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Evaluating the usefulness of existing environmental threshold concentrations (ETCs), with a focus on pharmaceuticals in surface water: a European perspective

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Abstract

Environmental Threshold Concentrations (ETCs), such as the Predicted No Effect Concentrations (PNECs) and European Environmental Quality Standards (EQSs), represent the concentration of a chemical in an environmental compartment at or below which no adverse effects are expected. While multiple ETCs may exist for a given substance across regulatory frameworks and scientific literature, selecting the most useful value can be challenging. Even when only one ETC exists, its usefulness must be evaluated. This paper addresses this challenge by providing a systematic and stepwise framework for selecting and interpreting ETCs, with a focus on human pharmaceuticals and European regulatory frameworks. However, the ideas behind this may be applied more broadly. The proposed approach begins by defining the context of the assessment and the associated protection goals. It then requires a systematic evaluation of all available ETCs, regarding their relevance and reliability. This includes the use of the most appropriate methodology and underlying data, as well as newly published information. It also considers overall uncertainties, the need to address chronic or short-term peak exposures, and whether the ETCs have been independently reviewed. We apply the framework to metoprolol to demonstrate its usefulness in ensuring that ETCs used in environmental assessments and management decisions are robust and fit for purpose.

Keywords Effects, Ecotoxicity, Risk assessment, Threshold concentrations, Pharmaceuticals

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Introduction

Environmental risk assessment aims to evaluate the impact of chemicals on ecosystems and human health, and is one of the tools that assist regulators and risk managers in decision making. In environmental risk assessment, measured or predicted concentrations of a substance in a given environmental compartment are typically compared with the concentration at or below which no adverse effects on the ecosystem are expected [1]. This concentration is often referred to as the Predicted No Effect Concentration (PNEC) [2–4], but other terms, such as Environmental Quality Standard (EQS) [5], Environmental Risk Limit, Water Quality Guideline, or Guidance Value, are also used depending on the regulatory context or formal status. In this paper, we use the term Environmental Threshold Concentration (ETC).

ETCs for active substances in human pharmaceutical products (further referred to as pharmaceuticals) may be available as PNECs reported in the (European) Public Assessment Reports (EPARs or PARs), reported by the European Medicines Agency (EMA) and national agencies. Since the marketing authorisation in the EU is product-based, and the same pharmaceutical may be used in products developed by different companies, several PNECs may be reported for the same pharmaceutical [6]. ETCs may also be available through pharmaceutical authorisation procedures in other geographic regions and jurisdictions. Since the active substances in pharmaceutical products may also be used for various purposes (e.g., veterinary pharmaceuticals, biocides, plant protection products, industrial chemicals), ETCs may have been derived in other regulatory frameworks with their own methodologies. Additionally, ETCs for pharmaceuticals may have been derived within the context of (inter) national environmental policy, or reported in public databases or peer-reviewed literature.

ETCs are usually based on experimental (eco)toxicity data, although sometimes in silico data or data generated by read-across approaches are used [7]. The basic approach to derive an ETC is similar across different frameworks, but differences exist in protection goals, purpose and formal status (e.g., screening values or legally binding standards). As a consequence underlying data requirements and methods may differ. This can result in multiple ETC values for individual compounds that can vary by orders of magnitude, which happens for pharmaceuticals [8, 9] as well as other compounds [10, 11]. As a result, it may be unclear for regulators as well as stakeholders (e.g., water managers, health care professionals) which ETC to select for the environmental risk assessment and subsequent management measures. Also, even when only one ETC exists, it must still be evaluated prior to use.

The IMI2 PREMIER project [12] is developing a Digital Assessment System (DAS) for identifying and addressing the environmental risks posed by pharmaceuticals. This includes the development of practical guidance for conducting a systematic and transparent risk assessment, including the evaluation of existing ETCs to select appropriate values. This paper reviews the differences between various existing ETCs. While stakeholders may also decide to derive new ETCs, this is not in scope of our publication. Deriving a new ETC, especially if new data has to be retrieved and evaluated, is much more time intensive and demands more and specific expertise, than the evaluation of existing ETCs. Thus, we focus on the evaluation of existing ETCs and provide a stepwise approach to determine their usefulness for the environmental risk assessment and subsequent risk management of human pharmaceuticals. We then apply this approach to metoprolol as a case study. Our focus is on the EU ETCs for protecting freshwater ecosystems from direct ecotoxicity (not addressing risks from food chain transfer or drinking water intake). However, the general principles of this approach can be applied to ETCs for other (micro)pollutants, environmental compartments, and geographical regions, as well as in other jurisdictions. To our knowledge, where multiple authors have shown that ETCs may differ within and between frameworks [8, 9, 11], and some recommendations are provided on evaluating their usefulness [13], a systematic and transparent assessment system like the one that we suggest is still lacking.

Existing regulatory ETCs in the European Union

Overview of ecotoxicological ETCs for freshwater

ETCs for the protection of surface waters are derived for prospective risk assessments in the context of market authorisation or for retrospective water quality assessments. Table A-1 (Supplemental file 1) provides an overview of EU regulatory ETCs for freshwater, which may be available for pharmaceuticals. These ETCs may have been derived in the context of authorisations of human pharmaceuticals (Directive 2001/83/EC; associated guidance [4]) and veterinary pharmaceuticals (Regulation EU 2019/6; [14]), and for the priority (hazardous) substances under the Water Framework Directive (2000/60/EC; [5]). Other relevant frameworks include the Biocidal Products Regulation (EU 528/212; [3]), the Plant Protection Products regulation (EC 1107/2009; [15]) and the REACH regulation for industrial chemicals (EC 1907/2006; [2]).

For the EU human pharmaceutical marketing authorisation, a PNEC is derived for chronic exposure, and should be based on chronic ecotoxicity tests. In contrast, a PNEC under REACH and an EU Water Framework Directive AA-EQS (Annual Average Environmental

Quality Standard) for chronic exposure may be derived based on both acute and chronic data as well as based on mesocosm data. To derive an ETC, varying assessment factors are applied which depend mainly on the data available, the application of which may vary across frameworks and jurisdictions. National authorities in and outside of the EU and the scientific community may apply similar procedures, but methods may differ depending on the purpose and context. An in-depth analysis of data requirements and assessment procedures can be found in Oltmanns, Macherey [17] for the EU and in Ceger, Garcia-Reyero Vinas [18] for the USA. Belanger, Beasley [19] identified global differences in the use of assessment factors and focused on the differences in PNEC derivation logic between the USA and EU. Although the common protection goal is freshwater ecosystem health and many aspects of ETC derivations may be similar, seemingly small differences in methodology can result in significant variations in ETCs for the same compound [9], and in how these values should be interpreted and used.

