Environmental Sciences Europe

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Screening and prioritising persistent, mobile and toxic chemicals: development and application of a robust scoring system

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Abstract

Background Lately scientific and societal concern has emerged about persistent (P), mobile (M) and toxic (T) chemicals. Such chemicals, like some polyfluoroalkyl acids (PFAAs), are of concern due to their high mobility and persistence in aquatic compartments which relates to long-term biotic exposure and difficult removal from drinking water. In this study, a screening approach for identification of PMT chemicals was developed and applied to 6158 diverse chemicals.

Results Chemicals are given a continuous score for P, M and T potential based on the modelled indicators (low to moderate potential is a score of 0–0.33, high potential is a score of 0.33–0.5 and very high potential a score of 0.5–1). The P score was based on the estimated aquatic environmental half life and the M score on the chemical's organic carbon/water partition coefficient (K_{OC}) using respectively the BIOWIN3 and KocWIN QSAR models of EPISuite™. The T score was based on the indicators for five human health endpoints: carcinogenicity (*c*), mutaganicity (*m*), reprotoxicity (*r*), endocrine disruption (ED) and general repeated dose systemic toxicity. Structural alerts for these endpoints taken from the OECD QSAR Toolbox™ and Toxtree™ were used as indicators of potential (human) toxicity. Chemical similarity values to Substances of Very High Concern (SVHC) with *c, m* and/or *r* properties were also included. Value functions were developed to translate the presence of alerts and similarity to the existing SVHCs to values between 0 and 1. Subsequently, all values were also aggregated to an overall PMT score, again ranging from 0 to 1. Applying the approach to chemicals from the Inventory of Existing Commercial chemical Substances, which are also REACH registered, resulted in 15% of the chemicals receiving high scores ($\geq$ 0.33) for all three (P-, M- and T-) indicators and 4% getting very high scores ($\geq$ 0.5) for both the P- and M-indicators.

Conclusions The approach confirmed the properties of chemicals classified as SVHC due to PMT properties (e.g. 1,4-dioxane), illustrating the ability of the approach to identify PMT chemicals of concern. Water regulators, drinking water suppliers and others can use this approach to identify potential PMT/vPvM chemicals that need further investigation.

Keywords Contaminants of emerging concern, Emerging contaminants, Drinking water, Continuous screening approach, Multi-criteria decision analysis, Prioritisation, PMT

Background

Manmade chemicals can be released to soil, air and water as a result of their production and use [1]. Examples of sources for chemical pollution of the aquatic environment include the discharge of municipal and industrial wastewater, the runoff of agricultural land and urban areas and the deposition of chemicals from air [2, 3].

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Figure 1 shows an overview of the different sources of chemical pollution of ground- and surface water and illustrates the diversity of potential pollution routes. Once present in surface- or groundwater, manmade chemicals can pose a risk to human health, if that water is used for recreation or for drinking water production, as well as to aquatic ecosystems.

The past examples of manmade chemicals that were found to be of great risk to humans and/or ecosystems are dichlorodiphenyltrichloroethane (DDT) [5], polychlorinated dibenzodioxins (PCDDs) [6] and polychlorinated biphenyls (PCBs) [7]. Although these chemicals differ in their molecular structure, they have specific properties in common. The first being that they are persistent in the environment, which means that even transient emission of these chemicals could lead to elevated environmental concentrations. Furthermore, these chemicals were found to bioaccumulate in the food chain and/or humans, and are toxic to humans and/or ecosystems. To limit the emission of such persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) chemicals in Europe, a PBT/vPvB assessment is required for chemicals manufactured in or imported to Europe in amounts of 10 tonnes or more per year following the European legislation No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Criteria for PBT/vPvB chemicals have been defined in Annex XIII of REACH, for this purpose. In addition, for the authorisation of plant protection products and biocides, a PBT assessment is required as stated in Regulations (EC) No 1107/2009 and 528/2012. Finally, a PBT assessment for human and veterinary products is also part of their Environmental Risk Assessment (ERA) following EC Directives 2004/27/EC and 2004/28/EC.

Lately, scientific and societal concern emerged about polar, persistent and toxic chemicals that are not bioaccumulative, but mobile (M), with mobility being loosely defined as "very water soluble, hard to remove from the aqueous phase" [8–12]. Substances with these properties are now known as "PMT chemicals" or "vPvM chemicals" (very persistent and very mobile). Mobile chemicals have a high affinity for water, and sorb poorly to soil or sediment, making them prone to travel large distances through rivers and to leach from the subsoil to groundwater [8, 9]. Persistent and mobile chemicals are known

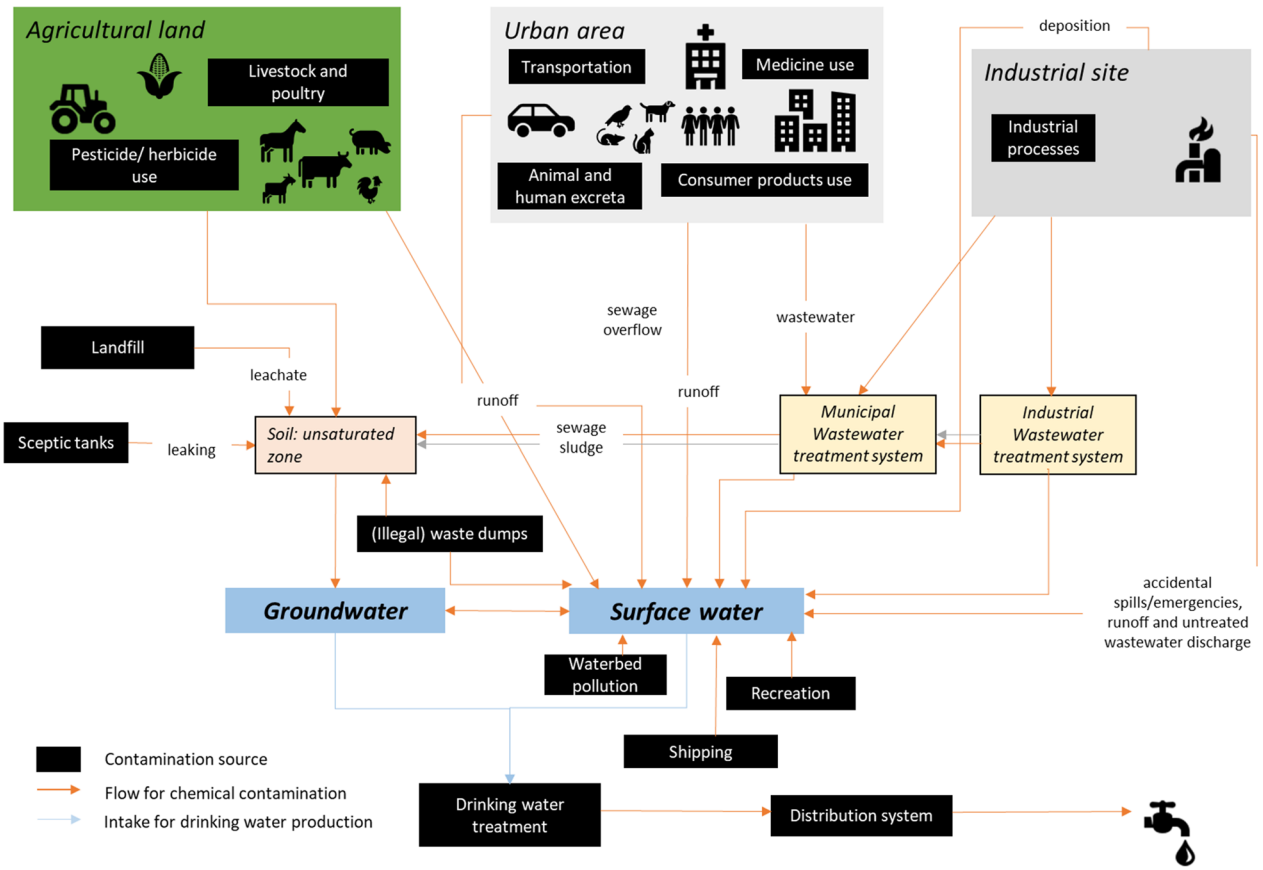

Fig. 1 Sources of manmade chemicals in ground- and surface water used for the production of drinking water [4]

