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Improving Environmental Risk Assessment of Human Pharmaceuticals

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ABSTRACT: This paper presents 10 recommendations for improving the European Medicines Agency's guidance for environmental risk assessment of human pharmaceutical products. The recommendations are based on up-to-date, available science in combination with experiences from other chemical frameworks such as the REACH-legislation for industrial chemicals. The recommendations concern: expanding the scope of the current guideline; requirements to assess the risk for development of antibiotic resistance; jointly performed assessments; refinement of the test proposal; mixture toxicity assessments on active pharmaceutical ingredients with similar modes of action; use of all available ecotoxicity studies; mandatory reviews; increased transparency; inclusion of emission data from production; and a risk management option. We believe that implementation of our recommendations would strengthen the protection of the environment and be beneficial to society. Legislation and guidance documents need to be updated at regular intervals in order to incorporate new knowledge from the scientific community. This is particularly important for regulatory documents concerning pharmaceuticals in the environment since this is a research field that has been growing substantially in the last decades.

INTRODUCTION

Pharmaceuticals were first identified to pose environmental risks in the 1990s, and since then the number of available monitoring and effect studies has increased steadily. Today, several hundred active pharmaceutical ingredients (APIs) have been found in sewage water, surface water, groundwater, soil, air, or biota in concentrations from sub-ng/L to more than μg/L.[1,2] Thus far, there are several examples of APIs convincingly shown to cause effects on organisms in the environment. The first example is the estrogenic substance ethinylestradiol causing impaired reproduction in fish.[3,4] The collapsing vulture populations in India and Pakistan, as a result of renal failure after feeding on dead cattle treated with the nonsteroidal painkiller diclofenac, constitutes the second example.[5] A third is the promotion of antibiotic resistance in bacteria in environments exposed to direct discharges from antibiotic manufacturing.[6−9] There are also examples of effects from antiparacitic agents such as sheep-dips and ivermectin.[10,11] Pharmaceutical classes identified to be of environmental concern include, for example, steroidal hormones, antibiotics, analgesics, parasiticides, and antianxiety-drugs.[2,12−15]

The purpose of safety assessments for pharmaceutical products is to show that the medicine is effective and that its benefits outweigh any potential side-effects. Before market approval of a new pharmaceutical product its pharmacological effects and side effects are therefore investigated extensively in preclinical and clinical tests. Consequently, the biological effects of APIs are well-known, certainly in comparison to the situation for industrial chemicals.

Based on the knowledge that APIs could constitute an environmental risk, the European Medicines Agency's (EMA) guideline on environmental risk assessment (ERA) of medicinal products for human use came into force in 2006.[16] The guideline is in accordance with the directive for medicinal products for human use (Article 8(3))[17] and has been reinforced through a Q&A-document that clarifies specific issues.[18] The EMA-guideline applies to all new marketing authorization applications. However, vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, and lipids are exempted since they are considered unlikely to result in significant risk to the environment. In addition, there are specific guidelines for pharmaceutical substances for veterinary

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Table 1. Ten Recommendations for Improving the European Medicines Agency's Guideline on Environmental Risk Assessment of Medicinal Products for Human Use

1. Require environmental risk assessment also for products put on the market before 2006

We recommend that environmental risk assessments are performed also on products approved before the European Medicines Agency's guideline came into force. This would provide relevant environmental information for all active pharmaceutical ingredients that could be found in the environment.

2. Add requirements to assess the risk for development of antibiotic resistance

We recommend that information that enables assessment of the risk for increased antibiotic resistance development is included in the environmental risk assessment for antibiotic substances. This would provide a more accurate picture of the risks connected to the environmental occurrence of antibiotics.

3. Perform only one environmental risk assessment per active pharmaceutical ingredient

We recommend that pharmaceutical companies that produce/import the same active pharmaceutical ingredient submit a joint environmental risk assessment instead of each company producing a separate one for the same substance. This would increase consistency, and reduce animal testing as well as duplication of work.

4. Refine the tiered approach

We recommend that the tiered approach is refined to include pharmacological and toxicological data from the drug discovery process, as well as bioconcentration data. This would improve the prioritization process so that the ecotoxicity testing is focused on the most problematic substances and the most relevant test species.

5. Perform mixture toxicity assessments on active pharmaceutical ingredients with similar modes of action

We recommend that environmental risk assessments are performed for groups of active pharmaceutical ingredients with similar modes of action. This would enable a more accurate environmental risk assessment.

6. Mandate use of all available ecotoxicity studies

We recommend that all available ecotoxicity studies, of sufficient reliability and relevance, are used in the decision process. This would make better use of the available knowledge and may thereby add important information to the environmental risk assessment.

7. Include environmental risks in the risk-benefit analysis

We recommend that environmental risks are included in the risk-benefit analysis when a product is considered for market authorization. This would increase the importance of the environmental risk assessment and motivate pharmaceutical companies to perform the assessment on time.

8. Require review of the environmental risk assessments at regular intervals

We recommend that environmental risk assessments must be updated when significant new environmental information is available. This would bring forward the regulatory use of new scientific data and increase collaboration between stakeholders.

9. Include data from production of active pharmaceutical ingredients and formulations in the environmental risk assessments

We recommend that the risk associated with active pharmaceutical ingredient discharges from manufacturing sites is included in environmental risk assessments when reviewing updated dossiers of products already on the market. This would increase the relevance of the assessments by including a part of the life cycle of the product responsible for the highest environmental concentrations detected.

10. Increase transparency

We recommend that environmental risk assessments and information about manufacturing sites are made publicly available. This would enable use of that information for other purposes such as research and evaluation, as well as stimulate companies to take more environmental responsibility throughout their supply chains.

use,[19,20] and for pharmaceutical substances consisting of genetically modified organisms (GMOs).[21]

In Phase I of the risk assessment procedure described in the EMA-guidance, the predicted environmental concentration (PEC) for surface water is calculated and the octanol−water partition coefficient (K_{ow}) is measured. If the PEC-value is equal to or above 0.01 μg/L, a Phase II assessment is performed. APIs with a logK_{ow} > 4.5 are screened for PBT-properties (Persistence, Bioaccumulation, Toxicity). APIs that are known a priori to affect reproduction of vertebrates or invertebrates at concentrations below 0.01 μg/L should also enter Phase II, following a tailored risk assessment strategy that addresses its specific mechanism of action. In Tier A of Phase II, physicochemical, fate, and effect studies (standard studies are recommended) are reviewed and the predicted no effect concentration (PNEC) for water, groundwater and micro-organisms is calculated. If the ratio $PEC_{surfacewater}$:$PNEC_{water}$ is above 1, an extended environmental fate and effect assessment, according to Tier B in Phase II, is required.[16]

A reliable and relevant prospective risk assessment procedure is the backbone of an effective and successful environmental policy. To achieve this, the assessment procedure has to be based on best available science, meaning that regular updates are needed. The legal requirement sets the lowest acceptable limits and it is therefore important to make sure that these limits correspond with the environmental protection goals. For pharmaceuticals, the primary purpose of the ERA is to provide information about the possible risks associated with a given product. An identified environmental risk with a pharmaceutical intended for human use is not considered a valid reason for denying market approval.

