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PBT - Quo vadis? Examination and further development of the PBT assessment approach for identification of environmental SVHC

Final report

For our Environment

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PBT - Quo vadis? Examination and further development of the PBT assessment approach for identification of environmental SVHC

Final report

by

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Abstract

The aim of the project was a review of the current version of the concept to identify persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) substances under the EU regulation (EC) No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), hereafter referred to as “PBT concept”.

The German Environment Agency (UBA) contracted Oeko-Institut, ETH Zürich and BiPRO to review the current PBT concept and to propose updates and adjustments. The project was designated to support UBA in its active contribution to the identification of new PBT substances.

In a first step, an evaluation of a number of already existing PBT/vPvB classifications was conducted, 57 of which were classified as non-PBT substances with a strong indication that 8 substances might be PBT substances.

For the assessment of environmental monitoring data, substances detected in remote areas were compiled and examined based on EpiSuite estimations for their P and B properties. .

In order to further strengthen the PBT concept two main steps were carried out: a review of the PBT/vPvB concept as implemented under REACH, and the implementation of the concept with the aim to identify substances of very high concern, and proposals for updating the PBT concept by developing suggestions on how to overcome the major challenges. Proposals for amendments or adjustments of PBT concept were discussed on a workshop with international PBT experts in June 2017.

Kurzbeschreibung

Ziel des Projekts war die Überprüfung der aktuellen Version des Konzepts zur Identifizierung persistenter, bioakkumulierbarer und toxischer (PBT)-Stoffe sowie sehr persistenter und sehr bioakkumulierbarer (vPvB)-Stoffe gemäß der EU-Verordnung (EG) Nr. 1907/2006 zur Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH), im Folgenden als PBT-Konzept bezeichnet.

Das Umweltbundesamt (UBA) hat das Öko-Institut, die ETH Zürich und BiPRO beauftragt, das aktuelle PBT-Konzept zu überprüfen und Aktualisierungen und Anpassungen vorzuschlagen. Das Projekt soll das UBA in seinem aktiven Beitrag zur Identifizierung neuer PBT-Stoffe unterstützen.

In einem ersten Schritt wurde eine Bewertung einer Auswahl bisher bekannter PBT/vPvB-Klassifizierungen durchgeführt. Siebenundfünfzig davon waren als Nicht-PBT-Stoffe eingestuft worden, wobei es wichtige Anhaltspunkte dafür gab, dass es sich bei 8 dieser Stoffe dennoch um PBT-Substanzen handeln könnte.

Im Hinblick auf die Bewertung von Daten aus der Umweltüberwachung wurden die in abgelegenen Gebieten nachgewiesenen Stoffe zusammengestellt und auf der Grundlage von EpiSuite-basierten Einschätzungen ihrer Persistenz und Bioakkumulierbarkeit untersucht.

Um das PBT-Konzept weiter zu stärken, wurden zwei Hauptschritte durchgeführt: zunächst eine Prüfung des PBT/vPvB-Konzepts gemäß der Umsetzung im Rahmen von REACH, sowie die Umsetzung des Konzepts mit dem Ziel der Identifizierung besonders besorgniserregender Stoffe sowie die Unterbreitung von Vorschlägen, wie das PBT-Konzept ausgebaut und gestärkt werden kann. Im Juni 2017 wurden im Rahmen eines Workshops mit internationalen PBT-Experten Vorschläge für Änderungen oder Anpassungen des PBT-Konzepts diskutiert.

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List of Abbreviations

6:2 FTS	6:2 fluorotelomer sulfonate
AMAP	Arctic Monitoring and Assessment Program
B	Bioaccumulative
BAF	Bio-accumulation factor
BCF	Bio-concentration factor
BMF	Bio-magnification factor
CAS	Chemical abstracts service
CCAMLR	Commission for the Conservation of Antarctic Marine Living Resources
CSA	Chemical safety assessment
DOC	Dissolved organic carbon
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EDC	Endocrine disrupting chemicals
EDC	Endocrine disrupting compounds
EEA	European Environment Agency
EEB	European Environmental Bureau
ESB	Environmental specimen banks
EU COM	European Commission
GMP	Global Monitoring Plan
HPV	High production volume
HSAC	Hazardous substances advisory committee
ICES	International Council for the Exploration of the Sea
IPCHEM	Information Platform for Chemical Monitoring
K_{oc}	Soil organic carbon-water partitioning coefficient
Log K_{aw}	Logarithm of the air-water partition coefficient
LogD	Logarithm of the octanol/water distribution coefficient
LogP or log K_{ow}	Logarithm of the octanol/water partition coefficient
LPVC	Low production volume chemicals
LRTAP	Long-range Transboundary Air Pollution
LRTP	Long-range transport potential
MONARPOP	Monitoring Network in the Alpine Region for Persistent and other Organic Pollutants
NER	Non-extractable residues
NILU	Norwegian Institute for Air Research
NORMAN	Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances
OECD	Organisation for Economic Cooperation and Development

OSPAR	OSPAR Convention - Convention for the Protection of the Marine Environment of the North-East Atlantic
P	Persistent
PBT	Persistent, bioaccumulative and toxic substances
PBTK	Physiologically based Toxicokinetic Model
PEC	Predicted environmental concentration
PFAS	Poly- and perfluoroalkyl substances
PFC	Perfluorochemicals
PFCAs	Perfluoroalkyl carboxylic acid
PNEC	Predicted no-effect concentration
POP	Persistent organic pollutant
POPRC	Persistent organic pollutants review committee
POPs	Persistent organic pollutants
P_{ov}	Overall Environmental Persistence
QSAR	Quantitative structure activity relationship
RBSPs	River basin-specific pollutants
REACH	Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
SETAC	Society of Environmental Toxicology and Chemistry
SPME	Solid-phase microextraction
SVHC	Substances of very high concern
T	Toxic
TCEP	Tris 2-chloroethyl phosphate
TCIPP	Tris(2-chloroisopropyl)phosphate
TCPP	Tris (1-chloro-2-propyl) phosphate
TMF	Trophic magnification factor
UBA	Umweltbundesamt (German Environment Agency)
UNECE	United Nations Economic Commission For Europe
UNEP	United Nations Environment Programme
UNIDO	United Nations Industrial Development Organization
US EPA	United States Environmental Protection Agency
UVCB	Substance of Unknown or variable composition, Complex reaction products or Biological materials
vPvB	Very persistent and very bioaccumulative substances
WFD	Water Framework Directive
WoE	Weight of Evidence

Summary

The aim of the project was a review of the current version of the concept for identifying persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) substances under the EU regulation (EC) No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), hereafter referred to as PBT concept.

The German Environment Agency (UBA) contracted Oeko-Institut, ETH Zürich and BiPRO for the above-mentioned review in order to submit proposals on updates and adjustments to the current PBT concept. The contractors' task was to evaluate methods and to develop a strategy for identifying further PBT candidate substances not yet covered by the current PBT criteria. The project is designated to support UBA in its active contribution to the identification of new PBT substances.

A first goal was to identify the reasons why suspected PBT/vPvB substances were finally concluded not to have PBT/vPvB properties by the former and current PBT expert group, and to discuss these reasons in order to identify directions for a future update of the present PBT concept. This analysis is based on the information provided for 71 substances selected by UBA. The aim was to analyse the argumentation and derive patterns, where such exist, especially for substances where the decision was not based on clear evidence.

The analysis illustrates why it was concluded by the expert group that the substances which met the screening criteria for PBT did not actually have PBT properties.

The following key questions were investigated for each substance with a non-PBT conclusion in the substance fact sheets provided by UBA:

1. Why were all of these substances eventually identified as non-PBT substances, although, in a screening, they had been recorded as being potential PBT/vPvB substances?
2. To what extent can these decisions be relied upon? Is it possible, for example, that a systematic error exists?
3. Was the precautionary principle adequately respected in cases of doubt?
4. Are there similarities between these substances or substance classes?
5. Which of these substances have been found in the environment, although they have not been identified or assessed as persistent and bio-accumulative?
6. Which of these substances have nevertheless to be classified as persistent and bio-accumulative?

The results of the analysis according to question 6 were presented by assigning "traffic-light" colours as follows:

- Green (23 substances) for substances for which the non-PBT decision is supported well by the presented data.
- Orange (22 substances) for which there is some indication for P, B, or T properties, but no values directly supporting a PBT classification of the substance, or where more information would be needed for a decision.
- Red (8 substances) for which there is a strong indication that the substance could be classified as a PBT substance.

It could be concluded:

- Conflicting results were not further assessed; instead results indicating non P and non B were given higher priority.
- Impurities/metabolites (or UVCBs) substances were not always sufficiently assessed, data were not available for all relevant constituents.

- Fast hydrolysis was mentioned as a support for non-persistence; however, the conclusion was not always sufficiently supported by data. Here, the question of relevant metabolites should be investigated.
- Questionable cut-offs for bioaccumulation considering molecular dimensions, octanol solubility or K_{ow} were reasons for a conclusion to classify a substance as non-PBT.

The ECHA Guidance on PBT assessment (Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11, PBT/vPvB assessment, ECHA 2017)) stipulates that monitoring data that are to be used for the assessment of persistence and bioaccumulation should be obtained in the Arctic sea or Alpine lakes or other remote areas or in top predators and biota from remote areas. Conversely, in the present work we analysed whether substances found in remote areas or higher trophic levels are potentially persistent and bioaccumulative, and compared the substance properties with estimated values obtained by use of the EpiSuite Software.

Our approach was based on using and updating a substance list that was compiled by Lambert et al. (2011) for identifying potential POP substances. The research focused on single studies and publications published between 2011 and 2016. Additionally, findings of monitoring programmes were also considered.

To strengthen the use of monitoring data, the following needs were identified:

- Generate a framework of data exchange, strengthen the collaboration between authorities with Monitoring Networks, and further develop IPCHEM (Information Platform for Chemical Monitoring) as one centralized centre.
- Establish approaches and protocols for data request and generation in order to make it easier for authorities to have a comparable approach and not to have to justify every approach individually. The protocols should ideally be approved by all stakeholders.
- Clarify who should contribute to the generation of monitoring data if needed in the substance evaluation, e.g. industry by information request or by e.g. the European Environment Agency (EEA) for the purpose of general environmental monitoring.
- Outline timeframe: The generation of monitoring data upon request is time-consuming and takes up to approximately two years. It is faster and easier to rely on existing data that were generated by established monitoring programmes. The timeline of a substance evaluation process is too short for the generation of new monitoring data.

Based on our review of the PBT/vPvB concept as implemented under REACH, we concluded that several options exist to further develop the concept regarding three different aspects.

Conceptual aspects:

- Toxicity, as operationally defined by acute or chronic testing on aquatic organisms, rather depicts short-term effects. Defined in this way, toxicity is not useful as a criterion, because continuous exposure of persistent and bioaccumulative substances may lead to a variety of effects that only become evident as a consequence of long-term exposure (i.e. months, years or even decades).
- Persistence together with mobility (i.e. partitioning of a chemical into a mobile phase such as water or air) is also of concern, as a wide distribution to potentially vulnerable ecosystems is possible and the contamination uncontrollable.

Several operational aspects are of importance for the further development of the PBT concept. They refer to the definition of the PBT/vPvB concept, i.e. identification of the substances based on the experimental setups, testing requirements and analytical limitations:

- The geometry of test vessels, presence of various environmental phases and sorption processes, and treatment of non-extractable residues can have an impact on persistence assessment and the sensitivity of the test.
- There is a lack of analytical tools for highly hydrophobic substances, e.g. measured BCF values can be obtained only up to a log K_{ow} of 7.8.
- For bioaccumulation, only aquatic species are considered. Different metabolisms in terrestrial organisms are not accounted for, nor are accumulation processes in specific tissues, as the BCF is normalized to the total lipid content. Therefore, the guidance should provide an indication on how to interpret dietary uptake results as an option within the OECD 305 test.

In addition, several procedural aspects should be further developed. They address the assessment process and its elements:

- There are no penalties for submission of non-compliant dossiers, and requesting missing data is a complicated and time-consuming process. In the case of substance evaluation, every decision has to go through a legal procedure which can lead to an unnecessary delay in regulating potentially hazardous substances.
- The selection of the substances that undergo a PBT assessment should be further refined. The status of the selection of the 71 substances when compared to screening results presented by Strempel et al. (2012) showed that only two of the 71 substances were potentially PBT/vPvB according to Strempel et al. (2012). The substance selection strongly depends on the data quality of registration dossiers. Besides, substances not registered under REACH will not enter the process.

Further development of the PBT concept and metrics could involve different approaches of accounting for other forms of bioaccumulation such as bioaccumulation in non-aquatic organisms and bioaccumulation in other tissues then storage lipids (i.e. membrane phospholipids, proteins).

Another issue to consider is the question of whether accumulation in functional tissues such as proteins and phospholipid membranes is of concern in terms of bioaccumulation or rather of toxicology. 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 that effects may occur far away from the source and with a time delay, the inclusion of a criterion for toxicity contradicts the concept. The combination of P and B properties would in any case lead to increasing levels in organisms over their lifetime if exposure continues; therefore, safe levels cannot be derived. However, outside of the PBT/vPvB assessment, toxicity is of 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 a lack of conceptual understanding and analytical tools. The focus should be on substances that are persistent but not bioaccumulative. In order to have a first indication of possible bioaccumulation, the application of a set of rather conservative trigger values based on already available data, and to some extent, of new/adapted QSARs that indicate non-lipid bioaccumulation in non-aquatic systems is recommended. Furthermore, authorities should be allowed to request data beyond standard information requirements if considered necessary. Further important aspects for the development of the PBT concept are substances which are very high persistent (exceeding even the thresholds set for high persistent substances in REACH Annex XIII) and the presence of substances in remote areas due to factors such as particle binding. Such properties should be discussed as of equivalent concern according to REACH article 57f.

As an incentive for submission of compliant dossiers, a maximum time span starting at the first information request by the competent authorities would be helpful. These and more proposals are described in detail in chapter 4 of this report.

Zusammenfassung

Ziel des Projekts war die Überprüfung der aktuellen Version des Konzepts zur Identifizierung persistenter, bioakkumulierender und toxischer (PBT-) sowie sehr persistenter und sehr bioakkumulierender (vPvB-) Stoffe gemäß EU-Verordnung (EG) Nr. 1907/2006 zur Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH), im Folgenden als PBT-Konzept bezeichnet.

Das Umweltbundesamt (UBA) hat das Öko-Institut, die ETH Zürich und BiPRO mit der oben genannten Überprüfung beauftragt, im Rahmen derer Vorschläge zur Aktualisierung und Anpassung des aktuellen PBT-Konzepts unterbreitet werden sollen. Aufgabe der Auftragnehmer war es, Methoden zu evaluieren und eine Strategie zur Identifizierung weiterer PBT-Kandidaten zu entwickeln, die noch nicht unter die aktuellen PBT-Kriterien fallen. Das Projekt soll das UBA in seinem aktiven Beitrag zur Identifizierung neuer PBT-Stoffe unterstützen.

Vorrangiges Ziel war es, die Gründe zu identifizieren, aufgrund derer sowohl die ehemalige als auch die aktuelle PBT-Expertengruppe zu dem Schluss gekommen war, dass die PBT/vPvB-Verdachtsstoffe nicht über PBT/vPvB-Eigenschaften verfügten. Darüber hinaus sollten diese Gründe erörtert werden um herauszufinden, in welche Richtung eine zukünftige Aktualisierung des aktuellen PBT-Konzepts gehen könnte. Grundlage dieser Analyse waren die Daten, die zu 71 vom UBA ausgewählten Stoffen vorgelegt worden waren. Eine weitere Zielvorgabe war es, die jeweilige Argumentation zu analysieren und zugrundeliegende Muster, sofern vorhanden, zu erkennen und abzuleiten, insbesondere für Stoffe, bei denen die Entscheidung nicht auf eindeutigen Belegen beruhte.

Die Analyse legt dar, warum die Expertengruppe zu dem Schluss gekommen war, dass die Stoffe, die die Kriterien für die Einstufung als PBT-Stoff erfüllen, letztlich doch keine PBT-Eigenschaften besitzen.

Die folgenden Schlüsselfragen wurden für jeden Stoff, der im Informationsblatt des UBA als Nicht-PBT-Stoff eingestuft wurde, untersucht:

1. Warum wurden all diese Stoffe letztendlich als nicht PBT-Stoffe eingestuft, obwohl sie im Screening als potentielle PBT/vPvB-Stoffe erfasst wurden?
2. Wie belastbar sind diese Entscheidungen? Kann möglicherweise ein systembedingter Fehler vorliegen?
3. Wurde im Zweifelsfall das Vorsorgeprinzip angemessen beachtet?
4. Gibt es Gemeinsamkeiten zwischen diesen Stoffen oder zwischen Stoffklassen?
5. Welche dieser Stoffe wurde in der Umwelt nachgewiesen, obwohl nicht als persistent und bioakkumulierend eingestuft/bewertet wurden?
6. Welche dieser Stoffe sind dennoch als persistent und bioakkumulierend zu bewerten?

Die Ergebnisse der Analyse entsprechend Frage 6 wurden durch die Zuordnung von Ampelfarben wie folgt dargestellt:

- Grün (23 Stoffe) für Stoffe, bei denen die Einstufung als Nicht-PBT-Stoff durch die vorgelegten Daten gut unterstützt wird.
- Orange (22 Stoffe) für Stoffe, bei denen zwar Hinweise auf das Vorhandensein von P-, B- oder T-Eigenschaften vorliegen, jedoch keine Werte, die unmittelbar eine PBT-Einstufung des Stoffes rechtfertigen würden, oder für die weitere Daten erforderlich sind, um eine Entscheidung treffen zu können.
- Rot (8 Stoffe), für Stoffe, bei denen es starke Anhaltspunkte dafür gibt, dass eine Einstufung des Stoffes als PBT-Stoff gerechtfertigt wäre.

Mögliche Schlussfolgerungen könnten lauten:

- Widersprüchliche Ergebnisse wurden nicht weiter bewertet; hingegen wurden Ergebnisse, die darauf hindeuteten, dass es sich nicht um einen P- bzw. B-Stoff handelt, höher gewichtet.
- Verunreinigungen/Metaboliten (oder UVCB-Stoffe) wurden nicht immer hinreichend bewertet. Es lagen nicht für alle relevanten Inhaltsstoffe Daten vor.
- Eine schnell verlaufende Hydrolyse wurde als Beleg dafür angeführt, dass es sich nicht um einen persistenten Stoff handelt. Diese Schlussfolgerung wurde jedoch nicht immer hinreichend durch Daten gestützt. Vor diesem Hintergrund sollte untersucht werden, ob relevante Metaboliten vorhanden sind.
- Fragwürdige Grenzwerte (Cut-offs) für eine Bioakkumulation unter Berücksichtigung der molekularen Dimensionen, der Octanol-Löslichkeit bzw. des K_{ow}-Wertes waren Gründe für die Entscheidung, einen Stoff als Nicht-PBT-Stoff einzustufen.

