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Towards a better consideration of endocrine disruption within the Technical Guidance for deriving Environmental Quality Standards

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Abstract

Endocrine-disrupting chemicals (EDCs) are a reason for growing concern because of their substantial and long-lasting deleterious effects on human health and wildlife populations. These include direct effects on aquatic organisms and may be a concern to species feeding on the aquatic food chains and water, including humans. In the European Community, the dedicated legislative tools to protect the aquatic environment and human health from contaminants released to surface waters is the Water Framework Directive (WFD). The achievement of protection goals is assessed through the comparison of concentrations measured in the media and thresholds of no effect called Environmental Quality Standards (EQSs). As EDCs are explicitly mentioned in the WFD, an analysis of the state of the art was undertaken on how far and how consistently ED properties were considered in the derivation of EQS values. Our results reveal substantial heterogeneity according to substance and that among substances with ED evidences, EQSs have been derived without considering ED properties for 70 % of them. A methodology to better consider endocrine disrupting properties is proposed and includes a logical and systematic approach to derive EQSs with a proposal to specify additional assessment factors based on the specific hazard and potential uncertainty.

Keywords

Endocrine disruption

Environmental Quality Standards

Water Framework Directive

Methodology

1 Introduction

Endocrine-disrupting chemicals (EDCs) have been recognised to be responsible for substantial and long-lasting deleterious effects on human health and wildlife populations. The number of species affected and the disappearance of species has been described for many years and has been the basis for EDCs' identification since the first World Wildlife Federation (WWF) Wingspread Conference focusing on EDCs (Colborn et Corlie, 1992). Their impact on human health has been estimated to be responsible for more than 160 million euros of care in Europe and more than 200 US dollars in the US annually (Trasande *et al.*, 2016; Attina *et al.*, 2016).

The European Union adopted a strategy on these substances more than twenty years ago (COM(1999) 706; E.C., 1999). This strategy has been, and still is, rather slow to find an operational implementation although some criteria have been set in the context of Plant Protection Products (E.C., 2017) and Biocidal Products (E.C., 2018a) regulations, and it has recently been the subject of an analysis of the adequacy of measures and the homogeneity of regulations with regard to EDCs (E.C., 2020; ECHA/EFSA, 2018). Further, the Regulation on classification, labelling and packaging of substances and mixtures (E.C., 2008) is currently being revised to *inter alia* add a new hazard class for endocrine disruptors (E.C., 2022). This analysis highlights the heterogeneity of treatments according to the regulations and the results obtained for a very small number of compounds.

The Water Framework Directive (WFD, E.C., 2000) structures the European Community water policy and aims at achieving or maintaining good quality status of aquatic ecosystems. To prevent the environment from chemical pollution, it introduced Environmental Quality Standards (EQSs) which are threshold values not to be exceeded by chemicals concentrations in the water bodies to protect human health and the environment. These standards are derived for several types of chemicals included in plant protection products, biocidal products or

industrial chemicals. Amongst them, some are likely to disturb functions of the hormonal system. To take this concern into consideration, the Technical Guidance for deriving EQSs, also called TGD EQS (E.C., 2018b) indicates that effects related to endocrine activity (EA) and to endocrine disrupting (ED) properties have to be taken into consideration while deriving an EQS, among other types of effects. It is not prescriptive though on how this should be achieved.

In the following, a state of the art is herein presented on how far and how consistently ED properties have been taken into consideration in the derivation of EQS until now. Our analysis indicates that EDCs are only incompletely taken into consideration and that a more explicit methodology is needed to better protect ecosystems from these compounds. Thus, a methodological proposal is formulated including additional assessment factors based on the specific ED hazard as well as potential uncertainty. It is worth noting that the methodology proposed does not provide guidance to identify EDCs as such, but to take knowledge on ED properties into account in EQS derivation to provide sufficient protection of the ecosystem. Finally, although this methodology is directly applied to the derivation of EQSs in a European legislative framework, it makes proposals that have a broader scope for the protection of ecosystems.

2 Existing strategy and methodology

2.1 EDCs specificities and thresholds of no effects

EDCs have been defined in several contexts, the most influential definition being the World Health Organisation (WHO) definition which introduced an EDC as “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” (WHO, 2002). Later, criteria allowing to define such substances have been confirmed and specified by EFSA and

ECHA in their “guidance for identification of EDCs” (ECHA/EFSA, 2018) as substances meeting all of the following criteria: (i) the substance shows an adverse effect in [an intact organism or its progeny]/[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; (ii) the substance has an endocrine mode of action, i.e. it alters the function(s) of the endocrine system, and (iii) the adverse effect is a consequence of the endocrine mode of action.” From a regulatory point of view, the possibility to define thresholds of no effects for EDCs has been discussed extensively. While experts acknowledge the difficulties to define a threshold of no effect for these substances, nobody is in a position to actually conclude on the inability to derive them (EFSA, 2013 ; JRC, 2013a; JRC, 2013b ; Lewis, 2013; Brescia, 2020). Difficulties in this exercise are partly due to an important lack of ED-related toxicity data. Amongst studies already available, other scientific issues for the analysis of data are linked to the existence of non-linear or non-monotonous dose-responses (NMDR, EFSA, 2021), to the existence of effects at (very) low exposure concentrations, to the issue of exposure windows (organisms are more sensitive at certain life cycle stages, e.g. foetal stage, perinatal period and puberty), to the delay in the occurrence of effects, and to the possible transgenerational effects. Because of these characteristics of EDCs, the derivation of thresholds of no effects for them are difficult and debated within the scientific community (Rhomberg et Goodman, 2012 ; Vandenberg *et al.*, 2012 ; Gross *et al.*, 2001 ; La Merrill *et al.*, 2020). However, there is relevance in deriving such values following a « Weight of Evidence » (WoE) approach in order to better regulate EDCs. In this process, biological plausibility and reproducibility of dose-responses relationships is a main step (Beausoleil *et al.*, 2016; Lagarde *et al.*, 2015). For this analysis, it is necessary to distinguish between mechanistic studies, providing effects observed *in vitro* and for which

NMDRs are often observed, from studies reporting adverse effects, also called apical effects, observed in *in vivo* tests and reporting of data at population level (Parrott *et al.*, 2017). The parallel distinction between EA and ED should also be highlighted. Endocrine active substances are substances that can interact or interfere with normal hormonal action. When this leads to adverse effects, they are called endocrine disruptors (ECHA/EFSA, 2018) or endocrine disrupting chemicals (EDCs). The document published recently by EFSA addresses this issue specifically and provides recommendations regarding the consideration of these data within risk assessment (EFSA, 2021).

In the context of EDCs assessment, more than for any other substances, the threshold for the biological effect which refers to the occurrence of adverse effects shall be distinguished from the threshold of experimental effect for which no effect was observed experimentally and from the threshold of mathematical effects (or « zero » effect) (Slob, 1999). Thus, it is very important to consider that it is technically impossible to determine the exact biological effect threshold for EDCs. In the context of some regulatory assessments (e.g., REACH), this makes it possible to consider only the adverse effects and to be more protective with regard to the risks posed by these substances. The scientific basis for a non-threshold effect is plausible as a single molecule can activate a hormone receptor. However, it may be doubtful whether this single activation leads to a substantial deleterious effect. Therefore, although necessarily imperfect, the consideration of thresholds makes it possible to calculate, in a homogeneous approach across regulations, EQS that would be more protective because they would consider results on endocrine disruption.

2.2 Environmental Quality Standards as defined in the Water Framework Directive

In order to meet its objectives, the WFD established quality objectives and monitoring programmes aiming at achieving good status of water bodies and non-accumulation of

pollutants in sediments and biota defined at the water body scale. The good chemical status is achieved when concentrations of pollutants or groups of pollutants in water, sediment or biota do not exceed a threshold concentration defined as « *Environmental Quality Standard* » (EQS), for freshwater and saltwater, respectively.

The EQS is selected from 5 quality standards (QS) calculated in order to protect aquatic organisms (by means of the quality standard QS_{water_eco}), benthic organisms (by means of the quality standard QS_{sediment}), predators and top predators from secondary poisoning (by means of the quality standard QS_{biota_sec pois}) and finally human health from the consumption of fishery products (by means of the quality standard QS_{hh_food}) and from the consumption of drinking water (by means of the quality standard QS_{dw_hh}).

In order to protect the structure and functions of aquatic ecosystems, and the organisms dependent on these (top predators and humans), the focus is on the most sensitive species. Thus, the EQS is defined as the lowest of the available specific Quality Standards (QS) as recommended in the « *Technical guidance document for deriving Environmental Quality Standards* » (TGD EQS, E.C., 2018b).

When toxicological data are available that are relevant and reliable for the purpose of deriving water quality thresholds, the quality standards are calculated by means of extrapolation from laboratory data or, where available, from mesocosm and field data. In most of the cases, the QS are calculated by dividing the lowest EC₁₀ (concentration tested for which 10% effects is observed experimentally) or the lowest NOEC (concentration tested for which no statistically significant effects are observed experimentally), or the lowest EC₅₀ (concentration tested for which 50% effects is observed experimentally) by an appropriate assessment factor (AF). When a sufficient number of data is available as defined by the TGD EQS, a species sensitivity distribution-based method can be applied that also requires application of an AF. AFs are used

to take into account uncertainty due to extrapolation, e.g. from laboratory to field or from acute to chronic, and uncertainties due to variability, e.g. between species or laboratory and within species and laboratory. Although AFs are recommended in the TGD EQS (E.C., 2018b) for each QS to be derived, the choice of the AF based on the available toxicity data is a crucial step of QS derivation, which partially remains under expert judgement.