Differences between ETCs: methodological aspects

For pharmaceuticals in the EU, ETCs are usually derived with a deterministic approach, using a limited set of ecotoxicity data and pre-defined assessment factors. Generally, the most critical (lowest) NOEC (No Observed Effect Concentration) or, preferably, EC10 (estimated concentration at which 10% effect is observed as compared to the control) is the point of departure for chronic ETCs (e.g., as for marketing authorisations of pharmaceuticals according to the EMA guidance [4]). Similarly, acute ETCs are based on the lowest of the available L(E)C50s (concentrations with 50% lethality or effect). The application of an assessment factor (AF) accounts for inter- and intra-species variation, inter- and intra-laboratory variation, acute-to-chronic extrapolation (where applicable), and extrapolation from laboratory to field data [5]. For the marketing authorisation of human pharmaceuticals an ETC for chronic exposure is based on chronic ecotoxicity tests involving at least three trophic levels, and an assessment factor of 10 [4]. In other regulations and frameworks, the size of the AF depends on the amount and type of data available (see Table A-1 in Supplemental file 1). For example, it may be reduced from 1000 for a limited set of acute toxicity values to 10 if chronic toxicity values for at least three trophic levels are present [2, 5].

Besides the deterministic approach described above, two other approaches can be used to derive an ETC: a probabilistic approach using Species Sensitivity Distributions (SSD), and using field data or mesocosm multispecies tests. In principle, there is nothing precluding the use of these methods when deriving ETCs for pharmaceuticals, but their relevance is limited as yet due to absence of data. Therefore, these refinements will not be discussed further.

Most EU frameworks include a separate assessment of secondary poisoning of birds and mammals in the case of bioaccumulating substances, resulting in separate ETCs. However, under the EU Water Framework Directive, the quality standard for direct ecotoxicity is compared to those for secondary poisoning and human exposure via fish consumption, and the lowest of these values is then taken forward as the final EQS [5]. In addition, in waters that may be used for the abstraction of drinking water, a standard for exposure of humans via drinking water is also added. Therefore, when comparing ETCs derived from varying regulations, it is important to consider which protection goals were taken into account when deriving the ETC.

Differences between ETCs: influence of underlying data

Besides generic differences in derivation methods described above, selection and treatment of data can also result in differences between ETCs.

Endpoints. Although this is not always explicitly stated in guidance documents, the majority of aquatic ecotoxicity data in the EU regulatory frameworks reflects endpoints that are traditionally considered population-relevant, such as mortality, growth, and reproduction. For example, in the Water Framework Directive EQS guidance [5], this is explicitly described in the main document with examples in its Annex A1. ETCs published in the peer-reviewed literature may include additional endpoints, such as behavioural responses, changes in biochemical or molecular biomarkers, and 'omics approaches. The inclusion of such endpoints in ETCs needs to be considered in relation to their population relevance and the protection goal.

Test type. The acceptance and use of in vitro studies and in silico data varies between frameworks. Quantitative Structure–Activity Relationships (QSARs) and read-across can be used under REACH to assist with data evaluation, to decide whether further testing is needed and to optimise the testing strategy [20, 21]. However, the results of QSARs may be less applicable to pharmaceuticals, as chronic toxicity for specific mechanisms of action may fall outside the application domain of the QSAR method. For the marketing authorisation of human pharmaceuticals, only chronic in vivo ecotoxicity data are used, and the use of in vitro or in silico tests is currently not accepted [4]. According to the Water Framework Directive, QSARs can provide supporting information, but they cannot be used to derive ETCs [5].

Sources and quality assessment of data. Historically, regulatory frameworks for marketing authorisation required that all ecotoxicity studies be performed under

Good Laboratory Practice (GLP) [17] and using validated test methods such as OECD (Organisation for Economic Co-operation and Development) test guidelines. However, this requirement has recently become less stringent, with the marketing authorisation of pharmaceuticals now stipulating the use of all available relevant and reliable data, although newly generated industry data should still adhere to OECD test guidelines and GLP. This is in line with assessments performed in the context of other regulations, such as the Water Framework Directive and for plant protection products.

ETCs derived outside of regulatory frameworks and published in peer-reviewed literature or online databases (e.g., the NORMAN Network [22]) may vary widely in the data sources used. These sources range from the use of QSARs or endpoints obtained experimentally in the study itself, to extensive literature reviews. Differences in data search strategies can lead to substantial variations in the datasets used for ETC derivation, resulting in different values even when the methods are comparable [9, 23, 24].

In regulatory frameworks, the relevance and reliability of the available ecotoxicity studies are evaluated using generic ranking systems [25, 26], or framework- and test-specific assessment tools [27–29]. For marketing authorisation of pharmaceuticals, toxicity tests should be evaluated according to the CRED method or a similar approach [4, 26]. In this case, GLP is not a strict requirement, which enables the use of peer-reviewed data as research in academic settings may not always be under GLP and/or follow OECD test guidelines. ETCs reported in peer-reviewed literature or databases may vary in how the data evaluation was performed. Unfortunately, this is not always transparently reported, but it may be described in supplementary information or in the relevant database structure. Failing to consider data quality issues may result in ETCs that are less reliable or even erroneous, making them irrelevant or even unenforceable. However, in cases of incidents or prioritisation exercises where an indicative screening value is sufficient, the evaluation of each individual study may be omitted or only performed on the most critical values.

Data handling. Regulatory frameworks may differ in the way results for the same endpoint/species are aggregated. In principle, the lowest reliable ecotoxicity effect value is used as a basis for ETC derivation when using the deterministic approach. Some EU frameworks stipulate that toxicity values may be aggregated into a geometric mean when multiple reliable data are available for the same species and the same endpoint, provided that life stage, test duration, and conditions are comparable [2, 3, 5], but this is not foreseen in the ERA for marketing authorisation of pharmaceuticals [4]. Other frameworks may allow for data aggregation at a higher level of biological organisation. For example, a geometric mean may be derived for different fish or invertebrate species in the regulatory assessment of plant protection products [15, 30], or for different species within a genus when water quality criteria are derived by the US EPA [31].

Expert judgement. As there is room for interpretation in all the above aspects, expert judgement is critical. Depending on the issue, there may be more than one interpretation. This means that two risk assessors using the same data and the same risk assessment methodology may reach two different conclusions, both of which could be legitimate, depending on the context of their assessment. For example, tests on different life stages of an organism may be evaluated to differ or not, leading to the aggregation or non-aggregation of the data on this species, and the subsequent derivation of differing ETCs.

Evaluation of the usefulness of ETCs

To identify whether an ETC is useful for risk assessment purposes, or to determine which is the most useful ETC in case of multiple values, a stepwise approach is suggested (Fig. 1). The evaluation of ETCs begins with determining the aim of the risk assessment and identifying available ETCs, followed by an evaluation of the transparency to determine whether all necessary information has been reported. In the next phase, the relevance, reliability and other considerations are evaluated. As some of these considerations overlap, these evaluations may be performed in parallel. In some cases, only a relevance is necessary and the other steps can be ignored, e.g., when a soil ETC is derived and the assessment is for freshwater. In the final phase, a conclusion is drawn on the usefulness of the assessed ETC(s). An Excel template to facilitate this evaluation is provided in the additional information (Supplemental file 2). Our approach is aimed at ETCs for fresh surface waters but could be generalized for other compartments.

In line with evaluation methods for ecotoxicity data (e.g., [26]), relevance and reliability are essential elements.

