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The accessibility of data on environmental risk assessment of pharmaceuticals: Is the marketing authorisation procedure in conflict with the international right of access to environmental information?

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Abstract

Background: For a large part of the active pharmaceutical ingredients (APIs) available on the market, there is no or no comprehensive environmental risk assessment (ERA) existent/available. Existing ERAs are, moreover, treated as commercially/industrial confidential information (CCI) and the information content on the ERAs contained in the Public Assessment Reports is very limited. Thus, neither the public can inform itself sufficient nor environmental authorities can use the ERAs to compile environmental quality standards. Environmental information law, on the other hand, requires the general accessibility of environmental information. Against this background, this investigation examines the following questions in conformity with the environmental information law: Which environmental information on pharmaceuticals is generated in the marketing authorisation? Which of the environmental information generated in the marketing authorisation is available to the public? Does the environmental information on pharmaceuticals concern CCI?

Results: According to international and European environmental information law, there is in principal a right of access to the ERAs of pharmaceuticals (environmental information according to Art. 2(3)(b) Aarhus Convention), which is ineffective due to product-based data and allegedly conflicting CCI. The practised blanket classification of CCI by the marketing authorisation holders is in conflict with the principle of transparency of environmental information law. In any case, the outcomes of the ERA (in particular the ecotoxicity endpoints) may not be classified as CCI. Furthermore, the publicly accessible information in the format of the Public Assessment Report does not sufficiently reflect the information from ERAs and thus does not fulfil the mandate of active access to information (Art. 5 Aarhus Convention). The conflict between the actual accessibility of environmental information on pharmaceuticals and the requirements of environmental information law could be resolved through an API-based publicly accessible database with the outcomes of the ERAs (including all underlying ecotoxicity endpoints). To fulfil the right of access to environmental information effectively, the database also needs to be extended to "old" APIs for which environmental risk assessments have not yet been carried out. This would be the basis for prioritisation of API and establishing a monograph system.

Conclusion: The environmental information law requires an improved accessibility of ERAs that could be achieved through an API-based publicly accessible database.

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Background

The pollution of surface water and drinking water with pharmaceuticals is an increasing global problem [1, 2]. More than 630 active pharmaceutical ingredients (APIs) are present in the environment above the detection limit [2]. Nevertheless, the effects of pharmaceuticals residues on environmental compartments have not yet been comprehensively investigated [3]. There is a lack of data for a reliable assessment [4–6]. 88% of pharmaceuticals targeting human proteins do not have comprehensive environmental toxicity data [7].

Environmental risk assessments (ERAs), including environmental toxicity data, play a key role in the entire substance management process beyond marketing authorisation: They are the basic prerequisite for prioritisation [8], for subsequent risk mitigation measures and monitoring measures in sectoral environmental protection and thus ultimately the prerequisite for a systematic reduction in the exposure of pharmaceuticals to the environment. However, even existing/comprehensive ERAs are insufficiently used for systematic reduction. In particular, there is a lack of information exchange between the authorities for the establishment of environmental quality standards (EQS). In fact, for reasons of confidentiality, the determined effect values are generally not passed on to environmental authorities, e.g., for environmental monitoring [9].

One of the most important factors directly affecting the existence and availability of data on environmental risks of pharmaceuticals is the statutory data generation and dissemination obligations.

Two different regulatory frameworks deal with information on environmental risks of pharmaceuticals. On the one hand, pharmaceutical authorisation law directly addresses the placing of pharmaceuticals on the market and generates and disseminates product information within the marketing authorisation procedure. On the other hand, the provisions of general environmental information law cover with all information relating to the environment without referring to specific hazardous substances. These regulations require that public authorities should have environmental information at their disposal that is relevant to their tasks (Art. 5 Aarhus Convention [10]) and that this information is also publicly available (Art. 4 and 5 Aarhus Convention).

The aim of this study is to investigate whether the authorisation procedure meets the requirements of environmental information law for the generation and availability of environmental information.

Marketing authorisation procedure

Information on pharmaceuticals is generated through the marketing authorisation procedure, which is regulated at EU level by Directive 2001/83/EC [11] [human medicinal products (HMPs)] and Directive 2001/82/EC [12] [veterinary medicinal products (VMPs)]. The latter will repeal on 28.01.2022 by Regulation (EU) 2019/6 [13]. There are four different kinds of authorisation procedure in the EU:

1. The centralised procedure in which pharmaceuticals are authorised in the entire EU simultaneously. This procedure is the responsibility of the European Medicines Agency (EMA) and is regulated by the Regulation (EC) No 726/2004 [14]. It is only available for new and high-technology pharmaceuticals, in particular for those that contain new APIs for the treatment of, e.g., cancer, diabetes, and orphan diseases or for particularly innovative pharmaceuticals.
2. The mutual recognition procedure in which a pharmaceutical is evaluated and approved by a Reference Member State in accordance with the national procedure followed by a consideration of the assessment report of the Reference Member State by other Concerned Member States.
3. The decentralised procedure in which the applications are submitted simultaneously to the Reference Member State (which is responsible for the procedure and the evaluation) and Concerned Member States.
4. The national procedure in which the pharmaceutical is authorised in one Member State only.

The core element of marketing authorisation is the generation of reliable and conclusive data/information on the risk and efficacy by the applicant and an authorisation decision based on this by the approval authority [15].

According to Art. 8(3)(ca) Directive 2001/83/EC, the application dossier of HMPs must include an "Evaluation of the potential environmental risks posed by the medicinal product.". In addition, part. I point 1.6 of Annex 1 of Directive 2001/83/EC specifies the information concerning the environmental risk. For VMPs, Art. 12(3)(j), fourth indent Directive 2001/82/EC requires the test results of the ERAs. This is reflected in Title I Part 3 (Safety and residue tests) Point 6 of Annex I of Directive 2001/82/EC, which already prescribes a two-phase test with data requirements on exposure, fate,

and effects of the VMP in the environment (so as well Title 1 Part 3 (Safety and residue tests) Point 6 of Annex II of Regulation (EU) 2019/6).

The aforementioned legal provisions of secondary law are naturally limited to the description of the regulatory framework in an abstract-general form, from which, however, no obligation of the applicant to submit certain test results can be derived [16]. The situation is different when the EMA guidelines on the ERA of HMPs [17, 18] and VMPs [19, 20] (EMA guidelines) are taken into account. These guidelines enable a uniform evaluation and specify for which types of marketing authorisation and to what extent an ERA must be carried out. They also include detailed scientific and technical instructions for the preparation of ERA documents, including concrete test procedures. These ERA guidelines are to be classified as "soft law" with a quasi-binding character [21, 22].

The EMA guideline of HMPs entered into force in December 2006 and is currently being revised. For VMPs, an EMA guideline for Phase I already exists since 1998 [19]. However, the guideline for Phase II did not enter into force until 2005 [20]. As the applicant's obligations to indicate potential environmental risks were not sufficiently specified without the guidelines, ERAs in the form and in the detail required by the guidelines can only be claimed from applicants, since the guidelines entered into force [23, 24]. On the basis of the dossier, the approval authority must prepare an assessment report, which is to be made available to the public after deletion of the commercially/industrial confidential information (CCI) (Art. 21(4) Directive 2001/83/EC; 25(4) Directive 2001/82/EC; Art. 47(3), 49(11), 51(11) Regulation (EU) 2019/6). In summary, there are two documents drawn up concerning the environmental risk of the APIs: The assessment document of the ERA created by the applicant and submitted to the approval authority and a corresponding assessment report of the authority. In the following, these documents are referred to as ERA and official assessment report.

The main substantive authorisation criterion is a positive risk–benefit balance of the pharmaceutical (Art. 26(1)(a) Directive 2001/83/EC; Art. 30(a) Directive 2001/82/EC; Art. 37(2)(b) Regulation (EU) 2019/6). The environmental risk of HMPs is not included in the assessment of the risk–benefit balance (Art. 1(28a)(28), first indent Directive 2001/83/EC). Therefore, environmental risks are not taken into account at all in the authorisation decision. For VMPs, on the other hand, the environmental risk must be taken into account within the framework of the risk–benefit balance (Art. 30(a) in connection with Art. 1(20)(19), second indent Directive 2001/82/EC, respectively Art. 37(2)(b) in connection with Art. 4(19)(b) Regulation (EU) 2019/6)) and can consequently also lead to refusal of authorisation. In addition, the new regulation explicitly mentions the adequate consideration of environmental risks as a prerequisite for authorisation (Art. 37(2)(i) Regulation (EU) 2019/6).

Environmental information law

The regulatory framework of environmental information is laid down at international level in the Aarhus Convention, at European level in the Environmental Information Directive (EID), and at national level in the German Environmental Information Act (UIG) [25].

