Safe and sustainable by design

A computer-based approach to redesign chemicals for reduced environmental hazards

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Safe and sustainable by design: A computer-based approach to redesign chemicals for reduced environmental hazards

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HIGHLIGHTS

- A systematic approach for the design of Safe and Sustainable chemicals is developed.
- The organophosphorus flame retardant TiBP was selected as a redesign example.
- An exhaustive set of suggested alternative structures were generated in silico.
- A final alternative was selected based on PBMT criteria and synthesizability.
- The approach helps to enable a safe, circular economy.

GRAPHICAL ABSTRACT
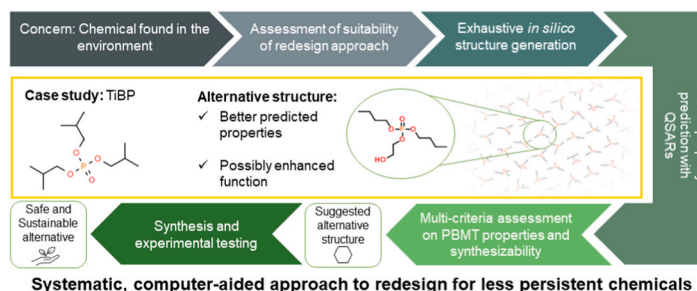
Systematic, computer-aided approach to redesign for less persistent chemicals

ARTICLE INFO

ABSTRACT

Persistency of chemicals in the environment is seen a pressing issue as it results in accumulation of chemicals over time. Persistent chemicals can be an asset in a well-functioning circular economy where products are more durable and can be reused or recycled. This objective can however not always be fulfilled as release of chemicals from products into the environment can be inherently coupled to their use. In these situations, chemicals should be designed for degradation. In this study, a systematic and computer-aided workflow was developed to facilitate the chemical redesign for reduced persistency. The approach includes elements of Essential Use, Alternatives Assessment and Green and Circular Chemistry and ties into goals recently formulated in the context of the EU Green Deal. The organophosphate chemical triisobutylphosphate (TiBP) was used as a case study for exploration of the approach, as its emission to the environment was expected to be inevitable when used as a flame retardant. Over 6.3 million alternative structures were created in silico and filtered based on QSAR outputs to remove potentially non-readily biodegradable structures. With a multi-criteria analysis based on predicted properties and synthesizability a top 500 of most desirable structures was identified. The target structure (di-n-butyl (2-hydroxyethyl) phosphate) was manually selected and synthesized. The approach can be expanded and further verified to reach its full potential in the mitigation of chemical pollution and to help enable a safe circular economy.

1. Introduction

Synthetic chemicals are pivotal for our society and economy, often contributing to our health and comfort. The overall production and use of these chemicals has been increasing over the past decades (Bernhardt et al., 2017). As a result, these human-made chemicals are omnipresent in the environment where they can cause adverse effects to both humans and other organisms (Naidu et al., 2021; Posthuma et al., 2020). Chemical pollution has consequently been identified as one of five main drivers for global biodiversity loss (IPBES, 2019). Moreover, chemical pollution ('novel entities') is one of the planetary boundaries humanity must not cross in order to avoid unacceptable global change although this specific planetary boundary is still unquantified (Li et al., 2021; Rockström et al., 2009). Recently however it was assumed that this planetary boundary is exceeded as the annual production and release of chemicals outpace the capacity for their assessment and monitoring (Persson et al., 2022). Worldwide, initiatives to reduce the impact of chemicals are lagging behind, underlining the urgent need for more ambitious action (United Nations Environment Programme, 2019; Wang et al., 2020).

Actions to manage chemical pollution consist for a major part of regulatory and technological (end-of-life) measures. Regulations are in place to register chemicals before market entry and hazard identification is a key part of this process. However, the influx of new chemicals on the market outpaces the speed with which such hazard assessments can be performed and for many chemicals adequate information on (environmental) hazards is lacking (Kristiansson et al., 2021). Consequently, problems are often identified long after the chemical has been approved (Johnson et al., 2020). Additionally, technological measures such as wastewater treatment are considered as resource-intensive and it can be even impossible to remove chemicals once present in waste streams (Kümmerer et al., 2018).

Chemicals can be emitted to the environment during their whole life cycle, from their production to waste phase (Wang and Hellweg, 2021). A combination of strategies covering the whole chemical life cycle will thus be most efficient to tackle the problem of chemical pollution (van Wezel et al., 2017). Technological curative measures will remain relevant at the end-of-life stage when emissions cannot be prevented, but preventive measures could be placed at the outset of the chemical life cycle. Designing Safe and Sustainable chemicals and materials is a promising option as its potential impact is expected to be high whilst costs are low (Peijnenburg et al., 2021; Puhlmann et al., 2021). As part of the EU Green Deal -the new growth strategy to transition the EU economy into a sustainable model and become climate-neutral by 2050- a Chemical Strategy for Sustainability was published. Here, the development of Safe and Sustainable chemicals is identified as a societal urgency and economic opportunity (European Commission, 2020). Products and materials are ideally designed for a circular economy using Safe and Sustainable chemicals to enable their recycling and reuse and to achieve a society where harm from chemicals is minimized (European Commission, 2020). The use of Safe and Sustainable chemicals is furthermore important as in many cases the release of substances from products or materials cannot be prevented.

The design of Safe and Sustainable chemicals requires an approach where a chemical's performance is not only seen as the ability to provide a certain function but inherently includes sustainability and hazard mitigation (Zimmerman et al., 2020). The concept of Green Chemistry provides a framework for this, aiming to generate more benign chemicals by taking into account a chemical's life cycle in order to increase resource efficiency and minimize waste (Anastas and Warner, 1998). This concept is further expanded to Circular Chemistry by making chemical processes circular when waste is used as a resource for new products (Keijer et al., 2019). In order to design chemicals that are not only sustainable but also safe, it is essential to consider the hazards of chemicals in the design phase. This is however seen as one of the least developed areas of Green and Circular Chemistry, and therefore requires urgent attention (Erythropel et al., 2018).

With regard to environmental hazards, substances that are persistent, bioaccumulative and toxic (PBT), or even very persistent and very bioaccumulative (vPvB), pose the highest risks. The mobility (M) of chemicals has been proposed as an additional criterion in order to identify substances that are highly polar as they put the quality of surface waters and drinking water at risk (Hale et al., 2020; Reemtsma et al., 2016; Schulze et al., 2019). These PBMT criteria are inherent properties of chemicals and can therefore be a design choice. Most pesticides and biocides, for example, are designed to be toxic to certain organisms as their desired function, yet their action should be highly selective, not harming other organisms and negatively impacting biodiversity and the environment. Persistency can be an asset for chemicals in closed loops in a functioning circular economy, but is a reason for concern when the emission of chemicals to the environment cannot be prevented (Kümmerer et al., 2020). This can result in accumulation of the chemical with its ongoing usage, increasing the likelihood of long-term exposure that result in adverse effects (Cousins et al., 2019b).

