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Developing a weight-of-evidence methodology for persistence assessment of substances in the environment

Christopher B. Hughes[1,#], Megan Griffiths[1,##], Simon Cook[1,*], Dik van de Meent[2], John Parsons[2,†], Delina Lyon[3,*], and Amelie Ott[4]

[1]Chemical Risk, Ricardo, Oxfordshire, United Kingdom
[2]Association of Retired Environmental Scientists (ARES), Odijk, The Netherlands
[3]Concawe, Brussels, Belgium
[4]International Collaboration on Cosmetics Safety (ICCS), New York, United States

*Corresponding authors: Simon Cook. Email: simon.h.cook@ricardo.com. Delina Lyon. Email: environment@concawe.eu

[#]Present address: Embark Chemical Consulting Ltd, Chester, UK

[##]Present address: Penman Consulting Ltd, Wantage, UK

[†]Author deceased: date of death: November 12, 2024.

Abstract

The environmental persistence of a substance plays a key role in determining its exposure to humans and other organisms, making this an important component in the risk assessment and management of chemicals. Regulatory persistence assessments generally involve a comparison of degradation half-lives against threshold criteria for different environmental compartments, typically water, sediment, and soil. Half-lives are commonly determined using OECD guideline biodegradation simulation tests. Other information may be considered relevant to persistence assessments, such as results from biodegradation screening tests, quantitative structure–activity relationships, field studies, monitoring data, and nonstandard laboratory experiments. All available relevant information should be considered together in a weight-of-evidence approach, but clear guidance is currently lacking both for evaluating the quality of individual studies and for combining these in a single weight-of-evidence determination. Here, we propose a systematic methodology to collate, evaluate, and integrate relevant information to reach robust, transparent, and consistent conclusions for persistence assessments. First, the quality (reliability and relevance) of individual studies within each information category, or "line of evidence," is evaluated using a novel scoring methodology. Then, information from different studies is combined to determine outcomes for each line of evidence. Finally, a stepwise weight-of-evidence approach is applied to integrate outcomes from different lines of evidence to reach an overall conclusion for the persistence assessment. Consistency of information is evaluated at various stages in line with weight-of-evidence best practice. The methodology has been developed in accordance with principles of the European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulatory framework, test guidelines, and guidance, while being flexible to accommodate different regulatory practices. The methodology has been implemented in a freely available Excel-based software tool, the Persistence Assessment Tool (PAT), and is demonstrated using a case study substance hexabromocyclododecane.

Keywords: persistence; biodegradation; weight-of-evidence; persistent, bioaccumulative and toxic or very persistent, very bioaccumulative (PBT/vPvB) assessment; persistent, mobile and toxic or very persistent, very mobile (PMT/vPvM) assessment

Introduction

Persistence assessment is a regulatory process to evaluate the potential of a substance to resist degradation processes in the environment. Persistent substances are associated with increased and potentially poorly reversible exposure, and hence greater risks, to humans and the environment (Boethling et al., 2009; Cousins et al., 2019; Mackay et al., 2014). Historically, persistence in combination with bioaccumulation and toxicity has led to substances being prioritized for regulatory action as part of so-called persistent, bioaccumulative, and toxic, very persistent, very bioaccumulative (PBT/vPvB), and persistent organic pollutant (POP) assessment frameworks (Matthies et al., 2016). More recently, the concept of persistence in combination with mobility has been introduced as a means to identify substances that may pose a threat to drinking water, with so-called persistent, mobile, and toxic, and very persistent, very mobile (PMT/vPvM) hazard classes being introduced under EU regulatory frameworks (Hale et al., 2022; Mohr et al., 2024). In 2023, PBT/vPvB and PMT/vPvM were also introduced as new hazard classes into the EU's Classification, Labelling and Packaging (CLP) regulation (EC, 2008).

Under established persistence assessment frameworks, substances are typically assessed by comparing their degradation half-lives in the environmental compartments water, sediment, and soil against fixed cut-off criteria (Moermond et al., 2012). The OECD guideline biodegradation simulation tests are typically

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used to generate degradation half-lives for this purpose, with OECD 307 (Aerobic and Anaerobic Transformation in Soil), 308 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems), and 309 (Aerobic Mineralisation in Surface Water—Simulation Biodegradation Test) supplying half-lives for soil, sediment, and water compartments, respectively (OECD, 2004, 2025a, 2025b).

Observable degradation half-lives of substances are inherently highly variable due to numerous environmental (e.g., concentration and diversity of degrading organisms, matrix characteristics, presence of oxygen or other electron acceptors, nutrients, pH, organic carbon, and mineral fractions) and experimental (e.g., test substance concentration and dosing, inoculum handling, test setup and system dimensions, aeration, agitation, temperature, light conditions, sampling, and analysis) factors (Boethling et al., 2009; Hughes et al., 2020; Hughes, Griffiths, & Swansborough, 2022; Mackay et al., 2014; Tian et al., 2024). Substances with difficult test properties (e.g., poor water solubility, high volatility or sorption) or complex composition can also present challenges in their testing and assessment (Birch et al., 2023; Davenport et al., 2022; Hughes, Griffiths, & Brown, 2022; Hughes, Griffiths, & Pemberton, 2022; Hughes, Griffiths, & Swansborough, 2022). Other types of information may be considered relevant when assessing persistence in addition to degradation half-lives. These include biodegradation screening tests (ready, inherent, enhanced ready), quantitative structure–activity relationship (QSAR) predictions, monitoring data, field studies, and nonstandard degradation experiments.

The EU framework for evaluating the persistence of industrial chemicals, biocides, and pharmaceuticals is laid out in Annex XIII of the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation, and detailed in European Chemicals Agency (ECHA) guidance (EC, 2006; ECHA, 2023a, 2023b). The guidance describes an Integrated Assessment and Testing Strategy (ITS) by which relevant information on persistence should be collated and analyzed to reach conclusions for a substance (Figure 1). Annex XIII of REACH requires that persistence assessments follow a "weight-of-evidence determination," considering all available relevant information together in a single determination.

Recent efforts have helped to improve the conceptual understanding and application of weight-of-evidence (WoE) in regulatory assessments (ECHA, 2017; European Food Safety Authority [EFSA], 2017; OECD, 2019; Suter et al., 2020). Approaches to evaluate the quality of individual studies and to weigh and combine these to reach overall conclusions are important elements of WoE, with substantial progress being made to support ecotoxicity and bioaccumulation assessments (Arnot et al., 2023; Moermond et al., 2016). Similar needs have been identified for persistence assessments, with guidance currently lacking both for evaluating the quality of individual studies and for combining these in a single WoE determination (Davis et al., 2024; Hughes, Griffiths, & Swansborough, 2022; Redman et al., 2022).