Free access to environmental information is intended to create an informed public which, on the basis of sufficient information, can ensure objective control of environmental management and thus help to identify and remedy deficits in decisions, policies and planning in environmental matters [26]. The term 'environmental information' is broad in scope. Among other things, this includes *"factors, such as substances, […] affecting or likely to affect the elements of the environment […]."*(Art. 2 No. 3 lit. b Aarhus Convention; Art. 2(1)(b) EID). The ERA and the official assessment report are information on substances (APIs) that are likely to affect the environmental elements water and soil.

It is the basic objective of the Aarhus Convention and the EID to ensure the widest possible availability and access to environmental information (recital 16 of the Aarhus Convention, Art. 1 EID). Environmental information law establishes access to information in different ways and it parallel lays down two essential obligations for the public authorities:

1. The obligation of public authorities to provide information on request and the corresponding right of the public to seek information from public authorities is stipulated at Art. 4 Aarhus Convention, Art. 3(1) EID). In principle, every person has the right of access to environmental information without having to state an interest (Art. 4(1) Aarhus Convention; Art. 3(1) EID). The information shall be made available as soon as possible and at the latest within 1 month of receipt of the application by the authority (Art. 4(2) Aarhus Convention; Art. 3(2)(a) EID). Only in the case of complex and extensive claims for information, environmental information law allows the possibility of extending the time-limit. Such an extension shall be justified to the applicant (Art. 4(2) Aarhus Convention; Art. 3(2)(b) EID). The blanket indication of an overload of the authority is not sufficient [27]. An extension of the time-limit due to the need to consult affected third parties [e.g., marketing

authorisation holders (MAHs)] is partly rejected in literature [27, 28] and politics [29]. In any case, however, the authority must inform the third party of the current legal time-limits and take appropriate procedural steps to comply with them [27]. The time-limits are mandatory [30].

The right of access to environmental information lays down that the disclosure of information should be the general rule and that public authorities may refuse access only in specific and well-defined cases (recital 16 of the EID). These cases are enumerated in Art. 4(3)(4) Aarhus Convention, Art. 4(1)(2) EID. Environmental information law also stipulates that the reasons for refusal must be interpreted restrictively and that the public interest in disclosure must be weighed against the interest in confidentiality (Art. 4(4), second sentence Aarhus Convention; Recital 16, Art. 4(2), second subpara EID). For this reason, each individual case requires a determination, evaluation, and weighting of the conflicting interests (public information interest vs. ground for refusal). Of particular importance for this investigation is the CCI as ground for refusal, since the environmental information on pharmaceuticals originates primarily from the pharmaceutical companies themselves and is generated there by elaborate studies (see below). In this context, the paper examines in particular whether the environmental information on pharmaceuticals concerns CCI of the MAHs.

2. The obligation to collect and disseminate information requires public authorities to possess and update information relevant to the decisions and measures which they take without the need for a specific request (Art. 5(1)(a) Aarhus Convention) [31]. A corresponding right of the individual does not exist. In correspondence with the individual right of access to information, this obligation ensures that the public can effectively pursue its claim to access environmental information and obtain a solid information base [32]. Only the availability of environmental information at the authorities ensures that the individual's right of access does not fail [26]. In addition, certain environmental information, including for example risk assessments on water and soil, has to be updated and actively and systematically disseminated to the public, in particular via the Internet (Art. 7 (2) (g) EID). The ERAs of pharmaceuticals assess the risk posed by APIs to water and soil, so that they are to be classified as risk assessments within the meaning of Art. 7(2)(g) EID.

Methods

The paper focuses on the question of the availability of environmental information on pharmaceuticals, measured against the requirements of environmental information law. In particular, the following questions were investigated:

1. Which environmental information on pharmaceuticals is generated in the marketing authorisation?
2. Which of the environmental information generated in the marketing authorisation is available to the public?
3. Does the environmental information on pharmaceuticals concern MAHs' CCI?

An analysis of the pharmaceutical approval law—based on a legal interpretation and literature review—should show which environmental information is generated by the marketing authorisation procedure. The enforcement of this legislation, i.e., administrative practice, has been reviewed to determine which of the environmental information generated on pharmaceuticals is publicly available. To this end, the right of access to environmental information has been used as an instrument. A formal request for access to environmental information to the competent authority in Germany for the authorisation of HMPs [The Federal Institute for Drugs and Medical Devices (BfArM)] and to the competent authority in Germany for the authorisation of VMPs [Federal Office of Consumer Protection and Food Safety (BVL)] should identify the accessibility of environmental information in the pharmaceutical sector as an example for an EU Member State.

On the one hand, access was requested API-based, i.e., for 19 HMP-APIs (Sulfamethoxazol, Trimethoprim, Ciprofloxacin, Doxycyclin, Amoxicillin, Clarithromycin, Erythromycin, Azithromycin, Florfenicol, Flumequine, Oxolinsäure, Oxytetracyclin, Sarafloxacin, Sulfadiazine, 17-alpha-Ethinylestradiol, 17-beta-Estradiol, Diclofenac, Ibuprofen, and Iomeprol) and for 14 VMP-APIs (Sulfamethoxazole, Trimethoprim, Ciprofloxacin, Doxycyclin, Amoxicillin, Clarithromycin, Erythromycin, Azithromycin, Florfenicol, Flumequine, Oxolinsäure, Oxytetracyclin, Sarafloxacin, and Sulfadiazin). On the other hand, access to environmental information on specific products was requested in Germany and only products for which an ERA was known to be included in the application dossier were selected (Tables 1 and 2).

The APIs considered were selected, because they are listed on the first [33] and/or second [34] watch list of Water Framework Directive, they have been detected in particularly high concentrations in the environment [2], or they are APIs from the group of antibiotics

Table 1 HMPs for which an application for access to environmental information has been submitted

HMP-API	Number of products listed in the application
Ciprofloxacin	2
Diclofenac	4
Ethinylestradiol	5
Ibuprofen	48
Iomeprol	3

Table 2 VMPs for which an application for access to environmental information has been submitted

VMP-API	Number of products listed in the application
Amoxicillin	4
Doxycyclin	2
Florfenicol	7
Oxytetracycline	1
Sulfadiazin/trimethoprim	2
Sulfadimethoxine/trimethoprim	1
Sulfadoxin/trimethoprim	1
Sulfamethoxazol/trimethoprim	1

which were focussed by the project PharmCycle [35] because of the high consumption of antibiotics as human and veterinary pharmaceuticals, their occurrence in aquatic ecosystems [2], and the problem of antibiotic resistance [36].

The selected medicinal products were authorised only under the decentralised or mutual recognition procedure, so that national authorities grant the authorisation and the information generated by this authorisation is available only to those national authorities. A corresponding application to the EMA as the approval authority exclusively for the above-mentioned centralised authorisations was, therefore, out of the question. In addition, the information systems on pharmaceuticals to be maintained by the national medicines agencies and the information system of the Heads of Medicines Agencies (HMA) [37] were analysed for the availability of environmental information on the above-mentioned pharmaceuticals. Based on a comparison of the data availability generally required according to the environmental information law with the data availability determined for the pharmaceutical sector, concrete deficits were identified and finally solution options were discussed.

Results

Which environmental information on pharmaceuticals is generated in the marketing authorisation?

During the authorisation process, two documents containing environmental information are generated for one pharmaceutical: The ERA created by the applicants and a corresponding assessment report of the approval authority. There are two different kinds of ERAs. On the one hand, there is an extensive dossier with ideally complete ERA studies (comprehensive ERA); on the other hand, the ERA is limited to a justification for not submitting ERA studies.

Justification for not submitting ERA studies

Instead of a complete ERA with ecotoxicity and environmental fate data, a justification for not submitting ERA studies can often be submitted with the marketing authorisation application, especially for HMPs (see Tables 3 and 4). Despite this problem identified in the concept paper on the revision of the EMA guideline for HMPs [38], the revised EMA guideline for HMPs does not sufficiently determine the substantive requirements to be met by this justification. In this respect, the EMA guidelines merely specify the requirement to take into account a possible significant increase in the environmental impact of the active substance. The guidelines do not specify a limit value for the increase here, but only list examples for which a significant increase can be assumed (see Tables 3 and 4, row 3). Tables 3 and 4 provide an overview of the cases in which a comprehensive ERA is required and the cases in which a justification for not submitting ERA is sufficient.

As a result, ecotoxicity and environmental fate data are regularly available only for new approvals from 2006 (HMPs) and 2005 (VMPs), for VMP generics from 2005 and possibly also for HMP generics in the future. Since, in case of variations and extensions, only the change is assessed and renewals in particular explicitly do not have to be evaluated, no complete data sets can be generated subsequently using this method either. Also in this respect, the marketing authorisation of pharmaceuticals deviates from the marketing authorisation regimes of the other environmental chemicals.