The ***relevance*** of an ETC can be defined as covering the extent to which ETCs are appropriate for a particular risk assessment goal, e.g., an ETC for acute toxicity in soil is not relevant to assess risks of chronic exposure in surface water. The relevance of an ETC is case-dependent and must be evaluated in the context of the goal of the risk assessment, for example a regulatory risk assessment for marketing authorisation, water quality assessment, discharge permitting, incident handling, prioritisation, or other (scientific) aims. Each of these purposes may differ in the desired aim and level of protection, and data requirements to meet these.

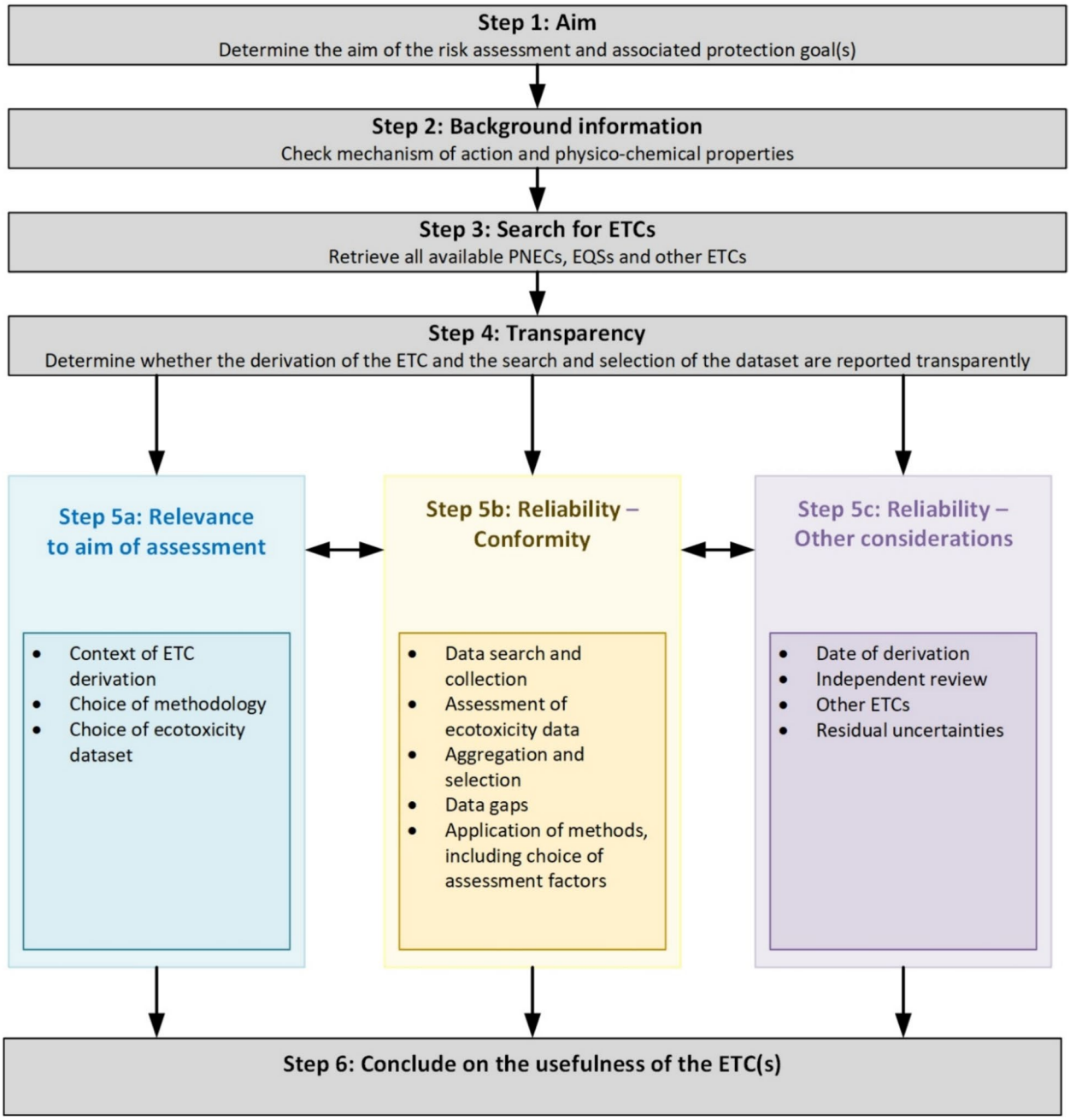


Fig. 1 Stepwise approach for the evaluation of Environmental Threshold Concentrations (ETCs)

The ***reliability*** of an ETC refers to whether it has been derived in conformity with the relevant methods (where applicable, compliant with the relevant guidance document), using data and evaluation methods that are recognised as robust and science-based. Other aspects of reliability are the overall uncertainties, newly published information or methodologies. Besides this, trust in the ETC may also be increased if the ETC has been derived conform the relevant methodology, if it has been independently reviewed, and if the review has not been biased or agenda-driven.

Since the purpose of the risk assessment determines what constitutes an appropriate ETC, there is no single answer to the question of whether an ETC is relevant; for another purpose, a previously non-relevant ETC may become highly relevant. Reliability may also be

considered as a relative term. In time, the likelihood of new data being generated increases. Even if every step in the derivation process followed the regulatory procedures at the time, the reliability of ETCs that were derived in the past could be questioned, given that new studies may have become available. Furthermore, scientific insights and/or guidance documents may have changed.

Transparent reporting of how and when data were collected and collated, and how the ETC was derived, is essential for the evaluation. Others must be able to assess the data on which an ETC is based and must be able to follow the quantitative derivation of the ETC. Adhering as much as possible to FAIR principles (Findable, Accessible, Interoperable, Reuseable [32]) may be helpful. The OECD recently released the "Guidance Document 417 on the Generation, Reporting and Use of Research Data for Regulatory Assessment". This document describes the lifecycle of research data in detail, from production to regulatory uptake, highlighting core considerations for researchers, assessors, and other stakeholder groups [33].

Step 1: Determine the aim of the assessment and associated protection goals

The context and aim of the risk assessment must be determined, as this information is required for the relevance evaluation and informs the next steps. It is important to establish whether the ETC is to be used within a specific regulatory framework, and which compartment is to be assessed (e.g., freshwater or marine water). It is also important to establish whether the ETC should address acute or chronic exposure, and which protection goals are to be addressed (e.g., direct ecotoxicity only, or protection goals such as secondary poisoning (Supplemental file 1)).

Step 2: Collect background information

Understanding the mode of action can also help to determine whether the ETC adequately covers potentially sensitive species or endpoints. For example, this could involve considering certain life stages in fish in the case of endocrine active substances. For pharmaceuticals, information about the API can be found in the Summary of Product Characteristics (SmPC) and/or the environmental risk assessment section of the (E)PAR. For centrally authorised products, EPARs are published on the European Medicines Agency's website, while (E)PARs for national or decentral authorised products are published by (some) national agencies. Like for evaluating individual studies, some basic knowledge on physico-chemical properties of the substance, such as volatility, lipophilicity and degradability may inform about the substance's fate and behaviour in test systems and the environment.

Step 3: Search for available ETCs

Depending on the aim, the search for available ETCs may be narrow or wide. In some regulatory frameworks, only ETCs derived within that same framework can be used, so a wider search may not be necessary. On the other hand, stakeholders like water managers typically do not derive an ETC themselves, but rather search for available ETCs in various sources before deciding which one to use.

