# WP 3: Discussion of the present PBT/vPvB concept

## Introduction and aim of the work package

Various legal frameworks have been developed in order to identify and regulate substances of concern, such as e.g. PBTs and POPs (Boethling et al. 2009). The regulatory assessment of POPs and PBTs, however, is not straightforward. Different regional and global legal frameworks use different criteria.

Criteria for POP and PBT identification are historically based on neutral hydrophobic substances and are derived under laboratory conditions. Compounds such as perfluoroalkyl substances, cyclic volatile methyl siloxanes and ionisable organic compounds show different properties but PBT behaviour (Matthies et al. 2016). At present, criteria for regulatory purposes are applied to all substances, but reflect properties of neutral organic substances only.

The aim of this work package is an evaluation of the PBT concept considering scientific findings, the legislative framework of REACH, guidance documents and experiences of regulators. This study focusses on REACH, as within EU legislation, the most comprehensive documentation and definition of the PBT/vPvB assessment is under REACH

The central question of WP3 is to check to which extent the present concept captures all the “*substances of concern, for which no safe environmental concentration exists”,* and if not, which are the most likely that it misses?

Besides the rather **“conceptual”** definition of the PBT/vPvB assessment which is mostly determined by the Annex III criteria and the legal framework, the outlined analytical approaches to the determination of P, B and T are also briefly reviewed. They do **“operationally”** define the single endpoints (i.e. P, B and T) and therefore have a direct impact on which substances are identified as PBT/vPvB, and which are not. Shortcomings as e.g. analytical challenges (e.g. limited solubility) for different kinds of substances (i.e. ranges of substance properties) can lead to systematic biases towards the identification of PBT/vPvB substances as well. The identification of PBT/vPvB substances, therefore, not only depends on the strength PBT concept, but to a considerable extent also on whether appropriate test methods can be applied with regard to the substances’ physical chemical properties.

Where a substance enters the process of substance evaluation because of potential PBT properties, the legal constraints of the evaluation process are finally having a direct impact on the control of the release of the substance to the environment. Therefore, the **“procedural”** dimension of the PBT-assessment is considered as well.

In section [1.3](#Ref491094989), PBT/vPvB assessment in various EU legislations is briefly mentioned. In section 1.4 the conceptual level of the identification of PBT/vPvB substances as well as procedural issues are discussed. Sections [1.5](#Ref491095478), [1.6](#Ref491095495) and [1.7](#Ref491095502) focus on operational definition of persistence, bioaccumulation and toxicity, respectively by discussing experimental constraints. In section [1.8](#Ref491096760), two case studies are presented, illustrating challenges for PBT assessment during evaluation.

## Summary

### Information requirements (Annex VII-X) and criteria (Annex XIII)

Based on the standard information requirements, conclusions on a substance’s PBT properties can only be drawn for those substances produced in amounts of 100 tons or more. Only if the substance is readily biodegradable and therefore not persistent, can a conclusive statement on persistence (i.e.: absence of persistence) be made for the lower tonnage substances, i.e. considering screening level information only.

Providing a legal background that makes use of non-standardized information for PBT/vPvB assessment is beneficial when it comes to capturing processes which otherwise would not be depicted by the criteria outlined in Annex XIII, as it is possible under the present legal framework of REACH. The appropriateness of the used data and methods is crucial in this context.

An evaluation of the application of the weight of evidence approach under REACH may provide an insight on its impact on PBT/vPvB assessment and possible needs for updating the ECHA guidance documents. An expert committee could review cases where substances are concluded to be non PBT/vPvB based on non-standardized information, in order to avoid release of potentially hazardous substances. Generation of standard information should always be given priority if feasible.

### Data availability and quality, estimation tools

Given the limited data quality and availability of some registration dossiers, a first identification of potentially PBT/vPvB substances, based on their chemical structure only, may be useful. The very first step for identification of potential PBT substances is the IT-mass screening, and it is the only screening step every registration dossier has to go through. Crosschecking the reported values by applying QSAR relationships and/or thermodynamic constraints might help identify errors in the reported data. Currently, the accuracy of the assessment is often limited by the accuracy of the data.

QSARs are often derived from empirical regressions based on experimental data. As such, they are very useful tools in order to fill data gaps or for identification of experimental errors or typos in the submitted registration dossiers. However, where the calibration dataset is biased due to experimental difficulties or not enough data points are available for a derivation of the relationship in a certain property range, the QSARs will provide biased results as well. It is to be avoided that empirical relationships based on biased data become applicable rules. A clear definition of the applicability domain and high quality data as input are crucial for establishing empirical relationships.

### Assessment procedure

There are no penalties for submission of non-compliant dossiers, which, given the effort needed to compile a high quality dossier, might lead to wrong incentives for the registrants. Applying the principle of “no data, no market”, market access should be denied until a full, compliant dossier is submitted.

### Substances analytically difficult to assess under present PBT/vPvB concept

Better **characterization of the testing setups** in general will lead to be better comparability of tests. Environmental parameters and system geometries have been shown to have a considerable impact on the results.

Interpretation of the **sorption** to organic matter (and in some cases formation of non-extractable residues, NER) is still an unsolved issue. The main challenge is that the operational definition of non-extractability does not distinguish between the part of the substance that is permanently incorporated into the matrix and the part that can be remobilized. Also, different extraction methods exist, which could be standardized. In a preventive approach, because of lack of understanding of the fate of NER, the NER-fraction should be considered as remobilizable, in order to prevent formation of reservoirs in the environment which could eventually lead to an uncontrollable release

For persistence assessment, reduced bioavailability due to e.g. sorption to organic matter and low water solubility might lead to false positives (i.e. underestimating the potential for biodegradation) or results that are difficult to interpret within the temporally limited test frame. However, for bioconcentration studies, reduced bioavailability and low water solubility might lead to an underestimation of bioconcentration, which would prevent identification of the substance as potentially PBT/vPvB. Use of state of the art analytics and reporting well-documented results is crucial when assessing this class of substances. A certain water solubility or Kow could be a trigger for a mandatory special testing approach determining B properties.

Biodegradation for (**highly) volatile substances** is difficult to assess, the OECD 301 ready test states a maximum of Henry’s law constant of 50 Pa m3 mol-1. An alternative might be to focus on long-range transport potential for highly volatile substances and assess temperature dependence (i.e. whether and under what conditions the substance is expected to partition out of the air). Also, assessment of biodegradability at lower temperatures where the substance is more likely to partition into solid and liquid phases could also be possible for volatile substances.

The current testing is designed for assessment of single constituents, therefore, for **UVCBs** the testing of the substance as a whole is inappropriate if the constituents are not sufficiently similar. Strategies for assessing UVCBs are being developed by ECHA. Analytical identification of the different constituents poses the main challenge from a PBT/vPvB assessment perspective. Discussion of the development of new concepts of PBT/vPvB assessment for different classes of UVCBs is beyond the scope of this project.

Assessing bioaccumulation (i.e. in terms of the Annex XIII criteria of bioconcentration) of **highly hydrophobic substance**s with a log Kow greater than 7.8 is analytically not possible. Cutoff values for bioaccumulation that have been proposed lack statistical and mechanistic support, as there is no measured BCF data in that Kow-range. The behaviour of this class of substances is not accessible with present analytical methods, but uptake cannot be excluded and is likely to be slow due to the high Kow. It includes “classical” PBT/vPvB substances conceptually captured by the PBT/vPvB framework, but with extreme properties and very slow kinetics and therefore analytically challenging.

See [Figure 1](#Ref491269118) for an overview over the analytical challenges identifies for persistence and bioaccumulation

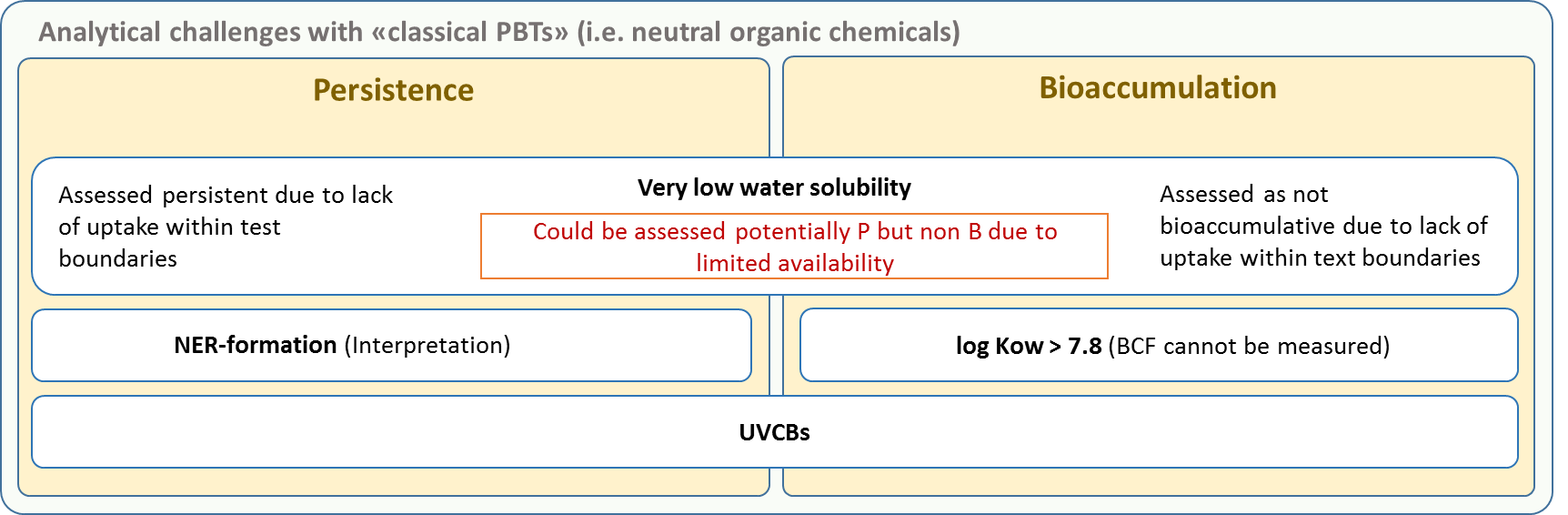


Figure 1: Overview over the analytical challenges with "classical PBTs" (i.e. neutral organic chemicals) for persistence and bioaccumulation

### Substances conceptually not covered by the present PVT/vPvB assessement

The only endpoint for **bioaccumulation** on assessment level is the fish BCF, i.e. the uptake of the substance from the water phase through gills. Due to the total lipid normalization, substances partitioning preferably into **phospholipid membranes** or **proteins** will be partially overlooked.

On screening level, substances which accumulate in **terrestrial systems** are identified based on log Koa (according to the guidance document or during IT-mass screening). However, there are no assessment level criteria nor agreed procedures how to identify substances accumulation only in terrestrial systems due to different metabolism pathways. Tests considering the terrestrial systems are outlined in the guidance document (ECHA 2017), but there is still need for a clear rules (e.g. criteria) on how to interpret the results in terms of PBT/vPvB-properties.

Also for substances, which are preferably taken up by **diet** (also in aquatic systems), the interpretation of the test results towards an identification as being bioaccumulative is not yet thoroughly defined.

Substances, which are **highly volatile and persistent in air** and could be taken up by air breading organisms, would not be captured by the present concept.

Conceptually, **toxicity** as an additional criterion for PBT assessment contradicts the paradigm of the concept itself as it introduces a “level” (i.e. a concentration), below which the substance can be considered “safe”, despite being persistent and bioaccumulative. For substances which are persistent and bioaccumulative, there are no safe levels, as in long lived organisms or through the food chain concentrations can raise uncontrollably, which cannot be assessed within a laboratory setup.

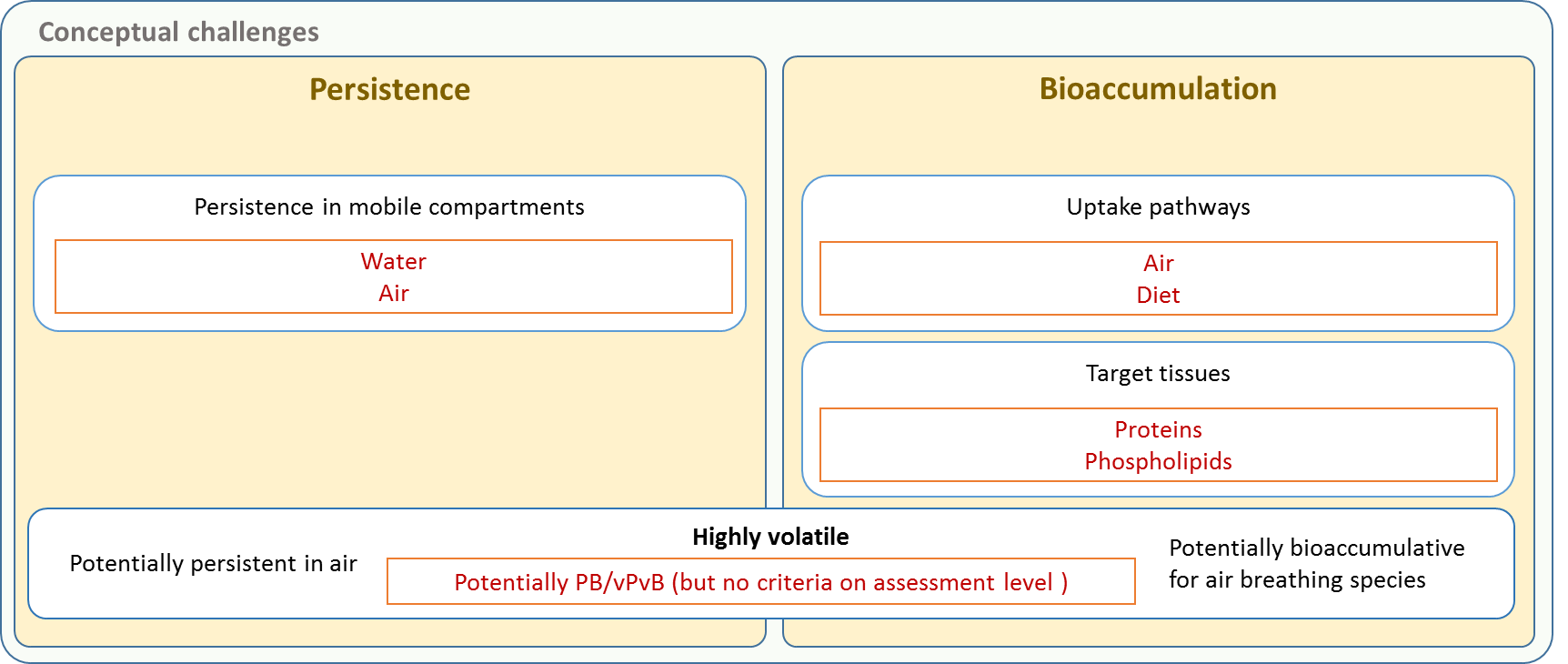


Figure 2: Conceptual challenges with the present PBT concept for persistence and bioaccumulation

## PBT Assessment of substances within the EU – regulations other than REACH

The PBT-assessment procedure is different for the different legal frameworks within EU. Besides REACH, four other European legislation frameworks exist, regulating substances according to their intended use. In contrast to REACH, where registration is warranted through the submission of the registration dossier, substances registered under the following regulations must get an authorization before they can be made available on the market:

* Biocidal Products Regulation BPR (Regulation EC No 528/2012)
* Veterinary Medicinal Products (Directive 2001/82/EC)
* Medicinal Products for Human Use (Directive 2001/83/EC)
* Plant Protection Products (PPP) (Regulation EC No 1107/2009)

The identification of PBT/vPvB substances is based on the same numerical criteria in all European regulations. As reviewed by a study (Rauert et al. 2014), the decision on whether the substance fulfills the PBT criteria or not, may in certain cases, also depend on the framework, under which the substance has been assessed. According to the authors, the same substance should not be treated differently under different legislations, as it is at present. Also, the same substances can be registered under different frameworks for different uses (Rauert et al. 2014). For human medicinal products, no consequences arise from the substance having met the PBT/vPvB criteria, as human health is prioritized over environmental issues, according to Directive 2001/83/EC. For veterinary medicinal products, environmental aspects are included for cost-benefit assessment according to Directive 2001/82/EC. The guidance for assessment of veterinary medicinal products (EMA 2015) also refers to ECHA’s guidance related to REACH (ECHA 2014a; ECHA 2016a). For PPP and Biocides, no authorization will be granted if the substance meets PBT/vPvB criteria, and additionally, substances that fulfill 2 of 3 PBT criteria are considered as candidates for substitution and have to undergo comparative assessment. The guidance focusses on the identification of candidates for substitution (DG SANCO 2012).