Comprehensive ERA

As with the risk assessments of other environmental chemicals under REACH Regulation [41], Biocidal Product Regulation [42], and Plant Protection Product Regulation [43], ERAs of pharmaceuticals require data on exposure, fate, and effects in the environment.

An exposure estimation [predicted environmental concentration (PEC)] must always be carried out for pharmaceuticals; it represents the so-called phase I. Fate and

Table 3 Comprehensive ERA or justification for not submitting ERA studies—HMPs [17, 18, 39]

	New marketing authorisation	Variation application	Extension application	Renewal	Application under Art. 10 (generic, hybrid, bibliographical, fixed combinations, informed consent, similar biological applications)
Comprehensive ERA	Since 2006 usually required	Usually not required, only type II, only if increase in environmental exposure is expected, and addressing only the change	Usually not required, only if increase in environmental exposure is expected and addressing only the change	Not required	Adopted guideline: Usually not required, only if increase in environmental exposure is expected Draft guideline: Usually required if there is no access to an earlier ERA for the same API Required, if the default Fpen was not used in earlier ERA and increase in environmental exposure is expected
Justification for not submitting ERA studies	If no environmental risk is expected, because the active substance is a naturally occurring substance	If no increase in environmental exposure is expected	If no increase in environmental exposure is expected	(–)	Adopted guideline: If no increase in environmental exposure is expected Draft guideline: Access to an earlier ERA for the same API in which no default Fpen was used but no increase in environmental exposure is expected
	Defined examples for naturally occurring substances: Vitamins Electrolytes Amino acids Peptides Proteins Nucleotides, carbohydrates Lipids as APIs	Defined examples for an increase: A new indication which results in an increase in the extent of the use	Defined examples for an increase: An extension application of an oral medicinal product to include a dermal patch	(–)	Defined examples for an increase: A new indication or a new patient population is added, the maximum daily dose is increased A new route of administration or a new pharmaceutical form is added A marketing authorisation is applied for in a member state with a higher prevalence of the disease

Table 4 Comprehensive ERA or justification for not submitting ERA studies—VMPs [19, 24, 40]

	New marketing authorisation	Variation application	Extension application	Renewal	Application under Art. 13 (generic, hybrid, bibliographical, informed consent)
Comprehensive ERA	Since 1998 (phase I) or 2005 (phase I + II) usually required	Usually not required, only type II, only if increase in environmental exposure is expected, and addressing only the change	Usually not required, only if increase in environmental exposure is expected and addressing only the change	Usually not required, only if A potential risk to the environment is identified on basis of existing information And/or Data have become available indicating a potential problem arising from the presence in the environment of an active substance related to the use of a veterinary medicinal product and in relation to the inherent ecotoxicity of the active substance and/or its metabolite(s)	Similar to new marketing authorisation (usually required)
Justification for not submitting ERA studies	If no environmental risk is expected, because the active substance is a naturally occurring substance	If no increase in environmental exposure is expected	If no increase in environmental exposure is expected	(–)	Similar to new marketing authorisation
	Defined examples for naturally occurring substances: Vitamins Electrolytes Amino acids Peptides Proteins Nucleotides Carbohydrates Lipids as APIs	Defined examples for an increase: Increase in dose rate for an existing food producing species Addition of an indication for an existing food producing species	Defined examples for an increase: Change or addition of a new route of administration Change or addition of food producing species	(–)	

effect studies including the derivation of PNEC and a risk characterization (PEC/PNEC) form phase II. These data need only be generated if the PEC determined in Phase I exceeds a trigger value or if the APIs are of particular concern due to their mechanism of action or physicochemical properties, namely endocrine active substances and antiparasitics (HMPs) or antiparasitics for animals reared on pasture (VMPs).

Estimation of exposure—phase I In phase I, a rather rough exposure assessment for surface waters or soil is carried out. This is done according to the revised EMA guideline for HMPs and the EMA guideline for VMPs using a decision tree. In the case of HMPs, the decision tree is dedicated in particular to the different types of authorisation, in the case of VMPs to the different areas of application and ends in both cases with a calculation of the PEC.

If the $PEC_{SURFACEWATER}$ determined accordingly is equal to or above 0.01 µg/L (trigger value HMPs) or the PEC_{SOIL} is equal to or above 100 µg/kg (trigger value VMPs) or the $EIC_{AQUATIC}$ is above 1 µg/L (trigger value VMP aquaculture), a risk for the environment is assumed. Consequently, a further test (phase II test) must be carried out. In view of the possible effects of the mixture of various APIs in the environmental compartment and the chronic effect of lower concentrations, it is questionable whether the trigger values mentioned are too high, taking the precautionary principle into account [6]. In the literature, there are recommendations for lower trigger values [0.004 µg/L (trigger value HMPs) or 1 µg/kg (trigger value VMPs)] [44]. In its first guideline for the evaluation of HMPs, the EMA also reserved the right to revise the trigger value based on acute toxicity data when a sufficient amount of chronic data is available [18]. The rough exposure estimation can be refined step-by-step in phase II.

Phase I of the marketing authorisation results in some products being exempted in practice from the obligation to prepare a complete ERA and thus to generate effect studies, i.e., ecotoxicity data. In the case of authorisation procedures carried out in Germany (i.e., Germany is a Reference Member State or a national authorisation), 15% of HMP and 37% of VMP assessments end in phase I [45].

Environmental fate and effect assessment—phase II The aim of Phase II is to determine the concentration of a substance below which no adverse effects in the environmental compartment are to be expected (PNEC). First, the "intrinsic" toxicity is estimated on the basis of standard data (Tier A). When a risk is identified in Tier A, a Tier B assessment with PEC refinement and if warranted further effect studies should be performed. In substance, the applicant shall generate a pool of information from which a "quantitative data set" for the derivation of PNEC values for each exposed environmental area shall be created. The framework of the data set is defined in the EMA guidelines. These are primarily ecotoxicological standard tests with standard OECD endpoints (growth, mortality, and reproduction), which are also required in REACH Regulation, the Biocidal Product Regulation, and the Plant Protection Product Regulation. For example, both the EMA guidelines [17, 20] and REACH Regulation (point 9 of Annexes VII and VIII of the REACH Regulation) require a base data set for aquatic toxicity with the species algae, daphnia (invertebrates), and fish (vertebrates) as representatives for all three trophic levels. While chronic effects are required for HMPs, "because the emission of pharmaceutical residues into surface water is continuous" [17], acute effect data are primarily to be generated for VMPs, as their inputs are diffuse and pulsed.

To determine the PNEC, the effect endpoint determined experimentally in laboratory studies is divided by an assessment factor. This takes into account the degree of uncertainty in the extrapolation from a limited number of test species to complex ecosystems in the actual environment and from short-term to long-term toxicity and accounts for, inter-species variations in sensitivity, intra-species variability, and laboratory data to field impact extrapolation [17, 20]. However, the assessment factors do not take into account summation effects of different APIs in the environmental compartment [46].

Since effects on growth, mortality, or reproduction of environmental organisms are to be expected when concentrations are exceeded, PNECs are important values in the context of hazard prevention (for industrial chemicals, see [47]). In addition, they are the base for deriving environmental quality standards (EQS) for API for surface water and other environmental compartments.

Risk characterisation The procedure for the characterisation of the risk of API (risk quotient approach) is implemented for the majority of substances within the EU regulation, according to toxicological-scientific procedures and irrespective of its intended use [48]. The risk characterisation is the product of the exposure, fate, and effect assessments. According to the risk quotient approach, the risk quotient (PEC/PNEC) indicates the occurrence of adverse environmental effects. If the risk quotient is ≥ 1, there is a high probability that an effect will occur. If the risk quotient is < 1, a risk is not excluded, but unlikely [17]. This scientifically based identification of the risk does not yet say anything about the political normative classification of the risk in the categories acceptable and unacceptable. This only happens in a further, evaluative step. Only

at this subsequent level, social and political considerations can be taken into account, such as, e.g., purpose or benefit [48].

Product-based ERAs In contrast to REACH Regulation, Biocidal Product Regulation, and Plant Protection Product Regulation, the creation and administration of ERAs for pharmaceuticals is exclusively product-based and not API-based, i.e., each applicant generates all data independently for his product. Although with the ERA for pharmaceuticals, as with biocides, plant protection products, and industrial chemicals, the environmental risks of the API contained in the product are focussed in the assessment, not the product itself. This creates the potential for different environmental information to be generated for an API. The extent of the tests to be performed and the result of the risk characterization depend on the one hand on the product-specific calculated PEC, which can vary considerably from product to another (in particular due to product-specific daily maximum doses or, in the case of VMPs, additionally due to target animal species). On the other hand, the specified test procedures may be waived in individual cases with appropriate justification. Consequently, ERAs with the result "risk" and also with the result "no risk" may be available for an API, as shown in Table 5 for the API Ibuprofen as an HMP example.