A systems level thinking is required to make choices on chemical design acknowledging that systems on Earth are interconnected (Matlin et al., 2016; Zimmerman, 2020). Systems level design thinking can be applied to design new chemicals, as well as to redesign chemicals that are already in use. By identifying relevant hazards and processes related to the environmental fate and behavior, the designer can choose to design for circularity, degradation, or in some cases a combination of the two (Cucciniello and Anastas, 2021; Keijer et al., 2019). Before choosing for a redesign approach, already existing alternatives and the essentiality of the use of the chemical are to be considered according to the frameworks of Essential Use and Alternatives Assessment (Cousins et al., 2019a; Tickner et al., 2015). A chemical can be phased out when suitable alternatives exist or when the chemical fulfils a non-essential function to society.

Redesign of chemicals to minimize persistency is relevant when emissions to the environment cannot be avoided, aiming for complete mineralization of the structure to prevent the generation of possible hazardous transformation products (Puhlmann et al., 2021). Various examples of chemicals designed with reduced persistency exist, including pharmaceuticals, ionic liquids and plasticizers (Erythropel et al., 2018; Jordan et al., 2016; Leder et al., 2015; Rastogi et al., 2015). In silico models such as quantitative structure–activity relationships (QSARs) are important tools in the design process to discover potential unwanted properties such as persistency early on (Erythropel et al., 2018; Gramatica et al., 2016). QSAR models assume that physio-chemical and environmental properties are linked to the chemical structure and molecular properties of a compound and are widely used to fill regulatory data gaps in registration dossiers (Pizzo et al., 2013). Elucidating unwanted effects can also prevent regrettable substitution; replacing a chemical with a structurally similar one that is less-studied, but ends up being equally or even more hazardous than the chemical it replaces (Maertens et al., 2021). Furthermore, in silico calculated properties can inform chemical design by prioritizing the most promising structures for further testing (Burello, 2015).

In the present study we aim to develop a framework to select chemicals for redesign and a systematic, computer-aided workflow to facilitate the redesign of these chemicals for reduced environmental and human health (PBMT) hazards with in silico generated structure suggestions. The organophosphate compound triisobutylphosphate (TiBP) was selected as case study to which we apply our computer-based approach for redesign. The method section gives an overview of the process to identify chemicals suitable for redesign, which includes considerations of available alternatives and essentiality. Then, the computer-aided redesign process is introduced, comprised of exhaustive structure generation, property prediction using QSARs and multi-criteria analysis of PBMT parameters and synthesizability. The results and implications of applying the developed redesign approach to TiBP

are subsequently discussed, as well as the experimental results obtained to verify QSAR predictions. We show how redesign for safety and sustainability can be facilitated by a systematic and exhaustive generation of alternative structure suggestions and assessment of predicted PBMT properties, uncovering the most benign molecules. Current shortcomings and future advancements of our redesign approach are discussed, which will promote further developments according to the principles of Green and Circular Chemistry.

2. Methods

Criteria to identify chemicals suitable for redesign were identified, including considerations of available alternatives and essentiality, and presented in Fig. 1. Following the flowchart, only chemicals which do not provide an essential function for society and/or health and for which no suitable alternatives are available are selected for a redesign approach (Cousins et al., 2019a; Tickner et al., 2015). Dependent on whether environmental emission of the chemical can be prevented or not, a redesign approach for recycling or degradation is chosen (Cucciniello and Anastas, 2021).

After the selection of the chemical for redesign -in our case TiBP- a three-step redesign process inspired on the design-make-test-analyze cycle used in drug discovery was followed (Fig. 2) (Plowright et al., 2012). First, (I) a set of alternative structure suggestions were generated *in silico*. Then, (II) QSARs were selected and applied to relevant hazardous properties of the generated structure suggestions. Subsequently, (III) the number of alternative structures was reduced by applying a filter for biodegradability followed by an analysis of PBMT properties and synthesizability. The structures were ranked and a target structure was selected manually, after which it was synthesized and tested. The redesign was implemented in python. Jupyter notebooks are available on GitHub (https://github.com/HannahFler/safedesign).

2.1. Generation of alternative structures

2D chemical structures were generated from chemical formulas with the Parallel Molecule Generator (PMG 1.0), the second version of the opensource software Open Molecule Generator (OMG) which allows for parallelization to reduce runtime (Jaghoori et al., 2013; Peironcely et al., 2012). PMG aims at an exhaustive generation of chemical structures, in SDF format, from a given elemental composition (expressed as chemical formula) and core structural fragment, hence generating every structure possible for that composition. It facilitates the systematic generation of alternative structures with moderate computational expense needed. As the software was created for analytics, some chemically unrealistic structures under normal conditions can be generated. The QSARs used in the subsequent steps to predict properties partly filter these out.