to resist conventional drinking water treatment [13]. Examples of these, so far not officially defined, PMT chemicals that already gained considerable scientific, regulatory and public attention are members of the group of perfluoralkylsubstances [14] and 1,4-dioxane [15]. The concern about PMT and vPvM chemicals is comparable to the concern about PBT/vPvB chemicals, as indicated by Hale et al. [10]. These authors argued that this concern is due to the fact that PMT/vPvM chemicals can accumulate in drinking water resources, just as PBT/vPvB chemicals accumulate in food chains and humans. The health impact of the long-term risk of exposure to both types of chemicals is difficult to determine [10] and might not be picked up by standard chronic toxicity testing used in current chemical risk assessments. In addition, the potential of PMT and vPvM chemicals for widespread and persistent contamination of the aquatic environment, makes their impact, if found to be problematic, difficult to control.

The European Commission (EC) acknowledged this concern as indicated by the Chemical's Strategy for Sustainability Towards a Toxic-Free Environment in which an objective is included to introduce PMT and vPvM substances as categories of Substances of Very High Concern (SVHC) [16]. On April 20th 2023 the revised regulation (EC) No 1272/2023 on Classification, Packaging and Labelling (CLP) entered into force. that the CLP regulation now included PMT/vPvM as a hazard class, with a substance fulfilling the persistence criterion in any of the following situations: (a) the degradation half life in marine water is higher than 60 days; (b) the degradation half life in fresh or estuarine water is higher than 40 days; (c) the degradation half life in marine sediment is higher than 180 days; (d) the degradation half life in fresh or estuarine water sediment is higher than 120 days; and (e) the degradation half life in soil is higher than 120 days. The mobility criterion is a log K_{oc} of less than 3 A substance fulfils the toxicity criterion (T) in any of the following situations: (a) the long-term no-observed effect concentration (NOEC) or EC10 for marine or freshwater organisms is less than 0.01 mg/l; (b) the substance meets the criteria for classification as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1A or 1B) or toxic for reproduction (category 1A, 1B or 2) according to Regulation (EC) No 1272/2008; (c) there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to Regulation (EC) No 1272/2008; (d) there is other evidence of chronic toxicity for terrestrial organisms, such as birds; (e) the substance meets the criteria for classification as endocrine disruptor (category 1) for human health or the environment according to Regulation (EC) No 1272/2008. Furthermore, a chemical should be classified as very persistent and very mobile, in any of the following situations: (a) the degradation half-life in marine, fresh or estuarine water is higher than 60 days; (b) the degradation half-life in marine, fresh or estuarine water sediment is higher than 180 days; (c) the degradation half-life in soil is higher than 180 days and the log K_{oc} is less than 2.

It is not until November 1st 2026 until all manufacturers, importers, downstream users and distributors have to confirm new CLP regulation No 1272/2023. Therefore, screening approaches are at the moment indispensable to identify potential PMT/vPvM chemicals that need further investigation.

Screening approaches for PM(T) chemicals were previously published by Holmberg et al. [18] and Arp et al. [19]. Holmberg et al. [18] screened 2,073 mono-constituent organic REACH registered substances for PMT properties using the criteria for PMT/vPvM chemicals as proposed by the German Environment Agency [12] (i.e. vP/P criteria as applied for PBT/vPvB substances and Log K_{oc} of < 4 for M and < 3 for vM) as well as alternative criteria employing quantitative structure–activity relationships (QSARs). Arp et al. [19] aimed to identify organic substances that may appear in drinking water based on the minimum cut-off criterion for persistence of a half life in freshwater > 40 days, and for mobility a log K_{oc} of < 4.5 (pH 4–10). Both approaches were thus based on the discrete criteria for PMT/vPvM chemicals.

In this study, a semi-continuous screening approach is developed for PMT chemicals, aiming to give the screening approach more distinctive power than discrete approaches do. Discrete screening approaches fail to distinguish borderline substances from clear PMT/non-PMT substances. However, regulatory interest (e.g. to require further testing) should especially be focussed on the 'borderline' chemicals, not those substances where experts agree on their (potential) PMT properties (like some PFAS). The semi-continuous screening approach is applied to 6158 chemicals, resulting in a ranking of these chemicals based on their PMT properties.

Methods

Development of a PMT screening approach: overview

The developed hazard-based screening approach is based on the earlier work by Hartmann et al. [20] and Rorije et al. [21]. The screening approach solely includes modelled data to allow for application to a wide range of chemicals, even those for which experimental data is lacking. The included modelled indicators are: (1) quantitative structure–activity relationships (QSARs), (2) structural alerts for a selection of human health endpoints and (3) chemical similarity to SVHCs [22]. A detailed

description of the screening approach is included in the results section. An overview of the various building blocks is given below.

The basic approach is to score chemicals from 0 (low to moderate PMT potential) to 1 (very high PMT potential). In addition, for persistence (P), mobility (M) and toxicity (T) as well as for the overall PMT score, the scores are constructed so that:

- a score of 0–0.33 indicates low to moderate P, M and/or T;
- a score of 0.33–0.5 indicates high P, M and/or T;
- and a score of 0.5–1 indicates very high P, M and/or T.

The PMT score was constructed using continuous scoring systems for a chemicals' persistence and mobility potential and a semi-continuous scoring system for a chemical's toxicity potential. The developed persistence score (P score) indicates a chemical's potential to persist in the aquatic environment based on its estimated half-life in water. A mobility score (M score) is developed based on the chemical's K_{oc}. The sigmoid functions used to transform a chemical's half-life and log K_{oc} to a 0–1 scale are based on Rorije et al. [21].

A novel aspect of the screening approach is the semi-continuous scoring system for a chemicals ' hazard potential (T score) on a scale from 0 to 1. Five human health endpoints are included: carcinogenicity (*c*), mutagenicity (*m*), reprotoxicity (*r*), endocrine disruption (ED) and general toxicity.

Application of screening approach: description of the database

A list of chemicals was prepared by combining:

1. chemicals from the European INventory of Existing Commercial chemical Substances (EINECS) which are also registered under REACH (from now on referred to as the EINCES/REACH list, $N=5316$); and
2. a list of chemicals that are monitored in surface water used for the production of drinking water in the Netherlands. This list was kindly provided by the Association of River water companies (RIWA) (from now on referred to as the RIWA list, $N=1161$).

Combining these lists yields 6,158 unique chemicals (based on CAS numbers) and includes, but is not limited to, industrial chemicals, pharmaceuticals, personal care products, biocides and plant protection products. This list of chemicals is screened using the developed approach. There is an overlap of 319 chemicals between the EINCES/REACH and the RIWA list. The overlap is limited, as many pharmaceuticals and plant protection products present on the RIWA suspect screening list are not present on the EINECS/REACH list.