Der ECHA-Leitfaden zur PBT-Bewertung (Leitlinie zu den Informationsanforderungen und der Stoffsicherheitsbeurteilung, Kapitel R.11, PBT/vPvB-Bewertung, ECHA 2017) legt fest, dass Überwachungsdaten, die für den Nachweis einer Persistenz oder Bioakkumulation verwendet werden sollen, in der Arktis oder in alpinen Seen oder anderen weit abgelegenen Regionen oder in Prädatoren bzw. Biota aus entlegenen Gebieten gewonnen werden sollten. Umgekehrt haben wir in der vorliegenden Arbeit analysiert, ob Stoffe, die in entlegenen Gebieten oder höheren trophischen Ebenen gefunden wurden, potentiell persistent und bioakkumulierend sind. Die jeweiligen Stoffeigenschaften wurden mit den Schätzwerten verglichen, die durch den Einsatz der EpiSuite-Software erhalten wurden.

Unser Ansatz basiert auf der Verwendung und Aktualisierung einer Stoffliste, die von Lambert et al. (2011) zur Identifizierung potenzieller POP-Stoffe erstellt wurde. Unsere Forschung konzentrierte sich auf einzelne Studien und Publikationen, die zwischen 2011 und 2016 veröffentlicht wurden. Darüber hinaus wurden auch die Ergebnisse der Überwachungsprogramme berücksichtigt.

Zur verstärkten Verwendung der vorliegenden Überwachungsdaten wurden folgende Anforderungen ermittelt:

- Schaffung eines Rahmens für den Datenaustausch, Stärkung der Zusammenarbeit zwischen den Behörden mit den Überwachungs- und Kontrollnetzen, und Weiterentwicklung von IPCheM (einer Informationsplattform für chemische Überwachung) als zentrales Zentrum.
- Erstellung von Konzepten und Protokollen für die Datenanfrage und -generierung, um den Behörden die Vergleichbarkeit zu erleichtern, so dass nicht jedes Konzept einzeln begründet werden muss. Die Protokolle sollten idealerweise von allen teilnehmenden Interessengruppen genehmigt werden.
- Klärung, wer bei Bedarf zur Generierung von Überwachungsdaten für die Stoffbewertung beitragen soll, z.B. die Industrie mittels einer Informationsanfrage oder die Europäische Umweltagentur (EEA) zum Zwecke der allgemeinen Umweltüberwachung.
- Festlegung eines Zeitrahmens: Die Generierung von Überwachungsdaten auf Anfrage, die bis zu zwei Jahre dauern kann, ist sehr zeitaufwändig. Es geht schneller und ist einfacher, sich auf vorhandene Daten zu stützen, die durch etablierte Überwachungsprogramme generiert wurden. Der zeitliche Rahmen einer Stoffbewertung ist zu kurz für die Generierung neuer Überwachungsdaten.

Unsere Überprüfung des im Rahmen von REACH angewandten PBT/vPvB-Konzepts ergab, dass es unter mehreren Gesichtspunkten Möglichkeiten zur Weiterentwicklung gibt,

Konzeptionelle Gesichtspunkte:

- Toxizität gemäß der operationellen Definition, also die Prüfung der akuten und chronischen toxischen Wirkung auf Wasserorganismen, bildet eher kurzfristige Effekte ab. Bei einer Definition in diesem Sinne ist Toxizität kein sinnvolles Kriterium, da eine kontinuierliche Exposition von persistenten und bioakkumulierenden Substanzen zu einer Vielzahl von Wirkungen führen kann, die nur

als Folge einer langfristigen Exposition (d.h. Monate, Jahre oder sogar Jahrzehnte) sichtbar werden.
- Weiterhin von Belang ist Persistenz in Zusammenhang mit Mobilität (d.h. Übergang einer Chemikalie in eine mobile Phase wie Wasser oder Luft), da eine weite Verbreitung in potentiell gefährdete Ökosysteme möglich ist und die Kontamination unkontrollierbar wird.

Mehrere operationelle Gesichtspunkte sind für die Weiterentwicklung wichtig. Sie beziehen sich auf die Definition des PBT/vPvB-Konzeptes, d.h. die Identifizierung von Substanzen auf der Grundlage der experimentellen Anordnung, die Testanforderungen und analytische Limitierungen:

- Die Geometrie der Testgefäße, das Vorhandensein verschiedener Umweltphasen und Sorptionsprozesse sowie die Behandlung nicht extrahierbarer Rückstände können einen Einfluss auf die Persistenzbewertung und die Empfindlichkeit des Tests haben.
- Es fehlen Analysewerkzeuge für sehr hydrophobe Substanzen, z.B. können BCF-Messwerte nur bis zu einem $\log_{Kow}$ von 7,8 bestimmt werden.
- In Bezug auf die Bioakkumulation werden nur Wasserlebewesen berücksichtigt. Da der BCF auf den Gesamtlipidgehalt normiert wird, werden unterschiedliche Stoffwechselvorgänge in Bodenorganismen nicht berücksichtigt, ebenso wenig wie Akkumulationsprozesse in bestimmten Geweben. Daher sollten die Leitlinien einen Hinweis darauf geben, wie die Ergebnisse der Nahrungsaufnahme im Rahmen des OECD 305-Tests zu interpretieren sind.

Außerdem sollten mehrere prozedurale Gesichtspunkte weiter entwickelt werden. Sie betreffen den Prozess der PBT Bewertung und die hierzu gehörenden Einzelschritte:

- Sanktionen für die Einreichung nicht konformer Dossiers gibt es nicht. Zudem ist das Anfordern fehlender Daten ein komplizierter und zeitaufwändiger Vorgang. Bei der Stoffbewertung muss jede Entscheidung ein rechtliches Verfahren durchlaufen, wodurch eine unnötige Verzögerung bei der Reglementierung potenzieller Gefahrstoffe eintreten kann.
- Die Auswahl der Stoffe, die einer PBT-Bewertung unterzogen werden, sollte weiter verfeinert werden. Der Abgleich zwischen der aktuellen Auswahl von 71 Stoffen und den Screening-Ergebnissen von Strempel et al. (2012) ergab, dass nur zwei der 71 Stoffe nach Strempel et al. (2012) potentielle PBT/vPvB-Stoffe waren. Die Auswahl der Stoffe hängt stark von der Datenqualität der Registrierungsdossiers ab. Außerdem werden Stoffe, die nicht unter REACH registriert sind, nicht in den Prozess aufgenommen.

Die Weiterentwicklung des PBT-Konzeptes und der entsprechenden Metriken könnte verschiedene Ansätze zur Berücksichtigung anderer Formen der Bioakkumulation einschließen, wie die Bioakkumulation in nichtaquatischen Organismen und die Bioakkumulation in anderen Geweben als Speicherlipiden (z.B. Membranphospholipide, Proteine).

Auch berücksichtigt werden sollte die Frage, ob die Anreicherung in funktionellen Geweben wie Proteinen und Phospholipidmembranen für die Bioakkumulation bzw. Toxikologie von Bedeutung ist. Sie kann auch außerhalb der PBT/vPvB-Bewertung in einem toxikologischen Kontext bewertet werden, d.h. durch Ableitung von Auslösewerten für die Bewertung der chronischen Toxizität, die auch für Stoffe gelten würden, die nach den PBT/vPvB-Kriterien nicht in der Umwelt persistent sind.

In Anbetracht der Tatsache, dass das Hauptproblem im Zusammenhang mit PBT/vPvB-Stoffen darin besteht, dass es keine sichere Umweltkonzentration gibt und dass Effekte räumlich weit entfernt von der Expositionsquelle und mit zeitlicher Verzögerung eintreten können, widerspricht das Vorhandensein eines Toxizitätskriteriums der Intention des PBT-Konzepts. Die Kombination von P- und B-Eigenschaften würde in jedem Fall dazu führen, dass sich die Schadstoffkonzentration in Organismen im Laufe ihres Lebens erhöhen, wenn die Exposition anhält; daher können keine sicheren Grenzwerte

abgeleitet werden. Außerhalb der PBT/vPvB-Bewertung ist die Toxizität jedoch von entscheidender Bedeutung (z.B. bei der Risikobewertung).

Wir schlagen eine neue Kategorie von "potenziell gefährlichen" Stoffen vor. Ziel ist es dabei, eine Prioritätenliste von Stoffen zu erstellen, deren Eigenschaften in Ermangelung des nötigen konzeptionellen Verständnisses und der geeigneten Analyseinstrumente noch nicht als PBT/vPvB bewertet werden können. Der Schwerpunkt sollte auf Substanzen liegen, die persistent, aber nicht bioakkumulierbar sind. Um einen ersten Hinweis auf eine mögliche Bioakkumulation zu erhalten, wird die Anwendung einer Reihe von eher konservativen Triggerwerten, auf der Grundlage bereits verfügbarer Daten und teilweise neuer/angepasster QSARs empfohlen, die eine fettfrei Bioakkumulation in nicht-aquatischen Systemen ermöglichen.. Darüber hinaus sollten die Behörden die Möglichkeit haben, über die üblichen Informationsanforderungen hinausgehende Daten anzufordern, wenn dies für notwendig erachtet wird. Weitere wichtige Gesichtspunkte für die Fortentwicklung des PBT Konzeptes sind Stoffe, die extrem persistent sind (very highly persistent, ihre Persistenz liegt deutlich über den Triggerwerten aus REACH Anhang XIII für sehr persistente Stoffe) und das Vorkommen von Stoffen in unberührten Gebieten aufgrund von Prozessen wie der Bindung an Partikel. Solche Eigenschaften sollten diskutiert werden als ähnlich besorgniserregend gemäß REACH Artikel 57f.

Als Anreiz für die Einreichung vollständiger Stoffdossiers wäre es sinnvoll, seitens der Behörden eine maximale Zeitspanne festzusetzen zwischen der ersten Nachforderung von Daten und deren Einreichung. Diese und weitere Vorschläge werden im Kapitel 4 dieses Berichtes beschrieben.

1 Objective of the study and the structure

The aim of the project was a review of the current version of the concept to identify persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) substances under the EU regulation (EC) No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), hereafter referred to as "PBT Concept". The criteria to specify the requirements for persistence, bioaccumulation and toxicity are laid down in REACH Article 57 and Annex XIII, while the identification procedure is set out in the European Chemicals Agency (ECHA) "Guidance on Information Requirements and Chemical Safety Assessment – Chapter R.11: PBT / vPvB Assessment"[1].

Among the substances registered under REACH, up to now (as of November 2018[2]) 33 substances have been recognized as PBT/vPvB substances. There are however screening studies that report a higher number of potential PBT substances. Strempel et al. (2012) for example screened a database of 95,000 substances and identified 2,783 potential PBT/vPvB substances[3]. Similarly, Rorije et al. (2011) screened a set of 65,000 substances and found around 7% of the substances being potentially PBT/vPvB. Regarding this gap between suspected PBT and actual categorised PBT substances we focussed on the questions:

► Are there more PBT/vPvB substances than identified under REACH with the current PBT concept?

► Are there other substance properties than already addressed, which need more attention?

Against this background, the German Environment Agency (UBA) contracted Oeko-Institut, ETH Zürich and BiPRO to review the current PBT concept and to propose updates and adjustments. This includes the evaluation of methods and the development of a strategy for identifying further PBT candidates not yet covered by the current PBT criteria. The overall goal is to identify measures to overcome the regulatory gaps addressing all substances for which a "safe concentration in the environment cannot be established with sufficient reliability" and where, therefore, a classical risk assessment applying ratio of PEC/PNEC is not sufficient. Moreover, the project is designated to support UBA in its active contribution to the identification of new PBT substances.

This report sets the focus on the following aspects:

In chapter 2 ("Analysis of previous PBT assessment results"), a comprehensive substance review of 71 PBT factsheets, the dossiers of the PBT expert group summarizing the data and the rationale for the assessment is presented. Special emphasis was given to the methods for assessing the PBT factsheets and their screening criteria related to persistence, bioaccumulation and toxicity.

Environmental monitoring results connected to possible PBT identifications were summarized and assessed in chapter 3 ("Environmental Monitoring"). Emerging substances were detected in environmental monitoring studies in remote areas and higher trophic level biota in a so-called iceberg list. For these substances, properties regarding persistence and bioconcentration were estimated by using the software package EpiSuite. Additional factors were discussed for some examples where substances despite not being assessed as persistent are found in remote areas.

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1 European Chemicals Agency (ECHA): Guidance on Information Requirements and Chemical Safety Assessment; Chapter R.11: PBT/vPvB assessment Version 3.0; November 2017; http://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf

2 As of 12 November 2018 at https://www.echa.europa.eu/web/guest/candidate-list-table

3 Strempel et al. (2012) assessed 94,483 chemicals with respect to PBT properties. The chemicals were obtained from three databases; the SMILECAS database, the European Inventory of Existing Commercial Chemical Substances (EINECS) and the European List of Notified Chemical Substances (ELINCS). For these chemicals, experimental data on PBT properties were collected from different public databases. Missing experimental data of substances were estimated by EpiSuite and the included tools. The PBT criteria according to REACH Annex XIII were applied for the identification of a chemical as PBT or vBvP. Based on these groups of substances, common structural elements of possible PBT substances were identified. Strempel et al. (2012) identified 2,783 potential PBT/vPvB substances.

A central aspect in this study was an evaluation of the PBT Concept considering new scientific findings and experiences of regulators (see chapter 4 " The present PBT concept and proposals for further development"). The focus was given to EU legislation, in particular to REACH, because the most comprehensive guidance on PBT assessment of substances has been developed under REACH when compared to other legislations. We concluded based on the discussion in the previous chapter that on various levels there are possible gaps in the assessment scheme and elaborated own proposals to examine and further develop the PBT Concept.

Moreover, within the context of the project an international workshop "PBT – Quo vadis?" was convened in June 2017. The workshop discussed conceptual and practical options and measures to improve the efficiency of the screening and assessment procedures under REACH. Furthermore, the workshop built on latest scientific knowledge about persistence, degradation, bioaccumulation and toxicity of organic substances. The main results of the workshop are part of this final report.

The general overview has been summarized in tabular form in the chapter 5.

2 Analysis of previous PBT assessment results

The first task started with the identification of the reasons why the former and current PBT-Expert Group[4] (later referred as PBT-EG) finally concluded for several suspected PBT/vPvB substances not to have PBT/vPvB properties and discuss the justifications in order to identify possible challenges for future adaptation of the present PBT-concept. A selection of 71 substance fact sheets (see Annex I, chapter 6.1) provided by UBA represented the basis for the analysis. Only the factsheets were considered in this study, no additional data were collected and assessed.

It was concluded that 57 of those 71 substances do not have PBT/vPvB properties (later referred to as nonPBT-substances), 6 substances are PBT/vPvB and for 8 substances the decision was deferred or is still ongoing.

The analysis of previous PBT assessment results was divided into four sub-chapters. First, a qualitative in-depth analysis of all decisions leading to a "nonPBT" outcome, which led to a compilation of a set of keywords that describe the background of the decisions and an identification of substances for which PBT-properties are possible. Second, we had a look at the current status of the 6 PBT substances under REACH (which were all considered PBT under the old legislation, i.e. before REACH entered into force). In a third step, we screened substances on other lists which address potential PBT/vPvB substances (i.e. in order to investigate whether the decisions of the PBT-EG are in line with other sources). Forth, we compared the decisions taken by the PBT-EG with EpiSuite-estimations. .These estimations have been taken into account in the following subsections.

2.1 Qualitative analysis of the arguments behind the decisions of the PBT-EG for nonPBT substances

As mentioned above, 57 nonPBT substances were initially included in this analysis; four of them had to be deleted as no data were available. Therefore, in total 53 substances were analysed in more detailed according to the following six guiding questions:

1. Why were all of these substances eventually identified as non-PBT substances, although, in a screening, they had been recorded as being potential PBT/vPvB substances?

[4] The PBT Expert Group focuses on PBT substances, which are substances that are persistent, bioaccumulative and toxic, whereas vPvB substances are very persistent and very bioaccumulative. These properties are further defined by the PBT/vPvB criteria in Annex XIII to the REACH Regulation. The group continues the work which has been done before by a PBT group of the Joint Research Centre of the EU Commission. In the following, if necessary a distinction is made between the "current" PBT Expert Group (organized by ECHA) and this earlier group ("former PBT expert Group") of JRC

2. To what extent can these decisions be relied upon? Is it possible, for example, that a systematic error exists?
3. Was the precautionary principle adequately respected in cases of doubt?
4. Are there similarities between these substances or substance classes?
5. Which of these substances have been found in the environment, although they have not been identified or assessed as persistent and bio-accumulative?
6. Which of these substances have nevertheless to be assessed as persistent and bio-accumulative?

The results of the analysis according to question 6 are summed up by assigning "traffic-light colours" as follows:

- Green (23 substances) for substances for which the nonPBT decision was supported well based on the presented data.
- Orange (22 substances) for substances for which there was some indication for P, B, or T properties but no data directly supporting a final PBT classification, or where more information would be needed for a decision.
- Red (8 substances) for substances for which there was a strong indication that the substance could be classified as a PBT substance.

The results of questions 1 and 2 are summed up by assigning keywords to the relevant substances. Overall, 12 different cases were differentiated; those 12 keywords were identified as arguments and challenges relevant for the final decision on PBT properties during the qualitative analysis of the substance fact sheets.

Table 1 below provides an explanation of the keywords, and their assignment to **P** (persistence), **B** (bioaccumulation) or general endpoints. Note that no keywords refer to T. Nevertheless, remarks on T were also identified in a first step. However, as there was no case in which the substance was considered to be P and B but not T, it will not be further discussed here.

The keywords *highK_{ow}_notB, nonB_lowoctanol, nonB_size* refer to cut off values where uptake of the substance is assumed not be relevant, but where the substance's partitioning properties still indicate a potential for bioaccumulation.

The last column in Table 1 gives the number of times the keyword was assigned. Only "red" and "orange" substances are considered here in order to identify key aspects for improvement. Note that for some substances, several keywords were attributed.

Table 1: Keywords assigned to „red" and „orange" substances in order to clarify the decision on its nonPBT properties

Keyword	Endpoint	Explanation	#
notP_readacross	P	Read-across with similar substances used for conclusion on P	1
fast_hydrolysis	P	Fast hydrolysis reason why the substance was considered non P	2
metabolite_not_assessed	P	The substance is considered not P due to degradation, however properties of the metabolites are not assessed	2
nonB_size	B	The substance is considered not B due to the size of the molecule	1
highK_{ow}_notB	B	The substance is considered not B due to a high log K_{ow}	3
nonB_lowoctanol	B	The substance is considered not B due to a low octanol solubility	3
nonB_readacross	B	Read-across with similar substances used for conclusion on B	3

Keyword	Endpoint	Explanation	#
nonB_experimental	B	Based on experimental K_{ow} or BCF values the substance was considered not B	2
conflicting_results	general	Values indicating non P/B as well as P/B were reported	12
no_data_4all _endpoints	general	Mostly assessment of P was neglected; decision on non PBT based on non B only, read-across, other reasons.	7
impurities	general	Where impurities/constituents could be present, that (might) have PBT properties but were not assessed or not considered for the decision on PBT	10
naturally_occurring	general	Where the reason for nonPBT conclusion was natural occurrence of the substance	2

Question 5, the presence of the substances in the environment, is discussed in chapter 3, together with other monitoring results of all substances found in remote areas or higher trophic levels. Question 4 is discussed only for the substances which were assigned to the "red" category. Question 3 is discussed on a general level.