2.3 EDCs within the WFD and specifically within the guidance for deriving EQSs

An analysis of the consideration of EDCs in EU legislation related to the presence of chemical substances was recently published by the European Commission (E.C., 2020). It states that the WFD takes EDCs into account on the basis of the presence of some identified EDCs in the lists of substances to be monitored (referring to Annex VIII of the Directive). It mentions, for example, that DEHP has been included in the list of priority hazardous substances, which should be phased out within 20 years, based on its endocrine effects.

In several occurrences, the TGD EQS (E.C., 2018) refers to ED properties for certain chemicals as a special concern to consider for the derivation of EQS but is being weakly prescriptive in its recommendations (Supplementary data Table S1). The document twice mentions the need to take into account available data on endocrine disruption without mentioning any specific methodology (Supplementary data Table S1). Among other things, the TGD EQS does not specify how ED-related toxicity data or endocrine MoA (Modes of Action) could or should be included in the toxicity dataset considered for EQS derivation. Similarly, the TGD EQS indicates in three sections the need to increase the assessment factor when calculating the EQS when ED-related effects are identified (Supplementary data Table S1). However, modalities of this requirement are not further specified, thus showing a significant gap in regulation preventing it to meet its objectives.

3 How are ED properties considered within TGD EQS?

In consideration of the lack of prescription included in the TGD EQS regarding ED, an analysis of the state of the art was undertaken on how far and how consistently endocrine disrupting (ED) properties were considered in the derivation of EQS based on the resources described in the following.

To achieve this goal, we compiled a list of 180 chemicals for which EU or national EQS were available with an explanatory document (« EQS factsheets/dossiers »). This list includes the 36 WFD EU « priority (hazardous) substances » (as defined in 2013/39/EU amending 2008/105/EC) as well as 144 other substances of interest (Supplementary data Table S2), and was used as the universe of candidate chemicals for our exercise. An analysis of the methodology used to establish the threshold values, as well as the associated rationale, was carried out with particular attention to the references to endocrine disrupting activities and how these activities were taken into account. The data used and their rationale were compared with data available in published databases.

3.1 Analysis of EDC lists and EA and ED data available for the 180 chemicals universe

Information on available EA and ED properties of chemicals are dispatched among several initiatives at national, European and international levels. The French Agency for Food, Environmental and Occupational Health & Safety (Anses) has recently reviewed all initiatives listing known or potential EDCs at national, European and international levels. The study shows that the lists are heterogeneous as they pursue different objectives, tackle different sets of substances, and take into account different criteria (ANSES, 2021).

For the purposes of our methodology, we considered the following lists:

- Some EU Member States (BE, DK, FR, NL, SE, SP) have recently established three lists of chemicals available on the website « edlists.org » informing on the conclusions of ED assessments, listing substances identified as EDCs at EU or national levels, as well as in ongoing EU evaluations (DK-EPA, 2021).

Further, two documents were published in the context of the European Community strategy for EDCs. They are the following:

- BKH 2000 list (Groshart et Okkerman, 2000): BKH consulting engineers was missioned by the European Commission to establish the very first European list of substances deemed « of priority » as regards their ED potential. Based on this list the European Commission built the text of its communication to the Council and the European Parliament untitled « Community Strategy for Endocrine Disruptors » (COM (1999) 706, E.C., 1999) and the « Commission staff working document on implementation of the Community Strategy for Endocrine Disruptors – a range of substances suspected of interfering with the hormone systems of humans and wildlife » (COM (1999) 706, E.C., 2004).
- DHI 2007 list (Petersen et al., 2007): DHI Water & Environment was missioned by the European Commission to update the existing list of priority chemicals produced by BKH, focusing on low tonnage chemicals. Based on this list the European Commission built the text of its « Community Strategy for Endocrine Disruptors – a range of substances suspected of interfering with the hormone systems of humans and wildlife. Third progress report on the implementation of the Strategy during the period 2004-2006. » (SEC (2007)1635, E.C., 2007)
- Moreover, data were collected from the SIN List (ChemSec, 2017) grouping *inter alia* information on hazard of chemicals foreseen for substitution, from scientific research

reports, and from scientific literature in general.

All these data were entered in a common database for the sake of our categorisation work.

3.2 Analysis of EQS factsheets for the 180 chemicals universe

For all 180 candidate chemicals, the following data were retrieved from the EQS factsheets available:

- EA or ED notification. This corresponds to references made of listing of chemicals in any document published within the context of an EDCs prioritisation initiatives (including European Commission Staff working document within the implementation of the EU Strategy on EDCs), and references of any EA or ED evidence within the scientific literature.
- Key information on the QSs and EQS derivation:
 - Key study(ies) and key effect(s) considered for the calculation of QS;
 - AF used for the calculation of QS and the reasoning-behind statement;
 - Any additional AF applied for the purpose of consideration of ED potential of the chemical.
 - Key QS for the derivation of the EQS

The information gathered was sequentially analysed with respect to the following questions:

- 1) Is there available information to highlight an ED potential?

- 2) Is the ED potential taken into account while deriving the EQS?
- 3) How clear is the rationale for the consideration of ED potential within the EQS derivation process and/or notification of the ED potential as stated in the factsheet?

3.3 Results

Based on the questions listed in section 3.2, existing EQS fell into four categories (Figure 1). In particular, of the 180 chemicals analysed, for 94 chemicals (52%) no ED evidence was shown neither within prioritisation initiatives nor within the scientific literature. The 86 other chemicals are listed at least once in these investigated sources. Among them, category 3 includes 14 chemicals (8%) for which ED potential was notified and taken account of appropriately and category 2 includes 12 chemicals (7%) for which the screening of the EQS value and factsheet showed that ED potential was considered but that the rationale stating choices made was not clear enough in this regard. Finally, 60 other chemicals were identified in category 1, meaning that one third of the EQS did not consider endocrine activity although there are substance-specific data suggesting or evidencing such activities (Figure 2).

Within category 1, three sub-categories were identified. The first two contain chemicals for which evidence of ED potential exists in the scientific literature (category 1C) or in a prioritisation initiative (category 1B) but without indication or consideration of this information in the EQS factsheet. Category 1A groups 15 chemicals for which ED effects were quoted in the EQS factsheets but not considered for EQS derivation. It is deemed that this latter category should be prioritised for revision.

An appendix detailing these results is provided (Supplementary data Table S2).

These results highlight how heterogeneous the derivation of EQS is concerning ED consideration; and that, out of the 86 compounds with ED potential, an EQS has been derived

for 70 % without these properties having been taken into account. This corresponds to 60 chemicals out of 86 for which we recommend an update of the respective EQS.

4 Proposed methodology for improving consideration of ED properties in EQS derivation

4.1 Overview

As EDCs represent a specific hazard due to their inherent toxicological properties, we suggest that additional assessment factors while deriving the effect thresholds should be considered to account for any risk to the environment and health. As for EQS derivation, the EDC specificities lead to increased uncertainties on threshold values and this shall be taken into account by application of an AF specific of this hazard.

The suggested methodology consists of three steps to be followed:

1. Identification of EDCs
2. Selection of specific ED threshold values
3. Selection of specific assessment factors

The main steps of the approach shall be applied in addition to the « conventional » approach of EQS derivation, i.e. assuming that minimum dataset requirement is met on acute and chronic effects. For example, for the derivation of $QS_{\text{water eco}}$ to protect aquatic organisms, this means that at least three reliable EC50 covering apical endpoints are available, preferably three EC10 or NOEC.

The first step addresses the knowledge on the EA and ED properties of the chemical and a systematic review of the corresponding data available. This first issue is a difficult one and the responsibility of a collective expertise. In a pragmatic approach, only the compounds on the official European Community lists are considered as EDCs. These are available on the website « edlists.org » (DK-EPA, 2021) in category I (« substances identified as endocrine disruptors at EU level »). All other substances present in category II or III on this site or on other sites or whose scientific publications mention endocrine effects can only be considered as suspected EDCs for the EQS derivation process. The European Union has proposed to include endocrine disruptors as a new hazard in the CLP regulation (E.C., 2022). CLP follows the United Nations' Globally Harmonized System (GHS) of classification and labelling of chemicals setting up criteria for classification and communication of physicochemical, health, and environmental hazards. Known, presumed and suspected endocrine disruptors will then be classified and these lists will be considered for the establishment of EQSs.