A critical review of the criteria and processes used in the PBT categorization of PPP concluded that, compared to REACH, for PPP the criteria are less clear and little guidance on the selection of data is provided. However the amount of data that has to be generated exceeds the substances addressed by REACH, as it must be provided to and evaluated by regulators prior to the placement of the product on the market (Solomon et al. 2013).

By application of QSAR models (i.e. Insubria-PBT-Index and EPA PBT Profiler), a screening study performed with 1200 pharmaceutical ingredients returned 35 pharmaceuticals which could have PBT properties. Given widespread use and quite often inadequate disposal of pharmaceuticals, the authors suggest considering environmental impact (Sangion & Gramatica 2016).

### Conclusion

Bringing experiences from different legislative frameworks together and enabling exchange of data may help to further strengthen, standardize and speed up evaluation of substances. Generally, more data is obtained for substances that are being registered under regulations, where they undergo an authorization process. However, the process PBT/vPvB identification is less defined within some legislations compared to REACH. The potential release to the environment together with the intrinsic hazard of a substance are in general considered for risk assessment. Therefore, PBT/vPvB assessment is to be done in the same way for all legislations, regardless of its use. Special treatment for different uses could then be considered in a following step, but relying on the same assessment results in all legislations. Even though protection goals might differ, the assessment of the properties is be done in the same way in order to avoid different conclusions on PBT/vPvB for the same substance under different legislative frameworks. The threat of widely used pharmaceuticals to the environment might also be considered e.g. in future monitoring programs.

## Overview of the Identification of PBT/vPvB substances under REACH

This study focusses on REACH, as it is the European legislation with the most comprehensive guidance and outline of criteria on PBT/vPvB identification of substances. The processes and documents, which define the concept are discussed in this chapter.

The Annex XIII (section [1.4.1](#Ref491096340)), the guidance document on IR&CSR Chapter R.11 (ECHA 2017), section [1.4.2](#Ref491096353), and the IT-mass-screening definition document (ECHA 2016b), section [1.4.3](#Ref491096369), have been identified as crucial for identification of PBT/vPvB substances and the definition of the concept. Besides those, also the data requirements, section [1.4.4](#bookmark), will set boundaries to the information available for the assessment of PBT/vPvB properties. Further, in some cases when a substance becomes subject to evaluation, several procedural aspects may also play an important role (see section [1.4.5](#Ref4910967601)).

### Legal Framework: Information requirements (Annex VII-X) and criteria (Annex XIII)

Within the REACH regulation, the criteria for identification of PBT/vPvB substances are outlined in Annex XIII, being the only actual legally binding definition of the PBT/vPvB concept. The numerical criteria can be compared to the substance property data in order to conclude on its PBT/vPvB properties. In cases where the criteria cannot directly be compared to the available information, the conclusion on PBT/vPvB properties of a substance can also be drawn considering all available information in a weight of evidence approach, e.g. not directly applying the criteria outlined in Annex XIII or information outlined in Annexes VII-X.

A tiered approach is applied for PBT assessment under REACH. It is differentiated between *screening level* and *assessment level.* The relevant information needed for the assessment on each of the two tiers is also given in section 3 of Annex XIII. If the results from screening tests or other information indicate that the substance may have PBT/vPvB properties, the registrant has to submit a testing proposal and generate higher tier (i.e. assessment level) information. Possible exceptions are outlined in Annex XI, i.e. “general rules for adaptation of the standard testing regime set out in Annexes VII – X”, e.g. where testing is not necessary, not possible or substance-tailored exposure driven testing can be performed (i.e. according to section 3 of Annex XI).

The required substance information to be initially submitted with the registration dossier varies according to the produced amount. Annexes VII-X list the required information:

* one tonne or more (Annex VII)
* 10 tonnes or more (Annex VIII)
* 100 tonnes or more (Annex IX)
* 1000 tonnes or more (Annex X)

Regarding PBT assessment, the information required for substances produced or imported in quantities of less than 100 tonnes per year according to Annex VII and VIII of REACH, corresponds to *screening level information* and the information required for substances of 100 tonnes and more per year according to Annex IX and X of REACH, as *assessment level information*.

#### Discussion and Conclusion

Based on the standard information requirements, only for substances produced in amounts > 100 t per year a definitive conclusion on PBT/vPvB can be made (unless the substance is ready biodegradable and therefore no further information is needed) with the information already submitted in the registration dossier. For substances registered as intermediates only, no PBT assessment is necessary a priori. In order to conclude a substance as persistent, the very expensive simulation test is needed, which is a standard information requirement only for substances which are produced in amounts > 100 t per year.

There is no criteria for bioaccumulation besides the fish-bioconcentration factor. Substances accumulating through other pathways than water cannot be identified by the criteria.

Some flexibility is given by also allowing other-than-standard information for PBT/vPvB-identification. This allows accounting for novel scientific findings or substances with peculiar properties. However, for an initial identification of a substance as PBT by the registrants, robust criteria and standard information requirements are crucial. If the registrants are not aware of the fact that additional information (i.e. information besides the standard information requirements as e.g. different forms of bioaccumulation) is needed or available in order to assess the substances behaviour in the environment properly, the substance will not be identified as a PBT/vPvB substance unless it is selected for (manual) substance evaluation.

Generation of standard information should always be given priority. Misinterpretation of non-standardized tests and use of inappropriate methods when concluding a substance not to exhibit PBT properties will be difficult to identify in an automatized way, and might lead to time-consuming expert-discussions. An evaluation of the first experiences with the application of the weight of evidence approach might help further develop the guidance documents and circumstances for application of weight of evidence, and eventually identify repeating cases, where criteria could apply.

A question would also be, whether there are substances which are concluded to be non-PBT based on non-standard information. The appropriateness of the applied non-standardized methods could also be evaluated.

### Guidance on IR&CSA. Chapter R.11. PBT/vPvB Assessment

In order to support the assessment procedure, ECHA has developed guidance documents. Those guidance documents are not legally binding, but provide explanation to regulatory processes and technical methods which are relevant for PBT/vPvB assessment as outlined in Annex XIII. Developed by ECHA involving stakeholders from Member States, industry and NGOs, they represent a mutually agreed procedure for the PBT/vPvB assessment. The Guidance on IR&CSR Chapter R.11 (ECHA 2017): PBT and vPvB assessment provides information about testing strategies and interpretation of the obtained results. In depth discussion of each REACH - required endpoint (i.e. not only regarding PBT-assessment) can be found in the Guidance on IR&CSR Chapter R.7 a-c: Endpoint specific guidance (ECHA 2016a).

The documents also provide guidance on interpretation of results and generation of information that go beyond the standard information requirements outlined in the Annexes VII-X (i.e. the standard information requirements for different tonnage) which are to be compared to the criteria for the identification of PBT/vPvB substances (i.e. as outlined in Annex XIII). According to Annex XIII, in a “weight of evidence” approach, also other-than-the-standard information can be used in order to assess PBT/vPvB properties of a substance.

#### Discussion and Conclusion

Although the guidance documents provide a very comprehensive discussion of different testing methods, the interpretation of e.g. bioaccumulation data (through feeding studies), terrestrial data etc. is not straightforward and there is no criteria that could be used for a clear identification of the substance as PBT or not PBT, which implies the need for work-intensive expert case by case judgements. Collecting experiences and more quantitative indicators toward developing criteria for at least some of the outlined testing in the guidance for which no criteria is outlined in the Annex XIII could be useful for registrants as well as for assessing authorities.

### IT-mass screening and application of QSARs

For substances regulated through REACH, the submission of the registration dossier (i.e. substance property information) allows for the placement of a substance on the market, whereas for active substances (e.g. biocides, which are regulated under different frameworks in the EU) authorization for use is granted after evaluation of the substance information by authorities. Given the number of chemicals registered under REACH, an automatized screening procedure is essential for identifying substances, that either potentially need further evaluation of dossiers, or which are not compliant with the information requirements.

As the ECHA is obliged to check at least 5% of the registration dossiers, the IT mass screening is the only review process where all registered substances will go through, and the criteria are crucial for identification of potentially PBT/vPvB substances which are not identified as PBT/vPvB by the registrants.

#### Discussion and Conclusion

Reviews of dossier compliance have shown that there are considerable issues with data availability and quality of the registration dossiers (Springer et al. 2015). This outlines the need for strengthening the IT-mass screening for identification of substances that potentially exhibit PBT/vPvB properties without relying solely on the reported data from the registration dossiers.

The IT-mass screening could be further enhanced by applying QSAR relationships and cross-checking the reported values and identifiers for plausibility with physico-chemical and thermodynamical constraints.

This could include correlations of endpoints in order to check the plausibility of the value. Approaches that consider experimental data together with physico-chemical constraints (e.g. using correlation with molecular mass for homologous series as presented in (Stieger et al. 2014) or logKow with BCF.

Thermodynamically related values such as Kow, Koa and H could be checked for consistency (Schenker et al. 2005).

Ranges of Kow and water solubility, where analytical difficulties can arise, could also be selected for a manual inspection.

Additionally, substance classes and substances similar to known PBT/vPvB substances, which show PBT behaviour but its PBT-properties are not captured by the common testing could be also prioritized in the future, where structure-activity-relationships for those group of substances are further developed.

QSARs are very powerful tools for checking the plausibility of measured values. However, the data used for calibration of QSARs has to be of very high quality and representative for the considered substances (i.e. in terms of applicability domain). Wrong QSARs relationships could be derived from systematically biased experimental data. The systematic bias in the experimental data could arise from a lack of appropriate methods for analysis of certain substance classes. This is for example the case with measuring log Kow for high (> 6) Kow substances in the past. For establishing and validating QSARs, experimental data are used in order to derive correlations between physico chemical properties and endpoints used for PBT/vPvB assessment on the one hand, and in order to validate the model on the other hand. Hence, development of QSARs also strongly relies on data sets of high quality.

## Persistence: state of the art and challenges

Substances that persist in the environment are a recognized global concern. Persistence is often inferred from a continued presence of a substance away from its sources of emission or from degradation studies (Boethling et al. 2009). Release of persistent pollutants to the environment can be considered an irreversible process, leading to unpredictable effects only after a very long time span, therefore it is important to apply a preventive approach when dealing with potentially persistent pollutants (Marvin 1977).

The aim of this literature review is to provide an overview of the different conceptual and operational definitions of persistence (i.e. regulatory criteria, required information, analytical methods) and to discuss possible consequences for identification of substances of concern and challenges for further development.

### Legal background and assessment processes

#### Persistence testing requirements and other EU frameworks

Definitive PBT assessment based on direct comparison to trigger values is possible for PPPs, medicinal products (veterinary and human) and biocides, where the necessary data is always available. For substances registered under REACH, the information requirements depend on the tonnage (see REACH Annex VII-X). Only for substances manufactured 100 tonnes per year or more, is a simulation study in the compartments of concern necessary, i.e. a direct comparison to the persistence criteria outlined in Annex XIII is possible.

#### Persistence assessment under REACH

The Guidance on IR&CSR Chapter R.11: PBT/vPvB assessment (ECHA 2014b) and its current draft version (ECHA 2017) more specifically deals with the use and applicability of different types of existing tests for persistence assessment. The Guidance on IR&CSR Chapter R.7b: Endpoint specific guidance (ECHA 2016a) gives the background on biodegradability and interpretation as well as use of existing guideline tests with respect to REACH.

Three types of tests are used for assessing persistence (i.e. in terms of biodegradation) within PBT/vPvB assessment under REACH: Tests on *ready or enhanced ready biodegradability,* tests on *inherent biodegradation* and *simulation tests*.

Irrespective of the tonnage band, a **ready biodegradability test** (i.e. OECD 301 series) is mandatory (REACH Annexes VII-X). The environment of those tests is artificial; therefore, no environmentally relevant degradation half-lives can be derived. Due to the very stringent conditions of this test, false negatives are not expected, but some false positives (Gartiser et al. 2015). Under the PBT/vPvB assessment, the outcome of the tests on ready biodegradability is considered screening level information. Based on the outcome of a ready test, the substance is *not persistent* or *potentially persistent*. **Enhanced ready biodegradability** or **inherent** biodegradability (i.e. OECD 302 series) tests allow for more favourable conditions than the very stringent ready biodegradability test.

**Simulation tests** (i.e. OECD 307, 308, 309) are mandatory for a registration of 100 tonnes per year and more according to REACH Annex IX and X. The testing conditions of simulation tests are environmentally representative and environmental degradation half lives can be derived for different compartments (e.g. soil, marine/fresh/estuary water, marine/fresh/estuary sediment) which then are compared to REACH Annex XIII criteria in order to finally determine whether a substance is persistent. Information about degradation products (metabolites, extracted residues), formation of non-extractable residues (NER) and mineralization can be obtained. The simulation study has to be performed in the relevant compartment. The compartment choice is based on emission scenarios and substance properties (ECHA 2017).

### Discussion of challenges

#### Ready biodegradability tests (OECD 301 series, OECD 310)

A test on ready biodegradability has to be performed for all tonnage bands. The criteria for ready biodegradability are very strict: there is a number of substances that fall in a gap between being “ready biodegradable” and “persistent”. A series of tests have been developed, the application of the different tests for substances according to their properties is outlined in the Guidance on IR&CSR Chapter 7b. For poorly water soluble substances, the OECD 301 B, C, D, F and 310 test is suitable. For volatile substances, OECD 301C, D, F and 310 test is suitable. For adsorptive substances, OECD 301B, C, D, F. According to the OECD guideline, for substances with a solubility in water exceeding 100 mg/L, all the 301 series tests are suitable. The OECD 310 guideline states a maximum for Henry’s law constant of 50 Pa m3 mol-1 for volatile substances.

A review on ready biodegradability test identified some shortcomings regarding their accuracy, reproducibility and comparability. First, better characterization of the inoculum would lead to a better reproducibility of the tests. Second, the number of replicates needed is too low. Third, for a test like OECD 301 A, where dissolved organic carbon is the endpoint, the influence of adsorption should be investigated: no threshold for maximum allowable elimination due to adsorption exists. Also for water-based systems, adsorption processes have to be defined. Finally, the authors propose compiling a set of poorly water soluble substances with known biodegradability for use as reference substances (Gartiser et al. 2015).