2.1.1 Substances with potential PBT/vBvP properties

Eight substances were identified as potentially PBT (i.e. assigned red, looking for patterns and similarities (i.e. considering question 4) between the substances for which there is a strong indication of PBT properties, we identified the following: see Table 2.

In three cases, the decision that the substance is not PBT is based on the assumption of a cutoff value for bioaccumulation, e.g. low octanol solubility, very high molecular size or reduced uptake due to a very high K_{ow}. In five cases, nevertheless higher values of BCF and log K_{ow} were also reported, but the decision was based on the lower values. In one case, a potential PBT impurity might be present.

Looking for patterns and similarities (i.e. considering question 4) between the substances for which there is a strong indication of PBT properties, we identified the following:

Table 2: Substances assigned red, keywords on the decision on nonPBT and the assessing national authority

Substance	CAS Nr.	Keywords	logK_{OW}
Pigment Yellow 13	5102-83-0	nonB_lowoctanol	8.1
Dibenzyltoluene	26898-17-9	conflicting_results	6.59
Hydrocarbons,_C4,_1,3-butadiene-free,_polymd.,_triisobutylene_fraction,_hydrogenated	93685-81-5	conflicting_results	6.4
Perylene-3,4:9,10-tetracarboxylic_dianhydride	128-69-8	nonB_lowoctanol	6.26
Ethylenebistetrabromophthalimide	32588-76-4	nonB_lowoctanol	9.8
Paraffin_waxes_and_Hydrocarbon_waxes,chloro	63449-39-8	highK_{ow}_notB impurities	17
2,6-di-tert-butyl-p-cresol(BHT)	128-37-0	conflicting_results metabolite_not_assessed no_data_4all_endpoints	5.1
Tetrabromophthalic_anhydride	632-79-1	fast_hydrolysis conflicting_results	5.63

- The substances are highly hydrophobic, most of them have a log K_{ow} above 6.
- In three cases, the decision on nonPBT is based on the substances' low octanol solubility (which is assumed to be an indicator of reduced storage capacity of the lipids for the substance, see discussion below).
- Conflicting results, indicating difficult experimental handling of the substances, were mentioned in three cases.

As highly hydrophobic substances are experimentally difficult and reliable data are scarce (Jonker and Van Der Heijden 2007; Müller and Nendza 2007), there are controversial discussions about the characteristics of those substances. See Annex II: Red (8 substances) for more details.

2.1.2 Discussion of nonPBT substances

2.1.2.1 Data availability and quality

In this chapter aspects that were identified as relevant for the decision on nonPBT will be further investigated. This analysis is focused on the substances labelled "red" and "orange", i.e. for which the decision on nonPBT is somehow questionable based on the presented substance information. 10 substances might have some constituents or impurities with PBT properties in considerable amounts. For 12 substances, experimental studies and or QSARs are presented which show conflicting results, and often, it is not clearly shown which of the presented studies is most reliable. For 8 substances, the nonPBT decision was based on the assessment of only one endpoint (usually exclusion by non-B and only screening-level P assessment without any decision on P). Those three aspects illustrate the big challenge in the context of PBT assessments: comprehensive and reliable data on all properties are the key factor for a sound decision, but the data are often lacking. Therefore, as the decisions are often associated with considerable uncertainties, potentially hazardous chemicals could be irreversibly introduced into the environment. Following one of the principles of REACH, no data – no market, setting up a framework in order to improve the data availability and quality is crucial to ensure a high level of protection for the environment.

2.1.2.2 Use of indicators for limited bioconcentration/bioaccumulation

Besides the experimental BCF, according in the ECHA Guidance on PBT/vPvB Assessment Chapter R.11[5] (ECHA 2017) data on molecular size and octanol solubility can be used in a weight of evidence approach as an indicator of limited bioaccumulation potential due to a lack of uptake. Those include the following (see Appendix R.11-1 of the Guidance):

- the maximum average diameter (>1.7nm) plus a molecular weight of greater than 1,100
- a maximum molecular length (MML) of greater than 4.3 nm
- octanol-water partition coefficient log K_{ow} >10
- a measured octanol solubility (mg/L) < 0.002 mmol/l x MW (g/mol) (without observed toxicity or other indicators of bioaccumulation)

According to the Guidance on PBT/vPvB Assessent, Chapter R.11, "if average molecular size, log K_{ow} and octanol solubility are above or below certain values (see above), they can be considered as indicator for a limited bioaccumulation potential due to the lack of uptake. However, these parameters should never be used on its own to conclude that a substance is not bioaccumulative. The information from these parameters should be accompanied by other information confirming the low uptake of the substance in living organisms, e.g. by read-across with similar substances, absence of toxicity or lack of uptake in toxicokinetic studies with mammals."

[5] ECHA, 2017. *Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB assessment*, Available at: https://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf.

As experimental indicators of hindrance of uptake are mentioned:

- no chronic toxicity for mammals and birds
- no uptake in mammalian toxicokinetic study
- very low uptake after chronic exposure

According to the Guidance, by combining those indicators (i.e. molecular properties together with experimental indicators of hindrance of uptake) in a "weight of evidence approach" it can be concluded that the substance is not B and no further information for B assessment needs to be generated, see chapter R.11 (ECHA 2017).

However, kinetic effects could lead to lack of observed uptake within a testing timeframe in toxicokinetic studies with mammals for the abovementioned large and highly hydrophobic substances, whereas in the case of lifelong exposure concentrations could possibly increase over time in long-lived organisms due to continuous exposure.

A literature study on the effects of molecular size and lipid solubility on bioaccumulation potential concluded that clear cut-offs in bioconcentration related to size or lipid solubility do not exist. The authors conclude that many studies that have investigated relationships between molecular dimensions and reduced uptake (i.e. based on lower BCFs than expected), may describe experimental shortcomings or artefacts. The reduced bioconcentration concerns hydrophobic chemicals with very low aquatic solubilities. Therefore, bioavailability, and dissolution kinetics are crucial influential factors which are contributing to the observed decrease of BCF for large, hydrophobic substances (Müller and Nendza 2007). Improvement of testing procedures has led to an increase of those proposed cut-offs with time. No cut-off for bioconcentration is observed up to the present technically feasible log K_{ow} of 7.8 (Jonker and Van Der Heijden 2007; Müller and Nendza 2007; Mayer and Reichenberg 2006)

Therefore, we conclude that there is no clear evidence that would justify considering a substance not being bioaccumulative based only on the discussed cut-off values and indicators as uptake cannot be excluded by experimental data for substances with the above discussed extreme properties, where at present experimental handling is very difficult if not impossible. The assessment would not be in line with the precautionary principle.

2.1.2.3 Persistence, fast hydrolysis and metabolites

For some substances[6], it was argued that they are not persistent due to fast hydrolysis. However, often references to studies are missing, the exact rate of hydrolysis is unknown (but "expected" to be fast). According to the REACH legislation (Guidance Chapter R 7.b: Endpoint specific guidance), hydrolysis as a function of pH must be reported for substances produced >= 10 t/y, unless the substance is highly insoluble in water or readily biodegradable. Identification of degradation products is mandatory for substances >= 100 t/y. Thus, the data that would be required according to the Guidance were not provided.

2.1.2.4 Read-across

Read-across is an acknowledged method under REACH, in order to fill data gaps on effects of chemicals and avoid testing on vertebrates by predicting unknown properties based on known properties of a similar chemical. A guidance outlining the procedure has been published by ECHA (Practical Guide: how to use alternatives to animal testing to fulfil your information requirements under REACH, 2016)[7]. However, the substance fact sheets did not provide a discussion on what the similarity is based on, as there was no compilation of guidelines at the time of the assessment. Read-across is a

[6] For example, tetrabromophthalic_anhydride (CAS 632-79-1)

[7] https://echa.europa.eu/documents/10162/13655/practical_guide_how_to_use_alternatives_en.pdf/148b30c7-c186-463c-a898-522a888a4404

promising approach in order to handle experimentally difficult chemicals, but clear rules are necessary in order to avoid misinterpretation and delays in substance assessments due to disputes on how similarity should be interpreted.

2.1.2.5 Impurities and UVCBs

Identifying relevant constituents is a very challenging task. According to ECHA (2017) Guidance on PBT/vPvB Assessment Chapter R.11, *"all known constituents, present at concentrations ≥10% should be specified by at least the English-language IUPAC name but preferably a CAS number; the typical concentrations and concentrations ranges of the known constituents should be given as well. Constituents that are relevant for the classification of the substance and/or for PBT/vPvB assessment must always be identified by the same identifiers. This means that substances with PBT or vPvB properties need to be considered for the PBT/vPvB assessment down to a threshold level of ≥0.1% (w/w)".* However, if there is a constituent that is not already an acknowledged PBT chemical, it might not even be identified (and therefore no data available for a PBT assessment) if the concentration is less than 10% before adverse effects become evident. Often, only the mixture as a whole can be assessed, which leads to uncertainties in the interpretation of the results, i.e. the PBT properties of minor constituents may not be detected.

At present, the PBT/vPvB assessment in general is based on knowing the substances' identity and properties, which is not the case for UVCBs. Where this is not the case, different conceptual frameworks are needed. Different approaches for different substance classes (sometimes specific to some) are presented in ECHA's guidance documents. The PBT assessment of UVCBs is therefore out of the scope of this study.

2.2 Comparison with other substance lists

In order to evaluate the outcome of the discussions in the former PBT working group and the current PBT expert group, we compared the conclusions with other expert judgments and compilations of potentially harmful substances. In particular the following two lists were used:

- SIN List (ChemSec). The compilation of the list is based on REACH criteria for SHVCs according to article 57 and aims to accelerate the process of regulating hazardous chemicals[8]. This list contains substances with property values that meet the criteria for PBT / vPvB according to REACH, but not all of them have been included in the Candidate list yet. Currently the list comprises more than 900 substances. For more details on inclusion of PBT/vPvB Substances into the SIN-List see the "Identification of PBT chemicals for inclusion in the SIN List: methodology" (ChemSec 2014)
- PBT List (Strempel et al. 2012). The list comprises 2,783 chemicals that meet the criteria defined in Annex D of the Stockholm Convention. Even if these criteria differ slightly from those of REACH (i.e. a degradation half-life of 60 days (water) or 180 days (soil, sediment) for persistence (P); a bioconcentration factor (BCF) or a bioaccumulation factor (BAF) of 5 000 for bioaccumulation (B); and a half-life in air of 2 days for long-range transport potential (LRTP) a comparison seems useful. (Strempel et al. 2012)

The following three substances were identified on the above-mentioned lists that are not regulated under REACH (considering PBT/vPvB properties). Information provided in the lists, however, gives an indication of PBT behaviour.

[8] http://chemsec.org/business-tool/sin-list/about-the-sin-list

Table 3: Three substances not regulated under REACH

Substance	Remark / comment
Tonalide (CAS 1506-02-1)	It has been concluded non PBT, however biomonitoring data indicate a potential for persistence and bioaccumulation. The chemical is therefore on the SIN-List. For the substance a non-standardized simulation test in water and activated sludge showed primary biodegradation (but no mineralization). The substance is potentially B. The substance is on the CoRAP-list as a potential endocrine disruptor.
chlorinated paraffins (CAS 63449-39-8)	Several congeners of the chlorinated paraffins are PBT/POP according to the SIN-List and PBTs-List. However, the CAS number mentioned is a generic number that covers all the congeners, but the properties vary with chain length. The properties considered in the PBT-List are those of short chain chlorinated paraffins which are already on the candidate list. For the SIN-List, all congeners are discussed together, i.e. it was not separated between the different chain lengths. However, under REACH the short chain chlorinated paraffins are on the candidate list and the medium-chain paraffins are still discussed (CoRAP). Reliable data for LCCP are generally lacking, however, e.g. the Canadian risk assessment concludes that the exposure level is too low to be of concern[9]. The UK risk assessment concludes that bioaccumulation is unlikely based on a relationship assuming decreasing BCF with high K_{ow}[10]
Cyclododecane (CAS 294-62-2)	Cyclododecane has been shown to have vPvB properties resulting from the assessment under the old legislation. In 2008, it was proposed for identification as PBT/vPvB substance. The substance meets PBT/vPvB screening criteria and fulfils the vB criterion. At present however, the substance is registered as intermediate only, therefore PBT assessment is not necessary. Because the substance was concluded to be PBT and vPvB by the PBT-EG, it is on the SIN-List.

2.3 Conclusion on the analysis of chemicals factsheets

A major challenge for the PBT/vPvB assessment is the substance data availability and quality. In several cases, the PBT-EG had to make a decision based on contradictory data. Accordingly, improvement of the quality of the submitted dossiers is crucial. The precautionary principle was not generally applied in the assessments. In light of the number of data points that were missing and the substantial uncertainties associated with the available data, some substances could have been evaluated differently. Major similarities shared by the substances with potential PBT properties were a high K_{ow}, and the fact that relevant transformation products have not been included. Thus, reassessment would be appropriate in some cases. Specific conclusions were:

- Substances identified as PBT in the fact sheets are not relevant for a PBT assessment under REACH because they are either only used as intermediates or already regulated;
- There are substantial problems with data availability and data quality;
- Assessments were not carried out comprehensively but were stopped too early, i.e. after consideration of only parts of the available information (i.e. only P, only B);
- Many complicated aspects were not considered in the assessments: relevant transformation products; extent and rate of hydrolysis; duration of BCF studies; evidence against BCF cut-off values.
- No criteria for long-range atmospheric transport exist in Annex XIII of REACH.

[9] http://www.ec.gc.ca/ese-ees/14B8724F-9BC3-432C-B155-B8BE7BBFC34E/Chlorinated Alkalenes - EN.pdf

[10] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/290855/scho0109bpgr-e-e.pdf

3 Environmental Monitoring

Globally, significant efforts are made to monitor numerous chemicals in various matrices (water, air, sediment, biota, soil, human milk, etc.) as a consequence of legislation, national and international initiatives as well as scientific endeavour combined with the fact that a growing number of substances are found in the environment[11]. The reason for their detection in the environment might be – besides a continuous emission – associated to persistence and bioaccumulation. The detection of substances in a remote area distant from the emission source is recognized as an indication for persistence and bioaccumulation. However, detection of substances in the environment can also be due to factors like direct releases, continuous emission and wide dispersive use.

The ECHA Guidance on PBT assessment (ECHA 2017) stipulates that monitoring data that are to be used for the assessment of persistence and bioaccumulation should be obtained in Arctic sea, Alpine lakes or other remote areas or in top predators and biota from remote areas. In our work, we analysed vice versa whether substances found in remote areas or higher trophic levels are potentially persistent and bioaccumulative and compared the substance properties with values estimated by the EPI (Estimation Programs Interface) Suite Software.

3.1 Approach

For this purpose, we revised and updated a substance list that was compiled by Lambert et al. (2011) for the purpose of identifying potential POP substances. The additional research focused on single studies and publications from 2011-2016. Additionally, findings of monitoring programmes were taken into account.

For the substances on our list called "iceberg list", persistence and bioconcentration estimates were generated with the software package EpiSuite. For persistence, BIOWIN was used to estimate the biodegradation (BIOWIN 2 for non-linear model prediction, BIOWIN 3 for ultimate biodegradation time and BIOWIN 6 for MITI non-linear model prediction). For bioaccumulation, the BCFBAF programme of EpiSuite was used to determine the bioconcentration factor BCF[12]. The KOWWIN and the KOAWIN programme of the EpiSuite package was used to determine the K_{ow} (octanol-water partition coefficient) and the Koa (octanol-air partition coefficient). The iceberg list was also compared to the list of identified PBT substances according to Strempel et al. (2012). Besides, the substances were checked for their REACH registration; when registered under REACH, the tonnage band was added.

3.2 Results and discussion

The iceberg list contains 125 REACH substances compared to 68 REACH substances compiled in 2011 by Lambert et al. These substances belong to substances groups that already have received special attention by scientists and public authorities because of different environmental concerns:

- flame retardants (brominated and chlorinated),
- organophosphates,
- phthalates,
- chlorinated substances,
- siloxanes,
- perfluorinated compounds (C8 – C18),
- organotin compounds,
- alkylphenols and

[11] The Norwegian Institute for Air Research states that "while 20 years ago we might measure roughly 50-100 compounds in an indoor air sample, we now find between 500 to 1000 substances using the same sampling and measurement methods."

[12] The BCF describes the ratio of the steady state chemical concentrations in aquatic water-respiring organism (Corg) and the water (Cw), exposure via water only.

- bromophenols.

Compared to the list of Lambert et al. (2011), the iceberg list shows the trend that a growing number of single substances within these substances groups are detected in the environment. Most scientific attention as for their presence in remote areas and higher trophic biota (based on the numbers of single studies cited in the iceberg list) received the substance group of brominated flame retardants, the organo phosphates and perfluorinated compounds. Substances of these groups were usually explored by several studies. The iceberg list shows that the studies on biota in remote areas focus on aquatic food web with sea birds and polar bear as top predators.

3.2.1 Limitations of the iceberg list

The iceberg list on substances detected in remote areas and higher trophic biota cannot be considered to be exhaustive because, among others, the present literature research focused on REACH chemicals. It can be expected that more substances are detectable in remote areas and higher trophic levels. The whole range of chemicals could be revealed by non-target screenings. Non-targeted screening results from remote areas would help to clarify the total number of substances that end up in the artic and other pristine regions and in top predators. Though Routti (2016) recently concluded based on a non-target screening of polar bear liver tissue that the chemical exposure is already well covered with target analyses, non-target screening results of different environmental compartments – in the best case with time trends from several years – will provide the optimal basis to monitor environmental contaminants in the future.

The data in the iceberg list are very often based on single studies that have been performed for different reasons. Every single field study has to be evaluated individually, which is time consuming. Furthermore, the data on the single substances are spatially and temporally limited and normally do not give time trends, which is however important for the evaluation of bioaccumulation. The studies used different biota and the authors mentioned other restrictions like e.g. small sample size in general or differences of the biota sampled that cannot be assessed like food availability, nutritional, and health status.

Thus, a better connection of monitoring networks with regulators is necessary to clarify regulatory needs. IPCHEM (Information Platform for Chemical Monitoring)[13] as a centralised initiative to bring all monitoring initiatives in Europe together might enable the exchange of monitoring data in the future. However, additionally a strategic approach for monitoring networks is needed to identify compartments or stations that are important for the identification of substances, define spatial and temporal resolution and standards as well as quality criteria in order to reach acceptance for assessors. Besides, specific concepts, standardization and guidance for monitoring networks are needed to clarify how to derive P and B (indication) from existing data in order to show bioaccumulation.

3.2.2 Estimated persistence and bioaccumulation

Persistence and bioaccumulation estimations were possible for 108 substances with EpiSuite[14].
61 substances of the iceberg list (56%) were found to be potentially P or vP. Although persistence as substance property tends to be connected with a potential for long-range transport, it is not a necessary prerequisite for a substance to end up in remote areas. In some cases, additional factors have been shown.

[13] https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html

[14] For 16 substances estimations were not possible due to a lack of the respective CAS number in SMILECAS-database of EpiSuite, a lack of CAS number at all or wrong CAS digits.

