Environmental Research 151 (2016) 478–492

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Integrated *in silico* strategy for PBT assessment and prioritization under REACH

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ARTICLE INFO

Article history:
Received 19 April 2016
Received in revised form
21 July 2016
Accepted 12 August 2016

Keywords:
Persistence
Bioaccumulation
Toxicity
In silico
Multi-criteria decision making

ABSTRACT

Chemicals may persist in the environment, bioaccumulate and be toxic for humans and wildlife, posing great concern. These three properties, persistence (P), bioaccumulation (B), and toxicity (T) are the key targets of the PBT-hazard assessment. The European regulation for the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) requires assessment of PBT-properties for all chemicals that are produced or imported in Europe in amounts exceeding 10 tonnes per year, checking whether the criteria set out in REACH Annex XIII are met, so the substance should therefore be considered to have properties of very high concern. Considering how many substances can fall under the REACH regulation, there is a pressing need for new strategies to identify and screen large numbers fast and inexpensively. An efficient non-testing screening approach to identify PBT candidates is necessary, as a valuable alternative to money- and time-consuming laboratory tests and a good start for prioritization since few tools exist (e.g. the PBT profiler developed by US EPA).

The aim of this work was to offer a conceptual scheme for identifying and prioritizing chemicals for further assessment and if appropriate further testing, based on their PBT-potential, using a non-testing screening approach. We integrated *in silico* models (using existing and developing new ones) in a final algorithm for screening and ranking PBT-potential, which uses experimental and predicted values as well as associated uncertainties. The Multi-Criteria Decision-Making (MCDM) theory was used to integrate the different values. Then we compiled a new set of data containing known PBT and non-PBT substances, in order to check how well our approach clearly differentiated compounds labeled as PBT from those labeled as non-PBT. This indicated that the integrated model distinguished between PBT from non-PBT compounds.

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1. Introduction

Annex XIII of the European Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH; Commission regulation (EU), 2011) specifies criteria for the hazard evaluation of substances regarding their P (persistent), B (bioaccumulative) and T (toxic) and also vP (very persistent) and vB (very bioaccumulative) properties. REACH aims at protecting human health and the environment and holds manufacturers, importers, and downstream users responsible for the safety of their manufactured, marketed and used substances (Moermond et al., 2011). This has to be documented in a mandatory registration dossier. Without registration no substance can be placed on

Abbreviations: REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; (Q)SAR, (quantitative) structure-activity relationship; ECHA, European Chemicals Agency; UBA, Umweltbundesamt; MCDM, multi-criteria decision making; WoE, weight of evidence; AD, applicability domain; P, persistent; B, bioaccumulative; T, toxic; vP, very persistent; vB, very bioaccumulative; nP, non-persistent; ADI, applicability domain index; SAs, structural alerts; SI, similarity index; ACR, acute-to-chronic ratio; LC50, lethal concentration 50; R^2, coefficient of determination; RMSE, root-mean-square error; BCF, bioconcentration factor; NOEC, no observed effect concentration; QSPR, quantitative structure-property relationship; LOEC, lowest observed effect concentration; SMILES, Simplified Molecular Input Line Entry System; k-NN, k-nearest neighbours; ChV, Chronic Value

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http://dx.doi.org/10.1016/j.envres.2016.08.014
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the European market ("No data, no market"). PBT/vPvB chemicals are of particular concern due to their properties. Indeed, these chemicals remain in the environment for a long time and, in some cases may reach remote areas. Even if the emission are low, their persistence into the environment may leads these chemicals to bioaccumulate and exert toxic effects. vPvB chemicals may accumulate in the organisms in high and not predictable levels, therefore they are of high concern even if they do not seem toxic (Moermond et al., 2011).

According to REACH, registrants not only are allowed but explicitly invited to use non-testing methods if available, such as (quantitative) structure-activity relationship ((Q)SAR) modeling and similarity-based approaches (read-across, chemical grouping) in addition to any empirical studies, in order to assess the toxicity and further hazard potentials of chemicals (van Wijk et al., 2009).

Non-testing methods are considered alternatives for investigating the PBT potential of chemicals, since they reduce time, costs and animals used and allow to screen a large number of chemicals (Dimitrov et al., 2014; Howard and Muir, 2010).