Regulatory-derived ETCs may be found on the website of the responsible regulatory authority (See Supplemental file 1 for an overview), or they may be published separately in legal documents (e.g., specific directives and regulations), or in publications that support such legal documents (e.g., EFSA opinions). For human pharmaceuticals authorised after the environmental risk assessment became mandatory in 2006, PNECs derived within marketing authorisation procedures are sometimes published in the (E)PAR. However, even for the fraction of substances with data in the (E)PARs, some effort is typically required to locate them, as the environmental risk assessment is reported per product and not per substance. Furthermore, some (E)PARs refer to an environmental risk assessment for a different product without specifying which product this is. For pharmaceuticals with other uses, ETCs may also be available in other regulatory frameworks (Supplemental file 1). ETCs may also be retrieved from the peer-reviewed literature and grey literature, the websites of marketing authorisation holders, and databases such as Fass [34], Norman [22], and the PREMIER project database [12]. For pharmaceuticals authorised before 2006, databases and the peer-reviewed literature may be the only sources. Useful keywords when searching for ETCs include (both derivations and full text): PNEC, EQS, RAC (Regulatory Acceptable Concentration), quality standard, environmental risk limit, guidance value, environmental thresholds, or similar (Supplemental file 1). Preferably, the search method is also documented so it can be reviewed, repeated, and/or expanded.

Step 4: Evaluate the transparency of the ETC derivation

Transparent documentation of how the ETC is derived is crucial for deciding on its usefulness. Even if the derivation is straightforward and uses limited data, clarity about data sources and collection methods remains critical. As datasets grow, expert judgement increasingly influences the compilation, evaluation, selection and weighing of data. Without sufficient documentation, the relevance and reliability of an ETC cannot be properly evaluated, limiting its usefulness.

The collection strategy for the dataset used to derive the ETC should be documented. This should include details of the data sources (e.g., scientific and regulatory databases, grey literature, and industry data), the search strings used, and the selection or exclusion criteria applied. The date of data collection should also be included, as new information may have been published since the ETC was derived (see Step 6). While ETC derivations do not require the same rigour as systematic literature reviews, applying established methods on search and reporting strategies can improve transparency and reliability [35, 36].

An overview of the collected data is necessary to confirm the appropriateness of the decisions made during the ETC derivation process. This applies to both the selected values and the deselected values. Evaluation of some of the aspects in Step 5 is only possible if the collected data are accessible.

Step 5a: Evaluate the relevance of ETCs

As many aspects of relevance and reliability interact, steps 5a, 5b and 5c are usually evaluated in parallel. The relevance evaluation (Table 1) is strongly linked to step 1, as it aims to establish whether the ETC derivation approach is appropriate for the purpose at hand, considering the aim and level of protection. The aspects that should be taken into account when evaluating the relevance of an ETC are summarised in Table 1 and further described below.

5a-1: context of the ETC derivation: relevant (non-)regulatory frameworks and associated guidance documents

Derived in a regulatory context. ETCs derived within a particular regulatory context can be considered relevant to that framework, provided that the applicable guidance document is followed. However, even if the guidance document is not followed, in some cases there may be legal requirements to use that specific ETC. Regulatory guidance from frameworks not specifically aimed at human pharmaceuticals may not always address the needs associated with a specific pharmacological mechanism of action. Therefore, ETCs derived from different regulatory frameworks cannot be used interchangeably without careful consideration. For example, under the Water Framework Directive and REACH, an ETC for chronic toxicity can be derived using acute ecotoxicity data and additional assessment factors that implicitly assume an acute-to-chronic ratio of 10 (Supplemental file 1). For most substances that would be protective enough, but not for pharmaceuticals with specific chronic mechanisms of action [37]. In such cases, expert judgment is needed to assess whether the ETC based on acute data only, despite its higher assessment factor, is still protective for the given protection goal.

If ETCs are based on refined effect assessment approaches, such as SSDs or mesocosms, careful consideration is required due to differences in the guidelines for using these methods across regulatory frameworks. Although mesocosms or SSDs are rarely performed for pharmaceuticals, they may be available for e.g., plant protection products, where different regulatory guidance applies for SSDs [15]. In addition, it should be noted that adapting regulatory guidance to new scientific insights, such as specific fungal ecotoxicity, behavioural effects, or new study protocols to assess specific endocrine effects, can take considerable time. Therefore, regulatory acceptance of an ETC should not be the sole basis for judging its relevance.

Derived in a non-regulatory context. ETCs derived in a non-regulatory context, such as in a peer-reviewed publication, are not required to adhere to regulatory guidance documents or formal methodologies. In practice, however, they often do so without explicitly stating it. Non-regulatory derived ETCs that point to critical endpoints relevant for a particular risk assessment, may also be useful and acceptable in a regulatory setting.

5a-2: choice of methodology, relating to protection goal and exposure scenarios

When using ETCs outside of the framework for which they were derived, it is critical to examine the methods used to derive the ETC and to evaluate whether they align with the assessment's objective. For example, PNECs for secondary poisoning could be relevant for the marketing authorisation of human pharmaceuticals with high lipophilicity, and an AA-EQS should preferably be compared to an exposure metric that reflects chronic exposure. ETCs for direct ecotoxicity, however, are not relevant if

Table 1 Aspects to consider when evaluating the relevance of an ETC

Number	Aspect for relevance evaluation
5a-1	Context of the ETC derivation: relevant (non)regulatory frameworks and associated guidance documents
5a-2	Choice of methodology, relating to the protection goal and exposure scenarios
5a-3	Choice of ecotoxicity dataset, corresponding to the aim of the assessment

there is an interest in secondary poisoning. ETCs from various frameworks or jurisdictions may be derived using design criteria that refer to different exposure profiles.

Another aspect to consider is the timescale of the risk assessment in relation to the exposure scenario. ETCs for acute exposure are relevant for incidental emission events at e.g., manufacturing locations, but are usually not protective when assessing continuous discharges of pharmaceuticals via wastewater treatment plants. Conversely, ETCs derived for chronic exposure like the AA-EQS mentioned above, will not only offer protection against chronic exposure, but also against acute peak exposures [5]. However, although these ETCs would indeed be protective from an environmental perspective, they may be overprotective and undesirable from an economic or societal perspective, and in that sense may sometimes not be considered relevant.

5a-3: choice of ecotoxicity dataset, corresponding to the aim of the assessment

When evaluating the dataset underlying the ETC derivation, the key question is whether the ecotoxicity data (i.e., organisms and endpoints) are consistent with the aim of the assessment and its protection goal. Depending on the research questions, ETCs published in the peer-reviewed literature may include methodologies and endpoints not currently accepted in regulatory contexts. Such ETCs should undergo critical assessment for use in other contexts (e.g., QSAR predictions should not overrule relevant experimental data, and non-standard datasets should be carefully evaluated in terms of the robustness of the assays and endpoints). As science progresses and our knowledge expands, our view of which endpoints are relevant for a particular protection goal also expands, as does our view on the robustness of the methods used to assess these endpoints. Examples are current discussions on behavioural effects in environmental risk assessment [38–40] and immune ecotoxicology [41].