This work aimed to develop a transparent and systematic WoE methodology for persistence assessments, including a scoring methodology for the quality evaluation of individual studies,

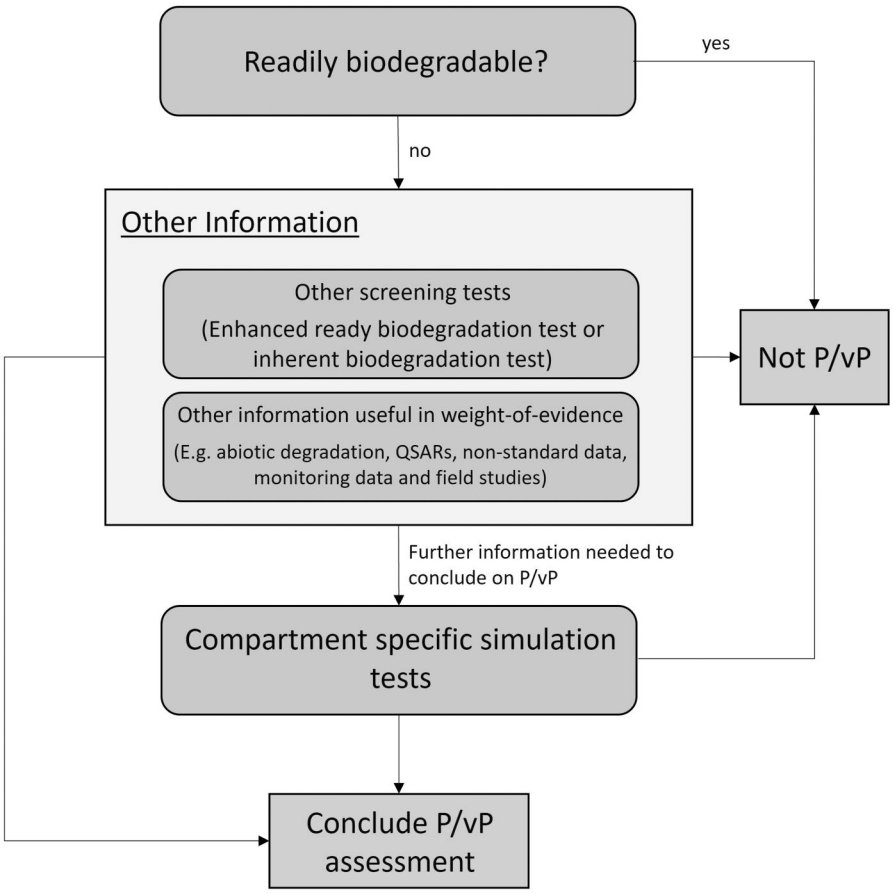

Figure 1. Simplified illustration of the Integrated Assessment and Testing Strategy (ITS) for persistence assessments under EU REACH (European Union Registration, Evaluation, Authorisation and Restriction of Chemicals), adapted from Hughes et al. (2020) under Creative Commons licence CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). P/vP = persistent or very persistent; QSAR = quantitative structure–activity relationship.

and a clear, stepwise approach for combining information and arriving at robust overall conclusions. The methodology has been implemented in a freely available software tool, the Persistence Assessment Tool (PAT v01.04; see online supplementary material 3). The methodology has been designed in accordance with the principles of the EU REACH regulatory framework, test guidelines, and guidance while being flexible to accommodate different regulatory practices. The study quality evaluation and WoE methodology represents a first attempt to codify various rules and principles applied in regulatory persistence assessments into a systematic approach, and further discussion and testing is envisaged to refine and build consensus around this. The methodology is presented herein and demonstrated using a case study substance hexabromocyclododecane (HBCDD).

Persistence assessment methodology

Overview of the method

The development of a persistence assessment methodology was informed by several previous detailed reviews, covering WoE (Hughes, Griffiths, & Swansborough, 2022), difficult substances (Hughes, Griffiths, & Brown, 2022), and complex substances (Hughes, Griffiths, & Pemberton, 2022). It is based upon the EU REACH Annex XIII framework and associated guidance for PBT/vPvB assessment (ECHA, 2023a, 2023b). The persistence assessment methodology utilizes various information on substance identity, physicochemical properties, degradation studies, and other information relevant to the assessment (see Table 1).

The methodology follows a sequential approach (see Figure 2) and should begin after all available, relevant information has been gathered. Studies are first organized into information categories, or lines of evidence (LoE). Individual studies are then scored for quality considering both reliability and relevance, using criteria specific to the LoE. Reliability and relevance are defined here as

- Reliability: robustness of methodologies to arrive at reliable, reproducible results. Experimental observations are in line with methodological principles and quality/validity criteria.
- Relevance: experimental conditions used relative to those that are considered most relevant in the regulatory context.

Once all studies within an LoE have been quality scored, the information is evaluated at the level of the LoE, taking into account the strength and indication of the various individual studies as well as specific rules relevant to that particular LoE. Finally, an overall conclusion on the persistence of a substance is determined, considering the ECHA ITS and weightings applied to each LoE. An assessment of the consistency of information is included for each LoE and for the overall assessment, in line with WoE principles (OECD, 2019).

The various elements of the persistence assessment methodology that have been developed are presented and discussed in the following sections. More detailed information, including specific criteria, rulesets, and calculations, are in the online supplementary material (see online supplementary material 1).

Substance identity and physicochemical properties

Information on the substance identity and physicochemical properties may be relevant to the assessment of persistence. A list of fields and criteria have been developed to capture this information and determine whether there are any implications for the assessment, in particular, whether the substance properties are likely to present challenges with testing or assessment and whether the substance has a complex composition. Information on the substance identity and various physicochemical properties are collected (see online supplementary material 1-1.1). Relevant physicochemical properties include molecular weight, water solubility, vapor pressure, Henry's Law constant, octanol–water partition coefficient (log K_{ow} or log D_{ow}), organic carbon normalized soil sorption coefficient (log K_{oc}), and acid dissociation constant (pK_a). In addition, it should be determined whether

Table 1. Overview of information considered in the persistence assessment methodology.

Information type	Description
Substance identity	Information related to the identity of the substance, including chemical name, CAS number, EC number, and whether the substance is a monoconstituent, multiconstituent, or UVCB substance.
Physicochemical properties	Properties of the substance that may be relevant to its environmental fate and persistence, including molecular weight, water solubility, vapor pressure, Henry's Law constant, octanol–water partition coefficient (log K_{ow} or log D_{ow}), organic carbon normalized soil–water partition coefficient (log K_{oc}), and acid dissociation constant (pK_a).
Screening tests	Biodegradation screening tests include ready (OECD 301 A-F, OECD 310, and OECD 306), enhanced ready (modified using increased test durations or vessel volumes), or inherent (OECD 302 A-C) biodegradability tests. These are standardized, relatively inexpensive tests providing information on the intrinsic potential for a substance to undergo biodegradation under a range of environmental conditions.
Simulation tests	Biodegradation simulation tests in surface water (OECD 309), water–sediment systems (OECD 308), and soil (OECD 307) are used to provide definitive information for the assessment of persistence in the form of degradation half-lives at low, environmentally relevant concentrations. These tests also provide information on the formation of transformation products. In addition to guideline simulation tests, other nonstandard studies may provide similar relevant information for consideration in a persistence assessment.
QSAR	*In silico* tools that predict substance properties based on chemical structure.
Monitoring data	Evidence of the occurrence of a substance in the environment can, under certain circumstances, be used in the assessment of persistence.
Other WoE	All other evidence that may be relevant to a persistence assessment, such as hydrolysis and photodegradation studies, field and mesocosm studies, other simulation tests, investigations with individual microbial strains, etc.

