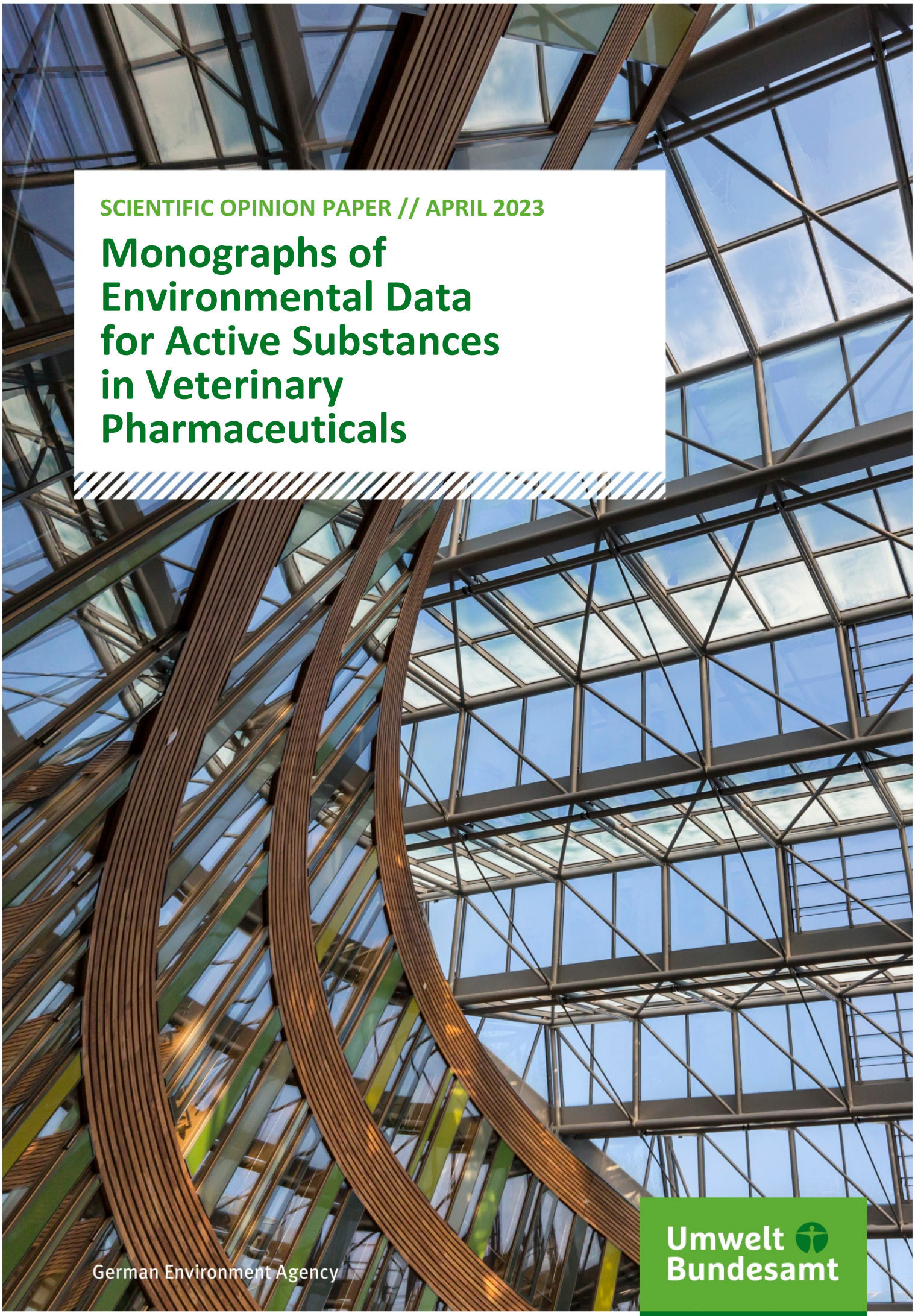

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Monographs of Environmental Data for Active Substances in Veterinary Pharmaceuticals

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Monographs of Environmental Data for Active Substances in Veterinary Pharmaceuticals

The essential base for assessing and managing risks

by

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Executive Summary

The European legislation on veterinary medicinal products (VMPs) takes the concern of potential adverse effects of pharmaceuticals on the environment into account by an authorisation procedure which requires for all new VMPs an environmental risk assessment (ERA) since 2005.[1] The European veterinary medicines legislation was revised with Regulation (EU) 2019/6, which came into force at the beginning of 2022. However, some issues relating to ensuring the environmental safety of veterinary medicines remain unresolved resp. still need decisions and implementing rules. This mainly concerns issues with the availability of ERA data, but also with (non)harmonised conclusions on similar VMPs in the pre-market phase and lack of surveillance in the post-market phase. The lack of environmental data, especially for medicinal products approved before 2005 poses a problem with regard to an efficient risk management. An active substance-based review system (monographs) that systematically and comprehensively collects and reviews data on fate and effects of active substances in the environment could help to address and to solve the above-mentioned issues of data gaps and data availability, as well as harmonisation of assessments. In this way, monographs will be crucial in improving the environmental safety of VMPs.