When evaluating the relevance of data, consideration should also be given to the mechanism of action of the substance (Step 2). This will help identify any potential data gaps, which will be part of the reliability evaluation in Step 5b-4. If no relevant ETC is found, it may be necessary to derive a new ETC.

Step 5b. evaluate the reliability of ETCs—conformity

In this step, the reliability of the ETC is evaluated regarding its conformity to the relevant methodology. This depends on whether the approach to derive an ETC has been applied accurately, e.g., following the regulatory or scientific procedures matching the goal of the assessment (see step 5a-1 and Table 2), with any deviations scientifically justified. Transparent reporting (Step 4) is essential to demonstrate that the procedure has been applied accurately. When no guidance document has been used, the reliability evaluation adopts a more interactive process along with the relevance evaluation (Step 5a).

Table 2 Aspects to consider when evaluating the reliability of an ETC

Number	Aspects for reliability evaluation—conformity
5b-1	Data search and collection
5b-2	Assessment of ecotoxicity data
5b-3	Aggregation and selection of ecotoxicity values
5b-4	Data gaps
5b-5	Application of methods, including choice of assessment factors

The reliability of the ETC does not depend solely on whether it is derived according to regulatory guidance, but additionally it should also be determined by the scientific rigor and robustness of the underlying approach. While adherence to regulatory guidance can support the development of a reliable ETC, clearly justified and well-supported deviations may be equally, or even more, appropriate in certain cases. This should only be done if scientifically justified, using expert judgement, and one should be aware that this would be a source of inconsistency, which may be undesired.

5b-1: data search and collection

For ETCs derived according to specific methods or (regulatory) guidance, the assessment should clearly demonstrate compliance with these methods or guidance. For instance, if the use of all available data is required, the reported search strategy should demonstrate this clearly. The selection and exclusion criteria for dataset compilation (e.g., freshwater vs. marine species, inclusion of non-standard behavioural studies, and adherence to GLP) should have been correctly applied, with any deviations fully justified.

5b-2: assessment of ecotoxicity data

Conform the framework for which the assessment is performed and the purpose of the risk assessment, all or only the critical ecotoxicity studies identified may need to be evaluated for relevance and reliability. Evaluation considerations include: the methods used to assess the relevance and reliability of the ecotoxicity studies underlying the ETC (e.g. [26]); whether all available studies were evaluated or only selected key studies; and whether evaluations were based on full study reports or on summaries. It should also be noted that the results of relevance and reliability assessments of underlying data are not always detailed directly in (public) assessment reports,

but the procedures followed may instead be documented within the relevant guidance document.

In deterministic approaches, the reliability of the critical value used for ETC derivation is an important factor when determining the reliability of the ETC, whereas the reliability of other individual datapoints mainly influence the choice of assessment factors (which depends on the availability of reliable data for different taxonomic groups). From a pragmatic perspective, it may sometimes be sufficient to evaluate only the most critical study or studies. However, a large, consistent dataset, even if it has not been fully evaluated, may offer greater confidence than a small but thoroughly evaluated dataset. However, datasets with conflicting results always require careful evaluation, not only of the most critical studies. Thus, when comparing ETCs, greater weight may be given to ETCs with fully evaluated datasets.

5b-3: aggregation and selection of ecotoxicity values

In regulatory frameworks that apply the deterministic approach, the selection of the key study, usually the lowest reliable value for population relevant effects, must be transparently justified. When multiple studies overlap in scope (e.g., the same species, duration or endpoints), the weighting and consideration of these studies in the ETC derivation should be clearly explained, particularly if the results are inconsistent (e.g., if one value is notably lower than in comparable studies). Geometric means or other aggregation methods may be applied when several reliable studies exist for the same species, life stage, and endpoint. This should be performed in accordance with the relevant methodology and/or guidance and be scientifically justified.

5b-4: data gaps

In some regulatory frameworks, an ETC cannot be derived if the dataset does not comply to the standards specified in the relevant guidance document (e.g., a study on algae, Daphnia and fish for marketing authorisation for human pharmaceuticals; and without fish but with additional blue-green algae for antibiotics) [4]. In other frameworks or scientific literature, this may be more flexible, and ETCs may be derived from incomplete datasets that do not cover potentially sensitive taxa or endpoints. Including such sensitive species could change the ETC, as was the case for the plant protection product imidacloprid, where mayflies turned out to be much more sensitive than the insects used in standard tests, leading to a revision of the Dutch national ETC [42, 43]. Potential data gaps may already have been identified during the relevance evaluation in Step 3. The current reliability step involves determining whether data gaps have been filled and if so, whether that was appropriately done (e.g., (not) using QSARs, see Sect. "Differences between ETCs: influence of underlying data") and whether this conforms to the relevant method/guidance and scientific knowledge.

5b-5: application of methods, including choice of assessment factors

Depending on the dataset and methodology, ETCs can be derived using a deterministic, SSD or mesocosm approach, either performed singularly, in parallel or in a tiered system. As explained in Sects. "Differences between ETCs: methodological aspects" and 2.3, the scientific opinions on which approach to choose, the data requirements, and the assessment factors may differ between frameworks. Where applicable, the methodology described in the relevant regulatory guidance should be used, and any deviations or selection of alternative approaches should be justified.

In the deterministic approach, assessment factors are applied, as described in Sect. "Differences between ETCs: methodological aspects". Although most frameworks apply standardised assessment factors to address data gaps and uncertainties, expert judgement may still be used. This often relates to questions whether potentially sensitive taxa are sufficiently represented in the dataset and whether missing data are critical or can be compensated for in a weight of evidence approach. Thus, the choice of assessment factor should be made transparent, compliant with the guidance document used (if applicable), and scientifically justified. This applies to ETCs derived in regulatory contexts, but also to those in non-regulatory frameworks.

Step 5c: reliability—other considerations

Conformity with (regulatory) methods alone is not enough to determine the reliability and thus usefulness of ETCs. Other considerations may play a role (Table 3) and are described below.

5c-1: date of ETC derivation

Especially in the case of older ETCs, it should be established whether they have been derived in line with the latest scientific insights and/or data, and whether regulatory requirements, guidance documents and test

Table 3 Additional aspects to consider for the evaluation of ETCs

Number	Aspect
5c-1	Date of ETC derivation
5c-2	Independent review of ETC derivation
5c-3	Comparison with other available ETC values
5c-4	Residual uncertainties

guidelines have been updated over time. For example, the assessment factors for deriving a MAC-EQS under the Water Framework Directive were modified in the 2018 guidance update.

In addition, new data may have become available that could affect the usefulness of previously derived ETCs. Additional research, especially on sensitive non-standard taxa, may result in lower ecotoxicity values. For example, this occurred with neonicotinoid insecticides [42, 44, 45]. In contrast, additional (chronic) data may also lead to lower assessment factors and higher ETCs, as demonstrated by Vestel et al. [37]. The availability of additional data may also enable an SSD to be performed [46]. It should be acknowledged however, that a newer ETC is not per se more useful, if e.g., methods have not been applied correctly (step 5b).