Trimethyl phosphate (SDF format, generated with ChemDraw Professional, version 19.0.1.28) was used as core structural fragment for PMG to preserve the organophosphate core as essential structural feature of TiBP for the function of flame retardancy. The phosphate core can form char residue by crosslinking, blocking access to fuel, and form phosphorus containing radicals in the gas phase inhibiting flames, therefore exhibiting flame retardant properties (Velencoso et al., 2018). Chemical formulas were systematically generated to be passed on to PMG. CH_2 units were added to a starting formula, which in turn was varied to include nitrogen or additional oxygen as heteroatoms and double bond equivalents, which result in rings or multiple bonds in the generated structures. For example, the starting formula $C_4H_{11}PO_4$ was used to generate organophosphate structures with different alkyl side chains upon addition of CH_2 units, and the starting formula $C_4H_{11}PO_5$ was used to include one additional oxygen as heteroatom in the side chains. The number of CH_2 units added per starting formula was determined mainly by computation time. An overview of all elemental
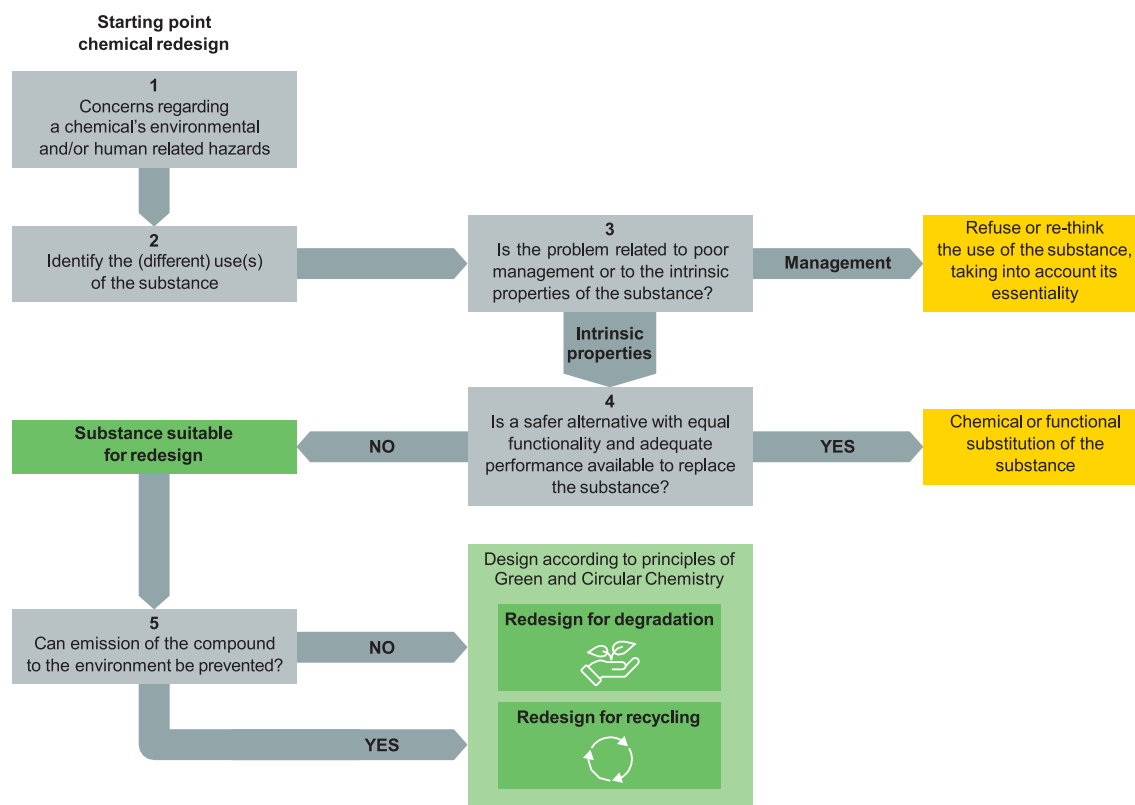
Fig. 1. Flowchart for selecting chemicals for a redesign approach, inspired by concepts of Essential Use, Alternative Assessment and Green and Circular Chemistry (Anastas and Warner, 1998; Cousins et al., 2019a; Cucciniello and Anastas, 2021; Keijer et al., 2019; Tickner et al., 2015; Wang and Hellweg, 2021). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)
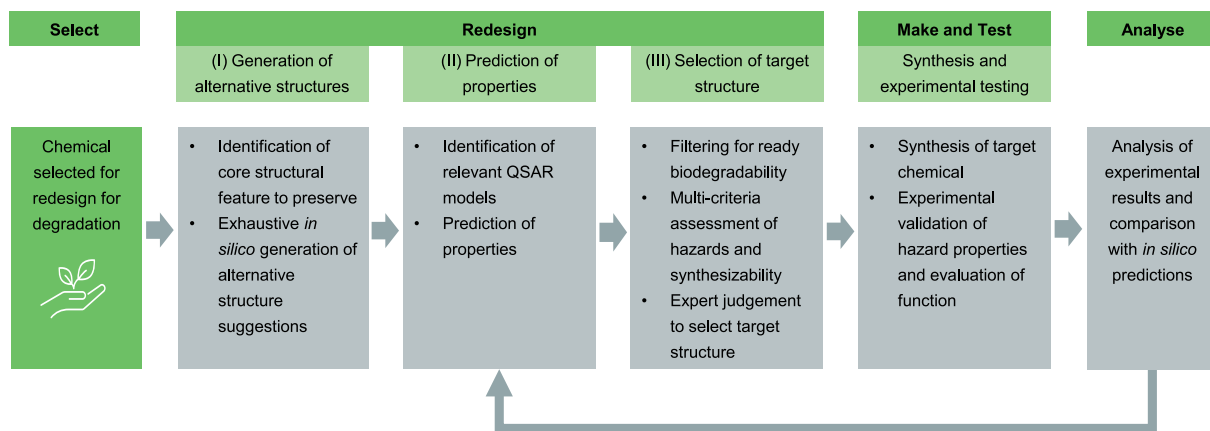
Fig. 2. Workflow for the systematic, computer aided redesign approach for Safe and Sustainable chemicals.

compositions for which structures were generated and the respective starting formulas is shown in Fig. 3. Generated enol structures were filtered out, as they would generally tautomerize to their keto form, which were already included in the structure set. The python package RDKit (Landrum et al., 2021) was used to handle chemical structures and translate SDF mol files to SMILES codes to be used in the subsequent steps.

2.2. Prediction of properties

A list was compounded with the generated structures as SMILES codes that were used as input to calculate P, B, M and T properties by using QSAR models from EPISuite (Epiweb version 4.1) and models included in the VEGA platform (Benfenati et al., 2019). The applicability domain of the models was manually checked by following the approach described in an OECD Guidance Document (OECD, 2007). Ranges of molecular weight and LogKow were defined for the model training and

test data sets. These data sets were also searched for structural similarities to the case study compound TiBP, of which a summary is presented in Table S1 in the SI. The number of endpoints able to be modeled was constrained, as our dataset fell outside the applicability domain of some QSARs. Some uncertainty regarding the applicability domain remains however, as the models are applied to a large number of diverse *in silico* generated structure suggestions. The QSAR results were thus treated as indications to guide the design.