Note. QSAR = quantitative structure–activity relationship; WoE = weight-of-evidence; UVCB = substance of unknown or variable composition, complex reaction products or biological materials.

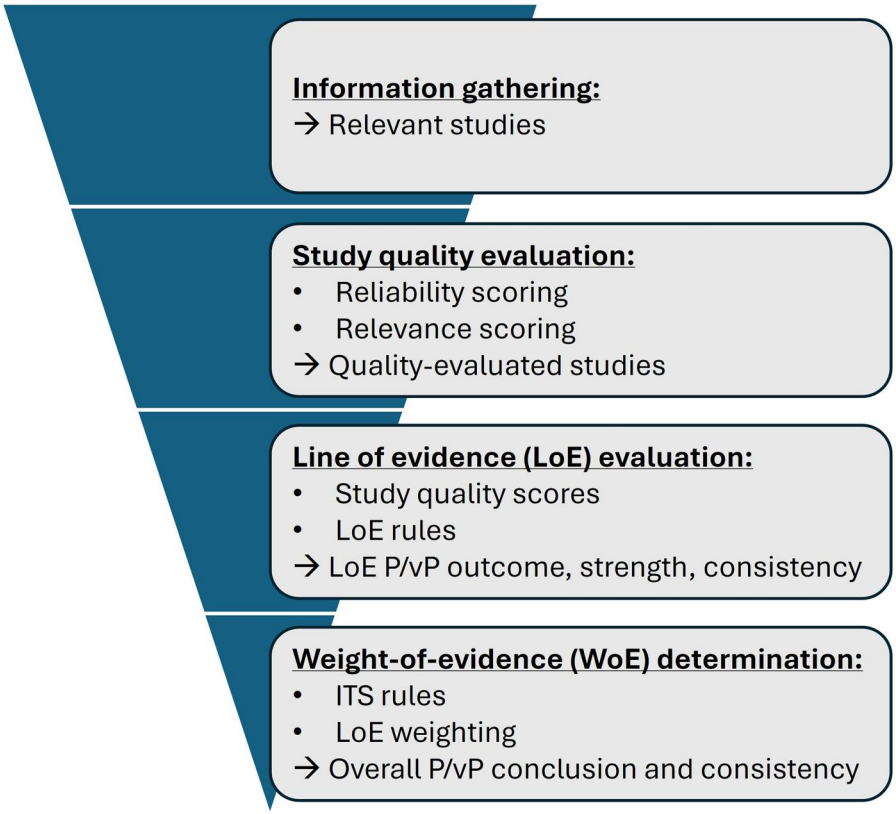

Figure 2. Illustration of the sequential approach applied in the persistence assessment weight-of-evidence methodology. LoE = line of evidence; P/vP = persistent or very persistent; WoE = weight-of-evidence; ITS = Integrated Assessment and Testing Strategy.

the substance has particular characteristics that may complicate its assessment, including being unstable, complexing, chiral, or toxic to microorganisms.

Substance information is used to identify whether the substance possesses so-called difficult substance properties (Table 2; online supplementary material 1-2.1). Properties that are anticipated to cause challenges with persistence assessment include being volatile, poorly soluble, sorbing, ionizable, unstable, complexing, chiral, toxic to microorganisms, and being composed of more than one constituent (Hughes, Griffiths, & Brown, 2022; Hughes, Griffiths, & Pemberton, 2022). The methodology is intended to alert the assessor to one or more properties of the substance that may complicate the assessment of persistence. Certain difficult substance properties are also considered in rulesets for the quality evaluation of studies within specific LoEs.

General approach to evaluating information related to persistence

Study information capture

Different types of information, or LoEs, are considered in the persistence assessment. These include biodegradation screening tests, simulation tests, QSARs, monitoring data, and other relevant information not fitting within these LoEs ("other WoE"), such as information from hydrolysis and photodegradation studies, field and mesocosm studies, investigations with individual microbial strains, etc. Templates to capture details of studies relevant to the persistence assessment have been developed across the various identified LoEs (see online supplementary material 1-1.2–1-1.8). These provide a systematic means of documenting and evaluating the available, relevant information pertaining to the persistence assessment of a substance.

Common information captured across LoEs includes study identifiers (e.g., author, year, description), method (e.g., guideline, Good Laboratory Practice [GLP] status, quality of reporting, where relevant) and test substance. Various additional study details are also captured, depending on the specific LoE (see *Further details of methodology for specific LoEs*).

Quality scoring of individual studies

Rules and criteria specific to each LoE have been developed to evaluate the quality of individual studies (see Figure 3; see online supplementary material 1-1.2–1-1.8) using similar principles to those of other methodologies developed for aquatic toxicity and bioaccumulation studies (Arnot et al., 2023; Moermond et al., 2016). Conditions, reporting requirements, and validity criteria of related OECD test guidelines have been taken into account, as well as EU REACH regulatory guidance. Fields under reliability and relevance are further divided into subcategories, such as method, test system, test substance, inoculum, and kinetics, depending on the specific LoE. Individual fields are scored numerically (either 0, 5, or 10) according to specific criteria, and study quality scores are calculated sequentially based on averages for each subcategory, then for reliability and relevance, and finally for the study overall. Scoring criteria for some fields are considered "critical fails" and lead to a score of zero for reliability and/or relevance. Numerical scores are assigned qualitative ratings of low (L), medium (M), or high (H) to aid with interpretation.

The quality of experimental studies is evaluated according to some general criteria. Studies that are not conducted in

Table 2. Characteristics of substances and associated criteria that can lead to challenges for persistence assessments.

Characteristic	Criteria	Implications
Poorly soluble	• Water solubility <1 mg/L	• Challenges with dosing and bioavailability of test substance
Volatile	• Henry's Law constant >1 Pa m^3/mol • Vapor pressure >1 Pa	• Loss of test substance from system/medium • Challenges with dosing, sampling and analysis • Affecting calculation of degradation kinetics
Sorbing	• n-Octanol/water partition coefficient (log K_{ow}) or distribution coefficient (log D_{ow}) >4 • Organic carbon normalized soil sorption coefficient (log K_{oc}) >3 • Highest base dissociation constant (pK_a) >4	• Loss of test substance from system/medium • Bioavailability and nonextractable residue (NER) formation
Ionizable	• Lowest acid dissociation constant (pK_a) <9 • Highest base dissociation constant (pK_a) >4	• Speciation of test substance potentially impacting degradation
Unstable	• Abiotic transformation (e.g., hydrolysis, oxidation, photodegradation) at pH 4–9	• Multiple potential transformation processes • Influence of matrix components/conditions • Potentially different transformation products
Complexing	• Chelating agent	• Bioavailability and influence of matrix components
Chiral	• One or more chiral centers	• Potential stereoselective degradation
Toxic to microorganisms	• Evidence of microbial toxicity	• Potential inhibition of biodegradation
More than one constituent	• Multiconstituent or UVCB	• Assessment should account for all relevant constituents

