Berkner and Brandt
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Comparing pharmaceutical persistence across terrestrial and aquatic environments: do studies according to OECD 307 and OECD 308 lead to similar outcomes?

Silvia Berkner[1*] and Ute Brandt[1]

Abstract

Information on transformation and persistence of chemical substances in the environment is important for hazard and risk assessment within a regulatory context or as a decision criterion in a safe and sustainable by design framework. Half-lives for human and veterinary medicinal products available from marketing authorization applications were compared between soil (OECD 307) and aquatic water/sediment systems (OECD 308). The comparison shows, that there is no obvious correlation between the total system half-lives in the two different compartments and that surpassing persistence criteria is compartment-specific in 45% of the cases.

Keywords Pharmaceuticals, Persistence, Transformation, OECD 307, OECD 308

Introduction

Information on transformation and persistence of chemical substances in the environment is important for risk and hazard assessment within a regulatory context or as a decision criterion in a safe and sustainable by design framework [1]. Data requirements and adherence to the requirements is different for regulatory frameworks. While for plant protection products different environmental compartments are covered, for other frameworks like pharmaceuticals or REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) chemicals only one compartment is tested initially, and only in some cases additional information on other compartments is required, depending on the outcome of the test, substance properties and regulatory framework [2, 3]. Therefore, it is interesting to examine if testing one compartment is sufficient or if differing results might be observed in aquatic and terrestrial compartments.

Methods

This question was examined using end point data from applications for marketing authorization for pharmaceuticals (21 human and one veterinary medicinal products) which are intended to be publicly available [4]. The terrestrial compartment was assessed by tests according to OECD (Organisation for Economic Cooperation and Development) TG (test guideline) 307 (transformation in soil, [5]). The aquatic compartment was examined in studies according to OECD TG 308 with water/sediment systems [6]. Studies conform to Good Laboratory Practice (GLP). All active ingredients (ai) from human pharmaceuticals and veterinary medicinal products were considered for which both data for soil and water/sediment systems were available (22 ai in total). Half-lives were calculated based on SFO (single first order) kinetics (DFOP (dual first order in parallel) for ceritinib in OECD 308) as geometric mean of different soils ($n = 1–4$) and different sediments ($n = 2$) for each ai. Only aerobic

*Correspondence:
Silvia Berkner
silvia.berkner@uba.de
[1] German Environment Agency, Unit IV2.2 Pharmaceuticals, Wörlitzer Platz 1, 06844 Dessau-Rosslau, Germany

studies were considered, however, it has to be taken into account that the sediment might contain anaerobic regions [7]. All studies were conducted at 20 °C. Half-lives were temperature corrected to 12 °C as described in [3]. The resulting total system (ts) half-lives are reported as DT_{50wsts} for OECD 308 studies and DT_{50soil} for OECD 307 studies. If half-lives could not be derived, because a plateau was observed or very high values were reported extrapolating far above the study duration, the values are given as > 1000 days and are marked in Fig. 1 by an arrow. Non-extractable residues were considered as sink (i.e., as equal to mineralized) in the present study. Additionally, K_{oc} (organic carbon normalized adsorption coefficient) values reported as part of the applications were collected. It should be noted that the available data are biased towards high K_{oc} values as generally only for compounds with a K_{oc} > 10,000 L/kg a terrestrial assessment is required. Table 1 gives an overview of the examined ai. As preference was given to use SFO kinetics to derive half-lives for better comparability between different substances and mean values are used, the results do not strictly correspond to a regulatory persistence classification which requires best fit kinetics (that may deviate from SFO kinetics more often) and worst case values from parallel test systems (instead of the geometric mean) to be used [8]. Pearson's coefficient of correlation was calculated using MSExcel 2019™.