2.3. Multicriteria analysis for selection of target structure

To reduce the size of the dataset, potential non-readily biodegradable substances were filtered out based on the EPISUITE cut-off criteria for combined results from the models BIOWIN 3 and 5, as described in the BIOWIN user manual (BIOWIN $3 \geq 3.25$ and BIOWIN $5 \geq 0.5$, US EPA, 2012). Structures which were predicted to be mutagenic by VEGA Ames test consensus model were also filtered out, as well as structures
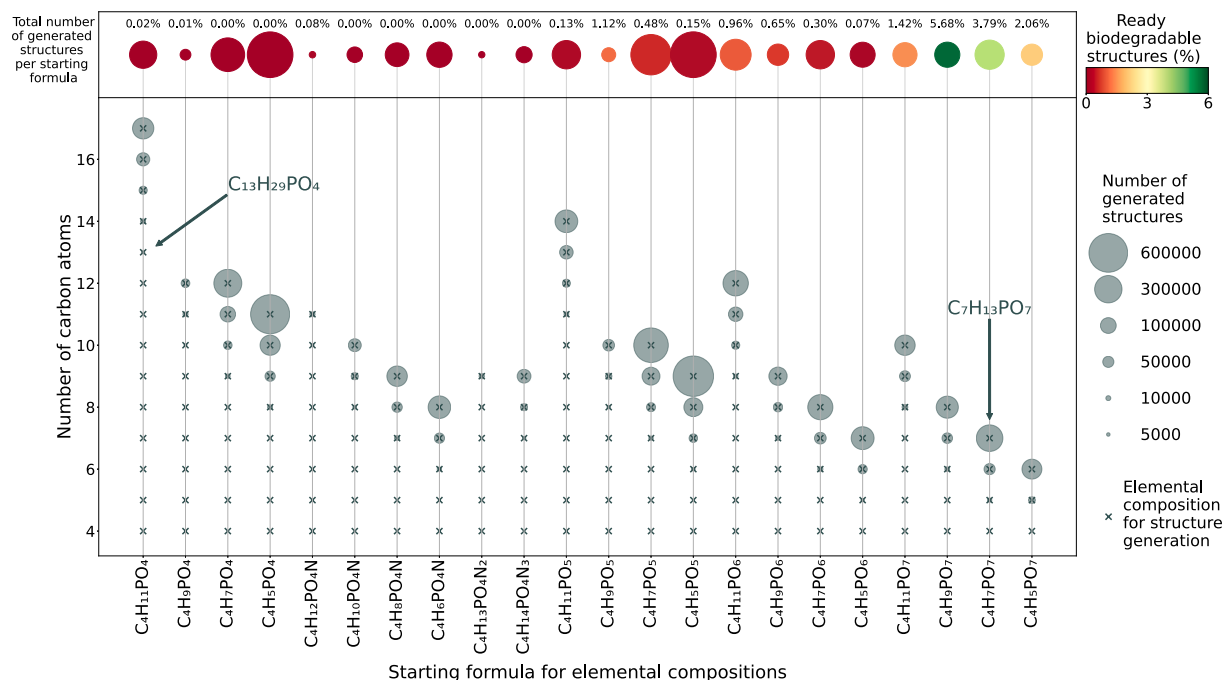
Fig. 3. Overview of the *in silico* generated structures and their ready-biodegradability. The starting formula for structure generation is shown on the x-axis. The y-axis shows the number of carbon atoms present in the elemental compositions. Each elemental composition for which structures were generated is marked by an x. Two formulas are shown as examples. The size of the bubbles indicates the number of structures generated for that particular elemental composition. The top plot shows the amount of generated structures per starting formula, and the colors represent the percentage of readily biodegradable structures as predicted by EPISUITE. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

which were predicted active in estrogen, androgen, thyroid alpha or beta receptor effects. Then, a multi-criteria analysis based on the Multi-Attribute Utility Theory (MAUT) principle was performed on hazard and synthesizability related endpoints. Criteria and endpoints used in the MAUT assessment are shown in Table 1. Values of an endpoint were scaled from 0 (worst) to 1 (best) based on results of the whole dataset for that specific endpoint to generate an endpoint sub-score. For LogKow and LogKoc, desirability functions were designed to calculate subscores, indicating optimal ranges for the values based on reported criteria and avoiding hard cut-off values (see SI Figure S1) (Segall, 2012).

Persistency was calculated based on biodegradability outcomes,

Table 1
QSAR models and their application used for the characterization of P, B, M, T and S properties for the MAUT assessment.

Criteria	Endpoint	QSAR model	Application of QSAR: Filter or Ranking (with desired value or range)	Weight for MAUT assessment
P	Ready biodegradability	EPISUITE: BIOWIN 3 and BIOWIN 5	Pre-selection filter	Not used for scoring
	Aerobic biodegradability	EPISUITE: BIOWIN 3 and BIOWIN 6 (average)	Ranking (desired value as high as possible)	0.5
	Anaerobic biodegradability	EPISUITE: BIOWIN 7	Ranking (desired value as high as possible)	0.5
B	BCF	EPISUITE: BCFBAF	All structures predicted non-concerning	Not used for scoring
	LogKow	EPISUITE: KOWWIN	Range between 1 and 3 [1].	1
M	LogKoc	EPISUITE: KOCWIN and VEGA: OPERA KOC (average)	Ranking (undesired below 1, soft lower cutoff between 1 and 2. Desired value between 2 and 4 [2])	1
T	Non-Mutagenicity	VEGA: consensus model	Pre-selection filter and ranking of reliability (desired value as high as possible)	1
	EDC properties: Estrogen, Androgen, Thyroid alpha and beta receptor effects	VEGA: Estrogen (IRFMN/CERAPP), Androgen (IRFMN/COMPARA), Thyroid alpha/beta (NRMEA)	Pre-selection filter with qualitative outputs	Not used for scoring
S	Synthesizability based on chemical symmetry (SynSymPoints)	None, score created using rdkit and SMARTS substructure matching	Ranking (desired value as high as possible)	0.5
	Exclusion of small rings (SynRingPoints)	None, score created using rdkit and SMARTS substructure matching	Ranking (negative value for rings, desired value as high as possible)	0.5

[1] (EU, 2006).
[2] (Arp and Hale, 2019).

which is composed of both aerobic and anaerobic processes. For aerobic degradation, model outputs of BIOWIN 3 and 6 models were combined for the MAUT assessment as this combination of models was shown to have the highest overall predictivity for biodegradation (Posthumus et al., 2005). Anaerobic degradation was predicted with BIOWIN 7. The LogKow, as predicted by KOWWIN, was used as a parameter for bio-accumulation. LogKoc values to estimate mobility were obtained by averaging predictions from KOC OPERA model from VEGA and KOCWIN model from EPISUITE. The BCF, which is used as a parameter to identify bioaccumulative substances under REACH (Regulation (EC) 1907/2009, Annex XIII), was predicted for all substances in our list to be non-concerning and therefore not further taken into account in the analysis. The non-mutagenicity score from VEGA ames test consensus model was included for toxicity. For synthesizability, two scores were created. One by rewarding organophosphate structures with equal side chains (SynSymPoints) as these more symmetric molecules are generally easier to synthesize than those with different side chains which requires more specificity of the synthetic strategy. Structures with no equal side chains received score 0, those with two equal side chains score 0.5 and those with all equal side chains a score of 1. Structures containing three- or four-membered rings were penalized with a score of −1 (SynRingPoints), as these rings are more difficult to synthesize. Furthermore, these rings rarely appear in the training datasets of the QSAR models used to predict properties, which makes the estimates for this kind of structures less reliable. After assigning scores for every endpoint between 0 and 1, partial scores for PBMTS were calculated by multiplying each criterion with the respective weight (see Table 1). All PBMTS criteria had a final weight of 1, treating them as equally important in the MAUT analysis. The partial scores were then summed up and normalized by dividing by the sum of weights to get a final PBMTS score. Accordingly, the alternative structures with the highest PBMTS score were expected to be the most desirable structures regarding their assessed PBMTS properties.

