European Journal of Pharmaceutical Sciences 192 (2024) 106614

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Designing greener active pharmaceutical ingredients: Insights from pharmaceutical industry into drug discovery and development

Neele Puhlmann [a], Rodrigo Vidaurre [b], Klaus Kümmerer [a,c,*]

[a] Institute of Sustainable Chemistry, Leuphana University of Lüneburg, Universitätsallee 1, 21335 Lüneburg, Germany
[b] Ecologic Institute, Pfalzburger Strasse 43/44, 10717 Berlin, Germany
[c] Research and Education Hub, International Sustainable Chemistry Collaborative Center ISC3, Niedersachsen, Germany

ARTICLE INFO

Keywords:
API
Sustainable
Environment
Feasibility
Interview
Experts

ABSTRACT

Active pharmaceutical ingredients (APIs), their metabolites and transformation products (TPs) are found as pollutants in the environment. They can impact human and environmental health. To address this issue, an efficient, long-term prevention strategy could be the design of APIs that have less impact on the natural environment, i.e. *the design of greener APIs,* by the implementation of environmental parameters into the drug discovery and development process (also abbreviated R&D for 'research and development'). Our study aimed to evaluate the feasibility of *the design of greener APIs* based on insights from drug design experts working in large, research-based pharmaceutical companies. The feasibility evaluation also identified needs and incentives for process modification. For this purpose, 30 R&D and environmental experts from seven globally active pharmaceutical companies were interviewed along a structured questionnaire.

Main findings are that the interviewed experts saw manifold opportunities to include properties rendering APIs greener in different stages along the R&D process. This implementation would be favoured by the fact that the pharmaceutical R&D process is very flexible and relies on balancing multiple parameters. Furthermore, some API properties that reduce environmental risks were considered compatible with common desirable properties for application. Environmental properties should be considered early during R&D, i.e. when molecules are screened and optimized. It has been found that availability of suitable *in silico* models and *in vitro* assays is crucial for this environmental consideration. Their attributes, e.g. throughput and costs, determine at which process stage they can be successfully applied.

An intensified exchange between R&D and environmental experts within and outside companies would push the industrial application of the benign by design approach for APIs forward. Collaboration across pharmaceutical companies, authorities, and academia is seen as highly promising in this respect. Financial, social, and regulatory incentives would support future design of greener APIs.

1. Introduction

Active pharmaceutical ingredients (APIs) are essential for human 'Good Health and Well-Being', one of the UN's Sustainable Development Goals (United Nations, 2015). At the same time, residues of APIs, their metabolites and transformation products (TPs) are frequently found as pollutants in the environment (aus der Beek et al., 2016; European Commission, 2020b, 2020a, 2020d; Hester and Harrison, 2015; Wilkinson et al., 2022). This is a long standing and well-known issue (Daughton and Ternes, 1999; Jones et al., 2001; Kümmerer and Hempel, 2010). Their presence potentially impacts ecosystems, drinking water resources, crops, and eventually humans (WHO, 2017). For example, some progestins and estrogens (hormones), oxazepam (anxiolytic), diclofenac (nonsteroidal anti-inflammatory drug), carbamazepine (anticonvulsant) and metoprolol (beta blocker) have been reported to chronically affect individual fitness and population health of aquatic organisms (Blazer et al., 2021; Brodin et al., 2013; Fent, 2015; Kidd et al., 2007; Triebskorn et al., 2007).

One of the concepts, which both the scientific and the policy community see as having potential to reduce pollution of the environment by pharmaceuticals, is the design of APIs that have less impact on the natural environment, i.e. *the design of greener APIs* (Kümmerer, 2007,

* Corresponding author.
E-mail address: Klaus.Kuemmerer@leuphana.de (K. Kümmerer).

https://doi.org/10.1016/j.ejps.2023.106614
Received 6 March 2023; Received in revised form 15 September 2023; Accepted 16 October 2023
Available online 17 October 2023
0928-0987/© 2023 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

2016). This concept is included amongst the proposed actions of policy initiatives addressing pharmaceutical pollution, including the European Union's 'Strategic Approach to Pharmaceuticals in the Environment' which highlights 'green pharmaceutical design' as a means to develop pharmaceuticals intrinsically less harmful to the environment (European Commission, 2019). Similarly, the OECD's work on pharmaceutical residues in freshwater includes amongst its proposed preventive measures the 'rational design' or 'benign by design' approach when developing pharmaceutical compounds (OECD, 2019).

The design of greener APIs is an approach directed at the source of pollution with the ultimate aim of designing APIs that have less impact on the environment (Kümmerer et al., 2020). The comparative of *green*, i.e. *greener*, is used to underline that it is about a comparison between common design and the design of more environmentally friendly APIs. Thus, the aimed-for environmental properties are not rigidly defined, but rather significant improvement is sought, analogous to the best-in-class approach (LaMattina, 2013). Moreover, it is not sufficient to consider only the impact by environmental pollution for a comprehensive assessment of the greenness of an API. For example, criteria for green production (Anastas and Warner, 1998) would also play a role, but are out of the scope of this study and the term *greener*. Recently the GREENER concept was published which proposes approaches for designing APIs with reduced environmental impacts after excretion based on well-known aspects (Moermond et al., 2022). These aspects can be divided into (i) those to reduce environmental exposure and (ii) those to reduce adverse environmental effects. The first aspect encompasses the second one and reduces environmental pollution by pharmaceuticals independently of known (in present) or to be discovered (in future) unwanted effects. In this respect the first approach is closer to the precautionary principle, which is a basic principle underlying all European environmental policy (European Parliament, 2015).

On this basis, we understand *greener APIs* as APIs that have less environmental impact after use, i.e. after excretion by patients, due to either reduced environmental exposure or at least reduced adverse environmental effects.

Reduced environmental exposure

A central approach to reduce environmental exposure significantly from the very beginning is the design of compounds that mineralize completely in the natural environment, i.e. degrade to innocuous inorganic compounds, such as carbon dioxide, water and inorganic salts (in the case of hetero atoms), by biotic and abiotic processes. Fast and full environmental mineralization leads to reduced environmental concentrations of the compound and its transformation products (TPs, i.e. molecules formed in the environment, including wastewater treatment plants, by incomplete biotic and abiotic transformation of the parent compound, e.g. an API) (Kümmerer, 2007; Puhlmann et al., 2021). In the best case, such a complete mineralization in the environment also occurs in the absence of sewage treatment, i.e. in surface waters. This presents a true sustainable solution of the problem as it is estimated that worldwide over 80% of wastewater (from municipalities, industry and agriculture) is released to the environment without adequate treatment (UN Water, 2017). Another design approach for achieving reduced environmental impact is having a lower therapeutic dose, which intrinsically leads to reduced API excretion by the patient. A lower dose may be achieved for example by improved bioavailability in patients, improved drug delivery or higher specificity (Baron, 2012; Daughton, 2003).

Reduced excretion can also be approached at a level other than drug design, e.g. through optimized drug prescribing (Daughton, 2003, 2014; Fortunak et al., 2015; Hamburg and Collins, 2010; Taylor, 2015). Environmental loads may also be reduced *via* wider adaptation of precision (personalized) medicine approaches that aim to replace suboptimal (e.g. ineffective) drug treatments with such that better account for individual genetic, environmental and lifestyle variabilities (European Commission, 2020c).

Reduced adverse environmental effects

Reduced adverse environmental effects could be achieved considering i) adverse environmental effects studied within regulatory environmental risk assessment (ERA; (EMA, 2006, 2018; European Commission, 2004a, 2004b)) and ii) adverse environmental effects that are linked to the therapeutic mode of action. For the latter, the presence/absence of drug-target orthologues in environmental organisms is a key factor to predict species susceptibility for drug exposure at low concentrations (Gunnarsson et al., 2019). Orthology predictions of drug targets can be obtained from the database Ecodrug.com (Verbruggen et al., 2018).

Ågerstrand et al. (2015) have proposed that potential ecotoxicity could be assessed earlier in the drug discovery and development process (also abbreviated R&D for 'research and development') to identify problematic APIs correspondingly earlier. They also recommend including environmental risks in the benefit-risk assessment when a medicinal product is considered for marketing authorization.

According to the Deloitte Report 'Options for a strategic approach to pharmaceuticals in the environment', the concept of designing greener substances has not yet been significantly explored by industry possibly because of concerns that it might be costly and technically challenging (Deloitte et al., 2018). Moreover, in contrast to the scientific and policy community's explicit backing, there is to the best of our knowledge no data so far in the public domain on how the pharmaceutical industry evaluates the feasibility of this concept, and which preconditions would have to be met for its implementation.

Addressing this gap, we conducted interviews with company experts, such as medicinal chemists, process chemists, and environmental risk assessors, from globally active, research-based pharmaceutical companies. A structured questionnaire was used to evaluate the feasibility of including environmental criteria for APIs into the drug discovery and development process (also abbreviated R&D for 'research and development') based on experts' insights. The feasibility evaluation also included identifying needs and incentives for *the design of greener APIs*.

2. Method

2.1. The questionnaire

A questionnaire (see supplementary) was developed consisting of two sections of five questions each:

Section I dealt with topics on the pharmaceutical R&D process, such as different phases and decision points within the process (Fig. 1), as well as criteria that play a role in decision-making. This section aimed to validate publicly available information on the R&D process provided, for example, by Blass (2015) and Summerton et al. (2015).

Moreover, the first section aimed to complement literature data with more detailed information on actual R&D practice. Understanding the main features of the R&D process was a prerequisite to evaluating the feasibility of *the design of greener APIs* based on interviewees' opinions.

Section II covered where environmental considerations are already implemented in a company's R&D process or can be integrated in future to enable *the design of greener APIs*. The aim of this section was to elicit information of interviewees on the current role of environmental criteria and their opinions regarding the feasibility of including environmental criteria into the pharmaceutical R&D process in future. The discussion on future integration of *the design of greener APIs* included key attributes for any *in silico* model or *in vitro* assay, related to their use at specific points in the R&D process.