As for potential bioaccumulation according to the BCF, no more than 24 substances have an estimated BCF > 2.000: 11 Substances from the iceberg list being potentially P&B, PvB, B and vB according to EpiSuite estimates (see Annex III, Table 7).

Five substances were potentially persistent and potentially bioaccumulative; three substances were potentially persistent and very bioaccumulative one substance was estimated being "only" potentially bioaccumulative and two substances being "only" potentially very bioaccumulative. 13 substances were identified as PBT substances according to Strempel et al. (2012)

We used the following additional considerations of e.g. Gottardo et al. (2014) who stated that the linear relationship between log K_{ow} and BCF seems not to apply to highly hydrophobic substances as BCF levels tend to either level off or decline at log K_{ow} higher than 5.5-6 ('hydrophobicity cut-off' phenomenon): Indeed, 71 substances of the iceberg list (65%) have a log K_{ow} > 4.5; therefrom 38 substances show an estimated log K_{ow} of > 6 and eight substances show an estimated log K_{ow} of > 10.
Based on the statement of Gottardo et al. (2014) that the combined use of criteria such as Koa (octanol-air partitioning coefficient) > 5 or 6 and K_{ow} > 2 should be considered within existing PBT/vPvB assessment frameworks, especially for screening purposes, we even found 80 of the 108 substances fulfilling this combination of K_{ow} and K_{oa}. This indicates that the bioaccumulative characteristics might be an important factor, as most substances of the iceberg list show this characteristic.

3.2.3 Iceberg list substances mostly not registered under REACH

From the 125 substances on the iceberg list, only 50[15] substances are registered under REACH according to ECHA's registered substances database. For three substances, only a use as intermediate is indicated. The tonnage bands indicated for the other registered substances show that they belong to high-production-volume chemicals with a tonnage band ranging from 1.000 to 10.000 tonnes per year being manufactured or imported in the EU (19 substances). For another eight substances, the tonnage band is higher than 10.000 tonnes per year. Thus, a high production volume might be a determining factor for substances being found in remote areas as even four of these substances are not estimated as neither potentially persistent nor potentially bioaccumulative.[16] However, there are 20 substances registered for less than 1.000 tonnes per year and 75 substances – about two third substances of the iceberg list – are not registered under REACH. Thus, the REACH registrations might not necessarily give an indication about the global use of certain substances.

Generally, use patterns and emission pathways are also important factors. Several substance groups of the iceberg list have a very widespread use as additives in polymers. Other uses such as for personal care products are responsible for a growing environmental release e.g. the detergent metabolic compound octylophenol or e.g. the sunscreen ingredient octocrylene. It has to be noted however that two thirds of the substances of the iceberg list are not registered under REACH according to ECHA's registered substances database.

The 13 PBT-substances according to Strempel et al. (2012) on the iceberg list are e.g. not registered under REACH (see Table 4). These 13 estimated PBT substances belong to chlorinated and brominated flame retardants as well as fluorinated alkyl sulfonamides. They show structural elements characteristic of PBTs according to Strempel et al. (2012), like chlorinated and brominated aromatic systems, chlorinated and brominated alicyclic compounds and per- and polyfluorinated alkyl substances. Two substances were proposed as POP candidates by Lambert et al. (2011) and one substance proposed as POP candidate by Blepp et al. (2012).

[15] A re-check for REACH registrations in March 2018 revealed additional registrations in the tonnage band of 1 to 10 tpa.

[16] Bis2-ethylhexylphthalate (DEHP, CAS 117-81-7), Dimethyl terephthalate (DMP, CAS 120-61-6), Diisononyl phthalate (DINP, CAS 28553-12-0) and Bisphenol A (BPA, CAS 80-05-7).

It is obvious that the work of the PBT expert group focuses on REACH registered substances. We understand that a registration under REACH is the key factor for the availability of data. The aim of the PBT concept is to ensure a high level of environmental protection in the EU. As PBT substances due to their P and B properties are very likely to be found far from their emission sources, it is obvious that not only the manufacture and use of PBT substances should be regulated but also their presence in articles.

Table 4: PBT substances according to Strempel et al. (2012)

Name of substances (CAS)	Further comments on the substance	Monitoring data
2,4,6-tribromo-phenyl allyl ether, ATE (3278-89-5)	Not registered under REACH; used as flame retardant.	One study was found which identified ATE in seal blubber and brain (von der Recke and Vetter 2007).
Pentabromophenol, PBP (608-71-9)	Not registered under REACH, used as flame retardant.	Huber et al. (2015) identified PBP in eggs of common eider, European shag and European herring gull in Norway.
Tetrabromo-p-xylene, p-TBX (23488-38-2)	Not registered under REACH; used as flame retardant.	p-TBX was identified in Greenland Shark and atmospheric particles in the Artic (Strid 2010, Salamova et al. 2014)
2,3-dibromopropyl-2,4,6-tribromo-phenyl ether, DPTE (35109-60-5)	Preregistered under REACH, used as flame retardant.	DPTE was found in different monitoring studies. The substance was found in environmental samples from remote areas (air samples, seawater) as well as in high trophic biota (polar bear, seal, black guillemot, glaucous gull) in remote areas (Möller et al. 2011, Von der Recke and Vetter, 2007, Vorkamp et al. 2015, Vetter et al. 2010). The detection frequencies were near 100% in high trophic biota from Greenland (Vorkamp et al. 2015),
Dechlorane 602, Dec 602 (31107-44-5)	Preregistered under REACH; used as flame retardant.	Dec 602 was found in air samples and seawater in remote areas by Möller et al. (2012and in high tropic biota (dolphin, bottlenose dolphin, pilot whale) in southern European waters (Baron et al. 2015). According to Baron et al. (2015), Dec 602 showed a significant positive correlation with trophic position.
Octachlorostyrene, OCS (29082-74-4)	Proposed as POP candidate by Lambert et al. (2011); not registered under REACH; by-product from the production of chlorinated hydrocarbons.	Different studies identified OCS in different animals at higher trophic level from remote areas (polar bear, ivory gulls) (McKinneya 2010, Braune 2007, Verreault 2005, Vorkamp et al. 2004, Verreault et al. 2006 a,b, Dietz et al. 2013) and in eggs of owls in Belgium (Jaspers et al. 2005). Vorkamp et al. (2004) identified OCS in the biota from Greenland. According to Vorkamp et al. (2004), OCS had the widest occurrence and the highest potential for bioaccumulation of the compounds analysed in the study (beside HCBD and PCA).
1,2,3,4-tetrachloro-benzene, 1,2,3,4-TeCB (634-66-2)	Not registered under REACH; proposed as POP candidate by Lambert et al. (2011)	One monitoring study was found which identified 1,2,3,4- TeCB in polar bear, air, ivory gull and sea gulls in remote areas (McKinneya 2010)

Name of substances (CAS)	Further comments on the substance	Monitoring data
Perfluorooctane sulfonamide, PFOSA (754-91-6)	Not registered under REACH; precursor substance of PFOS.	Dietz et al. (2012) identified PFOSA in harbour seal from different locations in Denmark.
N-etyl-perfluoro-octane sulfonamide, N-Et FOSA (4151-50-2)	Not registered under REACH; precursor substance of PFOS; used as insecticide according to the SIN list.[17]	One study identified N-Et FOSA in eggs of common eider, European shag and European herring gull in Norway (Huber et al. 2015).
N-metyl-perfluoro-octane sulfonamide, N-Me FOSA (31506-32-8)	Preregistered under REACH.	One study identified N-Me FOSA in eggs of common eider, European shag and European herring gull in Norway (Huber et al. 2015).
N-metyl-perfluoro-octane sulfonamidoetanol, N-Et FOSE (1691-99-2)	Not registered under REACH.	One study identified N-Et FOSE in eggs of common eider, European shag and European herring gull in Norway (Huber et al. 2015)
N-metyl-perfluoro-octane sulfonamide etylacrylat, N-Me-FOSEA (25268-77-3)	Not registered under REACH.	One study identified N-Me-FOSEA in eggs of common eider, European shag and European herring gull in Norway (Huber et al. 2015).
1H,1H,2H,2H-perfluorodecanol, 8:2 FTOH (678-39-7)	Precursor of PFOA; proposed as POP candidate by Blepp et al. (2012); used as intermediate and impregnating agent; used in coating of textiles, paper and carpets to achieve oil, stain and water repellent properties, in cleaning agents and is present as residual	Stock et al. (2007) identified 8:2 FTOH in air samples of remote areas.

3.2.4 Additional factors influencing the presence in remote areas

The iceberg list shows that there are substances found in remote areas for which the modelling data do not indicate a high persistence. Additional research on substance groups showed that there are additional factors that influence the presence in remote areas. As for organo phosphates, the iceberg list contains 16 organo phosphate substances wherefrom only the four chlorinated substances[18] are potentially persistent according to EpiSuite estimations. Salamova et al. (2014) explain that it has been shown that particle-bound organophosphates are persistent in the atmosphere with regard to OH-initiated oxidation. Due to association with particles the life time is prolonged and will be even longer in polar regions during UV–B darkness, when there is no energy to produce OH radicals and when the ambient temperatures are low, which helps to explain the detection of organophosphates in remote areas. Salamova et al. (2014) further reported that in contrast to previous studies reporting that chlorinated organophosphates dominated the sum of all organo phosphates congener profile, they found

[17] http://sinlist.chemsec.org/search/search?query=4151-50-2

[18] Tris 2-chloroethyl phosphate (TCEP, CAS 115-96-8), tris (1-chloro-2-propyl) phosphate / tris(2-chloroisopropyl)phosphate (TCPP / TCIPP, CAS 13674-84-5), tris (1,3-dichloro-2-propyl) phosphate (TDCPP / (TDCIPP), CAS 13674-87-8) and Tetrakis(2-chloroethyl)dichloroisopentyldiphosphate (V6, CAS 38051-10-4)

that non-chlorinated OPEs are the most abundant organophosphates congeners detected in their sample from the European Arctic site.

3.3 Conclusions

From the iceberg list it is apparent that as far as substance properties are concerned the potential for being persistent and for bioaccumulation reflected by a high K_{ow} and a high K_{oa} (indicating a potential to bioaccumulate in air-breathing organisms) correlates with the detection of substances in remote regions or higher trophic levels. It is however not a necessary prerequisite, as is demonstrated by other examples of the iceberg list: There are also substances that are not estimated for being persistent or bioaccumulative e.g. non-chlorinated organophosphates, alkylphenols and phthalates. As for the alkylphenols there is no analysis of the reasons why they have been found in remote areas so far. As for the organophosphates, an increased persistence by particle bounding and a resulting long-range transport has been found (Salamova et al. 2014). The presence of the substances in remote areas due to additional factors such as e.g. particle binding should be discussed as an equivalent concern according to REACH article 57(f).

Additionally, different uses also play an important role (tonnage used, application patterns and different pathways into the environment: see e.g. the different entry pathway into the environment of an ingredient in sunscreens (octocrylene/ octocrilene, CAS 6197-30-4) (2-ethylhexyl-2-cyano-3,3-diphenyl-2-propenoate) or rather emissions of e.g. flame retardant during use and waste phase.

A high production volume might also be a determining factor as indicated from the tonnage bands received through the REACH registered substances. However, as there are 20 out of the 50 substances registered under REACH for less than 1.000 tonnes per year and 75 substances – about two thirds of the substances of the iceberg list that are not registered under REACH –, REACH registrations and the tonnage bands indicated there might not in all cases be a good indicator for the global use of a substance. Analysis of use patterns and emission pathways were not taken into account for the iceberg list. However a wide-dispersive use of the substances on the iceberg list can generally be suspected.

Participants of the international project workshop formulated the following possibilities to make use of existing monitoring data for PBT assessment.

- ECHA Mass Screening of the pool of the registered chemicals for substance properties of concern: In this step, a comparison with the IPCHEM database should be done given that IPCHEM is established as centralized data centre. This would weigh occurrence alone as a criterion and a need for further assessment of the substance.
- Manual Screening on request, which is performed to further prioritize the outcome of the ECHA mass screening. This annual short list undergoes a manual, i.e. more detailed, screening by the member state authorities. In this step, monitoring data should also be gathered for prioritizing substances. It would however be necessary to further define criteria for monitoring data at this step e.g. is the substance found at point sources only or also found in different biota to further strengthen the evidence from the monitoring data.
- PBT Assessment: In this step monitoring can already be used in a Weight of Evidence (WoE) approach on a general basis. This flexible mechanism should further be explored. Monitoring data can indicate some extra evidence for P and B according to WoE could be helpful, e.g. by samples from different trophic levels.

For the purpose of strengthening the use of monitoring data the following needs were identified:

- Generate a framework of exchange, and to strengthen the collaboration between authorities with Monitoring Networks, and to further develop IPCHEM as one centralized centre.
- Establish approaches and protocols for data request and generation in order to make it easier for authorities to have a comparable approach and not to have to justify every approach each time. The protocols are ideally approved by all stakeholders.
- Clarify who has to contribute to the generation of monitoring data if needed in the substance evaluation, e.g. industry by information request or by e.g. the EEA for the purpose of general environmental monitoring.
- Outline timeframe: The generation of monitoring data upon request is time consuming and takes up to approximately two years. It is basically faster to rely on existing data that was generated on a daily routine. A substance evaluation process is a too short time line for the generation of new monitoring data.

4 The present PBT concept and proposals for further development

In the following sections, the present PBT concept is described and proposals are developed for its further development.

Some of the proposals were discussed with experts at an international workshop in June 2017 in Berlin. This workshop was organized in the course of the project. At the workshop, participants from the PBT-EG responsible for informal and non-binding scientific advice on questions related to identification of PBT and vPvB properties of chemicals, as well as invited scientific experts discussed the latest scientific findings. The need to evaluate existing or develop new methods was also discussed, as well as needs for additional approaches for identifying further PBT candidates. At the workshops initial findings from the analysis of several case studies of PBT assessments have been presented. Two of these case studies are documented in Annex 6.4

The assessment of the P,B and T properties of a substance is a quite complex task. It addresses a large number of aspects: the criteria to decide whether a substance is assessed as P,B or T, the tests and data needed for the assessment, analytical challenges and the sequence of steps from a first indication to a final decision regarding P, B and T. Even if many of these aspects have been discussed in the expert workshop and the project, the following compilation cannot be considered as complete. Nevertheless it describes important topics of the present discussion.

This chapter describes more than 40 aspects of the PBT concept and its application. In order to enhance the readability, the topics have been divided into three groups:

- **Conceptual aspects:** The concept of the PBT/vPvB assessment under REACH and the PBT/vPvB criteria in REACH Annex XIII (section 4.1).
- **Operational aspects:** Testing approaches for P, B and T and aspects of data interpretation. It includes analytical challenges such as low water solubility of substances or the assessment of non-extractable residues (NERs) (section 4.2).
- **Procedural aspects:** The steps which build the processes of PBT screening and PBT assessment. This includes aspects such as IT mass screening based on data from registration dossiers and insufficient data availability (section 4.3).

In each of these three groups, relevant aspects are described and conclusions are drawn separately for P, B and T. Based on these findings, proposals are developed for the further development of conceptual, operational and procedural aspects of the PBT concept.

For a number of aspects, an in-depth-discussion took place in the project. If appropriate, for these aspects additional information given (in brackets). For an understanding of the key findings of this project it is not necessary to read this. Readers interested in specific aspects are pleased to read these additional short sections.

4.1 Conceptual aspects: The PBT concept and PBT criteria in REACH Annex XIII

In the first part of this chapter a brief introduction into the present PBT concept is given (section 4.1.1). It is followed by three sections which describe relevant aspects of criteria setting separately for P, B and T (sections 4.1.2 - 4.1.4). For each of these parameters conclusions are drawn on the shortcomings of the present concept. If possible, options to overcome these shortcomings are described. Finally, in section 4.1.5 proposals are made how to further develop the criteria of the PBT concept.

4.1.1 The present PBT concept

The criteria for the identification of PBT/vPvB substances are outlined in REACH Annex XIII, which is the legally binding definition of the PBT/vPvB concept. The chemical property data of a chemical can be compared to the numerical criteria in order to conclude on the chemicals 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 by considering all available information in a weight-of-evidence (WoE) approach, e.g. by not directly applying the criteria outlined in Annex XIII or information outlined in Annexes VII-X.

For the PBT assessment under REACH, a tiered approach is applied differentiating between screening level and assessment level. Section 3 of Annex XIII specifies which information on the screening or assessment level is needed. If the results from a screening test indicates that the substance may have PBT/vPvB properties, the registrant has to submit a testing proposal and generate higher tier information (i.e. assessment level), regardless of the registered tonnage. 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 substance information that has to be submitted with the registration dossier varies according to the registered tonnage band:

- one tonne or more: submission of information according to Annex VII
- 10 tonnes or more: submission of information according to Annex VIII
- 100 tonnes or more: submission of information according to Annex IX
- 1000 tonnes or more: submission of information according to Annex X

Only for substances produced in amounts > 100 t per year a definitive conclusion on PBT/vPvB can be made based on the information of the registration dossier unless the substance is ready biodegradable and therefore no further information is needed. For substances registered as intermediates only, no PBT assessment is necessary a priori.

Some methodological flexibility is given also by allowing "other-than-standard" information for PBT/vPvB-identification. This makes it possible to account 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. In cases where 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, the substance will not be identified as a PBT/vPvB substance, unless it is selected for (manual) substance evaluation.

- The generation of standardized information should be given priority, when data for the registration dossier are generated. Due to the misinterpretation of non-standardized tests and the use of inappropriate methods there is a risk that in cases where it is concluded that a substance does not exhibit PBT properties the PBT assessment will be difficult and might lead to time-consuming expert discussions. In this context, an evaluation of the first experiences with the WoE approach might be helpful in order to further develop the guidance documents.
- A question would also be whether there are substances which are concluded to be nonPBT based on non-standard information. The appropriateness of these methods could also be evaluated.

4.1.2 Criteria for the assessment of persistence

4.1.2.1 Criteria for P assessment in the present PBT concept

The criteria for persistence and very peristence are given in REACH Annex XIII Article 1.1.1 (P), 1.2.1 (vP) and 3.1.1 (Screening criteria for P and vP). Four aspects have been identified in the project which are at present not adequately covered by the P criteria in the PBT concept:

- Persistence of substances in air and long-range transport of substances in air;
- Pseudo-persistence or continuous persistence
- Substances with very high persistence
- UVCBs

These aspects are described in the following sections 4.1.2.2 – 4.1.2.5

4.1.2.2 Criteria for persistence in air and long-range transport of substances in air

No criterion for persistence in air is considered in today's REACH legislation (i.e. Annex XIII) neither on screening nor on assessment level. Therefore chemicals that are persistent in air but not in water, soil or sediment cannot be identified with the present P criteria (Scheringer et al. 2006).

- A first indication of persistence in air on screening level could be obtained by EpiSuite's 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 generally applicable estimation methods. Further, many POPs/PBTs can be sorbed to particles. Their fate depends on physical atmospheric processes and the reactivity in their sorbed state is largely unknown (Boethling et al. 2009).

According to the Stockholm convention a substance is defined as prone to long-range transport when its atmospheric half-life exceeds 2 days. This time limit is set because it is assumed that within 2 days transboundary transport may occur (i.e. several 100 to over 1000 km).