A feasibility study carried out for the European Commission on the basis of Article 156 of Regulation 2019/6 comes to similar conclusions and also states that: *"Especially in view of the general EU goals stated in the EU Strategic Approach to Pharmaceuticals in the Environment (COM(2019)128) and in the Green Deal - zero emission – 'one substance, one risk assessment' approach (COM(2019)640), ... a monograph system is justified, proportionate and probably affordable."* Although it is recognised that the introduction of a monograph system is likely to be more resource-intensive than the existing system in the initial phase, the benefits of the system will clearly outweigh this. The report of the Commission published in early 2023, fulfilling its obligation under Article 156 of Regulation (EU) 2019/6 of the European Parliament and of the Council[2], also highlights the advantages of an active substance-based monograph system and the resulting improvements for the environmental safety of medicinal products. At the same time, it states that various details still need to be clarified before a monograph system can be successfully introduced, especially with regard to the effort involved and the fit with legislation. The report also states that the monograph system must be considered in a broader context, beyond the VMP sector, to create a comprehensive and coherent system. This means that a monograph system should apply in the longer term to active pharmaceutical substances used in both human and veterinary medicinal products. The current revision of the general legal framework for medicinal products for human use offers the opportunity to include such new and extended requirements for environmental risk assessment and environmental monographs.

[1] Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products
[2] Report from the Commission to the European Parliament and the council on a feasibility study of an active-substance-based review system ('monographs') and other potential alternatives for the environmental risk assessment of veterinary medicinal products; COM(2023) 9 final

The German Environment Agency (UBA) has been advocating a monograph system for pharmaceuticals for years and has discussed this topic in workshops[3],[4], [5] with various stakeholders. UBA fully supports the view of the feasibility study and the conclusions of the European Commission. UBA would like to encourage the European Commission to establish an environmental monograph system for active pharmaceutical substances, because we are convinced that this will be a crucial step towards effectively minimizing the environmental impact of pharmaceuticals by improving assessments, streamlining authorisation procedures, closing data gaps and risk management of pharmaceuticals and effectively minimising their environmental impact.

- **What advantages do monographs offer?**

In such monographs all relevant data on fate and effects of active pharmaceutical substances in the environment should be compiled and published in a publicly accessible database. These data could then be used for harmonised environmental risk assessments and conclusions on similar medicinal products with the same active substance. The data base would not only meet the Commission's objective of data transparency and availability, but could also allow the data to be used by various interested stakeholders and in different regulatory areas. Efficient risk management requires not only the availability of data but also the close interlinking of different regulatory areas. The validated substance data compiled in a monograph could, for instance, be used for deriving environmental quality standards and identification of priority substances according to the Water Framework Directive[6], setting of emission limits for production sites and decision making in sustainable procurement etc. as it is proposed in recital 32 of Regulation (EU) 2019/6. The detachment from product-specific data to active ingredient data as proposed with the environmental monographs sets the course for cross-regulatory use.

- **Establishing a system with shared responsibility and harmonised assessments**

A monograph system of environmental data for active pharmaceutical substances should be a system of shared responsibility and shared benefit. In this way a monograph system goes in the same direction as the 'one substance, one assessment'(1S1A)-approach, which is anchored in the zero-pollution action plan[7]. 1S1A aims to harmonise the registration and the outcome of risk assessment procedures of various individual chemical regulations, to standardise data, to provide

[3] Workshop (2014): *"An effective tool to strengthen the environmental safety of VMPs:Monograph system for active pharmaceutical substances".* 26.11.2014, Brussels(http://www.umweltbundesamt.de/node/28647) Science - Policy Event, Panel discussion (2015): *Environmental risks and effective environmental risk assessment of veterinary medicinal products*. 04.03.2015, Brussels https://www.umweltbundesamt.de/en/service/dates/lunch-debate-on-environmental-risks-of-veterinary

[4] UBA, TUKES (2015): *Environmental risk of veterinary medicines: Key measures for effective environmental risk assessment. A discussion paper on the Proposal for a Regulation of the European Parliament and of the Council on Veterinary Medicinal Products [COM (2014) 558 final]* https://www.umweltbundesamt.de/en/publikationen/environmental-risk-of-veterinary-medicines

[5] Workshop (2017): *"How to achieve an appropriate environmental risk assessment of veterinary medicinal products"*. 07.07.2017, Brussels (https://www.umweltbundesamt.de/en/service/dates/ws-2017-environmental-risk-ass-of-veterinary

[6] Directive 2000/60/EC of the European Parliament and of the Council establishing a framework for the Community action in the field of water policy

[7] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions - Pathway to a Healthy Planet for All EU Action Plan: 'Towards Zero Pollution for Air, Water and Soil'. COM(2021) 400 final

transparent access to data, to close data gaps and to avoid duplication of work and animal testing. In this light, monographs on active pharmaceutical substances can be seen as precursor to the implementation of the 1S1A-approach and would thus fulfil an important objective of the European Commission.

The added value of a monograph system should be considered in a wider policy context. In particular, veterinary and human medicinal products should be considered together, especially since the legislative shortcomings regarding environmental safety are very similar. Moreover, the existing data gaps that hamper effective risk management are even much larger for human medicines than for veterinary medicines. The currently ongoing revision of the European legislation on medicinal products for human use[8] offers the opportunity of introducing a monograph system for active substances for both veterinary medicinal products and medicinal products for human use.[9]

The monograph data should be published in a publicly accessible web-based database, preferable by using IUCLID, attached to an existing database for chemicals, if appropriate, and hosted by an EU agency, for instance the European Chemicals Agency ECHA or the European Medicines Agency EMA. If the European Commission considers a monograph system for pharmaceuticals as a valuable tool for improving environmental safety, it should be established in a timely manner.