The top 500 structure suggestions according to the scoring were examined manually to select a target molecule. This selection was guided by chemical stability (e.g., no structures with geminal diols, as they would undergo dehydration and form a carbonyl moiety), the identification of potential starting materials, such as the renewable ethylene glycol, and the possibility of systematic structural comparison with the original compound TiBP.

3. Results and discussion

3.1. Identifying chemicals for redesign

In the first step to select a substance for a redesign approach (Fig. 1), chemicals are considered that are present in the environment and for which concerns have been raised regarding risks to humans or ecosystems (Wang and Hellweg, 2021). Within this context, the organophosphate TiBP was selected as an example to showcase our new methodology. TiBP has been detected in water bodies and was added to the NORMAN list of emerging substances (Alygizakis et al., 2019). The second step is to identify the different uses of the substance. At present, there are 8 companies which have a registration for TiBP in the EU, each using between 1.000 and 10.000 tonnes annually as a solvent, plasticizer, anti-foaming agent and additive flame retardant (ECHA, 2020). Here, we focused on its use as an additive flame retardant for textiles as organophosphate flame retardants are generally known to be a group of concern (Blum et al., 2019; Pantelaki and Voutsa, 2019). Flame retardants are released from their textile matrix and potentially end up in the environment during washing or from wear and tear (Luongo et al., 2016). Emission of TiBP to the environment can thus be assigned to its intrinsic properties and specific uses, and not to mismanagement (step 3). In this step, the essentiality of the substance is considered as well to phase-out hazardous substances that don't contribute to health or society (Cousins et al., 2019a; European Commission, 2020). The outcome

of this step could change for certain chemicals depending on what uses can be considered essential (Cousins et al., 2021). It will, however, be hard to justify banning chemicals that are considered non-essential, but that contribute to society's comfort. For these functions, improved chemical or product design will play a pivotal role to reduce environmental emissions from manufacturing to end-of-life stages (Wang and Hellweg, 2021). In step 4 it is considered whether the function the chemical provides can be substituted by better alternatives. As no database with an overview of different flame retardants for textiles exists to our knowledge, it is difficult to evaluate for step 4 whether better alternatives for TiBP are already available and what the reasons would be that they are not used industrially. Phosphorus-based flame retardants are however already considered as a better alternative compared to e.g. brominated flame retardants, and therefore offer a promising starting point for the design of a benign additive. Chemicals containing phosphate are also of interest in the context of circularity as phosphate can be well recovered from wastewater effluents and subsequently reused (Jupp et al., 2021). A redesign approach for degradation was chosen, as emission of TiBP as a result of its use as an additive flame retardant cannot be prevented (step 5).

3.2. Generation of alternative structures

By repurposing software developed for metabolomics, we enabled a systematic search for alternatives for TiBP with a similar chemical structure. By combining the structure generation with data collection on potential PBMT properties, we aimed to prevent proposing a regrettable substitute as an alternative to TiBP.

More than 6.3 million structures were generated *in silico* to facilitate the redesign of TiBP. The difference in number of structures per elemental composition and in computing time resulted in a heterogenous number of CH_2-units added per starting formula, and thus in number of elemental compositions with the same double bond equivalents and heteroatoms. Fig. 3 shows the elemental compositions used for the PMG program for the exhaustive generation of structures. The combination of starting formula (x-axis of Fig. 3) and the total number of carbon atoms (y-axis of Fig. 3) yields the elemental composition, e.g. at the starting formula $C_4H_{11}PO_4$ (on the x-axis) with 13 carbon atoms (on the y-axis), the elemental composition $C_{13}H_{29}PO_4$ is represented (see left arrow in Fig. 3) for which PMG generated all possible structures. The starting formula $C_4H_7PO_7$ and 7 carbon atoms denotes the chemical formula $C_7H_{13}PO_7$ (see right arrow in Fig. 3), for which structures containing three additional oxygen atoms and two double bond equivalents were generated.

3.3. QSAR predicted properties

All generated structures were filtered based on their predicted ready-biodegradability according to EPISUITE cut-off criteria (US EPA, 2012), which greatly reduced the dataset from about 6.3 million generated structure suggestions to 32,350 structures. The fraction of structures predicted to be readily biodegradable according to this cut-off was generally highest in sets of structures generated from elemental compositions with more oxygen atoms (Fig. 3), in accordance with rules of thumb indicating increased biodegradability with the introduction of oxygen handles (Boethling et al., 2007). Structures which were predicted to be mutagenic by the VEGA mutagenicity consensus model were also filtered out (1057 structures), as well as structures which were predicted to be active in endocrine disruption according to VEGA models listed in Table 1 (46 structures).

Other relevant properties for the PBMT assessment were predicted with selected QSAR models from EPISUITE and VEGA platform. Results of all QSAR outcomes can be found on GitHub (https://github.com/HannahFler/safedesign). Uncertainties of QSAR-generated data are higher compared with experimental data, but these were partly addressed here by examining the applicability (Ballabio et al., 2017; Pizzo et al., 2016;

Posthumus et al., 2005). It is however important to note that some uncertainty always remains with setting the applicability domain (Netzeva et al., 2005).

Improvement of the reliability of QSAR predictions -especially of biodegradability-is greatly needed (Rücker and Kümmerer, 2012). Concerns have for example been raised regarding the potential (eco) toxicity of organophosphate flame retardants (Blum et al., 2019). Due to their toxic properties, some organophosphate flame retardants (including Trixylyl phosphate and Tris(2-chloroethyl) phosphate) are already included on the candidate list of SVHC for authorization under REACH (ECHA, n.d.). Models to predict endpoints such as carcinogenicity and ecotoxicity could however not yet be included in our approach as their applicability was considered to be unsatisfactory (see SI for further details). In order to improve the reliability of model outcomes in the future, a consensus approach could be applied in which outcomes of multiple models are combined and averaged (Gramatica et al., 2012). The PBT index as reported by Gramatica et al. (2016) offer for example promising tools to strengthen the assessment of persistency, bioaccumulation and toxicity related endpoints (Gramatica et al., 2016). In addition, QSARs to predict functionality as a flame retardant (Gu et al., 2019; Zhang et al., 2020) would be useful to include in order to enhance the approach and filter structures based on their functionality. However, these models currently don't seem suitable for the screening of a large library of structures with limited associated data (SMILES codes). In our framework, the preservation of the organophosphate core retains the key structural feature linked to flame retardancy (Velencoso et al., 2018). Beyond that, properties relating to the interaction with the material matrix are important to the success of an alternative, which depend on the specific application as well as manufacturing techniques.