The second step addresses the possible inclusion of EA and ED data within the dataset conventionally used for derivation of EQS. In fact, data conventionally collated, validated and used for the purpose of EQS derivation are EC₅₀, EC₁₀ or NOEC corresponding to apical effects, i.e. effects characterised by phenotypic or “observable” responses at individual scale with consequences on the population level (Krewski *et al.*, 2011). Therefore, the review of knowledge on and the assessment of ED potential will most probably allow to identify additional data. The new ecotoxicity and toxicity dataset will therefore be modified either with additional data showing a higher toxicity of the substance (availability of lower EC₅₀, EC₁₀ or NOEC values than the previous existing ones), either with additional data modifying the characteristics of the whole dataset (e.g. if new data address new endpoints or apply to new taxa or species or new exposure duration). These two cases may happen concomitantly.

Finally, the third step tackles the possible impact of EA and ED data inclusion within the ecotoxicological and toxicological dataset on the AF to apply, considering that there are two reasons for applying additional factors, the specific hazard related to endocrine disruption and the uncertainties related to the limited knowledge and data available.

4.2 Specific considerations

The derivation of EQS is not an assessment process during which specific data can be generated or requested to establish the threshold. The analysis can therefore only be done on the basis of available data and through a review of the scientific literature. This systematic review methodology is described, in particular, in an ECHA guidance dedicated to evaluation of available information (ECHA, 2011).

The data collation and ED potential assessment steps need to be screened regarding the list of tests methods and assessment of the endocrine activity of chemicals. This research can be based on tests recommended by the Organisation for Economic Co-operation and Development (OECD) in its « Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption » (OECD, 2018). These tests neither represent a mandatory nor sufficient test battery but an indicative list of tests which may be searched for in the scientific literature for the chemical investigated. Availability of tests conducted with aquatic organisms (invertebrates, amphibians, fish) sensitive to ED-related toxicity and classically investigated for $QS_{\text{water_eco}}$ derivation should be screened, but also tests with organisms potentially affected through the food chain (birds and rodents as representative of fish-eating predators and top predators) sensitive to ED-related toxicity and classically investigated for $QS_{\text{biota_sec pois}}$.

Regarding tests using invertebrates, it has to be noted that all tests exposing invertebrates “solely involve apical endpoints which are able to respond to some endocrine active substances and some non-endocrine active substances” (OECD, 2018) except the juvenile hormone screening test performed on *Daphnia magna*. For this reason, and until the scientific knowledge allows the opposite, they may be considered as tests indicative of the potential of reproductive toxicity, but they are not suited to demonstrate any ED potential in a stand-alone manner. Nevertheless, they may be screened and used in a weight of evidence (WoE) approach for the chemical ED assessment, as any other non-standardised tests on invertebrates.

More generally, any data deemed of interest for the expert and for which relevance and reliability can be justified should be considered as ED assessment relies on an empirical demonstration and the implementation of a line-of-evidence approach (Gross *et al.*, 2017 ; ECHA/EFSA, 2018 and La Merrill *et al.*, 2020).

The second step consists in including the EA and ED data related to any level of information of toxicity, i.e. mechanistic data showing endocrine activity or an endocrine MoA or adverse effects at individual or population level, in the dataset conventionally used for EQS derivation. In fact, although the dataset for derivation of EQS conventionally mostly includes apical effects observed in tests following standardised guidelines on algae, crustaceans and fish, the TGD EQS also recommends that “all available data for any taxonomic group or species should be considered, provided these data meet quality requirements for relevance and reliability” (E.C., 2018).

The expert has to evaluate how far the dataset is sufficient to consider the ED potential in EQS derivation based on the quantity and quality of the data and applying the line of evidence approach as recommended by ECHA/EFSA in its guidance for identification of EDCs (ECHA/EFSA, 2018). A minimal set of three required considerations is suggested:

- Are all the adverse effects identified in the ED assessment covered by the ecotoxicity and toxicity dataset represented by an EC10 or NOEC value?
- Do the chronic endpoints available in the ecotoxicity and toxicity dataset cover all the endocrine modes of action identified in the ED assessment (minimal investigation on EATS modalities) ?
- How many ED-related EC10 or NOEC values are available in the dataset ?

As a third step, the selection of AFs specific of ED concern should be considered. The identification of a substance as an EDC is a major concern considered by several EU regulatory framework, e.g., Plant Protection Products Regulation (E.C., 2009), Biocidal Product Regulation (E.C., 2012) and REACH (E.C., 2006). The distinctive characteristic of this concern is that its demonstration induces the ban or substitution of the chemical of concern on the European market. When a substance is identified as an EDC, we recommend applying an additional assessment factor for ED hazard (named $AF_{\text{add-ED-hazard}}$) to be multiplied by the conventional minimal assessment factor (e.g. an AF of 10 applied to the lowest of the 3 EC₁₀ or NOEC for $QS_{\text{water eco}}$ and an AF of 3 applied to the lowest NOAEL for $QS_{\text{biota sec pois}}$). We recommend that, except where expert judgement entails other need, this $AF_{\text{add-ED-hazard}}$ is a minimum of 5 for an identified EDC and a minimum of 2 for suspected EDCs.

Furthermore, another parameter to consider in the assessment factor is the residual uncertainty linked to a lack of investigation on effects on the endocrine system. The endocrine system is a complex network for which it is recommended to monitor at least the effects *via* EATS modalities, i.e. effects related to (anti-) estrogen (E), (anti-) androgen (A), thyroid disrupting (T) and steroid hormone synthesis disrupting (S) properties. It is important to have studies on a minimum of two modalities including at least one of the EAS modalities and on the thyroid axis or another relevant endocrine axis. The minimum data set should therefore include at least one

$EC_{10ED-mediated}$ (or one $NOEC_{ED-mediated}$) for each of the two relevant modalities. To take account of this residual uncertainty and the higher difficulty to complete the ED dataset, we recommend applying an additional assessment factor for uncertainty ($AF_{add-ED-uncertainty}$). We recommend that, except where expert judgement entails other need, this $AF_{add-ED-uncertainty}$ is a minimum of 2. It may be applied to the cases of suspected EDCs but also to identified EDCs.

Based on the criteria and steps detailed before, a decision tree is proposed to guide the expert deriving the EQS in better considering potential ED properties of the chemical of concern (Figure 3).

5 Discussion and recommendations for improvement of the TGD EQS

The specific characteristics of endocrine disruptors are prompting the European Commission to propose the introduction of these compounds as a new hazard class in the CLP regulation, which follows the United Nations' Globally Harmonized System (GHS) of classification and labelling of chemicals setting up criteria for classification and communication of physicochemical, health, and environmental hazards (Com, 2022). As stressed by the European Commission (E.C., 2019), in order to be effective, the various regulations must have coherence and aquatic environments, in particular, must be protected. In Europe this protection objective is enshrined in the WFD and involves the determination of reference values called EQSs, which designate concentrations that should be protective for human and environmental health. Our in-depth evaluation of selected EQSs showed that TGD EQS is not prescriptive enough regarding consideration of EA and ED properties. Among a sample of 180 existing EQSs derived in the European community, 60 chemicals were identified as “substances with EA or ED properties not taken account of within EQS derivation” (category 1) although there are substance-specific data suggesting or evidencing such properties. There is a consensus on the EU level on the definition of EDCs, but identifying these substances is particularly difficult and subject to the

qualitative assessment of expert groups. At least 27 initiatives and lists have been established and significant differences may exist between them (ANSES, 2021). Our screening work was based on selected lists and the scientific literature available but not in an exhaustive manner. Therefore, it cannot be excluded that, among the compounds for which no endocrine concerns were identified (and which represent 52% of the substances analysed in this exercise), other substances could be EDCs. Although this work is not intended to prioritise substances, it seems advisable to re-evaluate substances identified as endocrine disruptors and for which data have not been, or have been improperly, used in the derivation of EQS.

Based on the two statements that (1) TGD EQS is not prescriptive enough regarding consideration of potential ED properties and that (2) this can be demonstrated by an in-depth evaluation of the existing EQSs derived in the European community up to date, a decision tree is herein proposed to guide the expert deriving the EQS in better considering potential ED properties of the chemical of concern.

The process proposed in this decision tree includes three main steps, one of which is crucial among others, that is the choice of additional AFs considering ED properties. This corresponds to a usual practice in risk assessment. Alterations of the function of the endocrine system may arise from interaction with hormone receptors, changes in circulating hormone levels, effects on hormone synthesis, transport, metabolism, and other factors. Many of the critical events may occur during specific developmental stages that may be ignored or difficult to assess, thus obscuring any causal relationships that may exist. Furthermore, the endocrine system is a complex network involving many different hormones for which tests are still missing. Thus, determination of the exact biological effect threshold for EDCs is fraught with difficulties. The proposed $AF_{add-ED-hazard}$ is meant to take account of uncertainties linked to ED hazard itself, i.e. possible occurrence of effects at “very low doses”, NMDR, occurrence of transgenerational

effects, delay in responses and exposure windows issue. We propose an additional factor of at least 5 for identified EDCs for which the robust scientific assessments demonstrate that the specific hazard is undoubtful, and a factor of at least 2 for suspected endocrine disruptors.