#### Enhanced screening test for identification of a substance as PBT on screening level

At present, it is not possible to conclude a substance as persistent on screening level. However, concluding results on persistence at screening level are desired, as simulation testing is expensive and is only performed under certain circumstances (i.e. B or T criteria are fulfilled or cannot be excluded or environmental exposure assessment indicates a need), making this data rarely available (Gartiser et al. 2015).

The authors propose further developing enhanced screening tests, tests on inherent biodegradability and compartment-specific screening tests. Although due to the artificial setup,derivation of degradation rates for comparison with the Annex XIII criteria is not possible, the aim is to set a threshold for identification of a substance as persistent on screening level, by allowing for more favourable conditions than ready-biodegradability tests offer, but avoiding costly simulation studies. However, those tests, standards and pass levels still need to be developed (Gartiser et al. 2015).

According to the Guidance on IR&CSR Chapter R.11 (ECHA 2017), it is sufficient confirmation for a substance to be persistent if less than 20% degradation occurs in a standard test for inherent biodegradation (unless this occurs due to reduced bioavailability as a consequence of low water solubility). However, no such criteria are written down legally binding in the Annex XIII.

#### Simulation studies

##### Choice of compartment

The choice of compartment depends on the emission scenario and physico-chemical properties.

Testing in the water compartment (i.e. OECD 309) is generally a preferable choice, as formation of NER is to be avoided (ECHA 2017).

Testing on sediment and soil will be preferred if the water solubility of a substance is below 1ug/L (ECHA 2017).

##### Degradation half-lives in simulation studies

Degradation half-live values depend on the medium. This may be due to the adsorption to variable constituents of the matrix (e.g. clay minerals, metal oxides) and parameters like pH, cation exchange capacity, redox potential, microbial density or diversity, temperature and humidity (Gartiser et al. 2015). Normalization to specific conditions would enhance the comparability of data obtained for different purposes (e.g. under different regulatory frameworks) (Rauert et al. 2014).

##### Temperature dependence of degradation half-lives

Besides other factors, which are influential as well, temperature has shown to have a big impact on degradation but it is also quite well quantifiable. A temperature of 12°C is proposed as a reference for PBT identification, as it is established or suggested in many legal frameworks (Rauert et al. 2014). Further, a temperature of 12°C rather depicts European average environments than 20°C, which is often used as a reference temperature for laboratory settings.

##### Non-extractable residues (NER) (substances adsorbing or reacting with matrices)

NER pose a challenge for the interpretation of simulation studies in soil and sediment. Sediment and soils consist of a variety of organic and inorganic compounds, leading to a variety of interactions that might occur with the assessed substances: hydrophobic interaction, van der Waals forces, charge-transfer complexes, polar/ionic/covalent interactions. A combination of several of the interactions is also possible, as well as a function of time (e.g. ageing process, where hydrophobic compounds slowly sorb to organic matter and become increasingly recalcitrant to extraction). Entrapment into soil matrix pores leads to theoretically reversible but very slow released residues (Gartiser et al., 2015; Kästner et. al., 2014).

The nature of NER is largely unknown. A standardized methodology for characterization and quantification is still lacking. Several approaches are proposed as e.g. isotope mass balancing (labelling of the substances in order to assess its fate), sequential extraction (ECETOC 2013; Kästner et al. 2014; Gartiser et al. 2015).

Regarding the OECD 307 test on anaerobic and aerobic transformation in soil, NER and bound residues (BR) have been identified as the major challenges, i.e. how NER and BR should be defined, determined and interpreted (Gartiser et al. 2015). In a reflection paper on NER for veterinary medicines, applying the OECD 307, it is recommended to use a radiolabeled substance in order to quantify the volatile transformation products and the fraction lost during clean-up of the samples and bound to the soil particles as NER (EMA 2016).

The irreversible bound fraction is regarded as non-critical according to the Guidance on IR&CSA, Chapter R.11 (ECHA 2017). Extraction methods and type of chemical binding to soil and sediment is discussed in section R.7.9.4 and R.7.9.4 of the Guidance on IR&CSA, Chapter 7b (ECHA 2016a). The environmental relevance of various extraction methods is still under debate, and no standardization has been developed yet (Gartiser et al. 2015).

As a first steps towards regulatory treatment of NER, a scientifically based agreement is needed on (Gartiser et al. 2015):

1. *Developing experimental approach to non-extractractability*: the currently applied organic solvent based extraction is applicable for positively charged, hydrophobic compounds. It may not be suitable for (mostly positively charged) compounds bound by ionic interactions. In this case, solutions of chaotropic salts or complexing agents like EDTA might better simulate an environmentally relevant remobilization potential.
2. *Dealing with NER in biodegradation studies*: When can be NER disregarded from the mass balance (i.e. irreversibly bound to the matrix and therefore not critical), and when the potential for remobilization can be excluded.

##### Degradation half-lives in water systems

Different options performing the OECD test exist, however no guidance is provided in which cases which options should be used.

Addition of suspended solids is possible according to the OECD TG in water systems as well (ECHA 2017), however it induces the difficulties with NER and interpretation of a 2-phase system, i.e. the degradation in the water phase, degradation of the adsorbed fraction and NER formation (parent compound as well as possible metabolites).

The marine compartment is usually accounted for with a modified OECD 306 test and there is a separate criterion for the marine compartment in Annex XIII with a higher threshold value as for freshwater.

For poorly soluble substances, the limit of detection may also be a limiting factor, when degradation in the water compartment is assessed. However due to NER-formation in other compartments, the water compartment should be the first choice for assessment and the limit of detection can be enhanced using a radiolabelled form of the substance (ECHA 2017).

##### Degradation half-lives in sediment-water systems

According to the Guidance on IR&CSA, Chapter R.11 (ECHA 2017), for substances with a Koc (sediment) > 2000 aquatic sediment simulation may be considered. Although there are separate criteria for sediment and for water in Annex XIII of REACH, it is difficult to derive separate degradation half-lives from the OECD 308 test (i.e. anaerobic and aerobic degradation in sediment-water systems), which is referred to in the Guidance on IR&CSA, Chapter R.11 (ECHA 2017). Derivation of compartment-specific half-lives is not straightforward. Disappearance half-lives have been shown to have limited uncertainty, however, disappearance is a consequence of both, degradation and phase transfer (including formation of NER) and it has been shown that it is sensitive to the geometry of the test system, i.e. the water-sediment interface is an important factor as the substance is spiked into the water phase. Also, the sediment-water ratio is not representative of environmental systems (Honti & Fenner 2015).

Currently, several modifications of the sediment-water test are discussed:

* Spiking highly sorptive and substances of low water solubility into the sediment phase (discussion Partner Expert Group, September 2016). However, threshold values for water solubility and Koc are not yet available
* Stirring the system in order to increase the aerobic part of the sediment. It has been shown, that aeration of a bigger part of the sediment led to an increased biodegradation, however also grinding the sediment potentially leading to higher surface for sorption, which makes the interpretation of the results more difficult (Hennecke 2014).

Both modifications could lead to increased formation of NER.

A study concluded that the data from OECD 308 tests turned out to be insufficient in terms of robustness and uncertainty in order to derive the persistence indicator. However, the authors propose degradation half-life for the whole system together with standardization of the system geometry as an indicator (Honti & Fenner 2015). In order to overcome this problem, the ECHA guidance (ECHA 2017) proposes assuming rapid partitioning of the substance to sediment if log Koc is greater than or equal to 3. However, proposing log Koc 2 as the trigger for considering systems other than water, substances with 2 < Koc < 3 will be difficult to interpret in terms of single compartment half-lives.

##### Degradation half-lives from field studies

Compared to laboratory simulation studies, some conditions might be more realistic in field studies, e.g. the prolonged duration, fluctuating temperature and humidity, higher biological activity, larger system. However, it might be more difficult to reproduce, compare and interpret field studies compared to laboratory simulation studies. Laboratory field studies allow measurements of CO2-evolution, formation of metabolites and bound residues and therefore the estimation of a primary degradation rates. From a field study, a dissipation half-life will be derived and not a degradation half-life. Photolytic transformation and field dissipation processes like volatilization, leaching and runoff will also contribute to the substance loss (Rauert et al. 2014). The criteria outlined in Annex XIII are related to degradation processes and not dissipation processes, therefore a direct comparison to Annex XIII criteria with rates from field studies is not recommended.

For plant protection products, the European Food Safety Authority (EFSA) proposed a guidance on evaluating field studies, i.e. estimating dissipation processes on the soil surface (European Food Safety Authority 2014).

See also section on NER ([1.5.2.3.4](#Ref4919465021)) for discussion on challenges with interpreting soil biodegradation.

##### Sewage treatment plant simulation tests

Sewage treatment plant simulation tests are not explicitly mentioned in the REACH context, however their role was discussed within the PBT expert group. In a weight of evidence approach, also other data can be considered. OECD 303A and 314 are designed differently than the before mentioned simulation test. The test concentration of dissolved organic carbon is relatively high allowing for growth of degrading microorganisms. 14C-labelling is not foreseen, and therefore no carbon balance can be established. The synthetic sewage allows for co-metabolism processes. As this setup is very different from environmental compartments, comparing the results is not straightforward and therefore should not be used for P assessment due to its limited transferability.

#### Hydrolysis

Hydrolysis demonstrates only primary degradation, products need to be assessed for possible PBT/vPvB properties. Annex XIII points out the need for assessment of “relevant constituents of a substance, and relevant transformation and/or degradation products” for identification of PBT/vPvB substances. Hydrolysis rate constants measured in pure water may also not reflect rate constants in sediments or soil (ECHA 2017), e.g. partitioning behaviour and a potential for ionisation must be taken into account. Fast hydrolysis alone cannot lead to a conclusion on non-persistence (Gartiser et al. 2015). There is no criterion for hydrolysis in Annex XIII, however in a weight of evidence approach data on hydrolysis can be used for the assessment. As outlined in the ECHA guidance (ECHA 2017), hydrolysis kinetics depend strongly on the pH as well as other less predictable factors as dissolved organic carbon (i.e. the sorption behaviour of the substance). There are substances exhibiting rapid hydrolysis rates which are well known to be persistent in soil and/or sediment. Further, the fate of the potentially stable hydrolysis product should also be considered for potential PBT properties. Therefore, fast hydrolysis alone cannot be considered as an indicator of non-persistence.

#### Transformation products

Transformation products have to be determined when simulation tests are performed. However, even if some conclusion also can be drawn from the (enhanced) ready test, waiving further testing for readily biodegradable substances assumes that the degradation products are readily biodegradable as well, which might not be always true. Several studies show that transformation products can be even more persistent (Boxall et al. 2004). According to Annex XIII, “the identification shall also take account of the PBT/vPvB-properties of relevant transformation products”. Unfortunately, degradation pathways and half-lives of chemicals in the environment are highly variable and poorly characterized (Ng et al. 2011). Ongoing research is done in the field of better characterization of degradation pathways, however, for screening purposes estimation tools like EPISuite, the University of Minnesota Pathway Prediction System (UM-PPS) still represent the state of the art[[1]](#footnote-1).

An approach to jointly assess the persistence of parent compound and its transformation products has been developed using a combination of those tools, i.e. introducing a metric of “joint persistence”, however the authors address the need for better data on environmental half-lives of chemicals and knowledge on transformation pathways (Ng et al. 2011).

There are a few approaches, to estimate the formation degradation products and their properties on screening level:

The OECD QSAR Toolbox[[2]](#footnote-2), which is a freeware for grouping chemicals into categories and filling data gaps for endpoints needed in hazard assessment of chemical, contains a module accounting for the metabolism of chemicals.

CATALOGIC is a software suite for assessment of environmental fate and ecotoxicity endpoints, which predicts the endpoints for selected metabolites as well. The different endpoints estimated correspond to several OECD Standard test for biodegradation, abiotic degradation etc. under defined conditions (e.g. CATABOL 301B, which simulates the aerobic biodegradation according to OECD 301B test conditions, estimating the theoretical CO2 release after 28 days and the biodegradation products based on one single “preferred” pathway)[[3]](#footnote-3)

#### Concepts and metrics related to persistence: LRTP, Pov, CTD, mobility, multimedia fate modelling

##### Persistence criteria for air

No criteria for persistence in air is considered in today’s REACH legislation (i.e. Annex XIII) neither on screening nor on assessment level. Chemicals, that are persistent in air but not in water, soil or sediment are not identified (Scheringer et al. 2006). A first indication of persistence in air on screening level could be obtained by EPISuites AOPWIN, which considers hydroxyl-radicals and ozone reaction (i.e. the most prevalent atmospheric oxidants). For some compounds also nitrate radicals or direct photolysis is important. For direct photolysis, there are no broadly applicable estimation methods. Further, many POPs/PBTs are to a bigger or lesser extend sorbed to particles. Their fate depend on physical atmospheric processes and the reactivity in their sorbed state is largely unknown (Boethling et al. 2009).

The Stockholm convention defines a substance as prone to long-range transport when its atmospheric half-life exceeds 2 days. The idea behind is that within 2 days transboundary transport may occur (i.e. several 100 to over 1000 km).

It is important to note, that if a substances half-life in air is less than 2 days, this does not mean that the substance is not persistent. The substance can nevertheless meet the persistence criteria in another environmental compartment; therefore partitioning behaviour is also of considerable importance when assessing persistence (Scheringer et al. 2006). The concept of overall persistence (Pov) for example is combining information about partitioning behaviour of a substance (i.e. partitioning between air, water, soil and sediment) together with its half-lives in the different compartments, see next section.

##### Persistence, partitioning and mobility: Long-range transport as a persistence concern

Several tools for calculating different long range transport metrics exist. The common approach for most metrics modelling the fate of the substance with multimedia fate models, which account for partitioning and fluxes between different environmental compartments and degradation of the substance within the compartments.

In order to assess long range transport with a multimedia modelling approach, substance properties such as degradation half-lives for all considered compartments and partitioning coefficients (i.e. Kow, Koa) are needed. According to REACH, only for substances registered for 100 tonnes and more or if assessment level information is needed in order to conclude whether the substance is persistent or not, a simulation study in only one compartment has to be performed. Therefore, the standard information requirements do not provide enough data, but it could be estimated using property estimation tools (e.g. EPISuite).

Various metrics have been used as indicators, all of them combining the information of persistence, partitioning and transport. Some examples are:

* CTD (Characteristic travel distance): where the concentration in air of a substance has dropped to 1/e of its initial value (Beyer et al. 2000).
* Pov (Overall persistence): different metrics have been used: 1. Time necessary for disappearance of a substance for the overall environment to e.g. 10%. 2. Mass of the substance still remaining in the environment e.g. 30 years after emissions stopped. 3. Steady state residence time (Scheringer et al. 2009)
* LRTP (Long-range transport potential): The average distance that a molecule typically travels during its residence time in the environment (Scheringer et al. 2009).

Different multimedia models with different metrics as endpoints have been evaluated for a wide range of chemical properties (i.e. using hypothetical chemicals). The authors conclude, that the relative ranking of the chemicals was mostly the same, except for some group of substances, the different model parametrizations had a considerable impact on the result: 1. For chemicals with low volatility, high water solubility, high half-life in water, it is important whether and how transport in water is taken into account. 2. For chemicals that strongly bind to aerosols due to high Koa, it is important whether the aerosol fraction is assumed to be degradable. 3. For chemicals with high Kow and low Kaw, particle bound settling to the deep sea reduces their LRTP in global models containing oceanic water compartments. 4. For very volatile chemicals, distinction between target-oriented (i.e. addressing exposure in the compartments) and transport-oriented (addressing the hazard of widespread presence of the substance) models is important. For all models, the LRTP and Pov metrics were largely determined by chemical properties (Fenner et al. 2005).