In addition, the product-based ERA has the potential to underestimate the overall environmental risk for an API (regardless of HMP or VMP) if it is used to treat multiple clinical diseases with a high prevalence. If the different products have different applications, these are treated separately and may not address a total PEC (see for HMPs [7]). This means that there is neither a cross-product nor a harmonised assessment of the environmental risk for an API.

Literature data

For APIs already on the market, published scientific literature can or should (the new ERA guideline for HMPs in Section 6.1 explicitly calls for "a comprehensive literature search" [17]) be used instead of generating one's own data [17, 49–51]. The term "published scientific literature" implies that the literature should be freely accessible and published by a reputable source, preferably peer-reviewed [51]. The literature studies should be reliable, valid, and their design should be comparable with the study designs recommended in the EMA guidelines, e.g., classification according to criteria for reporting and evaluating ecotoxicity data (CRED) [17, 52, 53]. Finally, the principles of good laboratory practice (GLP) should have been respected [17].

In addition to using peer-review literature, it is also possible and desirable to submit data and study reports from other MAHs. MAHs which have already prepared relevant studies and applicants are invited to cooperate with their competitors in the exchange of existing data or the development of new ERA data [17, 24].

PAR, reviews, or summaries of data from other legal frameworks must not be used without the underlying study reports in the ERA dossier [17]. Furthermore, a reference or use of the studies contained in the original dossier is only possible if a letter of access is submitted [17]. This prohibition of referral and use applies both to applicants and to the competent authorities [24], an automatic cross-reference to ERA data is not possible [50]. In any case, the "foreign" information (study reports or peer

Table 5 Environmental information on pharmaceuticals that were publicly available in the PharmNet database in November 2018

API	Total number of HMPs/VMPs for which the author searched the public national database*	PAR available in database	PAR with a chapter called Ecotoxicity/Environmental Risk Assessment	Communicated result in PAR
Ciprofloxacin	1	1	1	No risk
Diclofenac	1	1	1	Risk
Ethinylestradiol	3	0	0	–
Ibuprofen	38	33	31	17× risk or risk cannot be excluded 8× no risk 6× no result
Iomeprol	3	0	0	–
Amoxicillin	2	2	2	2× no risk
Doxycyclin	2	0	–	–
Florfenicol	7	3	3	3× no risk
Sulfadoxin/Trimethoprim	1	0	–	–
Total	58	40	38	

* Authorised in Germany and for which an ERA was included in the dossier

review literature) can only be used as a substitute study if it contains a sufficient amount of data and sufficient details on the design and conduct of the studies to allow an evaluation of the reliability and quality of the studies performed and a complete and independent assessment of the pharmaceutical [17, 24]. The Notice to Applicants of VMPs [24] and the new draft EMA guideline of HMPs [17] explicitly stated that endpoints or a published summary of an assessment cannot be used by other MAHs to substitute for the autonomous production of an ERA.

Which of the environmental information generated in the marketing authorisation is available to the public?

Request for access to environmental information

The authors applied to the respective competent national approval authorities for access to ERAs and the corresponding official assessment reports on 19 HMP and 14 VMP-APIs. The competent authority for HMPs rejected access to the ERAs available for the 19 HMP-APIs on the grounds that they had no information on substances but only product-based environmental information. According to the authority, one has to search for environmental information on each individual product using various programmes. There would be no supporting filter or search function, rather all existing database entries for a product would have to be clicked and searched. A total of 5092 products would be listed under the 19 HMP-APIs. The search and compilation of all available ERAs for the 19 APIs would have led to such a high level of material and personnel effort that this would not have been covered by the right of access to environmental information. One would expect up to 9 months of administrative work and would reserve the right to charge the costs for each of the 5092 products to the author.

In substance, this means that access to environmental information for pharmaceuticals is only granted, if at all, for single products. In this respect, administrative practice differs significantly from that for other environmental chemicals for which environmental information is available on an active substance basis (cf. database on the website of the European Chemicals Agency (ECHA) [54]). For the authors and thus for consumers/scientists/authorities in general, it is already not transparent for which product on the market in a Member State there exists an ERA. According to the search described above, only the approval authority has access to this information. This results in immense obstacles for the preparation of the request. In addition, only the total emission of the API of all products is decisive for the environmental risk; only the API (not a single product) can be detected in the environment.

The interest in this environmental information cannot be satisfied by the isolated consideration of an ERA for only one product. This is because the PEC calculated in the ERA does not usually represent the total emission of all products with the same API. The PEC varies particularly depending on the maximum daily dose, which can vary considerably from product to product. In addition, the ERAs available for an API do not reflect the ideal case of identical ecotoxicity data in accordance with the guidelines. Rather, the ERAs are generally not in a harmonised format, show differences in the type of ERA (justification for not submitting ERA studies/comprehensive ERA), in the quality and quantity of the studies and a variance in the decisive PNEC values. This is demonstrated, for example, by the assessments made available by the approval authority for HMPs on two different HMPs contained the same API (ethinylestradiol) in the same dose (0.03 mg/tablet).

After Phase I and a total of 8 pages, one of the two HMPs comes to the following conclusion: "*The environmental risk assessment [...], demonstrates that the* $PEC_{SURFACEWATER}$ *values for CMA and EE [ethinylestradiol] are below 0.01 µ/L, and no other environmental concerns are apparent. Therefore it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.*"

The ERA of the other HMP, consisting of Phase I and II, comprises 83 pages and comes to the opposite conclusion: "*The ecotoxicological evaluation comes to the conclusion that concentrations of ethinylestradiol high enough to cause adverse effects actually can be reached in surface waters, that ethinylestradiol belongs to substances with environmental relevance, and that ethinylestradiol belongs to the known highly active compounds with predicted no effect concentrations below 10 ng/L. Ethinylestradiol is expected to pose a risk to the aquatic environment, especially to fish populations.*"

This heterogeneity of the ERAs to an API is also confirmed in the literature [6, 55]. Therefore, the isolated consideration of an ERA for a product is not representative of the risk of the total amount of substance approved. Rather, reliable statements about the total emissions of the API and their risk as well as the validity of the effect values can only be made with the aid of an overall view and analysis of all existing risk assessments for an API. For the identification and elimination of potential deficits in the marketing authorisation of pharmaceuticals, but also in the subsequent monitoring of APIs in sectoral environmental law, therefore, it is essential to analyse the entire information data set on an API. Even for access to environmental information on single products, the administrative burden was still so high that it was not possible to comply with the obligatory time-limits set

by environmental information law. Although an extension of the time-limit beyond the 2-month period is not even possible under environmental information law, the approval authority for VMPs announced this inadmissible extension in advance, in particular with reference to an extensive consultation procedure with the MAH. The approval authority for HMPs did not react at all for over 3 months, so that a so-called action for failure to act was admissible before the national Administrative Court and was filed by the author. Only after almost 9 (approval authority for HMPs) or 5 (approval authority for VMPs) months were the requests finally decided. In contrast to requests for information to the EMA, there is a lack of guidelines for the consultation of MAHs in the procedures for national authorisation authorities. For the former, the EMA has ruled that the MAH shall have a time-limit for reply which shall not be less than 5 working days and which shall enable the EMA to comply with its own time-limits for reply. It also stipulates that the EMA may decide on the notification even without a statement by the MAH if the MAH does not reply within the given time-limit [56, 57].

The author was only given access to the requested information if the MAH had expressly agreed to the disclosure beforehand. Moreover, both requests were rejected. The main reason cited for this was affected CCI. The classification of whether and to what extent CCI are involved was carried out by the MAH itself during the consultation. Some MAHs blacked out information in the ERAs; most of them completely refused access. This blanket classification by the MAH was complied with by the authorities without examination. The necessary weighing of the public interest in information against the interest in secrecy of the MAH was carried out according to the authorities, but was not presented to the author in a comprehensible manner. In practice, the confidentiality interest of the MAH in most cases will prevail over the public interest in transparency. Because of the possibility of making a mistake in the weighing of interests at the expense of the MAH and thus exposing themselves to expensive official liability claims, the authorities will in all likelihood always rather accept such a mistake in the weighing of interests at the expense of the public, whose violated interest could at best be an immaterial one. This means that there is in fact always a weighing failure.