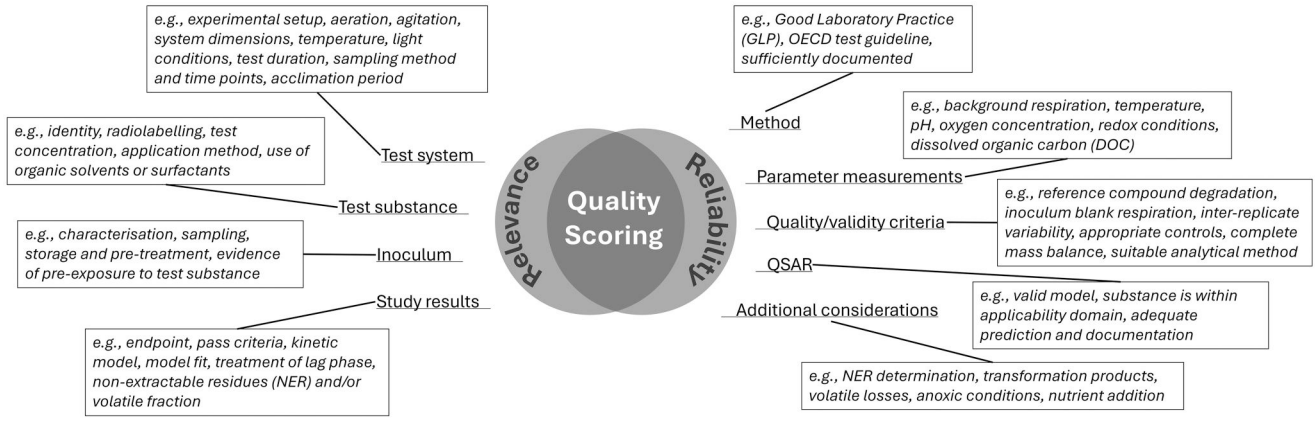

Figure 3. Overview of the study quality scoring methodology detailing aspects that are considered in evaluating study quality across various information categories connected to reliability and relevance (e.g., test system, test substance, inoculum, etc.). The precise information fields, criteria, and impact on study quality scoring are specific to the type of study (line of evidence) and are detailed in the online supplementary material (see online supplementary material 1-1.2–1-1.8). NER = nonextractable residues; QSAR = quantitative structure–activity relationship.

accordance with an appropriate OECD test guideline, GLP, or that are insufficiently reported (based on a subjective assessment) will have a cap placed on their maximum quality score. If a test substance contains more than one constituent, or is part of a composed mixture, the quality of the study is affected. Further, the use of nonadapted inocula is considered as a key principle for the quality evaluation of studies (ECHA, 2023a, 2023b). Details of the study quality scoring methodology for specific LoEs are further presented below (see *Further details of methodology for specific LoEs*).

LoE evaluation

Specific rulesets have been developed to evaluate individually scored studies at the level of the LoE (see Figure 4; online supplementary material 1-2.1 and 1-2.2). These rulesets have been developed taking account of the specifics of each LoE and their interpretation in the regulatory context. They take various elements into account, such as the quality, quantity, strength, and consistency of the evidence. The details of these evaluations for specific LoEs are discussed in the following sections.

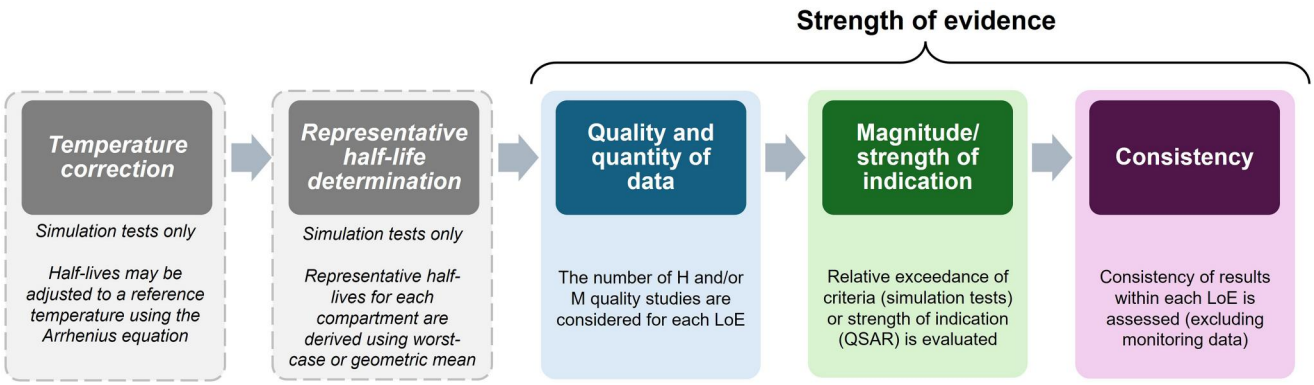

Figure 4. Overview of the different elements of the methodology for evaluating lines of evidence (LoE). Temperature correction and representative half-life determination are conducted for simulation tests only. The strength of the evidence within a particular LoE is then evaluated considering a combination of quality and quantity of data, the magnitude or strength of any indication, and the consistency of the evidence. H = high; M = medium; QSAR = quantitative structure–activity relationship.

Further details of methodology for specific LoEs

Screening tests

Biodegradation screening tests, such as ready biodegradability tests (OECD 301 A-F, OECD 310, and OECD 306), enhanced ready biodegradability tests (modified using increased test durations or vessel volumes), or inherent biodegradability tests (OECD 302 A-C), are standardized, relatively inexpensive tests designed to provide information on the intrinsic potential for a substance to undergo biodegradation under a range of environmental conditions (ECHA, 2023a; OECD, 2006). They are generally used in regulatory persistence assessments as screening tools, with positive results providing evidence of nonpersistence.

Biodegradation screening tests use relatively well-defined experimental systems, with specific requirements around inoculum source and concentration, test substance concentration, and mineral medium, as well as strict requirements on experimental controls and validity criteria. Despite this, their remaining degrees of freedom and biological inoculum are sources of variability in test outcomes, which are well documented (Davenport et al., 2022; ECHA, 2023a; Hughes, Griffiths, & Swansborough, 2022). This is one reason why the tests are generally used as positive screens, with negative results pointing to the need for further investigation rather than definitive conclusions of persistence. The tests generally measure biodegradation using nonspecific techniques, such as dissolved organic carbon (DOC) removal, carbon dioxide evolution, or biological oxygen demand; however, they can also incorporate targeted analysis to provide indications of primary degradation.

The persistence assessment methodology provides the same template for collecting information for different types of biodegradation screening test (see online supplementary material 1-1.2). This includes information on the test method, test system (e.g., study duration, test concentration, test volume, use of bioavailability improvement methods), inoculum (e.g., source, concentration, evidence of preexposure), controls, compliance with validity criteria, and results.

Quality scoring of biodegradation screening test data under the persistence assessment methodology is based on their adherence to the conditions detailed in the test guidelines and regulatory guidance. Studies that do not comply with these explicit conditions or validity criteria generally receive critical fails for reliability and/or relevance. Separate evaluation rules are applied for each type of test, reflecting differences in regulatory interpretation.

Ready biodegradability tests are stringent tests and generally considered a first-tier screen in persistence assessments. As such, these tests are generally the most widely available and have a special status within the EU REACH persistence assessment framework (ECHA, 2023b). In ready biodegradability tests, the extent of biodegradation over 28 days is assessed, with a pass criterion of 70% or 60%, depending on whether biodegradation is measured based on DOC or by respirometric techniques (biological oxygen demand or carbon dioxide evolution), respectively. For the test substance to be considered "readily biodegradable," this extent of degradation should normally be achieved within a "10-day window" following the lag phase (time to 10% degradation). However, for persistence assessment, the 10-day window is not considered (ECHA, 2023b).