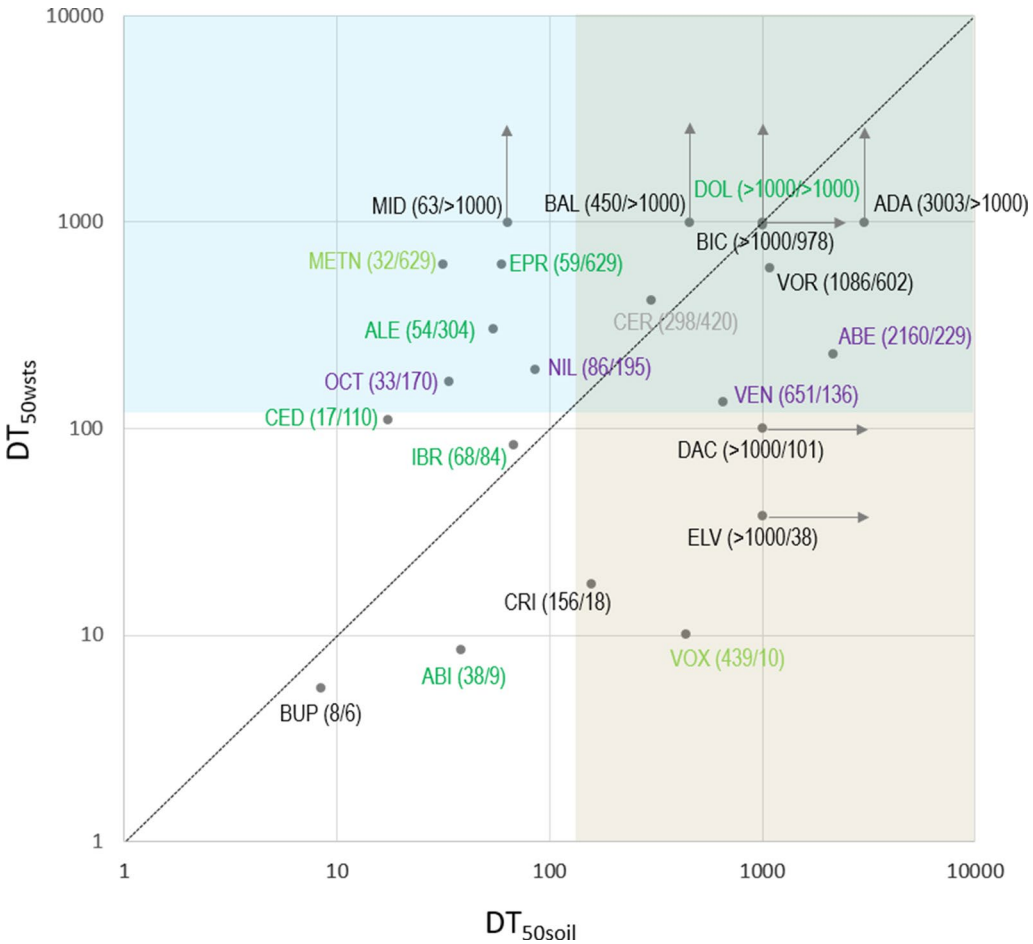

Fig. 1 Comparison of half-lives (@12 °C in d) for 22 ai (see Table 1) in soil and water/sediment systems; ai abbreviations (see Table 1) are given adjacent to the data point (the respective total system half-life for soil (DT_{50soil}) and water/sediment (DT_{50wsts}) is given in parentheses in days (d)). The 1:1 line is shown as dotted line. Values given as > 1000 d are marked with an arrow (arbitrary length). Persistence in water/sediment (total system) is indicated by blue shading of the region exceeding 120 d while persistence in soil is indicted by brown shading of the region exceeding 120 d. Individual ai names are color coded according to $logK_{oc}$ (3–4 light green; 4–5 dark green; 5–6 black; ≥ 6 violet; no data, light grey)

Table 1 Examined ai, abbreviations used in Fig. 1, and indication if human or veterinary medicinal product ai; for additional information see Table S1 in the supplementary information

ai	Abbreviation	Human (H) or veterinary (V) medicinal product ai
Abemaciclib	ABE	H
Abiraterone	ABI	H
Adapalene	ADA	H
Alectinib	ALE	H
Baloxavir	BAL	H
Bictegravir	BIC	H
Buprenorphine	BUP	H
Cediranib	CED	H
Ceritinib	CER	H
Crizotinib	CRI	H
Dacomitinib	DAC	H
Dolutegravir	DOL	H
Elvitegravir	ELV	H
Eprinomectin	EPR	V
Ibrutinib	IBR	H
Methylnaltrexone	METN	H
Midostaurin	MID	H
Nilotinib	NIL	H
Octenidine	OCT	H
Venetoclax	VEN	H
Vorapaxar	VOR	H
Voxilaprevir	VOX	H

Results and discussion

The comparison of terrestrial and aquatic half-lives is shown in Fig. 1 (see also Table S1 in the supplemantary information).

Four of the 22 compounds consistently show half-lives below the persistence threshold of 120 d [3] for both soil and water/sediment systems. Another eight compounds also consistently produce half-lives above the persistence threshold, independent of simulation study type. Six compounds are only classified as persistent when relying on data from OECD 308 studies and four compounds only exceed the 120 d persistence criterion when data from OECD 307 studies are used. For 55% of the compounds, persistence assessment shows the same outcome, regardless whether the terrestrial or the aquatic compartment is tested. Pearson's coefficient of correlation between soil and water/sediment is <0.1 (without values ≥ 1000 d), i.e., there is no correlation observable. The different $\log K_{oc}$ values of the compounds are color coded in Fig. 1. There is also no obvious correlation visible between half-lives and $\log K_{oc}$. Calculated Pearson's coefficients of correlation are 0.3 for soil half-lives and K_{oc}, and − 0.1 for water/sediment half-lives and K_{oc}. A tendency might be observable that extremely high $\log K_{oc}$ values (≥ 6) correspond to longer half-lives in water/sediment tests compared to soil, as all $\log K_{oc} \geq 6$ compounds are classified as persistent in OECD 308 studies but not necessarily in OECD 307 studies (see violet compounds in Fig. 1, $n=4$). It should be noted that some types of ai seem to be overrepresented among the study compounds. This is true for tyrosine kinase inhibitors, which are a class of antineoplastic agents (name ends in -ib). Additionally, antiviral compounds (ending in -vir) are also overrepresented. This should not be generalized however, as the sample of 22 ai is just a small subset of pharmaceutical ai on the market. It should be considered, that the sample of ai is biased for recently authorized compounds, as there are no or less data available for older ai, and for high K_{oc} compounds, as otherwise only the aquatic compartment is examined and data for soil are not available [2].

Conclusion and outlook

The results show that persistence assessment might yield different outcomes depending on the environmental compartment that is examined. In the studied examples, this concerns 45% of the test substances (10 out of 22 ai). It is therefore important to consider all compartments in persistence assessment to which emissions or subsequent transfer might occur. This has also been noted for REACH chemicals [9]. Consequently, skipping simulation type testing (i.e., OECD TG 308) for human pharmaceutical ai for the aquatic compartment in Phase II Tier A, as proposed by the revised draft guideline for environmental assessment for human medicinal products [10] will result in data gaps for persistence assessment of pharmaceutical compounds.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12302-023-00783-8.

Additional file 1: Table S1 Identities, pharmacological groups, identifiers, physico-chemical parameters and half-lives for the studied pharmaceutical ai.

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Data are included in the manuscript or are available at https://www.ema.europa.eu/en, materials: not applicable.

Declarations

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Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interest.

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