In summary, access to environmental information is granted only for single products. In the absence of information availability and a regulated MAH consultation procedure, the specified time-limits for access to information are exceeded many times over, with the result that the authorities are in fact unable to comply with the procedure laid down by environmental information law. In practice, the high costs involved prevent access to the necessary API-based data collections. This is contrary to the principle that fees must not hinder the effective exercise of the right to information [58]. It is not the authorities but the MAH who decide which parts of the ERA and the assessment report concern CCI and, therefore, are not made accessible, so that even a claim to access to the outcomes of ERAs (PEC and PNEC values) exists under current administrative practice only with the consent of the MAH. Overall, the rule exemption relationship between transparency (access to information) and secrecy (rejection), as laid down in international and European environmental information law, is reversed in the pharmaceutical sector.

Administrative information systems on pharmaceuticals

The obligation to collect and disseminate information laid down in Art. 5 Aarhus Convention; Art. 7 EID, according to which, inter alia, ERAs are to be disseminated via public telecommunications networks, is also not sufficiently taken into account in the pharmaceutical sector. ERAs of pharmaceuticals as such are not retrievable in electronic databases—neither study summaries nor endpoints or PEC/PNEC values. Environmental information is only disseminated, if at all, in the form of Public Assessment Reports (PARs), which are prepared by the competent national authority of the Reference Member State [59–61]. The European public assessment report (EPAR) is only prepared for centrally authorised pharmaceuticals (Article 13(3) of Regulation (EC) No 726/2004) and therefore is not subject of this investigation.

The inclusion of environmental risks in the PAR is expressly stipulated neither for HMPs nor for VMPs. For HMPs, reference is made only to the results of the pharmaceutical and pre-clinical tests, the clinical trials, the risk management system, and the pharmacovigilance system (Art. 21(4) Directive 2001/83/EC), but the environmental risks are not allocated to the pharmaceutical-, pre-clinical-, or clinical-dossier-section. However, there is a template of the Co-ordination Group for Mutual Recognition and Decentralised Procedures—Humans (established according to Art. 1(26) Directive 2004/27/EC [62]), which provides concrete recommendations for the ERA assessment [63]. In particular, a summary of the main study results (including the PEC value and all ecotoxicity endpoints) should be included in table format in the PAR.

In the case of VMPs, the PAR should take into account the safety and residue tests, which also include the ERA (Art. 25(4) Directive 2001/82/EC), and under the new regulation, only special precautions for the protection of the environment should be indicated in the PAR, but there is no mention of the results of the ERAs (Art. 33(1)(a) in combination with Art. 35(1)(c)(v) Regulation (EU) 2019/6).

The PAR is to be made available to the public after deleting any information of a commercially confidential nature by the competent national authority (Art. 21(4) Directive 2001/83/EC, Art. 25(4) Directive 2001/82/EC, Art. 47(3), 49(11), 51(11) Regulation (EU) 2019/6). It was indicated that, in practice, however, the draft PAR would be sent from the authority to the MAH, who carries out the deletion of the CCI independently. According to the BIO-Intelligence study, this is also confirmed by national approval authorities [6]. As a result, the MAH also determines the degree of transparency of environmental information within the framework of the active information obligation.

It has been shown that for the majority of the pharmaceuticals examined, PARs are available both in the national Internet information portal (PharmNet) and in the Internet information portal of the HMA (MRI-Product Index). The EMA database, which is also publicly accessible via the Internet, only contains information (EPARs) on pharmaceuticals that have been centrally approved. For the HMPs and VMPs covered by this investigation and in principle for pharmaceuticals with so-called "old" APIs, the EMA database does not contain any information [64].

The national information systems are not standardized and partly there is only the possibility to search for the product name, which can be different from one member state to another [6] and hinders to get an overview over the ERA of an API. In addition, the search functions/databases are predominantly configured in the national language (for example: France [65], Italy [66], Portugal [67], and Sweden [68]. In addition, there are considerable differences in the quality and quantity of the PARs, inter alia, depending on the Reference Member States [6].

The database of the HMA and the published PARs are available in English. However, with regard to the available environmental information, there are no differences in content between the database of the HAM and the national database as the same PARs are published.

The databases are product-based, so that for every single pharmaceutical that contains the examined API, it is necessary to search for each PAR and its ERA. For all HMPs and VMPs for which access to environmental information was requested and which are also on the market in Germany, the public national database (PharmNet) was searched for environmental information on the APIs examined. Table 5 shows the results of this research.

For some pharmaceuticals, the corresponding PARs are located under another pharmaceutical with the same API. For the above-mentioned HMPs, for whose API ethinylestradiol environmental risks have been identified, for example, no PAR is available in the database. For one-third of the examined pharmaceuticals, no environmental information is available at all. Most of the PARs contain a chapter called Ecotoxicity/Environmental Risk Assessment. For 13 of the HMPs examined, this chapter indicates that the ERA is incomplete or not accepted. For example, for some HMPs contained the API ibuprofen, the complete Phase II should have been submitted by 15 Nov. 2010. However, the chapter "Ecotoxicity/Environmental Risk Assessment" has still not been supplemented—more than 8 years later—although sensitive endpoints (NOEC 0.1 µg/L) for the API ibuprofen have meanwhile been documented in the public literature [69].

The environmental information contained in the PARs is very heterogeneous overall and is available only in the form of summaries with limited information content. They usually consist of only some of the following (summarised) sentences, without showing underlying data:

- *The applicant provided the necessary ecotoxicological studies.*
- *The product is not expected to pose a risk for the environment when the product is used as directed.*
- *Warnings and precautions as listed in the product literature are adequate to ensure safety to the environment when the product is used as directed.*
- *In Phase I, the $PEC_{SURFACEWATER}$ is below the action limit, so no further assessment is required.*
- *In conclusion, in Phase II, all risk quotients are below the trigger value, so it is unlikely that the pharmaceutical poses a risk for the environment.*
- *The applicant provided an ERA Phase I/an ERA Phase I and II/a revised ERA based on literature studies for the API/with a new study for the API.*
- *The ERA is in compliance with the relevant guideline and showed that no further assessment is required.*

In some cases, the PARs also provide statements about a remaining environmental risk. In a second sentence, however, this risk is usually relativised by a sentence such as "It is expected that the pharmaceutical will not pose a risk to the environment when used as directed". In addition, there is sometimes conflicting information about the risk of an API. For example, 8 out of a total of 31 PARs (with a chapter called Ecotoxicity/Environmental Risk Assessment) reviewed for the API ibuprofen state that there is no risk to the environment, while 17 reports in the PAR stated that there is a risk to the environment or at least that it cannot not be excluded. Of course, the risk quotient depends on the dose and its derived PEC, which might explain differences, but this does not emerge from the PAR. Thus, a more transparent and holistic approach and presentation for the same API is necessary and underlying data should be shown. Some exceptions

of PARs contain PEC and PNEC values. To find such information, however, dozens of pharmaceuticals must be searched. The 58 pharmaceuticals researched by the author included three PARs containing PEC and PNEC values.

In summary, there are considerable obstacles for the public to access environmental information via the databases. The environmental information available there is in part obsolete, incomplete, or contradictory. Getting concrete PEC and PNEC values for certain API is an exception. Overall, the public cannot derive a reliable picture of the actual environmental risk of pharmaceuticals from the publicly accessible information systems. This situation is incompatible with the active information obligation of environmental information law, which explicitly requires the updating and dissemination of ERAs.

Does the environmental information on pharmaceuticals concern MAHs' CCI?

The reasons for refusal of access to information, i.e., also the term CCI, must be interpreted restrictively within the framework of environmental information law (Art. 4(4), second sentence Aarhus Convention; Art. 4(2), second subpara EID). The term CCI is not legally defined, but Art. 4(4)(d) Aarhus Convention, Art. 4(2)(d) EID contain the restriction that it must be a matter of legitimate economic interests. In addition, when interpreting the terms in accordance with Art. 4(4), second sentence Aarhus Convention and Art. 4(2), second subpara, second sentence EID, the public interest in disclosure must be taken into account in each individual case. The EMA has formulated the aim specifically for the pharmaceutical sector to ensure the widest possible access to the documents in its possession [57].

The criterion of "legitimate" interest is intended in principle to ensure objective verifiability to prevent arbitrary secrecy of information which is not objectively confidential [26, 28]. A legitimate interest is to be assumed above all if the disclosure of the relevant information would be suitable to make exclusive technical or commercial knowledge available to competitors and thus adversely affect the competitive position of the involved MAH [28, 70–72]. In any case, the information in question must be objectively relevant to competition [73].