According to the guidance document, the ERAs should be performed by companies and evaluated by regulators. So far, it has been difficult to get an overview of how many ERAs for human pharmaceuticals have been performed since the guideline came into force. There is no publicly available record of ERAs and the responsibility for evaluation is divided between EMA and national competent authorities in Europe. During 2011−2012, EMA administrated and evaluated 42 ERAs, of which 20 required phase II assessments.[22] The German Federal Environment Agency (UBA), one of the largest contributing competent authorities on this matter, administrated and evaluated in total 120 ERAs during the years 2006−2014. Approximately 10% of the ERAs resulted in the conclusion that the pharmaceutical substance posed a potential environmental risk.[2]

We have analyzed the regulatory process for ERA of APIs and identified several aspects which are proposed to be included in future updates of the EMA-guideline. Ten recommendations for how to improve the current guideline are presented (Table 1). These recommendations are based on the results from research performed in the field of pharmaceuticals in the environment and on other types of regulatory frameworks for chemicals regulation, such as the REACH-legislation, and the biocide and plant protection product regulations.[23−25] The recommendations are presented here in the order of the risk assessment process, not in the order of importance. It is not our intention to rewrite the existing guidelines. Hence, we do not provide the detail that will be required in a new guideline; that detail would be agreed and written when the current guideline is updated.

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THE 10 RECOMMENDATIONS

1. Require Environmental Risk Assessment Also for Products Put on the Market Before 2006. The EMA-guideline only applies to new marketing authorization applications, that is, products that were put on the European Union (EU) market after the guideline came into force in 2006. Consequently, products approved before 2006 have not been, and will not be, assessed for environmental risk in the current system. There are no reasons to believe that the risks posed by a substance, or the need for a risk assessment, would depend on the date of market approval. German consumption data also show high and increasing sales numbers for some of the old APIs.[2] Consequently there are no scientific arguments for such a division and it can thus be seen more as a pragmatic approach to facilitate the phasing in of new rules.

A similar solution was previously used for industrial chemicals: up until 2007 there were separate rules for market introduction of "new" and "existing" industrial chemicals.[26−29] However, with the implementation of the new REACH-regulation this division is now abandoned. REACH covers all industrial chemicals regardless of the date when they were put on the market.[30] The same strategy is also used in the biocide and plant protection product regulations.

A reliable ERA is a prerequisite for proportionate risk management decisions such as the inclusion of a substance in the environmental monitoring program within the Water Framework Directive,[31] or attempts to reduce emissions. Unfortunately, recent studies show and acknowledge that environmental information is missing for many APIs.[32−35] When substances/products are exempted from testing, like "existing" pharmaceuticals are in the EMA-guideline, "no data" is treated as "no hazard", meaning that if no ecotoxicological information is available, then the API is considered nontoxic for organisms in the environment in a risk management situation. This approach is *risk seeking*, since it will underestimate environmental risks unless all APIs that lack ecotoxicity studies also lack environmental effects. In contrast, the hazard classifications of pharmaceutical products performed by the Stockholm County Council in Sweden build on a *risk averse* (precautionary) approach.[36] In that system, products lacking environmental information are assigned into the highest hazard classification category. This in turn may influence the risk management decisions since products without environmental data may be deselected in favor of products with information stating low environmental impact.[37] (For a discussion about risk-neutral approaches to risk management, see[38]).

Since the less strict rules for pharmaceutical products registered before 2006 are not motivated from a scientific perspective and since environmental data are missing for many APIs, we recommend that the information requirements and requirement to perform ERA should encompass all pharmaceutical products on the EU market.

One obvious disadvantage of widening the scope to include also products put on the EU market before 2006 is the increased costs, both for regulators and pharmaceutical companies. However, considering the overall cost of developing a new pharmaceutical product (often several billion USD[39]), the additional cost for the ERA is tiny. Companies could also perform the ERA in collaboration with other producers/importers of the same substance to reduce costs and animal testing (see recommendation number 3).

Today, all ERAs are evaluated by competent authorities and to be able to continue with this also for existing products, extra resources are probably needed. An alternative strategy could be to put greater responsibility on the pharmaceutical industry by using a similar approach as the REACH-legislation, where manufacturers/importers of chemicals are responsible for data submission and for performing risk assessments, and only a part of the submitted assessments are evaluated by regulators. It should also be stressed that a well-designed tiered risk assessment approach (see recommendation number 4) has the potential of limiting the workload for both regulators and the pharmaceutical companies and still improve the scientific basis for risk assessment.

Allocation of the responsibility for generic products also needs to be discussed. One possible solution is to use the same approach as is used within the REACH-legislation, where manufacturers as well as importers of substances and products are responsible for performing ERAs.

2. Add Requirements to Assess the Risk for Development of Antibiotic Resistance. The risk of promotion of antibiotic resistant bacteria is by far the greatest human health concern with regards to pharmaceuticals in the environment.[1] Antibiotics, possibly in conjunction with other chemicals such as heavy metals and antibacterial biocides, have the potential to select for resistant strains also outside of our bodies.[40] Given sufficient exposure, antibiotics in the environment may therefore favor the spread of resistant pathogens. Importantly, antibiotics can also promote harmless "environmental" bacteria carrying novel resistance factors, and when they increase in numbers under a selection pressure, there is increased risk for transfer of novel resistance elements to pathogens.[41,42] A comprehensive human health risk assessment for antibiotics in the environment is complicated,[43] but on the other hand a clearly recognized risk factor is if the antibiotics reach concentrations that select for resistant strains. Recent research suggests that such minimal selective concentrations (MSCs) can be very low.[44]

Several experimental methods have been proposed to generate MSCs for antibiotics, but it is recognized that there is a need to evaluate the sensitivity and relevance of such tests; also such data are still only available for a few antibiotics. One possible way to estimate MSCs broadly is to take advantage of already existing and publicly available data in the EUCAST database[45] on the potency of antibiotics to different pathogenic bacteria, as assessed by minimal inhibitory concentrations (MICs) (i.e., the concentration where no bacterial growth occur). The MSC for a resistant strain is, by necessity, lower than the MIC of the corresponding wild type bacterium, but how much lower would be dependent on the specific resistance mechanisms involved. The lowest MIC determined with confidence for any species would therefore provide an upper concentration limit of the possible MSC that would apply to, and be protective for, all bacterial species. Most likely, there will be species that are more sensitive (i.e., have a lower MIC), than those pathogens covered in the EUCAST database, and for that reason a safety factor is proposed to be added. Also, acknowledging that the MSC will be lower than the MIC, an additional safety margin should be included. Taken together, given the urgency to assess risk for resistance promotion, we therefore propose to include an assessment based on publicly available MIC data in the ERA for antibiotics. Similar ideas have earlier been proposed by Tello et al.[46] Eventually, the legislation should be refined by including data obtained from

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assays dedicated to directly assess the MSC rather than the MIC. This could for example involve the establishment of complex microbial communities in the lab under different antibiotic exposure concentrations, followed by analyses of changes in the abundance of resistant bacteria and resistance genes.

3. Perform Only One Environmental Risk Assessment Per Active Pharmaceutical Ingredient. According to the first line in the EMA-guideline, products are assessed one-by-one, meaning that there can be several ERAs for the same API. Apart from duplication of work and increased animal testing, this may also affect the credibility and coherence of the process, and the ability to assign a proper risk management option, if the different risk assessments come to different conclusions about risk.