Several tools for the calculation of long range transport metrics exist. The common approach for most of them consists of modelling the fate of the substance with multimedia models. These models cover the partitioning and fluxes between different environmental compartments and degradation of the substance within the compartments themselves.

> (Additional information: A study on "advancement of concepts for identification of SVHC under REACH" reviewed scientific findings 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 in rivers might be highly effective. This might be also true 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 cri-

teria for LRTP in freshwater would be 8-12 days (Zarfl et al. 2011), compared to the REACH criteria of 60 days.)

4.1.2.3 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 widespread use of drugs, of which some are not eliminated during waste water treatment, leading to 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).

Importantly, pseudo-persistence or continuous presence is not a substance property and is therefore impossible to predict based on the substance itself, as it depends only on external factors e.g. emission and usage patterns. Monitoring results would provide more certainty for the "continuous presence". However, this implies that action is taken only when problems have occurred, which is contradictory to the precautionary principle and the preventive policy of REACH. A regular risk assessment in terms of predicted environmental concentration versus predicted no effect concentration should be applicable to this class of substances. But chronic effects could arise from the chronic exposure, which are not captured within standard test durations (Mackay et al. 2014).

- Theoretically, it is possible that substances that are degradable in standard simulation environments might be persistent in vulnerable environments. Therefore, the continuous presence could be due to continuous emissions and the lack of degradation in the considered environment.

4.1.2.4 Substances with very high persistence

Substances with a very high persistence (exceeding even the criteria set in REACH Annex XIII for very persistent substances) can have adverse impacts over very long time periods. No test methods exist to detect experimentally adverse effects which occur after decades of exposure. Therefore, it is not possible to exclude that substances with very high persistence have such effects. This property should be an indication that the substance is of serious concern and should be considered as of equivalent concern according to REACH Art. 57f. At present, it is unclear how to measure the property "very high persistence" and no numerical criteria have been proposed.

4.1.2.5 UVCBs

UVCBs are substances of Unknown or Variable composition, Complex reaction products or Biological materials. The present concept of PBT/vPvB assessment is designed for pure substances only. There is a need for the identification of the single constituents, which are then assessed separately. Therefore, substances of unknown and variable composition are difficult to assess under the present concept. The lack of an a-priori determination of the identity and fractions of the relevant constituents remains the main challenge of their assessment.

While for registration purposes the single constituents of 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 the PBT assessment (ECHA 2017). Therefore, potentially relevant constituents are poorly defined. In addition, radioactive labelling and QSAR models are impossible in this case (Gartiser et al. 2015). Thus when the common biodegradation testing methods are used, they 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 days), it can be concluded that also 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 this summation is that the structural similarity is sufficient for describing similarity in susceptibility to degradation.

- However, in the case that not every single constituent is identified individually, there is a risk to overlook a persistent constituent, when testing is performed together. This is due to the fact that a sufficient level of degradation can be reached even if some constituents are not degradable.

4.1.2.6 Conclusions: Options for further development of the persistence criteria

Based on the findings described in the sections above and the discussions during the workshop, the following conceptual shortcomings in assessing persistence have been identified:

- 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) needs to be developed. This is of concern for volatile substances persistent in air and non-volatile, water-soluble substances persistent in water.
- 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 taking also into account 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. At this point we would like to note that the freely available software of The OECD P_{ov} & LRTP Screening Tool is for screening the environmental hazard potential of non-ionizing organic chemicals whose environmental partitioning can be described by absorptive capacities of environmental media estimated from partitioning between air, water and octanol in the laboratory (Wegmann et al. 2009)
- A continuous presence of a substance in a system may occur if the continuous input exceeds the degradation capacity. This leads to a long-term exposure, which possibly causing effects (Mackay et al. 2014). This aspect is clearly outside the PBT/vPvB concept, which aims at identifying intrinsic hazards in a preventive way. However, considering the "continuous presence" as a way of identifying substances of concern that have not been identified during hazard assessment.
- For substances with extreme (very high) persistence (i.e., exceeding the vP criteria under REACH) the following modification of the PBT concept should be considered: when released to the environment, extreme persistent substances cause nearly irreversible exposure with a potential for long-lasting and widespread adverse effects. Therefore, very high persistence (with trigger value to be defined) should be considered as a sufficient basis for including a substance in the SVHC list. An extreme persistency should be considered as sufficient base for giving a substance the SVHC status according to REACH Art. 57f. .
- In general, 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.
  The evaluation of substances found in remote areas (see chapter 3.3) has shown that additional mechanisms such as particle bounding can result in long-range transport of substances. Substances with such properties should be discussed as of equivalent concern according to REACH Article 57f.

4.1.3 Criteria for the assessment of bioaccumulation

4.1.3.1 Criteria for the assessment of bioaccumulation in the present PBT concept

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 it is higher than 5000[19].

Screening level information according to Annex XIII includes K_{ow}, 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 K_{ow} > 4.5,or log K_{ow} > 2 and log K_{oa} > 5 and uptake cannot be excluded by other indicators (see next section), the substance is potentially B/vB (ECHA 2017). The other way round, this also means that if the substance's log K_{ow} is less than 4.5, K_{oa} less than 5 and non-lipid bioaccumulation is not expected to occur, the substance can be concluded not B at the screening level.

Currently, there are no definitive criteria defined for bioaccumulation in terrestrial species and for aquatic species only the fish-bioconcentration factor. Therefore, substances accumulating through other pathways than water are not covered by the present BCF criteria in REACH Annex XIII. 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 measured 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. At the screening level, Koa is considered in the draft guidance in order to account for terrestrial bioaccumulation, but there are neither criteria on assessment level nor a developed standardized procedure for follow up assessment. Furthermore, applying the screening Koa criteria as proposed in the draft guidance would yield in the majority of registered chemicals being potentially PBT. Thus, an alternative or tiered approach would be necessary to for practical application.

4.1.3.2 Options for further development of the bioaccumulation criteria

Bioavailability and dissolution kinetics are crucial influential factors which contribute to the observed decrease of BCF for large, hydrophobic substances (Müller and Nendza 2007).

- For bioaccumulation, criteria that could help identify **substances suspected to undergo non-lipid bio-accumulation or bioaccumulate in non-aquatic organisms** are not available, neither at the level of screening nor at the assessment level. This fact shows the need for further investigations of the under-lying mechanisms and binding affinities so that criteria for regulatory purposes can be derived.
- The **detection of a substance far away from sources and in vulnerable populations and particularly in apex species** is an evidence for bioaccumulative behavior (for a retrospective assessment – the presence of a substance in such areas has to be avoided).

Pharmacokinetic models used for computer aided drug design could maybe be evaluated and adapted for a potential use in screening level assessments of protein bioaccumulation or rather considered for specific distribution ratios e.g. poly-parameter linear free-energy relationship (ppLFER). In this context, the **role of ionic substances** is important, especially the possible interactions of the ionic form. For regulatory purposes, further research is needed in this area.

As reviewed by another study, the only test for the terrestrial compartment looking at **air breathing animals** is the OECD 317 test on oligochaetes (Treu et al. 2015). However, in this test, dietary ingestion and uptake from the environment cannot be distinguished and the derived BSAF depends on the organic carbon fraction of the soil (ECHA 2017).

[19] The trigger values (BCF) reflect a value decision and cannot in principle be scientifically substantiated or derived.

There are also no threshold values for dietary studies in general. A solution could be the approach of deriving threshold values in terms of the elimination rate constant, which would be applicable to a variety of uptake pathways. Such an approach would still face the challenges of determining the bioavailable fraction of the substance and the uptake efficiency depending on the test setup and environment.

- The estimation of the elimination half-life based on mass-balance models could serve as a useful screening tool for both aquatic and terrestrial species, to decide whether further bioaccumulation testing is necessary and should be refined by in vitro studies on biotransformation (Goss et al. 2018).In principle, experimental elimination rate constants or elimination half-lives could serve as alternative B metric(Goss et al. 2018) if reliable worst-case trigger values can be established. This approach has been chosen in two recent OECD guidelines on hepatocytes and S9 in vitro transformation testing (OECD 319 A and OECD 319 B)[20].

4.1.4 Criteria for the assessment of toxicity

Given that the main concern of PBT/vPvB substances is that no safe environmental concentration exists and their effects may occur temporally and spatially removed from the source, using a criterion for toxicity contradicts the intention of the concept. The combination of P and B properties will potentially lead to increased levels in organisms over their lifetime, if exposure continues. Therefore, no safe levels can be derived. In particular, even for substances with P and B properties that are less toxic than the T criterion under REACH the effect threshold may be exceeded because of their long-term accumulation in the environment. See also subsections 4.1.2.3 and 4.1.2.4 above.

4.1.5 Criteria for P,B and T assessment: Proposals for a further development

The criteria for POP and PBT identification are historically based. They were derived from properties of neutral hydrophobic substances under laboratory conditions. Compounds such as perfluoroalkyl substances, cyclic volatile methyl siloxanes or ionisable organic compounds exhibit different properties but still a PBT like behaviour (Matthies et al. 2016). The criteria of the present PBT concept are still applied for all substances, but mainly reflect properties of neutral organic substances.

Based on the findings described above, the following proposals are made to further develop the criteria for PBT assessment:

- The **uncertainty about the "PBT-ness" of a substance** might also be used to prioritize substances for monitoring, for the case in which they behave as PBTs but their properties might not be captured by commonly used approaches.
  - In this context, it could be also useful to derive a category of "potentially hazardous" substances, having properties that make it difficult to establish a clear understanding of the substances' 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.
  - As summarized in a recent review, bioaccumulation is not fully understood when 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 K_{oa}/K_{ow} trigger

[20] 319 A: https://www.oecd-ilibrary.org/environment/test-no-319a-determination-of-in-vitro-intrinsic-clearance-using-cryopreserved-rainbow-trout-hepatocytes-rt-hep_9789264303218-en /
319 B: https://www.oecd-ilibrary.org/environment/test-no-319b-determination-of-in-vitro-intrinsic-clearance-using-rainbow-trout-liver-s9-sub-cellular-fraction-rt-s9_9789264303232-en

for terrestrial bioaccumulation, known experimental difficulties with BCF studies (i.e. log K_{ow} > 7.8). Preventive measures limiting release as well as putting those substances on a "watch-list" for monitoring could be possible.

- Very high persistency and occurrence of substances in remote areas due to particle binding or similiar processes should be considered as indications for an equivalent concern (REACH Art. 57f) (see 4.1.2.6).

4.2 Operational aspects: Testing approaches for P, B and T and data interpretation

This chapter describes different aspects of the complex issue of P, B and T testing approaches and the interpretation of the results obtained.

- In the first part of this section a brief introduction into the ECHA guidance documents for PBT/ vPvB assessment is given (section 4.2.1).
- It is followed by three parts which describe commonly used testing approaches for P, B and T assessment – and the related challenges of data interpretation for P, B and T (sections 4.2.2 – 4.2.4). For each of these parameters conclusions are drawn on the shortcomings of the present testing approaches. If possible, options to overcome these shortcomings are described.
- Finally, in section 4.2.5, proposals are made how to further develop testing approaches and data interpretation within the PBT concept.

Note to the reader: This chapter addresses more than 25 aspects of testing of PBT properties. It covers basic information about ready biodegradability tests, technical details on the documentation of results from the application of specific models as well as experimental challenges in testing highly hydrophobic substances. The separate discussion of aspects related to P, B and T testing could help the reader during reading. As in the previous section, for some aspects additional information is given in brackets.

4.2.1 The ECHA Guidances on PBT/vPvB assessment and endpoint-specific testing

To support the assessment on the operational level, ECHA has developed guidance documents that are not legally binding, but provide technical methods which are relevant for PBT/vPvB assessment as outlined in Annex XIII. Developed by ECHA and involving stakeholders from Member States, industry and NGOs, the guidance document represents a mutually agreed on procedure for the PBT/vPvB assessment:

- The Guidance on IR&CSR Chapter R.11 (ECHA 2017): The 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 guidance documents also provide the interpretation of results and the generation of information that goes 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-standard information can be used in order to assess the PBT/vPvB properties of a substance.

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. There are 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.

4.2.2 Testing approaches for assessment of persistence

In the following sections, three commonly used testing approaches for the assessment of persistence are discussed:

- Ready biodegradability tests (OECD 301 series, OECD 310)(see section 4.2.2.2)
- Enhanced screening test for identification of PBT substance (see section 4.2.2.3 and
- Simulation studies (see section 4.2.2.4).

The discussion of simulation studies in section 4.2.2.4 includes the following important aspects:

- Formation and assessment of non-extractable residues (NERs);
- Determination of degradation half life-times: impact of temperature and assessment in different experimental systems (water and sediment water);
- Degradation half-lives from field studies,
- Sewage treatment plant simulation tests,
- Hydrolysis and
- Identification of transformation products.

Poorly water soluble or sorptive substances are a specific challenge in different testing systems. This is described in section 4.2.2.5.

Experimental challenges in the testing of persistence are summarized in the chapter “Conclusions on testing of persistence” (section 4.2.2.6)

4.2.2.1 Testing of persistency in the present PBT concept

There are three types of tests for assessing persistence (i.e. in terms of biodegradation) within the present PBT/vPvB concept:

- 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, it is not expected that a persistent substance shows degradation (Gartiser et al. 2015). Under the PBT/vPvB assessment, the outcome of the tests on ready biodegradability is considered as screening level information. As a result, the substance is assessed as either not persistent or potentially persistent. In contrast to this very strict system, the enhanced ready biodegradability or inherent biodegradability (i.e. OECD 302 series) tests allow for conditions more favorable for biodegradation.

For substances which are manufactured or used in amounts > 100 t/a, relatively expensive simulation test are requested in order to conclude if a substance is persistent. These simulation tests cover i.e. OECD 307, 308, 309 according to REACH Annex IX and X. The testing conditions of simulation tests are environmentally representative thus realistic degradation half-lives can be derived for various compartments (e.g. soil, marine/fresh/estuarian water, marine/fresh/estuarian sediment). The derived values are then evaluated according 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). However, so far only for soil and water tests are standardized.

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

A test of ready biodegradability has to be performed for all tonnage bands. The criteria for ready biodegradability are very strict. A series of tests have been developed and the application of the different tests for substances according to their properties is outlined in the Guidance on IR&CSR Chapter 7b.

> (Additional information: For poorly water soluble substances, the OECD 301 B, C, D, F and 310 tests are suitable. For volatile substances, the OECD 301C, D, F and 310 tests are suitable. For adsorptive substances, the OECD 301B, C, D, F tests are suitable. According to the OECD guideline, for substances whose solubility in water exceeds 100 mg/L, all the 301 series tests are suitable. The OECD 310 guideline states a maximum for the Henry's law constant of 50 Pa m3 mol-1 for volatile substances).

A review of the ready biodegradability tests identified some shortcomings regarding their accuracy, reproducibility and comparability.

- a better characterization of the inoculum would lead to a better reproducibility of the tests.
- the number of replicates needed is too low.
- 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).

4.2.2.3 Enhanced screening test for identification of PBT substance on screening level

At present, it is not possible to identify a substance as persistent at the screening level. However, conclusive results on persistence at the 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).

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 included as legally binding in the Annex XIII.

4.2.2.4 Simulation studies

The outcome of a simulation test is strongly depending on the experimental approach used and the physico-chemical properties of the substance tested. In the following sections important aspects are described which have to be considered in simulation tests in order to derive correct degradation half life times.

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 non-

extractable residues (NER, see section below) is to be avoided (ECHA 2017).Testing on sediment and soil will be preferred if the water solubility of a substance is below 1 µg/L (ECHA 2017).

Non-extractable residues (NER)

Substances adsorbing or reacting with matrices pose a challenge for the interpretation of simulation studies in soil and sediment. These substances can form so-called "non-extractable residues", which cannot be extracted with common used solvents. In a test system formation of NER results in a reduction of the substance available in the aqueous phase. However, in the environment a release of NERs can take place, depending on the structure of the compound and the environmental conditions. 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 slowly released residues (Gartiser et al. 2015; Kästner et al. 2014, Wang et al. 2016; Trapp et al. 2017).

The nature of NER is largely unknown. A standardized methodology for characterization and quantification is still lacking. Several approaches are proposed such as e.g. isotope mass balancing (labelling of the substances in order to assess their fate), or 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 have been identified as the major challenges, including how NER and bound residues should be defined, determined and interpreted (Gartiser et al. 2015). In a reflection paper on NER for veterinary medicines that applies the OECD 307, it is recommended to use a radio-labeled substance in order to quantify the volatile transformation products, the fraction lost during clean-up of the samples and bound to the soil particles as NER (EMA 2016).

The irreversibly 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 a regulatory treatment of NER, a scientifically based agreement on the following aspects is needed (Gartiser et al. 2015):

- The development of an experimental approach to non-extractability: 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.
- NER in biodegradation studies: Insights on when NER can be disregarded in the mass balance (i.e. irreversibly bound to the matrix and therefore not critical), and when the potential for remobilization can be excluded need to be generated.

Degradation half-lives in simulation studies and impact of temperature

Besides other factors, which are influential as well (see additional information below), temperature has been shown to have a big impact on degradation as well as being readily quantifiable. A temperature of 12°C is proposed as a reference for PBT identification, as has been 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.

(Additional information: Degradation half-life values depend on the test 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 ex-change capacity, redox potential, microbial density or diversity, temperature and humidity (Gartiser et al. 2015). A normalization to specific conditions would enhance the comparability of data obtained for different purposes (e.g. under different regulatory frameworks) (Rauert et al. 2014).)

Degradation half-lives in various experimental systems

Different options for performing the OECD test exist. The substance can be tested in a water system or in sediment water systems. However, no guidance is provided in which cases which options should be used.

The addition of suspended solids in water systems is possible according to the OECD TG (ECHA 2017), however it induces the difficulties with NER and the interpretation of a 2-phase system, i.e. the degradation in the water phase, the degradation of the adsorbed fraction and the NER formation (parent compound as well as possible metabolites). 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 an assessment and the limit of detection can be enhanced using a radio-labelled form of the substance (ECHA 2017).

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 threshold value that lies higher than the one for freshwater.

Degradation half-lives in sediment-water systems

According to the Guidance on IR&CSA, Chapter R.11 (ECHA 2017), for substances with a K_{oc} (sediment) > 2000 an 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). It has been established that disappearance is sensitive to the set-up 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 and Fenner 2015).

Considering that the aerobic water phase in the environment is much bigger than the anaerobic part of the sediment phase when compared to test systems, the degradation rate obtained for substances undergoing fast degradation in anaerobic sediment but persisting in the aerobic water phase might be overestimated.

Currently, several modifications of the sediment-water test are being discussed. Both modifications could lead to an increased formation of NER, complicating the interpretation of the results.

- Spiking highly sorptive substances and substances of low water solubility into the sediment phase. However, threshold values for water solubility and K_{oc} are not yet available.
- Stirring the system to increase the aerobic part of the sediment. It has been shown that aeration of a bigger part of the sediment leads to an increased biodegradation, however the grinding of the

sediment potentially increases the surface for sorption, which makes the interpretation of the results more difficult (Hennecke 2014).

