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## To be or not to be degraded: in defense of persistence assessment of chemicals

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Characterizing the degradation behavior of chemicals in the environment is a key component of chemical hazard and risk assessment. Persistence has been successfully characterized for readily and for slowly degradable chemicals using standardized tests, but for the third group of chemicals with intermediate degradability ("middle group"), the assessment is less straightforward. Whether chemicals of this group behave as persistent or not in a given environment depends on environmental factors such as the presence of sorbents that can limit the bioavailability of chemicals. Uncertainties associated with current persistence assessments of chemicals in the middle group do not imply that persistence assessment is generally inconsistent, too ambiguous for regulatory use, and not useful in chemical hazard and risk assessment. Given the complexity of the environmental factors influencing chemical degradation, and the diversity of commercial chemicals, it has to be accepted though that for chemicals in the middle group even improved testing methods will not remove all of the immanent heterogeneity in their persistence data. For cases with widely different but technically valid persistence data, a weight-of-evidence approach is necessary and the "benefit of the doubt" should follow the precautionary principle in order to protect human and ecosystem health. We maintain that technically valid persistence data, although they might be considered dissatisfying from a scientific point of view because of high variability or even inconclusiveness, can well be sufficient for regulatory purposes. As with anything, also in persistence assessment, the scientific logic aims for a mechanistic description of the processes involved, low uncertainty, and a comprehensive understanding derived from a broad empirical basis. If the scientific logic is used as a benchmark in the regulatory context, this may easily lead to "paralysis by analysis". While regulatory decisions should be based on sound science, discrepancies between scientific goals and regulatory needs and, consequently, different levels of requirements (must-have *versus* nice-to-have) for degradation studies need to be recognized and appreciated. We further advocate for enhancing consistency between regulatory persistence assessments ("one substance–one assessment"), which is currently not the case.

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### Environmental significance

Persistence (*P*), even on its own, is an essential component of assessing the worldwide risk of chemicals to environmental and human health. Identifying existing uncertainties in the *P* assessment of chemicals and proposing steps to deal with these uncertainties in an assessment context is therefore environmentally significant. Regulatory *P* assessments have been successfully performed as part of many regulatory schemes to identify highly persistent chemicals for regulatory measures. Uncertainties and inconsistencies in the persistence assessment of chemicals seemingly complicate the classification of those chemicals that are not either clearly readily degradable or (highly) persistent. Reasons for the difficulties in classification of the intermediate group are, for instance, how to consider the bioavailability and the variability of environmental conditions which can lead to wide variations in empirical observations of degradation half-lives. Here we offer suggestions for improvement, including how to incorporate recent scientific findings and how to handle immanent and irreducible uncertainties.

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Both aspects, scientific and technical questions, as well as uncertainties in relation to regulatory schemes, are interwoven, which makes the situation complex, impeding a clear and effective discussion on future development of persistence assessment in a regulatory context. Here, we attempt to disentangle the two aspects, with a focus on matters learned on the scientific side and recommend a way forward for the overall discussion on *P* assessment.

## 2. What has worked in *P* assessment?

Over 350 000 chemicals and chemical mixtures have been registered for production and use globally<sup>2</sup> and production is still increasing.<sup>1</sup> Regarding persistence, chemicals can be assigned to three groups: readily degradable substances such as mono- and oligosaccharides, highly persistent substances such as perfluorooctanoic acid (PFOA) and other perfluoroalkyl acids, and a third group of substances that lie between these two extremes (“middle group”). *P* assessments typically provide unequivocal outcomes for the first two groups and have therefore been successfully performed as part of many regulatory schemes, including the EU REACH regulation and the Stockholm Convention on Persistent Organic Pollutants, to identify highly persistent chemicals for regulatory measures. Persistence can of course also be a desired property of chemicals, such as pigments in automotive paint, and there are numerous natural polymers such as lignin that are highly persistent. In this article, however, we are concerned with environmentally relevant non-polymeric organic substances whose persistence assessment is fraught with uncertainty.<sup>3</sup> In that case, *P* assessment is particularly challenging for those substances in the middle group whose classification as either readily degradable or persistent may not be clear-cut (Fig. 1). For example, degradation half-lives of the biocides triclosan and triclocarban in soil strongly vary depending on the soil's sorption potential. This is largely due to the reduced bioavailability of the sorbed chemicals with increasing soil organic matter contents, which may be modulated, for instance, by amendment of biosolids used in agriculture as fertilizers.<sup>12</sup>