In the context of WFD implementation, experts deriving EQSs are dependent on existing data and not in a position to require the production of missing information as is the case of risk assessment experts elaborating dossiers for risk regulation purposes for substances to be placed on the market. Thus, primary limitation to EQS derivation is often the lack of ecotoxicological data. This has been taken into account in the propositions made in the decision tree (**Error! Reference source not found.**) with the screening of the availability of data to identify the substance as an EDC and availability of EA and ED-related toxicity data within the dataset used for EQS derivation. The most important point to consider here is the lack of scientific investigation of the endocrine system and the different axes that can be disturbed by a given compound. The endocrine system is crucial for the development, homeostasis, behaviour, reproduction and breeding of organisms that can be affected in different ways. The ECHA/EFSA guidance on the identification of EDCs (ECHA/EFSA, 2018) recommends investigating the EATS modalities. However, these modalities are restrictive and other perturbations could be very important and go relatively unnoticed due to our lack of knowledge. Pragmatically, and considering the tests currently available, we recommend that at least two modalities be investigated in order to limit the uncertainties of endocrine action. The scientific data and the interpretation of the most widely used OECD regulatory tests suggest that E, A and S activities often produce similar reproductive or developmental effects (Christiansen et al. 2020; OECD 2018). Two modes corresponding to EAS on the one hand and T on the other seem to be in line with current requirements and knowledge. The introduction of this uncertainty factor is an incentive to document the modes of action of compounds that may be

particularly deleterious and thus to reduce uncertainty as is classically practised in threshold value calculations.

We recommend that a factor of 2 be used for endocrine system uncertainties where there is an insufficient number of specific endpoints available to describe two endocrine disruption modalities. Thus, in combination, providing no specific justification is raised by the expert to higher the by default additional factor, the additional factor for compounds identified as EDCs would be 10 (i.e. 5×2). This factor is also the one recommended by the French methodology to derive EQSs for River Basin Specific Pollutants (INERIS, 2011) and in a study to derive threshold values considering EDCs in the context of human health (DK-EPA, 2019).

Finally, within the implementation of WFD itself, there are a number of quotations of ED effects in the TGD EQS which would need to be specified or clarified for improvement of the guidance (e.g. consideration of tests focusing on non-apical endpoints, see Supplementary data Table S1).

6 Implications

The writing of a European Technical Guidance Document is a long-lasting process which involves several experts discussing scientifically sounded options to reach a relevant methodological text. This decision tree is proposed as a complement to the existing methodology to be applied for the derivation of specific QS within derivation of EQS where data are available and sufficient, guiding the expert more specifically through the steps of completing the dataset with ED effects where appropriate, and consider how this should influence the assessment factor where necessary. We think its inclusion within the existing European methodology in the TGD EQS would help harmonising the consideration of ED properties between the different Member States.

Whatever the regulatory context, studies addressing the derivation of thresholds of no effect for EDCs are based on an empirical approach which often raises the concern of the lack of specific and robust methods to depict individual steps in endocrine pathways, which in turn raises the concern of the lack of data. These lacks hamper a straightforward establishment of corresponding regulatory water quality standards. It is therefore very important to support active research to identify the effects of EDCs in wildlife species, to continue efforts to elucidate the mechanisms of action, without restricting them to EATS parameters or vertebrates, and to develop and enforce tests to identify EDCs. On top of that, it is worth adding that industry data availability is also a key to robust datasets. In any case, the existence of necessary debates within the scientific community and the many uncertainties and gaps in knowledge should not be a reason to delay efforts to better regulate and manage EDCs. It is important that regulations consider the hazards identified, and that regulations can be harmonised and consider all EDCs.

The presented suggestion ties in well with the existing EU framework on ED and takes account of data available in regulatory assessment and scientific literature. We think that inclusion of this approach in the TGD EQS could improve guidance on ED and would enable harmonisation of the consideration of ED properties within thresholds derivation exercise. Furthermore, this methodology will be an incentive to develop and to use a more complete range of tests to assess the endocrine effects of substances and will add consistency between EU regulations. More generally, the proposed methodology and the logic behind it provide a basis for reflection that could lead to transposition into regulations in other regions of the world in order to protect aquatic environments, particularly those impacted by chemicals not considered in Europe.

7 List of figures

Figure 1 – Analysis of ED substances considered in EQS and subsequent categorisation mentioning the number of chemicals per category. Cat. 1: chemicals for which EQS did not consider endocrine activity although there are substance-specific data suggesting or evidencing such activities; Cat. 2 : chemicals for which the screening of the EQS value and factsheet showed that ED potential was considered but that the rationale stating choices made was not clear enough in this regard; Cat. 3: chemicals for which ED potential was notified and taken account of appropriately; Cat. 4: chemicals for which no ED evidence is available.

Figure 2 –Results of the analysis of EQS factsheets for the 180 chemicals according to their use of the available knowledge on endocrine activity or effect of the substance, with grouping in categories 1A, 1B, 1C, 2, 3 or 4. For detailed legend of categories, see Figure 1.

Figure 3 – Decision tree for better considering endocrine disrupting properties within derivation of specific QS. Four categories of substances are considered: known EDC, suspected EDC, not an EDC and inconclusive substance (box 1) and two subcategories according to the available data on the endocrine activity and effects for a given substance: sufficiently documented or insufficiently documented (box 2). An additional assessment factor of 5 is applied for a known EDC and of 2 for a suspected EDC, while the lack of sufficient information on EA and ED leads to applying another factor of 2. Please refer to the explanatory notes to be guided through the decision tree.

8 List of tables

Table S1 – Complete list of quotations relating to EA and ED within TGD EQS (E.C., 2018) using the following keywords : « Endocrine », « Hormone », « Estrogen » (or « Oestrogen »), « Androgen » and « Thyroid » ; TGD EQS corresponding chapters ; parameters to which quotation refers (QS derivation in general or specific relation to Assessment Factor (AF) or to tests recommended for the building of the ecotoxicity and toxicity dataset used for the EQS derivation) ; numbers of quotes in the core text or in the appendices.

Table S2 : Outcome of the analysis of ED substances considered in EQS and subsequent categorisation for 180 candidates. Substances are ranked by category and alphabetical order. E.C. (2013) (2005) = EQS established by the European Commission in 2005 for priority substances and reported within the daughter Directive 2013/39/EC, E.C. (2013) (2011) = EQS established by the European Commission in 2011 for priority substances and reported within the daughter Directive 2013/39/EC ; JORF2015 + INERIS = EQS established by the French Ministry in charge of the environment based on INERIS proposal and applying for French RBSPs; VGE = Environmental Guideline Value proposed by INERIS for potential implementation as EQSs, but not legally-binding.

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Figures

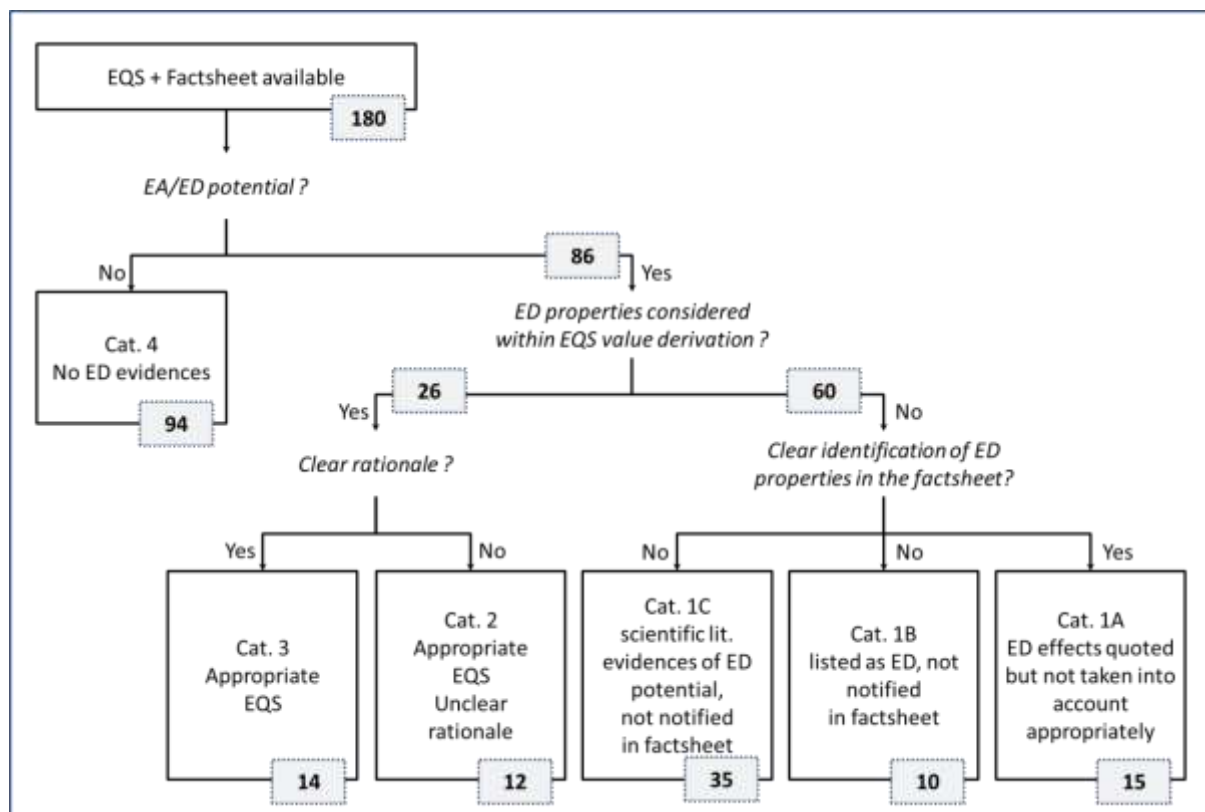


Figure 1 – Analysis of ED substances considered in EQS and subsequent categorisation mentioning the number of chemicals per category. Cat. 1: chemicals for which EQS did not consider endocrine activity although there are substance-specific data suggesting or evidencing such activities; Cat. 2 : chemicals for which the screening of the EQS value and factsheet showed that ED potential was considered but that the rationale stating choices made was not clear enough in this regard; Cat. 3: chemicals for which ED potential was notified and taken account of appropriately; Cat. 4: chemicals for which no ED evidence is available.