Results

Screening approach

Persistence (P) scoring

Persistence was estimated using the BIOWIN3 model of the EPI (Estimation Programs Interface) Suite™ 4.1 software. BIOWIN3 does not provide estimates of half-lives in water, but merely provides an indication of the time needed for complete biodegradation (mineralization) in the aquatic environment as a value between 1 and 5, where 5 = hours, 4 = days, 3 = weeks, 2 = months and 1 > months. The values given by BIOWIN3 are based on the expert knowledge. Here, the output of BIOWIN3 was converted to a continuous estimate of half-lives in water using the approach introduced by Rorije et al. [21]. Equation 1 shows the exponential function for the half life in freshwater in days ($t_{0.5}$), which was constructed by relating the half lives given by Aronson et al. [23] to the average value given by BIOWIN3. This function is an update of the function used in Rorije et al. [21] by a revision of the distribution of the score over the bins, including the extreme bins.

$$t_{0.5}(\text{fresh water}) = 5377 * e^{-1.95*\text{BIOWIN3}} \quad (1)$$

Next a sigmoid function was constructed that transforms the half-life in freshwater in days ($t_{0.5}$) to a value between 0 and 1. Others in the field of decision analysis and operations research have referred to such a function as the value function [24]. For this purpose, a sigmoid curved value function was used instead of a linear function or binning. A sigmoid curved relation gives the scoring system more distinctive power than a discrete or linear relation would [20, 21]. A sigmoid function is preferred over a discrete function as it describes a continuum instead of dividing all substances in categories. It therefore helps to answer the question 'How persistent/mobile/toxic is a chemical?' instead of 'Is the chemical (very) persistent/mobile/toxic?'. Furthermore, a sigmoid curved function provides, in contrast to a linear function, the opportunity to decrease the slope of the curve in the beginning and the end of the curve and increase the slope in the middle. This gives the sigmoid function more distinctive power around benchmark values of interest.

The sigmoid function is constructed following Rorije et al. [21], but amended so that persistent chemicals with a half-life between 40 and 60 days in freshwater get scores between 0.33 and 0.5, whereas very persistent chemicals with a half-life in excess of 60 days get a score of 0.5 or higher. The benchmark values of 40 and 60 days

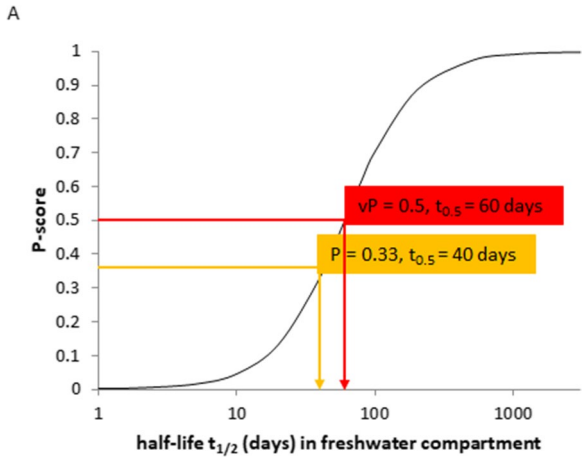

Fig. 2 Relation between a chemical's half-life in water and its P score calculated using Eq. 2

were chosen based on the criteria for persistent (half life in surface water ≥ 40 days) and very persistent (half life in surface water ≥ 60 days) chemicals according to Annex XIII of REACH. The values of 0.33 and 0.5 were chosen to ensure that the distinctive power of the sigmoid function is optimal around the benchmark values (60 days for vP, see also Fig. 2). Other values could have been selected (e.g. 0.33 and 0.66, in which case a score of 0.5 would correspond to a half life in water of 50 days), but currently used values are in line, and thus allow comparison, with earlier applied cut-off values for PBT screening [21, 22].

Equation 2 is the resulting function for the developed persistence score (*P*) (see also Fig. 2).

$$P-\text{score}=\frac{1}{1+10^{\log 2\left(\frac{\log 60-\log t_{0.5}}{\log 60-\log 40}\right)}} \quad (2)$$

Mobility (M) scoring

A chemical's K_{oc} is estimated using the KOCWIN™ model (log K_{ow}-based method) of EPI Suite™ 4.1. Mirroring the persistence scoring approach described above, a sigmoid function was constructed that covers the degree of fulfilment of the mobility criterion as a function of log K_{oc}. The sigmoid function was constructed using benchmark values for mobile and very mobile chemicals. Here, mobile chemicals were chemicals with an estimated log K_{oc} of 3 (i.e. a score of 0.33), whereas very mobile chemicals had a log K_{oc} of 2 or lower (i.e. a score of 0.5 or higher). These benchmarks are in line with the proposal on hazard classes for PMT/vPvM in CLP, as shared by the European Commission in October 2021 with Member States. Others (e.g. [12]) have suggested a log K_{oc} of 4 for mobile and a log K_{oc} of 3 for very mobile chemicals. These benchmarks were not applied in this work as these cut-off values might be considered to be too conservative. Particularly as the groundwater ubiquity score (GUS) indicates that chemicals with a log K_{oc} of 4 (or higher) are considered only mobile enough to reach the groundwater if there is no (observable) degradation at all in the environment [25, 26]. Equation 3 shows the resulting function for the mobility score (*M* (see also Fig. 3).

$$M-\text{score}=\frac{1}{1+10^{\log 2\left(\frac{2-\log Koc}{2-3}\right)}} \quad (3)$$

Toxicity (T) scoring

The hazard potential is estimated based on the five endpoints: carcinogenicity (*c*), mutagenicity (*m*), reprotoxicity (*r*), endocrine disruption (ED) and general toxicity. Structural alerts (known as profilers) from the QSAR Toolbox 4.4.1 and Toxtree 3.1.0 were used for all human health endpoints included in the scoring system for T (*c, m, r*, ED and general toxicity). Although CMR (uppercase) is the commonly used abbreviation for carcinogenic, mutagenic and reprotoxic chemicals, here we use cmr (lowercase) as the M (uppercase) is used for mobility.

Next to these profilers, indicators for structural similarity to known cmr chemicals, according to Wassenaar et al. [22] were used for a selection of the human-toxicological endpoints, namely *c*, *m* and *r*. Figure 4 illustrates the analytical hierarchy used to calculate a chemical's T score. It shows which (sub-)profilers and similarity values were used for each human health endpoint. Background information to each of the used (sub-)profilers and similarity models is included in Table 1.

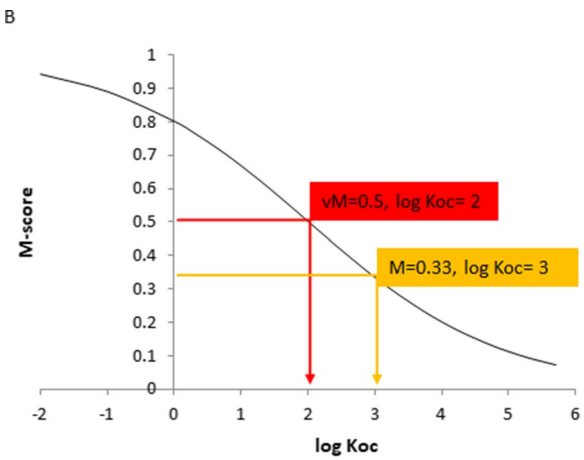

Fig. 3 Relation between a chemical's log K_{oc} and its M score calculated using Eqs. 3