Inherent biodegradability tests are another type of biodegradation screening test intended to provide a subsequent tier of testing under less stringent conditions. These are generally in the form of higher inoculum concentrations and lower test substance concentrations compared with ready biodegradability tests. However, they may also include preexposure of the inoculum (such as in OECD 302 A: Modified SCAS Test), which is generally not permitted in persistence assessments. Results of inherent biodegradability tests are subject to different interpretation than ready biodegradability tests. While using similar test durations and pass criteria in terms of extent of biodegradation, the timepoints by which these pass criteria must be achieved (seven days in OECD 302 B and 14 days in OECD 302 C) are notably shorter than in ready biodegradability tests. The lag phase in inherent tests must also not exceed three days for positive results to be valid for use in persistence assessments. The specific reasons for these additional constraints placed on inherent biodegradability tests are not fully clear; presumably, to counteract the more favorable conditions. However, they would seem to somewhat limit the usefulness of this test, because few substances failing the ready biodegradability test might be expected to pass these stricter requirements. A further specific aspect to the interpretation of inherent tests is that a result of <20% biodegradation may be considered as evidence that the substance fulfils the criteria for persistence.

A third type of biodegradation screening test is the enhanced ready biodegradability test. These are a relatively recent concept, intended to provide an additional option for assessing

persistence at the screening level (ECHA, 2023a). Possible enhancements include extended test durations of up to 60 days (for poorly soluble substances), and increased vessel sizes. Enhanced ready biodegradability tests utilize the same pass criteria as regular ready biodegradability tests. However, very long lag phases (e.g., >20 days) followed by fast degradation are considered signs of microbial adaptation and are not considered adequate for P/vP assessment.

Once all biodegradation screening studies have been evaluated individually for quality, they are evaluated at the level of LoE (see online supplementary material 1-2.2). For this purpose, ready biodegradability tests are evaluated separately from inherent and enhanced ready biodegradability tests, which are evaluated as a single LoE. Individual pass/fail outcomes of tests assessed to be of sufficient quality are used to determine the overall conclusion for the LoE. Positive outcomes correspond to a conclusion of "not P/vP," whereas negative outcomes correspond to "potentially P/vP."

Ready biodegradability tests are regarded as stringent tests, and therefore positive results are generally considered to supersede negative results under most circumstances (ECHA, 2023a; OECD, 2006). For purposes of the persistence assessment methodology, the same principle is applied for evaluating inherent and enhanced ready biodegradability tests. For each LoE, an assessment of strength and consistency is performed, with strength being based on the number of studies of sufficient quality that are available.

Simulation tests

Biodegradation simulation tests are used to provide definitive information for the assessment of persistence in the form of degradation half-lives at low, environmentally relevant concentrations (ECHA, 2023b). Degradation half-lives are compared to P and vP cut-offs for the environmental compartments water, sediment, and soil to determine whether a substance meets the criteria for persistence. According to established persistence assessment frameworks, a substance needs only to fulfil the criteria in one of these environmental compartments to be concluded as persistent. The OECD test guidelines 307 (Aerobic and Anaerobic Transformation in Soil), 308 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems), and 309 (Aerobic Mineralisation in Surface Water—Simulation Biodegradation Test) are typically used to generate degradation half-lives on substances and are considered the most relevant information under the EU REACH framework (ECHA, 2023b). These tests are complex and technically challenging, particularly for difficult substances, and require care in the evaluation of their overall quality (reliability and relevance).

In addition to guideline simulation tests, other nonstandard studies may provide information on degradation half-lives of substances and be relevant for consideration in a persistence assessment. An approach is therefore needed to evaluate information from these types of studies and determine their reliability and relevance for the assessment.

Guidance for evaluating the quality of simulation tests (and other studies producing degradation half-lives) has so far been lacking in the regulatory context, which can be a source of confusion and disagreement between assessors, and is problematic for applying robust and consistent WoE determinations (Hughes et al., 2020; Hughes, Griffiths, & Swansborough, 2022; Schäffer et al., 2022; Shrestha et al., 2023; Wassenaar & Verbruggen, 2021). The persistence assessment methodology herein addresses this issue by providing a systematic basis for the quality evaluation of such information. This approach is based on the principle discussed above, that OECD guideline simulation tests represent the most reliable and relevant information under the EU REACH regulatory framework. This principle has been used to define information fields and rulesets for determining the reliability and relevance of individual studies.

Separate templates have been developed for capturing information on water, sediment, and soil simulation tests (see online supplementary material 1-1.3–1.1.5). Each template follows a similar approach of capturing information on method, test system, test substance, inoculum, parameter measurements/quality criteria, kinetics, and transformation products.

Test system fields consider aspects related to the experimental design, such as whether the system is aerobic or anaerobic and open or closed (sealed). Experimental conditions such as temperature, light conditions, duration, and sampling frequency are captured. For water tests, the vessel volume, sampling method, and test concentration(s) are also considered. For sediment tests, additional inoculum-specific system parameters are recorded, as these are influenced by the sediment selection and are important to the determination of study quality. These include the water–sediment ratio, height of sediment layer, amount of sediment, and acclimation period.

The use of radiolabeled substances in simulation tests is considered important in persistence assessments and necessary to measure key aspects such as mass balances, transformation products, carbon dioxide, and nonextractable residues (NERs; ECHA, 2023b). Therefore, studies using nonlabeled test materials receive lower reliability and relevance scores. Information on the dosing of the substance is important in simulation tests, such as the application method, whether an organic solvent was used (and how much), and whether a homogenous distribution of the substance was achieved.

The inoculum is important in determining the outcome of simulation tests, and hence, various aspects are captured. These include those related to sampling, such as sampling date and location, sampling depth, and whether the inoculum is freshwater or marine water (for aquatic tests), as well inoculum parameters such as pH, organic carbon content, nutrient and suspended solids content (water tests), texture (sediment and soil tests), sampling temperature, and oxygen concentration (aquatic tests). In addition, inoculum preparation and storage conditions are recorded.

All tests include quality criteria for mass balance and a suitable analytical method. In addition, aqueous tests include parameter measurements for oxygen concentration, pH, DOC, and sediment redox potential (sediment tests only).

Degradation kinetics from each type of simulation test are captured. For soil and sediment tests, fields determining the kinetic model selection and acceptability of model fits are based on FOCUS guidance (FOCUS, 2014). In addition, fields are included to address inclusion and interpretation of NERs in the determination of the half-life, in line with recent guidance developments (ECHA, 2023b; Schäffer et al., 2018). In the case of water tests, a degradation half-life based on either parent compound removal or mineralization is assessed based on pseudo first-order kinetics, and may or may not include a lag phase (OECD, 2004). In all cases, detection of transformation products at concentrations >10% of initially applied radioactivity or continuously increasing during the study is an indication of potentially persistent transformation products that should be investigated further. Finally, the addition of supplementary nutrients or surfactants/emulsifiers is included as additional quality indicators, based on experience with nonstandard experimental methods.