A blanket classification by the MAH, consequently, cannot be sufficient to trigger the proviso on secrecy. Otherwise, in the pharmaceutical sector, the MAH could arbitrarily undermine the public's right to information. Therefore, there is a need for substantiated evidence from the entrepreneur of a requirement for secrecy or rather competition relevance [74] and correspondingly an obligation on the part of the authority to review and to state [26, 32]. This requirement is implemented exemplarily by the REACH Regulation: According to this, the confidential treatment of certain information on substances must first be applied for and justified by the registrants (Art. 10(a)(xi) REACH Regulation) and finally accepted as valid by the approval authority (Art. 119(2) REACH Regulation). Such a preliminary examination is unknown to pharmaceutical approval law, so that the classification in each individual case must be carried out by the authority obliged to provide information by means of an interpretation. The provisions of the REACH Regulation and general principles from the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) [75, 76] can be used for this purpose.

The author's request has shown that the approval authorities in practice assume that competitors can use the ERA documents for approval applications while saving their own resources. In the context of authorisation decisions, this assumption would subsequently mean that all documents generated by the MAH in principle would have to be assumed to have a legitimate interest in confidentiality. Regardless of whether and how in the concrete authorisation procedure an unfair commercial use of disclosed data is possible at all. In the case of environmental information generated within the framework of authorisation procedures of substances, the right of access to information in principle would be undermined. The "principle of transparency with reservation of secrecy" anchored in environmental information law is converted by this practice into a "principle of secrecy with reservation of disclosure".

Due to the obligation to interpret the reasons for refusal restrictively, not every economic disadvantage of any kind may result in a refusal to provide information [77]. Therefore, it must be demanded that the MAHs concerned prove the concrete cause of a competitive disadvantage through disclosure and the resulting use of the data for approval applications of competitors. Such a possibility of use by competitors is not apparent with regard to the ERA in the marketing authorisation. This is because a market competitor cannot use the ERA documents of the original manufacturer for its application without the latter's express consent (letter of access) [17, 50]. If such a letter of access is not available, each applicant must prepare its own ERA or refer to publicly available (peer-reviewed) literature, regardless of the type of authorisation it requests. The ERA documents would also not be "publicly available" through disclosure under the right of access to environmental information. Rather, this can only be assumed once the studies are freely available in the public domain and published by a reputable source preferably peer-reviewed [17, 50, 51]. Therefore, the consent of the person who owns the rights to the ERA

documents is also required at this point. The authorisation procedure is subjected to measures to ensure that ERA data are protected against unfair commercial use. This is precisely the case governed by Art. 39(3) of the TRIPS Agreement:

> *"Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use."*

Consequently, there is no justified interest in secrecy, so that the ERAs are not to be classified in general as CCI. No other conclusion is reached by the EMA, which in cooperation with the HMA has defined general principles for classifying information as confidential [78]. The EMA and the HMA also classify the information submitted with the dossier themselves in a guidance document [79]. The guidance differentiates between:

1. CCI = Commercially Confidential Information, which, as a main rule, cannot be released;
2. PPD = Protected Personal Data, which, as a main rule, cannot be released;
3. CBC = Case-by-Case Analysis, i.e., information which may contain CCI or PPD and which, therefore, require a case-by-case review;
4. CBR = Can Be Released, means that all of the section can be released, always after review.

The dossier section concerning the whole ERA (Module 1.6) is classified as 'CBR'.

The principles have so far only been laid down in a paper for HMPs, but in general they should also apply to VMPs [78]. In particular, in both authorisation regimes, the use of "third-party" environmental documents is only possible with the submission of a letter of access. In this respect, the EMA/HMA guidance document should also be used as an orientation for environmental dossiers of VMPs.

Even if a need for secrecy should be assumed for individual parts of the environmental dossier in the specific individual case based on plausible explanation, this may not apply in any case to the outcomes of ERA (PEC–PNEC values and its underlying ecotoxicity endpoints). After all, these are values of hazard prevention which, in isolation, do not benefit any competitor without its underlying studies and will not aid in the generation of the mandatory GLP studies [80]. The knowledge of the PEC and PNEC values, therefore, does not give rise to any commercial advantage [80]. With regard to the public interest to be taken into account, the PEC and PNEC values and its underlying ecotoxicity endpoints, consequently, cannot be classified as CCI. Otherwise, the interpretation of the reason for refusal "CCI" with regard to pharmaceuticals would be equivalent to an annulment of the right to information. In addition, a pharmaceutical is authorised based on a risk–benefit analysis in which an identified environmental risk is not even taken into account in the case of HMPs and does not necessarily result in a refusal of the authorisation in the case of VMPs. This means that the environmental risk is not sufficiently controlled by the approval law. Thus, this task is passed on to environmental protection law. Then, the information generated in the authorisation must also be available beyond the authorisation procedure. This information is at least necessary to determine whether environmental authorities, responsible for environmental quality, have to take protective and control measures for individual active substances. There is thus an overriding public interest. This conclusion was supported by the British approval authority, which initially rejected the request for access to environmental endpoints but finally granted access after the applicant's objection in 2006 [80].

Discussion

The author has analysed the implementation of the requirements of environmental information law in the marketing authorisation procedure of pharmaceuticals and has shown a conflict in this respect: The confidentiality principle identified in the pharmaceutical sector for environmental information is not compatible with the transparency requirement of environmental information law.

In addition, the data situation at the authorities is in conflict with the environmental information law, as well. The fact, for example, that no complete ecotoxicological data are already available for 88% of pharmaceuticals targeting human proteins [7] is contrary to Art. 5(1)(a) Aarhus Convention, which requires authorities to collect, possess, and update information relevant to their functions. As a result, the right of access to environmental information often fails due to a lack of availability.

To resolve these conflicts between the marketing authorisation procedure and the environmental information law and to eliminate the existing legal uncertainty among the authorities, there is a need for a legal clarification, which stipulate:

- that applicants should merge to jointly prepare or share ERA data on the same API. It should also be possible to replace a necessary agreement with a ruling by an independent body or by the approval authority.
- that the above-mentioned regulation also applies to "old" APIs, so that MAHs also have to merge and retroactively prepare an ERA to their "old" API.
- that possible CCI can only be classified as CCI with subject to secrecy in the context of authorisation upon application with a substantiated justification as to why publication is detrimental to the applicant's legitimate economic interests.
- which data must be excluded from the proviso of secrecy and which must be published. In any case, the results and PECs and PNECs (including all underlying ecotoxicity endpoints) of the ERAs should be excluded from the proviso of secrecy. In principle, the summary or robust study summary of the ecotoxicological studies should be published free of charge on the Internet in the format of an API-based publicly accessible database, unless they have exceptionally been classified as CCI according to the above procedure. In any case, the results, PECs and PNECs (including all underlying ecotoxicity endpoints) of the ERAs should be available in the database on the Internet. The database should be centralised and guided by EMA and/or HMA and the responsible member state authorities.

The regulations already established for industrial chemicals, plant protection products, and biocides for years under REACH Regulation (Titles III and XII); under the Biocides Regulation (Chapters XIV and XV) and under the Plant Protection Product Regulation (Chapters V and VI) can be used as a model in this respect. In addition to the legal regulations, EMA guidelines on data sharing and the associated cost sharing should be issued on the model of the ECHA Guidance on data sharing [81].

With the establishment of the aforementioned regulations, the public's interest in information based on active substances could be satisfied within the framework of the specified time-limits. Without the need for time-consuming, product-based research and then a month-long administrative procedure with consultation, examination and consideration of CCI and, following this, at least as long a judicial procedure with re-invitation of all third parties involved.

Only with such a legal clarification on the handling of CCI could the generated data also be forwarded to environmental authorities and used to derive EQS (limit values). This would additionally help to improve compliance with the requirements of the Water Framework Directive [82]. Valid, publicly available results of ERAs and endpoints could also help other stakeholders, such as water supply and disposal companies and water authorities, to manage problematic substances [9] and to assess environmental API concentrations in regions outside the EU [2].

Only if "old" APIs were also covered by this procedure, it could be ensured that the public's right to environmental information in the pharmaceutical sector would not fail and that a conflict with Art. 5(1) of the Aarhus Convention would not remain.

On this basis of the API database, guided by EMA and/or HMA and the responsible member state authorities, APIs should be prioritised with regard to their environmental risk and a monograph system for prioritised API should be developed.

Finally, the proposed regulations would contribute to a legal harmonisation of European substance law (Pharmaceutical Directives/Regulation with REACH Regulation, Biocides Regulation, and Plant Protection Products Regulation).