In scope of environmental criteria were aspects related to APIs that are greener due to less impact on the environment after patient excretion (cf. introduction for a more detailed discussion of our understanding of

Fig. 1. Generic workflow of a common R&D process inspired by Messinger et al. (2016). The first four phases – from target selection to candidate selection, which aim to discover an API candidate – are placed under the label drug discovery (Research, i.e. the R in R&D). The last two phases, i.e. preclinical and clinical studies, deal with the development of the formulated drug (drug Development, i.e. the D in R&D). Explanation of the terminologies 'target', 'hit', 'lead' and 'candidate' can be found elsewhere (Messinger et al., 2016).

the concept). Out of scope were aspects of green chemistry addressing greener production methods such as synthesis routes that use less inputs and the use of renewable materials within R&D.

The following four environmental criteria were used in the questionnaire:

a) *No/reduced environmental exposure* to the compound reduces risks in the environment. Exposure should not exceed a limit value for ecotoxicological effects, like the predicted no effect concentration (PNEC).
b) *Environmental (bio)degradability* or environmental persistence of an API has major influence on the actual environmental concentration and thereby exposure. Complete and fast environmental (bio) degradation (i.e. mineralization) reduces or even prevents environmental risks (no risk in case of no exposure).
c) *No/reduced adverse environmental effects* reduces risks in the environment. Adverse environmental effects include adverse effects studied within regulatory environmental risk assessment and those that are linked to the therapeutic mode of action.
d) The concept behind *no/reduced undesirable moieties* (e.g. PFAS moieties CF_2 and CF_3 including C-CF_3 as precursor of trifluoroacetic acid (Cahill, 2022; Joudan et al., 2021; Rüdel et al., 2020; Scheurer and Nödler, 2021)) is to avoid, if possible, the use of molecular groups that are known to have a negative impact on the environment (e.g. due to persistence or ecotoxicity). Thus, this concept is linked to all previous criteria.

Before conducting the interviews, the questionnaire was tested on two R&D experts from medicine agencies who worked in pharmaceutical companies' R&D earlier in their careers. Question scope, comprehensibility and scheduling feasibility were tested. The questionnaire was revised in favour of comprehensibility by using more common terms. Time slots for blocks of questions were adjusted.

2.2. Interview request and interviewees

An interview request was sent to representatives of 10 globally leading pharmaceutical companies, which do research, development and manufacturing of pharmaceutical products. The request was accompanied by a two-page background summary of the challenge of pharmaceuticals in the environment, and the questionnaire to show the interview scope and allow for preparation (both in supplementary). The contacted company representatives forwarded the request to the addressed R&D and environmental experts within their company; particularly medicinal chemists, but also computational chemists, process chemists responsible for the development of APIs and environmental risk assessors (in the following "company experts").

In total, 30 company experts working for seven out of the ten contacted companies accepted the request. All companies are large-sized pharmaceutical companies and members of the European Federation of Pharmaceutical Industries and Associations (EFPIA), with head offices in Europe (6 companies) or in the USA (1 company). Interviewed experts were mostly medicinal chemists (at least one per company), others were staff with expertise in other disciplines, e.g. environmental risk assessment (ERA) (Table 1).

2.3. Conducting and evaluating the interviews

Interviews lasted 2 h and were conducted online between April and July 2021 using the video conferencing platform *GoToMeeting*. After a brief round of introductions, the interview was conducted along the two sections of the questionnaire:

I description of the R&D process within the particular company (00h:10m - 01h:10m),
II current role of environmental considerations for APIs and potential in future (01h:11m - 02h:00m).

Before the interview started, interviewees agreed to a recording for the purposes of completing the transcript by the recorder. It was ensured that the group answers followed the questionnaire's structure, to obtain the specific data required for answering this study's research questions and to ensure comparability between the interviews. Interview transcripts were used as basis for a qualitative and systematic evaluation of all answers and additional comments. Statements that were not directly asked for were considered individually, but only if they were within the scope of this study. As confidentiality was agreed, results are presented anonymized and generalized, so that statements cannot be traced back to an individual company or employee.

2.4. Data analysis

Data generated in the interviews was predominantly qualitative. The qualitative data analysis conducted was abductive in nature (straddling a middle ground between deductive and inductive approaches; cf. Thompson, 2022). On the one hand, the analysis follows theoretical concepts related to the topic, such as the phases and decision points in the pharmaceutical R&D process and the environmental criteria presented in 2.1). On the other hand, the analysis engaged inductively with the empirical data generated, identifying relevant patterns and themes in the different responses to one and the same question and summarizing the data available for these patterns/themes. In particular, emphasis was placed on themes and patterns related to potential for uptake and implementation, as well as barriers hereto.

Analysis was conducted per question. For each question, data was condensed and restructured into a synthesis of the meaningful information provided in the responses.

Table 1
Number of company experts from different disciplines in the 7 interviews.

Discipline	Number per interview I-VII							Σ
	I	II	III	IV	V	VI	VII	
Medicinal chemistry	1	3	1	2	2	2	3	**14**
In silico chemistry						1		**1**
Process chemistry		2				1	1	**4**
Product Stewardship						1		**1**
ERA	1		1	2	1	2	3	**10**
∑ experts	**2**	**5**	**2**	**4**	**3**	**7**	**7**	**30**

3. Results

The interviewees usually answered the questions very comprehensively and were open-minded and interested towards the approach *the design of greener APIs*. Some of them expressed intrinsic motivation to contribute to this solution approach for pharmaceuticals in the environment. Interviewee's attitude led to lively, data-providing discussions – also between experts from the same company.

3.1. The drug discovery and development process, R&D (Q1–Q5)

3.1.1. Variability in pharmaceutical companies' R&D process (Q1–Q3)

All interviewees confirmed that in general terms their company's R&D workflow follows the generic workflow described in the literature (Fig. 1). Differences in how phases are named were seen as insignificant. Additional phases to those presented in Fig. 1 were mentioned by interviewees. However, they were not considered relevant to the design of a greener API. An example is synthesis route selection (deciding on the best process to synthesize the API for larger-scale production), which usually occurs after candidate selection and has therefore no impact on the drug design. Additional important decision points apart from those covered by Fig. 1 were not identified in the interviews.

In general, modification of the workflow of R&D occurs due to project- or programme-specific circumstances. For example, if a project is targeting a new or less well-known biological target it will require more intensive validation, leading to significantly more testing and thus to some R&D phases taking longer, than if the biological target is well known. However, whereas projects can have very significant differences in individual phase length, approach applied, resources and so on, such modifications do not change the overall picture and logic of the process. The overall picture is also still valid when taking into account that the R&D process evolves rapidly e.g. due to new testing methods and approaches, especially in the field of computational chemistry.

All interviewees highlighted that the R&D process is typically not linear, but rather highly cyclical and flexible due to significant learning steps within the process. Particularly, the phases of hit optimization and lead optimization, where multiple parameters are optimized (using Multi-Parameter Optimization, MPO), are highly iterative and flexible. This flexibility allows for the process to be changed by adding decision points or "stoppers" (red flags), or new parameters to be considered with further assays to filter out problems encountered in previous iterations. However, decision points are not significantly affected when returning to a previous stage in an iteration, as the same level of characterization of every potential API is needed. If information may be drawn from the failures that lead to the iteration, decision points can be merely refined by more extensive data (leading e.g. to specific follow-up assays). Interviews revealed that there is a trend towards more continuity of team members along the R&D chain, more exchange within and between teams, and more collaboration between different experts from different departments within companies. This indicates not only the possibility of flexibility but also that companies rate this as important. Accordingly, interviewees stated that these changes are seen as helping to lower compound failure rates during the process (attrition rates).

3.1.2. Decision criteria (Q4)

According to the interviewees, the parameters listed in the questionnaire (supplementary, Q4) are by default part of screening cascades in the R&D process as they are crucial for the development of an approvable pharmaceutical product. Examples are potency, physicochemical properties, adsorption, distribution, metabolism, excretion (ADME) parameters, stability (chemical, plasma, shelf life), pharmacokinetic, efficacy and safety related parameters such as off-target effects.

The list of parameters can be expanded to include project-specific parameters as needed. Some decision point criteria can vary with disease area (nervous system, oncology, etc.). For example, possible off-target effects for headache medication are less acceptable than for oncology drugs.

Several parameters being optimized for in R&D have been discussed during the interviews also in terms of their environmental significance (listed in the supplementary with literature-based information). Examples are lipophilicity and stability. It was highlighted by medicinal chemists that they try to strive for less lipophilic molecules. Regarding stability, interviewees said that results of experimental stability tests during lead optimization phase can lead to red flags. For example, if a lead compound is unstable under atmospheric, humid, or oxidative conditions this leads to a red flag for the decision criteria, as it would shorten the specified shelf life considered necessary to deliver the drug to the patient. Moreover, API stability in the human body is desired for treatment regimens conducive to patient compliance, e.g. no fast metabolism of compound, or half-lives in blood allowing for e.g. oral dosing no more than once or twice daily.

3.1.3. Company's use of a target product profile (Q5)

A so-called *target product profile* (TPP) builds the basis for the development of the pharmaceutical product. The TPP outlines the desired pharmaceutical profile of a new product. For example, topics such as dosage and administration are part of the TPP. Consistently, interviewees summarized their TPPs as living guidance documents which are systematically developed and refined along the entire R&D process.

3.2. Environmental considerations (Q6–Q10)

3.2.1. Current role of environmental considerations in any phase of the R&D process (Q6)

According to interviewees, current consideration of environmental aspects within their R&D process is limited to aspects related to manufacturing, for example, the use of fewer and safer raw materials, and lower carbon footprint. Since manufacturing-related aspects are out of the scope of this study they are not discussed here in more detail. Currently, then, the interviewed companies do not consider the environmental behaviour or profile of potential APIs when designing APIs.

Whereas there is currently no explicit consideration of environmental criteria of an API during the different phases of drug discovery, several interviewees identified aspects related to properties that medicinal chemists aim for in an API, and which may also result in better environmental properties. The consideration of these criteria by medicinal chemists may thus result in beneficial outcomes for the environment (albeit unintentionally) too, which can be seen as a win-win situation. These identified aspects are:

- low dose drugs (if enabled for reasons other than increased potency; see section Q8b)
- high target specificity
- aqueous solubility balanced against lipophilicity
- high bioavailability
- no toxicity (e.g. carcinogenic, mutagenic, reprotoxic)
- no/reduced adverse effects.

A low administered dose can be expected to translate into low amounts of API being excreted by the patient and thereby to result in lower environmental concentrations of an API or its metabolites. High specificity leads to less off-target effects in the human body, which may translate to less adverse effects in environmental organisms.