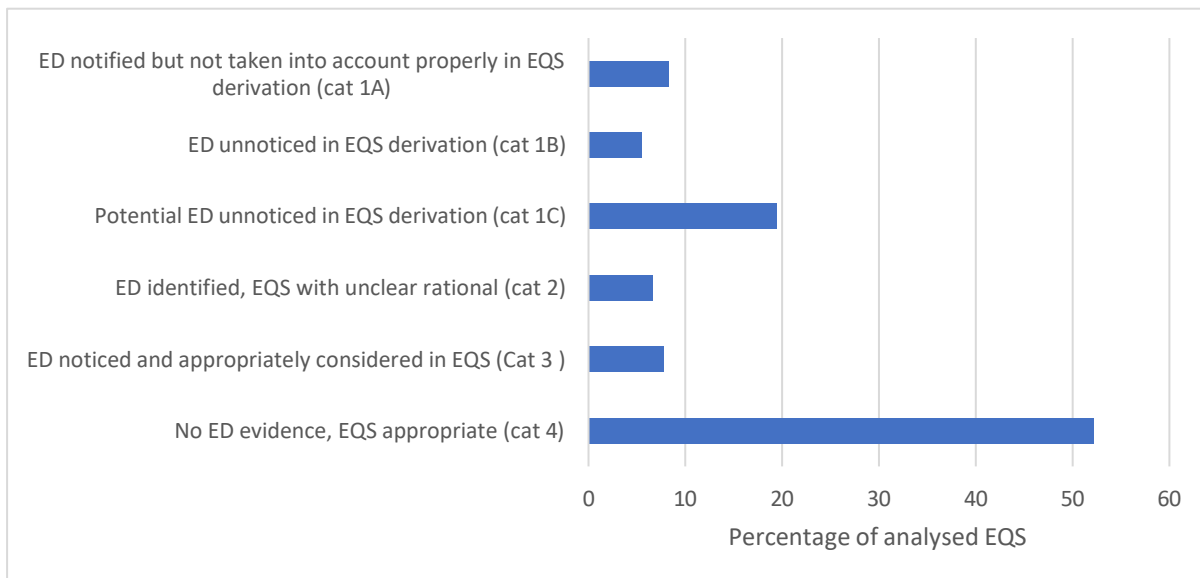


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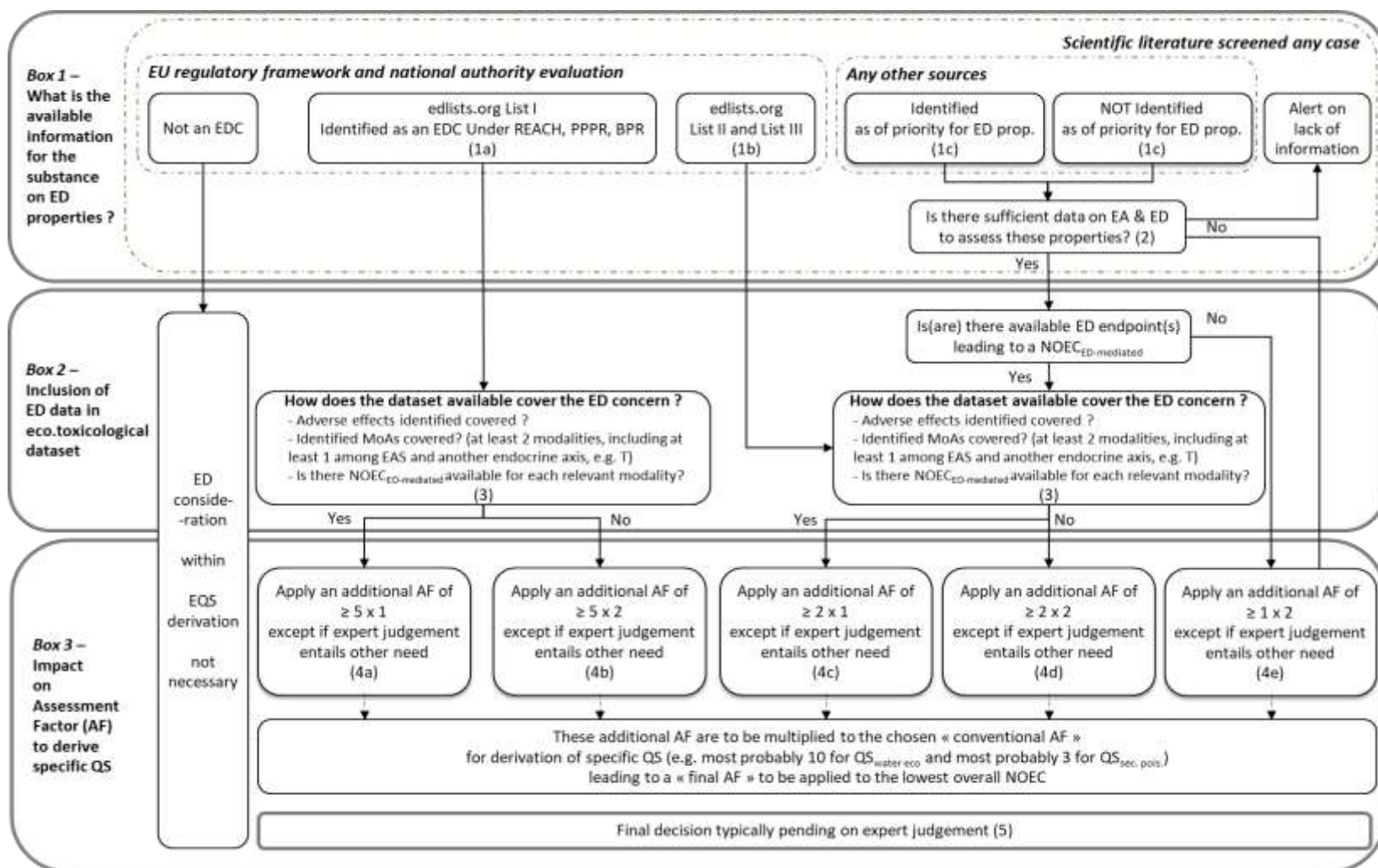


Figure 3 – Decision tree for better considering endocrine disrupting properties within derivation of specific QS. Four categories of substances are considered: known EDC, suspected EDC, not an EDC and inconclusive substance (box 1) and two subcategories according to the available data on the endocrine activity and effects for a given substance: sufficiently documented or insufficiently documented (box 2). An additional assessment factor of 5 is applied for a known EDC and of 2 for a suspected EDC, while the lack of sufficient information on EA and ED leads to applying another factor of 2. Please refer to the explanatory notes to be guided through the decision tree.

Context notes to accompany Figure 3:

The implementation of this flow chart implies that enough toxicity data is available to derive an EQS (at least enough aquatic toxicity data available to derive $QS_{\text{water eco}}$ (at least 3 EC50, preferably 3 NOEC or EC10) and enough oral mammalian and bird data available to derive $QS_{\text{biota sec pois}}$ and $QS_{\text{biota hb}}$) excluding consideration on availability of endocrine disrupting (ED) related toxicity data.

Box 1 – “Available information for my substance on ED properties”

(1a) Substances evaluation may originate from several EU regulatory framework (PPPR, BPR, REACH). Substances « identified as an EDC » are restricted to edlists.org Lists I = « Substances that have undergone an evaluation of endocrine disrupting properties, as regulated in the EU in PPPR, BPR or REACH, and which are identified as endocrine disruptors » (DK-EPA, 2021)

(1b) Substances evaluation may originate from several EU regulatory framework (PPPR, BPR, REACH) for which dossiers are not concluded. Screen edlists.org Lists II = « Substances under evaluation for endocrine disruption under an EU legislation ». Substances evaluation may also originate from EU Member States national authority evaluations. Screen edlists.org List III = « Substances considered, by the evaluating National Authority, to have endocrine disrupting properties » (DK-EPA, 2021).

(1c) Lists of prioritisation for ED properties/concern may originate from a high number of sources and corresponding evaluations or prioritisation processes. Here are some examples : E.C. Commission Staff working documents Cat 1 (« Presumed EDC ») and Cat 2 (« Suspected EDC »), ANSES Cat I (« Presumed EDC ») and Cat II or III (« Suspected EDC »), etc. For an exhaustive list of the international, EU, national initiatives, and any other initiatives to prioritise EDCs, at the date of the present report, see ANSES report (ANSES, 2021b).