Each simulation test type is evaluated for quality (reliability and relevance) in accordance with its specific quality evaluation scheme, based on the principles discussed above. Critical fail criteria are defined to address circumstances likely to cause major reliability issues or deviations from relevant conditions. These include anaerobic conditions, use of suspended sediment systems (water tests only), volatile losses, preadapted inocula, use of excessive amounts of organic solvents, persistent mass balance issues, or lack of a suitable analytical method.

Degradation half-lives from simulation tests are evaluated in one of five LoEs (freshwater, marine water, freshwater sediment, marine sediment, soil) (Figure 4; see online supplementary material 1-2.3). First, individual half-lives are temperature-corrected to a standard reference temperature (12 °C for soil and freshwater; 9 °C for marine and estuarine water) using the Arrhenius equation in accordance with regulatory guidance (ECHA, 2023a). A representative half-life is then determined for each LoE. This will consider the number and quality of half-life values available, with a geometric mean being calculated where greater than four half-lives of sufficient quality are available; otherwise, the worst-case half-life is used. The strength of evidence within a simulation test LoE considers the quality and quantity of half-life data, the magnitude of the representative half-life (i.e., by how much the half-life exceeds P/vP criteria), and the consistency of corresponding P/vP conclusions between half-lives.

Monitoring data

Under certain circumstances, monitoring data can provide evidence that a substance fulfils the criteria for persistence. Specifically, these are where a substance is detected in remote areas far away from populated areas and known point sources or in situations where there is a clear indication that a substance is fulfilling the P/vP criteria with a sufficient understanding of substance emissions, distribution, and transport behavior such that uncertainties are adequately addressed (ECHA, 2023b). The quality evaluation of monitoring data concerns whether or not sampling and analytical methods are considered reliable (see online supplementary material 1-1.7). The LoE evaluation of monitoring data considers the strength of evidence, with evidence from three or more independent studies being considered indicative of high strength (see online supplementary material 1-2.2).

QSAR

Quantitative structure–activity relationships are *in silico* tools that predict substance properties based on chemical structure. The persistence assessment methodology considers the type of endpoint predicted (e.g., screening test outcome, degradation half-life), as well as the environmental compartment (if applicable), and considers the prediction results in terms of the persistence conclusion indicated and the strength of the indication (to be determined by the assessor) (see online supplementary material 1-1.6). The evaluation of the quality of QSAR predictions is based on the OECD principles of QSAR validation (OECD, 2014). Predictions are considered high quality if they are (1) based on a valid QSAR model (considered the case if a QSAR model reporting format is available or if the QSAR is well-documented following the OECD principles of QSAR validation), (2) have a defined applicability domain that the substance falls within, and (3) are adequate (i.e., QSAR exhibits adequate performance) for the purpose of persistence assessment. The QSAR LoE evaluation provides an overall indication based the results and quality of individual predictions as well an indication of the strength and consistency of the evidence (see online supplementary material 1-2.2).

Other WoE

All other evidence that may be relevant to a persistence assessment can be considered under "Other WoE" (see online supplementary material 1-1.8). This LoE utilizes a flexible methodology to document the type of study and evaluate the reliability and relevance of the study using expert judgement according to Klimisch principles (Klimisch et al., 1997). The results of the study are then assessed according to whether the result provides quantitative or qualitative (i.e., type of) evidence, the persistence indication, and the strength of the indication. In doing so, disparate information relevant to the persistence assessment can be individually evaluated for quality and their outcomes weighed as a single LoE. The LoE evaluation determines an overall persistence outcome, considering the quality, type, persistence indication, and strength of each individual study. The overall strength and consistency of the LoE is also determined (see online supplementary material 1-2.2).

WoE determination

To reach overall conclusions for a persistence assessment, a further step has been developed to combine all information across the various LoEs. This step is intended to follow a WoE methodology while addressing specific rulesets required as part of the EU REACH persistence assessment framework.

The overall conclusion of the persistence assessment is reached following a stepwise workflow in accordance with the EU REACH Annex XIII framework and ITS (Figure 5; see online supplementary material 1-3). First, information from simulation test LoEs is considered, because these are considered to provide definitive information on persistence. If no definitive P/vP conclusion can be drawn based on information from simulation tests, the ready biodegradability test LoE is considered in a second step, with a positive outcome leading to a conclusion of not P/vP. If no conclusion can be drawn from Steps 1 and 2, a quantitative WoE methodology is used considering all LoEs together (see online supplementary material 1-3). Individual conclusions from LoEs are scored and weighed according to their persistence indication, strength of evidence (based on previous assessments of quality, quantity, magnitude, and consistency, see online supplementary material 1-2.2 and 1-2.3) and a default weighting coefficient. The default weightings are assigned to specific LoEs based on their overall importance to the assessment (simulation tests receive a score of 3; screening tests and "other WoE" receive a score of 2; QSARs and monitoring receive a score of 1). Persistence indications are assigned a numerical value according to the specific LoE and outcome and are scored either positively or negatively depending on whether they indicate a conclusion of not persistent or persistent, respectively. The sign of the average of scores determines an overall conclusion of the qWoE assessment (Step 3). Finally, the consistency of the overall conclusion is provided in relation to the conclusions of individual LoEs (Step 4).

Case study

The persistence assessment methodology was demonstrated using data for a case study substance, hexabromocyclododecane (HBCDD), which is commonly referred to under Chemical Abstracts Service (CAS) No. 25637-99-4 but is more precisely defined as 1,2,5,6,9,10-hexabromocyclododecane (CAS No. 3194-55-6). This substance consists of three diastereoisomers (α-HBCDD, CAS No. 134237-50-6; β-HBCDD, CAS No. 134237-51-7; and γ-HBCDD, CAS No. 134237-52-8). The substance HBCDD is a common brominated flame retardant and was selected owing to