[8] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en
[9] German Environment Agency, Scientific opinion paper (October 2022): Improving environmental protection in EU pharmaceutical legislation. Recommendations for reducing adverse environmental impacts from human pharmaceuticals

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1 Introduction

Pharmaceuticals have become an indispensable part of today's veterinary medicine especially in intensive livestock farming. Monitoring projects[10] show that residues of veterinary medicines enter agricultural land via manure (slurry, dung) from intensive livestock farming or are released directly into the environment by pasture-raised animals and in aquaculture. Although the benefits of a responsible use of pharmaceuticals are substantial and well-recognized, pollution with residues of pharmaceuticals is an environmental problem whose adverse effects on the organisms in the environment are well documented. Particularly in the context of antibiotic resistance, the impact on human health is also increasingly being discussed.[11]

The European legislation on medicinal products considers this concern by an authorisation procedure requiring an environmental risk assessment, besides the assessment of quality, user and target animal safety and efficacy. In 2005 an environmental risk assessment became mandatory for all marketing authorisations of veterinary medicinal products by implementation of Directive 2004/28/EC amending directive 2001/82/EC. Guidelines by EMA and VICH[12] for the environmental risk assessment (ERA) of veterinary medicinal products are available since 2005. A review program for products authorised prior to 2005 has never been implemented, resulting in a lack of ERA data for the majority of these "legacy" pharmaceuticals.

The Strategic Approach to Pharmaceuticals in the Environment (COM(2019) 128 final)[13] , published by the European Commission in March 2019, identifies as important action points the necessity to improve the ERA, to fill knowledge gaps on human and veterinary pharmaceuticals as well as the improvement of public access to main ERA results. The pharmaceutical strategy for Europe[14], published at the end of 2020 and focusing on medicines for human use, reinforces these objectives and also points to the need for environmental sustainability of medicines throughout their life cycle. The Pharmaceutical strategy calls for a sound and flexible regulatory system. One of the planned measures under the flagship initiatives on regulatory efficiency is to *"Provide for a single assessment process across Member States for active substances used for different generic medicines (active substance master files) to facilitate their authorisation and life-cycle management"*. In our view, an "active substance master file" should actually be the same as the proposed monograph system for active pharmaceutical substances.

In the Veterinary Regulation (EU) 2019/6, in force since beginning of 2022, the requirement of an ERA is waived for generic products with a reference product authorised after 2005 (Article 18). For products with reference products authorised before 2005 for which no ERA is available an ERA is still required unless similar products are authorised after 2005 (Article 18(7))[15]. This approach assumes that all relevant products have been evaluated uniformly and that the data

[10] https://www.umweltbundesamt.de/en/database-pharmaceuticals-in-the-environment-0.
[11] United Nations Environment Programme (2022): environmental Dimensions of antimicrobial Resistance: Summary for Policymakers.
[12] VICH: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
[13] 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 (COM(2019) 128 final)
[14] Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee: Pharmaceutical Strategy for Europe (COM(2020) 761 final)
[15] A reflection paper of the European Medicines Agency describes details of how Art 18(7) will be implemented: EMA/CVMP/ERA/622045/2020: Reflection paper on the interpretation of Article 18(7) of Regulation (EU) 2019/6

are available, which is not yet the case. However, the assessment of the active substance is done for each new product separately and not based on an agreed and harmonised data set. This fact had led to divergent assessments and conclusions for comparable products.

Environmental data collected as part of the approval of medicinal products have so far been published exclusively in tabular form in so-called public assessment reports for each individual medicinal product. This makes it extremely difficult to search for information of individual active substances. However, these data are of high public interest for various stakeholders and should therefore be more easily accessible to the public.

The need for a general review of the rules for environmental risk assessments was recognised in the new regulation on veterinary medicinal products (2019/6). According to Art. 156 of this regulation the Commission was asked to present a report to the European Parliament and to the Council on a feasibility study of an active substance-based review system ('monographs') and other potential alternatives for the environmental risk assessment of veterinary medicinal products by January 2022. The commissioned feasibility study[16] was published in September 2021 and sees a number of advantages of an active substance-based review system.

The lack of environmental data, especially for medicinal products approved before 2005, is a problem with regard to an efficient risk management. The availability of valid ERA data is the basis of a scientifically sound risk assessment and thus an essential prerequisite for any kind of risk management, be it within the framework of pharmaceutical legislation or in other areas of legislation for the protection of the environment.

The German Environment Agency (UBA) is supporting the development of environmental monographs for active pharmaceutical substances for years and has discussed its views in workshops with relevant stakeholders as the pharmaceutical industry, competent authorities and the European Commission.[17]

a[16] European Commission, Directorate-General for Health and Food Safety, Floeter, C., Schwonbeck, S., Vidaurre, R., et al., Feasibility study of an active-substance-based review system ('monographs') and other potential alternatives for the environmental risk assessment of veterinary medicinal products : final report, Publications Office, 2021, https://data.europa.eu/doi/10.2875/94477

[17] - Workshop (2014): *"An effective tool to strengthen the environmental safety of VMPs: Monograph system for active pharmaceutical substances".* 26.11.2014, Brussels (http://www.umweltbundesamt.de/node/28647)

- Science - Policy Event, Panel discussion (2015): *Environmental risks and effective environmental risk assessment of veterinary medicinal products*. 04.03.2015, Brussels (https://www.umweltbundesamt.de/en/service/dates/lunch-debate-on-environmental-risks-of-veterinary)
- UBA, TUKES (2015): *Environmental risk of veterinary medicines: Key measures for effective environment tal risk assessment. A discussion paper on the Proposal for a Regulation of the European Parliament and of the Council on Veterinary Medicinal Products [COM (2014) 558 final]* (https://www.umweltbundesamt.de/en/publikationen/environmental-risk-of-veterinary-medicines)
- Workshop (2017): *"How to achieve an appropriate environmental risk assessment of veterinary medicinal products"*. 07.07.2017, Brussels (https://www.umweltbundesamt.de/en/service/dates/ws-2017-environmental-risk-ass-of-veterinary)

2 Using monographs on active substances to address data shortcomings

2.1 Harmonised conclusions on similar VMPs in the pre-market phase

Status quo and necessary improvements:

Environmental risk assessment (ERA) as part of the regulatory process is well established and capable of identifying potential risks to the environment from the use of a medicinal product. However, because the assessment is performed separately for each medicinal product and the data originate in most cases from different study reports, this can lead to inconsistent conclusions on the ERA and thus to different consequences and product information for similar products[18]. This also applies to reference products of generic products.