There is currently a trend in drug design to aim for lower lipophilicity (which enables better plasma solubility and minimizes non-specific, off-target binding, amongst other things). A consequence of the design towards lower lipophilicity is that newly developed APIs have lower potential for bioaccumulation. On the other hand, the development towards more molecular complexity appears not to be positive from an environmental perspective. According to an interviewee, complexity is generally on the rise because of the exploration of a wider

chemical space aiming for drugs that are superior to current drugs. API complexity (e.g. due to more extensive branching and number of functional groups) might hinder complete mineralization in the environment.

3.2.2. Potential for uptake of environmental considerations in the pharmaceutical R&D process (Q7–Q8)

On the general question if environmental considerations can be included amongst other criteria in the target product profile, interviewees in six of the seven interviews tended towards an uptake being potentially possible, associated with conditionalities, however. The implementation would depend on suitable models or assays being available to evaluate the environmentally relevant criteria. Environmental criteria would need to be clearly defined, be translatable to parameters that play a role in environmental evaluation, and have an importance attached to them, e.g. if there were legal requirements to meet these criteria.

3.2.2.1. Potential uptake of environmental considerations in the different phases of the R&D process. According to interviewees, already at **target selection** a first environmental risk evaluation for an API could be possible based on intended volume of use and population. For example, contraceptives would be a high-risk area, which contrasts strongly in volume of use and population with e.g. some antineoplastics for small patient populations and specific indications. An evaluation at this stage could inform the degree and extent of uptake of environmental criteria in the R&D process.

Hit identification is the phase where the highest number of compounds is screened and therefore the phase with the highest chances of finding promising structures meeting environmental criteria. The minimum requirement for a potential assay would be that it has "at least a medium throughput, is not too costly, and does not require a too large amount of substance." However, adding further criteria to the early stages could hamper drug discovery, in the opinion of some interviewees. Medicinal chemists generally want to avoid potentially filtering out promising scaffolds. Moreover, it would be difficult to evaluate compound's environmental properties in early phases as there would be a very large question mark regarding a compound's characteristics, including metabolites. One interviewee highlighted that hit structures selected will not necessarily resemble the evolved lead structures.

At **hit selection and optimization**, a standard toolbox would be needed that is suitable for routine screening of environmental parameters. For example, problematic structural elements could be identified at an early stage using a standard filter. Models could be based on parameters that are measured anyway in the process. Several interviewees mentioned the possibility that environmental criteria could be part of the parameters evaluated in the design-make-test-analyse (DMTA) cycle. DMTA consists of the **d**esign of new analogues, their synthesis (**m**ake) and **t**esting, and **a**nalysis of results. The cycle is performed iteratively in hit optimization and lead optimization to optimize multiple parameters using MPO. Analogues result from various modifications in the molecular structure. Whether structural changes are kept, developed further, or discarded is decided on the basis of test results. For example, structural changes are kept if improved potency (and/or other properties) results from the change. According to interviewees, it would be ambitious to implement molecular changes to the minimum environmental impact within MPO, but feasible.

Lead optimization was seen as the phase where environmental considerations should play an important role, because in this phase *in vitro* assays to characterize a compound's environmental properties can have much lower throughput and greater expense. The more precise evaluation of environmental parameters possible in this phase could ensure that any decisions taken are based on adequate and relevant data. Longer assay turnarounds, while not desirable, would not necessarily slow down processes in this phase, as the significantly smaller number of molecules that reach this phase will already undergo a detailed characterization. Interviewees also highlighted the potential to use the high-quality data that could be generated in this phase for improving the corresponding *in silico* models.

Moreover, at this phase a selection of compounds is prioritized, and choices can still be made when optimising parameters as part of MPO. Some parameters, such as dose-related ones, may go hand in hand with environmental risk. Opportunities were identified to consider environmental biodegradability in this phase by using *in silico* testing in combination with the ADME profile, as an extension of it. An interviewee showed interest in the approach of benign by design and mentioned the literature example of the β-blocker propranolol optimized regarding biodegradability (Rastogi et al., 2015).

When considering environmental criteria in MPO, it could be difficult to weigh different parameters (e.g. different ecotoxicity parameters against each other, or ecotoxicity parameters and those related to other issues) since there would already be a balance between the standard pharmaceutical parameters. The question arose of how to decide which is the most important environmental parameter. Interviewees highlighted that in medicinal chemistry, tests are almost never a yes-no decision, but rather balancing several criteria on different sliding scales of acceptability. Interviewees assumed that an evaluation of environmental criteria and prioritising compounds based on an environmental score is possible. In case of a selection of compounds that are similar in terms of pharmaceutical properties, prioritization due to environmental properties is considered feasible. It may become challenging if the outcome of an assay evaluation greatly reduces the variety of structures of different scaffolds, resulting in only one series of a compound with a solid scaffold, but with poor environmental characteristics.

The latest process point identified with potential for incorporating environmental criteria in decision-making is right before **candidate selection** (effectively the "spout of the funnel"). The reason is that the molecular structure is set with candidate selection. Once a development candidate builds momentum it is considered very difficult to go back to design alternatives that may have better properties. However, results of environmental tests at these later stages would be valuable for data and knowledge-generation purposes.

In **preclinical and clinical studies** metabolites could potentially be investigated, e.g. regarding potency, to figure out how they should be assessed from an environmental perspective. In clinical phases I and II, the therapeutic range of dosing is determined. There could be some potential for choices that can be made to the dosing regimen (e.g. choosing a lower individual dose with several daily doses, while considering patient compliance) which could reduce the amount of unchanged compound excreted by the patient.

3.2.3. Suitability of environmental criteria for uptake (Q8b)

Asked for concrete environmental criteria that could be suitable for uptake in pharmaceutical R&D, interviewees discussed the following greener aspects (Section 2.1, a - d) proposed in the questionnaire.

3.2.3.1. No/reduced environmental exposure. Exposure data is needed (together with effect data) to estimate a potential environmental risk. Early on in the R&D process, environmental exposure of the API could be estimated very roughly based on assumed dosage and market penetration which impacts environmental concentration. Compound dosage becomes more clearly specified later, typically during preclinical and clinical studies.

According to some interviewees, there are possibilities for adjusting drug dosage in ways that could lead to reduced excretion from the human body, and thus emissions into the environment. Interviewees, however, stressed that the efficacious dose in humans needed for administration would be one of the most important of multiple criteria, i.e. the dose would never be lower than needed for efficacy.

For the interviewees of six of the seven companies, no/reduced low dose toxicity is compatible with parameters currently optimized in the R&D process, as meeting toxicity requirements is necessary from a pharmaceutical point of view. APIs after all need to be safe for the patient. All the efforts carried out during the R&D process to reach a low dose can in general be seen as reducing risks of toxic effects on patients, and potentially also on the environment.

The feasibility of a lower dose is favoured by higher compound potency. However, highly potent APIs may already exert toxicity to environmental organisms at low doses. Therefore, high potency needs a more detailed consideration than the use of a simple rule of thumb. An interviewee explained that, in general, the more potent one would make the drug, the more one would have to build in some additional properties to avoid side effects, for example, a very specific way of drug delivery. After *in vivo* efficacy it would be desirable that the API is metabolized to less potent metabolites.

In addition to the aspect of low dose, an interviewee argued that for new substances designed for specific diseases of a small patient population, no release in huge quantities is expected. The low quantities of these substances would never provoke any risks in the environment.

3.2.3.2. Environmental (bio)degradability. All interviewees agreed in principle on the desirability of APIs with a higher environmental (bio) degradability, but there was no clear agreement amongst them on the potential to implement this criterion in practice. An interviewed medicinal chemist feared that the consequences of designing APIs that are degradable in the environment have not yet been sufficiently researched, and was therefore sceptical of the aim of environmentally biodegradable drugs. Multiple transformation products could be formed in the water that are more soluble, and therefore harder to extract from water.

In two interviews it was mentioned that environmental (bio)degradability could clash with the need to design for API stability against enzymes in the human body. However, in four interviews it was argued that the different conditions affecting the API along its lifecycle should be considered in detail when evaluating the potential of environmental (bio)degradability. It would be interesting to find some kind of 'window of opportunity' for compounds to be both sufficiently stable in the human body and (bio)degrade in the environment: the compound could be made so that it is sufficiently stable to have an effect in the human body, and later degrade relatively quickly in the environment.

Another concept for APIs designed to be only as stable as necessary was the antedrug[1] approach. Antedrugs could result in molecules that are smaller, more polar, more easily excreted and probably also readily biodegraded in the environment. An interviewee proposed that data on a molecule's behaviour in the patient (e.g. molecule clearance from the body) could be made available for environmental studies. In this context, it was recognized that modifying lead structures using certain functional groups to block metabolism (e.g. groups containing fluorine) could hinder biodegradation in the environment.

3.2.3.3. No/reduced adverse environmental effects. The aim of no/reduced adverse environmental effects in the environment would be strongly compatible with several established R&D practices, in the opinion of interviewees of six of the seven participating companies.

In particular, interviewees mentioned medicinal chemistry's aim of very high target specificity of their active substances – high specificity being an established strategy to reduce off-target (side-) effects in the patient. High specificity is synergistic with reducing off-target effects in the environment, as specific drugs, once excreted, might be expected to show fewer off-target environmental effects than less specific drugs dosed at similar levels (due to the high specificity to the drug target in the human body).

Several interviewees suggested that *in silico* testing with mouse enzymes or human enzymes could possibly inspire the testing with fish enzymes (off-targets). Off-target assay panels for human safety existing in pharmaceutical R&D could be of great interest to integrate targets of environmental species that are associated with adverse effects.

At the moment of this study, no concrete off-targets in environmental species (e.g. concrete enzymes) were known to the interviewees. If one would know concrete off-targets one could look at structural similarities and build selectivity into the molecule. However, this could be contradictory to environmental biodegradability and no/reduced undesirable moieties (next paragraph). To overcome such a consequence of increased specificity, targeted delivery and pro-drugs were mentioned as further strategies to reduce adverse effects. An interviewee mentioned ecotoxicity screens, developed by OECD (e.g. OECD test 201, 210, 211), the use of which could be generally plausible.

3.2.3.4. No/reduced undesirable moieties. Many interviewees saw high potential for implementing the criterion *no/reduced undesirable moieties* in future R&D, based on lists of moieties of concern. They suggested it should be considered as a parameter which weighs decisions in favour of molecules without problematic moieties, or a parameter which flags particular concerns and increase awareness, rather than a hard rule or 'blacklist' of forbidden structural elements, as a 'blacklist' could hinder the ability of the pharmaceutical industry to treat diseases (e.g. in the case of a complete ban on fluorinated groups).