As science progresses and our knowledge expands, our views on which endpoints are relevant for a particular protection goal change. However, regulatory guidance often progresses more slowly and may not immediately reflect emerging scientific insights. Evaluating the applicability of new research for the regulatory protection goals and its impact on existing authorisations, developing and validating new test methods, and translating these findings into formal data requirements all take time. At present, there is a growing awareness that psychoactive pharmaceuticals may cause behavioural responses in wildlife species. This is important for understanding population dynamics and maintaining ecosystem function, but this has not yet been incorporated into regulatory frameworks [38–40].

5c-2: independent review of ETC derivation

The independence of the derivation (i.e., whether it was conducted by regulatory authorities or by a company with commercial interests) and whether it has been independently reviewed should be assessed. Where an ETC is derived within a regulatory framework, the applicable guidance documents and procedures indicate the review process applied. For market authorisation of new pharmaceuticals, the industry derives PNEC values as part of the environmental risk assessment. This is then reviewed by regulatory authorities and, if necessary, revised until agreement is reached. Some pharmaceuticals appear as industrial chemicals (e.g., when used as intermediates) under REACH, with PNECs available via the European Chemicals Agency (Registered substances—ECHA). The regulatory scrutiny applied there may differ from that applied within marketing authorisation procedures for medicinal products and only a part of the substances has been reviewed [47].

For ETCs derived by national agencies for ad-hoc risk assessments or in the scientific literature, transparency on internal or external review is often limited, and peer review may not focus specifically on the relevance or reliability of the ETC outside the context of that individual publication. Databases such as NORMAN [22] or Fass [34] are also commonly used sources of ETCs for pharmaceuticals. However, the extent of independent verification may be limited, and critical evaluation is often warranted (e.g., many ETCs in the NORMAN database are based on QSAR data, see 5a-3).

5c-3: comparison with other available ETC values

When several ETCs exist for the same substance, derived by different stakeholders using different methods or datasets, comparing them can provide information on the level of consensus. This would iterate with the reliability evaluation. Marked differences may arise from variations in underlying data, endpoints, or derivation approaches (including assessment factors), and understanding these differences is essential.

ETCs may be compromised if key studies are omitted or if the most critical endpoint is taken from a low-reliability study. Such issues may only become apparent when ETCs are compared side-by-side. Differences in data interpretation can also contribute to variability. For example, the inclusion of borderline reliable studies or the choice between nominal or measured exposure concentrations determine the value of the most critical endpoint.

Selecting the lowest ETC as a default conservative worst-case value is not appropriate without justification, as it may be based on less reliable or less relevant information (e.g., QSAR-based value with an assessment factor of 1000). The same applies to selecting the most recent ETC without justification.

5c-4: residual uncertainties

Assessment factors are intended to address uncertainties related to extrapolations from limited laboratory studies to complex species-rich field situations, intra- and interspecies variation, lab-to-lab variation, and short-term to chronic scenarios [20]. However, it may be unclear which uncertainties have been considered. Generally, uncertainty decreases as more robust and diverse data become available, though new or conflicting findings may initially increase uncertainty before ultimately improving coverage of sensitive taxa or endpoints.

Uncertainty may also stem from the results of the underlying studies themselves, for instance, when no adverse effects are observed at the highest test concentration, when solubility limits interfere with applying correct test concentrations, when effects are observed at the lowest test concentration, when the dose–response curve is very flat, or when EC10s and NOECs in a study

show large discrepancies. If such studies form the basis of the ETC, these uncertainties propagate to the final value, risking either over-conservatism or insufficient protection.

Step 6. Conclude on the usefulness of the ETC(s)

The proposed structured approach for evaluating ETCs supports transparent decision-making and reporting. Concluding on their usefulness requires transparency on the expert judgment applied, including the weighing and reasoning of the aspects addressed.

Application of the evaluation system to a case study

As an illustrative example, we present an ETC evaluation for metoprolol (CAS no. 37350-58-6), for which several ETCs are available in the public domain. The detailed application of the scheme is included in the supplemental information (Supplemental file 3).

Step 1. Aim of the assessment

In our fictional case study, a regional water authority wants to assess the impact of metoprolol on surface water quality. Metoprolol is emitted into the environment via wastewater treatment plants that receive household wastewater. The primary objective of the water managers is to protect freshwater aquatic organisms from the direct toxic effects of long-term exposure to metoprolol. The water authority prefers to use ETC values that are derived using a methodology similar to that used to derive Environmental Quality Standards for the Water Framework Directive [5], as these are the most relevant to the water sector.

Step 2. Background information

Metoprolol is a pharmaceutical prescribed to treat hypertension and angina. As a betablocker it blocks beta-1 adrenergic receptors. Based on this, it is expected that a broad range of species may be affected by metoprolol [48]. It is commonly formulated as a salt in pharmaceutical products, most frequently as metoprolol succinate (CAS no. 98418-47-4) or metoprolol tartinate (CAS no. 56392-17-7). These salts rapidly dissociate into metoprolol base, which is the active compound and the corresponding counter ion. Thus, the relevant substance for the ETC is the metoprolol base. This has implications for how the ETC is derived and how (If at all) data for the metoprolol salts are recalculated into the base form.

The physicochemical properties of metoprolol are presented in Table A 4 in Supplemental file 4, based on the work of [49]. No further search for these properties was performed. The substance is soluble and not very hydrophobic or volatile, and thus it is unlikely that testing was performed above its solubility limit or that losses have occurred due to sorption or volatilisation. Because of this, reliability of the underlying data is likely not influenced by its physicochemical properties.

Step 3. Search for available ETCs

ETCs were found in the Water Framework Directive at national and EU levels, the Fass database, and in the peer-reviewed literature. The search led to 7 ETCs: a mix of AA-EQS, MAC-EQS and PNEC values (Supplemental file 3).

Step 4. Evaluation of transparency

The methodology used to derive the ETC was reported for most ETCs. However, other aspects were not consistently reported. Information on the data collection strategy was missing for multiple ETCs (e.g., in [49–53]). Additionally, detailed information on relevance and/or reliability assessment of underlying data was not consistently provided, like in Besse and Garric [50] and Fass [53]. Some authors acknowledge ETC derivations from other institutes, e.g., Oekotoxzentrum [51] and Coors et al. [52].

It is noted that studies by Besse and Garric [50] and the Oekotoxzentrum [51] are written in German and French, respectively, and may be less accessible to non-native speakers. The transparency of the derivation of all ETCs was still found to be sufficient to proceed to the next evaluation steps (Excel table in Supplemental file 3).

Step 5a. Evaluation of the relevance of the ETCs

Table 4 presents the chronic freshwater ETC values for metoprolol. ETCs that were derived to protect against short-term (peak) exposure (e.g., MAC-EQS and some PNECs) or the marine environment were not included as they are not relevant for chronic exposure scenarios. All ETCs refer to direct ecotoxicity and are relevant for this assessment. For metoprolol, with a relatively low log K_{OW} of 1.88 (Supplemental file 4), an ETC for secondary poisoning would not need to be derived or evaluated.