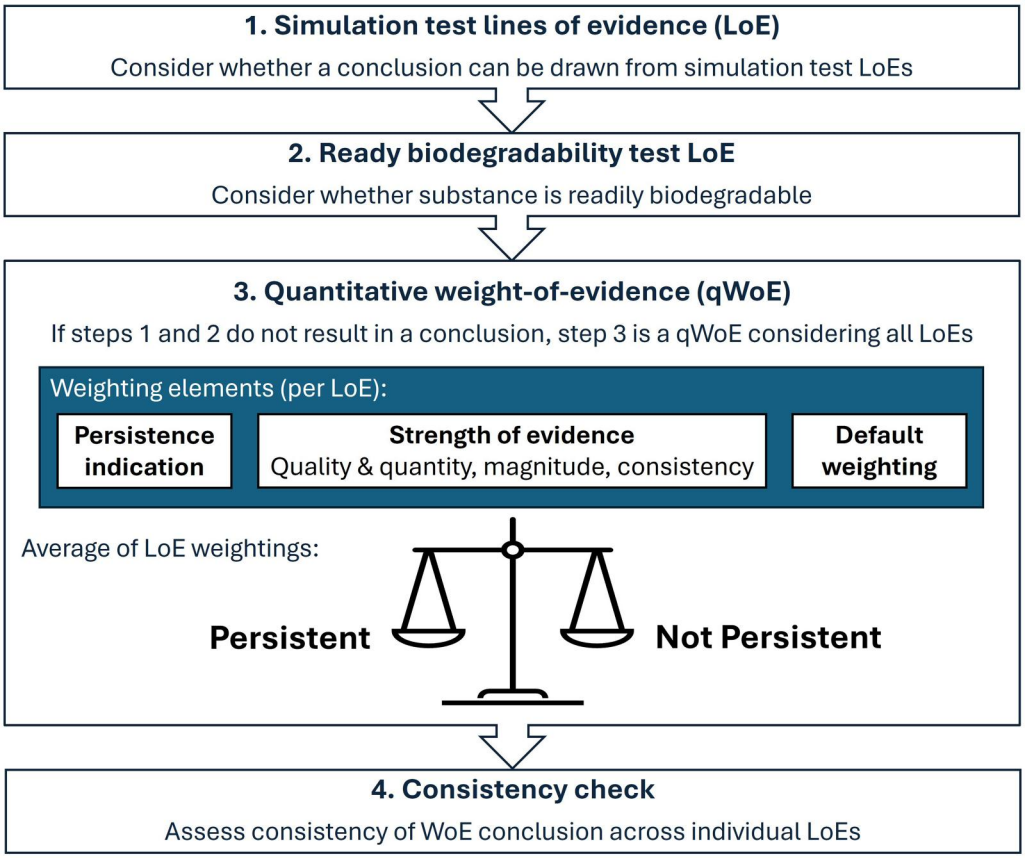

Figure 5. Scheme for determining persistence assessment conclusions following the weight-of-evidence (WoE) methodology. LoE = line of evidence; qWoE = quantitative weight-of-evidence.

its regulatory scrutiny and availability of simulation test data in different environmental compartments. It is listed on the EU REACH Authorisation List (Annex XIV) due to its PBT properties, and in Annex A of the Stockholm Convention on Persistent Organic Pollutants (UNEP, 2013). The information regarding the persistence of HBCDD has been evaluated in several authoritative reports. The information used in this case study was obtained from sources pertaining to the EU REACH regulation, specifically the substance of very high concern support document, risk assessment report, and registration dossier (ECHA, 2008a, 2008b).

Details of the properties and information relevant to the persistence assessment of HBCDD are presented in the supplementary material (see online supplementary material 2). Based on the physicochemical properties of the substance, the methodology flagged HBCDD as a poorly soluble, sorbing, and chiral substance. Data for specific diastereoisomers are reported where relevant. Available studies with quality scoring, results, and persistence indications are summarized in Table 3.

Information from biodegradation screening tests was limited, with only one reliable ready biodegradation test in which no biodegradation was observed (Schaefer & Haberlein, 1996). In one monitoring study, γ-HBCDD was detected in a remote region, in freshwater sediment cores in Svalbard, with the α- and β-diastereomers below the analytical limit of detection (Christensen et al., 2004).

Multiple simulation studies have been conducted using HBCDD across different environmental compartments. Two aerobic simulation studies were reported for soil. The OECD 307 study of Davis et al. (2003b) tested HBCDD (5.8% α-, 19.3% β-, and 74.9% γ-HBCDD), generating a half-life of 63 days at 20 °C for γ-HBCDD; the other diastereomers were not followed. Davis et al. (2004) conducted an OECD 307 soil simulation study, but no degradation of ^{14}C-HBCDD (8.7% α-, 6.1% β- and 85.2% γ-HBCDD) was observed during the 112 days of the study at 20 °C. A further two simulation tests exist for HBCDD in freshwater water–sediment systems. Davis et al. (2003a) determined half-lives for γ-HBCDD of 11 and 32 days in two different sediments at 20 °C. A half-life for total HBCDD of 101 days at 20 °C was determined by Davis et al. (2004). The study of Davis et al. (2004) also included degradation experiments with anaerobic sediments, which were included as other WoE. No water simulation tests were available.

The results of quality scoring and persistence indications of the available simulation tests for HCBDD are summarized in Table 3. Results from both sediments in Davis et al. (2003a) indicated a conclusion of not P/vP. The Schuylkill sediment was rated medium quality (score 5.3) according to the methodology, with the use of an organic solvent, lack of radiolabeling, insufficient kinetic information, and absence of a mass balance all contributing to the reduced score. The Neshaminy sediment, however, received a critical fail for relevance due to evidence of preexposure to the test substance, resulting in an overall quality score of 0. The Davis et al. (2004) sediment study supported a conclusion of vP and was scored as high quality (score 8.2) owing to the inclusion of radiolabeling and associated kinetic information generated. The soil simulation studies by Davis et al. (2003b) and Davis et al. (2004) both received high-quality scores of 7.0 and 7.9 and supported persistence conclusions of P and vP, respectively. Both studies received scores of zero for the "kinetics" relevance category due to missing information. Although the 2004 study

Table 3. Summary of studies available for hexabromocyclododecane (HBCDD) with their associated quality evaluation, results, and persistence indications.

LoE	Reference	Description	Test material	Reliability score	Relevance score	Overall quality score (and rating)	Result	Indication
Screening	Schaefer and Haberlein (1996)	Ready biodegradation	HBCDD (CAS No. 25637-99-4)	10	10	10 (H)	0% biodegradation at 28 days	Potentially P
Soil simulation	Davis et al. (2003b)	Soil study 1	HBCDD consisting of 5.8% α-HBCDD, 19.3% β-HBCDD and 74.9% γ-HBCDD. Only the disappearance of the γ-diastereomer was followed.	7.5	6.6	7.0 (H)	γ-HBCDD dissipation half-life: 63 days at 20°C (134 days when normalized to 12 °C)	P
Soil simulation	Davis et al. (2004)	Soil study 2	HBCDD consisting of 8.7% α-HBCDD, 6.1% β-HBCDD and 85.2% γ-HBCDD	9.4	6.3	7.9 (H)	No degradation observed during the 112-day study. Half-life entered as 112 days at 20 °C (238 days when normalized to 12 °C)	vP
Sediment simulation	Davis et al. (2003a)	Aerobic freshwater sediment study 1 (Schuylkill)	HBCDD consisting of 5.8% α-HBCDD, 19.3% β-HBCDD and, 74.9% γ-HBCDD.	5.2	5.4	5.3 (M)	γ-HBCDD dissipation half-life: 11 days at 20 °C (23 days when normalized to 12 °C)	Not P/vP
Sediment simulation	Davis (2003a)	Aerobic freshwater sediment study 1 (Neshaminy)	Only the disappearance of the γ-diastereomer was followed.	6.2	0	0 (L) Critical fail due to evidence of pre-exposure to test substance	γ-HBCDD dissipation half-life: 32 days at 20°C (68 days when normalized to 12 °C)	Not P/vP
Sediment simulation	Davis et al. (2004)	Aerobic freshwater sediment study 2	HBCDD consisting of 8.7% α-HBCDD, 6.1% β-HBCDD and 85.2% γ-HBCDD	8.1	8.3	8.2 (H)	Total HBCDD degradation half-life: 101 days at 20 °C (214 days when normalized to 12 °C)	vP
Monitoring	Christensen et al. (2004)	Arctic freshwater sediment core layer corresponding to 1973-1987	γ-HBCDD. α- and β-HBCDD were below LOD.	OK	Not considered	OK Sampling and analytical method are considered reliable	γ-HBCDD detected at 3.8 ng/g dry weight	P/vP
Other WoE	Davis et al. (2004)	Anaerobic freshwater sediment	HBCDD consisting of 8.7% α-HBCDD, 6.1% β-HBCDD and 85.2% γ-HBCDD	H	L	L Anaerobic conditions not directly comparable to P/vP criteria	Total HBCDD degradation half-life: 125 days at 12 °C	P/vP