A computational chemist highlighted the potential of *in silico* approaches for developing databases of matched molecular pairs that could, for a given molecule, on the one hand identify undesirable structural moieties in it, and on the other suggest better structural moieties for it. Pooling industry data and resources for a common large database with this purpose was seen as a great opportunity.

3.2.4. Key attributes of environmental models/assays (Q9)

Future integration of environmental criteria in the pharmaceutical R&D process requires that models and assays be developed that predict or assess environmentally relevant properties of APIs. Interviewees identified key attributes of these potential environmental screening

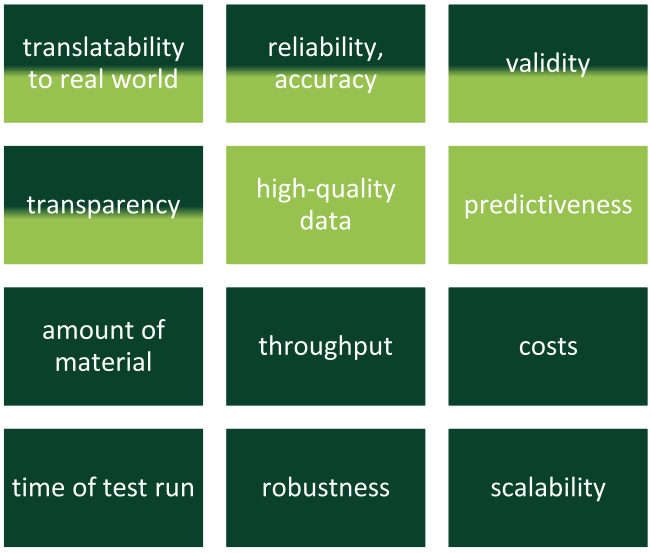

Fig. 2. Key attributes for environmental *in silico* screening models (light green) and *in vitro* assays (dark green). Note, high-quality data is a key attribute to build/improve *in silico* models, but comes from *in vitro* tests. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[1] An antedrug is defined as an active synthetic derivative that is designed to undergo biotransformation to the readily excretable inactive form upon entry in the systemic circulation (Khan et al. (2005)).

models and assays, which would facilitate their future integration into the R&D process (Fig. 2).

Two attributes often mentioned, both for *in vitro* and for *in silico* tests, are reliability and translatability to the real world, i.e. the natural environment. Assays need to be reliable and sufficiently reflective of the natural environmental to play a role in an R&D project's TPP. Attributes mentioned for *in vitro* tests are the amount of substance needed for the assay, throughput, and test costs. An aspect of special relevance for *in silico* tests is high-quality experimental data as the basis for the models. It remained unclear to which extent companies already have such data and whether they would share it.

3.2.4.1. In silico models. Most interviewees stressed the very high potential of *in silico* models: they were considered enormously helpful, and quite an "easy sell", due to time and cost savings when compared to *in vitro* or *in vivo* assays. *In silico* models also have high potential because they would make it as easy as possible for medicinal chemists to include environmental considerations in their workflows and decision-making. Computational screening is well implemented for a range of desirable API parameters, from physicochemical properties to target binding. *In silico* models based on large compound databases are already available for physicochemical properties (e.g. lipophilicity, solubility, vapour pressure), which are also relevant for environmental properties.

The importance of the size of the applicability domain of the model as well as good predictiveness was stressed – qualities based on the availability of high-quality data for a wide variety of compounds. Reaching the necessary level of model predictiveness would just be a matter of time, hinging on the database eventually incorporating sufficient data on new compounds also from different sources (i.e. companies' and public data). Several companies expressed interest in developing *in silico* models for environmentally relevant parameters, required for environmental endpoints where high-quality data are missing. Three companies emphasized that they are open-minded regarding a cooperation across the pharmaceutical industry and academia on such models. Furthermore, the possibility of using already generated data for existing drugs was highlighted, including the environmental test data generated in the past 15 years in the context of EU authorisation.

3.2.4.2. In vitro assays. Aspects highlighted by interviewees as important for *in vitro* assays, independent of the phase in which an *in vitro* assay is implemented, were reproducibility and reliability, as well as its being well-defined, standardized and validated. Having defined cut-off criteria for environmental parameters, i.e. a concrete value for what would be acceptable, would be helpful.

Complexity, throughput, and costs of an assay as well as the amount of material required will influence where the assay is placed in the screening cascade along the drug discovery pathway. This means that there is not one set of attributes that *in vitro* assays for environmental properties need to meet for their being taken up in the R&D process; rather, environmental screen/assay characteristics will determine in which phase uptake could take place.

Interviewees highlighted the benefits of using models and assays at several different points along the R&D process, for example, during hit selection to get an idea on the environmental impact, and during lead optimization using a high-quality test to drive the molecule design with data allowing for a better understanding of the property. Repeating the evaluation of an environmental criterion by a high-quality test can also be desirable at a later stage to feed back into the models applied in earlier stages.

3.2.5. Incentives for the design of greener APIs (Q10)

Incentives in fostering *the design of greener APIs* are viewed by interviewees as potentially helpful in stimulating efforts in research and development in the field of greener APIs.

Incentives identified by interviewees can be described as either hard or soft (Fig. 3). Regarding hard incentives, proposals put forward often related to policy incentives with economic implications, such as fast-track approval in the authorisation process, and increased patent lifetime exclusivity for medicines that meet specific environmental criteria. It was speculated (by non-legal experts) that regulated patentability for reduced environmental impact as novelty could be helpful. Furthermore, a green label (which builds trust with society) could encourage companies to invest in environmental considerations. It would create a social incentive[2] as it may project a positive reputation in society. Financial support, e.g. by subsidizing testing for environmental impact, was also suggested as a viable incentive.

Interviewees observed that regulations in many fields are becoming more stringent; some saw the possibility that in future there could be "*a must*" around this topic for pharmaceuticals. Companies would thus have an intrinsic incentive for acting sooner rather than later, as they should be prepared for upcoming regulatory developments.

Soft incentives include creating awareness and motivation within teams of medicinal chemists. Awareness of a compound's environmental impact, based on in-depth knowledge (regarding environmental issues, and tools to avoid those), would be important to make good decisions in the R&D process. An interviewee mentioned that so as to increase their intrinsic motivation, companies should be exposed to and familiarized with test methods. Once this exposure has taken place, acceptance for integration would increase. Another soft incentive would relate to reputational issues, as implementing environmental considerations would be beneficial for the reputation of pharmaceutical companies.

Some interviewees suggested no policy incentives would be needed, as the direction society is travelling in was already creating 'soft' incentives; it generates public pressure, company willingness, and even personal interest of medicinal chemists. Personal interest and intrinsic motivation were indeed noticeable in each of the conducted interviews.

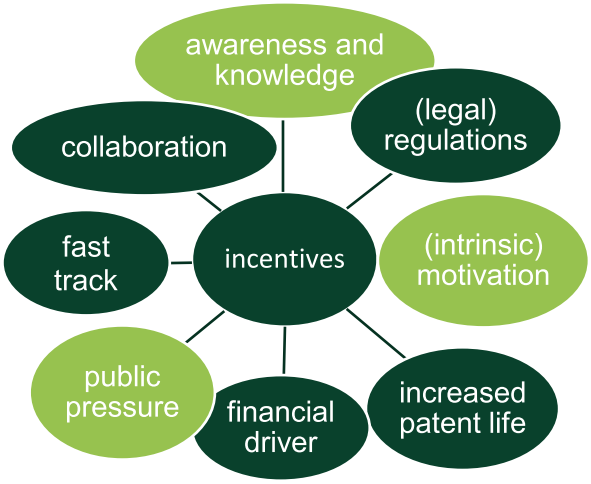

Fig. 3. Soft incentives (light green) and hard incentives (dark green) mentioned in the interviews (Q10). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[2] Social incentives cover a wide spectrum of interpersonal rewards and motivations, encouraging people (here, companies' actors) to behave in a socially valued and approved manner. Examples are projecting a positive social image and reputation and gaining social acceptance (Dorfman and Grossmann (2020)).

4. Discussion

Current application of green chemistry principles by pharmaceutical companies interviewed is limited to the manufacturing process, e.g. using fewer and safer raw materials, or reducing a product's carbon footprint. Reducing the environmental impact of an API itself by minimizing its environmental exposure and adverse effects does not play a role in their drug discovery and development. This finding is in line with the study by Di Soete et al. (2017) who intensively discussed the application of green chemistry principles by the pharmaceutical industry beyond *the design of greener APIs*. However, Di Soete et al. (2017) highlighted the need to evaluate the feasibility of *the design of greener APIs* from the perspective of R&D experts, including needs and incentives. Our interview study should lead to a better understanding of the feasibility of this concept according to the medicinal chemists and other experts who work on discovering and developing APIs.

4.1. The R&D process and environmental considerations

No significant, company-specific deviations from the general approach to the pharmaceutical R&D process were identified when interviewing experts of seven global pharmaceutical companies. Differences in nomenclature and intermediate decision points exist, but are not necessarily linked to a governance process and can be neglected. As the overall process in different companies is largely the same, the potential for uptake of environmental parameters in the pharmaceutical R&D process identified in this paper can be generalized to other research-based pharmaceutical companies.

The finding that the pharmaceutical R&D process is highly flexible is consistent with literature data. Companies try to operate in a very nimble, agile nature to improve R&D productivity (Berggren et al., 2018), for example applying an agile, iterative test-and-learn approach (Gyurjyan et al., 2017). A study of the operational practices of more than 25 global pharmaceutical companies found that all companies had launched lean or Six Sigma projects in the recent past (Cremer et al., 2009). Thus, the R&D culture in pharmaceutical companies is familiar with highly dynamic processes and continuous changes. This process flexibility and flexible R&D culture show that there are no intrinsic barriers to the uptake of novel criteria of a different type to the criteria already playing a role in pharmaceutical R&D decision-making.

The interviewees saw numerous opportunities for uptake of environmental parameters in different phases of the R&D process. Environmental parameters could already play a role in the earliest phases of R&D, for example in hit identification approaches based on *in silico* screens and *in vitro* high throughput screens, all the way up to the final stages of lead optimization. With candidate selection the molecular structure is established, and environmental parameters will not lead to structural changes after that point. After candidate selection, relevant environmental data could however still be collected to improve the scientific knowledge base and the predictive capability of *in silico* models.