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

Due to the need for a more robust indicator of persistence and comparability between different aquatic systems (i.e. OECD 308 and 309), a bioavailability-corrected and sediment-mass normalized second order degradation constant was proposed by a study. The authors used data from OECD 309 and 308 together with an inverse modelling framework deriving the rate constant. They outline its potential as a system-independent descriptor of degradation in aerobic aquatic systems (Honti et al. 2016).

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, the fluctuation of temperature and humidity, the higher biological activity and the size of the system. However, it might be more difficult to reproduce, compare and interpret field studies in relation to laboratory simulation studies.

Laboratory simulation studies allow the measurement of CO_2-evolution, formation of metabolites and bound residues and therefore enable the estimation of primary degradation rates. From a field study, a dissipation half-life and not a degradation half-life will be derived. 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 guidance on evaluating field studies, i.e. estimating dissipation processes on the soil surface (European Food Safety Authority 2014) (see also the subsection on NERs above for a discussion of the challenges in the interpretation of 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, other data can be considered as well. 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 a carbon balance cannot be established. The synthetic sewage allows for co-metabolism processes. As this setup is very different from environmental compartments, comparing the results is not straight forward and should therefore not be used for P assessment due to its limited transferability.

Hydrolysis

Hydrolysis of a substance (e.g. by opening of an ester bond) demonstrates only primary degradation. The resulting 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 considered. 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 such as dissolved organic carbon (i.e. the sorption behaviour of the substance). There are sub-stances 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.

Identification of transformation products

For substances in the tonnage band > 100 t/yr, transformation products have to be identified 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). Research is being conducted to achieve a 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[21].

An approach for a joint assessment of the persistence of parent compound and its transformation products has been developed using a combination of those tools, i.e. by introducing a metric of "joint persistence". However, the authors also point to the need for better data on environmental half-lives of chemicals and more knowledge on transformation pathways (Ng et al. 2011).

There are a few approaches that can be used to estimate the formation of degradation products and their properties at the screening level.

(Additional information: The **OECD QSAR Toolbox**[22] 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 the 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 tests 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)[23]).

[21] Personal Communication Kathrin Fenner, Eawag, Überlandstrasse 133, CH-8600 Dübendorf, 05.03.2018

[22] http://oasis-lmc.org/products/software/toolbox.aspx

[23] http://oasis-lmc.org/products/models/environmental-fate-and-ecotoxicity/catabol-301b.aspx

4.2.2.5 Poorly water soluble or sorptive substances and underestimation of biodegradability

For poorly soluble substances, biodegradability can be underestimated, as in 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 to homogenize the solution.

According to the OECD 301 guidance, substances above 100 mg/L are considered soluble. The term poorly soluble is however not numerically defined. Due to its sorptive behaviour, part of the substance might be (temporally) not bioavailable, thus the interpretation of simulation studies in soil and sediment systems, as well as field data on soil is difficult (see also section on NER). Dissolved organic carbon (DOC) 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 covalent binding, therefore other structural features might also be important besides K_{oc}. This is a challenge related to NER formation in soil and sediment studies. Defining persistence becomes difficult for sorptive substances because when using radio-labeling 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 the persistence of those substances.

4.2.2.6 Conclusions: Challenges in the testing approaches for persistence and options for further development

Conceptually, persistence is understood as an inherent property of a substance. However, whether a substance will persist in the environment will be determined by a combination of substance-specific characteristics in combination with environmental conditions.

- Therefore, standardization and better characterization of test environments, clear trigger values regarding substance properties for different test types and well-documented experimental reports are crucial.

The choice of the 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 where the substance will reside.

Although some substances might be degraded under anaerobic conditions, those environments will rarely be the compartment the chemical is discharged to. Therefore, it is likely to persist in other (i.e. oxygenated) compartments.

- Degradation data obtained under very specific conditions which are not representative of the average conditions should not be used for drawing a conclusion on persistence.

Mostly due to experimental challenges, volatile, sorptive, poorly water-soluble substances are challenging for P assessment.

- Trigger values (for water solubility, Henry's law constant, K_{oc}) could help identify substances which deserve special attention.
- Enhanced screening tests - on inherent biodegradability and compartment-specific screening tests – should be further developed.. Although the derivation of degradation half-lives for a comparison with the Annex XIII criteria is not possible due to the artificial setup, the aim is to set a threshold for the identification of a substance as persistent at the screening level. This can be achieved by al-

lowing for more favourable conditions than the ones ready-biodegradability tests offer, but avoiding costly simulation studies. However, those tests as well as standards and pass levels still need to be developed (Gartiser et al. 2015).

4.2.3 Testing approaches for the assessment of bioaccumulation

In the following sections, commonly used as well as newly introduced testing approaches for the assessment of bioaccumulation are discussed. The mechanisms responsible for bioaccumulation can be quite different depending on the structural properties of the substances assessed. Bioaccumulation includes bioconcentration as well as biomagnification which can be assessed in aquatic and non-aquatic food webs.

Similar to the assessment of persistence, a large number of aspects are relevant to select the appropriate testing approach for bioaccumulation and to ensure a correct interpretation of the results. The following seven aspects are described in this chapter:

- Bioconcentration factors (BCF) derived from the OECD 305 fish test (section 4.2.3.1)
- Octanol-Water Partition Coefficient (Log K_{ow}) as a screening indicator for bioaccumulation (section 4.2.3.2)
- Cut off values to exclude bioaccumulation (section 4.2.3.3)
- Bioaccumulation and biomagnification in non-aquatic organisms and food webs (section 4.2.3.4)
- Highly hydrophobic substances: bioaccumulation and biomagnification (section 4.2.3.5)
- Ionic substances (section 4.2.3.6) and
- Organ- and tissue-specific bioaccumulation: interactions with proteins and phospholipids (section 4.2.3.7).

Experimental challenges in the testing of bioaccumulation and in the identification of cut off values are summarized in the chapter “Conclusions on testing of bioaccumulation” (section 4.2.3.8)

4.2.3.1 Bioconcentration factors (BCF) derived from the OECD 305 fish 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 a 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 is equal to the ratio of the uptake rate constant divided by the elimination rate constant (i.e. the kinetic BCF). Reporting both factors is desirable to check whether a steady state was reached.

According to the OECD guideline, fish growth during the 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 exists no agreed-upon 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: According to the OECD-Guideline, this 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, a log K_{ow} < 6 and sufficient water solubility may support minimized testing and, thereby, a reduced consumption of fish.
- The dietary bioaccumulation test OECD 305-III: 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 with log K_{ow} > 5 and water solubility below around 0.01-0.1 mg/L dietary studies could be considered, but the aqueous test is always pre-

ferred if possible. However the results of this test 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 K_{ow} 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 K_{ow} of 7.8, and for substances above log K_{ow} > 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 K_{ow} < 6, and if 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. K_{ow} or water solubility, where one or another test should be performed is recommended. For example, for substances with very low water solubility, use of radio-labelling and reporting of the dissolved concentration should be mandatory.

4.2.3.2 Octanol-Water Partition Coefficient K_{ow} as screening criteria for bioaccumulation

Experimental as well as estimated K_{ow} values may be subject to considerable uncertainties, varying often by orders of magnitude (Stieger et al. 2014; Buser et al. 2013). Nevertheless, the K_{ow} is a crucial value determining the fate of the substances, i.e. their partitioning into fatty tissue and serves also as a benchmark for regulatory purposes. For very high K_{ow}, analytical determination is not technically feasible. At present, combining solid-phase microexaction with the well-established "slow-stirring" method allows for measurements of log K_{ow} up to 9 (Jonker 2016).

QSARs can be used for derivation of K_{ow} -values instead, however there is very few (or no) data for validation beyond log K_{ow} ~ 8, which was considered the upper limit for the slow-stirring method (De Bruijn et al. 1989).

Other predictive methods based on polyparameter-linear-free-energy-relationships (ppLFER) are less limited by the application domain than the K_{ow} QSARs, as pointed out in a review of bioaccumulation (Goss et al. 2013). Such relationships describe partitioning to specific storage compartments (such as e.g. phospholipids, storage lipids, proteins) based on several thermodynamic parameters. The use for regulatory purposes is not yet straightforward due to the absence of specific criteria or overall guidance.

4.2.3.3 Cut-off values to exclude bioaccumulation

According to the guidance, several indicators (i.e. average maximum diameter, maximum molecular length, log K_{ow}, octanol solubility) can be used as indicators of a limited uptake in a weight of evidence approach. When this information is combined with "other information" that confirms for example the substances' low uptake in living organisms e.g. by read-across, absence of toxicity or lack of uptake in toxicokinetic studies with animals or also other methods or biomimetic exposure (ECHA 2017), 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 are 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 and Van Der Heijden 2007; Muller and Nendza 2007). A study investigating possible cut-offs for bioconcentration found that the data allow 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 and Nendza 2007). A study investigating field bioaccumulation factors of several brominated flame retardants showed a relationship between BAF and increasing log K_{ow} (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 cut-off either, up to a membrane-water partitioning coefficient of 7.8 (Endo et al. 2011).

Currently, obtaining experimental BCFs for substances with a K_{ow} > 7.8 is not possible. This analytical threshold has been increasing over the past year, as are the assumed "bioaccumulation cut-offs".

Care must be taken in interpreting different endpoints in a weight of evidence approach – an aspect that is in our opinion not sufficiently outlined in the guidance. If the same analytical challenge persists - e.g. slow, but existent uptake kinetics for large, highly hydrophobic molecules - this might 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, such as for example slow uptake due to kinetic effects - an aspect that will not be observed within the time constraints of the tests. Two endpoints that are potentially biased in the same way, should not be considered as supportive of each other.

4.2.3.4 Bioaccumulation and biomagnification in non-aquatic food webs

Substances with a log K_{ow} 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 for biomagnification of in the terrestrial food chain was developed (Armitage and Gobas 2007).

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, which makes an inclusion of data on terrestrial organisms necessary (Goss et al. 2013). For the IT-mass screening as well as for screening level identification of terrestrial biomagnification, a K_{ow}/K_{oa} trigger has been implemented. However, no mandatory procedure and no criteria at the assessment level exist and, only weight of evidence can lead to a conclusion on bioaccumulation properties based on the substance's behaviour in the terrestrial food chain.

An approach of a unifying metric as an alternative to the BCF and which can be related to the BMF is the elimination half-life which can be applied to terrestrial or aquatic species.

New approaches have recently been suggested to include metabolic rate constants derived from *in vitro* test with fish hepatocytes or S9 liver cells in a PBTK model to extrapolate the BCF by in vitro to in vivo extrapolation (Nichols et al. 2013, Armitage and Gobas 2007). The OECD test guideline on the use of in vitro testing for B-assessment is currently under development. However, certain limitations and shortcomings remain.

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, which is why 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).

4.2.3.5 Highly hydrophobic substances: bioconcentration and biomagnification

Experimental challenges

A recent publication on an approach for the development of solutions for highly hydrophobic test substances (i.e. solid phase desorption system) showed that it was possible to test substances up to a log K_{ow} of 7.8 for 8 weeks (Schlechtriem et al. 2016). According to the guidance on IR&CSR Chapter R.11, testing via the aqueous phase becomes increasingly difficult for strongly hydrophobic substances (log K_{ow} > 5 and water solubility below around 0.01-0.1 mg/L). The difficulties include the maintenance of a stable concentration and the detection limit of the substance. The use of radio-labelled 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 a stable concentration is maintained during the test and the detection limit does not allow for aqueous phase testing. It is assumed that substances with high K_{oc} will partition into organic matter and therefore rather be taken up with food. It is possible to translate data from dietary studies into a kinetic BCF to compare it with the Annex XIII criteria. However, only the elimination rate constant can be directly derived from the study and it is therefore recommended to use those studies only as a body of evidence. Nevertheless, the dietary exposure test delivers other valuable parameters such as the dietary chemical absorption efficiency and the whole body elimination rate constant (ECHA 2017). During the preparation of this study, research projects on this topic are in progress and the results could be elaborated due to lack of resources.

A review study on the further development of regulatory bioaccumulation criteria (Schlechtriem et al. 2016) also concludes that for substances with a log K_{ow} > 5 other tests 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 an estimation of the uptake rate constant were reviewed, as it would be very valuable to compare dietary fish bioaccumulation studies with the Annex XIII criteria of REACH. However, the authors concluded, that the accuracy of those models is not high enough (Schlechtriem et al. 2016).

Therefore, for substances with K_{ow} > 5, a clear identification as bioaccumulative substance is difficult within the present Annex XIII criteria of REACH (this also applies to other legislative frameworks relying on the same or similar criteria).

Challenges with estimation software

The BCFBAF module from EpiSuite software (US EPA 2012) assumes a decreasing BCF with increasing log K_{ow} for log K_{ow} above 7. The training data set and the relationships of the previous BCFWIN and the updated BCFBAF model show a linear increase in BCF with increasing log K_{ow} until a log K_{ow} of 7 followed by a decrease. However, there are very little data for substances above log K_{ow} 7. This relationship is not in agreement with the newer findings summarized above, which indicate that there is no solubility or K_{ow} cutoff value that would limit the BCF for high K_{ow}. The number of available data points is rapidly decreasing for very high log K_{ow} (US EPA 2012).

A high K_{ow} 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 and Reichenberg 2006). Because of the slow uptake, an acute toxicity test is not the appropriate way of describing the substances' toxicity: The test duration is too short for the effects to become visible. The same mechanism might also lead to lower measured BCF values (Jonker and Van Der Heijden 2007). Again, data measured more recently indicates that there is no "hydrophobicity cutoff" (Endo et al. 2011).

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

A study investigating sorption of highly hydrophobic substances (log K_{ow} 5.5-7.8) to organic matter in a 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 constantly delivers freely dissolved substance, and feed residues and feces can be removed, equilibrium or the substance with the organic matter is unlikely to be achieved. The presence of organic matter can lead to an underestimation of the BCF by decreasing 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).

4.2.3.6 Ionic substances

Based on an evaluation of preregistered chemicals, it has been estimated that up to 50 % of the 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 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 form 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 that mechanistically model the 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, interactions with various proteins are also possible as discussed for e.g. PFAA (Ng and Hungerbühler 2014).

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

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

- 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, evidence exist that ions can sorb more strongly than their corresponding neutral. However, the authors conclude that no validated model exists to predict the behaviour yet.

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

Proteins can include positively and negatively charged side chains, making sorption (or covalent) binding to proteins more important for the ionic species than for the neutral ones. However, protein

interaction can be very complex and depends on a variety of factors. QSARs have been established 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 and Hungerbühler 2014; Endo et al. 2011).

- In summary, the following 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 K_{ow}-driven bioaccumulation, which is today's state of the art of describing bioaccumulation that can be directly 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 to correctly account for non-lipid bioaccumulation. Bioaccumulation-related processes that could be more relevant for the ionic species than for the neutral form are still not understood well enough to derive quantitative criteria.

4.2.3.7 Organ- and tissue-specific accumulation: protein- and phospholipid-interactions

A class of substances which received a lot of scientific attention during the past years are perfluorinated alkyl acids (PFAAs). By 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 also preferably occurs in certain organs and tissues (Ng and 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 not only vary 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 a specific pKa as a trigger value).

One approach could be the a focus on molecular interactions, as shown for PFAAs in a explorative study(Ng and Hungerbühler 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 to deal 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 with regards to the variety of possible bioaccumulation mechanisms.

Use of PBTK-Models

A study by Schlechtriem et al. (2015) used a "Physiologically based Toxicokinetic Model" (PBTK-model) to model lipid-based bioconcentration factors. This model describes an organism and accounts for different organs as different compartments and different uptake regimes. The model describes lipid-based bioaccumulation. The model has been validated and seems to generate accurate BCF and kinetic uptake and elimination rates in rainbow trout for substances with a log $K_{ow} > 0$. The authors propose to use modelled BCF, BAF, kinetic uptake or elimination rate constants and to compare them with measured data (i.e. OECD 305 test) to enable an assessment of the potential importance of non-lipid bioconcentration. If the experimental and modelled values are in the same range, it can be concluded that the bioconcentration is lipid-driven, if not, further testing might be required. The authors also point out that the bioaccumulation of polar substances will be a future challenge (Schlechtriem et al. 2015).

The approach is useful for assessing organ-specific bioaccumulation and serves as a first indication on the question of whether lipid-driven or other mechanisms led to the resulting experimental BCF. How-

ever, at the present stage the need for a high quality of the experimental data limits the use of the model for regulatory purposes.

Interactions with proteins

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

A study measuring the 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 also present correlations with K_{ow} and poly-parameter linear free energy relationships. However, they also indicate that further research on ionic compounds is needed (Endo et al. 2012).

Another study 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 and Hungerbuehler 2015).

Interactions with phospholipids

Phospholipids have been target tissues for research on the partitioning of neutral as well as ionic compounds (See also the section on ionic substances). Membrane phospholipids exhibit different partitioning properties for a variety of substances other than storage lipids. Recent experimental data and ppLFER-models for neutral organic compounds indicate a higher affinity of H-bond donor compounds to membrane lipids than to storage lipids. Given that, normalization is usually done to a total lipid content (Endo et al. 2011) and accumulation might hence be overlooked.

The membrane-water partition coefficient correlates with the K_{ow} 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 ionic compounds, affinity of membrane phospholipids exceeds the affinity of storage lipids (Escher et al. 2000).

4.2.3.8 Conclusions: Challenges in the testing approaches for bioaccumulation

The **proposed cut-offs (e.g. molecular dimensions, hydrophobicity) for bioaccumulation** are not supported by data, as substances with those properties pose a major analytical challenge. A detailed mechanistic understanding of all the relevant uptake, storage and elimination mechanisms for the different substance classes would help to identify possible cut-off-values, however present state-of-the-art science does not yet allow for it. Substances exhibiting properties that go beyond the current analytical capabilities presently still pose a challenge, as theoretical assumptions cannot be validated.

- As a potential hazard cannot be ruled out, we recommend a conservative approach that altogether avoids the release of such substances to the environment.

Introducing **organic matter** to the system will reduce the overall bioavailability as shown in an aquatic environment (Böhm et al. 2016).

- To assess bioaccumulation in a proper way, it is important that the bioavailable fraction of the chemical is reported, as otherwise bioaccumulation might be underestimated.

Solid-phase microextraction (SPME) tools have proven 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 and they are also listed in the 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 a 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 a failure to differentiate between the bioavailable and bound fraction will lead to false negatives.

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

4.2.4 Toxicity testing of PB or vPvB substances?

The toxicity of a chemical describes its effect within an organism after exposure and is hence linked to bioaccumulation. This effect is dependent on the chemical and environmental conditions. Chemicals that are strongly bioaccumulative often tend to be toxic as well. They show a baseline toxicity, a non-specific narcotic effect. .

Given that the main concern of PBT/vPvB substances is that no safe environmental concentration exists and effects may occur temporally and spatially far away from the source, using a criterion for toxicity stands in contradiction to the PBT-concept. The toxicity criterion does presume a “safe level” indeed, e.g. a NOEC threshold of 0.01 mg/L, implying that no organism will ever be exposed to a level of this substance in which effects might become evident.

- The combination of P and B properties will potentially lead to increased levels in organisms over their lifespan if exposure continues - therefore, no safe levels can be derived.