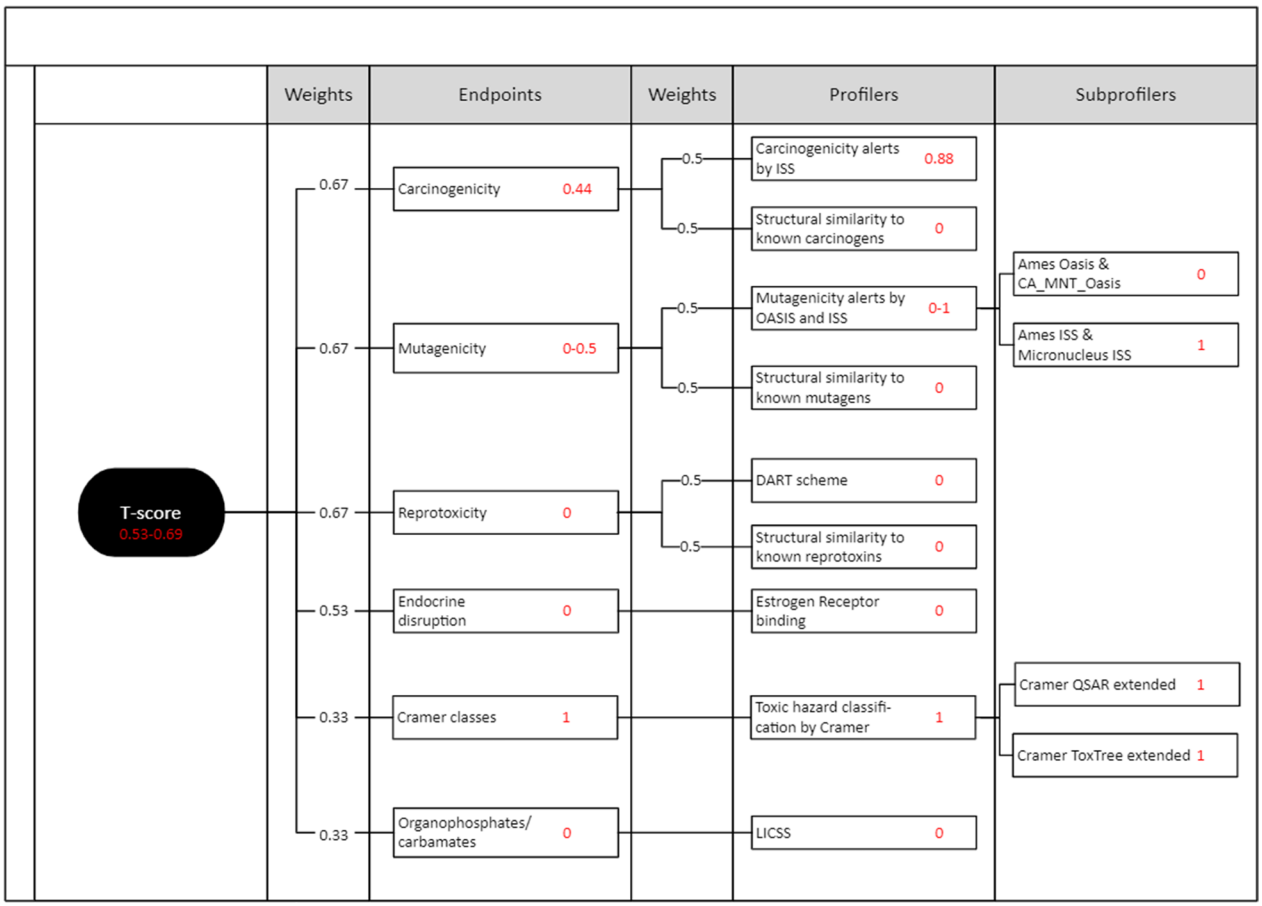

Fig. 4 The analytical hierarchy* and weighting used to calculate a chemical's T score. In red the scores for Melamine as an example calculation are given. *The T score includes (sub-)profilers from the QSAR Toolbox 4.4.1, Toxtree 3.1.0 and structural similarity values by Wassenaar et al. [22]. Table 1 provides background information to the (sub-)profilers and similarity models. These (sub-)profilers and similarity measures were used to indicate each of the endpoints (c, m, r, ED and general toxicity) which were aggregated to indicate a chemical's hazard potential on a scale from 0 to 1. In red the T score calculation for melamine (1,3,5-triazine-2,4,6-triamine, CAS number: 108-78-1), as presented in "Application of screening approach" section, is shown as an example

For the endpoints *c*, *m* and *r*, the scores were based on the structural alerts from the QSAR Toolbox (called profilers) and on similarity measures by Wassenaar et al. [22]. The potential of a chemical for endocrine disruption is solely based on the oestrogen receptor binding profiler from the QSAR Toolbox. General toxicity of a chemical was indicated by two profilers: Cramer classes and whether a chemical is an organophosphate or carbamate as these substances are known to cause neurotoxicity at low doses [34]. Using the Cramer decision tree, organic chemicals can be subdivided into one of three classes based on their molecular structure: Cramer Class I indicates low toxic potential, Cramer Class II indicates intermediate toxic potential, and Cramer Class III indicates high toxic potential of a chemical [35]. The categorization into Cramer classes was based on the extended Cramer profiler from the QSAR Toolbox and ToxTree. Whether a chemical is an organophosphate or carbamate was determined using the excel add-in LICSS (GitHub—KevinLawson/excel-cdk: Enable chemical informatics functionality in MS Excel spreadsheets).

Some of the (sub-)profilers provided a binary output, meaning that these profilers provide information on whether a chemical contained a structural alert for the specific endpoint (sub-score is 1) or not (sub-score is 0). This applied to the following (sub-)profilers: Ames Oasis & CA_MNT_Oasis, Ames ISS & Micronucleus ISS and DART from the QSAR Toolbox 4.4.1, and LICSS. The other profilers and similarity values were either categorical (carcinogenicity alerts by ISS, oestrogen receptor binding and both of the Cramer profilers) or continuous (structural similarity to known carcinogens, mutagens and reprotoxicants).

The output provided by these categorical and continuous profilers is transformed to a value between 0 and 1 using the value functions presented in Fig. 5. The

Table 1 Background information* to the (sub-)profilers and similarity models used to calculate a chemical's T score (see Fig. 4)

Profiler and similarity models	Background information	Source
Carcinogenicity alerts by ISS	This profiler works as a decision tree for estimating carcinogenicity, based on the list of 55 structural alerts. The structural alerts for carcinogenicity are molecular functional groups or substructures known to be linked to the carcinogenicity activity of chemicals	QSAR Toolbox 4.4.1
Structural similarity to known carcinogens, mutagens and reprotoxins	The model indicates structural similarity to chemicals that are on a Dutch list of SVHCs (including REACH-SVHCs and cmr category 1A and 1B CLP classified substances). The model consist of a combination of a binary fingerprint, similarity coefficient and similarity threshold, and suggested a high predictive performance (≥ 80%) on an internal dataset consisting of SVHC and non-SVHC substances. The model was developed based on the analysis of 112 different similarity measures for varying SVHC-subgroups	Wassenaar et al. [22]
Mutagenicity alerts by OASIS and ISS	The alerts for DNA damage are based on the Ames Mutagenicity model of the OASIS TIMES QSAR system (85 alerts) [27, 28] and the 43 in vitro mutagenicity (Ames test) alerts for DNA damage as derived by Istituto Superiore di Sanità (ISS), Rome, Italy and implemented in the Mutagenicity module of the ToxTree software [29]	QSAR Toolbox 4.4.1,), Mekenyan et al. [27], Serafimova et al. [28] and Benigni et al. [29]
DART scheme	The DART scheme is a framework for identifying chemicals with structural features associated with the potential to act as reproductive or developmental toxicants, based on Wu et al. [30]. It was developed on the basis of the combination of known modes of action (MOA) and associated structural features, as well as an empirical association of structural fragments within molecules of reproductive or developmental toxic (DART) chemicals when MOA information was lacking. The design of this tool is based on the detailed review of 716 chemicals (664 positive, 16 negative, and 36 with insufficient data) that have been evaluated for their DART potential	QSAR Toolbox 4.4.1 and Wu et al. [30]
Estrogen receptor binding	The Estrogen Receptor binding profiling scheme is based on the structural and parametric rules extracted from literature sources and supported by experimental data. The ER-binding profiler classifies chemicals as non-binders or binders depending on molecular weight (MW) and structural characteristics of the chemicals	QSAR Toolbox 4.4.1
Toxic hazard classification by Cramer	Toxic hazard classification by Cramer profiler (extension) is built on the basis of Cramer et al. [31], Patlewicz et al. [32] and Munro et al. [33]. The decision tree comprises 33 basic structural rules. The entered target chemicals are classified in one of the three toxic classes: - Low (Class I) - Intermediate(Class II) - High (Class III)	QSAR Toolbox 4.4.1, Toxtree 3.1.0, Cramer et al. [31], Patlewicz et al. [32] and Munro et al. [33]
LICSS	This profiler gives an alert when the chemical is a organophosphate or carbamate	LICSS

*The background information is extracted from the description of the profilers in the QSAR toolbox and from Wassenaar et al. [22]

structural alerts for the indicators from the QSAR toolbox, LICSS and ToxTree were transformed to a 0–1 scale based on the pairwise comparison experiment performed by the authors using the 'Potentially All Pairwise RanKings of all possible Alternatives' (PAPRIKA) method. This method is explained in detail in [36]. The PAPRIKA method helps its users to rank levels of criteria (e.g. Cramer Class I, II and III) by asking the user to choose multiple times between two hypothetical alternatives with two criteria. The output of the PAPRIKA method was the score for each level of a profiler (e.g. 0 for Cramer Class 1, 0.375 for Cramer Class II and 1 for Cramer Class III).