The opinions of medicinal chemists differed when it came to their preference for including environmental criteria earlier or later within phases of drug discovery. Different opinions can be explained by a lack of clarity on how strategies for decision-making could look like, including an approach on how to weigh parameters of different nature (pharmaceutical and environmental aspects). A strategy for decision-making to include environmental parameters in overall compound scores, or as flags, was seen as more promising by medicinal chemists than strict cut-off limits or go/no-go criteria.

4.2. Environmental parameters

According to many interviewees, some environmental properties can go hand in hand with common desirable API properties, leading to potential win-wins. For instance, physicochemical or fate properties such as plasma solubility or permeability also influence the uptake by environmental organisms, required for biodegradation by intracellular enzymes. Environmental bioaccumulation is often associated with high lipophilicity of the compound, combined with lack of enzymatic clearance in the non-target species. The current trend in drug design is toward lower lipophilicity (to enable better plasma solubility and minimize off-target binding, amongst other things) and thus only very few newly developed APIs should show bioaccumulative properties. Conversely, hydrophilic APIs and their transformation products that are persistent and mobile in the aquatic environment are more likely to be a concern for the future (Hale et al., 2020).

Furthermore, compounds that are highly selective in the human body may also cause fewer adverse effects on non-target species. Effects based on a mode of action needed for applications, e.g. of antibiotics, might be challenging to avoid in the environment. Orthology predictions of drug targets in the human body and environmental organisms can be obtained from the database Ecodrug.com (Verbruggen et al., 2018). Options to mitigate risks of adverse effects based on a mode of action are largely limited to reducing environmental exposure e.g. through degradation.

There was less consensus on the compatibility of the criteria 'no/reduced environmental exposure', 'no/reduced undesirable moieties', and 'environmental (bio)degradability'. Regarding environmental exposure, low dose drugs (leading to reduced excretion by patients into the environment) potentially go hand in hand with desirable environmental considerations. However, some interviewees highlighted that approaches aiming for lower dosing (which reduces exposure) are limited due to therapeutic dose requirements. Moreover, strategies of dose reduction require a more precise examination. Lower dose due to higher potency may also result in greater ecotoxicological potency in case of greater potency enhancement than dose reduction. A well-known example are endocrine disrupters, which are potent at low environmental concentrations (Vandenberg, 2014). This is possibly the reason for frequent hazard- and risk-based prioritization for environmental assessments but no consideration by exposure-based methods (Burns et al., 2018). Lower dose due to better bioavailability is considered beneficial from an environmental perspective not only because of reduced emissions, but also because of potentially better bioavailability for bacteria, which is required for biodegradability in the environment (Boethling et al., 2007; Daughton, 2003). The latter is true only if bioavailability is improved by optimizing the API structure, not the drug delivery system (Baron, 2012). Higher on-target specificity to enable a lower dose and reduced off-target effects in the patient will likely result in fewer effects on related targets conserved in environmental organisms (Moermond et al., 2022). Environmental adverse effects based on interaction with more distant targets are still possible, especially for bioaccumulating substances.

Regarding no/reduced undesirable moieties, it was not covered during the interviews which ones are undesirable. Regardless of this, an early flagging was considered generally feasible, keeping in mind that the importance of such moiety for the bioactivity is rather unclear at early stages. For the classification as undesirable moiety, a starting point might be looking at regulations for other product categories such as cosmetics, plant protection products, and chemicals in general. A highly topical example is the proposal by the Netherlands, Germany, Norway, Denmark and Sweden to restrict per- and polyfluoroalkyl substances (PFAS) under REACH. It covers a wide range of PFAS uses (ECHA, 2022). Even if the restriction proposal does not apply to pharmaceuticals, the criteria for a greener API can be guided by it.

At first glance, environmental (bio)degradability does not seem compatible with the required chemical stability for an API. However, in some interviews it was discussed that conditions such as pH, access to light and bacteria concentration and diversity (and therefore the set of enzymes that interacts with the compound) change continually during the API's lifetime (i.e. from synthesis to excretion and presence in the environment), possibly creating significant windows of opportunity for

compounds to be both sufficiently stable in the human body and (bio) degradable in the environment. Environmental conditions changing along the lifetime of a compound are described in literature in the context of 'benign by design' as an opportunity (Kümmerer, 2007; Puhlmann et al., 2021). For example, a compound could be designed that, after use, will be cleaved by light to TPs, which are then mineralizable by enzymes in the natural environment. Such consideration requires expertise in environmental processes within the teams of drug designers or by close collaboration with environmental scientists. At the moment, most R&D experts interviewed seem to not be aware of the debate of fate and effects of pharmaceuticals, leading to e.g. scepticism about aiming for degradability of APIs, not because of doubts about the feasibility but because of concerns of supposedly unknown consequences regarding TPs. However, research on TPs has been going on for more than 25 years, e.g. TPs of pesticides, demonstrated by search results using e.g. the literature data base 'Web of Science' and keywords "transformation products" combined with "environment".

Furthermore, the growing API complexity mentioned by an interviewee can hinder complete (bio)degradability (e.g. in case of carbon chain branching or amine functional groups carrying further substituents), but not necessarily, as (bio)degradability depends on the specific structural units and the molecule as a whole. Nonetheless, this knowledge could serve as rough guiding principles ('rules of thumb') for the design for environmental biodegradation (Boethling et al., 2007). For example, biomolecules such as the group of monoclonal antibodies can be very complex (with repeating structural features) and biodegradable at the same time as long as they carry natural function groups and are attached in a natural manner (Website Roche). Thus, it is too early for a final conclusion at this point in time. Environmental (bio) degradation has to be better understood.

The ideal outcome from an environmental perspective would be ready and complete environmental biodegradation of an API to inorganic compounds such as carbon dioxide and inorganic salts, i.e. complete mineralization. This would mean that neither parent compound nor any TPs are persistent and there would therefore be no risks in the environment, as there would be no meaningful exposure (DeVito, 2016; Kümmerer, 2010; Kümmerer and Hempel, 2010; Taylor, 2015).

Complete mineralization is probably not feasible for all APIs, but could be aspired to for a share of new APIs. According to publicly available ERA data from pharmaceutical companies, there are examples of APIs on the market which are unintentionally (i.e. without targeted design) biodegradable in the environment, e.g. rosiglitazone (inherently), interferon alfa-2a (readily), and enfuvirtide (readily), as well as monoclonal antibodies (readily), such as emicizumab and ocrelizumab (Websites GSK; Roche). Examples of high-volume marketed APIs which are readily biodegradable include several β-lactams (such as Penicillin V), valproic acid, and acetylsalicylic acid (Kümmerer and Al-Ahmad, 1997; Längin et al., 2009; Puhlmann et al., 2021). But overall, many of registered pharmaceuticals are persistent. For example, Schwarz et al. found that approx. 50% of APIs are persistent according to ERA datasets of around 300 APIs (Schwarz et al., 2021).

Interviewees would like to have a set of clearly defined, measurable and optimizable parameters for greener APIs, either related to ecotoxicity or to fate endpoints. Exchange of knowledge between R&D experts and environmental scientists is needed to clarify how to measure and optimize environmental parameters in practice. The GREENER approach by Moermond et al. (2022) proposing environmental criteria is a good starting point for such an exchange.

4.3. Needs of models and assays and incentives for this process modification

Interviewees often argued that incorporating environmental considerations into R&D is possible when suitable models or assays are available for clearly defined parameters. Standardized assays for ecotoxicity or environmental fate, such as OECD tests, are well established, e.g. as part of the marketing authorisation procedure (EMA, 2006, 2016, 2018). However, these are low-throughput assays and less suitable for uptake in early R&D processes. Approaches are needed to screen a higher number of compounds at an earlier phase of R&D, e.g. *in silico* tools for predictions or *in vitro* medium- or high-throughput screens. For chronic ecotoxicity, using less complex test systems than whole organisms enables shorter time of test run. Examples are enzymes (as a panel of targets related to effects in environmental species), cells (including bacteria) and embryos (e.g. embryo-larval zebrafish).

Development of *in silico* tools could play an important role in considering environmental parameters due to e.g. high throughput and comparatively low costs, and the possibility of prioritizing compounds for synthesis. The last years have seen a growing role of *in silico* approaches in different areas of pharmaceutical R&D and this growth is expected to continue (Leveridge et al., 2018; Trenfield et al., 2022; Wang et al., 2021), a development that underscores their potential for environmental parameters. Environmental *in silico* models could help e.g. predict a compound's binding affinity to relevant off-targets from wildlife species, or predict its environmental (bio)degradability and resulting transformation products and their properties. Furthermore, structural moieties (i.e. desired / undesired including rules of thumb from an environmental perspective) could be identified.

In silico tools like QSARs (Quantitative Structure-Activity Relationships) have been used to predict toxicity of industrial chemicals to algae, daphnia and fish, e.g. through ECOSAR (US EPA, 2012), with varying results. Predictions are best for neutral compounds in acute studies. However, many pharmaceuticals are ionisable rather than neutral, and concern regarding their environmental effects relates to chronic toxicity at low environmentally relevant concentrations rather than acute toxicity at high concentrations. Prediction of presence or absence of drug targets in the most susceptible species was found to be possible (Gunnarsson et al., 2019). Within the VEGA platform (https://www.vegahub.eu/), there are several *in silico* models to predict persistence of chemicals in soil, sediment and water, including ready biodegradability. Using the prediction system JANUS, transformation products formed in the environment can be evaluated. JANUS is also available within VEGA. Further examples for models to predict biodegradability are Biowin1–7 of the US EPA, CASE Ultra from Multicase, Model Applier from Leadscope, VEGA, and the OECD QSAR Toolbox (Rücker and Kümmerer, 2012). However, the applicability domain of *in silico* methods for environmental (bio)degradability is generally limited for pharmaceuticals as experimental data is missing to build (better) models with an applicability domain of considerable size. A practical *in-silico* workflow addressing such limitations was suggested by Lorenz et al. (2021) to support the design of new environmentally mineralizing compounds.

Generally, chemical and taxonomic read-across approaches may overcome the limited applicability domain of QSARs, and other future *in silico* approaches of artificial intelligence could also help, but their use requires great expertise, standardization, and rigorous validation (Benigni, 2019; ECHA, 2017; Fenner et al., 2020).