In our example, relevant chronic freshwater data are available, therefore PNECs based on acute data, such as reported by Besse and Garric [50], AstraZeneca [54] and Fass [53], were considered less relevant.

Step 5b. Evaluation of reliability—conformity

For the purpose of this case study, we have only evaluated the reliability of the ETCs, not of the underlying ecotoxicity data. We assume that reliability evaluations on the underlying data by the respective authors of the derivation were correct and are still aligned to current guidelines. In case of revised test guidelines and/or where there are conflicting study results, it can add value to

Table 4 Evaluation of ETC-values for metoprolol

ETC	Value (µg L^{-1})	Type of ecotoxicity data; lowest value and species name[a]; assessment factor	Derived by	Conclusion
AA-$EQS_{fw, eco}$[b]	43	Chronic; 430 µg·L^{-1} for *D. subspicatus*; 10	Federal Environment Agency (UBA; Germany); [49]	Most useful
AA-$EQS_{fw, eco}$[b]	62	(Semi-)chronic[c]; 3100 µg·L^{-1} for *D. magna*; 50	National Institute for Public Health and the Environment (RIVM; Netherlands); [55]	Useful
AA-$EQS_{fs, eco}$[b]	8.6	Chronic; 430 µg·L^{-1} for *D. subspicatus*; 50	Oekotoxzentrum (Switzerland); [51]	Useful
PNEC freshwater	7.3	Acute; 7300 µg·L^{-1} for *D. subspicatus*; 1000	[50]	Not useful: Relevant, but not reliable (methods not applied correctly)
PNEC freshwater	7.3	Acute; 7300 µg·L^{-1} for *D. subspicatus*; 1000	Fass.se; [53]	Less useful: Less relevant (acute data used for chronic ETC); less reliable (No/limited data search, critical data not included)
PNEC freshwater	7.3	Acute; 7300 µg·L^{-1} for *D. subspicatus*; 1000	AstraZeneca Company website; [54]	Less useful: Less relevant (acute data used for chronic ETC); less reliable (no reference to chronic data found in other derivations; critical data not included)
PNEC freshwater	610	Chronic; 6100 µg·L^{-1} for *D. magna*; 10	[52]	Less useful: Relevant, but less reliable (no/limited data search; critical data not included; choice of assessment factor)

[a] *D. subspicatus* = *Desmodesmus subspicatus* (algae); *D. magna* = *Daphnia magna* (crustacean)

[b] fw = freshwater, eco = direct ecotoxicity

[c] Moermond [55] assigned this study as chronic, but referred to it as semi-chronic, explaining that '*this test is neither acute nor chronic, it is included in the chronic dataset because the "true" chronic endpoint reproduction was included*'. The 9-day exposure period is longer than that of standard acute tests (48 h), but shorter than that of standard chronic tests with *Daphnia magna* (21 days). However, as it covers multiple life stages, it was considered acceptable as a chronic study according to the WFD EQS guidance [5]

re-evaluate studies regarding their adherence to current standards and guidance documents, to ensure the most relevant and reliable data is used for its intended purpose. The ETCs by Nendza [49], Moermond [55] and the Oekotoxzentrum [51] are based on extensive literature reviews and large datasets. However, the EQS derivation by the Oekotoxzentrum does not state how the literature search was performed (see step 4), solely that data up to 17 May 2016 were considered, which hampers assessment. On the other hand, this report does acknowledge and makes use of the AA-EQS derived by Nendza [49] and [55], who report a search strategy. This enhances confidence in its reliability.

The derivation of the AA-EQS_{fw} values was well-reported and aligned with the Technical Guidance for Deriving Environmental Quality Standards [5]. All chronic ecotoxicity data were tabulated and sorted per trophic level and species. A reliability score was assigned to each endpoint and toxicity value, and the data sources were cited. The lowest reliable experimental result for each trophic level was tabulated and discussed. Then, an assessment factor was assigned to derive the AA-QS_{fw} using the deterministic approach. The three AA-EQS_{fw} values were considered reliable. The other ETCs were considered less reliable, primarily because critical studies were not included, data were not used, and assessment factors were not chosen according to the currently accepted methodology. For more details, seeSupplemental file 3.

Step 5c. Evaluation of reliability—other considerations

The three ETC values remaining after step 5b were derived around the same time (2014–2016), with the ETC derived by Oekotoxzentrum in 2016 [51] reflecting the values of both Moermond [55] and Nendza [49]. Please note that these were all derived according to WFD EQS methodology, but before the WFD EQS guidance was updated in 2018. When these ETCs are compared, it appears that Nendza [49] and the Oekotoxzentrum [51] included a reliable critical effect value that had not been included by Moermond [55]. A further comparison reveals differences in the choice of the assessment factors. Moermond et al. (2014) and Oekotoxzentrum (2016) followed a different approach for dealing with the

presence of a 'lower than' result (NOEC < 3.1 mg/L for *Daphnia*). Moermond [55] increased the AF to 50 and applied this on the lowest uncensored ecotoxicity value of 3.1 mg/L. The Oekotoxzentrum used the same argumentation, while applying the assessment factor of 50 on their lowest uncensored value of 0.43 mg/L for the alga *Desmodesmus subspicatus*. It is noted, however, that this is a different species (algae versus water flea) and an EQS based on 0.43 mg/L for algae with an assessment factor of 10 would have been protective for *Daphnia* too, as a further look into the raw data of the *Daphnia* study revealed that the EC10 likely would have been around 2.5 mg/L.

Step 6. Conclusion on the usefulness of the ETC

Based on the information collated in steps 1 to 5, the ETC derived by Nendza [49] using the lowest available chronic ecotoxicity value with an assessment factor of 10 was considered most useful by the authors of the current paper. Please note that this is neither the lowest nor the most recent value, but the result of our step-wise evaluation, which provides a pragmatic approach to make initial assessments of potentially complex and/or historic ETCs. The selected ETC is derived using a full dataset and is based on the lowest ecotoxicity value known at the time, following the principles of the EQS guidance current at the time, which is largely similar to the current EQS guidance [5]. Thus, the AA-QS_{fw} of 43 µg/L can be used by the regional water authority to assess the risks to regional fresh surface waters.

When significant action is required as a result of the use of any ETC (e.g., restriction of product use or capital investment decisions for water treatments), it may be wise to review the availability of more recent data and/or new guidance documents, and revise the ETC accordingly. For the current case study too, if an ETC would be derived de novo, evaluation of all currently available individual ecotoxicity studies, and use of methodology of current guidance documents, may lead to a different ETC. A de novo ETC derivation may also be necessary if the evaluation of available ETCs shows that none of them is useful, either because they are not relevant or reliable. However, a de novo ETC derivation would require expert evaluation of reliability and relevance of all available data according to current standards, which requires more resources and expertise than the evaluation of existing ETCs. Re-evaluation of individual ecotoxicity studies was beyond the scope of this study.

Discussion

The evaluation and reuse of existing ETCs is essential for achieving both scientific robustness and efficient use of resources. Considerable investments have been made in generating ecotoxicity data and performing assessments for regulatory and academic purposes. Re-using and harmonising these data and assessments maximises the value of existing knowledge while minimising duplication of work [33]. This is in line with the One Substance, One Assessment (OSOA) approach from the European Commission that strives towards increased dialogue and harmonisation of data requirements and methodology across frameworks [9].