3.4. Multi-criteria analysis

A multi-criteria ranking of the remaining 31,247 structures was made based on PBMTS properties to find the most desirable structures (Fig. 4). For persistency, the endpoints for aerobic biodegradability and anaerobic biodegradability were evaluated, for bioaccumulation the LogKow was used and for mobility the LogKoc was considered. For toxicity, only the non-mutagenic score given by the VEGA consensus model could be included as our dataset fell outside the applicability domain of other relevant QSAR models. To include the synthesizability in the analysis, identical side chains (SynSymPoints) were rewarded and small rings (SynRingPoints) were penalized (Table 1). The distributions of the dataset of alternative structures for each endpoint are presented in the SI.

The combined use of QSAR-generated data and MAUT analysis to identify the most desirable alternative structure has been previously reported (Zheng et al., 2019). The selection of appropriate parameters and QSAR models is a key step in this process, but the type of parameters and models that are useful might differ on a case-by-case basis as the redesign goals and the endpoints that are considered relevant might differ. Furthermore, the weight applied on the parameters in the PBMTS MAUT assessment is a key factor which affects the order of the list of most suitable structures. This emphasizes that the (re)design for Safe and Sustainable chemicals requires a combination of different expertise working together to ensure that all relevant parameters and issues considering a chemical's function and hazard are properly understood and taken into account (Plowright et al., 2012; Zimmerman et al., 2020).

3.5. Manual target selection

The top 500 structures according to the PBMTS score ranking were inspected to search for suitable targets. By inspecting the alternative structures based on the PBMTS MAUT ranking, di-*n*-butyl (2-hydroxyethyl) phosphate, which ranked 22nd in the analysis, was selected as the target compound. Figure S1 in the SI shows the top 25 structures of the PBMTS scoring for illustrative purposes (see Jupyter notebooks on
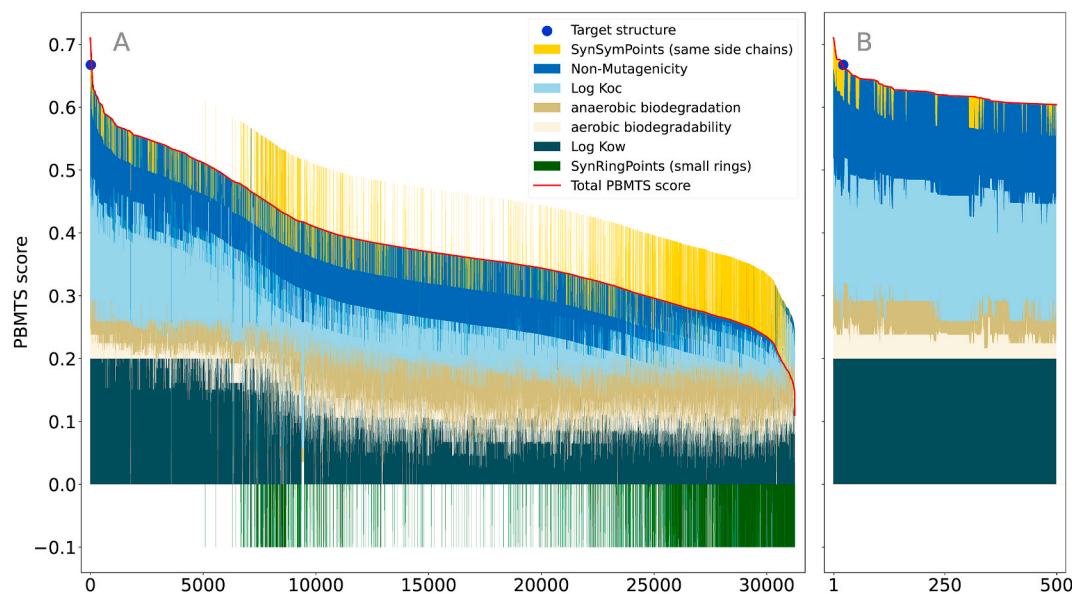
Fig. 4. Composition of the PBMTS score of the complete set of *in silico* generated structures which were predicted to be readily biodegradable (A) and the 500 top-scoring structures (B), sorted from highest to lowest ranking structure. Structures containing 3- or 4-membered rings were penalized with a negative sub score (SynRingPoints, plotted in dark grey), leading to a lower total PBMTS score (plotted as red line) for the respective structures. The selected target compound is shown as blue dot. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

GitHub for the complete overview). In contrast to many of the top 500 structures, the target compound is chemically stable and has a 2-hydroxyethyl moiety which offers the possibility of using commercially available ethylene glycol and di-*n*-butyl phosphate for the synthesis. The higher ranked structures often contain a hydroxymethyl group which is generally harder to obtain as the C_1-diol building block methanediol is not stable and can oligomerize to $HO(CH_2O)_nH$. Furthermore, the chosen target allows for structural comparison with the original compound TiBP, as the two other side chains have a chain length of four carbon atoms, as compared to higher ranked structures with longer side chains. Moreover, phosphates with C_4 chains are more common in industry, e.g. di-*n*-butyl phosphate is more attainable and economical than di-*n*-pentyl phosphate. The di-*iso*-butyl isomer of the target compound was not predicted to be readily biodegradable and was thus not included in the dataset of possible alternative structures. Consistently, branched hydrocarbon chains are reported to result in lower biodegradation rates compared to similar structures with linear chains (Liang and Liu, 2016). The selected alternative structure was expected to be better water soluble due to its lower LogKow as a result of the added hydroxyl group. Water-soluble substances usually biodegrade faster than substances with a high LogKow, as the latter sorb strongly to the sediment diminishing their bioavailability. In addition, the added hydroxyl group and the linear alkyl chains were expected to increase the biodegradation potential of the structure as well (Boethling et al., 2007).

In addition to the chemical stability and hazard profile of the chemical, attention was paid to the sustainability of potential production routes of the designed alternative. As an organophosphate chemical, the starting materials could be renewably sourced from P-rich waste streams. Furthermore, the hydroxyethyl side chain of the target could be introduced using ethylene glycol, which is a readily available base chemical with a high potential for sustainable production (Figueiredo, 2020; Kandasamy et al., 2019). The target di-*n*-butyl (2-hydroxyethyl) phosphate is a known compound (CAS 130525-77-8) with mentioned potential applications as a flame retardant and as additive in lubricant oils (Matsumura and Tokuyasu, 1999; Shono and Ogata, 2018). It has also been identified as a metabolite of tri-*n*-butyl phosphate in earthworms (Wang et al., 2018). One preparation of the compound is described in patent literature, starting with di-*n*-butyl phosphate and ethylene oxide (Matsumura and Tokuyasu, 1999) yet no characterization of this compound was reported to date. Furthermore, the compound is not registered in the EU under REACH, nor does it seem to be registered in another region (OECD, n.d.) indicating the compound is currently not produced and used at industrial levels.
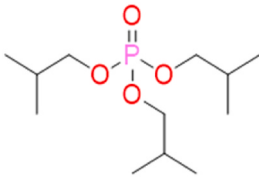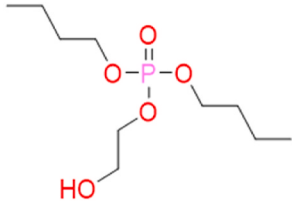
3.6. Experimental and in silico properties: TiBP vs target compound