Attributes of the screening tools (throughput, costs, etc.) will decide for which phase in R&D a particular tool or assay is suitable. For instance, new tools and assays with lower throughput and more complexity will be helpful in later stages of drug discovery (e.g. lead optimization), as well as help improve knowledge and validate models used in the earlier stages. New tools with higher throughput and lower complexity could in turn prove helpful in the earlier stages of drug discovery (e.g. hit selection and optimization). In the long-term, a standard toolbox that is suitable for routine screens in analogy e.g. to the OECD QSAR toolbox (OECD, 2021) would be helpful for successful application of environmental considerations in R&D processes.

Efforts to develop screening tools are needed to close the identified gaps in methodology. Collaborations within and across pharmaceutical companies and between industry and academia on these topics was seen as highly promising. The incorporation of environmental parameters

into early R&D would benefit from an earlier involvement of environmental experts (including industry's own environmental experts) in the R&D process. Currently, these experts become involved around preclinical studies only (cf. Fig. 1). Including environmental expertise in the earlier phases could be beneficial, in a similar fashion to previous process transformations in pharmaceutical R&D in which other areas (e.g. formulation) were addressed earlier in the R&D process, as it was realized that an earlier evaluation of these topics was potentially profitable in the long term. R&D experts need to become aware of the issue of pharmaceuticals in the environment and how they can use models and assays. This will facilitate further discussions on the feasibility and follow up developments of incorporating *the design of greener APIs* in the R&D process. Furthermore, pharmaceutical companies could cooperate to pool data for a common large database needed for development of prediction models. Moreover, exchange with other sectors facing the same challenge of designing more environmentally friendly products, e.g. agrochemical or detergent industries, could also support efficient research and development of tools.

Important for the addressing of identified needs in research and development are financial, social, and regulatory incentives. Interviewees proposed a number of soft and hard drivers that would be reasonable 'carrots and sticks' to encourage industry investment: creating awareness and knowledge, (intrinsic) motivation, and public pressure, as well as pharmaceutical sector internal standards, increased patent life, fast track approval, financial drivers, and regulations. The European Union's 'Strategic Approach to Pharmaceuticals in the Environment' highlighting "the green pharmaceutical design" (European Commission, 2019) might generate pressure on the research-based pharmaceutical companies. According to Ågerstrand et al. (2015) an inclusion of environmental risks into the benefit-risk assessment of a medicinal product under consideration for marketing authorisation would consequentially lead to an early consideration of environmental aspects.

Based on the identified needs for process modifications, we propose a roadmap with sequential actions that would facilitate industry moving towards *the design of greener APIs*. It consists of four phases: i) uptake of novel approaches, ii) data gathering, iii) toolbox development and iv) ongoing tasks (Fig. 4). Especially for step i) and ii), collaboration across pharmaceutical industry, academia, authorities and all other stakeholders is essential. These changes would profit from guidance and regulation.

4.4. Discussion of the study design

Due to the COVID-19 pandemic the interviews could not be conducted face-to-face, leading to a loss of personal atmosphere and body language on the one hand. On the other hand, this format allowed for more interview participants, as no travel time was required. Interviews resulted in fruitful discussions between the interviewees of the same company. The different numbers of participants per interview (2 - 7) might have led to losses in comparability between the seven interviews due to differences in the diversity of opinions and dynamics of the discussions between company members. However, the different numbers of participants per interview is considered to have less impact on the data evaluation, as interview data was evaluated qualitatively. The same applies to differences in statements between companies due to corporate culture and policy.

Since all interviewed experts work for major pharmaceutical companies, the perspective of smaller pharmaceutical companies and biomedical start-ups was not captured by this study. It would be desirable to elicit the perspective of smaller companies in future research, given their significant share of newly approved and marketed drugs (Ioannou, 2018).

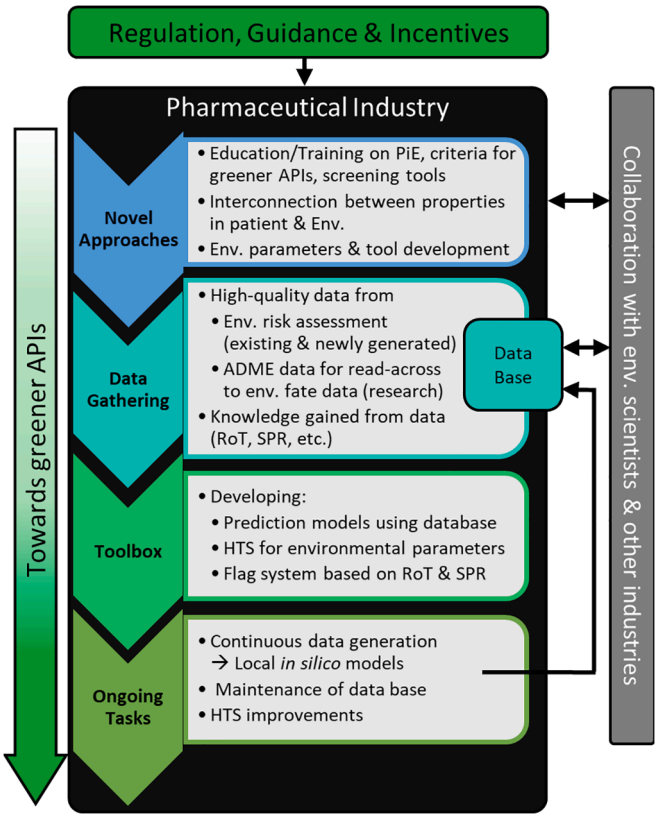

Fig. 4. Proposal of a roadmap towards *the design of greener APIs*.
Abbreviation: Env.: environment(al), PiE: pharmaceuticals in the env., HTS: high throughput screen, RoT: rules of thumb, SPR: structure-property relationship.

5. Conclusion

This study breaks new ground in that it managed to elucidate state, needs and opportunities for *the design of greener APIs* within pharmaceutical industry, based on in-depth interviews with medicinal chemists and other experts of major global pharmaceutical companies. Information on the technical feasibility of implementing *the design of greener APIs* was gained. Needs (e.g. tools and their attributes) and incentives for this process modification were identified.

The results indicate that including environmental considerations in pharmaceutical R&D is possible and could take place at several stages in the R&D process, from the hit selection phase to late stages of lead optimization. In addition, it could also result in new business opportunities, both in general terms and against the background of on-going policy developments e.g. in the EU. Environmental properties that are determined by the molecular structure should be considered early during R&D. The latest opportunity would be at late stages of lead optimization, as the molecular structure of an API candidate will no longer be subject to change thereafter. Uptake of environmental considerations is possible due to the highly flexible nature of the R&D process (with processes adapting continuously over time, but also individual projects updating continuously their approaches) and due to the fact that medicinal chemists are highly experienced in optimizing numerous interdependent parameters in parallel. Moreover, some properties that reduce environmental risks were considered compatible with common desirable API's properties in the human body, which are already optimized for in pharmaceutical R&D.

However, barriers exist to actually including environmental considerations in pharmaceutical R&D. Most significant are the challenges related to the current state of knowledge and the availability of appropriate *in silico* models and *in vitro* assays that can help evaluate

environmental parameters. For their uptake in R&D, environmental parameters should ideally be clearly defined, measurable and relevant. Furthermore, identified interdependencies between environmental aspects and the desirable API parameters need to be further investigated to understand exactly how any molecular modification affects its environmental behaviour and impact in order to identify synergies and possible hurdles. Collaboration between R&D experts and environmental scientists within and outside pharmaceutical companies and authorities would help R&D experts to better understand needs and possible future drivers on the one hand and existing tools to assess environmental properties and how to include environmental data into the decision-making during drug discovery on the other hand. For the development of new environmental assessment tools, financial, social, and regulatory incentives would be beneficial.

In future research, the scope of *the design of greener APIs* should be expanded to i) greener pharmaceutical products, i.e. considering excipients, and ii) further principles of green chemistry, e.g. reduced carbon footprint.

CRediT authorship contribution statement

Neele Puhlmann: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization. **Rodrigo Vidaurre:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Klaus Kümmerer:** Conceptualization, Writing – review & editing, Supervision.

Data availability

The data that has been used is confidential.

Acknowledgements

This study was conducted as part of the EU project PREMIER. PREMIER has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 875508. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. http://www.imi-premier.eu

This publication reflects only the authors' view and the Joint Undertaking is not responsible for any use that may be made of the information it contains.

The authors thank all interviewees for their time and valuable insights, as well as the PREMIER consortium for valuable feedback during the writing process, especially Daniela Angst, Helen Sneddon, Caroline Moermond, and Emilio Benfenati.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2023.106614.

References

Ågerstrand, M., Berg, C., Björlenius, B., Breitholtz, M., Brunström, B., Fick, J., Gunnarsson, L., Larsson, D.G.J., Sumpter, J.P., Tysklind, M., Rudén, C., 2015. Improving environmental risk assessment of human pharmaceuticals. Environ. Sci. Technol. 49 (9), 5336–5345. https://doi.org/10.1021/acs.est.5b00302.

Anastas, P.T., Warner, J.C. (Eds.), 1998. Green Chemistry: Theory and Practice. Oxford University Press, Oxford [England], New York.

aus der Beek, T., Weber, F.-A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A., 2016. Pharmaceuticals in the environment—Global occurrences and perspectives. Environ. Toxicol. Chem. 35 (4), 823–835. https://doi.org/10.1002/etc.3339.

Baron, M., 2012. Towards a greener pharmacy by More Eco design. Waste Biomass Valoriz. 3 (4), 395–407. https://doi.org/10.1007/s12649-012-9146-2.

Benigni, R., 2019. Towards quantitative read across: prediction of Ames mutagenicity in a large database. Regul. Toxicol. Pharmacol.: RTP 108, 104434. https://doi.org/10.1016/j.yrtph.2019.104434.

Berggren, R., Fleming, E., Keane, H., Moss, R., 2018. R&D in the 'age of agile'. <https://www.mckinsey.com/industries/life-sciences/our-insights/r-and-D-in-the-age-of-agile>.

Blass, B., 2015. Basic Principles of Drug Discovery and Development. Elsevier Science, Burlington, p. 591.