Information may also be available in the scientific literature for substances NOT identified in any list of priority for ED properties. The attached list of OECD CF Level 2, 3, 4 or 5 tests (*) is indicative and neither necessary, nor sufficient. It is indicative of tests results relating to ED toxicity showing mechanistic information on endocrine activity and/or endocrine adverse effects.

(2) This step typically includes possible implementation of ECHA/EFSA Guidance on identification of EDCs (ECHA/EFSA, 2018). The corresponding methodology may be applied strictly (systematic review) or according to a less in-depth work depending on time and resources allocated to the EQS derivation. In anycase, it corresponds to a Weight of Evidence approach to try to identify ED. This step requires at least to check compliance with the list of most relevant tests while raising ED concern (*)

Box 2 – “Impact on eco.toxicological dataset”

(3) This step is preparatory to the choice of the Assessment Factor (AF) and refers to the need to be able to assess if the existing key $NOEC_{\text{non-ED}}$ or key $NOEC_{\text{ED-mediated}}$ (***) and the whole toxicity dataset in general cover the adverse effects and relates to the relevant ED MoA through the available endpoint(s). More generally, it aims at assessing whether the dataset available for EQS derivation is deemed to cover the ED concern. This may be performed via answering a list of questions, e.g:

- “Are the adverse effects identified covered ?”
- “Are the MoAs identified covered?” (studies available on a minimum of 2 modalities, including at least one of the EAS modalities and on the T axis or another relevant endocrine axis (E: Estrogenic, A: androgenic, T: Thyroidal and S: Steroidogenic)
- “How many $NOEC_{\text{ED-mediated}}$ are available in the dataset ?” (at least one $EC10_{\text{ED-mediated}}$ (or one $NOEC_{\text{ED-mediated}}$) for each of the two relevant modalities)

(***) Key NOEC = lowest relevant and reliable NOEC value from which the QS is derived

Box 3 – “Impact on Assessment Factor (AF) to derive specific QS”

The identification of a substance as an EDC is a high-level concern which is considered by many EU regulations (PPPR, BPR or REACH) which implies the substance to be banned or substituted on the market. This ED concern is implied by the occurrence of effects at very low doses for which complete consideration is not possible because of the non-linearity of these (Non-Monotonous Dose Response, NMDR). This ED concern justifies the application of an additional assessment factor (AF_{add}) to account for extrapolation of ED, except if expert judgement entails other need (cf. note (5) below). To this aim, a minimal AF_{add} of 5 is proposed for a substance “identified as an EDC” and a minimal AF_{add} of 2 is proposed for a substance “presumed” or “suspected” to be an EDC.

The residual uncertainty in the dataset implied by a lack of data (e.g. on MoA, or when less than 3 $NOEC_{\text{ED-mediated}}$ are available) is accounted for by an additional AF of 2. Typical example is if adverse effects are observed and attributed to ED MoA with no associated $NOEC_{\text{ED-mediated}}$ while other apical toxicity data are not available to cover these effects in the dataset underlying the QS.

(4a) & (4c) $AF_{\text{add}} = 5 \times 1$: Cases where ED concern is identified and the residual uncertainty for adequately protecting the environment via a threshold based on the available dataset is low.

(4b) $AF_{\text{add}} = 5 \times 2$: Cases where the substance is identified as an EDC in an EU regulatory framework but with significant residual uncertainty in the available dataset to adequately protect the environment.

(4d) ED concern is not demonstrated but only presumed or suspected, and dataset do not cover all adverse effects and/or MoA suspected in Box 1.

(4e) ED concern is not demonstrated but only presumed or suspected, and dataset is not sufficient for the ED evaluation to be led.

(5) It is worth noting that final decision on AF is typically pending on expert judgement and should be duly justified. Recommendations may be further specified, if possible, while pursuing the methodological work on this topic.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Supplementary material

Content

EDCs within the WFD and specifically within the guidance for deriving EQSs

Table S1 – Complete list of quotations relating to EA and ED within TGD EQS (E.C., 2018)

Analysis of EQS factsheets for the 180 chemicals universe

Table S2 : Outcome of the analysis of ED substances considered in EQS and subsequent categorisation for 180 candidates. Substances are ranked by category and alphabetical order. E.C. (2013) (2005) = EQS established by the European Commission in 2005 for priority substances and reported within the daughter Directive 2013/39/EC, E.C. (2013) (2011) = EQS established by the European Commission in 2011 for priority substances and reported within the daughter Directive 2013/39/EC ; JORF2015 + INERIS = EQS established by the French Ministry in charge of the environment based on INERIS proposal and applying for French RBSPs; VGE = Environmental Guideline Value proposed by INERIS for potential implementation as EQSs, but not legally-binding.

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Table S1 – Complete list of quotations relating to EA and ED within TGD EQS (E.C., 2018) using the following keywords : « Endocrine », « Hormone », « Estrogen » (or « Oestrogen »), « Androgen » and « Thyroid » ; TGD EQS corresponding chapters ; parameters to which quotation refers (QS derivation in general or specific relation to Assessment Factor (AF) or to tests recommended for the building of the ecotoxicity and toxicity dataset used for the EQS derivation) ; numbers of quotes in the core text or in the appendices.

Keywords	Quotes	Section	Relating to...			Nb of quotes	
			QS	AF	Tests	in core text	in App.
Endocrine	<i>If there are indications of endocrine activity (e.g. bioassays), but no studies are available that allow assessment of adverse effects through this mechanism, this should be highlighted as an uncertainty in the technical report.</i>	2. GENERIC ISSUES 2.6 Data... 2.6.1 Types of data required... 2.6.1.2 Ecotoxicological data	✓	(✓)		5	6
	Regarding the recommendation for the adoption of EQS Predicted No Effect Concentrations (PNECs) as QSs and the <i>circumstances that could prompt a review of the RAR PNEC:</i> * <i>If there is new evidence for a mode of toxic action that was not considered in the RAR e.g. new evidence of endocrine disrupting properties.</i>	2. GENERIC ISSUES 2.8 Using existing risk assessments 2.8.1 Risk assessments under Existing Substances Regulations	✓	(✓)			
	If there are indications of adverse effects via endocrine activity (e.g. <i>in vivo</i> bioassays) or other specific effects that have not been adequately reflected in bird or mammal studies used to derive the NOAELoral (e.g. only 28-day studies are available), an additional assessment factor may be considered to cover the anticipated effects.	2.9 Extrapolation 2.9.1 Mode of action	✓	✓			
	When there are indications that a substance may cause adverse effects via disruption of the endocrine system of mammals, birds, aquatic or other wildlife species, the assessor should consider whether the assessment factor would be sufficient to protect against effects caused by such a mode of action, or whether a larger AF is needed (Section 2.9.1).	3 STANDARDS TO PROTECT WATER QUALITY 3.3 Deriving a $QS_{fw, eco}$ 3.3.1 Derivation of a $QS_{fw, eco}$ 3.3.1.1 Extrapolation using AF method	✓	✓			
	When there are indications that a substance may cause adverse	3 STANDARDS TO	✓	✓			

Keywords	Quotes	Section	Relating to...			Nb of quotes	
	effects via disruption of the endocrine system of mammals, birds, aquatic or other wildlife species, it should be considered whether the assessment factor would also be sufficient to protect against effects caused by such a mode of action, or whether an increase of the factor would be appropriate.	PROTECT WATER QUALITY 3.3 Deriving a QS _{fw, eco} 3.3.2 Derivation of a QS _{sw, eco} 3.3.2.1 Extrapolation using AF method					
	Description of toxicity tests and their purpose(s)/endpoints meanings <u>Invertebrates</u> • OECD guideline 211: Daphnia magna Reproduction Test. <u>Fish</u> • OECD guideline 234: Fish Sexual Development Test. • OECD guideline 240: Medaka Extended One Generation Reproduction Test (MEOGRT) * screening tests / only be used as supporting information with regard to EQS-derivation: • OECD guideline 229: Fish Short Term Reproduction Assay • OECD guideline 230: 21-day Fish Assay <u>Amphibians</u> • cf. keyword “Thyroid” : OECD guideline 241	APPENDIX 1: DATA COLLECTION, EVALUATION AND SELECTION A1.3. TOXICITY DATA A1.3.2. Data evaluation and data tables A1.3.2.10. Use of toxicity tests performed according to established guidelines			✓		
	OECD (2012). Guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption. Series on Testing and Assessment. No. 150, OECD Environment Directorate, Paris	APPENDIX 1: DATA COLLECTION, EVALUATION AND SELECTION A1.6. REFERENCES TO APPENDIX 1			✓		
	Table 2 Existing evaluations and Regulatory information <i>Endocrine disrupter: Available information / Not investigated</i>	APPENDIX 2: PROFORMA FOR EQS DATASHEET					
Hormone*	-	-				0	0
Estrogen*	<i>Under some circumstances, a MAC-QS may not be justified, e.g. for substances that exert only sub-lethal effects after prolonged exposure. Steroid oestrogens could be one example.</i>	3 STANDARDS TO PROTECT WATER QUALITY	✓			1	0