Still, one of the major challenges in the management of chemicals is the lack of comprehensive and accessible data on environmental hazards and effects. For many substances, crucial ecotoxicological and/or exposure data are missing, inconsistent, scattered across databases and institutions, or not publicly available, and thus only subsets of data are used. This limits the ability to assess and address risks efficiently and identify substances of concern. Besides access to data, access to existing ETCs including their derivation, would facilitate their reuse and systematic evaluation. This enhances scientific and societal trust, but also helps to fill critical knowledge gaps and makes better use of the information already produced. In future, artificial intelligence (AI) applications may help stakeholders to mine the literature for available ETCs and pre-select the most useful one. However, the interpretation of the strengths, weaknesses and uncertainties of AI results will still require specific expertise [56] and conclusions should be evaluated with scrutiny.

One of the aims of OSOA is to improve data sharing amongst frameworks, eventually leading to a shared data platform, which will help to harmonise the ETCs that are derived using this data. Making additional use of existing ETCs in assessment and management decisions strengthens the ability to address the twin crises of pollution and biodiversity loss in a sound way. Data-driven identification and prioritisation of hazardous substances enables more consistent and transparent environmental protection, and the lowest ETC is not always the best value. An overly conservative value will not accurately reflect the real risk, and could potentially lead to erroneous prioritisations, e.g., for risk mitigation measures. Vice versa, use of an ETC that is too high will result in an underestimation of risk and insufficient risk management. We consider the approach presented in the current paper to provide much needed guidance, which would help improve the impact of such analyses in future as well as increase the usefulness of publicly available ETC databases such as the NORMAN database. This database provides an invaluable tool to risk assessors with significant transparency on the underlying data on which PNECs are based, as well as the assessment factors used. However, users tend to ignore the statement that '*in case of no or insufficient empirical endpoints, QSAR predictions were used to estimate a provisional P-PNEC value to allow for*

a first screening', and just use the lowest PNEC value for all types of risk assessments.

Equally important is the integration of perspectives across disciplines and sectors. Effective environmental management requires collaboration between researchers, risk assessors, regulators, water authorities, and other practitioners. The stepwise evaluation scheme developed in this paper contributes to bridging these communities by providing a common, transparent basis for comparing and interpreting ETCs. Too often, ETCs are only used and reported in the regulatory framework for which they were derived, leading to knowledge gaps in other contexts. Improved cross-sectoral approaches and data-sharing, including sharing of ETCs and their derivations, are vital for developing coherent policies that address pollution and biodiversity together, supporting more holistic and preventive environmental governance.

The proposed stepwise approach provides support for this, enhancing the transparency of the assessment and identifying uncertainties. Key aspects include relating the ETCs to the purpose of the risk assessment and carefully scrutinising the data search, selected data, and application of assessment factors. Although we acknowledge that expert judgement may still be needed and not all stakeholders will be able to fully grasp the detailed methodology, the stepwise approach at least would lead to a transparent, systematic evaluation that can be adapted and reused by others, and can help to justify choices made for risk assessment and subsequent risk management. The metoprolol case study demonstrated that multiple ETCs may be available for a single compound and that the proposed method can help determine the most useful ETCs. The example also shows that even when the same type of dataset and the same guidance documents are used, experts may come to different conclusions because they miss data, or apply different assessment factors.

A transparent and systematic evaluation tool like the one we proposed will facilitate discussions. The importance of transparency is reflected in step 4 of our assessment scheme. Even within mature regulatory procedures there often remains a lack of transparency on how such reviews are conducted and/or how consensus is reached and the decisions taken over specific studies or endpoints. A study assessing the benefits of REACH for other regulatory frameworks observed large deviations when comparing registrants' PNECs with ETCs derived by the Dutch authorities [57]. Although some improvements have been made, the level of detail and quality of the publicly available study summaries still is highly variable and the reliability of resulting PNECs is difficult to evaluate due to a lack of details about how it was derived. ETCs derived under the Water Framework Directive undergo an iterative process with multiple stakeholders and committees involved. Similar to what is observed above for pharmaceutical marketing authorization, there is a lack of transparency on the level of consensus and dispute, and the way final choices have been made [58], which may hamper the acceptance and use of these ETCs in other frameworks. Full transparency is needed to be able to evaluate and interpret ETCs, and should therefore be the priority in regulatory frameworks and peer reviewed literature.

OSOA does not mean that the same ETC is always the most suitable, as this depends on the aim of the assessment (e.g., peak exposures or chronic exposures) and the protection goals (e.g., direct ecotoxicity, secondary poisoning, drinking water protection), and thus different ETCs may still have to be used in different frameworks. However, the aim should be to use the same ETC when the protection goal is the same (e.g., chronic exposure in freshwater), regardless of the framework. Selecting an appropriate ETC can be challenging, also for experts. Moreover, it is highly unlikely that there are any perfect ETCs. The aim of the ETC should always be to estimate the true threshold level for effects in the environment as accurately as possible, but uncertainties will always remain. As there is not a standard environment, the 'real' threshold value may also vary between seasons, geographic locations, type of surface water, and other factors. Besides this, a substance will never occur in the environment just by itself, and ETCs for single substances may not protect against possible mixture effects [59]. Although it may be impossible to know the 'real' threshold value, a structured, science-based derivation and evaluation method, including justifications of choices made, will at least help to make the derivation and choice of ETCs as robust as possible. By systematically evaluating and integrating data from various regulatory and non-regulatory sources, as proposed here, decision-makers can better prioritise chemicals of concern and take measures to mitigate risks to the environment.

In conclusion, using an existing ETC often is the preferred option in risk assessment since it saves time and resources. However, the usefulness of a particular ETC is not always obvious, since it depends on the quality of the derivation process and the underlying data. Particularly if multiple ETCs are available, selecting a useful ETC can be challenging. We present a systematic and stepwise framework for selecting and quality-assessing ETCs, with a focus on human pharmaceuticals and European regulatory frameworks. The framework is based on assessing the relevance and reliability of existing ETCs. The framework was demonstrated in a case study, showing how a suitable ETC for metoprolol can

be selected. The presented framework is a step forward in the (international) harmonisation of risk assessment procedures.

Our systematic stepwise evaluation approach guides stakeholders helping them with a consistent, scientifically sound, and transparent evaluation and documentation of ETCs. While we primarily focused on pharmaceuticals, the approach is generally applicable to substances across other industrial sectors. Our approach helps understanding the usefulness of existing ETCs for specific purposes enabling better decision-making in, e.g., prioritisation of substances, risk assessment and environmental management. By using a transparent ETC evaluation scheme, discussions between stakeholders may be structured and the useability of various ETCs and their evaluations among regulatory frameworks and academia will be improved.

Supplementary Information

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Supplemental file 1.

Supplemental file 2.

Supplemental file 3.

Supplemental file 4.

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Availability of data and materials
The dataset supporting the conclusions of this article is included within the article (and its Supplemental file(s)).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Samuel Maynard is employed by AstraZeneca, a marketing authorization holder of the case study compound metoprolol.

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