Blazer, V.S., Gordon, S., Jones, D.K., Iwanowicz, L.R., Walsh, H.L., Sperry, A.J., Smalling, K.L., 2021. Retrospective analysis of estrogenic endocrine disruption and land-use influences in the Chesapeake Bay watershed. Chemosphere 266, 129009. https://doi.org/10.1016/j.chemosphere.2020.129009.

Boethling, R.S., Sommer, E., DiFiore, D., 2007. Designing small molecules for biodegradability. Chem. Rev. 107 (6), 2207–2227. https://doi.org/10.1021/cr050952t.

Brodin, T., Fick, J., Jonsson, M., Klaminder, J., 2013. Dilute concentrations of a psychiatric drug alter behavior of fish from natural populations. Science 339 (6121), 814–815. https://doi.org/10.1126/science.1226850.

Burns, E.E., Carter, L.J., Snape, J., Thomas-Oates, J., Boxall, A.B., 2018. Application of prioritization approaches to optimize environmental monitoring and testing of pharmaceuticals. J. Toxicol. Environ. Health, Part B 21 (3), 115–141. https://doi.org/10.1080/10937404.2018.1465873.

Cahill, T.M., 2022. Increases in trifluoroacetate concentrations in surface waters over two decades. Environ. Sci. Technol. 56 (13), 9428–9434. https://doi.org/10.1021/acs.est.2c01826.

Cremer, P., Lösch, M., Schrader, U., 2009. Maximizing efficiency in pharma operations. <https://www.mckinsey.com/~/media/McKinsey/Business%20Functions/Operations/Our%20Insights/Maximizing%20efficiency%20in%20pharma%20operations/Maximizing%20efficiency%20in%20pharma%20operations.pdf>.

Daughton, C.G., 2003. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. Environ. Health Perspect. 111 (5), 757–774. https://doi.org/10.1289/ehp.5947.

Daughton, C.G., 2014. Eco-directed sustainable prescribing: feasibility for reducing water contamination by drugs. Sci. Total Environ. 493, 392–404. https://doi.org/10.1016/j.scitotenv.2014.06.013.

Daughton, C.G., Ternes, T.A., 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change? Environ. Health Perspect. 107 (suppl 6), 907–938. https://doi.org/10.1289/ehp.99107s6907.

De Soete, W., Jiménez-González, C., Dahlin, P., Dewulf, J., 2017. Challenges and recommendations for environmental sustainability assessments of pharmaceutical products in the healthcare sector. Green Chem. 19 (15), 3493–3509. https://doi.org/10.1039/C7GC00833C.

Deloitte, Directorate-General for Environment (European Commission), INERIS, Milieu Ltd, Kümmerer, K., 2018. Options for a strategic approach to pharmaceuticals in the environment, Final report.

DeVito, S.C., 2016. On the design of safer chemicals: a path forward. Green Chem. 18 (16), 4332–4347. https://doi.org/10.1039/C6GC00526H.

Dorfman, A., Grossmann, I., 2020. Social Incentives. In: Zeigler-Hill, V., Shackelford, T.K. (Eds.), Encyclopedia of Personality and Individual Differences. Springer International Publishing, Cham, pp. 5067–5070.

ECHA, 2017. Read-Across Assessment Framework (RAAF). <. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf. > (retrieved 18.02.21).

ECHA, 2022. Perfluoroalkyl Chemicals (PFAS). <. https://echa.europa.eu/en/hot-topics/perfluoroalkyl-chemicals-pfas. > (retrieved 03.06.22).

EMA, 2006. Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use - First version (EMEA/CHMP/SWP/4447/00 corr 2). <. https://www.ema.europa.eu/en/environmental-risk-assessment-medicinal-products-human-use. >.

EMA, 2016. Questions and Answers on 'Guideline on the Environmental Risk Assessment Of Medicinal Products for Human Use': EMA/CHMP/SWP/44609/2010 Rev. <. https://www.ema.europa.eu/en/questions-answers-guideline-environmental-risk-assessment-medicinal-products-human-use. >.

EMA, 2018. Draft Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Rev. 1). <. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-environmental-risk-assessment-medicinal-products-human-use-revision-1_en.pdf. >.

European Commission, 2004a. Art. 1, Definitions 28 and 28a, 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. <. https://op.europa.eu/en/publication-detail/-/publication/61bbe31e-fc11-4f11-b2a7-e175a7529f8d/language-en/format-PDF. > (retrieved 18.02.21).

European Commission, 2004b. Art. 8 (3), 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. <. https://op.europa.eu/en/publication-detail/-/publication/61bbe31e-fc11-4f11-b2a7-e175a7529f8d/language-en/format-PDF. > (retrieved 18.02.21).

European Commission, 2019. Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee: european Union Strategic Approach to Pharmaceuticals in the Environment. <. https://ec.europa.eu/environment/water/water-dangersub/pdf/strategic_approach_pharmaceuticals_env.PDF. > (retrieved 07.07.22).

European Commission, 2020a. A New Circular Economy Action PlanFor a Cleaner and More Competitive Europe. <. https://eur-lex.europa.eu/resource.html?uri=cellar:9903b325-6388-11ea-b735-01aa75ed71a1.0017.02/DOC_1&format=PDF. > (retrieved 18.02.21).

European Commission, 2020b. Chemicals Strategy for Sustainability Towards a Toxic-Free Environment. <. https://ec.europa.eu/environment/pdf/chemicals/2020/10/Strategy.pdf. > (retrieved 18.02.21).

European Commission, 2020c. Personalised Medicine. <. https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/personalised-medicine_en. > (retrieved 03. June .2022).