A study on advancement of concepts for identification of SVHC under REACH (UFOPLAN 3709 65 409) reviewed scientific findings on LRTP and possibilities to include LRTP as a critical substance property for SVHC identification under REACH (Matthies et al. 2011). The authors conclude that for sufficiently water soluble chemicals transport with rivers might be highly effective also for chemicals having half-lives shorter than the present REACH criteria. Screening for chemicals with LRTP properties revealed, that all the non-PBT substances were persistent, but not bioaccumulative (Matthies et al. 2011). Taking an average European riverine flow velocity of 0.7-1 ms-1 and a regional scale of 700 km as the threshold, the half-life criteria for LRTP in freshwater would be 8-12 days (Zarfl et al. 2011), compared to the REACH persistence criteria of 60 days.

##### Pseudo-persistence or continuous persistence

There is an ongoing discussion about another dimension of persistence, namely “pseudo-persistence”. This concept was first introduced in the context of the consequences of the widespread use of drugs, of which some do not get eliminated during waste water treatment, leading continuous input and exposure (Daughton 2002). This idea was recently brought up again in the context of persistence assessment. The authors propose using the term “continuously present”. Harm could result from this class of substances if continuous exposure occurs before degradation processes have had time to reduce the quantity of chemicals to an acceptable level (Mackay et al. 2014).

The property pseudo-persistence or continuous presence is difficult to predict on the level of the substance, as it depends also on external factors e.g. emission and usage patterns. Monitoring results would provide more certainty for the “continuous presence”, however this would imply that action is taken only after problems have already risen, which is against the preventive policy of REACH. A normal risk assessment in terms of predicted environmental concentration versus predicted no effect concentration should be applicable to this class of substances. But some chronic effects could arise from the chronic exposure, which are not captured within standard test durations (Mackay et al. 2014).

Introducing emission scenarios into the PBT/vPvB context is to be avoided, as the basic idea is to identify substances for which there is no safe concentration based on intrinsic hazardous properties. However, environmental half-lives are not intrinsic properties neither, but the testing environments are controlled laboratory setups where comparable data can be obtained.

Theoretically, it is possible that substances, which are degradable in standard simulation environments might be persistent in vulnerable environments, lacking a degrading a capacity. Therefore, continuous presence could be due to continuous emissions but also lack of degradation in the considered environment.

#### Substances potentially difficult to assess

##### Highly volatile substances

The closed bottle test (OECD 301D) and CO2-Headspace test OECD 310 are suitable for volatile substances, where the upper limit for Henry’s law coefficient or the OECD 310 is 50 Pa m3 mol-1. On assessment level, there is no criterion for persistence in air or long range transport, which might be of concern (also for less volatile substances). Also, no trigger value for Henry’s law constant is indicated, where the substance has to be treated as “volatile”. Assessment over a range of European temperatures might give an indication of the relevant environmental phase, i.e. lowering the temperature might increase sorption/partitioning into other phases than air.

##### UVCBs

The lack of an a-priori determination of the identity and fractions of the relevant constituents with a reasonable effort still remains a challenge assessing UVCBs under the present PBT/vPvB concept, as there is a need for identifying the single constituents and assessing each separately. The PBT/vPvB assessment framework is designed for assessing pure substances.

While for registration purposes the single constituents for UVCBs have to be identified if they make up more than 1 % w/w, single constituents down to 0.1 % w/w are relevant for PBT assessment (ECHA 2017). Therefore, potentially relevant constituents are poorly defined, radioactive labelling as well as application of QSAR models is impossible in this case (Gartiser et al. 2015). Using the common biodegradation testing methods will not provide information on the individual constituents.

Effort is undertaken towards improving assessment of UVCBs, but it remains a challenging task. Strategies often aim to describe how to deal with different categories of constituents. For example, as outlined in the ECHA Guidance (ECHA 2017), if the test item (i.e. UVCB substance) consists of sufficiently homologous structures and is shown to meet the ready biodegradability criterion (> 60% degradation in 28 day), it can be concluded that the underlying constituents are not expected to be persistent. For assessment of single constituents with a close structural similarity, their weight fractions have to be summed up for the assessment, assuming similar mode of action (ECHA 2017). This approach is particularly important for assessing persistence when most or all constituents are below 0.1% w/w, even though the summation – justified by same mode-of-action – rather refers to bioaccumulation and toxicity than to persistence. The assumption behind the summation is that structural similarity is sufficient in describing similarity for susceptibility to degradation. However, where not every single constituent is identified, there will always be the risk of overlooking a persistent constituent when testing is performed for several constituents together, as a sufficient level of degradation can be reached even if some constituents are not degradable.

##### Poorly water soluble or sorptive substances

For poorly soluble substances, biodegradability can be underestimated as for most substances only the soluble fraction is accessible for biodegradation. For substances that can be degraded in the solid state, the accessible surface area will have a considerable impact on biodegradation (Gartiser et al. 2015). Annex III of OECD 301 TG (i.e. test on ready biodegradability) describes options for testing of poorly soluble substances, mostly by using chemical or mechanical aid in order to homogenize the solution.

According to OECD 301 guidance, substances above 100 mg/L are considered soluble. The term poorly soluble is however not numerically defined.

Due to its sorptive behavior, part of the substance might be (temporally) not bioavailable, thus interpretation of simulation studies in soil and sediment systems, as well as field data on soil is difficult. See also section on NER. DOC-based testing (e.g. OEDC 301 A and E) is not appropriate for sorptive substances.

However, not all sorptive processes are fully understood. Some of them include also covalent binding, therefore also other structural features might be important besides Koc. This is a challenge related to NER formation in soil and sediment studies. Defining persistence becomes difficult for sorptive substances because when using radiolabeling methods, the fraction which is assimilated into biomolecules and the fraction which is bound (through sorptive processes or covalent binding) to the soil/sediment matrix cannot be distinguished. Where assimilation into biomolecules can be seen as biotransformation, the sorbed fraction is not (Gartiser et al. 2015). Therefore, the presence and properties of the matrix are a very determining factor for persistence of those substances.

### Conclusion on persistence assessment

Conceptually, persistence is understood as an inherent property of a substance. However, regarding present concepts of assessing persistence, there is no inherent property of a substance related to persistence that can be easily measured. It is a combination of substance specific characteristics, together with environmental conditions that finally determine whether the substance will persist in the environment or not. Therefore, standardization and better characterization of test environments, clear trigger values regarding substance properties for different test types and well-documented experimental reports are of crucial importance.

Mostly due to **experimental challenges** volatile, sorptive, poorly water soluble substances are challenging for P assessment. Trigger values (water solubility, Henrys law constant, Koc) could help identify substances which deserve special attention.

For **UVCBs**, in general, it is not possible to conclude on non-persistence down to 0.1 w/w % when the substance is assessed as a mixture and not the single constituents.

A broader understanding of persistence in terms of **mobility** (i.e. partitioning into mobile phases with sufficient persistence within the phase, potentially reaching vulnerable areas or ecosystems) could prevent distribution of potentially harmful substances. This is of concern for volatile substances persistent in air and non-volatile, water substances persistent in water.

Concern might also arise from a **continuous presence** of a substance, if the continuous input exceeds the purification capacity of the system, allowing for long term exposure possibly causing effects (Mackay et al. 2014). This dimension of persistence is somehow outside the PBT/vPvB concept, which aims identifying intrinsic hazards in a preventive way. However, considering the “continuous presence” as a way of identifying substances of concern, which have not been identified during assessment.

On the screening level, no definitive conclusion on persistence can be made unless the substance is ready biodegradable and therefore not persistent. Simulation studies are very expensive and are therefore often not performed if bioaccumulation or toxicity can be excluded, However, as there are other ways of bioaccumulation than depicted by the BCF, i.e. also bioaccumulation through air or terrestrial organisms, potentially persistent and bioaccumulative chemicals might not be identified. Further, also experimental challenges with the bioaccumulation or toxicity assessment of certain compounds (e.g. highly hydrophobic, poorly water soluble, mixture effects) can lead to an underestimation of bioaccumulation or chronic toxic effects or mixtures.

Besides bioaccumulation and toxicity, the combination of persistence and partitioning into mobile media can lead to an unpredictable widespread contamination with potentially hazardous chemicals. Therefore, a detailed assessment of persistence and minimizing release of such substances to the environment is a crucial precautionary measure, as the release is irreversible and adverse effects can arise temporally and far away from its sources.

As mentioned above, “measurable persistence” is not an inherent property of a substance; therefore persistence will be a function of the environment. Choice of environmental conditions (i.e. compartment) could potentially be a critical step in the assessment. The environment should therefore represent the phase where discharge of the substance is likely and were the substance will reside. Although some substances might be degraded under anaerobic conditions, those environments rarely will be the department the chemical is discharged to. Therefore, it is likely to persist in other (i.e. oxygenated) compartments. Degradation data obtained under very specific conditions that are not representative of the average conditions should not be used for a conclusion on persistence.

## Bioaccumulation: state of the art and challenges

### Legal background and assessment processes

#### Bioaccumulation testing requirements within REACH and other EU frameworks

The bioconcentration factor (BCF) determined by the OECD 305 flow through fish test is considered as a standard endpoint in all EU legislative frameworks. For biocides, plant protection products and human medicinal products the test is mandatory for risk assessment if the substances log Kow exceeds 3, for veterinary pharmaceuticals if log Kow exceeds 4 and for REACH registered substances if the production volume is above 100t/a and log Kow > 4.5. Thus, “bioaccumulation” from a present regulatory point of view is operationally defined through the bioconcentration from the aqueous phase. Although also other data can be used in a weight of evidence approach, the outlined criteria in Annex XIII of REACH refer to bioconcentration in an aquatic environment.

The BCF is not the most relevant indicator of bioaccumulation for all substances (Klecka & Muir 2008). Therefore, the need of considering all available information in a weight of evidence approach is proposed by a recent review (Rauert et al. 2014).

#### Guidance for bioaccumulation assessment under REACH

The Guidance on IR&CSR Chapter R.11: PBT/vPvB assessment (ECHA 2017) more specifically deal with the use and applicability of different types of existing tests for bioaccumulation assessment. The Guidance on IR&CSR Chapter R.7c: Endpoint specific guidance (ECHA 2014b) gives the background on specific endpoints and interpretation as well as use of existing guideline tests with respect to REACH.

#### Assessment levels and required information under REACH

Annex XIII provides criteria on screening level and assessment level. For substances produced in amounts higher than 100 t/year, assessment level information has to be generated in any case.

According to Annex XIII, a substance fulfils the bioaccumulation criterion if the bioconcentration factor (BCF) is higher than 2000 and is considered to be very bioaccumulative if the BCF is higher than 5000.

Screening level information according to Annex XIII includes Kow, which can be experimentally derived or estimated, and may indicate B or vB properties. According to the Guidance on IR&CSR Chapter R.11, if a substance has log Kow > 4.5,or log Kow > 2 and log Koa > 5 and uptake cannot be excluded by other indicators (see next section), the substance is potentially B (ECHA 2017). This also means, that if the substance’s log Kow is less than 4.5, Koa less than 5 and non-lipid bioaccumulation is not expected to occur, the substance can be concluded not B on screening level.

There are no screening level criteria yet for non-lipid bioaccumulation.

Assessment level information on bioaccumulation corresponds to a bioconcentration from a bioaccumulation study in aquatic species, where a BCF is to be compared to the outlined criteria.

Nevertheless there are screening Koa – indicators which should account for lipid based accumulation of air breading organisms, final assessment level data and criteria are based on BCF for aquatic organisms only.

### Discussion of challenges

#### Kow as screening criteria for bioaccumulation

Experimental as well as estimated Kow values may be subject to considerable uncertainties, varying often over orders of magnitude (Stieger et al. 2014; Buser et al. 2013). Nevertheless, the Kow is a crucial value determining the substances fate and serves also as a benchmark for regulatory purposes.

#### BCF derived from the OECD 305 test

The Annex XIII criteria for bioaccumulation refer to bioconcentration in fish only (i.e. BCF obtained from OECD 305 test).

The BCF can be calculated from the study results in two ways: Assuming steady state to be reached, BCF can be described by the ratio of steady-state-concentration in fish divided by the steady state concentration in the water (i.e. steady-state BCF). For steady state conditions, this equals to the ratio of the uptake rate constant divided by the elimination rate constant (i.e. the kinetic BCF). Reporting both factors is desirable, in order to check whether steady state was reached.

According to the OECD guideline, fish growth during depuration phase can lead to an overestimation of the depuration rate, therefore, the kinetic BCF should be corrected for growth. Also, steady state BCF is influenced by growth but there is no agreed procedure for correction. Normalization to a 5% of fish lipid content is also necessary as lipid content varies among fish.

There are two options besides the standard OECD 305 fish bioconcentration test mentioned in the Guidance on IR&CSR Chapter R.11 (ECHA 2017):

* The minimized OECD 305-II Test: According to the OECD-Guideline, the test can refute or confirm BCF estimates based on QSARs. If the substance behaves as expected and does not exhibit borderline-properties, further testing can be omitted. Criteria such as first-order uptake and depuration kinetics, log Kow < 6, sufficient water allow considering minimized testing which encounters less fish.
* The dietary bioaccumulation test OECD 305-III test: According to the OECD guideline this test should be performed for substances for which no stable aqueous solution can be maintained. The Guidance on IR&CSR Chapter R.11 states that for substances log Kow > 5 and water solubility below around 0.01-0.1 mg/L dietary studies could be considered, but the aqueous test always preferred if possible. The result however will be a biomagnification factor, BMF, for which no Annex XIII criteria exist yet.

According to the OECD 305 guidance, solid phase desorption dosing systems have been successfully applied to substances up to a log Kow of 7.8, without using solvents and dispersants, which themselves can potentially affect the fate of the chemical.

Given that aqueous testing seems to be feasible up to a log Kow of 7.8, and for substances above log Kow > 5 and water solubility below around 0.01-0.1 mg/L dietary studies can be used and minimized test design could apply for substances with log Kow < 6, where there is an indication of low BCF, the choice of the appropriate testing is not straightforward.

Developing a **clear and binding guidance for the choice of the right BCF testing strategy by deriving threshold values for e.g. Kow or water solubility**, where one or another test should be performed. For example, for substances with very low water solubility, use of radiolabelling and reporting of the dissolved concentration should be mandatory.

##### Sorption of highly hydrophobic chemicals to organic matter in fish bioconcentration studies

A study investigating sorption of highly hydrophobic substances (log Kow 5.5-7.8) to organic matter in batch equilibrium showed that decreased bioavailability of the test substances occurred even in the presence of very low concentrations of organic matter. The presence of organic matter is due to feed residues and feces. Compared to an OECD 305 test setup, this represents a worst-case scenario: as the flow-through setup delivers constant freely dissolved substance, and feed residues and feces can be removed, equilibrium or the substance with the organic matter is unlikely to be achieved. Nevertheless, organic matter can lead to an underestimation of the BCF by lowering the bioavailable fraction. Automated monitoring with SPME (solid-phase microextraction) can provide information on the dissolved (i.e. bioavailable) fraction of the substance (Böhm et al. 2016)

#### Bioaccumulation and biomagnification in non-aquatic food webs

Substances with a log Kow between 2 and 5 and high log Koa above 6 do not biomagnify in aquatic food webs but do biomagnify in terrestrial food webs due to low rate of respiratory elimination to air (Kelly et al. 2007). Subsequently, a model was developed (Armitage & Gobas 2007) for biomagnification of in the terrestrial food chain.