The structural similarity to known carcinogens, mutagens and reprotoxins was converted to a 0–1 scale using the optimised threshold for the similarity score (the thresholds of 0.851 and 0.941 in the formulas in Fig. 5) as derived by Wassenaar et al. [22]. The underlying CMR similarity models as developed by Wassenaar et al. [22] consist of two sub-models, of which one is specifically optimised for relatively small molecular structures (< 85 fragment bits) and the other for relatively large molecular structures (≥ 85 fragment bits). Fragments bits are defined as the number of present chemical substructures according to the CDK Extended fingerprint [37].

The sub-scores for c, m, r, ED and general toxicity were then calculated as shown in Table 2.

The sub-scores on each endpoint were combined to an overall T score. The function to combine the sub-scores was based on two assumptions:

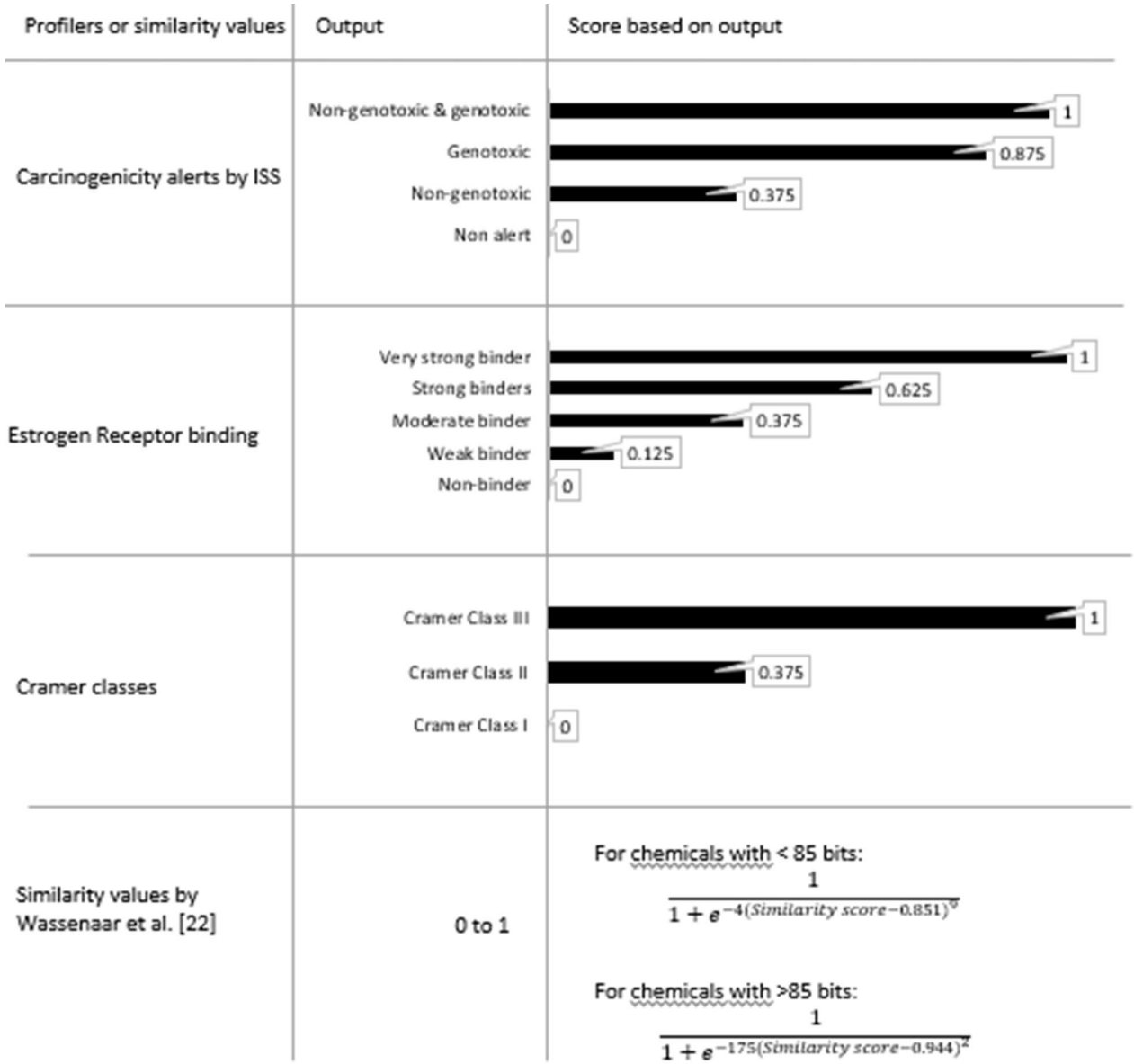

Fig. 5 Transformation of the categorical and continuous profilers and similarity values to a value between 0 and 1

Table 2 Sub-score calculation of human health endpoints based on the (sub-)profilers and similarity values shown in Fig. 4

Endpoint	Function for sub-score calculation
Carcinogenicity	$C-\text{score}=\sum_{\text{carcinogenicityISS},c-\text{similarity}}0.5\text{score}$
Mutagenicity	$M-\text{score}=\sum_{\text{QSARprofilersmutagenicity},m-\text{similarity}}0.5\text{score}$
Reprotoxicity	$R-\text{score}=\sum_{\text{DART},r-\text{similarity}}0.5\text{score}$
Endocrine disruption	$\text{ED}-\text{score}=\text{score}_{\text{ERbinding}}$
General toxicity	$\text{Cramer}-\text{score}=\text{score}_{\text{Cramerclasses}}$ $\text{OPester}-\text{score}=\text{score}_{\text{LICSSToxTree}}$

1. An alert for any of the endpoints c, m, r, ed or general tox should be sufficient for a T score of 0.33 or higher. This mirrors the approach used for the P and M scoring approaches; and
2. Two endpoints fulfilled is considered a higher concern than one.

Using these assumptions, a function based on the response addition equation was constructed to combine the sub-scores on each endpoint to a toxicity score (T), as shown in Eq. 4, and ensures that the T score cannot be above 1.

$$T - \text{score} = 1 - \prod (1 - \text{weight} * \text{score}_{C,M,R,ED,\text{Cramer,LICSSToxTree}}) \quad (4)$$

The weights used for each endpoint are presented in the second column in Fig. 4. Because two of the five endpoints (mutagenicity and Cramer classes) were based on a profiler with two sub-profilers, a $T\text{-}_{min}$ and a T_{max} were calculated. The average between these values ($T_{average}$) was used to calculate the PMT score (see section "PMT scoring" below).

PMT scoring

The scores for P, M and T were combined to construct a PMT score, where potential PMT chemicals are identified by a score of at least 0.33. A PMT score of 0.5 or higher, indicates very high PMT potential. The aggregation function was constructed so that the score not filled by one endpoint could be filled by another, which is comparable to the way of thinking of the GUS, where multiplication of P and M is also used to indicate the potential of a chemical for leaching and dispersion [26]. This is considered a valuable addition to the existing screening approaches as this enables the identification of chemicals of concern that may not score high on all three indicators (P, M and T), but that do cause a concern based on the combination of (some of) these indicators. Equation 5 shows the resulting function used to calculate a chemical's PMT score.

$$\text{PMT} - \text{score} = P - \text{score}^a * M - \text{score}^b * T - \text{score}^c \quad (5)$$

where the sum of the weights ($\sum a, b, c$) should be 1. Here, we used equal weights $a = \frac{1}{3}, b = \frac{1}{3}$ and $c = \frac{1}{3}$.