An example of when risk assessors arrived at different conclusions comes from the Swedish voluntary classification system for pharmaceuticals (often called the FASS-system).[47] Here, the sex hormone estradiol was assessed by eight pharmaceutical companies and this resulted in four different conclusions regarding the environmental risk associated with this substance. In five of the risk assessments it was concluded that too few ecotoxicity studies were available to enable a classification. In the three other assessments, three different classifications were proposed: insignificant risk, moderate risk and high risk. Reasons for the variations in the conclusions can be attributed to differences in the exposure assessments, use of different assessments factors and use of different ecotoxicity studies.[47] Reviews of risk assessments for other types of chemicals show similar inconsistencies when several institutions assess the same substance. How toxicity studies were weighted and evaluated was an important aspect explaining the different conclusions for these substances.[48,49]

The REACH-legislation uses the opposite approach by encouraging producers/importers of the same chemical substance to share data from animal testing. Only in specific cases where proper justifications are provided are companies allowed to hand in a separate risk assessment (Article 11(1,3)).[23] The motivation behind this approach is the 3R principle (replacement, reduction and refinement), which is aimed at reducing animal testing. Also the plant protection product regulation offers producers the option to hand in a joint application for the active substance (Article 7(1)).

To deal with possible inconsistencies in ERAs for APIs, to reduce duplication of work, and to avoid redundant animal testing, we therefore recommend that ERAs are performed on the API level instead of product level. Since different exposure scenarios may occur, especially in connection to manufacturing, it may be necessary for each company to provide their own exposure assessment. This is also in accordance with the REACH-legislation.

4. Refine the Tiered Approach. The vast majority of the APIs for which an ERA is required go through the same test battery. An efficient test strategy must take into account the limitations in resources and testing capacity, as well as the overall aim to reduce the use of animals in ecotoxicity testing. Furthermore, relevant and sensitive end points have to be studied. This implies that the selected test methods for lower tier test should minimize the probability of false negatives (type II errors), while allowing for some false positives (type I errors). The reason for this is that false positives can be corrected at higher tiers, while the false negatives will not reach higher tiers and hence cannot be corrected. The purpose of a tiered approach is to separate APIs that are unlikely to be of environmental concern and focus resources on testing those APIs that could pose an environmental risk. Since resources for testing are limited, useful and adequate prioritization schemes for in-depth ecotoxicity testing of APIs are of great environmental importance.[50−52]

The EMA-guideline has a clear tiered approach. First, APIs that are considered unlikely to result in significant risk to the environment are exempted (e.g., vitamins, electrolytes, and amino acids). In the next step, referred to as phase I, environmental exposure is modeled and logK_{ow} is determined. In phase II, fate and effect testing are performed for products that exceed the trigger values in phase I.[53] However, ecotoxicity testing is still based on traditional studies developed for identifying toxic industrial chemicals, using end points such as lethality, growth and fecundity. Most APIs are designed to be nontoxic, but still affect biological systems in specific ways. Therefore, they may cause other types of effects compared to industrial chemicals. This should be reflected in a relevant test strategy, and therefore we suggest that the recommended effect studies in Phase II, Tier A are refined. The improvements that are needed are mainly related to aquatic vertebrates and not to invertebrates and algae, where we think the testing approach does not fall short in the same way.

An interesting alternative approach would be to use preclinical and clinical toxicological and pharmacological data from the drug discovery process in ERAs when conserved drug targets are likely to be present in the test organisms.[34,54,55] The testing may be optimized by first requiring simplified bioconcentration studies (e.g., without a depuration phase, and with a long duration time) on fish. APIs that show blood plasma or target tissue concentrations in fish far below those known to give rise to pharmacological responses in mammals when exposed at the PEC could be considered unlikely to cause effects on aquatic vertebrates, and further testing on fish may not be required.[56−58] The action limit for requiring in-depth testing, such as full lifecycle test or a mode of action based test, could be defined as a ratio between the plasma concentration in fish and the human (or mammalian) therapeutic plasma concentration. But how large that ratio should be needs to be evaluated with more data to strike a good balance between increased testing and risks of missing important information.[59]

The lipophilic property of a substance gives a rough estimate of its bioconcentration potential but good bioconcentration models are currently lacking. Fick et al. performed a screening study on blood plasma of fish exposed to sewage effluents.[56] When comparing the theoretically calculated plasma concentrations with the experimentally determined values, some APIs did not bioconcentrate to blood plasma as expected. The progestin levonorgestrel exceeded the predicted value considerably, possibly due to the presence of specific binding proteins.[60] Such high bioconcentration of levonorgestrel agrees well with its ability to reduce egg production in fish and frogs already at exposure concentrations of 1 ng/L.[13,61] In addition, in the screening study with fish exposed to sewage effluents, other APIs bioconcentrated less than expected based on calculated lipophilic properties.[56] This demonstrates the value of using actual empirical data to estimate bioconcentration in a tiered risk assessment context.

Pharmacological and toxicological data could also be used to guide in the selection of test species and test design.[34,54] Knowledge about the presence of drug targets in different species may facilitate identification of species and end points

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that are expected to be sensitive to the pharmacological or toxicological mode of action, and hence provide a guide to what species and end points that are suitable to include in the ERA.[55,57] The current chronic tests in phase II could however not be (completely) replaced by tests with end points related to modes of action, since potential effects that are not related to interactions with effects/targets known in mammals are not likely to be accurately reflected using a mode of action approach.

The most important advantage of this recommendation is that resources are focused and tailored. The pharmaceutical industry, with its long tradition of showing safety of their products, is given the possibility to use available substance-specific knowledge in the environmental field as well. Specific methods and strategies for transfer of pharmacological and toxicological data to be used in ERA do however need to be developed and standardized. An example demonstrating the methodology to use when designing a specific mode-of-action test can be found in Margiotta-Casaluci et al.[62] Disadvantages with the recommendation include increased demand on pharmaceutical companies and regulatory agencies, since it will result in a wider range of studies that need to be performed and assessed.[34] To handle this, additional training and guidance may be needed.

5. Perform Mixture Toxicity Assessments on Active Pharmaceutical Ingredients with Similar Modes of Action. Estrogenic chemicals have been demonstrated to have additive effects at environmentally relevant concentrations.[63] It has also been shown to be possible to accurately model the effects of complex mixtures of estrogenic chemicals at the whole river catchment scale.[64] This highlights the possibility for underestimating the exposure and, therefore, the risk posed by real-life mixtures of chemicals that act via a similar mode of action. In addition, environmentally relevant concentrations of three progestagenic APIs (levonorgestrel, norethindrone, and progesterone) inhibit egg development in frogs in a similar manner. The three progestagens interrupted formation of vitellogenic oocytes, indicating suppressed vitellogenesis, after exposure to low ng/L concentrations in adult frogs.[65] This implies that these progestagens may act additively and that the current approach to evaluate the risk for single APIs may underestimate the risk for this group of APIs.