European Commission, 2020d. Pharmaceutical Strategy for Europe. <. https://ec.europa.eu/commission/presscorner/detail/en/ip_20_2173. > (retrieved 18.02.21).
European Parliament, 2015. The Precautionary Principle: Definitions, Applications and Governance. <. https://www.europarl.europa.eu/thinktank/en/document/EPRS_IDA(2015)573876. > (retrieved 30th October 2022).
Fenner, K., Screpanti, C., Renold, P., Rouchdi, M., Vogler, B., Rich, S., 2020. Comparison of small molecule biotransformation half-lives between activated sludge and soil: opportunities for read-across? Environ. Sci. Technol. 54 (6), 3148–3158. https://doi.org/10.1021/acs.est.9b05104.
Fent, K., 2015. Progestins as endocrine disrupters in aquatic ecosystems: concentrations, effects and risk assessment. Environ. Int. 84, 115–130. https://doi.org/10.1016/j.envint.2015.06.012.
Fortunak, J.M.D., Emeje, M.O., Kammendi, H., Tilahun, E.L., Wang, X.S., 2015. Chapter 13 the business case for green chemistry in drug discovery. In: Summerton, L., Sneddon, H.F., Jones, L.C., Clark, J.H. (Eds.), Green Chemistry Strategies For Drug Discovery. The Royal Society of Chemistry, pp. 280–313.
GSK, 2021. Safety Data Sheets & Environmental Risk Assessments. <. https://www.msds-gsk.com/ERAList.aspx. > (retrieved 18.02).
Gunnarsson, L., Snape, J.R., Verbruggen, B., Owen, S.F., Kristiansson, E., Margiotta-Casaluci, L., Österlund, T., Hutchinson, K., Leverett, D., Marks, B., Tyler, C.R., 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.
Gyurjyan, G., Thaker, S., Westhues, K., Zwaanstra, C., 2017. Rethinking pharma productivity. <https://www.mckinsey.com.br/~/media/McKinsey/Industries/Pharmaceuticals%20and%20Medical%20Products/Our%20Insights/Rethinking%20pharma%20productivity/Rethinking-pharma-productivity.pdf>.
Hale, S.E., Arp, H.P.H., Schliebner, I., Neumann, M., 2020. Persistent, mobile and toxic (PMT) and very persistent and very mobile (vPvM) substances pose an equivalent level of concern to persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) substances under REACH. Environ. Sci. Eur. 32 (1), 155. https://doi.org/10.1186/s12302-020-00440-4.
Hamburg, M.A., Collins, F.S., 2010. The path to personalized medicine. N. Engl. J. Med. 363 (4), 301–304. https://doi.org/10.1056/NEJMp1006304.
Hester, R.E., Harrison, R.M. (Eds.), 2015. Pharmaceuticals in the Environment. Royal Society of Chemistry, Cambridge.
Ioannou, L., 2018. Big Pharma's billion-dollar scramble to invest in start-ups to fuel innovation. <https://www.cnbc.com/2018/03/26/big-pharmas-scramble-to-invest-in-start-ups-to-fuel-innovation.html>.
Jones, O.H., Voulvoulis, N., Lester, J.N., 2001. Human pharmaceuticals in the aquatic environment a review. Environ. Technol. 22 (12), 1383–1394. https://doi.org/10.1080/09593332208618186.
Joudan, S., Silva, A.O.de, Young, C.J., 2021. Insufficient evidence for the existence of natural trifluoroacetic acid. Environ. Sci.: Process. Impacts 23 (11), 1641–1649. https://doi.org/10.1039/D1EM00306B.
Khan, M.O.F., Park, K.K., Lee, H.J., 2005. Antedrugs: an approach to safer drugs. Curr. Med. Chem. 12 (19), 2227–2239. https://doi.org/10.2174/0929867054864840.
Kidd, K.A., Blanchfield, P.J., Mills, K.H., Palace, V.P., Evans, R.E., Lazorchak, J.M., Flick, R.W., 2007. Collapse of a fish population after exposure to a synthetic estrogen. Proc. Natl. Acad. Sci. 104 (21), 8897. https://doi.org/10.1073/pnas.0609568104.
Kümmerer, K., 2007. Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry. Green Chem. 9 (8), 899–907. https://doi.org/10.1039/b618298b.
Kümmerer, K., 2010. Why green and sustainable pharmacy? In: Kümmerer, K., Hempel, M. (Eds.), Green and Sustainable Pharmacy. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 3–10.
Kümmerer, K., 2016. Chapter 7 Benign by Design. In: Summerton, L., Sneddon, H.F., Jones, L.C., Clark, J.H. (Eds.), Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry. The Royal Society of Chemistry, pp. 73–81.
Kümmerer, K., Al-Ahmad, A., 1997. Biodegradability of the anti-tumour agents 5-fluorouracil, cytarabine, and gemcitabine: impact of the chemical structure and synergistic toxicity with hospital effluent. Acta Hydrochim. Hydrobiol. 25 (4), 166–172. https://doi.org/10.1002/aheh.19970250402.
Kümmerer, K., Clark, J.H., Zuin, V.G., 2020. Rethinking chemistry for a circular economy. Science 367 (6476), 369–370. https://doi.org/10.1126/science.aba4979.
Kümmerer, K., Hempel, M. (Eds.), 2010. Green and Sustainable Pharmacy. Springer Berlin Heidelberg, Berlin, Heidelberg.
LaMattina, J., 2013. BCG weighs in on first-in-class vs. best-in-class drugs. How valuable is their advice? <https://www.forbes.com/sites/johnlamattina/2013/06/17/bcg-weighs-in-on-first-in-class-vs-best-in-class-drugs-how-valuable-is-their-advice/>.
Längin, A., Alexy, R., König, A., Kümmerer, K., 2009. Deactivation and transformation products in biodegradability testing of beta-lactams amoxicillin and piperacillin. Chemosphere 75 (3), 347–354. https://doi.org/10.1016/j.chemosphere.2008.12.032.
Leveridge, M., Chung, C.-W., Gross, J.W., Phelps, C.B., Green, D., 2018. Integration of lead discovery tactics and the evolution of the lead discovery toolbox. SLAS DISCOVERY: Adv. Life Sci. R&D 23 (9), 881–897.
Lorenz, S., Amsel, A.-K., Puhlmann, N., Reich, M., Olsson, O., Kümmerer, K., 2021. Toward Application and Implementation of in Silico Tools and Workflows within Benign by Design Approaches. ACS Sustain. Chem. Eng. 9 (37), 12461–12475. https://doi.org/10.1021/acssuschemeng.1c03070.
Messinger, J., Otsomaa, L., Rasku, S., 2016. Chapter 9 medicinal chemistry: how "green" is our synthetic tool box? In: Summerton, L., Sneddon, H.F., Jones, L.C., Clark, J.H. (Eds.), Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry. The Royal Society of Chemistry, pp. 101–115.
Moermond, C.T.A., Puhlmann, N., Brown, A.R., Owen, S.F., Ryan, J., Snape, J., Venhuis, B.J., Kümmerer, K., 2022. GREENER pharmaceuticals for more sustainable healthcare. Environ. Sci. Technol. Lett. 9 (9), 699–705. https://doi.org/10.1021/acs.estlett.2c00446.
OECD, 2019. Pharmaceutical Residues in Freshwater: hazards and Policy Responses. <. https://www.oecd.org/chemicalsafety/pharmaceutical-residues-in-freshwater-c936f42d-en.htm. > (retrieved 22.09.21).
OECD, 2021. The OECD QSAR Toolbox. <. https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm. > (retrieved 20.12.22).
Puhlmann, N., Mols, R., Olsson, O., Slootweg, J.C., Kümmerer, K., 2021. Towards the design of active pharmaceutical ingredients mineralizing readily in the environment. Green Chem. 23 (14), 5006–5023. https://doi.org/10.1039/D1GC01048D.
Rastogi, T., Leder, C., Kümmerer, K., 2015. Re-designing of existing pharmaceuticals for environmental biodegradability: a tiered approach with β-blocker propranolol as an example. Environ. Sci. Technol. 49 (19), 11756–11763. https://doi.org/10.1021/acs.est.5b03051.
Roche, 2021. Environmental Risk Assessments (ERA) for Roche's Active Pharmaceutical Ingredients (API). <. https://www.roche.com/sustainability/environment/environmental-risk-assessment-downloads.htm. > (retrieved 18.02).
Rücker, C., Kümmerer, K., 2012. Modeling and predicting aquatic aerobic biodegradation – a review from a user's perspective. Green Chem. 14 (4), 875. https://doi.org/10.1039/c2gc16267a.
Rüdel, H., Körner, W., Letzel, T., Neumann, M., Nödler, K., Reemtsma, T., 2020. Persistent, mobile and toxic substances in the environment: a spotlight on current research and regulatory activities. Environ. Sci. Eur. 32 (1), 5. https://doi.org/10.1186/s12302-019-0286-x.
Scheurer, M., Nödler, K., 2021. Ultrashort-chain perfluoroalkyl substance trifluoroacetate (TFA) in beer and tea – An unintended aqueous extraction. Food Chem. 351, 129304 https://doi.org/10.1016/j.foodchem.2021.129304.
Schwarz, S., Gildemeister, D., Hein, A., Schröder, P., Bachmann, J., 2021. Environmental fate and effects assessment of human pharmaceuticals: lessons learnt from regulatory data. Environ. Sci. Eur. 33 (1) https://doi.org/10.1186/s12302-021-00503-0.
Summerton, L., Sneddon, H.F., Jones, L.C., Clark, J.H. (Eds.), 2015. Green Chemistry Strategies For Drug Discovery. The Royal Society of Chemistry.
Taylor, D., 2015. The pharmaceutical industry and the future of drug development. In: Hester, R.E., Harrison, R.M. (Eds.), Pharmaceuticals in the Environment. Royal Society of Chemistry, Cambridge, pp. 1–33.
Thompson, J., 2022. A guide to abductive thematic analysis. Qual. Rep. 27 (5), 1410–1421. https://doi.org/10.46743/2160-3715/2022.5340.
Trenfield, S.J., Awad, A., McCoubrey, L.E., Elbadawi, M., Goyanes, A., Gaisford, S., Basit, A.W., 2022. Advancing pharmacy and healthcare with virtual digital technologies. Adv. Drug Deliv. Rev. 182, 114098 https://doi.org/10.1016/j.addr.2021.114098.
Triebskorn, R., Casper, H., Scheil, V., Schwaiger, J., 2007. Ultrastructural effects of pharmaceuticals (carbamazepine, clofibric acid, metoprolol, diclofenac) in rainbow trout (Oncorhynchus mykiss) and common carp (Cyprinus carpio). Anal. Bioanal. Chem. 387 (4), 1405–1416. https://doi.org/10.1007/s00216-006-1033-x.
UN Water, 2017. Wastewater. The Untapped Resource Report 2017, The United Nations World Water Development Report 2017. <. http://www.unesco.org/new/en/natural-sciences/environment/water/wwap/wwdr/2017-wastewater-the-untapped-resource/. > (retrieved 18.02.21).
United Nations, 2015. THE 17 GOALS. <. https://sdgs.un.org/goals#goals. > (retrieved 16.09.22).
US EPA, 2012. Estimation Programs Interface Suite™ for Microsoft® Windows V4.11. <. https://www.epa.gov/tscascreening-tools/epi-suitetm-estimation-program-interface. >.
Vandenberg, L.N., 2014. Low-dose effects of hormones and endocrine disruptors. Vitam. Horm. 94, 129–165. https://doi.org/10.1016/B978-0-12-800095-3.00005-5.
Verbruggen, B., Gunnarsson, L., Kristiansson, E., Österlund, T., Owen, S.F., Snape, J.R., Tyler, C.R., 2018. ECOdrug: a database connecting drugs and conservation of their targets across species. Nucleic Acids Res. 46 (D1), D930–D936. https://doi.org/10.1093/nar/gkx1024.
Wang, W., Ye, Z., Gao, H., Ouyang, D., 2021. Computational pharmaceutics - A new paradigm of drug delivery. J. Control. Rel.: Off. J. Control. Rel. Soc. 338, 119–136. https://doi.org/10.1016/j.jconrel.2021.08.030.
WHO, 2017. Chemical Mixtures in Source Water and Drinking-Water. <. https://www.who.int/publications/i/item/9789241512374. > (retrieved 07.07.22).
Wilkinson, J.L., Boxall, A.B.A., Kolpin, D.W., Leung, K.M.Y., Lai, R.W.S., Galbán-Malagón, C., Adell, A.D., Mondon, J., Metian, M., Marchant, R.A., Bouzas-Monroy, A., Cuni-Sanchez, A., Coors, A., Carriquiriborde, P., Rojo, M., Gordon, C., Cara, M., Moermond, M., Luarte, T., Petrosyan, V., Perikhanyan, Y., Mahon, C.S., McGurk, C.J., Hofmann, T., Kormoker, T., Iniguez, V., Guzman-Otazo, J., Tavares, J.L., Gildasio De Figueiredo, F., Razzolini, M.T.P., Dougnon, V., Gbaguidi, G., Traoré, O., Blais, J.M., Kimpe, L.E., Wong, M., Wong, D., Ntchantcho, R., Pizarro, J., Ying, G.-G., Chen, C.-E., Páez, M., Martínez-Lara, J., Otamonga, J.-P., Poté, J., Ifo, S.A., Wilson, P., Echeverría-Sáenz, S., Udikovic-Kolic, N., Milakovic, M., Fatta-Kassinos, D., Ioannou-Ttofa, L., Belušová, V., Vymazal, J., Cárdenas-Bustamante, M., Kassa, B.A., Garric, J., Chaumot, A., Gibba, P., Kunchulia, I., Seidensticker, S., Lyberatos, G., Halldórsson, H.P., Melling, M., Shashidhar, T., Lamba, M., Nastiti, A., Supriatin, A., Pourang, N., Abedini, A., Abdullah, O., Gharbia, S.S., Pilla, F., Chefetz, B., Topaz, T., Yao, K.M., Aubakirova, B., Beisenova, R., Olaka, L., Mulu, J.K., Chatanga, P., Ntuli, V., Blama, N.T., Sherif, S., Aris, A.Z., Looi, L.J., Niang, M., Traore, S.T., Oldenkamp, R., Ogunbanwo, O., Ashfaq, M., Iqbal, M., Abdeen, Z., O'Dea, A., Morales-Saldaña, J.M., Custodio, M., La Cruz, H.de, Navarrete, I.,

Carvalho, F., Gogra, A.B., Koroma, B.M., Cerkvenik-Flajs, V., Gombač, M., Thwala, M., Choi, K., Kang, H., Ladu, J.L.C., Rico, A., Amerasinghe, P., Sobek, A., Horlitz, G., Zenker, A.K., King, A.C., Jiang, J.-J., Kariuki, R., Tumbo, M., Tezel, U., Onay, T.T., Lejju, J.B., Vystavna, Y., Vergeles, Y., Heinzen, H., Pérez-Parada, A., Sims, D.B., Figy, M., Good, D., Teta, C., 2022. Pharmaceutical pollution of the world's rivers. Proc. Natl. Acad. Sci. 119 (8), e2113947119 https://doi.org/10.1073/pnas.2113947119.