Keywords	Quotes	Section	Relating to...			Nb of quotes	
		3.4 Deriving a MAC-QS					
Androgen*	<p>Description of toxicity tests and their purpose(s)/endpoints meanings</p> <p><u>Fish</u></p> <p>* screening tests / only be used as supporting information with regard to EQS-derivation:</p> <ul style="list-style-type: none"> • OECD Guidance document on the Androgenised Female Stickleback Screen (series on Testing and Assessment No. 148) (AFSS) 	<p>APPENDIX 1: DATA COLLECTION, EVALUATION AND SELECTION</p> <p>A1.3. TOXICITY DATA</p> <p>A1.3.2. Data evaluation and data tables</p> <p>A1.3.2.10. Use of toxicity tests...</p>			✓	0	1
Thyroid*	<p>Description of toxicity tests and their purpose(s)/endpoints meanings</p> <p><u>Amphibians</u></p> <ul style="list-style-type: none"> • OECD guideline 231: Amphibian Metamorphosis Assay (AMA) • OECD guideline 241: The Larval Amphibian Growth and Development Assay (LAGDA) 	<p>APPENDIX 1: DATA COLLECTION, EVALUATION AND SELECTION</p> <p>A1.3. TOXICITY DATA</p> <p>A1.3.2. Data evaluation and data tables</p> <p>A1.3.2.10. Use of toxicity tests...</p>			✓	0	2
Steroid*	cf. keyword "Estrogen*"	<p>3 STANDARDS TO PROTECT WATER QUALITY</p> <p>3.4 Deriving a MAC-QS</p>	✓			1	0

Analysis of EQS factsheets for the 180 chemicals universe

In consideration of the lack of prescription included in the TGD EQS regarding ED, an analysis of the state of the art was undertaken on how far and how consistently endocrine disrupting (ED) properties were considered in the derivation of EQS.

To achieve this goal, a list of 180 chemicals was compiled for which EU or national EQS were available with an explanatory document (« EQS factsheets/dossiers »).

For all 180 candidate chemicals, data were retrieved from the EQS factsheets available: EA or ED notification published within the context of an EDCs prioritisation initiatives and within the scientific literature, key information on the QSs and EQS derivation (Key study(ies) and key effect(s) considered for the calculation of QS, AF used for the calculation of QS and the reasoning-behind statement, possible additional AF applied for the purpose of consideration of ED potential of the chemical, key QS for the derivation of the EQS).

The information gathered was sequentially analysed and allowed the categorisation of existing EQS into 4 categories:

- Cat. 4: chemicals for which no ED evidence is available;
- Cat. 3: chemicals for which ED potential was notified and taken account of appropriately;
- Cat. 2 : chemicals for which the screening of the EQS value and factsheet showed that ED potential was considered but that the rationale stating choices made was not clear enough in this regard;
- Cat. 1: chemicals for which EQS did not consider endocrine activity although there are substance-specific data suggesting or evidencing such activities:
 - Cat. 1 C: no indication or consideration of the ED potential in the EQS factsheet although it exists in the scientific literature
 - Cat. 1 B: no indication or consideration of the ED potential in the EQS factsheet although it exists in a prioritisation initiative
 - Cat. 1 A: ED effects were quoted in the EQS factsheets but not considered for EQS derivation

Detailed results of this analysis are presented herein in Table S2

Table S2 : Outcome of the analysis of ED substances considered in EQS and subsequent categorisation for 180 candidates. Substances are ranked by category and alphabetical order. E.C. (2013) (2005) = EQS established by the European Commission in 2005 for priority substances and reported within the daughter Directive 2013/39/EC, E.C. (2013) (2011) = EQS established by the European Commission in 2011 for priority substances and reported within the daughter Directive 2013/39/EC ; JORF2015 + INERIS = EQS established by the French Ministry in charge of the environment based on INERIS proposal and applying for French RBSPs; VGE = Environmental Guideline Value proposed by INERIS for potential implementation as EQSs, but not legally-binding.

Substance name	CAS Number	EQS Source	CATEGORY	edlists.org (updated Sept. 2021)
Acetochlore	34256-82-1	INERIS (2014)	1A	
Alachlore	15972-60-8	E.C. (2013) (2005)	1A	
Atrazine	1912-24-9	E.C. (2013) (2005)	1A	
Chloro-4 Methylphenol-3	59-50-7	INERIS (2011)	1A	
Diuron	330-54-1	E.C. (2013) (2005)	1A	List II
Endosulfan	115-29-7	E.C. (2013) (2005)	1A	
ETU (ethylene thiouree)	96-45-7	INERIS (2015)	1A	
Fenitrothion	122-14-5	INERIS (2011)	1A	
Hexachlorobenzene	118-74-1	E.C. (2013) (2005)	1A	
Hexachlorocyclohexane (all isomers, including lindane)	608-73-1	E.C. (2013) (2005)	1A	
Lambda-cyhalothrine	91465-08-6	INERIS (2011)	1A	
Nonylphenol-4 (ramifie)	84852-15-3	E.C. (2013) (2005)	1A	List I
Nonylphenols	25154-52-3	E.C. (2013) (2005)	1A	List I
Octylphenol-para-tert-	140-66-9	E.C. (2013) (2005)	1A	List I
Octylphenols	1806-26-4	E.C. (2013) (2005)	1A	
Trichlorfon	52-68-6	INERIS (2009)	1A	
Bifentrine	82657-04-3	INERIS (2011)	1B	
C10-13-chloroalcanes	85535-84-8	E.C. (2013) (2005)	1B	
Chlorfenvinphos	470-90-6	E.C. (2013) (2005)	1B	
Cypermethrine	52315-07-8	E.C. (2013) (2011)	1B	
Nonylphenol-4-(para)-	104-40-5	E.C. (2013) (2005)	1B	List I
Pentachlorobenzene	608-93-5	E.C. (2013) (2005)	1B	
Pentachlorophenol	87-86-5	E.C. (2013) (2005)	1B	
Terbutryne	886-50-0	E.C. (2013) (2011)	1B	
Trichlorobenzene	12002-48-1	E.C. (2013) (2005)	1B	
Trifluraline	1582-09-8	E.C. (2013) (2005)	1B	
Acide perfluoro sulfone (PFOA) et ses derives (PFOS)	1763-23-1	E.C. (2013) (2011)	1C	
Anthracene	120-12-7	E.C. (2013)	1C	
Antimoine	7440-36-0	INERIS (2014)	1C	
Arsenic et composes mineraux	7440-38-2	INERIS (2015)	1C	
Benzene	71-43-2	E.C. (2013)	1C	
Cadmium et composes	7440-43-9	E.C. (2013) (2005)	1C	
Carbamazepine	298-46-4	INERIS (2012)	1C	
Chloroaniline-2	95-51-2	INERIS (2012)	1C	
Chloroforme	67-66-3	E.C. (2013)	1C	
Chlorophenol-4	106-48-9	INERIS (2011)	1C	
Chlorpyriphos-Ethyl	2921-88-2	E.C. (2013) (2005)	1C	
Dichloromethane	75-09-2	E.C. (2013) (2005)	1C	List II
Dichlorure de dibutyletain	683-18-1	INERIS (2009)	1C	
Dichlorvos	62-73-7	E.C. (2013)	1C	
Diclofenac sodium	15307-86-5	INERIS (2015)	1C	
Difenoconazole	119446-68-3	INERIS (2013)	1C	
Epoxiconazole	133855-98-8	INERIS (2011)	1C	
Fenbuconazole	114369-43-6	INERIS (2013)	1C	
Glyphosate	1071-83-6	JORF2015 + INERIS (2014)	1C	
Hexachlorobutadiene	87-68-3	E.C. (2013) (2005)	1C	
Hexaconazole	79983-71-4	INERIS (2011)	1C	
Mercure et composes	7439-97-6	E.C. (2013) (2005)	1C	
Naphtalene	91-20-3	E.C. (2013) (2011)	1C	