We synthesized the target compound from di-*n*-butyl phosphate using oxalyl chloride for activation and subsequent addition of excess ethylene glycol. No attempts were undertaken to optimize the synthesis in this study, but the development of organophosphate synthesis protocols adhering to the principles of Green and Circular Chemistry is ongoing in our laboratories. For example, the design of TiBP can be made circular when degradation products are used as the starting materials for a new cycle (Cucciniello and Anastas, 2021). This can be achieved by mineralization of a structure, generating phosphate that can be retrieved from wastewater and used as a source for the production of new chemicals (Jupp et al., 2021). Mineralization is furthermore desirable as metabolites and transformation products might be equally or even more hazardous than the initial structure (Noguera-Oviedo and Aga, 2016).

In silico predicted properties and results of experimental testing of TiBP and the target compound are summarized in Table 2. The *in-silico* properties of the target compound show an improvement regarding environmental hazards as, contrary to TiBP, it is predicted to be both readily biodegradable and degradable under anaerobic conditions. Furthermore, the predicted LogKow of the target compound is lower than the regulatory trigger value of 3 for bioaccumulation. Model outcomes should be considered with due prudence and need to be validated with relevant experimental testing.

For both TiBP and the target compound, results of the OECD301F test show that degradation is started after an adaptation period of 10 days. The results furthermore suggest that the substances are equally degradable (SI), but neither of them can be considered as readily biodegradable because the degradation rate did not reach 60% within 28 days. Contrary to the *in silico* prediction, the target compound is not more biodegradable than TiBP in this experiment, opening two pathways for further investigation. Following these results, another structure can be selected to reiterate and continue the design cycle (Fig. 2). On the

Table 2
Comparison of experimental and *in silico* predicted properties of TiBP and the target compound.

	Original compound: TiBP	Target Compound: di-*n*-butyl (2-hydroxyethyl) phosphate
Structure		
CAS number	126-71-6	130,525-77-8
SMILES	CC(C)COP(=O) (OCC(C)C)OCC(C)C	CCCCOP(=O) (OCCO)OCCCC
Mw	266.31 g/mol	254.27 g/mol
In silico predicted properties		
LogKow	3.6	1.37
LogKoc	3.15	1.79
BCF	16 (does not bioaccumulate)	2 (does not bioaccumulate)
Readily Biodegradable (BIOWIN 3 & 5)	No	Yes
Anaerobic degradation (BIOWIN 7)	Does not biodegrade fast	Biodegrades fast
Experimental properties		
Biodegradation (OECD301F)	Non-readily biodegradable after 28 days	Non-readily biodegradable after 28 days
Agonistic effects on the hormone system	No	No
Antagonistic effects on the hormone system	No	No
Functionality as FR	Yes (ECHA, 2020)	Yes (Matsumura and Tokuyasu, 1999)
TGA char yield (Figure SI1)	7%	20%

other hand, the biodegradation process can be experimentally assessed in more detail to arrive at more definite conclusions for a more limited set of compounds. Many issues can make the outcomes of biodegradation tests difficult to interpret. For example, it is interesting to note that TiBP is considered to be readily biodegradable in the REACH dossier based on an OECD 301 test (ECHA, 2020). The use of different inocula is shown to yield highly variable biodegradation outcomes, resulting in a lack of reproducibility of these tests (Poursat et al., 2019). This lack of reproducibility could partly be overcome by using chemostats and by introducing an adaptation period of the inoculum to the chemical in future testing (Gresham and Hong, 2015; Poursat et al., 2020). Furthermore, other types of testing such as OECD 308 and 309 tests can be performed to gain better insights on the behavior of a compound in specific environmental media (Seller et al., 2021). These tests could also generate insights into the mechanisms of the degradation process and hint at further possibilities to improve the molecular design process and the predictive tools used in the design process.

Thermogravimetric analyses (TGA) suggest that the function of TiBP as a flame retardant is successfully retained in the designed alternative structure. The TGA monitors the weight loss as a function of temperature and the remaining char yield, which hints both at condensed phase activity for flame retardancy and at reduced emission of potentially combustible gases (Markwart et al., 2019; Rakotomalala et al., 2010). The functionality might even be enhanced due to a higher char yield of 20% for the target compound compared to a yield of 7% for TiBP (Table 2). The target compound could exhibit benefits compared to TiBP as, due to its potentially enhanced functionality as a flame retardant, less material might be needed to provide the same level of protection. More extensive testing must be performed to confirm flame retardant properties of the target compound, especially by application to the material that the substance aims to protect. Additionally, environmental fate needs to be further assessed in realistic conditions to evaluate the suitability of the target as a benign alternative to TiBP.

4. Improvements needed to account for biodegradability in the design process

Despite the need to further improve QSARs that predict ready biodegradability (Mamy et al., 2015), they are useful tools to screen large amounts of substances to guide the (re)design of Safe and Sustainable chemicals in an early stage. Since biodegradation occurs via a

variety of different mechanisms, induced by different environmental variables that are currently not completely understood (Fenner et al., 2021), it will remain difficult to accurately predict the biodegradation of a chemical in the environment. The vast number of variables that influence the degradation of a substance in the environment can, for example, not only result in different outcomes between laboratory and field, but also in space and time (Seller et al., 2021). Alternative techniques are being developed that can cope with these aspects (Fenner et al., 2021), yet these methods are all experiment-based and therefore not suitable for incorporation in our redesign approach to screen vast amounts of novel structures. These techniques will provide valuable insights into the various biodegradation processes, however, which we are currently exploiting in our laboratories to advance our *in silico* tools used in the (re)design process.