Also, a PBPK (physiologically based pharmacokinetic) modelling study suggests, that highly volatile substances lacking elimination mechanisms can bioaccumulate, also in blood tissues (Andersen et al. 2008).

As concluded in a review on bioaccumulation, terrestrial species lack the efficient elimination mechanism of water ventilation. Those substances will not be captured by the aquatic BCF, therefore taking also data on terrestrial organisms in account is needed (Goss et al. 2013). For the IT-mass screening and also for screening level indentification of terrestrial biomagnification, a Kow/Koa trigger has been implemented. However, there is no mandatory procedure nor criteria on assessment level, only weight of evidence can lead to a conclusion on bioaccumulation properties bases on the substances behaviour in the terrestrial food chain.

Experimental sediment bioaccumulation (i.e. OECD 315, biota-sediment accumulation factor, BSAF), soil bioaccumulation (i.e. OECD 317 biota-soil accumulation factor, BSAF) and field data on biomagnification is also discussed in the Guidance on IR&CSR. However, no direct criteria exist in Annex XIII which could be compared to the resulting endpoints, and as it is not possible to give any threshold values for BSAF, so that they have to be interpreted on a case by case basis. For hydrophobic substances, the BSAF is highly dependent on the organic carbon content of the soil, therefore it is usually normalized to the organic content of the soil. Generally the bioavailability of the substance decreases with increasing soil organic content (ECHA 2017).

Those studies become relevant when a fish bioaccumulation test is not available and when exposure from the sediment is likely to be relevant (ECHA 2017).

An approach of a common metric in order to compare BCF and BMF data is the elimination half-life, see section [1.6.2.9](#Ref482550219).

#### Cutoffs for bioaccumulation

According to the guidance, several indicators (i.e. average maximum diameter, maximum molecular length, log Kow, octanol solubility) can be used in a weight of evidence approach as indicators of a limited uptake. When this information is combined with “other information confirming the low uptake of the substance in living organisms e.g. by read-across with different substances, absence of toxicity of lack of uptake in toxicokinetic studies with animals or also other methods or biomimetic exposure” (ECHA 2017).

The Guidance on IR&CSR Chapter R.11 outlines the possibility of concluding a substance as not bioaccumlative if there is indication physicochemical indicators such as:

* Average maximum diameter > 17.4 A (i.e. hindered uptake due to molecular size)
* Log Kow > 10 (i.e. hindered uptake and distribution in general)
* Octanol solubility (mg/L) < 0.02 (mM) x molecular weight (g/mol)

Together with other indicators of uptake such as:

* No chronic toxicity for mammals and birds
* No uptake in mammalian toxicokinetic study
* Very low uptake after chronic exposure

It can be concluded that no bioaccumulation will occur and no generation of additional data is mandatory (ECHA 2017).

This approach has several shortcomings, which can lead to false negatives. There is very little data on chemicals with properties in those ranges. Experimental artefacts are known to lead to an underestimation of bioaccumulation for hydrophobic substances (Jonker & Van Der Heijden 2007; Muller & Nendza 2007). A study investigating possible cut-offs for bioconcentration concluded that the data allows no conclusion on the cut-offs. Further, highly hydrophobic substances with very low aqueous solubilites are difficult to test, and many reduced BCFs can be attributed to shortcomings in the interpretation of experimental results (Muller & Nendza 2007). A study investigating field bioaccumulation factors of several brominated flame retardants concluded a positive relationship of BAF with increasing log Kow (range: 5.07-7.8), indicating no reduced uptake (Wu et al. 2011). A study on partitioning of neutral organic compounds to membrane lipids did not observe a cutoff neither up to a mebrane-water partitioning coefficient of 7.8 (Endo et al. 2011).

Obtaining experimental BCFs for substances with a Kow > 7.8 is not possible at the moment. This analytical threshold has been increasing over the past year, and so were the assumed “bioaccumulation cutoffs”.

Care must be taken when interpreting different endpoints in a weight of evidence approach, which is to our opinion not sufficiently outlined in the guidance. If the same analytical challenge, e.g. slow but not missing uptake kinetics for large, highly hydrophobic molecules lead to the same systematic errors in the data. Considering different endpoints will not strengthen the hypothesis of a lack of bioaccumulation if both endpoints encounter the same problem of e.g. a slow uptake due to kinetic effects, which will not be observed within the time constraints of the tests. Two endpoints, which are potentially biased in the same way, should not be considered as supportive of each other.

#### High log Kow – bioaccumulation relationship

##### Experimental challenges

A recent publication on an approach (i.e. solid phase desorption system) of developing solutions for highly hydrophobic test substances showed that it was possible to test substances up to a log Kow of 7.8 for 8 weeks (Schlechtriem et al. 2016). According to the ECHA Guidance on IR&CSR Chapter R.11, for strongly hydrophobic substances (log Kow > 5 and water solubility below around 0.01-0.1 mg/L), testing via aqueous phase becomes increasingly difficult. The constraints are maintaining a stable concentration and the detection limit of the substance. Use of radiolabelled substance could improve the detection limit (ECHA 2017).

A dietary study such as OECD 305 III (dietary exposure bioaccumulation fish test) is considered appropriate, when maintaining a stable concentration during the test and the detection limit do not allow for aqueous phase testing. It is assumed that substances with high Koc will partition into organic matter and therefore rather be taken up with food. It is possible to translate data from dietary studies to a kinetic BCF in order to compare it with the Annex III criteria, however only the elimination rate constant can be directly derived from the study, therefore, it is recommended to use those studies only as a body of evidence. But the dietary exposure test delivers other valuable parameters such as the dietary chemical absorption efficiency and the whole body elimination rate constant (ECHA 2017).

A review study on further development of regulatory bioaccumulation criteria (Schlechtriem et al. 2015) also concludes, that for substances with a log Kow > 5 other than the aqueous bioconcentration test are suitable (i.e. biomagnification (BMF) through feeding). The revised OECD 305 guidance will offer this opportunity, however there is no threshold level for BMF criteria for identification of substances as B or vB in the Annex XIII.

Various models for estimation of the uptake rate constant were reviewed, as it would be very valuable in order to compare dietary fish bioaccumulation studies with the Annex XIII criteria of REACH. However, they came to the conclusion, that the accuracy of those models is not high enough (Schlechtriem et al. 2015).

Therefore, for substances with Kow > 5, it is difficult to identify them as bioaccumulative with the present Annex XIII criteria of REACH (but also other legislative frameworks relying on the same criterion).

Threshold values for BMF would overcome the problem with inducing uncertainties by estimating the uptake rate constant in order to calculate a kinetic BCF from the BMF data. It might be useful to derive separate numerical criteria for dietary studies using a set of reference chemicals with well known kinetic BCFs in a log Kow range, where both methods could be applied. However, data availability might be a constraint as well as the theoretical applicability of the threshold values for chemicals in a different Kow range than used for its derivation.

##### Challenges with estimation software

The BCFBAF module from EpiSuite software (US EPA 2012) (here shown for non-ionic substances) assumes a decreasing BCF with increasing log Kow for log Kow above 7, see [Figure 1](#Ref478395032). Note that the number of available datapoints is rapidly decreasing for very high log Kow (US EPA 2012).

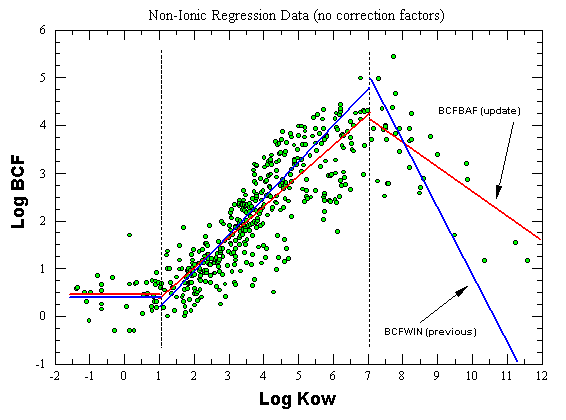


Figure 3 The training data set (green dots) and the relationships of the previous BCFWIN and the updated BCFBAF model, showing al linear increase of BCF with increasing log Kow until a log Kow of 7 followed by a decrease. However, there is very little data for substances above log Kow 7. From EPiSuite documentation (US EPA 2012)

A high Kow also implies slow uptake of the substance by the organism. Therefore, typical test durations might be too short for this class of substances, leading to lower BCF values (Mayer & Reichenberg 2006). As a consequence of the slow uptake, an acute toxicity test is not the appropriate way of describing the substances toxicity, as its duration is too short for the effects to become visible. The same mechanism might also lead to lower measured BCF values (Jonker & Van Der Heijden 2007). Also, data measured more recently indicate that there is no “hydrophobicity cutoff” (Endo et al. 2011).

#### Ionic substances

Based on an evaluation of preregistered chemicals it has been estimated that about 50 % of REACH chemicals on the market could be present in the environment in an ionized form (i.e. acids, bases or zwitterionics) (Franco et al. 2010). The simplest approach accounting for bioconcentration of ionic compounds is considers the fraction in the neutral form only (given by the substances pKa and environmental pH).

Attempts to mechanistically interpret bioconcentration of ionic compounds in their ionic for include *pH dependent absorption efficiency* at the respiratory surface, *membrane-water distribution ratios (i.e. phospho-lipids*) and *octanol-water distribution (i.e. neutral lipids) ratios* (Armitage et al. 2013).

An approach to account for ionic species is estimating membrane-water partitioning coefficients (i.e. phospholipids). Several studies mechanistically modelling interaction of ionic species with membrane phospholipids conclude, that ionic species seem to have a higher affinity for membrane phospholipids than for storage lipids (Armitage et al. 2013; Bittermann et al. 2014).

Besides phospholipids, also interactions with various proteins are possible as discussed for e.g. PFAA (Ng & Hungerbühler 2014).

As concluded by a reviewing study, todays scientific understanding of bioaccumulation of ionic compounds does not yet allow specific regulatory treatment of this class of substances (Goss et al. 2013).

Efforts have been made toward quantification and characterization of ionic species, however overall As summarized in a review study (Goss et al. 2013), four sorption mechanisms are identified:

* Sorption of free organic ions together with free counter ions
* Formation of ion-pairs and subsequent partitioning of the ion pair
* Sorption at an aqueous interface so that the ionic group stays fully immerged in water and only the non-ionic part of the molecule is attached to the interface
* Ion exchange

Theoretically, sorption of ions into storage lipids can occur by the first two processes, however it will be always smaller than partitioning of the neutral species and is therefore not likely to contribute significantly to the bioaccumulation of a chemical.

For **phospholipid partitioning**, indication exist that ions can sorb stronger than their corresponding neutral, however the authors conclude no validated model exists yet in order to predict the behaviour.

**Active transport** of ionic species through membranes is also shown to occur, however no quantitative methods are available yet.

**Proteins** can include positively and negatively side chains, making sorption (or covalent) binding to proteins more important for ionic species than for the neutral ones. However, protein interaction can be very complex and depending on a variety of factors. QSARs have been established in order to predict pharmaceutical interaction with blood serum proteins. Current knowledge is not sufficient to draw any conclusions for ion partitioning to structural proteins (Goss et al. 2013; Ng & Hungerbühler 2014; Endo et al. 2011).

Summarized it can be concluded: considering the neutral form (i.e. the fraction that will be present in the neutral form) will give some indication of the log Kow driven bioaccumulation which is todays state of the art of describing bioaccumulation which directly can be compared to the Annex XIII criteria. Due to the variety of possible target tissues other than storage lipids, normalization of BCFs to the corresponding target tissues as well as derivation of new threshold values for BCFs related to non-storage-lipid bioaccumulation might be necessary in order to correctly account for non-lipid bioaccumulation. Bioaccumuation related processes, which could be more relevant for the ionic species than for the neutral form are still not enough understood in order to derive quantitative criteria.

#### Organ- and tissue-specific accumulation

A class of substances which received a lot of scientific attention during the past years are perfluorinated alkyl acids (PFAAs). Reviewing various data sources and modelling approaches, it has been shown that there is a big variation in the reported elimination half-lives between genders and species. The authors conclude after reviewing several studies, that the observed bioaccumulation patterns have to be explained with phospholipid but also protein interaction. Further, accumulation of PFAAs occurs preferably also in specific organs and tissues (Ng & Hungerbühler 2014).

Therefore, applying a traditional approach of normalization to the lipid content of an organism might not be suitable, as the target tissue for bioaccumulation might vary not only with the substance but also with the target species. Given the variability of potential bioaccumulation mechanism of the ionic substances (or the ionic form of a substance), it might be useful, to develop a separate bioaccumulation framework (with the pKa as a trigger value for generating entering this path).

One approach could be the focus on molecular interactions, as shown for PFAAs in a explorative study (Ng & Hungerbuehler 2015). A review of models used for computer aided drug design that aim to describe molecular interactions between drugs and receptor molecules might be one approach dealing with the variability of possible interaction pathways which lead to organ- and tissue-specific accumulation. Defining standards such as target tissues and/or species for regulatory purposes will be one big challenge regarding the variety of possible bioaccumulation mechanisms.

##### Use of PBTK-Models

Another study (Schlechtriem et al. 2015) used a “Physiologically based Toxicokinetic Model” (PBTK-model) in for modelling lipid-based bioconcentration factors. This model describes an organism, accounting for different organs as different compartments and different uptake regimes. The model describes lipid-based bioaccumulation. The model has been validated and seems to predict BCF and kinetic uptake and elimination rates for rainbow trout quite well for substances with a log Kow > 0. The authors propose using modelled BCF, BAF, kinetic uptake or elimination rate constants and compare them with measured data (i.e. OECD 305 test) in order to assess whether also non-lipid bioconcentration could be important. If the experimental and modelled values are in the same range, the bioconcentration can be concluded to be lipid-driven, if not, further testing might be required. The authors also point out, that a future challenge will be bioaccumulation of polar substances (Schlechtriem et al. 2015).

The approach is useful for assessing organ specific bioaccumulation and for a first indication of whether lipid-driven or other mechanisms led to the resulting experimental BCF. However, need for high quality experimental data limits the use of the model for regulatory purposes at the present stage.

##### Interactions with proteins

The general conclusion is that interactions with proteins are potentially important for ionic species (and for neutral maybe as well), but it is not yet possible to derive criteria for regulatory purposes (Goss et al. 2013; Schlechtriem et al. 2015).

A study measuring partitioning of neutral organic compound to structural proteins (i.e. muscle protein, collagen, gelatin) concluded that it occurred less than it was the case for bovine serum albumin, which is frequently studied. The authors present also correlations with Kow and poly-parameter linear free energy relationships, however indicate that further research on ionic compounds is needed (Endo et al. 2012)

Another explored the approach of molecular docking (i.e. modelling the interaction of the substance and the protein given its 3D-configuration). The method was illustrated with perfluorinated alkyl acids. The authors conclude, that there is a variety of possible protein that can interact with substances and thus affect its fate, however data for validation of such approaches is still limited in order to develop a screening tool (Ng & Hungerbuehler 2015).

##### Interactions with phospholipids

Phospholipids have been target tissues for research of partitioning of neutral as well as ionic compounds.

Membrane phospholipids exhibit different partitioning properties for a variety of substances than storage lipids. Recent experimental data and ppLFER-models for neutral organic compounds indicate a higher affintity of H-bond donor compounds to membrane lipids than to storage lipids. Given that normalization is ususally done to a total lipid content (Endo et al. 2011)

The membrane-water partition coefficient correlates with the log Kow for neutral organic compounds (Endo et al. 2011), but it does not for ionic species. Therefore, a mechanistic model such as proposed by ref (Bittermann et al. 2014) could better describe the relevant interactions. For hydrophobic ionogenic compounds, affinity of membrane phospholipids exceeds the affinity or storage lipids (Escher et al. 2000).