To further increase the relevance of the ERA process, we therefore recommend that the cumulative risk for groups of APIs with similar modes of action is assessed. Such an approach could give important insights regarding actual risk and, to some degree, how to handle mixture effects in a transparent and readily applicable manner.[50,66,67] Several theoretical models have been developed and applied to predict mixture toxicity in the context of ERA. These models are largely based on two principles referred to as concentration addition (CA) and independent action (IA), which were proposed to describe mixture effect of components having similar and dissimilar modes of action, respectively (e.g.,[68,69]). Although we are fully aware that it may be difficult to establish the exact mode of action for many APIs in nontarget organisms, the examples on estrogenic chemicals and progestagenic APIs in fish and frogs provided above still indicate that the CA-model could be used for deriving more refined risk estimates. The most straightforward approach would be to apply the so-called PEC/PNEC summation method, which simply sums up the PEC/PNEC quotient for all those APIs that have similar mode of action and are of relevance for a particular exposure scenario.[66] It uses available ecotoxicity data and does not require environmental measurements, which means that the PECs and PNECs that are required for individual APIs in the EMA-guideline are already available, at least for those APIs for which Phase II analyses have been made. Another simple approach is to multiply each individual PNEC-value with a mixture correction factor that equals the number of chemicals present in a mixture.[66] Analogous to the PEC/PNEC summation method, as chronic data for individual APIs are available, this method does not require additional data demands.

6. Mandate Use of All Available Ecotoxicity Studies. The EMA-guideline recommends use of ecotoxicity studies following Good Laboratory Practices (GLP) and internationally standardized guidelines provided by the Organisation for Economic Co-operation and Development (OECD). Standard studies have, if the strict instructions for how to perform and report them are followed, high reliability (i.e., intrinsic quality). The OECD standard tests were developed for testing of industrial chemicals with a focus on traditional toxicological end points including acute effects, organ toxicity, cancer, and reproductive toxicity. Nevertheless, many APIs are not expected to be toxic in the traditional sense. Instead it is the pharmacological effect that is expected to be the main effect occurring at low doses (also described for recommendation 4). Therefore, for many APIs, standard studies might not be the most relevant choice.[70] Systematic exclusion of nonstandard studies in regulatory risk assessment was presented as one of the shortcomings in the U.S. Environmental Protection Agency's (USEPA) pesticide risk assessment process. For the herbicide atrazine, 74 nonstandard studies were excluded since they did not meet the USEPA criteria for inclusion in quantitative assessments, even though some of the studies were evaluated to be useful for investigating possible effects from atrazine. The risk assessment was instead based on a single standard study funded by the manufacturer showing no effect on reproduction.[71]

Alteration in natural behaviors, such as activity and feeding rate, are examples of end points that are not included in ERAs on a regular basis, even though they have ecological consequences. Recent ecotoxicity studies on a benzodiazepine anxiolytic drug reported increased activity, reduced sociality, and higher feeding rate in fish at concentrations close to those encountered in effluent-influenced surface waters.[12,72,73] Nonstandard studies may also open up for use of other test species than the standard set (i.e., fish, crustacean, and algae). In amphibians, the Müllerian ducts (precursors of the female reproductive tract in higher vertebrates) are sensitive targets for endocrine disrupting APIs and other substances. As a consequence, frogs exposed to the progestagen levonorgestrel during the larval period showed serious effects on female reproduction (a lack of oviducts and sterility) that would not have been discovered using standard test species.[74]

Due to the limitations with standard studies, we recommend that the ERAs should utilize all available ecotoxicity studies of sufficient reliability and relevance. The guidance document should explicitly state that the peer-reviewed literature has to be searched for relevant studies for all substances. A major advantage of this is that state of the art scientific knowledge may be used in a way that directly benefits society. Nonstandard studies also have the possibility of filling some of the existing data gaps. From an ethical point of view, by considering the use of animals in (eco)toxicity testing, and also that much research is paid by taxpayers' money, it is important

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to make use of already performed studies in all possible ways. This is also supported in other legislation, for example, REACH and the biocide regulation.

A disadvantage with including all available ecotoxicity data is the added workload for risk assessors, both in the data selection phase and when evaluating and interpreting ecotoxicity studies, since nonstandard studies in general include a variety of test designs, species and end points. Studies from the peer-reviewed literature have also been seen to lack in the necessary detailed reporting of methods and results,[75,76] which adds to the complexity of the evaluation process.[77] A new validated evaluation method, which puts equal demand on standard and nonstandard studies, can act as a guide in this process.[78]

7. Include Environmental Risks in the Risk-Benefit Analysis. The EMA-guideline states that the ERA "should not constitute a criterion for refusal of a marketing authorization". As a consequence, and because there is no penalty for noncompliance, the ERA is not prioritized by pharmaceutical companies and they can fail to deliver data or to deliver data in time. A recent study shows that 37% of the ERAs performed during 2011−2012 were submitted after the deadline, and studies were missing or of unsatisfactory quality for 83% of the submitted ERAs.[22] Including environmental risk in the risk-benefit analysis has therefore been suggested as a way to emphasize the importance of the ERA, although the intention is not to block marketing of new products. For veterinary pharmaceuticals it has, since 2004, been possible to refuse approval of products due to their environmental risk; however this has so far never happened.[2] Potentially, inclusion of environmental risks in the risk-benefit analysis could be an incentive for pharmaceutical companies to generate all requested studies, and to do this on time, since market introduction might be delayed otherwise. In addition, environmental risk assessment could be performed earlier in the drug development process for prompt identification of potentially problematic APIs.

A Swedish expert group for pharmaceuticals in the environment, appointed by the Government, suggested that the ERA should be included in the risk-benefit analysis, but emphasized that the extent of the environmental impact has to be weighed against the expected clinical benefits, from a medical and social perspective, and against the availability of alternative and equivalent treatments with less environmental impact.[79] The potential impact on public health from exposure to pharmaceutical residues in the environment should also be considered. The possibility to consider the environmental aspects in the authorization should only aim at denying further approvals of products containing a known problematic API when there are already products on the market that cover that cover the specific medical need to the same extent though associated with a lower environmental risk. The availability of effective drug treatments would therefore not be affected significantly if the environmental aspects were considered in the risk-benefit analysis.[79] Therefore, we recommend that the ERA is included in the risk-benefit analysis. This recommendation is also supported by regulators, and it is included in the Swedish Government's bill on chemicals.[2,80] Knowledge concerning risk-benefit analyses where environmental aspects are included can be transferred from other fields where this has been standard procedure for many years, for example, the biocide and plant protection product regulations.

8. Require Review of the Environmental Risk Assessments at Regular intervals. There are no formal demands in the EMA-guideline to review and update the ERAs for approved products. Hence, new knowledge can only impact future market authorizations, that is, new products. The flexibility needed to make use of new knowledge, such as results from ecotoxicity studies, sales statistics, and environmental monitoring is not present. This is problematic since environmental studies are scarce but new knowledge may emerge at any time. Knowledge from the European database on suspected adverse drug reactions could also be an important contribution to an updated assessment. Furthermore, knowledge generated in other legislation, such as monitoring data from the Water Framework Directive, could add important information to the ERAs.[81] Therefore, we recommend that the guidance document should include a requirement that the ERAs are reviewed at regular intervals and updated whenever new information that may lead to a change in the risk assessment conclusions become available. This recommendation is similar to the wording in Article 22 of the REACH-legislation: "Following registration, a registrant shall be responsible on his own initiative for updating his registration without undue delay with relevant new information and submitting it to the Agency in the following cases: [...] e) new knowledge of the risks of the substance to human health and/or the environment of which he may reasonably be expected to have become aware which leads to changes in the safety data sheet or the chemical safety report". For biocides and plant protection products the initial approval shall not exceed 10 years, and in some cases 5 years (Article 4(1) in the biocide regulation, Article 5 in the plant protection product regulation).