If the ERA of VMPs were based on the same data of the respective active pharmaceutical substance, this would automatically result in harmonised risk assessment and conclusions and product information for similar products. Another aspect is that, from a scientific point of view, it would be desirable to bundle the partially large number of valid data available on the fate and effects of an active substance, to derive reliable values for an in-depth risk assessment, and thus to harmonise the data relevant for the assessment of medicinal products.

What advantages do monographs offer?

The introduction of an active substance-based monograph system would de facto not change the well-established authorisation system for veterinary medicinal products. Only the data on the fate and effects of active pharmaceutical substances in the environment required for the ERA of medicinal products will be unified. For example, if an applicant performs a VICH[19] guideline compliant ERA for a new product containing active substances already on the market and for which environmental monographs are available, no new studies need to be carried out by the applicant as the data compiled in the monograph are to be used.

In this way, the use of active ingredient monographs enables robust and consistent assessments, and thus consistent conclusions and harmonised product information (SPC, PI[20]) for medicinal products. The ERA within authorisation procedures for individual medicinal products would also be significantly simplified if the underlying active substance data had already been reviewed as part of an active substance monograph.

[18] Similar products: VMPs containing the same active substance and intended for the same target species and indication
[19] VICH: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
[20] SPC – Summary of Product Characteristics; PI – Package Information

2.2 Surveillance in the post-market phase

Status quo and necessary improvements:

The safety and efficacy of medicinal products in use is monitored via the pharmacovigilance system (PhV). If an adverse reaction or risk is identified, this may lead to a review of the benefit-risk balance and appropriate consequences as e.g. changes to the product information. The PhV also provides for reporting environmental incidents as suspected adverse effects observed following the administration of a veterinary medicinal product to target animals. However, reporting environmental incidents proves to be quite difficult as it is almost impossible to observe environmental impacts, e.g., on insects, plants or aquatic organisms directly following the treatment of livestock on pastures or the application of manure from treated animals on agricultural land. Even if effects were to be observed, it may be difficult to establish a direct link to a particular treatment.

In addition, the Union's pharmacovigilance database is currently not able to adequately capture environmental incidents. The Union pharmacovigilance database for VMP is purely product-based and there is only one code for environmental incidents, under which all reported environmental incidents of any type must be recorded. This considerably limits the possible use of the data e.g. through automated evaluations etc. The collection of information on the occurrence and effects of active pharmaceutical substances in the environment is de facto not foreseen in the Union’s pharmacovigilance database.

However, the scientific literature repeatedly reports on the occurrence of active substances in the environment and also on harmful effects on environmental organisms. To date, however, there is no uniform procedure leading to a reassessment of medicinal products on the market that contain the specific active substance, based on new scientific findings. There are practically no ERA updates of approved medicinal products or even a regular adjustment of the ERA to the state of the art in science and technology. The latter, however, is a deeply justified requirement to ensure the environmental safety of medicinal products in use.

Because of these systemic problems, it must be assumed that effects on the environment from the use of veterinary medicinal products are not sufficiently detected and reported under the current pharmacovigilance system.

What advantages do monographs offer?

In principle, a close interaction of the monograph system with the pharmacovigilance system would be advisable. Since monographs focus on active pharmaceutical substances and not on medicinal products, environmental incidents detected within the framework of pharmacovigilance or new publicly available scientific findings could be stored in the respective active substance monograph. This could lead to a reassessment of the environmental risk of the active substance, which in turn could result in the reassessment of medicinal products with the corresponding active substance in the context of pharmacovigilance.

In this way, linking monographs of active pharmaceutical substances to the pharmacovigilance system could be a promising option to monitor potential environmental impacts of VMPs post-market. This would contribute significantly to increasing the environmental safety of pharmaceuticals in use.

2.3 Environmental data for 'legacy' VMPs

Status quo and necessary improvements:

For pharmaceutical products authorised prior to 2005 it can be assumed that an environmental risk assessment according to the present standards had not been performed. However, a review program for legacy products approved before an environmental risk assessment for all new VMPs became legally mandatory, had not been implemented yet.

An analysis of VMPs on the German market[21] revealed a total of 162 active substances used in veterinary medicinal products for food-producing animals. If the criteria of the VICH guidelines are followed, only 59 of these active substances would require an in-depth risk assessment based on experimental studies. In Germany ERA data are available for 33 of these 59 active pharmaceutical substances, submitted within authorisation procedures. This means that for more than half of the relevant active substances the data required for an environmental monograph are already available. However, for the remaining 26 substances ERA data are lacking, i.e. data are non-existent for 17 substance and for 9 substances the data sets are incomplete. Consequently, definitive conclusions on possible environmental risks of theses active substances cannot be drawn.

These data gaps urgently need to be closed in order to perform a full environmental risk assessment in line with the respective guidelines and, if necessary, impose risk mitigation measures to minimise potential environmental impacts.

What advantages do monographs offer?

A monograph system that compiles, completes, and validates ERA data for active pharmaceutical substances is key to filling existing data gaps, especially for legacy products. In a stepwise catch-up process, it would be sufficient to generate one valid data set for an active substance, if necessary. The availability of complete and valid ERA data is an essential prerequisite for any kind of risk management, and consequently, closing data gaps increase the protection of the environment. In particular, for active substances approved before 2005, ERA data may be become available for the first time when the corresponding monograph has been prepared. Consequently, this would allow to conduct an environmental risk assessment, benefit-risk assessment, risk communication via product literature and risk management for several legacy medicinal products in a harmonised way. This could be done via referral procedures and/or variations.