## 3. Confounding factors and how they affect *P* assessments of chemicals of intermediate degradability

Many factors can contribute to the uncertainty of *P* assessment outcomes for substances belonging to the group with intermediate degradability. There are factors related to the testing conditions, including the environmental conditions such as temperature, pH, exposure to light, the presence of further contaminants<sup>13–15</sup> as well as the state of the environmental matrix such as its nutrient status, microbial activity, and potential adaptation due to pre-exposure to the pollutant or structurally related chemicals.<sup>8,16</sup>

Apart from these natural variabilities, another particular factor that renders *P* assessments difficult for this group of chemicals is bioavailability limitations due to the interaction of substances with solid environmental media such as soils,

sediments, and particulate matter, which leads to sorption and covalent binding, with the latter particularly resulting in the formation of non-extractable residues (NER).

Yet, bioavailability is a pre-requisite for microbial degradation. Micropollutants in the pore water of soils are taken up by microorganisms and degraded, if chemical structures are fit for direct catabolism, to products that can be used for anabolic biomass formation and energy gain. Alternatively, degradation may occur co-metabolically if readily degradable alternative substrates are available. Although sorbed chemicals can also be metabolized,<sup>17–19</sup> microbial degradation of dissolved substrates is more rapid and efficient. Examples for the challenges in *P* assessment in this context are the above-mentioned triclosan and triclocarban, as well as phenanthrene, for which Hughes *et al.* (2020) provided an extensive literature review of environmental fate and degradation tests.<sup>20</sup> The authors concluded that phenanthrene was non-persistent because the ready-biodegradability tests demonstrated that the corresponding cut-off value of mineralization was met, *i.e.*, 60% of the theoretical CO<sub>2</sub> produced in a 10-day time window following the attainment of 10% biodegradation within the 28-day period of the test. However, in soil, and even more so in soils containing strongly sorbing components such as black carbon<sup>21,22</sup> or sewage-sludge amendment,<sup>23</sup> a significant fraction of phenanthrene is not bioavailable for microbes due to strong sorption. Consequently, much longer degradation half-lives of phenanthrene in soil have been observed under such conditions.

One may argue that strongly sorbed chemicals and NER will not result in environmental and human exposure and thus can be neglected. However, this is not true. The herbicide atrazine according to the data of Koskinen and Clay (1997) has a degradation half-life of weeks to months<sup>24</sup> in dependence on environmental conditions.<sup>5</sup> Still, after the ban of atrazine some thirty years ago in the EU, atrazine residues at low concentrations are detected in aquatic media<sup>25</sup> and soil,<sup>26</sup> likely due to sequestration in the pores of the soil matrix and continuous release from this reservoir if the concentration in the soil pore water decreases upon degradation. Also, other pesticides remain in agricultural soils for long periods of time<sup>27,28</sup> and, therefore, often mixtures of various substances are detected<sup>29</sup> because they have been accumulating for years from previous applications. Such accumulated mixtures harm exposed organisms in soil.<sup>30</sup> Therefore, these examples point to a critical discrepancy between the limited range of conditions that can be covered by regulatory *P* assessment, and the conditions of actual degradation in the environment. Finding ways to accommodate this discrepancy is a key task for regulatory persistence assessment.

## 4. Way forward for regulatory *P* assessment

A first important point for persistence-related regulatory decision-making is that the uncertainties associated with *P* assessments of chemicals in the middle group between those classified as readily degradable and highly persistent do not



imply that persistence assessment schemes are generally inconsistent, too uncertain for regulatory use, and hence not useful in chemical hazard and risk assessment. Chemicals with (very) high and (very) low persistence can be reliably identified, and the uncertainties in the middle group do not negate the importance of persistence as a key dimension in chemical hazard and risk assessment.<sup>3</sup>

For the middle group, two points are important: first, as far as technically and conceptually possible, the assessment methods need to be improved, particularly for substances that strongly adsorb onto soil, sediment, and other particulate matter. As a way forward to evaluate whether bioavailability limitation of chemicals is a reason to consider them as persistent, we propose remobilization tests under environmentally relevant conditions for exposure assessment. As an example for remobilization under natural conditions, a soil containing strongly sorbed chemicals or NER could be treated physically (simulation of heavy rain events, freezing/thawing, wet/dry cycles), chemically (change in pH), and biologically (solubilizing enzymes, treatment with soil feeding organisms, growth of plants).<sup>31</sup> If the parent chemical or relevant metabolites are released and can be identified and quantified, the amounts of such residues should be considered in the *P* assessment, just as the sequestered fraction of NER.<sup>32</sup> If residues remain immobilized in the matrix and are not released by such treatment, they may be considered as too strongly bound to be of environmental relevance as it is the case for the covalently bound fraction of NER. This proposal, which is based on scientific evidence on sequestration and potential release mechanisms, could be taken up by regulatory bodies, *i.e.*, they could request such additional information from the applicants in the registration process if there are large discrepancies in *P* assessment outcomes and if the data point towards a strong influence of bioavailability on those *P* outcomes.