Application of screening approach

Example PMT-score calculation: melamine

To illustrate the screening approach, the calculation of the PMT score for melamine (1,3,5-triazine-2,4,6-triamine, CAS number: 108-78-1) is explained as an example. The output of BIOWIN3 for melamine is 2.27, which is converted to a $t_{0.5}$ of 64.2 days using Eq. 1. The $t_{0.5}$ of 64.2 days converts to a P score of 0.53 (slightly above the threshold score of 0.5 which reflects the P-criterion of 60 days) using Eq. 2. The KOCWIN™ model estimates the log K_{oc} of melamine to be 0.0002, which is converted to a M score of 0.80 using Eq. 3. The profilers from the QSAR toolbox give the following output for melamine: Ames/Micronucleus alert ISS, no Ames/Micronucleus alert OASIS, not known precedent for reproductive or developmental toxic (DART) effects, genotoxic carcinogen by ISS, no oestrogen receptor binder and Cramer Class III. ToxTree indicates melamine as being no organophosphate or carbamate and also classifies melamine as a Cramer Class III chemical. The similarity tool by Wassenaar et al. [22] gave the following similarity scores for melamine: 0.63 for both *c* and *m*, 0.60 for *r*. The output of the QSAR toolbox, ToxTree and the similarity tool is transformed to values between 0 and 1 using the functions as described in Fig. 5. The results of the T-score calculation with Eq. 4 and Table 2 is shown in red in Fig. 4. For the calculation of $\text{PMT} - \text{score}_{\text{melamine}}$ the average of $T_{\text{melaminemax}}$ (=0.69) and $T_{\text{melaminemin}}$ (=0.53) was used.

$$\text{PMT} - \text{score}_{\text{melamine}} = 0.53^{0.33} \times 0.8^{0.33} \times 0.61^{0.33} = 0.64$$

Melamine is thus categorised as a chemical with a very high PMT potential by the screening approach. The individual score above 0.5 for both the P- and the M score indicate that this substance could possibly even be categorised as a vPvM substance. Melamine is currently under investigation in the REACH legislation as a potential PBT/PMT substance [38].

PMT scores of database

The P, M, T scores for both the EINECS/REACH and RIWA list are included as supplementary material. The screened database contains 42 inorganic substances (all part of the RIWA list), for which the screening approach should not be used, because the QSARs/profiles used to derive the PMT scores are not developed for these kind of chemicals. An example is lead (CAS number: 7439-93-1). These inorganic compounds were kept in the database as points of reference, but they are labelled and the estimated PMT scores should be carefully evaluated.

Figure 5 shows the percentage distribution of the P, M, and T scores of the organic chemicals from the EINECS/REACH and the RIWA list. From the EINECS/REACH list, 2,714 chemicals (51%) have an overall PMT score ≥ 0.33, and 762 chemicals (14%) had a PMT score ≥ 0.5, although scores for individual criteria may be below the respective thresholds. Regarding persistence and mobility separately, 32% of all chemicals had a P score ≥ 0.33, the same percentage had an M score ≥ 0.33. Furthermore, 221 chemicals (4%) had both a P- and M score above 0.5. Finally, 4,139 chemicals (78%) had a T score of ≥ 0.33.

Estimating the PMT scores for organic chemicals from the RIWA list revealed a slightly different pattern. The 42 inorganic chemicals are not taken into account. In this sub-list, a higher percentage of chemicals had a PMT score ≥ 0.33 (910 chemicals; 81%), with 366 chemicals (33%) having a PMT score ≥ 0.5. In addition, a higher percentage, as compared to the EINECS/REACH list, was classified as persistent or mobile (617 chemicals with a P score ≥ 0.33; 55%) and 520 chemicals with a M score ≥ 0.33 (46%), respectively, with 48 chemicals (4%) classified as vPvM (i.e. P- and M score ≥ 0.5). Finally, 1,055 chemicals (94%) had a T score ≥ 0.33 (Fig. 6).

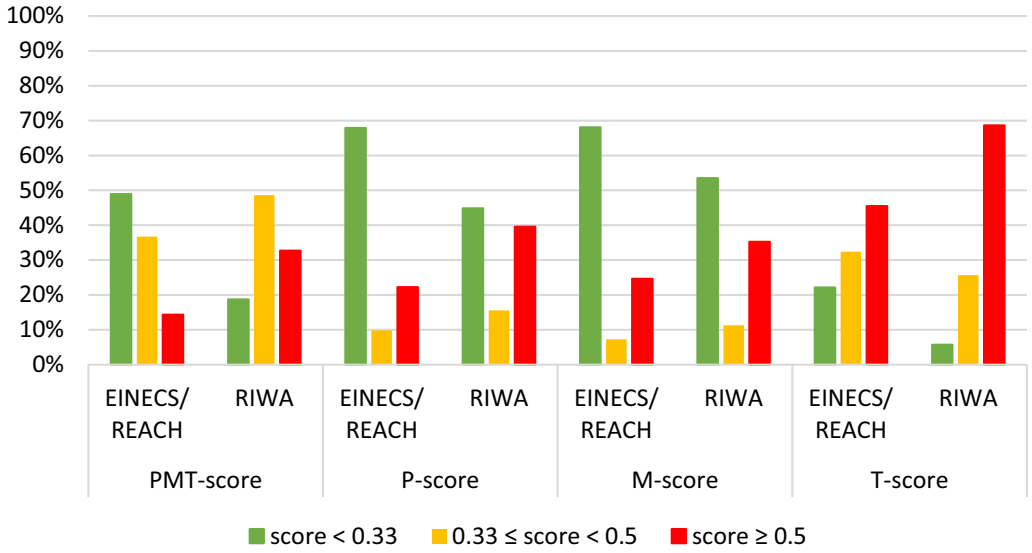

Fig. 6 Percentage distribution of P, M, and T scores of chemicals in the EINECS/REACH (*N* = 5316 organic chemicals) and the RIWA (*N* = 1119 organic chemicals) list

The three chemicals with the highest PMT scores were tylosin (CAS number 1401-69-0, used as veterinary antibiotic [39], PMT score = 0.82), C.I. Reactive Yellow 2 (CAS number 50662-99-2, used in cotton, wool and silk dyeing [40], PMT score = 0.81), and chlortetracycline (CAS number 57-62-5, used as veterinary antibiotic [41], PMT score = 0.81). For 115 unique chemicals, a PMT score of 0 was calculated, including aspartame (CAS number 22839-47-0) and maltose (69-79-4).

Table 3 shows the estimated PMT scores for a few chemicals that have gained scientific, public and regulatory attention over the past few years. The first three are members of the group of polyfluoroalkyl substances (PFAS): trifluoroacetic acid (TFA), perfluorooctanoic acid (PFOA) and perfluorobutanesulfonic acid (PFBS).