#### Elimination half-life as an alternative bioaccumulation metric

A study on the enhancement of criteria for bioaccumulation proposed the elimination half-life of a chemical as an alternative to the bioconcentration factor. The authors stress the ability of the organism to recover from a contamination as the primary protection goal, which is directly addressed by the elimination half-life but not by the biomagnification factor (BMF), because if a small elimination rate occurs with a small dietary uptake rate, it can still result in a BMF < 1. The advantage of the elimination half-life is also, that it does not depend on the uptake route. First illustrative calculations are shown, the authors conclude that deriving threshold values for regulatory purposes is still a pending task. Assuming 100% uptake efficiency, an elimination half-life of 70 days is derived meeting the criterion of BMF < 1. Taking some generic assumptions, recalculation of the elimination threshold value back to Kow/Koa criteria can be done. The threshold values vary considerably for water breading (log Kow < 6 for an elimination half-life < 70 d) and air breading organisms (log Kow < 1.3 and log Koa < 5.5 for an elimination half-life < 70 d). The authors explain the difference with the lack of an efficient elimination route for terrestrial organisms, such as the water ventilation (Goss et al. 2013).

### Conclusion on bioaccumulation assessment

There are **no threshold values** **for non-lipid bioaccumulation** or bioaccumulation in **non-aquatic organisms**.

For bioaccumulation, neither on screening nor on assessment level, criteria exist that could help identify substances suspected to undergo **non-lipid bioaccumulation**. The underlying mechanisms and binding affinities should be further investigated in order to derive criteria for regulatory purposes. The detection of a substance far away from sources and in vulnerable populations might be an evidence for bioaccumulative behaviour, however, this is to be avoided. Pharmacokinetic models used for computer aided drug design could maybe be evaluated and adapted for their use in a screening level assessment of protein bioaccumulation. In this context, the role of ionic substances is important, especially possible interactions of the ionic form, for which further research is needed for regulatory purposes.

As reviewed, the only test for the **terrestrial compartment** with air breathing animal is the OECD 317 test on oligochaetes (Treu et al. 2015). However, in this test dietary and uptake from the environment cannot be distinguished and the derived BSAF will depend on the organic carbon fraction of the soil (ECHA 2017). There are also no threshold values for dietary studies in general. A solution could be the approach of deriving an elimination rate constant threshold values, which would be applicable to a variety of uptake pathways, it will still face the challenges of determining the bioavailable fraction of the substance and the uptake efficiency depending on the test setup and environment.

An **elimination half-live approach** could serve as a useful tool in order to compare results from BCF and BMF studies, but further validation is needed (Goss et al. 2013)

The proposed **cut-offs (e.g. molecular dimensions, hydrophobicity**) for bioaccumulation are not statistically supported by data, as substances with those properties pose major analytical challenges. A detailed mechanistic understanding of all the relevant uptake, storage and elimination mechanisms for different substance classes would help identify possible cutoff-values, however present state-of-the-art science does not yet allow for it. Substances exhibiting properties beyond the analytical capabilities presently pose a challenge, as theoretical assumptions cannot be validated. As a hazard cannot be excluded, we recommend a conservative approach avoiding release of such substances to the environment.

Although for chemicals with low water solubility, testing in an aqueous environment might be challenging, introducing organic matter to the system will reduce its **bioavailability** as shown in an aquatic environment (Böhm et al. 2016). In order to assess bioaccumulation in a proper way, it is important, that the bioavailable fraction of the chemical is reported, otherwise bioaccumulation might be underestimated. SPME tools have shown to be useful for aqueous BCF fish studies. For BMF and BSAF studies in soil and sediment the issue is more complex. To our knowledge, no tools are available in order to assess the bioavailable fraction in those compartments. Neither can the derived values be compared to the present bioaccumulation criterion of Annex XIII, i.e. the bioconcentration factor for aquatic species. The Annex XIII allows for the use of such studies (according to section 3.2.2) and they are also listed Guidance on IR&CSR Chapter R.11. However, it is still not clearly defined under which circumstances the tests are to be performed (instead of an BCF) and how the results should be interpreted. Also, no guidance on how to quantify the **bioavailable fraction** is given. This might be a difficult issue, comparable to the non-extractable residues in persistence assessment, but with a different implication. When bioaccumulation is assessed, overestimating the bioavailable fraction will underestimate bioaccumulation potential, whereas with persistence it is the other way around. Defining a protective worst case scenario is therefore much more difficult, and not differentiating between the bioavailable and bound fraction will lead to false negatives.

For persistent substances with a Kow > 7.8 where BCF studies become technically unfeasible, bioaccumulation still cannot be excluded (Muller & Nendza 2007; Jonker & Van Der Heijden 2007). Further, due to slow kinetic, effects might not be captured within the time resolution of the tests (Mayer & Reichenberg 2006).

## Toxicity: State of the Art and Challenges

Given that the main concern of PBT/vPvB substances is that no safe environmental concentration exists and effects may occur temporally and locally far away from the source, adding a criterion for toxicity does contradict the concept. The toxicity criterion does imply a “safe level” indeed, e.g. a NOEC threshold of 0.01 mg/L, implying that no organism will ever be exposed to levels of a substance, where effects become evident. The combination of P and B properties will potentially lead increasing levels in organisms over its life if exposure continues; therefore, no safe levels can be derived.

Several endpoints that are considered for T identification in Annex XIII Section 3.2.3. (d) are assessed as outlined in the CLP Regulation. The concern with PBT/vPvB substances is that be persistence and bioaccumulation can lead to effects only observed in the long-term, possibly affecting long-living species exhibiting exposure for their lifetime, leading to an unpredictable rise in the organisms concentration if there is no elimination pathway. Therefore, the long-term toxicity tests on invertebrates, fish and growth inhibition on aquatic plants might not be sufficient to capture the hazard. Given that persistence and bioaccumulation potentially leads to a rise of levels of the substance that can cause effects. This is already taken into account with the vPvB – concept.

Besides the long-term rise of concentration due to accumulation, there is also a general analytical challenge: A high Kow also implies slow uptake of the substance by the organism. PB-substances are expected to have a high Kow. Therefore, typical test durations might be too short depicting the behavior of this class of substances (Mayer & Reichenberg 2006; Jonker & Van Der Heijden 2007).

Nonpolar chemicals with a log Kow > 4 are likely to exhibit baseline toxicity. Baseline toxicity is a consequence of the substances hydrophobicity and tendency to partition into membranes. LC50 data for fathead minnow was used together with the substances log Kow. The threshold value for LC50 of 1 mg/L was translated into mmol/L using an empirically derived relation between log Kow and molecular mass. Then, a relationship between the LC50 (in mmol/L) and log Kow for chemical known to act by narcosis derived. The intersection of the threshold of LC50 of 1 mg/L and line of “narcotic action” was at log Kow 4. About 800 Substances in a log Kow range of -0.5 and 7.5 were considered. Detailed calculations are shown in the publications supporting information (Maeder et al. 2004). This shows that substances with a tendency to bioaccumulate already exhibit baseline toxicity, making an additional criterion for toxicity obsolete. The relevance of toxicity is given without a substances persistent or bioaccumulative properties, and can be assessed in a PEC/PNEC-approach, also chronic toxicity where long-term exposure is expected.

## Evaluation of substances – case study

Each year, substances listed in the community rolling action plan (CoRAP), which can be evaluated by the member states are updated. The outcome of IT-mass screening plays a crucial role for the selection of the substances for evaluation. Substance evaluation is performed in order to clarify whether the substance poses a risk to human health or the environment. We present two examples, that illustrate the process of decision on PBT/vPvB properties, when registrants and authorities disagree, the data is not clear cut or there are no analytical possibilities to assess the properties needed.

### Case study - DBDPE

DBDPE (1,1’-(ethane-l,2-diyl)bis[pentabromobenzene], CAS 84852-53-9) was included in the Commu-nity rolling action plan (CoRAP) for substance evaluation on the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to unclear bioaccumulation potential and possibility of PBT/vPvB transformation products. The competent authority of United Kingdom was appointed to carry out the evaluation in 2012.

During evaluation, additional concerns arose: endocrine disruption effects, concerns about the reliability of aquatic toxicity studies in the registration dossiers as other published studies suggested effects in fish and aquatic invertebrates. The BCF study was performed at concentrations above water solubility,using as inappropriate method and too few fish. DBPE was found in the environment in organisms at low concentrations. A review of the compositional data provided by the registrants revealed that the level of brominated diphenyl ethane congeners present as impurities (which, by analogy with polybromodiphenyl ethers, might have PBT properties) in some commercial products was higher than expected. For this reasons, 22.5.2014 a decision on requesting further data in order to clarify the properties was made. On 22.8.2014, an appeal was launched by the registrants requiring to annul the decision on requesting further data. Discussions arose about the structural similarity with decaBDE, whether if it is a contradiction to demand “the purest form of the substance” while requiring to radiolabel the substance for testing. The appeal was mostly dismissed, the registrants have to provide the necessary information until January 2019. Registration of the substance was first published in February 2011, for 10 000-100 000 t/a.

There is an incentive to provide less information than required if a potentially profitable substance (e.g. a major substitute for an already widely used substance as it is the case here) is suspected to have adverse effects on the environment, as can be shown in the present case, as substance can still be marketed for at least 8 years without any restrictions.

### Case study - Dechlorane Plus

For Dechlorane Plus (13560-89-9), no Kow is reported (data waiving), the substance is considered “unsoluble” (ECHA). The log Kow predicted by EPISuite (US EPA 2012) is 11.27. The substance is potentially persistent. There is a lack of analytical tools in order to assess the substances properties needed for PBT/vPvB assessment. Further, the substance has been included in ChemSec’s SIN List[[4]](#footnote-4) because it has been detected in environmental and human samples and estimated and experimental data show P, B and T properties. The discussion went on for a few years, the Environmental Agency of UK has concluded that the chemical is vPvB, however the Hazardous Substances Advisory Committee (HSAC) pointed out that the evidence for bioaccumulation is not so clear cut[[5]](#footnote-5). The substance was first registered 25. Juni 2013. Since April 2017, the substance is handled “as if it is a PBT”, as the manufacturer accepted to do so. Finally, an autonomous expert panel concluded on vPvB properties of the substance in a weight of evidence approach.

The agreement of the manufacturer on handling the substance as if it is a PBT finally led to a conclusion. However, this example shows the difficulty of assessing a substances PBT/vPvB properties having neither the analytical tools nor clear guidance on how to proceed in such a case.

### Conclusion

As illustrated by the two case studies, requesting further information during substance evaluation (i.e. when there is an indication that the substance might exhibit PBT/vPvB properties) can be a very time consuming process, leading to an unnecessary delay of restricting use of potentially hazardous substances.

According to the guidance (ECHA 2017), first P is assessed, than B, than T. This is in order to avoid unnecessary consumption of animals. For substances where the initially submitted dossier did not clarify the PBT/vPvB properties sufficiently, this leads also to very long timespans until a final conclusion on the properties can be reached: For each requested test, the registrants are provided a certain time to deliver the data. Sequential performance of several simulation studies (18 months for each) has also been observed.

In order to avoid or minimize release of potentially hazardous substances to the environment, the timespan a substance can remain on the market even though not all hazards have been clarified has to be controllable. This is illustrated by the DBDPE case study, where the process of requesting information can last several years for high-tonnage substances with potentially considerable release to the environment if registrants appeal against the decision of requesting information.

Also, the competent authority carrying out the evaluation of the substance on behalf of the member state committee is meeting the challenge of requesting the lowest amount of data but still enough for a sound assessment. Requesting more data leads to a longer timespan until risk management options can be faced.

In order to create in incentive for submission of compliant dossiers and avoiding time consuming legal cases, a maximum timespan of 2 years starting with the first information request by the competent authorities, in order to deliver all the requested information was proposed. In cases where the clarification of potential hazards takes longer or the registrants appeal against the decision, the registration will “freeze”, i.e. placement of the substance on the market will only be possible after the required information is provided.

# WP4: Proposals for further development of the PBT concept

Based on the findings of WP3 and scientific literature, the main task for WP4 was “closing” the gaps identified in WP3 by proposing amendments or adjustments where possible and identifying needs for further research.

## Summary

**Long range transport** is a persistence-related **mobility** metric which refers to mobile environmental phases like water and air. It is a combination of a substance’s partitioning behaviour, persistence and emissions target compartment. Measures preventing release are desirable for substances that are persistent and mobile, as an uncontrollable widespread pollution might threaten vulnerable and pristine ecosystems not represented by the common testing procedure.

Another concern besides persistence could arise from a **continuous presence** of a substance. When **monitoring data** is used as an evidence for persistence. However, this is not an intrinsic property that can be assessed in a preventive approach. Considering the threat of “continuous presence” on a smaller local scale as similar to “persistence” on a wide scale could nevertheless be a trigger for allowing for a re-evaluation of the substances properties and possibly helping identify emerging pollutants which have not been identified by the present assessment scheme. Inducing the continuous presence of a substance as a legally accepted concern and trigger for preventive measures would give more weight to monitoring data with the potential of using non-target monitoring studies for identification of emerging pollutants with novel properties that are not captures by present hazard assessment schemes, even before the substances reach remote pristine areas, which is a prerequisite for use of monitoring data as indication of persistence at present (ECHA 2017).

Different approaches of **accounting for other forms bioaccumulation than only storage lipids** such as bioaccumulation in non-aquatic organisms and bioaccumulation in other tissues then storage lipids (i.e. membrane phospholipids, proteins) is an ongoing research topic. At present, derivation of quantitative criteria on the assessment level based on the scientific knowledge is not possible yet, but different approaches exist that need to be validated.

Further research into interspecies-variability and factors driving dietary uptake, storage and elimination rate constants is highly desirable. Terrestrial bioaccumulation is driven by different uptake and elimination mechanisms than bioaccumulation in aquatic phases.

In the future, following additional testing could be possibly implemented in order to assess non-lipid non-aquatic bioaccumulation:

* experimental determination liposome-water partitioning coefficients
* modelled protein-ligand interactions
* measured elimination rate constants in terrestrial organisms if the trigger for possible terrestrial bioaccumulation is passed
* ppLFER approaches for obtaining log Kow

Another question however is, whether accumulation in functional tissues such as proteins and phospholipid membranes is a **bioaccumulation concern or rather of toxicological concern.** It might also be assessed outside of the PBT/vPvB assessment in a toxicological context, i.e. by deriving trigger values for chronic toxicity assessment which would also apply to substances which are not persistent in the environment according to the PBT/vPvB criteria.

Given that the main concern of PBT/vPvB substances is that no safe environmental concentration exists and effects may occur temporally and locally far away from the source, adding an additional criterion for toxicity does contradict the concept. The **combination of P and B properties will in any case lead increasing levels in organisms over its life if exposure continues**; therefore, no safe levels can be derived. However, besides PBT/vPvB assessment toxicity has its crucial importance (i.e. in risk assessment).