Besides the availability of validated, well documented models for specific endpoints, non-testing methods need to be relevant, reliable and adequate in order to replace experimental data for a certain endpoint (Worth et al., 2007). There are few platforms for the identification and assessment of PBT substances. The most widely used is the "PBT Profiler" software developed by the United States Environmental Protection Agency (US EPA) (http://www.pbtprofiler.net). Some authors have focused on developing integrated methods to predict and estimate the PBT potential of chemicals. A not exhaustive list include: RAIDAR proposed by Arnot and Mackay (2008), PBT index published in Papa and Gramatica (2010) and tested on different categories of compounds (Cassani et al., 2015, Gramatica et al., 2015; Gramatica et al., 2016), a classification strategy proposed by Strempel et al. (2012). These methods will be better explained in Section 3.8. The Dutch National Institute for Public Health and the Environment (RIVM) too has developed a method for screening and assessment of substances, based on their ability to persist in the environment and accumulate in biological systems without taking into account the T criteria (Rorije et al., 2011). The European Joint Research Center (JRC) applied the Decision Analysis by Ranking Techniques (DART) to rank chemicals for environmental safety assessment (Pavan and Worth, 2008).

The overall aim of the present study was to use a series of existing and new *in silico* tools for assessing P, B and T in an integrated assessment approach. This framework provides an innovative weight-of-evidence (WoE) architecture for each parameter (P, B, T, vP, and vB) applying the Multi-Criteria Decision-Making (MCDM) theory (Pavan and Todeschini, 2008). Basically, the outcomes of the tools for each endpoint were integrated in a unified concept which merges the values associated with different properties and their related uncertainties into a single index, suitable for prioritizing chemicals of concern for regulatory activities. In particular, the calculation of the uncertainties is a new element that was not considered before. Assessing the availability of experimental data was the first step in integrated process. Secondly, where experimental data were missing or to support published values, *in silico* models were used in a consensus approach in order to provide a prediction for each single P, B, T, vP, and vB parameter. In addition, we calculated the uncertainty associated with either the experimental values available or the calculated ones for each endpoint.

This work was carried out as part of the project named "PRioritization Of chemicals: a METHodology Embracing PBT parameters into a Unified Strategy" (PROMETHEUS) commissioned by the German Environment Agency Umweltbundesamt (UBA). This project aims at drawing up a strategy to identify and prioritize PBT/vPvB chemicals which may be of concern for the environment and human health, for further closer assessment using a screening approach. The output of the project was a program that ranks chemicals in descending order based on their critical effects and their underlying uncertainties in predicted and/or experimental values. The focus was on the identification of candidate chemicals of very high concern. We outlined a conceptual scheme for integrating different evaluation tools within a PBT-framework that will be implemented in the VEGA platform (www.vega-qsar.eu) in the future.

2. Materials and methods

To build the integrated *in silico* strategy for the PBT/vPvB assessment, we proceeded according to the following steps. First we searched and evaluated the available computational models (focusing on freely available tools like VEGA, EPISuite™ and T.E.S.T.) for the specific P/vP, B/vB and T properties in order to see whether they were suitable for our purposes. Then we compiled datasets for each P/vP, B/vB and T endpoint in order to build new *in silico* models for the different endpoints. Considering the poor performance of QSAR models for the other ecotoxicological endpoints (e.g. *Daphnia magna* as reported in Golbamaki et al., 2014), for the T-parameter we focused on both acute and chronic toxicity on fish. Some existing and new models for each endpoint were integrated, creating conceptual workflows for each endpoint to provide a prediction and judge their reliability. The reliability evaluation takes into account several sides of the property value: if it is coming only from predictive models or some experimental values were available, the applicability domain (AD) of the predictive models, and the potential disagreement of the used experimental/predicted values. Depending on the model, the AD was obtained either automatically from its output if available, or manually evaluated according to the specific guidelines of the model for the ones that have not an automatic evaluation of the AD. Finally we combined all the workflows for each endpoint in a single *in silico* system and we assessed its performance in a testing exercise. Thus, experimental values were used for three purposes: to build up new models, if necessary, to run the testing exercise for PBT prioritization and they were also the preferred input in the workflows.

2.1. Data collection for building new in silico models

The experimental data to build up new models refer to persistence, log Kow and fish toxicity (acute and chronic). It was not necessary to develop new models for the bioconcentration factor (BCF) as the existing ones are suitable for our purposes. Supplementary materials 4 reports the dataset used both for the model building (except the UBA data and the already published datasets) and for the testing exercise.

2.1.1. Persistence

The data used for building models for P in the three compartments (sediment, soil and water) are presented in Manganaro et al. (2016) and Pizzo et al. (2016). Briefly, we collected half-life (HL) and disappearance time 50 (DT50) data for sediment, soil and water compartments. Since the majority of the data were categorical, all the data were classified in four classes: nP (with HL/DT50 below the P threshold), nP/P (with both nP and P compounds), P/vP (with both P and vP compounds) and vP (with compounds above the vP threshold). The hybrid classes were due to the original classes that were not set according to the PBT/vPvB classes.

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