The basic principle of monographs is the shared responsibility of all marketing authorisation holders of products containing the respective active substances and shared benefit. Significant benefits would be cost reduction for applicants as multiple ERA tests for the same active substance for each marketing authorisation became obsolete as well as the administrative burden would be reduced for both applicants and competent authorities.

[21] Hein, Arne et al: Monographs for active substances in veterinary medical products – Data gaps and availability of environmental information. Poster SETAC Europe 2022

2.4 Publicly available ERA data of active pharmaceutical substances

Status quo and necessary improvements:

In recent years, the conclusions on the environmental risk assessment and the underlying data for the active substances (only study endpoints in tabular form) submitted as part of the authorisation procedure of VMPs have increasingly been published in (European) public assessment reports ((E)PARs) for specific products. These (E)PARs of medicinal products are published on the websites of the European Medicines Agency (EMA), the Heads of Medicines Agencies (HMA) or nationally by the competent authorities. This comparable uniform reporting of environmental data was established only a few years ago. As a result, there are significant gaps in publicly available environmental data generated and used in a regulatory context.

Furthermore, environmental information on fate and effects are usually searched for individual active substances. However, environmental data submitted within marketing authorisation procedures are published in (E)PARs for the respective products and are not detectable by a general data search for an active substance. Hence, as not all available data for active substances are retrievable in the public domain, only an incomplete picture of the overall environmental information exists.

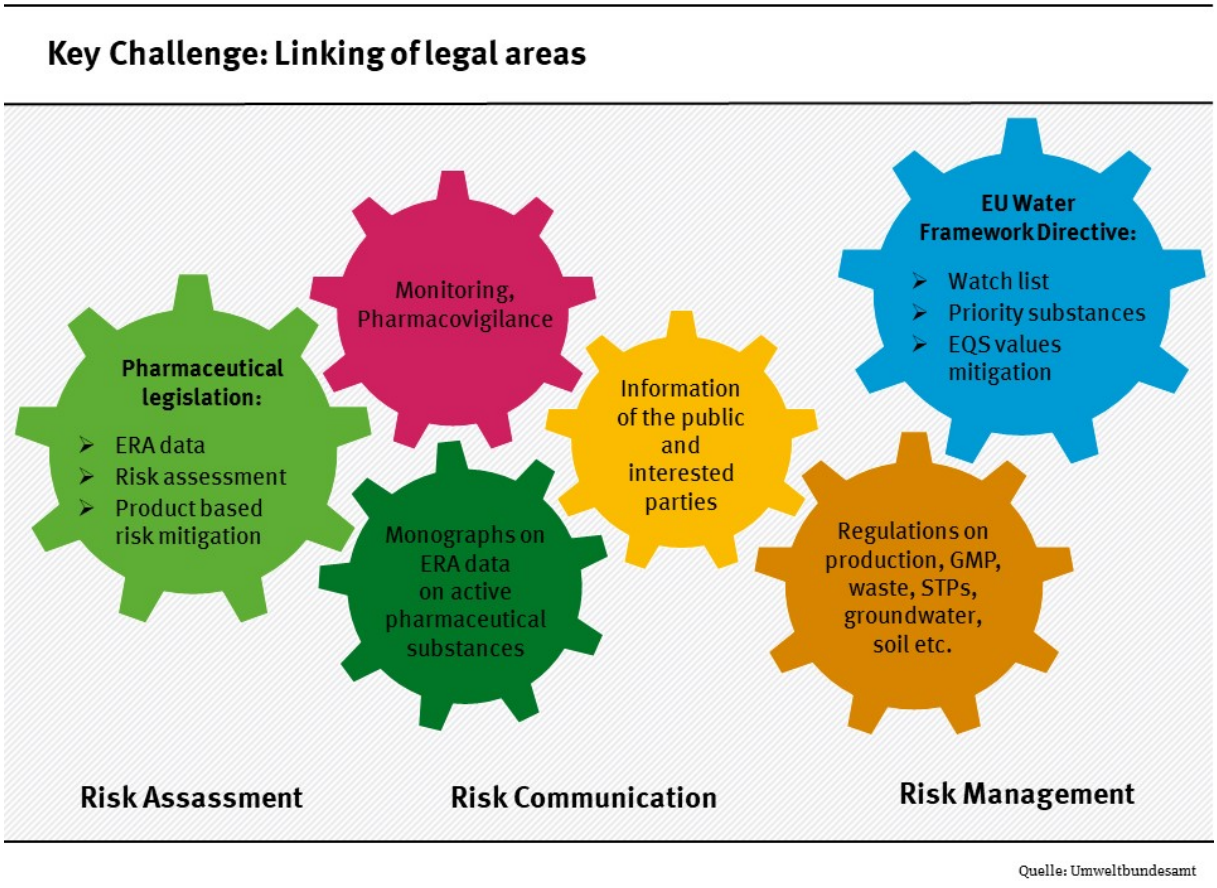
Efficient risk management requires the accessibility of data which should preferably published in a publicly accessible database (see 3.3). Availability of environmental data for chemicals is part of the EU Commission Chemicals strategy. In principle there is a right of access to the ERA data of pharmaceuticals (environmental information according to Art. 2(3)(b) Aarhus Convention)[22]. They should be made available substance-related and easily searchable for various stakeholders such as water suppliers, academics, authorities and the public.

[22] Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters, United Nations, Treaty Series, vol. 2161, p. 447

What advantages do monographs offer?

Monographs could be the crucial bridge between risk assessment on the one hand and risk management on the other, and this across different regulatory areas. Moreover, a monograph system could play a key role in terms of risk communication and public information.