Several endpoints that are considered for toxicity identification in Annex XIII are assessed as outlined in the CLP Regulation. The concern about PBT/vPvB substances is that persistence and bioaccumulation can lead to effects that will only be observed in the long-term. This means: in time periods which are much longer than the duration of chronic toxicity tests. This might then possibly affect long-living species that exhibit an exposure over their lifetime, leading to an unpredictable rise in the organism’s concentration if an elimination pathway does not exist.

- Therefore, the long-term toxicity tests being conducted on the growth inhibition in invertebrates, fish and aquatic plants might not be sufficient to capture the hazard.

Given that persistence and bioaccumulation can potentially lead to a rise in levels of the substance that can cause effects. This is already taken into account within the vPvB – concept.

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

(Additional information: Non-polar chemicals with a log K_{ow} > 4 are likely to exhibit baseline toxicity. Baseline toxicity is a consequence of the substances’ hydrophobicity and their tendency to

partition into membranes. LC50 data for fathead minnow was used together with the substances' K_{ow}. The threshold value for LC50 of 1 mg/L was translated into mmol/L using an empirically derived relation between log K_{ow} and molecular mass. Then, a relationship between the LC50 (in mmol/L) and log K_{ow} for a chemical that is known to act by narcosis was derived. The intersection of the threshold of LC50 of 1 mg/L and the line of "narcotic action" was at log K_{ow} 4. About 800 substances in a log K_{ow} range of -0.5 and 7.5 were considered. Detailed calculations are displayed in the publications' supporting information (Maeder et al. 2004).)

- Substances with a tendency to bioaccumulate already exhibit baseline toxicity, making an additional criterion for toxicity obsolete.

4.2.5 Testing of P and B: Operational proposals for a further development

In sections 4.2.2 – 4.2.4, many aspects have been described which are important for the testing of substances on persistence and bioaccumulation. Conclusions for P and B have been drawn separately in the subsections 4.2.2.6 and 4.2.3.8. In this section, we want to summarize some important findings related to the testing of persistence and/ or bioaccumulation.

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 assessments. The difficulties associated with a P assessment will lead to false positives. The uptake into microorganisms might be slowed down or hindered within the boundaries of the test setup, leading to a reduction in the observed biodegradation that is larger than theoretically possible under environmental conditions. In the B assessment, for the same reasons the opposite will be the case, i.e. the test will tend to 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 and Van Der Heijden 2007). Improved analytical procedures for **poorly water soluble substances** exist, allowing for determination of the freely dissolved fraction (Schlechtriem et al. 2016).

- Therefore, for substances with limited water solubility and high tendency to sorb, we recommend the establishment of a mandatory testing strategy for bioaccumulation that accounts for its analytical difficulties. This could take the form of e.g. a **mandatory reporting of freely dissolved fractions or the radiolabelling of the substance** to increase the detection limit in BCF studies. The trigger could be set at certain water solubility, and be 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 for neutral, hydrophic substances.

- However, the **definition of the term "highly sorptive"** needs improvement depending on the context. Then this definition could be applied even for different molecular interactions, such as for example NER "sorption", as this process may not only include K_{oc}/K_{ow} but also ionic interactions or covalent bonding.
- Deriving **trigger values through a consideration of 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 or reduced bioavailability due to limited solubility).

Besides substances for which potential bioaccumulation patterns are unknown, the classical **neutral hydrophobics with extreme properties** exist. In those, measuring the K_{ow}, and BCF becomes analyti-

cally impossible. Regulatory treatment of such substances is far from straightforward. First, cut-offs were proposed based on the assumption of a limited uptake at a certain K_{ow}. However, as the analytical techniques progressed, the cut-offs were progressing as well, towards a higher K_{ow} (Müller and Nendza 2007). Choosing a preventive approach in order to avoid the release of potentially persistent and highly bioaccumulative substances, the proposed physicochemical indicators (ECHA 2017) for hinderance 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).

4.3 Procedural aspects: The processes of PBT screening and PBT assessment

4.3.1 Introduction

Various legal frameworks have been developed that 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. All around the world, national, regional and international bodies are developing ways to reduce the risk posed by chemical substances of different concern by using different criteria – all the while paying special attention to PBT and vPvB substances.

The legal constraints of the evaluation process have a direct impact on the control of the release of (potential) PBT substances to the environment. The longer the process of PBT assessment lasts, the longer the use and the emission of the substance continue. Therefore it is important to discuss procedural aspects and to identify options to improve the efficiency of the processes of PBT screening and PBT assessment. Some of these procedural aspects are closely related to conceptual or operational aspects discussed before, there are some overlaps.

The following three procedural aspects have been discussed in the project and in the workshop:

- IT mass screening for potential PBT substances based on data from registration dossiers (see section 4.3.2)
- Experience with PBT assessment in regulations other than REACH (see section 4.3.3)
- Substance evaluation and the sequence of steps for the PBT assessment (see section 4.3.4)

Finally, five proposals are made for a further development of the processes of PBT screening and PBT assessment (see section4.3.5).

4.3.2 IT mass screening for potential PBT substances based on data from registration dossiers

For substances regulated under REACH, the submission of the registration dossier (i.e. substance property information) automatically permits the placement of a substance on the market, whereas for active substances (e.g. biocides, which are regulated under different frameworks in the EU), an authorization for use is only granted after an evaluation of the substance information by the authorities. Given the number of chemicals registered under REACH, an automatized screening procedure is essential to identify substances that might either require a further evaluation of their dossiers, or that 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 through which all registered substances will have to pass. Hence, the criteria used in this process are crucial for the identification of potential PBT/vPvB substances which are not identified as PBT/vPvB by the registrants.

Reviews of dossier compliance have shown that there are considerable issues with the data availability and quality of the registration dossiers (Springer et al. 2015). This shows the need for a strengthening of the IT-mass screening used in the identification of substances that potentially exhibit PBT/vPvB properties that should not rely 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.

QSARs are powerful tools for checking the plausibility of measured values. However, the data used for calibration of QSARs must be of very high quality as well as representative for the considered substances (i.e. in terms of applicability domain). Wrong QSARs 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 has for example been the case in the past with measuring log K_{ow} for high (> 6) K_{ow} substances. For establishing and validating QSARs, experimental data is used on the one hand to derive correlations between physico-chemical properties and endpoints used for PBT/vPvB assessment, and on the other hand also to validate the model. Hence, development of QSARs also strongly relies on high quality data sets.

4.3.3 Experience with PBT Assessment in regulations other than REACH

The PBT-assessment procedure differs within the various legal frameworks within EU. Besides REACH, four other European legislation frameworks exist, that regulate substances according to their intended use. In contrast to REACH, in which registration is warranted through the submission of the registration dossier, substances registered under the following regulations must obtain 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 of 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.

In general, more data are obtained for substances that are registered under regulations which require them to undergo an authorization process. However, the process of PBT/vPvB identification is less clearly defined within some legislation as compared to REACH. The potential releases to the environment are in general considered together with the intrinsic hazard of a substance for its risk assessment.

- Therefore, PBT/vPvB assessment should be done in the same way for all legislations, regardless of its use. A special treatment for different uses could then be considered in a subsequent step, however relying on the same assessment results under all legislations. Even though protection goals might differ, the assessment of the properties should be conducted 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.

First attempts of drugs modelling interactions with proteins show there is a potential but also considerable effort involved in application of those models for regulatory purposes (Ng and Hungerbühler 2014)[24]. In the future, this might result in a screening tool that identifies chemical structures that are

[24] Substances that would make bad oral drugs because of their low solubility and slow adsorption kinetics, can be highly bioaccumulative environmental contaminants (Müller and Nendza 2007)

likely to interact with a set of certain proteins, whose relevance was previously defined. Generation of data for a validation of the model results will be necessary.

- Such a tool could be used also for other groups of chemicals.

4.3.4 Substance evaluation and the sequence of steps for PBT assessment

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. When registrants and authorities disagree, the data are not clear-cut or there are no analytical possibilities to assess the properties needed.

Requesting further information during substance evaluation (can be a very time consuming process, leading to an unnecessary delay of restricting use of potentially hazardous substances.

- There is no incentive to provide all information on adverse effects of a potentially profitable substance (e.g. a major substitute for an already widely used substance as it is the case here) despite rather clear indication for potentially PBT properties.

Moreover, according to the guidance (ECHA 2017), first P is assessed, then B, then 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 also leads 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. For example for DBDPE[25] 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.

4.3.5 Proposals for a further development of the processes of PBT screening and PBT assessment

Within the complex processes of PBT screening and PBT assessment several options exist for further development. Based on the aspects discussed in the previous section 4.3.1 – 4.3.4, we make the following five proposals:

- Extension of the IT mass screening for P and B;
- Increased exchange of experience with PBT assessment between different regulations
- Stronger implementation of the precautionary principle;
- Enhanced use of monitoring data and
- Maximum timespan of two years for data clarification.

These proposals aim to further develop PBT screening and PBT assessment and to enhance their efficiency and effectiveness.

[25] DBDPE (1,1'-(ethane-l,2-diyl)bis[pentabromobenzene], (CAS 84852-53-9)

Extension of IT-mass screening for P and B

Existing criteria (ECHA 2016b) focus on single reported values and only consider screening level information. We propose to additionally include simple checks on whether the chosen tests (e.g. for ready biodegradability) are suitable for the substance in question. Trigger values could include ranges of K_{oc} (or K_{ow}) (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 (see section 4.1.2.2).
- BIOWIN predictions for ranges of degradation half-lives in the different compartments could also be used together with the OECD Pov and LRTP Screening tool[26] for a screening on persistence as a function not only of the degradation rates but also its partitioning behaviour. Furthermore, this tool could also be used to check whether the appropriate compartment for the biodegradation simulation study was chosen, as the fraction of the substances that depend on the compartment where the emissions occur can be calculated.

Additionally, known correlations of endpoints (ECHA 2016b) could be used to check the value's plausibility. E.g., to check whether the bioavailable concentration was reported for the experimental BCF, it could be compared to the water solubility. Thermodynamically predetermined values such as K_{ow}, Koa and H could be checked for their consistency. For known substance classes, also 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 K_{ow} with BCF could be used. Ranges of K_{ow} and water solubility, where analytical difficulties exist, could also be selected for a manual inspection.

Substance classes and substances similar to known PBT/vPvB substances, which show PBT behaviour but whose 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 to be expected to be further developed.

Increased exchange of experience with PBT assessment between various regulations

Bringing experiences from different legislative frameworks together and enabling an exchange of data may help to further strengthen, standardize and speed up the evaluation of substances.

Stronger implementation of the precautionary principle

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

Flexibility in the 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 that show PBT behaviour but which are not captured by the criteria. However, there is little incentive for the registrants to conduct a time consuming comprehensive research on alternative PBT-properties that go beyond the standard information requirements. On the other hand, where non-appropriate and non-standardized methods are applied, a case-by-case discussion without clearly defined criteria can be very time-consuming.

[26] http://www.oecd.org/exposure/povlrtp

Enhanced use of monitoring data

In a WoE 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 are considered to be suitable to give a persistence indication. However, the fact that remote regions are reached also implies partitioning into a mobile phase and transport (and not only persistence), which will not be the case for all potentially persistent substances (i.e. substances that persists in soil and sediment).

It is also expected that substances that are found in the environment in urbanized areas and are continuously present might also pose a risk. This is the effect of long-term continuous exposure, however, the substance might not meet the P criteria in terms of degradation half-lives.

Identification of substances based on their presence in the environment should be understood as a "second choice" option, where an adequate identification has failed in the first place. Considering the possible hazards resulting from continuous substance exposure and/or presence can trigger corresponding regulation. This may affect the discharge or certain usage patterns, even if the substance does not fulfil the persistence criteria outlined in the PBT concept. An inclusion of the factor of "continuous presence" will make the increased use of already available monitoring data for prioritizing substances for further assessment possible.

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. In such a case, a re-assessment of the PBT/vPvB properties could be an option, as their presence could not only be due to continuous discharge but also due to overlooked intrinsic substance persistence. This might result to use non-target screening data as a screening criterion or as additional scenario in IT Mass screening

Maximum time span of two years for data clarification

The analysis of case studies of PBT assessments (see Annex 6.4) has shown that requesting further information during substance evaluation (i.e. if there is an indication that the substance might exhibit PBT/vPvB properties) can be a very time-consuming process, that can cause an unnecessary delay in the restriction of potentially hazardous substances.

For the creation of an incentive for submission of compliant dossiers and to avoid time consuming legal cases, a maximum timespan of two years starting at the first information request by the competent authorities 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. In specific cases the time span could be elongated if the required tests need a longer time span.

5 Overview

In the following table, the most important proposals for further development of the PBT concept from chapter 4 are clearly summarized in a table, divided into the three aspects as well in P, B and T. For details, see subsections of chapter 4.

Table 5: Overview on the main proposals for further development of the PBT concept. For details, see chapter 4.

Level	General proposals	P	B	T
Conceptual aspects	► Uncertainty of the "PBT-ness": prioritize substances for monitoring ► Develop criteria for the combination of persistence and mobility ► Developing a group of "P and potentially B": 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 ► Giving more weight to persistence. Avoid release of substances which are persistent.	► Develop of P criterion for air – screening and assessment level ► Develop a broader understanding of partitioning and persistence ► Consider very high persistent substances as substances of equivalent concern ► Consider substances found in remote areas due to processes such as particle binding as substances of very high concern	► Develop screening level criteria for non-lipid bioaccumulation ► Adopt elimination rate constant or elimination half-life ► Approach determination of the bioavailability and the uptake efficiency	► Consider uncoupling T from PB assessment, as it contradicts the "no safe level"-paradigm
Operational aspects	► Substances with limited water solubility ► Dissolution kinetics ► "poorly water soluble" and "highly sorptive" ► Neutral hydrophobics with extreme properties	► Update tests requirements on ready biodegradability regarding better characterization of the inoculum, higher number of replicates, definition of a threshold for maximum allowable elimination due to adsorption ► Develop enhanced screening tests, tests on inherent biodegradability and compartment-specific screening tests ► Review testing conditions of simulation studies e.g. temperature dependence of degradation half-lives, non-extractable residues	► Define K_{ow} as screening criteria for bioaccumulation ► Develop cutoffs for indicators of a limited uptake (average maximum diameter, maximum molecular length, log K_{ow}, octanol solubility) ► Develop guidance on how to quantify the bioavailable fraction	► Bioaccumulative substances are already baseline toxicants.

Level	General proposals	P	B	T
		► Approach substances difficult to assess: Highly volatile substances and Poorly water soluble or sorptive substances		
Procedural aspects	► Increased exchange of experience from other regulations, evaluation of tools and approaches from research on pharmaceuticals. ► Stronger implementation of the precautionary principle in substance identification ► Enhanced use of monitoring data ► Process efficiency: maximum time span as an incentive for submission of compliant dossiers; consideration of "freezing" of registrations until required information on potential hazard is provided	► IT-mass screening for P	► IT-mass screening for B	

6 List of Annexes

- Annex I: Overview of the evaluated substances
- Annex II: Red (8 substances)
- Annex III: Substances from the Iceberg List
- Annex IV: Analysis of PBT assessments: case studies

6.1 Annex I: Overview of the evaluated substances (see chapter 2)

Table 6: Overview of the evaluated substances

Substance	CAS	Rappoteur	Conclusion/ Proposal	Comment[27]
1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naph-thyl)ethan-1-one	1506-02-1	Netherlands	nonPBT	Old PBT evaluation
1,2,3-trichlorobenzene	87-61-6	Denmark	PBT	Old PBT evaluation
1,2,4-trichlorobenzene	120-82-1	Denmark	PBT	Old PBT evaluation
2,2'[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[N-(2,4-dimethylphenyl)-3-oxobutyramide], (Synonym; Pigment Yellow 13)	5102-83-0	United Kingdom	nonPBT	Old PBT evaluation
2,4,6-trichlorophenol	88-06-2	Austria	nonPBT	Old PBT evaluation
2,4-dinitrotoluene_(2,4-DNT)	121-14-2	Germany	nonPBT	Old PBT evaluation
2-ethylhexyl10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	15571-58-1	United Kingdom	under evaluation	Old PBT evaluation
2-Propenoic_acid,_2-methyl-,_C9-11-isoalkyl_esters,_C10-rich	90552-07-1	United Kingdom	nonPBT	Old PBT evaluation
4,4'-methylenedicyclohexyl_diisocyanate	5124-30-1	France	nonPBT	Old PBT evaluation
4-chloro-1-(2,4-dichlorophenoxy)-2-nitrobenzene	2392-48-5	Sweden	nonPBT	Old PBT evaluation
Alpha,alpha,alpha,4-tetrachlorotoluene	*5216-25-1*	*Spain*	*nonPBT*	Old PBT evaluation *Substance is also on the new list (86), however with a different CAS-Nr.*
Benzenesulfonicacid,C1444-branchedandlinearalkylderives.,calciumsalts	91696-73-0	France	under evaluation	Old PBT evaluation
Cyclododecane	294-62-2	Sweden	vPvB	Old PBT evaluation

[27] The group continues the work which has been done before by a PBT group of the Joint Research Centre of the EU Commission. In the following, if necessary a distinction is made between the "current" PBT Expert Group (organized by ECHA) and this earlier group ("former PBT expert Group") of JRC

Substance	CAS	Rappoteur	Conclusion/ Proposal	Comment[27]
Decanoic_acid,ester_with_2-ethyl-2-(hydroxymethyl)-1,3-propanediol_octanoate	11138-60-6	Sweden	nonPBT	Old PBT evaluation
Di(tertdodecyl)pentasulphide	31565-23-8	United_Kingdom	under evaluation	Old PBT evaluation
Dibenzyltoluene	26898-17-9	France	nonPBT	Old PBT evaluation
Diisodecyl_phenyl_phosphite	25550-98-5	United_Kingdom	nonPBT	Old PBT evaluation
Dioxobis(stearato)trilead	12578-12-0	Norway	nonPBT	Old PBT evaluation
Dodecylphenol	27193-86-8	United_Kingdom	nonPBT	Old PBT evaluation
Ethanol,2,2'-iminobis-,N-C12-18-alkyl_derivs.	71786-60-2	Sweden	nonPBT	Old PBT evaluation
Hydrocarbons,_C4,_1,3-butadiene-free,_polymd.,_dibutylene_fraction,_hydrogenated	93685-78-0	Finland	nonPBT	Old PBT evaluation
Hydrocarbons,_C4,_1,3-butadiene-free,_polymd.,_triisobutylene_fraction,_hydrogenated	93685-81-5	Finland	nonPBT	Old PBT evaluation
Methyl_2-(4-(2,4-dichlorophenoxy)phenoxy)propionate	51338-27-3	France	nonPBT	Old PBT evaluation
N,N-dicyclohexylbenzothiazole-2-sulphenamide	4979-32-2	Germany	nonPBT	Old PBT evaluation
4-(2,4-dichlorophenoxy)aniline	14861-17-7	Sweden	nonPBT	Old PBT evaluation
Nitrofen	1836-75-5	Netherlands	PBT	Old PBT evaluation
Nonylphenol	25154-52-3	United_Kingdom	nonPBT	Old PBT evaluation
N-tert-butylbenzothiazole-2-sulphenamide	95-31-8	Germany	nonPBT	Old PBT evaluation
Octabenzone	1843-05-6	France	nonPBT	Old PBT evaluation
Pentachlorobenzenethiol	133-49-3	Finland	vPvB	Old PBT evaluation
Perylene-3,4:9,10-tetracarboxylic_dianhydride	128-69-8	Finland	nonPBT	Old PBT evaluation
Sulfonicacids,_C1021-alkane,_Ph_esters	91082-17-6	Denmark	nonPBT	Old PBT evaluation
Sulfonylchlorides,C1634-alkane,chloro	91082-32-5	Denmark	nonPBT	Old PBT evaluation
Terpenes_and_Terpenoids,_turpentine-oil,3-carene_fraction	91770-80-8	Finland	nonPBT	Old PBT evaluation
Terpenes_and_Terpenoids,_turpentine-oil,_alpha-pinenefraction	65996-96-5	Finland	nonPBT	Old PBT evaluation