We propose a new category of **“potentially hazardous”** substances. The aim is to develop a priority list of substances whose properties might not be yet assessed as PBT/vPvB due to lack of conceptual understanding and analytical tools. Focus would be on substances that are **persistent but not bioaccumulative**. In order to have a first indication on possible bioaccumulation, applying a set or rather conservative trigger values based on already available data and to some extend new/adapted QSARs that indicate bioaccumulation in non-aquatic systems, phospholipids or proteins and allow authorities to request data beyond standard information requirements if considered necessary. However, at present, criteria are only available for terrestrial bioaccumulation in terms of Koa/Kow. Ionic speciation at environmental pH could be used a generic indication for possible phospholipid or protein interaction, but might lead to several false positive. Some measures in order to minimize release of persistent substances should be possible, as determination of bioaccumulation is not straightforward.

The overall concept of moving away from an additional toxicity criterion but additionally accounting for mobility is presented in [Figure 3](#Ref482692268) below. Adding the possibility of a broader definition of persistence in terms of continuous presence and bioaccumulation in terms of potential bioaccumulation accounts for the possibility of substances exhibiting P and B behavior in the environment, but lack of analytical or conceptual understanding in order to assess them as P or B in the first place.

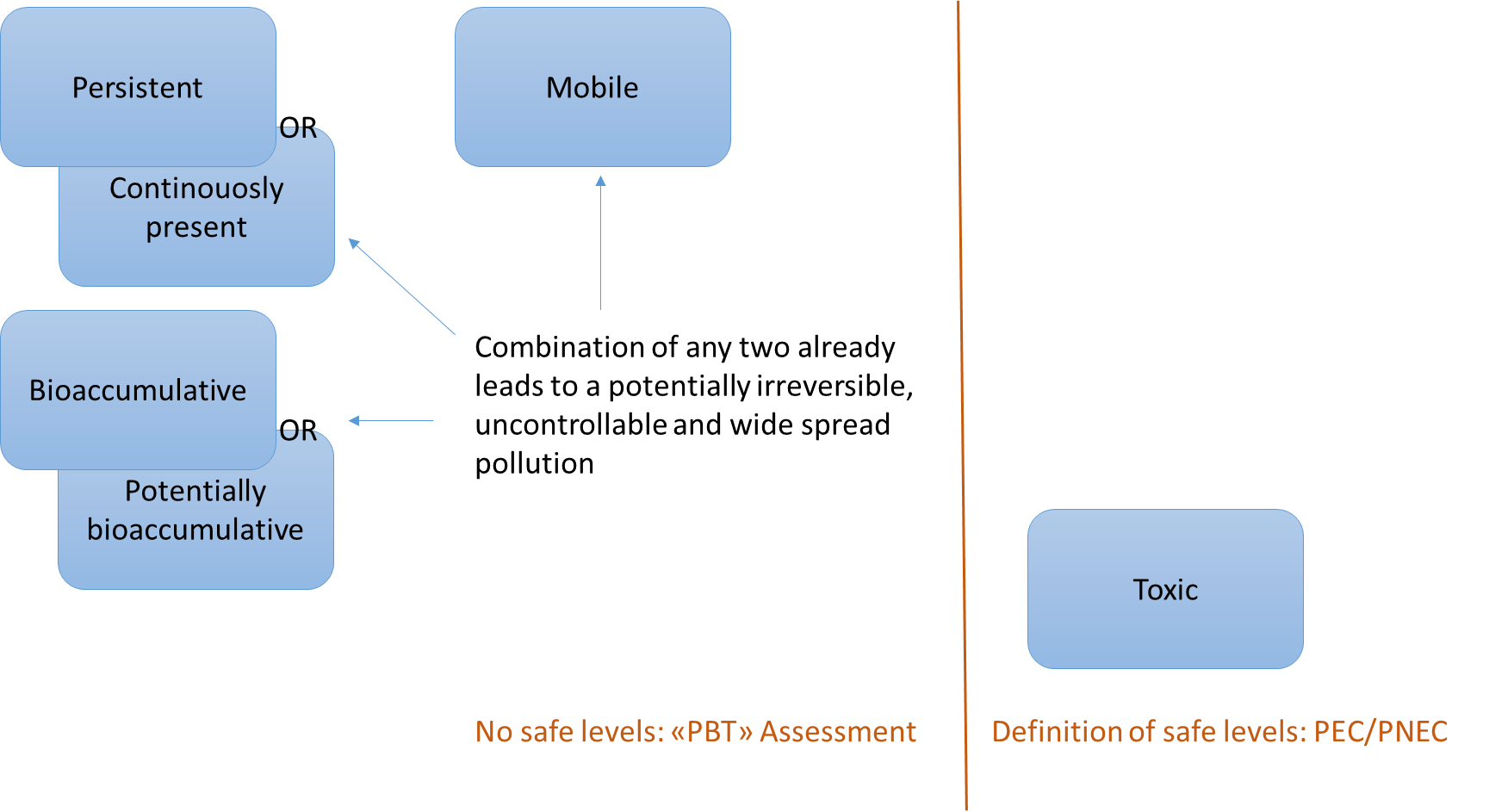


Figure 5: Generic outline of a future «PBT» or «potentially hazardous» substances assessment. The toxicity criterion is considered separately, as per se of concern. Concern for PBT substances arises due to a substances intrinsic properties allowing the spread over long distances, accumulation in organisms and persistence in ecosystems.

## Enhancement of identification of identification of PBT substances

* + 1. **IT-mass screening for P and proposed enhancement**

The following criteria for persistence within the screening for potentially persistent substances include the following (ECHA 2016b):

1. Registrant declares substance P or vP
2. Experimental Data (ready biodegradation)
   1. Not ready biodegradable or at least one water/sediment/soil endpoint meets half-life criteria of Annex XIII REACH
   2. Highest reported value of biodegradation among studies reported in registration dossier is <60%
   3. Lowest percentage of biodegradation is <60% (taking into account only measurements after 21 days) and the highest is above 60% (regardless of time).
3. BIOWIN model predicts potential P/vP properties (interpretation outlined in Guidance on IR&CSR Chapter R.11)

Existing criteria focus on single reported values, considering only screening level information. We propose including also simple checks whether the chosen tests for (e.g. for ready biodegradability) are suitable for the substance in question. Trigger values could include ranges of Koc (or Kow) (describing sorptive behaviour), Henry’s law constant (describing volatility) and water solubility.

Besides the already used BIOWIN model, the EPISuite Package offers two more models related to persistence:

* A first indication of whether a substance might be persistent in air and therefore prone to long range transport could be estimated with AOPWIN, i.e. the half-life of the substance in air considering reactions with OH radicals and Ozone.
* BIOWIN predictions for ranges degradation half-lives in the different compartments could also be used together with the OECD Pov and LRTP Screening tool (<http://www.oecd.org/exposure/povlrtp>) for a screening on persistence as a function not only of the degradation rates but also its partitioning behaviour. Further, this tool could be also used in order to check whether the appropriate compartment for the biodegradation simulation study was chosen, as the fraction of the substances depending on the compartment the emissions occur to can be calculated.
  + 1. **IT-mass screening for B and proposed enhancement**

The IT-mass screening criteria for bioaccumulation are indicated below(ECHA 2016b):

1. Kow: 3 < logKow < 7
2. Koa: recognized as indicator of bioaccumulation for terrestrial organizms not required reporting under REACH.
3. Estimated from Kow and H (Henry’s law constant)
4. If parameters in a.) not available: water solubility, vapor pressure, molecular weight.
5. If parameters in b.) not available: H estimated from HENRYWIN

KOAWIN estimation: estimated log Koa >= 5 (because inherent capacity to biomagnify in food webs) AND at least one reported log Kow >= 2 (because < 2 eliminated by urinary excretion, do not bioaccumulate even if Koa high)

1. BCF, BAF, BSAF, BMF, TMF

Indication of biaccumulation potential: (BCF, BAF, BSAF > 1000) because some fish-BCF are not interpreted correctly in the report (e.g. not lipid-normalized)

1. BMF or TMF reported

In addition, we propose where possible to investigate correlations of endpoints such as BCF and log Kow in order to check the plausibility of the value. Further, in order to check whether the bioavailable concentration was reported for the experimental BCF, it could be compared to the water solubility. Thermodynamically related values such as Kow, Koa and H could be checked for consistency. For known substance classes, correlations of molecular mass and Kow could also offer a possibility for assessing quality of the reported Kow.

* + 1. **Monitoring data**

In a weight of evidence approach, monitoring data can already be used as an indication for PBT properties of a substance, given the substance is found in remote areas. Traditionally, only data from remote regions is considered suitable in order to give an indication for P. However, reaching remote regions also implies partitioning into a mobile phase and transport (and not only persistence), which will not the case for all potentially persistent substances (i.e. substances being persistent in soils and sediments).

Considering also substances, which are found in the environment in urbanized areas and are continuously present might also pose a risk as effect could arise as a consequence of long-term continuous exposure, nevertheless the substance might not meet the “traditional” P criteria.

Besides the emission-related continuous presence, presence in the environment could also be a consequence of overlooked inherent (i.e. “traditional”) persistence of a substance. Therefore, presence of a substance in the environment can be considered as a trigger for further assessment.

Identification of substances based on its presence in the environment should be understood as a “second choice” option, where identification has failed in the first place. Given the possible hazard resulting from continuous exposure, continuous presence of a substance can be a trigger for regulating its discharge or certain usage pattern, even if the substance does not fulfil the persistence criteria outlined in the PBT concept. But considering “continuous presence” as well will give the opportunity to make use of much more already available monitoring data for prioritizing substances of further assessment.

By analysing results from non-target screenings, substances could be identified which pass the persistence criteria as non-persistent, but are ubiquitously found or continuously present in compartments where they potentially can cause harm due to long-term exposure. A re-assessment of their PBT/vPvB properties in such a case could also be an option, as its presence could not only be due to continuous discharge but also due to overlooked intrinsic substance persistence.

Continuous presence, as observed by monitoring, could be a trigger for considering measures reducing discharge of some human medicines, where PBT status has no consequences on the substances use.

## Challenging substance classes

### Substances with very low bioavailability

Substances with limited water solubility and substances with a tendency to sorb to environmental matrices or test vessels have been identified as challenging substances for P as well as for B assessment. The difficulties associated to P assessment will rather lead to false positives. The uptake into microorganisms might be slowed down or hindered within the boundaries of the test setup, leading to a reduced observed biodegradation then theoretically possible under environmental conditions. For B assessment, for the same reasons the opposite will be the case, i.e. the test will rather lead to false negatives.

Only the dissolved fraction of the substance is available for uptake in the BCF test, but dissolution kinetics is slow and the substance might also sorb to the test vessels. This might lead to an underestimation of the BCF within the test setup (Jonker & Van Der Heijden 2007). Improved analytical procedures for poorly water soluble substances exist, allowing determination of the freely dissolved fraction (Schlechtriem et al. 2016). Therefore, for substances with limited water solubility and high tendency to sorb, we recommend establishing a mandatory testing strategy for bioaccumulation that accounts for its analytical difficulties, such as e.g. *mandatory reporting* of freely dissolved fraction or radiolabelling the substance in order to increase the limit of detection in BCF studies. The trigger could be set at a certain water solubility, and also implemented into the IT-mass screening for identification of potentially biased BCF studies.

The terms “poorly water soluble” and “highly sorptive” are sometimes used interchangeably, which makes sense considering neutral, hydrophic substances. However, the term “highly sorptive” could be better defined, depending on the context, maybe even for different molecular interactions: As for e.g. NER “sorption” may not only include Koc/Kow driven sorption but also ionic interactions or covalent bonding. Deriving trigger values considering physico-chemical properties related to water solubility and sorption could help choose the appropriate testing regimes and identify possible uncertainties (e.g. loss of substance due to sorption, reduced bioavailability due to limited solubility).

### Evaluation of tools and approaches from research on pharmaceuticals.

As outlined also by (Muller & Nendza 2007), substances that would make bad oral drugs because of low solubility and slow adsorption kinetics, can be very bioaccumulative environmental contaminants. An evaluation of models used for computer aided drug design might be a first step towards identifying other interactions than lipid partitioning or assessing potential elimination kinetics. Generation of data for validation of the model results will be necessary. First attempts of modelling interactions with proteins show there is a potential but also considerable effort involved in application of those models for regulatory purposes (Ng & Hungerbühler 2014).

In the future, this might result in a screening tool that identifies chemical structures likely to interact with a set of proteins, which are defined to be relevant.

### Dealing with substances “conceptually” not covered by present PBT/vPvB

Including a **measure of suitability** of the commonly used testing approaches regarding PBT assessment for different substance classes might help prioritize the ones that need special attention and develop methods of addressing potentially new pathways. This measure could be based on a “**proximity**” of commonly measured physico-chemical properties, structural features etc. for the substances it was developed for and commonly used, to the physico-chemical properties of the substance in question. A concept for “proximity” is still to be developed and validated.

The **uncertainty of the “PBT-ness”** of a substance might also be used in order to prioritize substances for monitoring, for the case they behave as PBTs but their properties might not be captured by commonly used approaches. In this context, it could be also useful deriving a **category of “potentially hazardous” substances**, having properties where there is a lack of knowledge about their behaviour in the environment. An example would be superhydrophobic substances, where the analytical possibilities are limited and clear conclusion on PBT is not possible due to analytical challenges. Also, “continuously present” substances identified by non-target screening could be termed potentially “P”. This also leads to leads to a lack of quality data for establishing and validating QSARs. Precautionary measures should be taken avoiding the release of those substances to the environment, as they are potentially not only P or B but a combination of those. Even though uptake might be limited or slow, so will be the case for elimination, which leads to a potential for bioaccumulation, especially if an uptake pathway is overlooked by standard testing procedures.

As summarized in a recent review, bioaccumulation is not fully understood where it goes beyond lipid-driven bioaccumulation for neutral organic chemicals, e.g. protein sorption or bioaccumulation of polar substances (Schlechtriem et al. 2015). Neither regulatory criteria can be derived yet, nor a reliable set of properties or standard analytical procedures for identification. We propose developing a group of **“P and potentially B”** substances, defining protective trigger values where available such as ionic speciation at environmental pH, log Koa/Kow trigger for terrestrial bioaccumulation, known experimental difficulties with BCF studies (i.e. log Kow > 7.8). Preventive measures limiting release as well as putting those substances on a “watch-list” for monitoring could be possible.

Besides the combination of persistence and bioaccumulation, also the combination **persistence and mobility** is of concern. A wide spread distribution of a chemical can lead to unpredictable effects in sensitive environments far away from sources, leading to an irreversible and widespread pollution. Discharge of mobile substances into mobile compartments is to be avoided.

Historically, the PBT criteria have been developed based on a set of reference chemicals, i.e. neutral hydrophobic. Today, new chemicals with different properties could be grouped into different sets of reference chemicals, and their behaviour in the environment is still largely unknown. Among them are perfluoroalkyl substances, cyclic volatile methyl siloxanes and ionisable organic compounds. In order to refine or update the PBT criteria however, from a today’s point of view, deeper understanding of the relevant pathways and more data on emerging contaminants is needed, in order to adjust numerical values and/or propose or develop new testing regimes (Matthies et al. 2016).

Generally, there is more data available for pharmaceuticals, biocides and veterinary chemicals as for chemicals regulated under REACH (Rauert et al. 2014). However, many of those are ionic substances, for which the understanding of sorption, degradation, bioaccumulation and toxicity is less developed than for neutral organic chemicals (Matthies et al. 2016). Therefore, even though enough data is available, other endpoints and maybe even numerical criteria might be necessary in order to depict PBT behaviour of ionic substances (e.g. ionic interactions with functional biomolecules such as proteins or DNA).