Table 3 PMT scores of seven chemicals that have gained public attention over the past few years

Chemical name	CAS number	Usage	SVHC	PMT score	P score	M score	T score
Trifluoroacetic acid (TFA)	76-05-1	Precursor to other fluorinated compounds, also used as a strong acid to remove t-butyl derived side-chain protecting groups. Persistent metabolite of substances that contain a trifluoromethyl functionality, f.e. a number of fluoro-coolants HFCs	–	0.34	0.16	0.75	0.34
Perfluorooctanoic acid (PFOA)	335-67-1	Used in several applications, such as in firefighting foam and in coatings	SVHC	0.60	0.99	0.36	0.61
Perfluorobutanesulfonic acid (PFBS)	375-73-5	Fluorosurfactant, used as replacement for PFOS	SVHC	0.63	0.92	0.51	0.53
1,4-Dioxane	123-91-1	Solvent and stabiliser for the transport of chlorinated hydrocarbons in aluminium containers	SVHC	0.38	0.09	0.73	0.84
Melamine (1,3,5-triazine-2,4,6-triamine)	108-78-1	Used in, for example, plastic dishware	–[1]	0.64	0.53	0.80	0.61
Methyl Tert-butyl Ether (MTBE)	1634-04-4	Additive for unleaded gasoline	–	0.42	0.17	0.61	0.74
Glyphosate	1071-83-6	Active ingredient in herbicides and crop desiccant	–	0.25	0.05	0.96	0.34
Perfluorheptanoic acid (PFHpA)	375-85-9	Used as a stain or water repellent	–[1]	0.63	0.98	0.42	0.61

SVHC = Substance of Very High Concern according to Article 57(f) of regulation 1907/2006 (REACH)

[1] Melamine and PFHpA are on the Candidate List of SVHCs

The next chemical is 1,4-dioxane, which is used as a solvent and is widely detected in both groundwater and surface water [15]. The PMT score for melamine estimated with the presented screening approach was already discussed in "Application of screening approach" section ("Example PMT score calculation: melamine"), but is also included in Table 3. The final two chemicals included in Table 3 are methyl tert-butyl ether (MTBE) and glyphosate. MTBE has been used as a gasoline additive and glyphosate is the most commonly used active ingredient in herbicides [42, 43].

The PMT scores estimated by the developed screening approach are discussed in more detail in the Discussion section below.

Discussion

This screening approach is able to identify potential PMT chemicals of concern, illustrated by the fact that several PMT-SVHCs are classified as such by the screening approach (see Table 3), even though limitations of the method were found. First, this section comprises a discussion of the results presented in Table 3 in order to elucidate the effectivity of the screening approach for identification of PMT/vPvM chemicals. Second, the strengths and limitations of the approach are discussed and finally suggestions for further improvement are provided.

Estimated PMT scores for known aquatic contaminants of concern

All in Table 3 listed known aquatic contaminants of concern were accurately scored by the screening approach. Meaning that those contaminants that are of concern for their PMT properties received a PMT score of above 0.33. First, this was achieved for the contaminants that are classified as SVHCs because of these PMT properties (Perfluorooctanoic acid (PFOA), Perfluorobutanesulfonic acid (PFBS) and 1,4-dioxane. For some other concerns exist. HFPO-DA is also classified as a SVHC because of its PMT properties, but is not included in the database underlying this paper.

Furthermore, the two contaminants that are on the candidate list of SVHCs, melamine and Perfluorheptanoic acid (PFHpA) were also picked up by the screening approach. TFA and MTBE were also scored above 0.33, which is in line with the experimental data on these chemicals (TFA [14, 44] and MTBE [12]). Finally, glyphosate, which is not a substance of very high concern because of its PMT properties [43, 45], was also not identified as such by the screening approach (< 0.33).

Despite the fact that the calculated PMT scores for the in Table 3 listed contaminants were accurate, the underlying persistence score was for some contaminants not in line with experimental data. BIOWIN 3 underestimated the persistence for TFA [9, 46], 1,4-dioxane [47]and MTBE [12], which led to an, based on the experimental evidence, unrealistically low P score for these chemicals [10, 14, 42–45, 47–51].

Strengths and limitations

Interpretation of screening results and follow-up

What does an estimated PMT score of ≥ 0.33 mean and what should be the next steps for evaluation of such chemicals? This is a relevant question when interpreting the results obtained with the presented screening approach. It is suggested to use a stepwise approach. The first step that should be looked at for chemicals with a PMT score of ≥ 0.33, is what the separate scores for P, M and T are. When there is relevant and reliable experimental evidence available, this should be used to overrule one or more of these scores. For example, for melamine, the recently identified hepatoxic effects of melamine are not picked up by the QSARs, which would justify a higher T score [52]. Another example is the low P score for 1,4-dioxane, which can be overruled by the empirical evidence as provided e.g. by Hofman-Caris et al. [47]. In addition, expert users could evaluate whether the chemical falls within the applicability domains of the underlying models. Regarding the similarity scores to known SVHCs, based on Wassenaar et al. [22], it is worth looking at the compound to which the highest similarity was found. A next step could be to add monitoring and/or emission data to the PMT screening results, to prioritise action on widely used potential PMT chemicals over sporadically used ones. The screening approach was intentionally designed based on the modelled indicators to make it widely (even for those chemicals for which experimental data is lacking) and easily (applying the screening approach can be done for thousands of chemicals at once) applicable. The necessary follow-up steps should be assessed case by case (checking for experimental data, adding emission data etc.) and are therefore intentionally not included in the screening approach.

Some chemicals are included in the database which could be represented by different Simplified Molecular-Input Line-Entry System (SMILES) (e.g. isomers), and these different SMILES could result in different PMT scores. An example is ibuprofen. This chemical (CAS number 15687-27-1) is included in the RIWA list as well as in the EINECS/REACH list, but with a different SMILES representing their structure, one representing the neutral structure, and one the charged (dissociated) structure. The T score is different between these two entries, because of a different Cramer Class assigned and absence/presence of a developmental toxicity (DART) alert by the QSAR Toolbox for these different SMILES.

This illustrates the sensitivity of the used QSAR and alert models for small differences in the SMILES input and thus the importance of providing unambiguous structures. It could be advised to use multiple SMILES representations of a single chemical in the screening process in order not to miss a possible alert.

Comparison with other screening approaches for PMT chemicals

Holmberg et al. [18] and Arp et al. [19] published screening results for PMT chemicals. As the screening approach developed in this study is solely based on the modelled data, the study by Holmberg et al. [18] is the most comparable approach as they also almost exclusively based their screening on QSAR-based predictions. However, Holmberg et al. [18] used different criteria for M, namely Log K_{oc} of < 4 for M and < 3 for vM. Arp et al. [19] applied a different approach by mainly using experimental data. In those cases were experimental data was unavailable, QSAR predictions and expert judgement were used.

Holmberg et al. [18] found 23% of the 2073 screened REACH registered chemicals to be PM, 8% to be PMT and 4.6% to be vPvM. The toxicity was not only based on indicators for human health endpoints, but also on ecotoxicity. In comparison, the current study found 16% of the EINECS/REACH list to be PM (P score ≥ 0.33 and M score ≥ 0.33), 15% to be PMT (P score ≥ 0.33, M score ≥ 0.33 and T score ≥ 0.33) and 4% to be vPvM (P score ≥ 0.5 and M score ≥ 0.5). These percentages differ from percentages introduced in the results section "PMT scoring" as the percentages mentioned in the previous sentence only cover chemicals with scores above ≥ 0.33 for P, M and T (fraction of PMT chemicals), and ≥ 0.5 for P and M (fraction of vPvM chemicals) (see section 'Interpretation of screening results'). The identified fraction of PM and vPvM chemicals thus resembles the results of the study by Holmberg et al. [18], despite the difference in QSAR models and interpretation of results. The screening approach introduced in this study identifies a higher percentage of PMT substances, which is probably due to a more conservative toxicity screening. A more conservative approach is warranted for screening purposes. The conservativity here relates to the fact that the transformation function for T is constructed so that an alert on one of the endpoints is enough for a T score of 0.33. This is done by choosing the weights for the different endpoints accordingly (see Fig. 4). If a user prefers a less conservative approach, these weights can be adjusted while being mindful that the weights on each level of the hierarchy need to sum up to 1.

The developed screening approach uses benchmark values to shape the transformation functions for P and M (i.e. $t_{0.5}$ of 40 and 60 days and log K_{oc} of 3 and 2) to be able to score chemicals using that transformation function on a scale between 0 and 1. Scores of 0.33 and 0.5 are related to the benchmark values. The developed screening approach thereby enables the identification of borderline PMT/not PMT chemicals which are not identified by the screening approach by Holmberg et al. [18] and Arp et al. [19]. This specifically considers chemicals with a PMT score just below or above 0.33 (i.e. the PMT criterion). Identifying also these borderline chemicals is considered a valuable improvement as screening approaches are most helpful when they can direct regulatory interest to these 'borderline' chemicals, as well as to those chemicals where experts agree on their PMT/not PMT properties (like PFAS).