Monographs could closely link different regulatory areas for efficient risk management (see figure). For example, environmentally relevant active substances identified in marketing authorisation procedures of pharmaceuticals can hardly be regulated as the pharmaceutical legislation offers only few options for this. Hence, such substances would need to be regulated in other environmental regulatory frameworks. As mentioned in recital 32 of Regulation (EU) 2019/6, environmental information could be used, for example, for the inclusion of active substances in the list of priority substances according to the Water Framework Directive or for the derivation of environmental quality standards (EQS). This requires that these data are publicly available, can be used and that detailed information on the underlying test methodology, etc., is also available to allow independent scientific assessment in a different context.[23] Other regulatory areas that may be relevant for the risk management of pharmaceutically active substances and medicinal products include are, for example, regulations for the manufacturing of medicinal products including Good Manufacturing Practice (GMP), as well as regulations for waste, wastewater, sewage treatment plants (STPs), groundwater and soil.



Quelle: Umweltbundesamt

[23] European Commission: Technical Guidance for Deriving Environmental Quality Standards; Guidance Document No. 27, updated Version 2018

3 Brief outline of environmental monographs

3.1 What data should a monograph contain?

Environmental monographs are understood as compilations of data for single active pharmaceutical substances needed for an ERA. The data on physico-chemical properties, fate and effects of an active substance should ideally originate from standard OECD tests according to the requirements as laid out in the respective EMA/VICH guidelines[24]. All these data should be evaluated by competent authorities (see 3.2). If there are several valid data of an active substance on one specific endpoint, as e.g. toxicity to algae available, monographs offer the possibility of pooling the data and finally obtaining reliable values for a more in-depth risk assessment and thus to provide a harmonised data set. In any way, the final data to be used in the environmental risk assessment for regulatory purposes should be identified, and also the relevant intrinsic properties and related hazards such as PBT properties (Persistent – Bioaccumulative – Toxic) should be indicated. It might also be useful to include information obtained through the pharmacovigilance system, such as e.g. data from post-authorisation studies, surveillance, monitoring or literature.

3.2 How to operate a monograph based on shared responsibility and harmonised assessments

Monographs of environmental data of active pharmaceutical substances should be generated based on the principle of shared responsibility of all relevant marketing authorisation holders (MAHs). In order to collect all necessary environmental data for a monograph, the MAHs of medicinal products containing the same active substance should be required to submit the necessary data as a consortium - regardless of whether data are already available from previous applications or whether data need to be generated to fill data gaps.

A fair cost sharing system should be established for both, the performance and assessment of required experimental studies and the services provided by the authorities. It could be conceivable that fees charged for the authorisation of a medicinal product may be reduced accordingly if the ERA is based on the monograph data for the respective active pharmaceutical substance.

Under Regulation (EU) 2019/6, generic applicants refer directly to the ERA of the reference product, if one exists. Once a monograph for an active ingredient is finalised, a separate process must ensure that the risk assessment, risk-benefit analysis, and ultimately the product information for all reference products and associated generics are harmonised.

In the case the marketing authorisation application concerns a medicinal product containing a new active pharmaceutical substance, the respective monograph has to be drafted solely by the applicant. This can be done either before or in parallel with the respective marketing authorisation procedure, so that there is no time delay and the applicant is not disadvantaged.

Official bodies to be involved in the monograph system could be the European Commission, the European Medicines Agency (EMA) and competent authorities of the EU Regulatory Network. Since the number of relevant active substances is manageable and data are already available for many active substances (see 2.3), a time frame of 10 years should be sufficient to prepare the necessary monographs for all environmentally relevant active substances - according to a certain prioritization scheme. Drawing up a monograph could follow in principle the centralised

[24] CVMP/VICH/592/98, CVMP/VICH/790/03-Final and EMEA/CVMP/ERA/418282/ 2005-Rev.1

marketing authorisation procedure, i.e. assessment of the data package and drafting of the monograph by a rapporteur/co-rapporteur, discussion and adoption by CVMP[25] and final decision by the European Commission. In this way the monographs are approved by the EU member states in a harmonised procedure.

3.3 Selecting a suitable database for compiling and publishing environmental monograph data

Besides the evaluation of the available environmental data, the monograph system would also require the collection and publication of the respective environmental data in a database in order to enhance the transparency of environmental risk assessments. The respective environmental data could be compiled in a database on EU level, hosted preferably by an European Agency, and accessible for various users with different access levels, if necessary. Existing database structures and tools (e.g. IUCLID) could be used for this purpose (see Annex). This centralised collection in monographs and publication would also allow an easy search of environmental data of active pharmaceutical active substances.

In our view, publication of environment data should meet the following criteria:

- Publication in a web-based database at Union level, hosted by an EU agency.
- It should include only data verified and validated by national competent authorities of the EU medicines regulatory network or an EU agency in accordance with the criteria laid out in the respective OECD technical guidelines or according to the CRED-evaluation system[26].
- Access should be granted for regulators, applicants, marketing authorisation holders, academics and the public with different access levels, if necessary. For instance, access for the general public could be restricted to main study results only, study summaries for academics and official bodies, full access, e.g. including the respective study reports, for EU regulators and fee based full access for applicants for marketing authorisations, if applicable.
- Data confidentiality must be guaranteed, e.g. the use of published data by applicants other than the data owner in ERA for marketing authorisations are not acceptable, unless otherwise agreed. Furthermore, disclosure of a full set of monograph data to a third party without consent from the data owner must be prevented and respective measures should be introduced, e.g. a binding statement of commitment.
- Automated data input via established tools / templates (e.g. IUCLID / OHT) should be possible.
- Maintenance of the database must be guaranteed

Options for publication of 'monograph' data could be either the establishment of a stand-alone database under consideration of well-established technologies or the attachment to existing platforms / databases.