Conclusion

According to international and European environmental information law, there is in principle a right of access to the ERAs of pharmaceuticals and their official assessment reports. The rule exemption relationship between transparency (access to information) and secrecy (rejection), as laid down in the environmental information law, is reversed in the pharmaceutical sector, in particular due to the practised blanket classification as CCI by the MAH, without any obligatory rules of procedure or administrative verification. As a result, the MAH could arbitrarily undermine the public's right to information. This is not compatible with the transparency requirement of environmental information law. Even if a need for secrecy should be assumed for individual parts of the environmental dossier, this may not apply in any case to the outcomes of ERA (PEC/PNEC values including all underlying ecotoxicity endpoints). With regard to the public interest to be taken into account in the adoption of a reason for refusal, the secrecy of PEC/PNEC as values of hazard prevention would not be compatible with environmental information law.

In addition, the dissemination of superficial information in the format of the PAR does not fulfil the mandate of active access to information, which explicitly requires the updating and dissemination of ERAs. Also for this, conflicting CCI is partly responsible.

The identified contradiction could be resolved through a publicly accessible database of APIs and their ERA results (including PECs and PNECs and underlying ecotoxicity endpoints). The prerequisites for this are binding

rules for data sharing and for classification procedures for CCI. This would be the basis for a monograph system, as under the European regulations on chemicals, plant protection products, and biocides. The database should also be extended to "old" APIs for which environmental risk assessments have not yet been carried out.

The improved accessibility of data will allow developing EQS and risk mitigation measures and further research to be undertaken to reduce systematically the impact of pharmaceuticals on the environment.

Abbreviations

API: active pharmaceutical ingredient; CCI: commercially/industrial confidential information; CRED: criteria for reporting and evaluating ecotoxicity data; ECHA: European Chemicals Agency; EIC: environmental introduction concentration; EID: Environmental Information Directive; EMA: European Medicines Agency; EPAR: European public assessment report; EQS: environmental quality standards; ERA: environmental risk assessment; GLP: good laboratory practice; HMA: Heads of Medicines Agencies; HMP: human medicinal product; MAH: marketing authorisation holder; PAR: public assessment report; PEC: predicted environmental concentration; PNEC: predicted no effect concentration; TRIPS: Agreement on Trade-Related Aspects of Intellectual Property Rights; UIG: German Environmental Information Act; VMP: veterinary medicinal product.

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Authors' contributions

Carolin Floeter contributed to the chapter Background, initiating the legal analysis. Kim Oelkers is the main author of the article. Both authors read and approved the final manuscript.

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Availability of data and materials

The database "PharmNet" analysed during the current study is available under the link https://www.pharmnet-bund.de/static/en/index.html.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. European Commission (2017) Strategic approach to pharmaceuticals in the environment: Roadmap
2. Beek T aus der, Weber F-A, Bergmann A et al. (2016) Pharmaceuticals in the environment: global occurrence and potential cooperative action under the Strategic Approach to International Chemicals Management (SAICM)
3. Vidaurre R, Lukat E, Steinhoff-Wagner J et al (2016) Konzepte zur Minderung von Arzneimitteleinträgen aus der landwirtschaftlichen Tierhaltung in die Umwelt. UBA Fachbroschüre, Dessau-Roßlau
4. Ebert I, Amato R, Hein A et al (2015) Pharmaceuticals in the environment-avoidance, reduction and monitoring. UBA Background, Dessau-Roßlau
5. European Commission (2019) European Union Strategic approach to pharmaceuticals in the environment: communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee. COM(2019) 128 final
6. BIO Intelligence Service (2013) Study on the environmental risks of medicinal product: Final Report. Prepared for Executive Agency for Health and Consumers
7. Gunnarsson L, Snape JR, Verbruggen B et al (2019) Pharmacology beyond the patient—the environmental risks of human drugs. Environ Int 129:320–332. https://doi.org/10.1016/j.envint.2019.04.075
8. Ebert I, Hein A (2016) Veterinary pharmaceuticals—environmental risk assessment of pharmaceuticals: how to prioritise the active substances? Dessau-Roßlau
9. Athing M, Brauer F, Duffek A et al (2018) Recommendations for reducing micropollutants in waters. UBA Background, Dessau-Roßlau
10. Do OR, Informacij U, Zadevah O (1998) Convention on access to information, public participation in decision-making and access to justice in environmental matters. Aarhus Convention, Aarhus
11. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, pp 67–128), last amended by Article 2 of Amending Regulation (EU) 2019/5 of 11.12.2018 (OJ 2019 No L 4, p 24)
12. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, pp 1–66), last amended by Art. 149 para. 1 Amending Regulation (EU) 2019/6 of 11.12.2018 (OJ 2019 No. L 4 p 43)
13. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (OJ L 4, 7.1.2019, pp 43–167)
14. Regulation (EC) No 726/2004 of the European Parliament and of the council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, pp 1–33), last amended by Article 1 of Amending Regulation (EU) 2019/5 of 11.12.2018 (OJ 2019 No L 4, p 24)
15. Dettling H-U, Apeltauer J (2017) Informationsschutz nach der neuen EMA_Transparenz-Politik und der Verordnung (EU) Nr. 536/2014 über klinische Prüfungen. In: Voit W (ed) Transparenz/Neue Produkte. Nomos Verlagsgesellschaft mbH & Co. KG, Baden-Baden, pp 9–158
16. Gärtner S (1998) Rechtliche Regelungen zu den Umweltauswirkungen von Arzneimitteln. In: Hessische Landesanstalt fütr Umweltschutz (ed) Arzneimittel in Gewässern - Risiko für Mensch, Tier und Umwelt, vol 254, Wiesbaden, pp 59–64
17. EMA/CHMP (2018) Guideline on the environmental risk assessment of medicinal products for human use. Draft: EMEA/CHMP/SWP/4447/00 Rev. 1
18. EMEA/CHMP (2006) Guideline on the environmental risk assessment of medicinal products for human use: EMEA/CHMP/SWP/4447/00 corr 2
19. EMEA/CVMP/VICH (2000) Guideline on environmental impact assessment for veterinary medicinal products—phase 1: CVMP/VICH/592/98-FINAL. VICH GL 6
20. EMEA/CVMP/VICH (2004) Environmental impact assessment for veterinary medicinal products—phase II Guidance: CVMP/VICH/790/03-FINAL. VICH GL 38
21. EMA (2009) Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework: EMEA/P/24143/2004
22. EMEA (2008) Status of EMEA scientific guidelines and European pharmacopoeia monographs and chapters in the regulatory framework applicable to medicinal products: EMEA/42371/2008
23. Kern K (2010) Rechtliche Regulierung der Umweltrisiken von Human- und Tierarzneimitteln, 1. Aufl. Berliner stoffrechtliche Schriften, vol 8. Lexxion Der Jur. Verl., Berlin