Updates of the ERAs should include a thorough review of the peer-reviewed literature and other publicly available sources such as reports from stakeholders. If new data become available and are assessed for possible inclusion in the ERA, but the data are not considered sufficient to change the conclusions in the ERA, the new data should still be included in the list of references, and the ERA should include an explanation on why the new data did not motivate an update of the conclusions. The date of the latest update should also be clearly available in the ERA.

In general, there is often a delay between generation of new scientific data and societal use of that particular information. The advantage of this recommendation is that new knowledge can potentially be considered and used as soon as it becomes available, or shortly thereafter. A requirement to carry out reviews at regular intervals also has potential to increase collaboration between stakeholders. Increased collaboration has been identified as a future need in risk assessments.[82] In addition, it would make better use of resources, in terms of laboratory animals and taxpayers' money.

9. Include Data from Production of APIs and Formulations in the Environmental Risk Assessments. The EMA-guideline only considers API use by patients, leaving out other parts of the pharmaceutical product's lifecycle, such as production of APIs and formulation. Due to the nature of industrial discharges, it is considerably more difficult to generate PECs for such emission routes than for patient usage and excretion.[9] Hence, an assessment based on MECs rather than PECs is proposed for manufacturing discharges, and this can normally only be done after marketing authorization. Discharges of APIs are very rarely regulated in any part of the world, but it is clear that pharmaceutical production can lead to substantial API discharges to the environment. There are

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several examples of discharges in the mg/L range, also of highly toxic APIs, including antibiotics, leading to unprecedented environmental contamination. Most examples of high discharges so far are from Asia, but there are also examples from U.S. and within the EU.[9] Importantly, that European citizens consume pharmaceutical products produced outside of the EU boarders, where discharges to the environment may be significant, creates a moral dilemma.[83] We firmly believe that our concern for the environment should go beyond boarders and therefore such environmental aspects must be handled within European legislation. Finally, discharges of antibiotics may lead to the promotion of antibiotic resistance, which clearly is of everyone's concern regardless of where the discharges take place.[7,8,42] Therefore, we recommend that the risk associated with API discharges from manufacturing sites is included in ERAs when reviewing dossiers, even if the discharges take place outside of EU borders.

If the risks associated with manufacturing discharges are assessed during the review, we also recommend that it should be possible to withdraw market authorization when discharges are considered "severe" and the companies have failed to reduce emissions despite being given warnings and appropriate time to adjust. There are presently no agreed methods for how to define acceptable API-emissions from production. However, there are risk-based methods available that identify safe long-term and short-term concentrations using approaches similar to those used in several legal frameworks.[84] Notably, the strategy proposed by Murray-Smith et al. does not encompass risks for antibiotic resistance development. It should be stressed that there are well documented examples of industrial API-discharges that we believe very few would consider "acceptable", even though they may not violate current laws,[9] motivating the need to create incentives to reduce such emissions.

10. Increase Transparency. There is currently low transparency in the ERA process for pharmaceutical products.[2] The EMA publishes European public assessment reports (EPARs) containing a summary of the environmental information, and such documents are currently available for 41 products, but ERA dossiers are not publicly available.[22] As a consequence, it is not possible for a third party to review and/or make use of the studies and conclusions from the pharmaceutical companies and the competent authorities. Therefore, we recommend that the ERA dossiers are made publicly available by EMA, preferably on the Web site for faster and more flexible access. For industrial chemicals under the REACH-legislation this is possible; registration data without confidential business information are available at the European Chemicals Agency's webpage (http://echa.europa.eu/information-on-chemicals/registered-substances).

Advantages with this recommendation are that external evaluation and comparison between different ERA dossiers would be possible. Previous evaluations of chemical risk assessments have identified several shortages in the process that should be considered. Examples include: how toxicity studies are interpreted differently in different assessments; how values influence assessments; differences in data selection between risk assessments for the same substance; and nontransparent use of assessment factors.[48,49,85−87] In addition, increased transparency can also be beneficial for the research community, since new environmental data can guide the design and prioritization of future studies. Unnecessary repetitive testing can also be avoided, thereby reducing animal testing. Regulatory work within other legal frameworks, for example, environmental monitoring, could moreover benefit from a greater access to environmental data.[2]

To improve transparency in this ERA process and to facilitate and safeguard use of nonstandard environmental data from the peer-reviewed literature in the regulatory process, steps toward increased collaboration between academia, governmental agencies and pharmaceutical industry need to be taken. We recommend that EMA develops an open access database containing summaries and references to all available ecotoxicity data, both industry study reports and peer-reviewed literature. As a starting point, the WikiPharma database from the MistraPharma program can be used.[35] To facilitate the process of adding studies to the database, collaborations with scientific journals could be established to ensure that all peer-reviewed studies for APIs are made available for ERA.

We also suggest that information on the manufacturer of the API and the specific manufacturing site(s), both for API production and formulation, becomes publicly available.[83] This would motivate producers to more carefully control discharges and improve wastewater treatment in the production chain, since this information would enable interested parties (for example researchers and journalists) to identify cases of severe environmental pollution and link it to the company selling the final product. This would in turn make it possible for consumers and the healthcare sector to deselect products that are produced in an environmentally unfriendly way. Today, the origin of APIs in pharmaceutical products is most often considered confidential information, which prevents consumers and purchasers from making environmentally informed decisions. Reporting the site of origin is common for various groups of consumer products and food items (e.g., fruit, meat, fish, seafood, clothes, and cars), and it should therefore also be possible for pharmaceutical products.

■ CONCLUSIONS

One could argue, from an ethical and resource effective perspective, that society has a responsibility to make use of research by incorporating new knowledge into legislation and guidance documents. The European Medicines Agency's guideline for environmental risk assessment for human pharmaceutical products is one example of a process that could benefit from doing this. In this paper we provide 10 recommendations for how this can be done. The recommendations vary in complexity and controversy, which makes the implementation of them differ in amount of effort needed for gaining acceptance of the change. Some recommendations might also need changes in the European Directive.[17]All of the recommendations are based on research performed in the field of pharmaceuticals in the environment, and from studying other European regulatory frameworks for chemicals. We believe that society as a whole would benefit from carefully considering the implementation of our recommendations, and that they could contribute to strengthening the protection of the environment.

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Notes

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■ REFERENCES

(1) BIO Intelligence Service. Study on the environmental risks of medicinal products. Final Report prepared for Executive Agency for Health and Consumers. 2013. http://ec.europa.eu/health/files/environment/study_environment.pdf.

(2) Küster, A.; Adler, N. Pharmaceuticals in the environment: Scientific evidence of risks and its regulation. *Philos. Trans. R. Soc., B* **2014**, *369*, 20130587.

(3) Jobling, S.; Nolan, M.; Tyler, C. R.; Brighty, G.; Sumpter, J. P. Widespread sexual disruption in wild fish. *Environ. Sci. Technol.* **1998**, *32*, 2498−2506.

(4) Desbrow, C.; Routledge, E. J.; Brighty, G. C.; Sumpter, J. P.; Waldock, M. Identification of estrogenic chemicals in STW effluent. 1. Chemical fractionation and in vitro biological screening. *Environ. Sci. Technol.* **1998**, *32*, 1549−1558.

(5) Oaks, J. L.; Gilbert, M.; Virani, M. Z.; Watson, R. T.; Meteyer, C. U.; Rideout, B. A.; Shivaprasad, H. L.; Ahmed, S.; Chaudhry, M. J.; Arshad, M.; Mahmood, S.; Ali, A.; Khan, A. A. Diclofenac residues as the cause of vulture population decline in Pakistan. *Nature* **2004**, *427*, 630−633.