Second, given the multitude and complexity of environmental factors influencing chemical degradation, and the variability and diversity of the reactivity and behavior of many chemicals, it has to be accepted that for chemicals in the middle group even improved testing methods will not remove all of the often considerable heterogeneity in the persistence data. A lot of this heterogeneity is irreducible, as many years of research into persistence assessments have shown.<sup>33</sup> This implies that a certain extent of heterogeneity has to be processed as such by the regulatory system.

For cases with widely different persistence data, as long as the diverging results are technically valid, a weight-of-evidence approach is necessary in order to determine the meaning and relative importance of the results. Generally, the “benefit of the doubt” should be used in favor of human and ecosystem health. In practice, this would mean, for example, that technically valid half-life data above a certain persistence threshold should be prioritized and considered as a strong indication for the chemical to be classified as persistent rather than to dilute these findings by merging them with shorter half-lives and using the average. It is the regulators’ task and responsibility to check the validity of data to protect human and environmental health, which is the foundation of long-term economic and societal

prosperity, in particular in light of the mounting evidence that current schemes of chemical risk assessment are underprotective.<sup>34–37</sup>

It is often stated that the “bright-line” criteria of fixed cut-off values are not suitable for assessments that involve so much uncertainty. In response to this, it should be noted that it is not necessarily uncertainty that is reflected by diverging persistence data, but real heterogeneity of how rapidly or slowly the same chemical may be degraded. In such a situation, the cut-off criteria are still useful as a basis for decision making, but the task is to decide on which side of the line a chemical should be placed (Fig. 1), given the available persistence data. This requires a careful analysis of the individual data so that their relative importance can be determined, but the decision-making task is still well-defined, and the situation does not imply that cut-off criteria are inappropriate.

A key point that illustrates why and how a stricter differentiation between scientific and regulatory aspects of persistence assessments is helpful is the following: scientifically, the outcomes of persistence studies may be considered dissatisfying (meaning that the results are highly noisy or even inconclusive although all data considered are technically valid), and improved assessment methods may be asked for. However, a scientifically dissatisfying result may well be sufficient for regulatory purposes. The scientific logic aims for a mechanistic description of the processes involved, low uncertainty, and a comprehensive understanding derived from a broad empirical basis. If this logic is used as a benchmark in the regulatory context, this may easily lead to “paralysis by analysis”. This does not at all imply that regulatory decisions should not be based on sound science, but the point is that scientific goals and regulatory needs are different and lead to different requirements regarding, *e.g.*, the level of detail in the results obtained, the extent of mechanistic understanding, and the type and extent of uncertainty that can be accommodated.

Uncertainties similar to those in the *P* assessment of the middle group apply in principle also to the other two important elements of hazard assessment, the bioaccumulation potential and toxicity of chemicals. For example, in toxicity, non-monotonic dose–response relationships lead to uncertainties of assessment; for bioaccumulation, uncertainties may arise from comparison of *in vitro* and *in silico* predictions, but these aspects need to be considered in further work. Also, difficulties in the persistence assessment for other types of chemicals, such as substances of unknown or variable composition, complex reaction products or biological materials (UVCBs) as well as polymers, do exist, but treatment of these topics would go beyond the scope of the present work.<sup>38–40</sup>

## 5. Conclusion

In conclusion, to strengthen the regulatory assessment of chemical persistence, improvements on both the scientific and the regulatory side are desirable. Scientifically, it is important to better understand confounding factors, particularly those that can cause significant underestimation of persistence in the standardized testing, and to exploit the potential of data-driven



analyses of persistence data. On the regulatory side, consistency between regulations should be achieved (“one substance–one assessment”), for instance as to whether the formation of NER is considered as degradation or not (in the EU, currently the way in which NER are treated by different agencies is not consistent). Most important, however, may be that the inherent and irreducible heterogeneity of persistence data needs to be appreciated, and that weight-of-evidence schemes used in regulatory decision-making accommodate this heterogeneity as a challenging but unavoidable feature of persistence assessment.<sup>41</sup>

## Conflicts of interest

All authors confirm that they have no conflict of interest.

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