Potential areas for improvement of screening approach

First, an important area for future research is to apply the screening approach to a broader database. The database used in this study did not include all REACH registered chemicals, nor did it cover all biocides, plant protection products and pharmaceuticals used in Europe. Application of the screening approach to a broader database might reveal flaws in the screening approach that were not yet discovered in this study. Such flaws could potentially be related to inaccuracies in specific sub-models for specific groups of chemicals (e.g. as observed for the persistence prediction of several PFAS).

Furthermore, the analysis of the screening results for both the EINECS/REACH and RIWA list, showed a high percentage of chemicals being classified as potentially toxic (78% and 94%, respectively). This could indicate that the calculation of the T score is too conservative. However, from a screening point of view this could possibly be justified. In addition, this observation could also be related to the data used in this study. For example, the RIWA list specifically contains chemicals that are monitored in surface water as they are (potentially) toxic and could risk the production of drinking water. Furthermore, in the RIWA list pharmaceuticals are overrepresented. In addition, this is due to the fact that this list is specifically focussed on those chemicals monitored in surface water. This possibly also explains the high percentage of PM chemicals on this list. Moreover, the endpoints included in the calculation for the T score are not yet all-encompassing, which also justifies a more conservative scoring system. An example is that ED is currently only based on the potential of the chemical for oestrogen binding. Similarity values for ED based on Wassenaar et al. [22] were not included because the dataset of chemicals that are classified as SVHC because of their ED properties is currently too limited.

Another potential area for improvement of the screening approach is a different weighing of P, M and T. The

presented results were calculated with Eq. 5, where $a = \frac{1}{3}$, $b = \frac{1}{3}$ and $c = \frac{1}{3}$. This even weighing of P, M, T results for some chemicals, in a similar PMT and PBT score, meaning that the chemical would be classified as both a potential PMT and PBT chemical. This is counterintuitive, as one would label a chemical usually either as PMT or PBT (with the exception of some PFAS). This issue could be solved by giving more weight to M (and B). Following Cousins et al. [53], it could even be argued that highly persistent (and toxic) chemicals are a cause of concern, irrespective of their mobility or bioaccumulation. This argument could be valid for the extremely persistent substances like PFAS—that have such long environmental residence times that inevitably exposure concentrations will reach a certain concern level. The environmental half-life for such substances (where persistence in itself is sufficient for concern) is thought to be much higher than the threshold values for PBT/PMT substances (40 days in the aquatic environment).

A fourth area for improvement could be the addition of volatility in the screening approach as mobile chemicals that are highly volatile are easily removed by simple drinking water treatment processes. However, the concern caused by PMT chemicals is not limited to drinking water safety. Therefore, including volatility for a general screening approach of PMT chemicals is hard to justify. When one would want to screen PMT chemicals of concern specifically for drinking water safety, the addition of volatility to the M score could be considered. Furthermore, other descriptors for mobility (in addition to K_{oc}) could potentially be added in future as K_{oc} may not be fully representative for mobility for all chemicals. The estimation of the K_{oc} in the current screening approach is solely based on the traditional method based on the log K_{ow}, and an estimation of the K_{oc} using the Molecular Connectivity Index (MCI) could possibly be added in future to reflect uncertainty when the output of these two methods is different. In addition, it is well known that the octanol water partition coefficient (and the log Koc) is dependent on pH for dissociating substances. Experimentally, the log D (pH dependent log Kow) could therefore be a better screening criterion for dissociating substances. QSAR models are available that estimate dissociation constants (pKa) which can be used to correct the log K_{ow} to environmentally relevant pH. Including dissociation behaviour (pKa estimate) in the screening approach is something that will probably improve screening especially for the mobility estimation.

A fifth area for improvement could be to apply other models to estimate a chemical's persistence in the aquatic environment. However, other generic estimation models for estimation of aquatic half-life are currently not known. If models are available they can be added in addition to the current BIOWIN model to reflect uncertainty using the hierarchy as shown in Fig. 4.

A final area for improvement could be the addition of other indicators for toxicity, e.g. adding ecotoxicity to the T-score calculation. Currently, the screening approach does only include human health endpoints. This could be established by including the QSAR for ecotoxicity from the Danish database [18]. However, it is not expected that the addition of an ecotoxicity indicator will identify many additional PMT chemicals, as most QSAR-based models for ecotoxicity are based on the chemical's Log K_{ow}, which is also directly related to a chemical's bioaccumulation potential and mobility (via Log K_{oc}). Another valuable area for improvement would be the update of the existing and addition of other models, for instance with improved similarity models [54] and addition of models to indicate a chemical's potential for ED. ED is currently solely based on the oestrogen receptor binding profiler from the QSAR Toolbox, which is likely to give an underestimation of the ED potential of a chemical as disturbing other hormonal systems and pathways can also lead to concern for ED [55].

Conclusions

Emissions of chemicals that are persistent (P) and mobile (M) in the aquatic environment as well as hazardous to humans and/or ecosystems (T), should be avoided. For this purpose, screening approaches are needed to identify these so-called PMT chemicals as early as possible. The screening approach developed in this study can be used by permit officers, risk assessors, drinking water suppliers, industry and others to screen chemical databases for potential PMT chemicals of concern. The screening approach should be used as a first step, followed by further investigation of chemicals with high PMT scores, by, for instance, collecting emission data and empirical persistence, mobility and toxicity data. The screening approach is also useful as part of the safe by design principle to prevent the development of potential PMT chemicals. Novel aspects of the developed screening approach were the use of continuous value functions for persistence and mobility, and a semi-continuous hazard based T score, giving the screening approach more distinctive power (following Hartmann et al. [20]). This kind of screening approaches are indispensable in protecting environmental and human health by identifying potential PMT/vPvM chemicals that need further investigation.

Abbreviations

c	Carcinogenic
DDT	Dichlorodiphenyltrichloroethane
ED	Endocrine disruption
M	Mobile
m	Mutagenic

PBT	Persistent, bioaccumulative and toxic
PCBs	Polychlorinated biphenyls
PMT	Persistent, mobile and toxic
r	Reprotoxic
REACH	European legislation No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals
SVHC	Substance of very high concern
vPvB	Very persistent and very bioaccumulative
vPvM	Very persistent and very mobile

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12302-023-00749-w.

Additional file 1. The P,M,T-scores for the EINECS/REACH and RIWA list

Acknowledgements
The authors thank Monique van der Aa, Els Smit, Theo Traas and Joop de Knecht (RIVM) for their valuable input on earlier versions of the manuscript. Furthermore, the authors would like to acknowledge the other members of the Working Group on PMT substances: André Bannink (RIWA Meuse), Anne Jans (Rijkswaterstaat), Henny Sonnemans (Water authority Limburg), Harrie Timmer (Vewin) and Erik Verhofstad (Ministry of Infrastructure and Water Management). This research was partially funded by the Dutch Ministry of Infrastructure and Water Management.

Author contributions
JH, EV and ER have made substantial contributions to the conception and design of the work. JH, EV, ER and PW have analysed and interpreted the data. JH, EV, ER and PW have drafted and revised the manuscript. JH, EV, ER and PW have approved the submitted version and have agreed both to be personally accountable for their contributions and ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

Funding
This research was funded by the Dutch ministry of Infrastructure and Water Management.

Availability of data and materials
The dataset(s) supporting the conclusions of this article are included within the article and its additional file(s). This is a preliminary list of chemicals. A more extensive list is planned to be published on https://rvs.rivm.nl/ in 2023.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.The P,M,T-scores for both the EINECS/REACH and RIWA list

Competing interests
The authors declare that they have no competing interests.

Received: 3 November 2022 Accepted: 19 May 2023
Published online: 02 June 2023

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