5. Conclusions

Here, we developed a systematic approach to facilitate the design of Safe and Sustainable chemicals in order to reduce hazards whilst the chemical's function is maintained. The approach was applied to TiBP as a case study, yet can be applied to other molecular structures. At first, we evaluated whether TiBP would classify for a redesign approach. By incorporating aspects from the EU Green Deal's Chemicals Strategy for Sustainability, only chemicals that provide an essential function and for which no suitable alternatives are available are of relevance to be selected for redesign. Depending on whether emission of the chemical to the environment can be prevented or not, a redesign approach for recycling or degradation is chosen. Considering that TiBP can leach out of textiles during washing, a redesign approach for degradation was chosen. Next, a three-step redesign process was developed in which alternative structures were generated *in silico* and ranked based on their QSAR-predicted PBMT hazards and synthesizability. Predicted properties of the selected alternative (di-*n*-butyl (2-hydroxyethyl) phosphate) show favorable characteristics compared to TiBP, while first experimental results do not confirm enhanced biodegradability. The implementation of our approach to design chemicals that are functional, safe and sustainable is largely dependent on the availability of suitable tools and methods to predict environmental fate and related hazards. It is therefore key that the knowledge on the mechanisms of biodegradation will be improved so that testing methods can be improved in order to advance the much-needed Chemicals Strategy for Sustainability and

help mitigate chemical pollution. Studies like the present can provide valuable input for this strategy and can help taking Green and Circular Chemistry principles for the design of Safe and Sustainable chemicals into practice. By using future advances of testing methods and by looking beyond a chemical's intended function only, environmental hazards can be minimized to allow chemicals to continue to provide vital functions to society.

6. Experimental section

6.1. Synthesis of the target compound: di-n-butyl (2-hydroxyethyl) phosphate

The synthesis was performed with standard Schlenk technique under an atmosphere of dry nitrogen. Dry solvents were obtained from a solvent purification system, where DCM was dried over $CaCl_2$. DMF was dried with $MgSO_4$ or molecular sieves and distilled. Triethylamine was purified by distillation. Other reagents were used as received. NMR spectra were measured with a 400 MHz Bruker Avance NMR spectrometer and calibrated internally to residual solvent resonances (^{1}H, δ 7.26 ppm (chloroform-d); ^{13}C, 77.36 ppm (chloroform-d)). The software "Bruker TopSpin" (version 4.1.3) was used to analyze the spectra. The IR spectrum was measured with a Bruker Alpha FT-IR spectrometer equipped with a Platinum ATR module. High resolution electrospray ionization (ESI) mass spectra were recorded with flow injection (flow rate 0.01 mL/min) on an AccuTOF LC, JMS-T100LP mass spectrometer (JEOL, Japan) in positive-ion mode with a needle potential of 2500 V. The synthesis protocol was oriented on procedures described in literature (Hilken et al., 2014; Pahor et al., 2016).

Synthesis of di-n-butyl (2-hydroxyethyl) phosphate: A solution of 9.9 mL (10.5 g, 50 mmol) di-*n*-butyl phosphate and 0.5 mL (0.46 g, 6.25 mmol) DMF in 100 mL DCM was added dropwise to a solution of 21.5 mL (31.7 g, 250 mmol) oxalyl chloride in 100 mL DCM at room temperature. Gas evolution was observed. The mixture was stirred for 3 h at room temperature. The solvent and excess oxalyl chloride were removed by vacuum distillation under nitrogen atmosphere. The remaining yellow solid was dissolved in 140 mL DCM. The resulting clear yellow solution was added dropwise over 25 min to a mixture of 14 mL (10.1 g, 100 mmol) triethylamine and 28 mL (31.0 g, 500 mmol) ethylene glycol in 40 mL DCM, while stirring in an ice bath. The mixture was stirred at room temperature for 1.5 h and then refluxed for 18 h. The reaction mixture was quenched with 200 mL water and the aqueous layer was extracted with 2x 100 mL DCM. The combined organic phases were washed (100 mL water, 100 mL sat. aq. NH_4Cl, 100 mL water), dried with $MgSO_4$ and filtered. The solvent was removed in vacuo, leaving 9.53 g (75% crude yield) of an orange oil behind. The product was purified by silica gel column chromatography. Two columns were run using diethyl and diethyl ether:ethanol 98:2 as eluent, respectively, yielding one pure fraction of a pale-yellow oil (2.27 g). Some other fractions containing products and few impurities were combined and purified on a second column (*n*-hexane: ethyl acetate 30:70 to 0:1) giving 2.37 g of a pale yellow oil (4.64 g purified product, 37% yield). R_f(diethyl ether) = 0.18, R_f(*n*-hexane: ethyl acetate) = 0.43. ^{1}H NMR (400 MHz, chloroform-d, 298 K): δ 4.11 (m, 2H; CH_2), 4.03 (q, AB-type, $^3J(H,H) = 6.7$ Hz, 4H; CH_2), 3.78 (m, 2H; CH_2), 3.14 (s, 1H; OH), 1.64 (quintet, $^3J(H,H) = 7.1$ Hz, 4H; CH_2), 1.38 (sextet, $^3J(H,H) = 7.5$ Hz, 4H; CH_2), 0.91 (t, $^3J(H,H) = 7.4$ Hz, 6H; CH_3). ^{13}C NMR (400 MHz, chloroform-d, 298 K): δ 69.8 (d, $^3J(C,P) = 23.4$ Hz, 1C; CH_2), 68.1 (d, $^3J(C,P) = 24.7$ Hz, 2C; CH_2), 62.3 (d, $^3J(C,P) = 21.1$ Hz, 1C; CH_2), 32.5 (d, $^3J(C,P) = 26.6$ Hz, 2C; CH_2), 18.9 (s, 2C; CH_2), 13.8 (s, 3C; CH_3). ^{31}P{^{1}H}-NMR (400 MHz, chloroform-d, 298 K): δ 0.1 (s, 1P). IR ν (cm^{-1}): 3406 (O–H, s), 2960–2875 (C–H, CH_3, s), 1463–1382 (C–H, CH_2, m), 1252 ((C–O)$_3$P=O), s), 1018 (P–O–C, s), 909–809 (C–C–O, m). HR-MS (70 eV, ESI) calculated for $[C_{10}H_{23}O_5P + H]^+$ 255.1361, found: 255.1350; calculated for $[C_{10}H_{23}O_5P + Na]^+$ 277.1181, found: 277.1221. *m/z*: 143 $[HOC_2H_4PO_4H_2+H]^+$, 199 $[HOC_2H_4PO_4HC_4H_9+H]^+$.

6.2. Testing the target compound with regard to functionality and hazard-related properties

To get a first indication about the functionality of the designed and synthesized alternative compound as a flame retardant, a TGA was performed. CALUX (Chemically Activated LUciferase eXpression) assays were performed by the company Bio Detection Systems (BDS) at Amsterdam Science Park to test for agonistic and antagonistic properties on hormone systems. Biodegradation was tested according to the OECD 301F test (OECD, 1992), performed by the company Ibacon GmbH (Rossdorf, Germany). Detailed description of the methods and results are presented in the SI.

Author contributions

Joanke van Dijk: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft preparation, Writing – review & editing, Visualisation. **Hannah Flerlage:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft preparation, Writing – review & editing, Visualisation. **Steven Beijer:** Conceptualization, Investigation, Writing – review & editing. **Chris Slootweg:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Annemarie van Wezel:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2022.134050.

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