Substance name	CAS Number	EQS Source	CATEGORY	edlists.org (updated Sept. 2021)
Nickel	7440-02-0	E.C. (2013) (2011)	1C	
Oxyde d'heptachlore (cis)	1024-57-3	E.C. (2013) (2011)	1C	
Oxydemeton-methyl	301-12-2	INERIS (2009)	1C	
Paraquat	4685-14-7	INERIS (2012)	1C	
Penconazole	66246-88-6	INERIS (2013)	1C	
Pendimethaline	40487-42-1	JORF2015 + INERIS (2015)	1C	
Plomb	7439-92-1	E.C. (2013) (2011)	1C	
Propiconazole	60207-90-1	INERIS (2015)	1C	
Pyrimethanil	53112-28-0	INERIS (2011)	1C	
tebuconazole	107534-96-3	JORF2015 + INERIS (2011)	1C	
Terbutylazine	5915-41-3	INERIS (2011)	1C	
Triclosan	3380-34-5	INERIS (2012)	1C	List II
2,4,5-T	93-76-5	INERIS (2013)	2	
Carbendazime	10605-21-7	INERIS (2011)	2	
Chlordane	57-74-9	INERIS (2012)	2	
Chlordecone	143-50-0	JORF2015 + INERIS (2013)	2	
Composes du tributyletain	688-73-3	E.C. (2013) (2005)	2	
Dibromoethane-1,2	106-93-4	INERIS (2009)	2	
Dimethoate	60-51-5	INERIS (2009)	2	
Epichlorohydrine	106-89-8	INERIS (2009)	2	
octaBDE	32536-52-0	E.C. (2013) (2011)	2	
pentaBDE	32534-81-9	E.C. (2013) (2011)	2	
Simazine	122-34-9	E.C. (2013) (2005)	2	
Tributyletain cation	36643-28-4	E.C. (2013) (2005)	2	
2,4-D (including 2,4-D salt and esters)	94-75-7	JORF2015 + INERIS (2012)	3	
Aminotriazole	61-82-5	JORF2015 + INERIS (2011)	3	
Di(2-ethylhexyl)phtalate (DEHP)	117-81-7	E.C. (2013) (2005)	3	List I
Dichloroaniline-3,4	95-76-1	INERIS (2012)	3	
Dicofol	115-32-2	E.C. (2013) + INERIS (2012)	3	
Heptachlore	76-44-8	E.C. (2013) (2011)	3	
Iprodione	36734-19-7	JORF2015 + INERIS (2015)	3	
Linuron	330-55-2	JORF2015 + INERIS (2009)	3	
Mancozebe	8018-01-7	INERIS (2014)	3	List I
Omethoate	1113-02-6	INERIS (2009)	3	
Perchlorate d'ammonium	7790-98-9	INERIS (2012)	3	List II
Procymidone	32809-16-8	INERIS (2011)	3	
Propanil	709-98-8	INERIS (2009)	3	
Acide monochloroacetique	79-11-8	INERIS (2013)	4	
Aclonifen	74070-46-5	E.C. (2013) (2011)	4	
AMPA	1066-51-9	JORF2015 + INERIS (2014)	4	
azoxystrobine	131860-33-8	JORF2015 + INERIS (2011)	4	
bentazone	25057-89-0	JORF2015 + INERIS (2009)	4	
Benzidine	92-87-5	INERIS (2013)	4	
Bifenox	42576-02-3	E.C. (2013) (2011)	4	
Biphenyle	92-52-4	JORF2015 + INERIS (2013)	4	
Boscalid	188425-85-6	JORF2015 + INERIS (2014)	4	
Chloro-1 Dinitrobenzene-2,4	97-00-7	INERIS (2012)	4	
Chloro-4 Nitroaniline-2	89-63-4	INERIS (2012)	4	
Chloroaniline-3	108-42-9	INERIS (2011)	4	
Chloroaniline-4	106-47-8	INERIS (2011)	4	
Chloronaphtalene-1	90-13-1	INERIS (2011)	4	
Chloronaphtalene-2	91-58-7	INERIS (2011)	4	
Chloronitrobenzene-1,2	88-73-3	INERIS (2012)	4	
Chloronitrobenzene-1,3	121-73-3	INERIS (2012)	4	
Chloronitrobenzene-1,4	100-00-5	INERIS (2011)	4	
Chlorophenol-2	95-57-8	INERIS (2012)	4	
Chlorophenol-3	108-43-0	INERIS (2011)	4	
Chlorotoluene-2	95-49-8	INERIS (2012)	4	
Chlorotoluene-3	108-41-8	INERIS (2011)	4	
Chlorotoluene-4	106-43-4	INERIS (2009)	4	
chlorprophame	101-21-3	JORF2015 + INERIS (2014)	4	

Substance name	CAS Number	EQS Source	CATEGORY	edlists.org (updated Sept. 2021)
Chlortoluron	15545-48-9	JORF2015 + INERIS (2013)	4	
Chlorure de vinyle	75-01-4	INERIS (2009)	4	
Cybutryne	28159-98-0	E.C. (2013) (2011)	4	
Cyproconazole	94361-06-5	INERIS (2011)	4	
Cyprodinil	121552-61-2	JORF2015 + INERIS (2011)	4	
Dicamba	1918-00-9	INERIS (2011)	4	
Dichlorobenzidine-3,3'	91-94-1	INERIS (2013)	4	
Dichloro-di-isopropyl ether	108-60-1	INERIS (2012)	4	
Dichloroethane-1,2	107-06-2	E.C. (2013) (2005)	4	
Dichloroethene-1,2	540-59-0	INERIS (2009)	4	
Dichloroethylene-1,1	75-35-4	INERIS (2015)	4	
Dichloronitrobenzene-2,3	3209-22-1	INERIS (2009)	4	
Dichloronitrobenzene-2,4	611-06-3	INERIS (2009)	4	
Dichloronitrobenzene-3,4	99-54-7	INERIS (2009)	4	
Dichloropropene-1,3	542-75-6	INERIS (2009)	4	
Dichlorprop	120-36-5	INERIS (2009)	4	
Diflufenicanil	83164-33-4	JORF2015 + INERIS (2012)	4	
Dimethenamide	87674-68-8	INERIS (2011)	4	
Dimethenamid-P	163515-14-8	INERIS (2011)	4	
Dimethomorphe	110488-70-5	INERIS (2011)	4	
EDTA	60-00-4	INERIS (2012)	4	
Flufenacet	142459-58-3	INERIS (2015)	4	
Flumioxazine	103361-09-7	INERIS (2015)	4	
Fluoranthene	206-44-0	E.C. (2013) (2011)	4	
Fluroxypyr	69377-81-7	INERIS (2015)	4	
Fluroxypyr methyl heptyl ester	81406-37-3	INERIS (2015)	4	
Formaldehyde	50-00-0	INERIS (2011)	4	
HexaBromoCycloDoDecane (HBCDD)	25637-99-4	E.C. (2013) + INERIS (2012)	4	
Hexabromocyclododecane-1,2,5,6,9,10	3194-55-6	E.C. (2013) (2011)	4	
Hexabromocyclododecane-alpha	134237-50-6	E.C. (2013) (2011)	4	
Hexabromocyclododecane-beta	134237-51-7	E.C. (2013) (2011)	4	
Hexabromocyclododecane-gamma	134237-52-8	E.C. (2013) (2011)	4	
Hexachlorocyclohexane alpha	319-84-6	E.C. (2013) (2005)	4	
Hexachloroethane	67-72-1	INERIS (2009)	4	
Imazalil	35554-44-0	INERIS (2015)	4	
Imidaclopride	138261-41-3	JORF2015 + INERIS (2011)	4	
Isopropylbenzene	98-82-8	INERIS (2012)	4	
Isoproturon	34123-59-6	E.C. (2013) (2005)	4	
Isoxaben	82558-50-7	INERIS (2014)	4	
Isoxaflutole	141112-29-0	INERIS (2015)	4	
MCPA-2,4	94-74-6	JORF2015 + INERIS (2013)	4	
Mecoprop	93-65-2	INERIS (2013)	4	
Metaldehyde	108-62-3	JORF2015	4	
Metamitron	41394-05-2	INERIS (2011)	4	
metazachlore	67129-08-2	JORF2015 + INERIS (2011)	4	
Methabenzthiazuron	18691-97-9	INERIS (2011)	4	
Methamidophos	10265-92-6	INERIS (2012)	4	
Monochloramine	10599-90-3	INERIS (2009)	4	
Monolinuron	1746-81-2	INERIS (2009)	4	
Nicosulfuron	111991-09-4	JORF2015 + INERIS (2011)	4	
Oxadiazon	19666-30-9	JORF2015 + INERIS (2014)	4	
Oxyde de dibutyletain	818-08-6	INERIS (2011)	4	
Oxyfluorfe	42874-03-3	INERIS (2014)	4	
Phosphate de tributyle	126-73-8	JORF2015 + INERIS (2013)	4	
Phoxime	14816-18-3	INERIS (2009)	4	
Prosulfocarbe	52888-80-9	INERIS (2014)	4	
Pyrazon/chloridazon	1698-60-8	INERIS (2009)	4	
Quinoxyfen	124495-18-7	E.C. (2013) + INERIS (2011)	4	
Rimsulfuron	122931-48-0	INERIS (2011)	4	
Sulcotrione	99105-77-8	INERIS (2011)	4	
Tetrachloroethane-1,1,2,2	79-34-5	INERIS (2013)	4	

Substance name	CAS Number	EQS Source	CATEGORY	edlists.org (updated Sept. 2021)
Tetraconazole	112281-77-3	INERIS (2011)	4	
Thiabendazole	148-79-8	JORF2015	4	
Toluene	108-88-3	JORF2015 + INERIS (2009)	4	
Triazole-1,2,4	288-88-0	INERIS (2015)	4	
Trichloroethane -1,1,2	79-00-5	INERIS (2013)	4	
Trichlorophenol-2,4,5	95-95-4	INERIS (2012)	4	
Trichlorotrifluoroethane-1,1,2	76-13-1	INERIS (2013)	4	
Triclopyr	55335-06-3	INERIS (2011)	4	
Xylenes	1330-20-7	JORF2015 + INERIS (2009)	4	