The aforementioned restrictive approach to the criteria for determination has served as the basis for criticism against the European Commission, which has even been accused of serving the interests of the chemical industry and not protecting European citizens from certain substances considered potentially harmful to health [110]. Specifically, the above criticism is rooted in the fact that the Regulation proposes the exclusion only of substances with a known and fully proven ability to cause endocrine disruptions, and disregards the existing database of potential endocrine disruptors, thus excluding only a small subset of hazardous substances [112]. In order to cover a greater number of substances, such a large amount of evidence is required that it is practically impossible to achieve. Furthermore, the Regulation ignores substances for which there are only indications of possible endocrine action and therefore does not ensure the desired levels of safety for health and the environment, as previously stipulated in earlier legal texts [113]. The above concerns and criticisms are related to the fundamental question of whether risk assessment is a transparent process. Under the current regulatory framework of the EU, the applicant company (which benefits from the approval of its chemical product) is the primary supplier of the scientific studies that will be evaluated by EFSA and ECHA [114]. Moreover, the risk assessment studies conducted by the industry are not available to the public, with the excuse of preserving commercial confidentiality [115]. Thus, risk assessments carried out by companies are considered more important than an open and transparent scientific evaluation of the documents. Such a choice in the way knowledge is generated is problematic and raises suspicions of serving vested interests [116]. The issue of scientific credibility has also been raised by European citizens who, through the ECI (European Citizens' Initiative), have called on the Commission to make reforms to ensure that the scientific assessment of pesticides for EU regulatory approval is based solely on published studies conducted by competent public authorities, rather than the pesticide industry (The European Citizens' Initiative (ECI) is a mechanism in the European Union (EU) that allows citizens to directly participate in the EU legislative process by proposing new laws or changes to existing ones) [117].

8. Conclusions

As is evident from the above, EU legislation does not provide sufficient regulatory approaches for the effective management of EDs, and this has raised serious concerns among European citizens. Moreover, no unified assessment has yet been carried out covering all the different (vertical and horizontal) aspects of EDs [118]. Therefore, there is a need to take action at both European and national levels with four objectives: (a) reducing exposure to endocrine disruptors, with accompanying further development of relevant scientific knowledge and the dissemination of appropriate information to society; (b) protecting the

environment and health as a single goal, including all data related to the presentation of EDs; (c) strengthening and deepening scientific assessment and the search for substitutes for these substances to reduce exposure to hazardous substances through the enforcement of regulatory regulations; (d) involvement of stakeholders in the decision-making process regarding the designation of a chemical substance as an ED.

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