(6) Larsson, D. G. J.; de Pedro, C.; Paxeus, N. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J. Hazard. Mater.* **2007**, *148*, 751−755.

(7) Kristiansson, E.; Fick, J.; Janzon, A.; Grabic, R.; Rutgersson, C.; Weijdegård, B.; Söderström, H.; Larsson, D. G. J. Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. *PloS One* **2011**, *6*, e17038.

(8) Bengtsson-Palme, J.; Boulund, F.; Fick, J.; Kristiansson, E.; Larsson, D. G. J. Shotgun metagenomics reveals a wide array of antibiotic resistance genes and mobile elements in a polluted lake in India. *Antimicrob. Resist. Chemother.* **2014**, *5*, 648.

(9) Larsson, D. G. J. Pollution from drug manufacturing: review and perspectives. *Philos. Trans. R. Soc., B* **2014**, *369*, 20130571.

(10) Virtue, W. A.; Clayton, J. W. Sheep dip chemicals and water pollution. *Sci. Total Environ.* **194−1997**, *195*, 207−217.

(11) Floate, K. D. Endectocide use in cattle and fecal residues: environmental effects in Canada. *Can. J. Vet. Res.* **2006**, *70*, 1−10.

(12) Brodin, T.; Fick, J.; Jonsson, M.; Klaminder, J. Dilute concentrations of a psychiatric drug alter behavior of fish from natural populations. *Science* **2013**, *339*, 814−815.

(13) Säfholm, M.; Norder, A.; Fick, J.; Berg, C. Disrupted oogenesis in the frog *Xenopus tropicalis* after exposure to environmental progestin concentrations. *Biol. Reprod.* **2012**, *86*, 126.

(14) Liebig, M.; Fernandez, A. A.; Blübaum-Gronau, E.; Boxall, A.; Brinke, M.; Carbonell, G.; Egeler, P.; Fenner, K.; Fernandez, C.; Fink, G.; Garric, J.; Halling-Sørensen, B.; Knacker, T.; Krogh, K. A.; Küster, A.; Löffler, D.; Cots, M. A.; Pope, L.; Prasse, C.; Römbke, J.; Rönnefahrt, I.; Schneider, M. K.; Schweitzer, N.; Tarazona, J. V.; Ternes, T. A.; Traunspurger, W.; Wehrhan, A.; Duis, K. Environmental risk assessment of ivermectin: A case study. *Integr. Environ. Assess. Manage.* **2010**, *6* (Suppl), 567−587.

(15) Runnalls, T. J.; Margiotta-Casaluci, L.; Kugathas, S.; Sumpter, J. P. Pharmaceuticals in the aquatic environment: Steroids and anti-steroids as high priorities for research. *Hum. Ecol. Risk Assess. Int. J.* **2010**, *16*, 1318−1338.

(16) *Committee for Medicinal Products for Human Use (CHMP). Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. Ref EMEA/CHMP/SWP/4447/00 corr 2*; European Medicines Agency: London, United Kingdom, 2006.

(17) *Directive 2001/83/EC of the European Parliament and the council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use*; European Parliament, 2001.

(18) *Questions and Answers on 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use'*, EMA/CHMP/SWP/44609/2010; European Medicines Agency, 2010.

(19) *Guideline on Environmental Impact Assessmenst (EIAS) for Veterinary Medicinal Products—Phase 1*, CVMP/VICH/592/98; CVMP/VICH/790/03; European Medicines Agency, 2000.

(20) *Guideline on the environmental impact assessment for veterinary medicinal products phase II*; European Medicines Agency: London, UK, 2004.

(21) *Environmental Risk Assessment for Medicinal Products Containing, Or Consisting, Of Genetically Modified Organisms (GMOs)*, CHMP/BWP/135148/04; European Medicines Agency, 2005.

(22) Caneva, L.; Bonelli, M.; Papaluca-Amati, M.; Vidal, J.-M. Critical review on the environmental risk assessment of medicinal products for human use in the centralised procedure. *Regul. Toxicol. Pharmacol.* **2014**, *68*, 312−316.

(23) *Regulation (EC) No 1907/2006 of the European Parliament and of the Council. 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*; European Parliament, 2006.

(24) *Regulation (EU) No 528/2012 of the European Parliament and the council of 22 May 2012 Concerning the Making Available on the Market and Use of Biocidal Products*; European Parliament, 2012.

(25) *Regulation (EC) No 1107/2009 of the European Parliament and 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*; European Parliament, 2009.

(26) *Council Directive 79/831/EEC of 18 September 1979 Amending for the Sixth Time Directive 67/548/EEC on the Approximation of the Laws, Regulations and Administrative Provisions Relating to the Classification, Packaging and Labelling of Dangerous Substances*; Council of the European Communities, 1979.

(27) *Commission regulation (EC) No 1488/94 of 28 June 1994 Laying down the Principles for the Assessment of Risks to Man and the Environment of Existing Substances in Accordance with Council Regulation (EEC) No793/93*; Commission of the European Communities, 1994.

(28) *Council Directive 92/32/EEC of 30 April 1992 Amending for the Seventh Time Directive 67/548/EEC on the Approximation of the Laws, Regulations and Administrative Provisions Relating to the Classification, Packaging and Labelling of Dangerous Substances*; Council of the European Communities, 1992.

(29) *Council Regulation (EEC) No 793/93 of 23 March 1993 on the Evaluation and Control of the Risks of Existing Substances*; Council of the European Communities, 1993.

(30) European Commission. White paper. Strategy for a future Chemicals Policy. 2001http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2001:0088:FIN:EN:PDF.

(31) *Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Guidance Document No. 27. Technical Guidance for Deriving Environmental Quality Standards*; European Commission, 2011.

(32) Carlsson, C.; Johansson, A.-K.; Alvan, G.; Bergman, K.; Kühler, T. Are pharmaceuticals potent environmental pollutants?: Part I: Environmental risk assessments of selected active pharmaceutical ingredients. *Sci. Total Environ.* **2006**, *364*, 67−87.

(33) Boxall, A. B. A.; Rudd, M. A.; Brooks, B. W.; Caldwell, D. J.; Choi, K.; Hickmann, S.; Innes, E.; Ostapyk, K.; Staveley, J. P.; Verslycke, T.; Ankley, G. T.; Beazley, K. F.; Belanger, S. E.; Berninger, J. P.; Carriquiriborde, P.; Coors, A.; DeLeo, P. C.; Dyer, S. D.; Ericson, J. F.; Gagné, F.; Giesy, J. P.; Gouin, T.; Hallstrom, L.; Karlsson, M. V.; Larsson, D. G. J.; Lazorchak, J. M.; Mastrocco, F.; McLaughlin, A.; McMaster, M. E.; Meyerhoff, R. D.; Moore, R.; Parrott, J. L.; Snape, J. R.; Murray-Smith, R.; Servos, M. R.; Sibley, P. K.; Straub, J. O.; Szabo, N. D.; Topp, E.; Tetreault, G. R.; Trudeau, V. L.; Van Der Kraak, G.