[25] CVMP: Committee for Veterinary Medicinal Products of the European Medicines Agency
[26] Moermond, C.T.A. et al. 2016: CRED: Criteria for reporting and evaluating ecotoxicity data. Environmental Toxicology and Chemistry, Vol. 35, No. 5, pp. 1297–1309, https://doi.org/10.1002/etc.3259

A number of publicly accessible databases containing environmental data are already available online. A brief description of a selection of web-based databases is given in the Annex. These databases differ considerably, e.g. with regard to their origin, purpose, structure, host and content. Taking these aspects into account, the Annex also presents the pros and cons of the selected databases from UBA's point of view.

Having evaluated the databases listed in the Annex, under consideration of the criteria as outlined above, we consider the IUCLID database to be the database of choice because it offers several advantages over other databases:

- IUCLID is established for decades. The first version had been launched in 1993 for the European Existing Substances Regulation 793/93/EEC, the most recent version IUCLID 6 was released in 2016.
- It is the tool to be used for data collection and submission and dossier preparation under REACH and the EU Biocides regulation. It is accepted e.g. in the OECD Chemical Assessment Programme, the US HPV Challenge Programme and the Japan HPV Challenge.
- The software is maintained by the European Chemicals Agency
- Harmonised templates for standardised data exchange are provided by the OECD
- The application is expandable and customisable to specific requirements
- Data are searchable through the eChemPortal[27], the Global Portal to Information on Chemical Substances by OECD that provides data search on 36 databases at present.

However, although IUCLID appears to be the most suitable application for the reasons mentioned above, consideration is needed as to whether environmental data of pharmaceutical monographs could be attached to an existing database or a stand-alone solution would be more appropriate.

3.4 Keeping data up to date

Monographs are the focal point for the collection and availability of environmental information on individual active pharmaceutical substances. Relevant new information and research results should therefore be incorporated into the respective monographs. This will ensure that the monographs remain at the cutting edge of science and technology, thus enabling an up-to-date and technically sound risk and hazard assessment at all times.

A review and update of a monograph could be initiated, for example, either periodically or when new scientific evidence becomes available, when there is a suspicion that potential environmental risks are underestimated, or to ensure that they are up to date for regulatory compliance. These reasonable grounds may also arise from post-authorisation studies or from observations within the scope of the pharmacovigilance system.

[27] https://www.echemportal.org/echemportal/

4 Conclusions

By establishing a system of environmental monographs for active pharmaceutical substances, a number of improvements of the current pharmaceutical system could be achieved, particularly in the following areas:

- Closing data gaps for 'legacy' VMPs,
- Harmonised conclusions on similar VMPs in the pre-market phase,
- Surveillance in the post-market phase, and
- Making ERA data of active pharmaceutical substances available to the public and other interested parties.

Reliable ERA data are the essential prerequisite for risk assessment and risk management under the pharmaceutical legislation and other regulatory areas. In our opinion, monographs containing data on the fate and effects of active pharmaceutical substances in the environment could contribute significantly to improving the environmental safety of VMPs, as monographs have positive effects in both pre-market and post-market control of VMPs and can fill data gaps.

An environmental monograph system is considered the appropriate tool to achieve the necessary improvements in the field of the environmental protection as outlined in various EU strategies, such as the pharmaceutical strategy (2021) resp. the strategic approach to pharmaceuticals in the environment (2019), the European Green Deal with the zero-pollution ambition (2021) and the 'one substance, one assessment'-approach. Like the monograph system, the "one substance, one assessment" (1S1A) approach also aims at harmonising the registration and risk assessment procedures of the various legal frameworks on chemical safety such as for pesticides, biocides, human and veterinary medicines and industrial chemicals. Similar to the monograph system, the intent is to harmonise data and close data gaps, avoid duplication of work and animal testing and enhance data transparency.

By compiling data for active substances in monographs and making these data publicly available in a database, the stage is set for cross-regulatory use. The monograph system can therefore be seen as a precursor to the implementation of the 1S1A-approach and thus facilitates an important priority of the European Commission.

The benefit of an active substance-based monograph system would be enhanced if already existing database structures and tools are used. We recommend to publish the data in a publicly accessible web-based database and using the IUCLID software application. However, consideration should be given to whether environmental data of pharmaceutical monographs should be attached to an existing database or a stand-alone solution would be more appropriate. In principle, various existing instruments and experiences from other European regulatory frameworks, such as plant protection products, biocides or chemicals, can be used for the establishment of a monograph system for active pharmaceutical substances.

A feasibility study[28], carried out on behalf of the European Commission on the basis of Article 156 of Regulation (EU) 2019/6 also states that, particularly in view of the EU's strategic objectives "... a monograph system is justified, proportionate and probably affordable." Although it is

[28] European Commission, Directorate-General for Health and Food Safety, Floeter, C., Schwonbeck, S., Vidaurre, R., et al., Feasibility study of an active-substance-based review system ('monographs') and other potential alternatives for the environmental risk assessment of veterinary medicinal products: final report, Publications Office, 2021

recognised that in the initial phase the implementation of a monograph system is likely to be more resource intensive than the existing system, the benefits of the system will clearly outweigh this. According to this study monographs on environmental data of active pharmaceutical substances would allow environmental information to be gained more efficiently, give environmental authorities, experts and the public access to ERA data and improve in this way the knowledge about relevant environmental risks.

The Commission's report on the feasibility study [29], fulfilling its obligation under Article 156 of Regulation (EU) 2019/6 of the European Parliament and of the Council, also highlights the benefits of an active substance-based monograph system and the resulting improvements to the environmental safety of medicines. At the same time, it notes that before a monograph system can be successfully implemented, various details still need to be clarified, particularly with regard to the effort involved and compatibility with the legislation. The German Environment Agency sees many potentials for improving the veterinary pharmaceutical legislation in order to enhance the environmental safety of VMPs. The added value of a monograph system should also be considered in a wider policy context, as the Commission's report also noted. In particular, such a system would also be necessary for active substances used in human medicinal products, since the problems described with regard to ensuring environmental safety are very similar.