### Dealing with analytically difficult substances

Besides substances with potential bioaccumulation patterns that are unknown, there are the classical neutral hydrophobics with extreme properties, where measuring the Kow, and BCF becomes analytically impossible. Regulatory treatment of such substances is not straightforward. Cut-offs were proposed, assuming limited uptake at a certain Kow, but as the analytical techniques progressed, the cut-offs were progressing as well, towards a higher Kow (Muller & Nendza 2007). Choosing a preventive approach in order to avoid release of potentially persistent and highly bioaccumulative substances, the proposed physicochemical indicators (ECHA 2017) for hindered should be considered with care, as they lack scientific support (i.e neither uptake nor lack of uptake can be demonstrated as analytical methods for substances exhibiting such extreme properties are no available yet).

## Process efficiency and harmonization

### Identification of substances

A lot more testing approaches are described in ECHAs guidance document then Annex XIII offers direct criteria for. Additionally, on screening level, Koa is considered in the draft guidance in order to account for terrestrial bioaccumulation, but there is no criteria on assessment level neither a developed standardized procedure for follow up assessment. The assessment is stopping at a dead end. There is a need for assessment level criteria on terrestrial bioaccumulation for substances which do not show bioaccumulation in the aquatic systems. However, no methods or criteria are elaborated yet for regulatory use.

According to the IT-mass screening criteria, substances will be selected according to much more preventive criteria than screening level criteria. However, they will be disregarded for further evaluation right after, as they do not meet the screening criteria. From a process efficiency view it would be beneficial to avoid such obvious false positives and focus on identification of possible measurement errors (e.g. by screening for substance with properties that pose analytical difficulties or applying QSARs in order to compare the experimental value) and wrong conclusions.

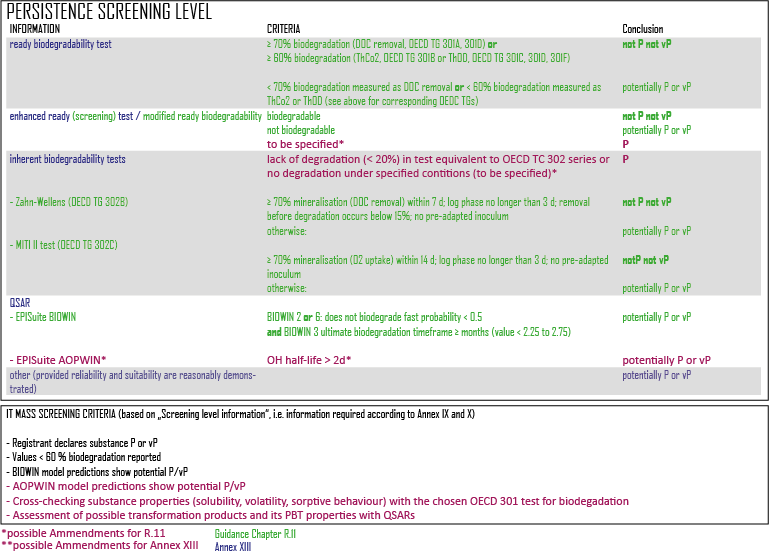
Flexibility for identification of PBT substances such as the weight of evidence approach which is allowed by the Annex XIII is beneficial for the identification of substances, which show PBT behaviour but are not captured by the criteria. However, there is little incentive for the registrants to do a time consuming comprehensive research on alternative PBT-properties that go beyond the standard information requirements. On the other hand, where non-appropriate non-standardized methods are applied, a case-by-case discussion without clear set criteria can be very time-consuming.

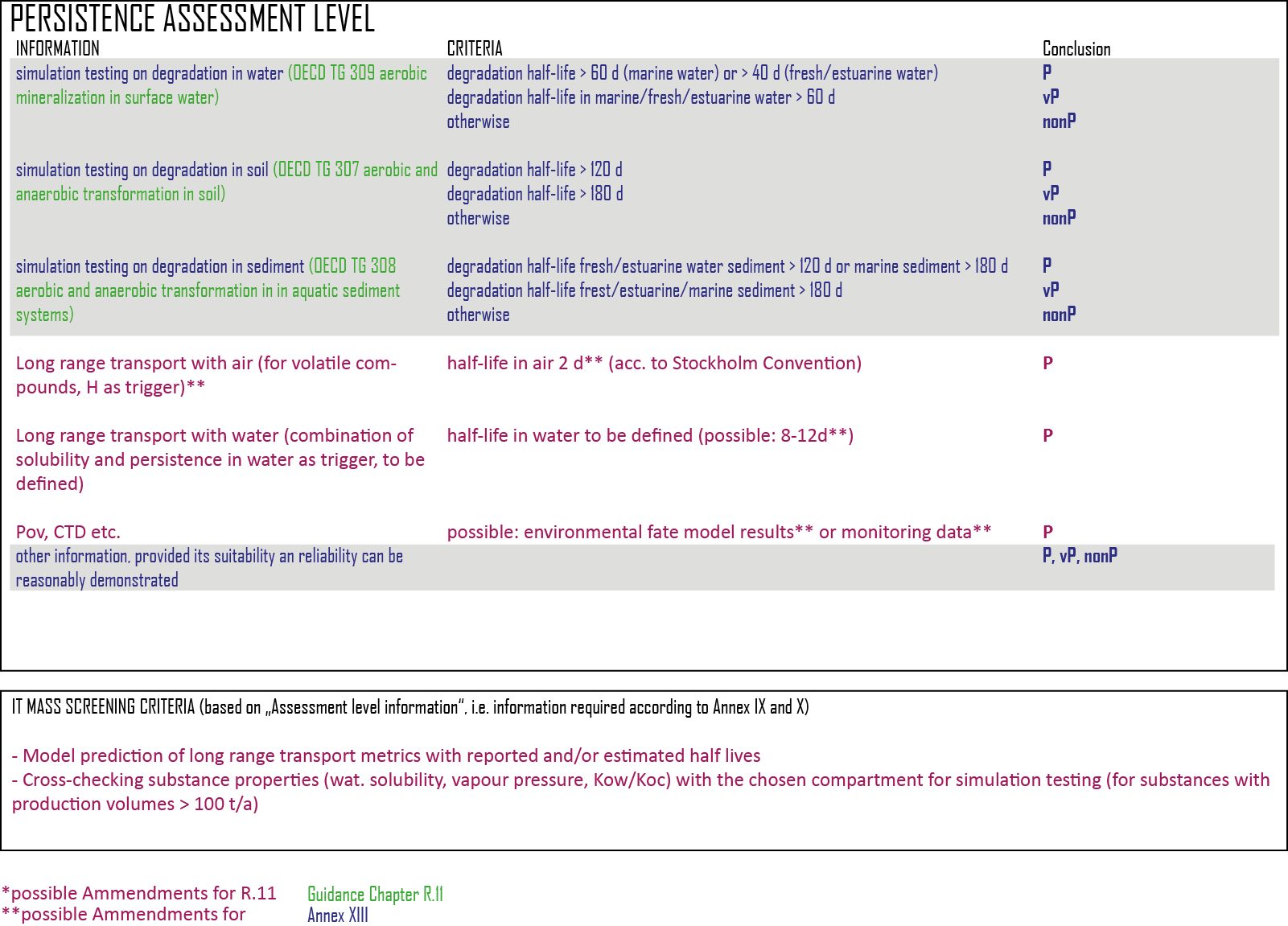
### Procedural aspects

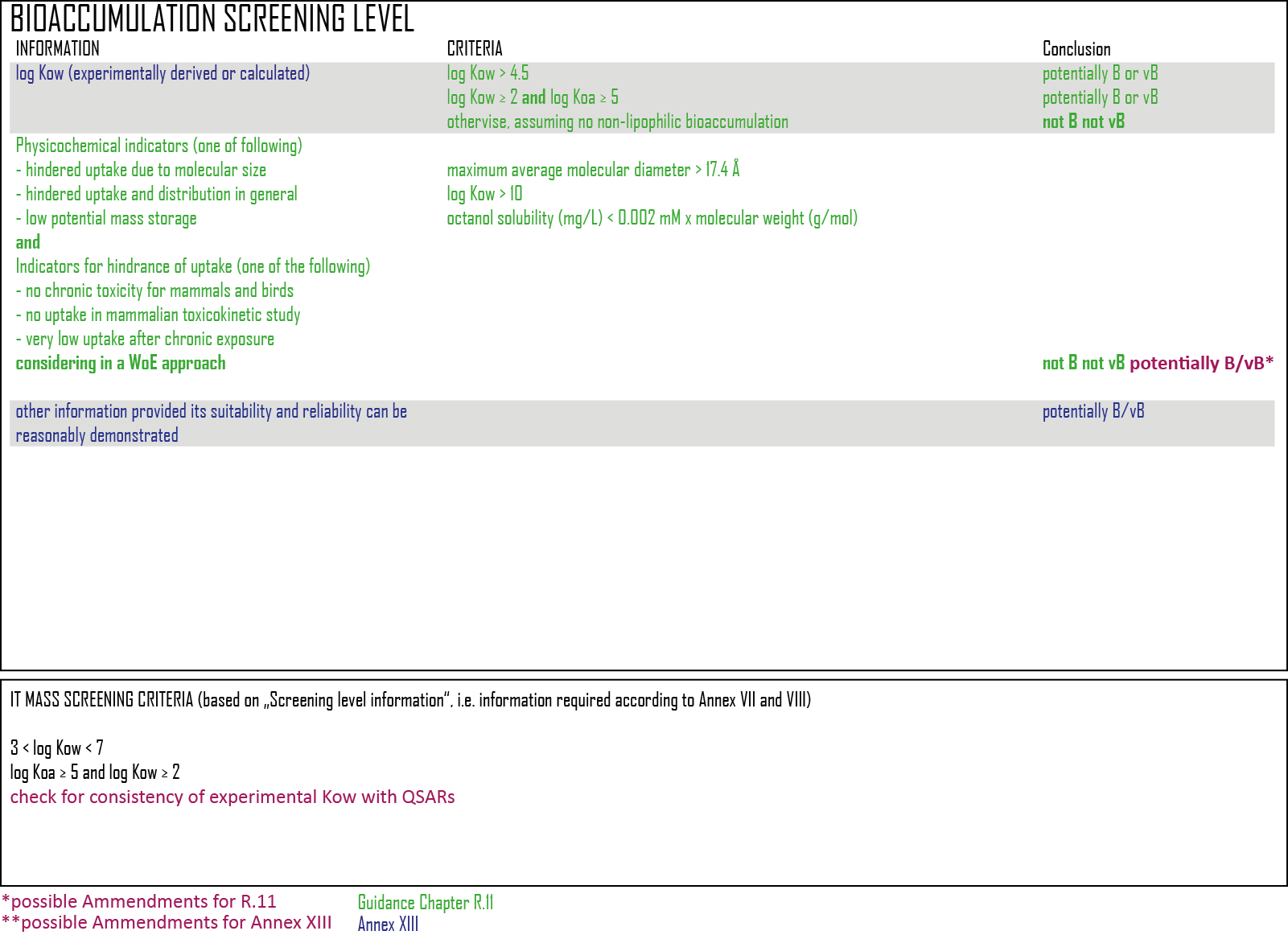
Requesting further information during substance evaluation (i.e. when there is an indication that the substance might exhibit PBT/vPvB properties) can be a very time-consuming process, leading to an unnecessary delay of restricting use of potentially hazardous substances. A maximum timespan for delivering the requested information during substance evaluation could help prevent potentially irreversible release of PBT/vPvB substances. After this timespan, the registration could be temporally suspended until the data are delivered.

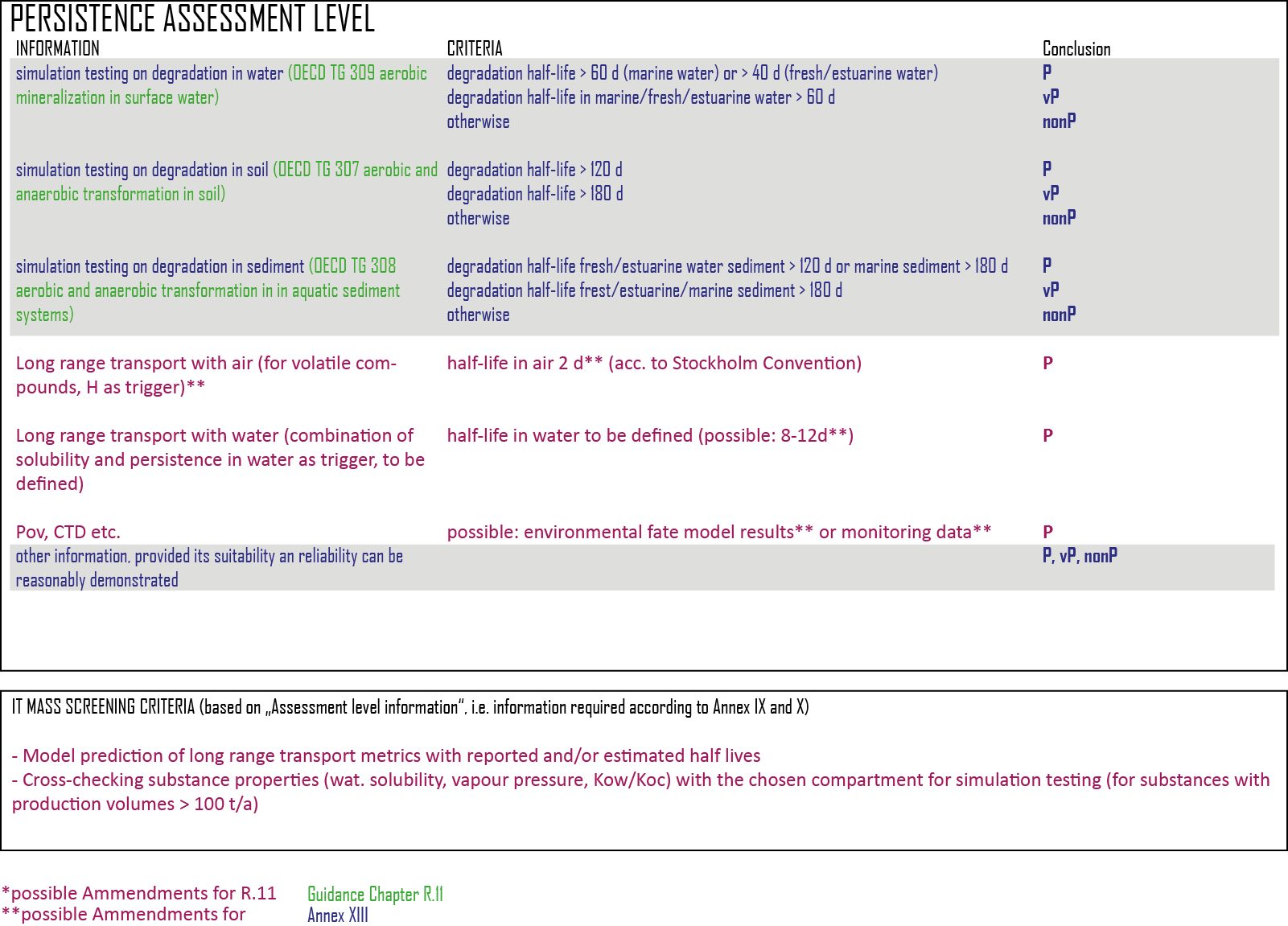
## Overview of the possible enhancements

The following tables present an overview of the present assessment procedure and possibilities for enhancement of the PBT/vPvB assessment on the level of IT-mass screening, Annex XIII or the guidance documents. For more details, see the chapters on the endpoints in WP3.









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