24. European Commission (2009) Volume 6C guidance on the assessment of environmental risks of veterinary medicinal products: notice to applicants veterinary medicinal products
25. Umweltinformationsgesetz in der Fassung der Bekanntmachung vom 27. Oktober 2014 (BGBl. I S. 1643), Last amended by Article 2(17) G of 20.7.2017 on modernising the law on environmental impact assessment 4 (BGBl. I p. 2808): UIG
26. Epiney A, Diezig S, Pirker B et al. (eds) (2018) Aarhus-Konvention, 1st ed. nomos
27. Karg M (2018) §§ 1-14 UIG. In: Gersdorf H, Paal B (eds) BeckOK Informations- und Medienrecht
28. Reidt O, Schiller G (2017) UIG. In: Landmann Rv, Hansmann K, Rohmer G et al. (eds) Umweltrecht: Kommentar, 79. Erg.-Lfg., Stand: Februar 2016. Beck, München
29. Deutscher Bundestag (2004) Drucksache 15/3406
30. European Court of Justice (2005) Directive 90/313/EEC - Freedom of access to information on the environment - Request for information - Requirement to give reasons in the event of refusal - Mandatory time-limit - Failure of a public authority to respond within the time-limit for reply - Implied refusal - Fundamental right to effective judicial protection. European Court Reports 2005 I-03299
31. United Nations, Economic Commission for Europe (2014) The Aarhus convention: an implementation guide, 2nd edn. Economic Commission for Europe, Geneva
32. Schlacke S, Schrader C, Bunge T (2010) Informationsrechte, Öffentlichkeitsbeteiligung und Rechtsschutz im Umweltrecht: Aarhus-Handbuch. E. Schmidt, Berlin
33. European Commission (2015) Commission Implementing Decision (EU) 2015/495 of 20 March 2015 establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council
34. European Commission (2018) Commission Implementing Decision (EU) 2018/840 - of 5 June 2018 - establishing a watch list of substances for Union-wide monitoring in the field of water policy pursuant to Directive 2008/105/EC of the European Parliament and of the Council and repealing Commission Implementing Decision (EU) 2015/495
35. Andrä J, Beyer F, Cornelissen G et al (2018) PharmCycle: a holistic approach to reduce the contamination of the aquatic environment with antibiotics by developing sustainable antibiotics, improving the environmental risk assessment of antibiotics, and reducing the discharges of antibiotics in the wastewater outlet. Environ Sci Eur 30(1):18692. https://doi.org/10.1186/s12302-018-0156-y
36. Schmitt H, ter Laak T, Duis K (2017) Development and dissemination of antibiotic resistance in the environment under environmentally relevant concentrations of antibiotics and its risk assessment. UBA Texte 01/2017, Dessau
37. Heads of Medicines Agencies. http://mri.medagencies.org/. Accessed 01 July 2019
38. EMA/CHMP (2016) Concept paper on the revision of the 'Guideline on the environmental risk assessment of medicinal products for human use' (EMEA/CHMP/SWP/4447/00 corr 2): EMA/CHMP/SWP/65429/2016
39. EMA/CHMP (2016) Q&A on the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use: EMA/CHMP/SWP/44609/2010, Rev.1
40. EMA/CVMP (2016) Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH Guidelines GL 6 and GL 38: EMA/CVMP/ERA/418282/2005-Rev.1-Corr
41. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (Text with EEA relevance) (OJ L 396, 30.12.2006, pp 1–849), last amended by Article 1 of Amending Regulation (EU) 2019/957 of 11.6.2019 (OJ No L 154, p 37): REACH Regulation
42. Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products Text with EEA relevance (OJ L 167, 27.6.2012, pp 1–123), last amended by Article 1 of Amending Regulation (EU) No 334/2014 of 11.3.2014 (OJ No L 103, p 22; OJ No L 305, p 55): Biocidal Product Regulation
43. Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC (OJ L 309, 24.11.2009, pp 1–50), last amended by Art. 47 EU Fertiliser Products Regulation of 5.6.2019 (OJ No. L 170 p 1): Plant Protection Product Regulation
44. Montforts MHMM The trigger values in the environmental risk assessment for (veterinary) medicines in the European Union: a critical appraisal. RIVM rapport 601500002. RIVM report 601500002/2005, Bilthoven
45. Brückner J, Westphal K (2018) Risikobewertung von Tier- und Human-Arzneimitteln. SETAC GLB GDCh Regulatorische Ökotoxikologie 2018, Dessau-Roßlau
46. Schäffer A, Filser J, Frische T et al. (2018) The Silent Spring: On the need for sustainable plant protection. Diskussion/Deutsche Akademie der Naturforscher Leopoldina, Nr. 16. Deutsche Akademie der Naturforscher Leopoldina e.V. - Nationale Akademie der Wissenschaften, Halle (Saale)
47. Führ M, Kleihauer S (2012) Bestimmung von stoffbezogenen Umweltqualitätskriterien: Ein Methodenvergleich von nationalen und internationalen Bewertungsgrundlagen. UBA Texte 38/2012, Dessau-Roßlau
48. Bund/Länderausschuss für Chemikaliensicherheit (2003) Arzneimittel in der Umwelt Auswertung der Untersuchungsergebnisse: Bericht an die 61. Umweltministerkonferenz (UMK) am 19./20. November 2003 in Hamburg
49. EMA (2018) European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure: EMA/821278/2015
50. EMEA/CVMP (2008) Reflection Paper on the implementation of Directive 2001/82/EC, as amended, in respect to the assessment of environmental risks of veterinary medicinal products: EMEA/CVMP/182112/2006-consultation
51. European Commission (2017) Volume 6A procedures for marketing authorisation. Chapter 1. Marketing authorisation: notice to applicants veterinary medicinal products
52. Moermond CTA, Kase R, Korkaric M et al (2016) CRED: criteria for reporting and evaluating ecotoxicity data. Environ Toxicol Chem 35(5):1297–1309. https://doi.org/10.1002/etc.3259
53. Ågerstrand M, Küster A, Bachmann J et al (2011) Reporting and evaluation criteria as means towards a transparent use of ecotoxicity data for environmental risk assessment of pharmaceuticals. Environ Pollut 154:2487–2492. https://doi.org/10.1016/j.envpol.2011.06.023
54. European Chemicals Agency ECHA (2019) information on chemicals. https://echa.europa.eu/information-on-chemicals. Accessed 20 June 2019
55. Rönnefahrt I (2014) Monograph system of active pharmaceutical substances: necessity, challenges and perspectives. Workshop "Monograph system on active pharmaceutical substances", Brussels
56. EMEA (2006) European Medicines Agency policy on access to documents: (related to pharmaceuticals for human and veterinary use), EMA/729522/2016. Policy/0043
57. EMA (2018) EMA policy on access to documents: POLICY/0043, EMA/729522/2016
58. European Court of Justice (1999) Commission of the European Communities v. Federal Republic of Germany, judgement of the Court (Sixth Chamber). InfoCuria - Case-law of the Court of Justice ECLI:EU:C:1999:395
59. CMDv (2017) Best Practice Guide for Veterinary Decentralised Procedure (DCP): EMA/CMDv/63793/2006
60. CMDv (2017) Best Practice Guide for Veterinary Mutual Recognition Procedure (MRP): EMA/CMDv/83618/2006
61. CMDh (2017) Q&A—Product Information/Information on Medicinal Products: CMDh/275/2012, Rev.1
62. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use
63. HMA/CMDh (2014) Public Assessment Report. Scientific discussion: CMDh/223/2005
64. EMA. https://www.ema.europa.eu/en/medicines/. Accessed 17 Jun 2019
65. Agence nationale de sécurité du médicament et des produits de santé. http://agence-prd.ansm.sante.fr. Accessed 17 Aug 2019

66. Agenzia Italiana del Farmaco. farmaci.agenziafarmaco.gov.it/bancadati-farmaci/. Accessed 17 Aug 2019
67. National Authority of Medicines and Health Products. www.infarmed.pt/infomed/inicio.php. Accessed 17 Aug 2019
68. Medical Products Agency. http://www.lakemedelsverket.se/LMF/. Accessed 17 Aug 2019
69. Ji K, Liu X, Lee S et al (2013) Effects of non-steroidal anti-inflammatory drugs on hormones and genes of the hypothalamic-pituitary-gonad axis, and reproduction of zebrafish. J Hazard Mater 254–255:242–251. https://doi.org/10.1016/j.jhazmat.2013.03.036
70. Bundesverwaltungsgericht (2009). ECLI:DE:BVerwG:2009:190109B 20F23.07.0
71. Bundesverwaltungsgericht (2009). ECLI:DE:BVerwG:2009:240909 U7C2.09.0
72. Bundesverwaltungsgericht (2008). ECLI:DE:BVerwG:2009:280509 U7C18.08.0]
73. Prinz M (2014) Der Schutz von Betriebs- und Geschäftsgeheimnissen im Informationsfreiheitsrecht. Wissenschaftliche Schriften der WWU Münster, vol 11. MV-Verlag
74. Meßerschmidt K (2011) Europäisches Umweltrecht: Ein Studienbuch. Beck, München
75. Agreement on Trade-Related Aspects of Intellectual Property Rights, Annex 1C of the Agreement Establishing the World Trade Organization (WTO), which was signed in Marrakesh on 15 April 1994 and approved on behalf of the European Community by Council Decision 94/800/EC of 22 December 1994 concerning the conclusion on behalf of the European Community, as regards matters within its competence, of the agreements reached in the Uruguay Round multilateral negotiations (1986–1994): TRIPS Agreement
76. Kokott J (2016) Opinion of Advocate General Kokott: Case C-442/14.Bayer CropScience SA-NV Stichting De Bijenstichting v College voor de toelating van gewasbeschermingsmiddelen en biociden. Reports of Cases
77. Gersdorf H, Paal B (eds) (2018) BeckOK Informations- und Medienrecht
78. HMA/EMA Working Group on Transparency (2012) Principles to be applied for the implementation of the HMA/EMA guidance on the identification of CCI and PPD in MA applications
79. EMA/HMA Working Group on Transparency (2012) Guidance Document on the Identification of Commercially Confidential Information and Personal Data within the Structure of the Marketing Authorisation (Ma) Application - Release of Information after the Granting of a Marketing Authorisation
80. Montforts MHMM, Keessen A (2008) Openbaarheid van milieu-informatie bij registratie van (dier)geneesmiddelen. RIVM Briefrapport 601500006/2007. RIVM Briefrapport 601500006/2007
81. ECHA (2017) Guidance on data-sharing. Version 3:1
82. Küster A, Adler N (2016) Pharmaceuticals in the environment—make ideas work: key measures to reduce pharmaceuticals' emissions. UBA Position, Dessau-Roßlau

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