Against this background, we fully support the European Commission’s decision to establish an environmental monograph system for active pharmaceutical substances in human and veterinary medicinal products.

[29] Report from the Commission to the European Parliament and the Council on a feasibility study of an active-substance-based review system (‘monographs’) and other potential alternatives for the environmental risk assessment of veterinary medicinal products. Final report 13 January 2023

Annex

Examples of existing databases for substance dossiers /environmental data

Options for publication of 'monograph' data could be either the establishment of a stand-alone database under consideration of well-established technologies or the attachment to existing platforms / databases.

A number of publicly accessible databases containing environmental data are available online. In the following, we present a short description of a selection of web-based databases.

- **IUCLID** (**I**nternational **U**niform **C**hemica**L** **I**nformation **D**atabase)

  IUCLID is a software application for recording, storing, maintaining and exchanging environmental data of chemical substances and mixtures. Both regulatory bodies and chemical industry use the software in the implementation of various regulatory programmes. The software and its underlying format are developed and maintained by the European Chemicals Agency (ECHA) in collaboration with the OECD. The backbone of IUCLID are the OHTs (OECD Harmonised Templates). This strategic approach for structured and harmonised data of properties and endpoints is essential for the IUCLID data base. This collaboration aims at reaching harmonisation of the way data on chemicals are collected and exchanged in regulatory settings between countries.

  IUCLID is used by ECHA amongst others for data on chemical registration under REACH and Biocides regulation.

  ECHA – https://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation

  IUCLID - https://iuclid6.echa.europa.eu/

  OECD - Use of IUCLID software - https://www.oecd.org./chemicalsafety/risk-assessment/electronictoolsfordatasubmissionevaluationandexchangeintheo-ecdcooperativechemicalsassessmentprogramme.htm

- **EFSA – Register of Questions – Pesticides Dossier**:

  The EFSA Register of Questions provides access to pesticides dossiers, evaluated by EFSA within the EU peer review of active substances used in plant protection products. http://registerofquestions.efsa.europa.eu/roqFrontend/wicket/bookmarkable/eu.europa.efsa.raw.gui.pages.substance.SubstanceSearchPage?2

  Data Warehouse http://www.efsa.europa.eu/en/science/data

- **NORMAN Database Systems - ecotoxicological database**:

  The NORMAN database contains substances with their lowest predicted no effect concentrations (PNEC), either predicted by QSAR methods or derived experimentally. These data submitted to and voted by the NORMAN ecotoxicology experts are addressed as 'verified'. The data are used primarily for prioritisation purposes. https://www.norman-network.com/nds/ecotox/ecotoxIndex.php

- **FASS Sweden** – Swedish environmental and classification system for pharmaceuticals, launched and developed in 2005 by the Swedish association of the pharmaceutical industry. Review and classification of the data is done by IVL (Swedish Environmental Research Institute), an independent consultancy. Data are not verified by a competent authority.

  https://www.fass.se/LIF/product?userType=2&nplId=20090306000013&docType=78&scrollPosition=310 (website in Swedish only, ecotox data available in English)

- **US EPA Ecotoxicology Knowledgebase** The publicly available ECOTOX database is a compilation of summarised single chemical environmental toxicity data on aquatic life, terrestrial plants and wildlife from various publications. These data are not verified by the US EPA. For further information on the data, the respective original scientific literature has to be consulted.

  https://cfpub.epa.gov/ecotox/

- **IPIE database**

  The iPiE database was developed within an IMI (**I**nnovative **M**edicines **I**nitiative) project, run by a consortium consisting of EFPIA (European Federation of Pharmaceutical Industries and Associations) and other pharmaceutical industries as well as universities, research organisations, public bodies and non-profit groups. The database contains data from study reports selected by the pharmaceutical industry. The validity and plausibility of these data were neither assessed within the IME project nor verified and validated by a competent authority. This database will be continued in the IMI project PREMIER.

  http://i-pie.org/ipiesum/

Suitability of selected databases

The databases described above vary considerably, for instance in terms of their origin, purpose, structure, host and content. The following table summarises our view on the main pros and cons of the considered databases without claiming to be exhaustive. Our main focus herewith is on their hosts, purpose and quality of the data included.

Table 1: Overview of UBA view on Pros and Cons of selected databases

Database	Pros	Cons
IUCLID / ECHA	• Hosted and maintained by an EU agency (ECHA) • Standardised data exchange (OECD templates) • Established processes • Extension possible • Customisable to specific needs	• ECHA not related to pharmaceuticals
EFSA	• Hosted and maintained by an EU agency (EFSA)	• EFSA not related to pharmaceuticals
NORMAN Ecotoxicological database	• Tool for the compilation of findings in the environment worldwide	• Database not hosted by a national competent authority / EU agency • Designed mainly for monitoring data
FASS Sweden	• Tool for information of the general public & medical professionals	• Database not hosed by a national competent authority /EU agency • Classification by a consultancy • Data not verified by competent agency/EU agency
US EPA Knowledgebase	• Hosted by a competent authority • Tool for information of the general public	• Database not hosted by a national competent authority / EU agency • Only data compilation, data not verified by competent agency / EU agency
iPiE Sum	• Tool for information of the general public & information for interested parties (e.g. generic industry) on the availability of studies on ecotoxicity, fate & behaviour for approx. 280 active substances	• Database not hosted by a national competent authority /EU agency • Hosting and maintenance unclear • Selected data input by industry • Data not verified by a national competent authority / EU agency