DOI: 10.1021/acs.est.5b00302
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

Pharmaceuticals and personal care products in the environment: What are the big questions? *Environ. Health Perspect.* **2012**, *120*, 1221−1229.
(34) Laenge, R.; Steger-Hartmann, T.; Schweinfurth, H. The environmental risk assessment of human pharmaceuticals in the overall EU regulatory affairs process. *Regul. Toxicol. Pharmacol.* **2006**, *45*, 223−228.
(35) Molander, L.; Ågerstrand, M.; Rudén, C. WikiPharma—A freely available, easily accessible, interactive and comprehensive database for environmental effect data for pharmaceuticals. *Regul. Toxicol. Pharmacol.* **2009**, *55*, 367−371.
(36) Wennmalm, Å.; Gunnarsson, B. Public health care management of water pollution with pharmaceuticals: Environmental classification and analysis of pharmaceutical residues in sewage water. *Drug Inf. J.* **2005**, *39*, 291−297.
(37) Stockholm County Council. www.sll.se.
(38) Hansson, S. O.; Rudén, C. A risk-neutral default for chemical risk management. *Am. J. Ind. Med.* **2008**, *51*, 964−967.
(39) Herper, M. How Much Does Pharmaceutical Innovation Cost? A Look At 100 Companies. *Forbes* **2014**. http://www.forbes.com/sites/matthewherper/2013/08/11/the-cost-of-inventing-a-new-drug-98-companies-ranked/.
(40) Pal, C.; Bengtsson-Palme, J.; Rensing, C.; Kristiansson, E.; Larsson, D. G. J. BacMet: Antibacterial biocide and metal resistance genes database. *Nucleic Acids Res.* **2014**, *42*, D737−743.
(41) Finley, R. L.; Collignon, P.; Larsson, D. G. J.; McEwen, S. M.; Li, X.-Z.; Gaze, W. H.; Reid-Smith, R.; Timinouni, M.; Graham, D. W.; Topp, E. The scourge of antibiotic resistance: The important role of the environment. *Clin. Infect. Dis.* cit 355, **2013**, DOI: 10.1093/cid/cit355.
(42) Pruden, A.; Larsson, D. G. J.; Amézquita, A.; Collignon, P.; Brandt, K. K.; Graham, D. W.; Lazorchak, J. M.; Suzuki, S.; Silley, P.; Snape, J. R.; Topp, E.; Zhang, T.; Zhu, Y.-G. Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. *Environ. Health Perspect.* **2013**, *121*, 878−885.
(43) Ashbolt, N. J.; Amézquita, A.; Backhaus, T.; Borriello, P.; Brandt, K. K.; Collignon, P.; Coors, A.; Finley, R.; Gaze, W. H.; Heberer, T.; Lawrence, J. R.; Larsson, D. G. J.; McEwen, S. A.; Ryan, J. J.; Schönfeld, J.; Silley, P.; Snape, J. R.; Van den Eede, C.; Topp, E. Human health risk assessment (HHRA) for environmental development and transfer of antibiotic resistance. *Environ. Health Perspect.* **2013**, *121*, 993−1001.
(44) Gullberg, E.; Cao, S.; Berg, O. G.; Ilbäck, C.; Sandegren, L.; Hughes, D.; Andersson, D. I. Selection of resistant bacteria at very low antibiotic concentrations. *PLoS Pathog* **2011**, *7*, e1002158.
(45) European committee on antimicrobial susceptibility testing. Website: http://www.eucast.org/mic_distributions/.
(46) Tello, A.; Austin, B.; Telfer, T. C. Selective pressure of antibiotic pollution on bacteria of importance to public health. *Environ. Health Perspect.* **2012**, *120*, 1100−1106.
(47) Ågerstrand, M.; Rudén, C. Evaluation of the accuracy and consistency of the Swedish Environmental Classification and Information System for pharmaceuticals. *Sci. Total Environ.* **2010**, *408*, 2327−2339.
(48) Rudén, C. From data to decision. A case study of comtroversies in cancer risk assessments. Doctoral thesis. Karolinska Institutet, Sweden. 2002.
(49) Beronius, A.; Rudén, C.; Håkansson, H.; Hanberg, A. Risk to all or none?: A comparative analysis of controversies in the health risk assessment of Bisphenol A. *Reprod. Toxicol.* **2010**, *29*, 132−146.
(50) Roos, V.; Gunnarsson, L.; Fick, J.; Larsson, D. G. J.; Rudén, C. Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection. *Sci. Total Environ.* **2012**, *421*−*422*, 102−110.
(51) Caldwell, D. J.; Mastrocco, F.; Margiotta-Casaluci, L.; Brooks, B. W. An integrated approach for prioritizing pharmaceuticals found in the environment for risk assessment, monitoring and advanced research. *Chemosphere* **2014**, *115*, 4−12.
(52) Kostich, M. S.; Lazorchak, J. M. Risks to aquatic organisms posed by human pharmaceutical use. *Sci. Total Environ.* **2008**, *389*, 329−339.
(53) *Committee for Medicinal Products for Human Use (Chmp). Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. Ref EMEA/CRMP/SWP/4447/00*; European Medicines Agency: London, UK, 2006.
(54) Winter, M. J.; Owen, S. F.; Murray-Smith, R.; Panter, G. H.; Hetheridge, M. J.; Kinter, L. B. Using data from drug discovery and development to aid the aquatic environmental risk assessment of human pharmaceuticals: Concepts, considerations, and challenges. *Integr. Environ. Assess. Manage.* **2010**, *6*, 38−51.
(55) Gunnarsson, L.; Kristiansson, E.; Larsson, D. G. J. Environmental comparative pharmacology: Theory and application. In *Human Pharmaceuticals in the Environment*; Brooks, B. W., Huggett, D. B., Eds.; Springer: New York, 2012; pp 85−108.
(56) Fick, J.; Lindberg, R. H.; Parkkonen, J.; Arvidsson, B.; Tysklind, M.; Larsson, D. G. J. Therapeutic levels of levonorgestrel detected in blood plasma of fish: Results from screening rainbow trout exposed to treated sewage effluents. *Environ. Sci. Technol.* **2010**, *44*, 2661−2666.
(57) Gunnarsson, L.; Jauhiainen, A.; Kristiansson, E.; Nerman, O.; Larsson, D. G. J. Evolutionary conservation of human drug targets in organisms used for environmental risk assessments. *Environ. Sci. Technol.* **2008**, *42*, 5807−5813.
(58) Grabicova, K.; Lindberg, R. H.; Ostman, M.; Grabic, R.; Randak, T.; Larsson, D. G. J.; Fick, J. Tissue-specific bioconcentration of antidepressants in fish exposed to effluent from a municipal sewage treatment plant. *Sci. Total Environ.* **2014**, *488*−*489*, 46−50.
(59) Rand-Weaver, M.; Margiotta-Casaluci, L.; Patel, A.; Panter, G. H.; Owen, S. F.; Sumpter, J. P. The read-across hypothesis and environmental risk assessment of pharmaceuticals. *Environ. Sci. Technol.* **2013**, *47*, 11384−11395.
(60) Miguel-Queralt, S.; Hammond, G. L. Sex hormone-binding globulin in fish gills is a portal for sex steroids breached by xenobiotics. *Endocrinology* **2008**, *149*, 4269−4275.
(61) Zeilinger, J.; Steger-Hartmann, T.; Maser, E.; Goller, S.; Vonk, R.; Länge, R. Effects of synthetic gestagens on fish reproduction. *Environ. Toxicol. Chem.* **2009**, *28*, 2663−2670.
(62) Margiotta-Casaluci, L.; Hannah, R. E.; Sumpter, J. P. Mode of action of human pharmaceuticals in fish: The effects of the 5-alpha-reductase inhibitor, dutasteride, on reproduction as a case study. *Aquat. Toxicol.* **2013**, *128*−*129*, 113−123.
(63) Brian, J. V.; Harris, C. A.; Scholze, M.; Backhaus, T.; Booy, P.; Lamoree, M.; Pojana, G.; Jonkers, N.; Runnalls, T.; Bonfà, A.; Marcomini, A.; Sumpter, J. P. Accurate prediction of the response of freshwater fish to a mixture of estrogenic chemicals. *Environ. Health Perspect.* **2005**, *113*, 721−728.
(64) Sumpter, J. P.; Johnson, A. C.; Williams, R. J.; Kortenkamp, A.; Scholze, M. Modeling effects of mixtures of endocrine disrupting chemicals at the river catchment scale. *Environ. Sci. Technol.* **2006**, *40*, 5478−5489.
(65) Säfholm, M.; Ribbenstedt, A.; Fick, J.; Berg, C. Risks of hormonally active pharmaceuticals to amphibians: a growing concern regarding progestagens. *Philos. Trans. R. Soc., B* **2014**, *369*, 20130577.
(66) Kortenkamp, A.; Backhaus, T.; Faust, M. *State of the Art Report on Mixture Toxicity. Final Report*; London, UK, 2009.
(67) Sumpter, J. P. Protecting aquatic organisms from chemicals: the harsh realities. *Philos. Trans. R. Soc., A* **2009**, *367*, 3877−3894.
(68) Walter, H.; Consolaro, F.; Gramatica, P.; Scholze, M.; Altenburger, R. Mixture toxicity of priority pollutants at no observed effect concentrations (NOECs). *Ecotoxicology* **2002**, *11*, 299−310.
(69) Backhaus, T.; Altenburger, R.; Arrhenius, Å.; Blanck, H.; Faust, M.; Finizio, A.; Gramatica, P.; Grote, M.; Junghans, M.; Meyer, W.; Pavan, M.; Porsbring, T.; Scholze, M.; Todeschini, R.; Vighid, M.; Walter, H.; Grimme, L. H. The BEAM-project: Prediction and assessment of mixture toxicities in the aquatic environment. *Cont. Shelf Res.* **2003**, *23*, 1757−1769.