Substance	CAS	Rappoteur	Conclusion/ Proposal	Comment[27]
Tetrachlorophthalic_anhydride	117-08-8	Spain	nonPBT	Old PBT evaluation
Tetraethyl_lead	78-00-2	United_Kingdom	nonPBT	Old PBT evaluation
Triphenylphosphine	603-35-0	Germany	nonPBT	Old PBT evaluation
Bis(tributyltin)_oxide_(TBTO)	56-35-9	Norway	PBT	Old PBT evaluation
N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine_(6PPD)	793-24-8	United_Kingdom	nonPBT	Old PBT evaluation
Tert-dodecanethiol	*25103-58-6*	*United_Kingdom*	*under evaluation*	Old PBT evaluation
Ethylenebistetrabromophthalimide	32588-76-4	France	nonPBT	Old PBT evaluation
1,4_Benzenediamine,_N,N'-mixed_Phand_tolyl_derivs	68953-84-4	Germany	nonPBT	Old PBT evaluation
2,4_Dinonylphenol,_branched	84852-14-2	United_Kingdom	deferred	Old PBT evaluation
1H3a,7-Methanoazulene,2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-,3R-(3.alpha.,3a.beta.,7.beta.,8a.alpha.)-	469-61-4	France	nonPBT	Old PBT evaluation
Methylnaphthalene	91-57-6	Germany	nonPBT	Old PBT evaluation
Amines,_coco_alkyl	61788-46-3	Germany	nonPBT	Old PBT evaluation
Hexachlorocyclopentadiene	77-47-4	Norway	deferred	Old PBT evaluation
1H-Indene-5-ethanol,_2,3-dihydro-beta.,1,1,2,3,3-hexamethyl-	1217-08-9	Sweden	nonPBT	Old PBT evaluation
Paraffin_waxes_and_Hydrocarbon_waxes,chloro	63449-39-8	Finland	nonPBT	Old PBT evaluation
2,6-di-tert-butyl-p-cresol(BHT)	128-37-0	Sweden	nonPBT	Old PBT evaluation
retinol	68-26-8	Sweden	nonPBT	Current PBT evaluation
2-(4-tert-butylbenzyl)propionaldehyde_(Lysmeral)	80-54-6	Sweden	nonPBT	Current PBT evaluation
N-1-naphthylaniline	90-30-2	Germany	under evaluation	Current PBT evaluation
tetrabromophthalic_anhydride	632-79-1	United_Kingdom	nonPBT	Current PBT evaluation
2-ethylhexyl_diphenyl_phosphate	1241-94-7	United_Kingdom	nonPBT	Current PBT evaluation
Ionone,_methyl-	1335-46-2	United_Kingdom	nonPBT	Current PBT evaluation
3,7,11,15-tetramethylhexadec-1-en-3-ol (Isophytol)	505-32-8	na	nonPBT	Current PBT evaluation

Substance	CAS	Rappoteur	Conclusion/ Proposal	Comment[27]
α,α,α,2-tetrachlorotoluene	*2136-89-2*	*na*	*nonPBT*	Current PBT evaluation *Substance is also on the old list, however with a different CAS-Nr.*
2-hexyldecan-1-ol	2425-77-6	na	nonPBT	Current PBT evaluation
2-octyldodecan-1-ol	5333-42-6	France	nonPBT	Current PBT evaluation
retinyl propionate	7069-42-3	Sweden	not classified/ or not evaluated	Current PBT evaluation
3,7,11-trimethyldodeca-1,6,10-trien-3-ol,mixed_isomers_(Nerolidol)	7212-44-4	Austria	nonPBT	Current PBT evaluation
Cashew,_nutshell_liq.	8007-24-7	United_Kingdom	nonPBT	Current PBT evaluation
Rosin	8050-09-7	Finland	nonPBT	Current PBT evaluation
Rosin,maleated	8050-28-0	Finland	nonPBT	Current PBT evaluation
1,2-dichloro-4-(trichloromethyl)benzene	13014-24-9	na	under evaluation	Current PBT evaluation
tert-dodecyl_mercaptan,TDM,tert-dodecanethiol	*25103-58-6*	United_Kingdom	*nonPBT*	Current PBT evaluation *Substance is also on the old list, however with a different CAS-Nr*
2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol	28219-61-6	na	nonPBT	Current PBT evaluation
isodecyl_diphenyl_phosphate	29761-21-5	United_Kingdom	nonPBT	Current PBT evaluation
2,5-Furandione,dihydro-,mono-C15-20-alkenyl_derivs.	68784-12-3	Norway	nonPBT	Current PBT evaluation

6.2 Annex II: Red (8 substances) (see chapter 2.1.1)

2,2'[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[N-(2,4-dimethylphenyl)-3-oxobutyramide] (C.I.Pigment Yellow 13) (CAS 5102-83-0)

Keywords: nonB_lowoctanol (cutoff for octanol solubility)

A calculated log K_{ow} of 8.1 was reported, BCF is 22000 (according to TGD 2003) and 10 (according to EPISuite's BCFBAF). This difference is due to the fact, that BCFBAF equation is based on an assumption, that for substances with log K_{ow} > 7 the BCF decreases with increasing log K_{ow}. The decision itself however is not based on K_{ow} or BCF, but on the octanol solubility, supported by a discussion paper which proposed a cutoff level (Discussion paper for the TC NES subgroup on PBTs, Mike Comber, Steve Robertson and Dick Sijm, 2005). Without further information provided in order to prove a lack of uptake, this decision is neither supported by the ECHA Guidance Chapter R.11 nor is scientifically backed up (nendza2007). As the substance is clearly P (and vP) and its log K_{ow} indicates a high potential for bioaccumulation, vPvB properties cannot be excluded.

Dibenzyltoluene (CAS 26898-17-9)

Keywords: conflicting results (for P)

Conflicting results exist regarding persistence: The substance is not readily biodegradable according to BIOWIN and CATABOL predictions and OECD 301 C test. BIOWIN 2 and 3 predict biodegradation for dibenzyltoluene and its expected metabolite according to CATABOL is benzoic acid. A closed bottle test showed disappearance of aromatic rings (58% by 62 days). The test result is in conflict with CATABOL prediction showing < 1% probability for metabolites with less than 2 aromatic rings, the first metabo-lite predicted by CATABOL is a benzoic acid derivative of dibenzyltoluene. It is therefore unclear, which metabolites are expected.
The benzoic acid derivative (i.e. the metabolite predicted by CATABOL) has a high log K_{ow} (5.58 esti-mated by KOWWIN), however it is expected to be in ionized form in the environment, which is also reflected by is estimated BCF of 5.6 (BCFWIN). The parent compound's estimated log K_{ow} is 6.59 (KOWWIN) and BCF 23480 (BCFWIN)
An OECD 305 test with dibenzyltoluene provided BCFs of up to 8180 during a 10-week test. 4 different peaks were identified, indicating that the test substance was an isomer mixture, for each of the peaks, BCF range above 2000 were reported. It was argued, that due to the uncertainty regarding the identity of the peaks, the identity of the test substance cannot be reliably connected to the substance and there-fore, this results are not considered for further assessment.
Regarding the high potential for bioaccumulation of both (i.e. parent substance and possible metabolite) and the conflicting data regarding persistence and possible metabolites, we conclude that it cannot be excluded, that a persistent and bioaccumulative metabolite is formed or there are bioaccumulative constituents in the commercial mixtures.

Hydrocarbons, C4,_1,3-butadiene-free,_polymd.,_triisobutylene_fraction,_hydrogenated (CAS 93685-81-5)

Keywords: conflicting_results (for B); impurities

Very high estimated BCF for the main constituent (2,2,4,6,6,-pentamethylheptane) are available, i.e. 7464 (with log K_{ow} of 5.94) and 16900 (with log K_{ow} 6.4), experimental BCF show conflicting results, i.e. 880 in a flow through bioconcentration study where steady state has been reached after 4 days. A dietary accumulation test reports a BCF of 3141, however it is argued, that direct BCFs obtained from dietary may generally provide too conservative impression on bioaccumulation.
The big difference between estimated and measured BCFs is attributed to the known ability of fish to metabolize this type of hydrocarbons. It is noted that there is only information on bioaccumulation potential in fish, and other animals may not have the capability to metabolize hydrocarbons as effectively. It is concluded that the substance has a moderate to high potential for bioaccumulation, but it is concluded not to meet B criterion as a borderline case.
The decision on non B is questionable, especially as it is known that fish metabolize this type of hydrocarbons very well, whereas this might not be true for other animals. The predicted bioaccumulation potential is high, also experimental BCF >2000 are obtained in a dietary study. Further, considering a BCF-K_{ow} relationship according to Connell et al. 1988, time to equilibrium would be around 9 months for substances with K_{ow} of 6. Four days to steady state seem to be rather low.
Only the main constituent was assessed, making up 85%. It would be theoretically possible, that other constituents (3-7%) also exhibit PBT properties.

Perylene-3,4:9,10-tetracarboxylic_dianhydride (CAS 128-69-8)

Keywords: nonB_lowoctanol (cutoff for octanol solubility)

The substance is considered as non B due to its low octanol solubility. This neither is not scientifically supported (Nendza2007) nor outlined this way in the present ECHA guidance document. Low octanol solubility has to be supported with more information on e.g. critical body burden, toxicokinetics or others (Chapter R.11).

Ethylenebistetrabromophtathalimide (CAS 32588-76-4)

Keywords: nonB_lowoctanol (cutoff for octanol solubility)

The substance is potentially P/vP. The substances' calculated K_{ow} is very high 9.79 according to (KOWWIN v1.67). A low bioaccumulation potential was assumed due to reduced storage and uptake, argued with its low octanol solubility and molecular dimensions as proposed by in the discussion paper (Discussion paper for the TC NES subgroup on PBTs, Mike Comber, Steve Robertson and Dick Sijm, 2005), however this cutoff levels lack scientific support (Nendza2007).

Paraffin_waxes_and_Hydrocarbon_waxes,chloro (CAS 63449-39-8)

Keywords: impurites; conflicting_results; highK_{ow}_notB (**not B due to estimated BCF, potential PBT impuritie)**

The indicated CAS number is a generic CAS number referring to an unspecified chain length. Regarding chlorinated paraffins, a variety of CAS numbers exists

Chemical Name	CAS Number
Alkanes C10-13, chloro	85535-84-8
Alkanes C14-17, chloro	85535-85-9
Alkanes C18-28, chloro	85535-86-0
Alkanes, C10-21, chloro	84082-38-2
Alkanes, C18-20, chloro	106232-85-3
Alkanes, C6-18, chloro	68920-70-7
Alkanes, chloro; chloroparaffins	61788-76-9
Alkanes, C12-13, chloro	71011-12-6
Alkenes, polymerized, chlorinated	68410-99-1
Alkenes, C12-24, chloro	68527-02-6
Chlorowax	51990-12-6
Paraffin waxes, chloro	63449-39-8

Three main categories of the strait chain paraffins are distinguished: Short (SCCP, C10-C13), medium (MCCP, C14-C17), and long (LCCP, C18-C30), depending on the carbon chain length.
However, only the long chain (C18-30) chlorinated paraffins are considered for the assessment in the substance fact sheet, concluding there is no bioaccumulation. Bioaccumulation strongly depends on chain length. As pointed out in the substance fact sheet, studies indicate decreasing bioaccumulation with increasing chain length.
Accordingly, within REACH legislation, the SCCPs (CAS 85535-84-8) are on the candidate list for its PBT/vPvB properties and the MCCPs (CAS 85535-85-9) are on the CoRAP list suspected for PBT/vPvB properties.
There is a full registration under the generic CAS Nr. (63449-39-8), with PBT assessment done for the LCCP only concluding non PBT.
The Canadian (EC, 2008) and the UK (EA, 2009) risk assessments agree that at least some congeners of the LCCPs have a high bioaccumulation potential, but empirical data is lacking.
According to the substance fact sheets, impurities of C17-paraffins are in the range of 10-20%. Belonging to the MCCPs, which are suspected PBT/vPvB substances, the assessed mixture itself could contain considerable amount of a potentially PBT/vPvB substance.
The decreasing trend regarding bioaccumulation could also be a consequence of kinetic disequilibrium or analytical challenges faced with substances with such high K_{ow} (meyerreichenberg2006, heijden2007).
All BCF studies were performed above water solubility, and therefore are considered unreliable. Although in the dietary studies, the concentrations in the diet exceeded the concentrations in the animals, it is not clear whether the studies were long enough to reach steady state conditions. As there has been shown that uptake can occur via diet and the substance is highly hydrophobic according to its high log K_{ow}, bioaccumulation may occur, however it takes longer for the concentration achieve their steady state levels. The decision on nonB relies on the estimated BCF, derived from a relation assuming de-creasing BCF with increasing log K_{ow}.

2,6-di-tert-butyl-p-cresol(BHT) (CAS 128-37-0)

Keywords: conflicting_results; metabolite_not_assessed; no_data_4all_endpoints (**conflicting results for B, persistence and possible metabolite not assessed)**

Experimental BCF values range from 200 to 2800. Despite use of dispersants (with concentrations below the solubility limit) and non-optimal sampling regime the study is regarded reliable. However, use of dispersants might lower the obtained BCF values as a fraction of the substance might form micelles and will therefore not be bioavailable, but still contribute to the measured concentration in the water which will lead to lower BCF values. The log K_{ow} ranges between 4.2 and 6.2, indicating potential for bioaccumulation. Based on the statement that the substance does not meet the B criterion, neither P nor T is further discussed. 2,6-di-tert-butyl-m-cresol degrades in water to several transformation products with unknown properties.

tetrabromophthalic_anhydride (CAS 632-79-1)

Keywords: fast_hydrolysis; conflicting_results (**fast hydrolysis and conflicting_results)**

According to the registration dossier, the substance does not meet the PBT or vPvB criterion as it undergoes rapid hydrolysis to tetrabromophthalic acid which itself does not meet the criteria for B, vB or T. The rate of hydrolysis is not currently known but is expected to be reasonably rapid.
Regarding hydrolysis, as stated in the report, it is crucial to know the rate as this determines whether the substance is able reach environmental compartments as sediment/soil where hydrolysis is not relevant.
The water solubility (241 mg/l at 25°C) reported CSR (chemical safety report) is also considered uncertain, EPISuite's WSKOWWIN (0.019 mg/l) and WATERNT (64.9 mg/l) predict much lower solubility, which then questions the relevance of the hydrolysis.
A measured log K_{ow} value of 1.98 for the anhydride was reported in the CSR (unpublished industry study), however the reliability of this value is considered questionable by PBT EG and rather attributed to the hydrolysis product then to the substance itself. Values calculated with KOWWIN indicate 5.63 for the anhydride and 4.63 for the acid.
The substance itself is concluded to be potentially bioaccumulative, the hydrolysis product is not.
A slower hydrolysis rate rate and lower water solubility than expected could mean that the substance is P and B, possibly vPvB.

6.3 Annex III: 11 Substances from the Iceberg List (see chapter 3.2.2 and 3.2.3)

Table 7: Substances from the iceberg list being potentially PB, PvB, B and vB according to EpiSuite estimates

	Name of substances (CAS)	non-linear probability	ultimate biodegradation	MITI non-linear model prediction	BCF estimation	$logK_{ow}$ (KOAWIN estimate)
PB	Dimethyl-TBBPA (Me-TBBPA, 37853-61-5)	0,00	1,06	0,01	2.983	8,33
	Hexabromobenzene (HBB / HxBBz, 87-82-1)	0,00	1,16	0,01	4.699	7,33
	Hexachlorocyclo-pentenyl-dibromocyclooctane (HCDBCO, 51936-55-1)	0,00	0,39	0,00	4.754	7,91
	Hexamethylcyclot-risiloxane (D3, 541-05-9)	0,46	2,71	0,02	2.457	5,64
	Perfluorooctanesul-fonamide (PFOSA, 754-91-6)	0,00	0,10	0,00	3.126	5,80
PvB	Tetrabromo-bisphenol A (TBBPA, 79-94-7)	0,00	1,35	0,01	10.580	7,20
	Pentabromoeth-ylbenzene (PBEB, 85-22-3)	0,00	1,34	0,01	7.729	7,48
	Pentabromotoluene (PBT, 87-83-2)	0,00	1,37	0,02	19.020	6,99
B	Alkanes, C14-17, chloro medium chain chlorinated paraffin (MCCP, 85535-85-9)	0,42	2,81	0,46	2.152	7,40
vB	Triphenyltin (TPhT, 639-58-7)	0,95	2,41	0,00	6.785	4,19
	octocrylene (2-ethylhexyl-2-cyano-3,3-diphenyl-2-propenoate) (OCT, 6197-30-4)	1,00	2,80	0,13	16.120	6,88

6.4 PBT assessment of substances: Case studies

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.

Remark: These case studies have been made in the first part of the project. They correspond to the dtate of the discussion of the substances by spring 2016.

6.4.1 Case study - DBDPE

DBDPE (1,1'-(ethane-l,2-diyl)bis[pentabromobenzene], CAS 84852-53-9) was included in the Community 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 an 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 these 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.

6.4.2 Case study - Dechlorane Plus

For Dechlorane Plus (13560-89-9), no K_{ow} is reported (data waiving), the substance is considered "unsoluble" (ECHA). The log K_{ow} 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 substance's properties needed for PBT/vPvB assessment. Further, the substance has been included in ChemSec's SIN List[28] 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[29]. The substance was first registered 25. June 2013. Since April 2017, the substance is handled "as if it is a PBT", as the manufacturer accepted to do so. Finally, an expert panel concluded on vPvB properties of the substance in a weight of evidence approach.

[28] http://chemsec.org/business-tool/sin-list/

[29] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/442688/HSAC-comments-on-Dechlorane-Plus-fact-sheet.pdf

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.

6.4.3 Conclusion

As illustrated by the two case studies, requesting further information during the assessment of the substance (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.

There is no incentive to provide all information on adverse effects of a potentially profitable substance (e.g. a major substitute for an already widely used substance as it is the case here). As can be shown in the present case, a substance can still be marketed for at least 8 years without any restrictions, despite rather clear indication for potentially PBT properties.

According to the guidance (ECHA 2017), first P is assessed, then B, then 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 also leads 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. There is no harmonized strategy regarding the requests for additional tests between the MS CA. E. g. simulation studies. Some MS CA request first OECD 309, followed by 308. Other request in addition OECD 307. Requesting more data leads to a longer timespan until risk management options can be faced.

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