Note. H = high; M = medium; L = low; P/vP = persistent/very persistent; LOD = limit of detection.

achieved a higher overall score, it still exhibited quality issues related to inconsistent compliance with mass balance criteria. The 2003 study scored lower overall due to the use of an organic solvent and the absence of radiolabeling, which also prevented a mass balance assessment. For all simulation studies, NERs were either not measured or not included in the determination of degradation kinetics, meaning that half-lives would likely have been underestimated according to current ECHA guidance (ECHA, 2023b). Based on the available half-lives determined for both the total α/β/γ-HBCDD mixture and γ-HBCDD, the predominant diastereoisomer in technical HBCDD, HBCDD can be considered vP according to the persistence assessment methodology described herein. The remaining evidence from other LoEs were supportive of this persistence conclusion. The conclusion reached in this assessment is in line with the regulatory persistence assessments of HBCDD under EU REACH and the Stockholm Convention.

Discussion

Regulatory persistence assessments require a range of disparate, relevant information to be considered together in a WoE determination. As such, they are complex and challenging. The methodology proposed herein is intended to support the work of assessors, leading to increased consistency, transparency, and robustness in these assessments. The systematic information capture, quality evaluation, and WoE methodology is designed in accordance with the EU REACH regulatory framework and addresses gaps in existing regulatory guidance. The methodology has been implemented in a freely available software tool, the PAT; see online supplementary material 3).

It is important to recognize that the methodology presented is not intended to replace the role of assessors in evaluating studies and applying their expert judgement to specific cases. Although clear rulesets and a structured approach are advantageous to promote consistent assessments, the nature of WoE assessments is such that this need for certainty must be balanced with the flexibility to deviate from a standardized approach according to the particulars of the situation at hand (Suter et al., 2020). Further, a key overarching requirement supported by this methodology is that information and assessments are transparently documented.

The study quality evaluation and WoE methodology represents a first attempt to codify various rules and principles applied in regulatory persistence assessments into a systematic approach. Certain aspects of the methodology are necessarily based on expert judgement and, although the methodology was subject to appraisal and testing by an external team of experts from industry, academia, and regulatory bodies (the project monitoring team), further discussion and testing should be considered to refine and build consensus around the methodology. The case study on HBCDD presented in this article is also relatively noncontentious, and the methodology should be applied to additional, more borderline cases and cases with varying amounts and types of data available. Further investigation of such real (and hypothetical) cases will provide deeper insights into sensitivities and support further refinement and calibration of the study quality evaluation and WoE methodology. This would seem particularly important because the effectiveness of similar score-based data quality assessments has recently been questioned (Kuo & Shih, 2024). Further, the methodology should be continuously refined in accordance with ongoing scientific and policy developments.

It should be borne in mind that the methodology is based on the EU REACH persistence framework and that assessments may follow different rules and processes in different regions and/or regulations. For instance, current assessment practices in the EU are notably different for the assessment of plant protection products (Hughes, Griffiths, & Swansborough, 2022; Moermond et al., 2012; Rauert et al., 2014). Potential customization of the methodology to account for these differences is envisaged, and several options are included within the PAT software (see online supplementary material 1-4). These include considerations on NERs and microbial adaptation, temperature correction of half-lives, representative half-life determination, half-life cut-offs, minimum study quality scores, and the WoE workflow. The PAT also includes a multimedia fate model ("SimpleBoxTreat4PAT") based on SimpleBox v4.0, which enables steady state overall persistence (P_{OV}) to be calculated for a range of emission scenarios (Hollander et al., 2016; van de Meent et al., 2023). The P_{OV} concept has been suggested as an option to further refine persistence assessments that are based on single compartment-specific half-life thresholds (Redman et al., 2022; Scheringer et al., 2009).

In addition to the need for ongoing testing, refinement, and consensus-building around the methodology (discussed above), the following additional limitations are highlighted:

- The methodology relies upon the assumption that assessors have already compiled all available relevant information pertaining to the persistence assessment of the substance. If this is not the case it could lead to meaningful differences in persistence assessment outcomes.
- Although the majority of decisions in the methodology are based on clear and objective criteria, certain inputs remain somewhat subjective. This is, to some extent, an unavoidable general feature of such WoE-based environmental assessments. However, it may be possible to further reduce this as a source of uncertainty through refinements to the methodology and supporting information.
- The other WoE LoE represents a general "catch-all" category for all relevant evidence that does not fall under one of the more well-defined categories. It is therefore necessarily more generic and subjective than other parts of the methodology. There is scope to develop additional LoE categories in future iterations of the methodology.
- The methodology follows a substance-by-substance approach and does not currently consider read-across of data from related substances.
- Aspects of the methodology related to difficult test substances are somewhat limited and mostly relate to alerting the assessor to potential issues with the available data.
- Substances with complex compositions, such as UVCBs and polymers, present unique challenges for persistence assessments (Hughes, Griffiths, & Pemberton, 2022). The methodology could be further expanded in the future to better support the assessment of these substances.

Conclusion

Environmental persistence is becoming increasingly important as an issue of concern for chemicals. Regulatory persistence frameworks are used to assess and prioritize substances for further action. However, the implementation of these frameworks is challenging due to the need to evaluate complex and disparate information in a weight-of-evidence determination. In the present work, a methodology has been developed to support

compilation, evaluation, and integration of relevant information in these assessments. An approach is presented for evaluating the quality of individual studies and combining these in a stepwise weight-of-evidence determination, in accordance with the EU REACH regulatory framework. The approach addresses several gaps in existing guidance and is anticipated to support improved consistency, transparency, and robustness in assessments.

The methodology has been incorporated into a freely available software tool (the PAT) and has been demonstrated using a known PBT substance. Further discussion and refinement of the methodology is envisaged to build consensus, address uncertainties, and support greater regulatory utilization in the future.

Supplementary material

Supplementary material is available online at *Integrated Environmental Assessment and Management*.

Data availability

Data, associated metadata and calculation tools are available in the online supplementary material. A preprint of this article is published at https://doi.org/10.26434/chemrxiv-2025-g1jpg.

Author contributions

Christopher Hughes (Conceptualization, Methodology, Software, Writing—original draft, Writing—review & editing), Megan Griffiths (Data curation, Methodology, Software, Writing—original draft, Writing—review & editing), Simon Cook (Data curation, Software), Dik van de Meent (Conceptualization, Software), John Parsons (Conceptualization, Methodology), Delina Lyon (Conceptualization, Writing—review & editing), and Amelie Ott (Conceptualization, Writing—review & editing)

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Conflicts of interest

The following authors work for consulting companies providing services in chemical regulatory assessment and compliance, including work related to the topics discussed in this article: C.B.H., M.G., and S.C.

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The remaining authors declare no conflicts of interest.

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