DOI: 10.1021/acs.est.5b00302
Environ. Sci. Technol. XXXX, XXX, XXX−XXX

(70) Bound, J. P.; Voulvoulis, N. Pharmaceuticals in the aquatic environment—A comparison of risk assessment strategies. *Chemosphere* **2004**, *56*, 1143−1155.
(71) Boone, M. D.; Bishop, C. A.; Boswell, L. A.; Brodman, R. D.; Burger, J.; Davidson, C.; Gochfeld, M.; Hoverman, J. T.; Neuman-Lee, L. A.; Relyea, R. A.; Rohr, J. R.; Salice, C.; Semlitsch, R. D.; Sparling, D.; Weir, S. Pesticide Regulation amid the Influence of Industry. *BioScience* **2014**, DOI: 10.1093/biosci/biu138.
(72) Klaminder, J.; Jonsson, M.; Fick, J.; Sundelin, A.; Brodin, T. The conceptual imperfection of aquatic risk assessment tests: Highlighting the need for tests designed to detect therapeutic effects of pharmaceutical contaminants. *Environ. Res. Lett.* **2014**, *9*, 084003.
(73) Brodin, T.; Piovano, S.; Fick, J.; Klaminder, J.; Heynen, M.; Jonsson, M. Ecological effects of pharmaceuticals in aquatic systems—impacts through behavioural alterations. *Philos. Trans. R. Soc., B* **2014**, *369*, 20130580.
(74) Kvarnryd, M.; Grabic, R.; Brandt, I.; Berg, C. Early life progestin exposure causes arrested oocyte development, oviductal agenesis and sterility in adult *Xenopus tropicalis* frogs. *Aquat. Toxicol.* **2011**, *103*, 18−24.
(75) Ågerstrand, M.; Breitholtz, M.; Rudén, C. Comparison of four different methods for reliability evaluation of ecotoxicity data: a case study of non-standard test data used in environmental risk assessments of pharmaceutical substances. *Environ. Sci. Eur.* **2011**, *23*, 17.
(76) Ågerstrand, M.; Edvardsson, L.; Rudén, C. Bad reporting or bad science? Systematic data evaluation as a means to improve the use of peer-reviewed studies in risk assessments of chemicals. *Hum. Ecol. Risk Assess. Int. J.* **2013**, *20*, 1427−1445.
(77) Küster, A.; Bachmann, J.; Brandt, U.; Ebert, I.; Hickmann, S.; Klein-Goedicke, J.; Maack, G.; Schmitz, S.; Thumm, E.; Rechenberg, B. Regulatory demands on data quality for the environmental risk assessment of pharmaceuticals. *Regul. Toxicol. Pharmacol.* **2009**, *55*, 276−28.
(78) Moermond, C.; Kase, R..; Korkaric, M.; Ågerstrand, M. CRED—Criteria for Reporting and Evaluating ecotoxicity Data. Submitted.
(79) *Minska riskerna med farliga ämnen! Strategi för Sveriges arbete for en giftfri miljö. Statens Offentliga Utredningar SOU*; Miljömålsberedningen, 2012; Vol. *38*. 2012 (in Swedish).
(80) Swedish Government. Bill number: 2013/14:39 In Swedish: På väg mot en giftfri vardag - plattform för kemikaliepolitiken. www.riksdagen.se/sv/Dokument-Lagar/Forslag/Propositioner-och-skrivelser/Pa-vag-mot-en-giftfri-vardag--_H10339/.
(81) Molander, L.; Breitholtz, M.; Rudén, C. Missing links in the regulatory chain controlling life cycle emissions of hazardous chemicals from articles. *Toxicol. Lett.* **2011**, *205*, S243−S243.
(82) Buonsante, V. A.; Muilerman, H.; Santos, T.; Robinson, C.; Tweedale, A. C. Risk assessment's insensitive toxicity testing may cause it to fail. *Environ. Res.* **2014**, *135C*, 139−147.
(83) Larsson, D. G. J.; Fick, J. Transparency throughout the production chain—a way to reduce pollution from the manufacturing of pharmaceuticals? *Regul. Toxicol. Pharmacol.* **2009**, *53*, 161−163.
(84) Murray-Smith, R. J.; Coombe, V. T.; Grönlund, M. H.; Waern, F.; Baird, J. A. Managing emissions of active pharmaceutical ingredients from manufacturing facilities: An environmental quality standard approach. *Integr. Environ. Assess. Manag.* **2012**, *8*, 320−330.
(85) Wandall, B. Values in science and risk assessment. *Toxicol. Lett.* **2004**, *152*, 265−272.
(86) Schenk, L. Comparison of data used for setting occupational exposure limits. *Int. J. Occup. Environ. Health* **2010**, *16*, 249−262.
(87) Schenk, L.; Johanson, G. Use of uncertainty factors by the SCOEL in their derivation of health-based occupational exposure limits. *Crit. Rev. Toxicol.* **2010**, *40*, 791−798.

DOI: 10.1021/acs.est.5b00302
Environ. Sci. Technol. XXXX, XXX, XXX−XXX